CLINICAL GUIDELINES

Lab Management Program

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EviCore healthcare Clinical Decision Support Tool Diagnostic Strategies: This tool addresses common symptoms and symptom complexes. Imaging requests for individuals with atypical symptoms or clinical presentations that are not specifically addressed will require physician review. Consultation with the referring physician, specialist, and/or individual's Primary Care Physician (PCP) may provide additional insight.

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Clinical Use Guidelines

Clinical Use Guidelines

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Confirmatory Genetic Testing

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Description

The Centers for Medicare and Medicaid Services (CMS) developed the Clinical Laboratory Amendments (CLIA) in order to help regulate laboratory tests. CMS intended to use this program as a way to ensure that quality laboratory testing was performed. Laboratories that receive reimbursement from Medicare or Medicaid must be CLIA certified.[1]

Most genetic or genomic tests are performed in a CLIA certified laboratory and used for a clear medical purpose. However, some genetic or genomic tests are performed in a research laboratory that is not CLIA certified or as part of a direct to consumer test that is not necessarily performed for a medical purpose.

When genetic testing is performed in a research laboratory or in a laboratory that is not CLIA certified, it is important to confirm any genetic change found prior to using this information to change an individual's medical treatment.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for confirmatory genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

Criteria

Confirmatory single site genetic testing in a CLIA certified laboratory is medically necessary when the following criteria are met:

- A disease-causing genetic mutation (documented to be pathogenic or likely pathogenic by the laboratory, healthcare provider, or reporting service) was identified by a laboratory that is not CLIA certified (e.g. research lab), AND
- Healthcare providers can use the test results to directly impact medical care for the individual (e.g. change in surveillance or treatment plan)

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Exclusions

- Confirmatory genetic testing is not considered medically necessary if the original testing was performed in a CLIA certified laboratory.
- Confirmatory genetic testing is not considered medically necessary if healthcare providers cannot use the test results to directly impact medical care for the individual.
- Confirmatory genetic testing is not considered medically necessary for variants of unknown significance (VUS).
- Tests that are considered not medically necessary (e.g., APOE for Alzheimer's risk assessment) or experimental, investigational, or unproven (e.g., MTHFR) per eviCore clinical guidelines are not eligible for confirmatory testing.

References

1. Clinical Laboratory Improvement Amendments (CLIA). CMS.gov website. Available at: **https://www.cms.gov/regulations-and-guidance/legislation/clia**

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Experimental, Investigational, or Unproven Laboratory Testing

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Experimental, investigational, or unproven (E/I/U) molecular and genomic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures address by this guideline	Procedure codes
9p21 Genotype	81479
AidaBreast	0597U
AlloSure	0540U
Altera	81479
Apolipoprotein E Genotype (APOE)	81401
Apolipoprotein L1 (APOL1) Renal Risk Variant Genotyping	0355U
ARISk Autism Risk Assessment Test	81479
AssureMDx	81479
Augusta Hematology Optical Genome Mapping	0331U
Augusta Optical Genome Mapping	0260U
Avantect Ovarian Cancer Test	0507U
Avantect Pancreatic Cancer Test	0410U
BarreGEN	81599
BBDRisk Dx	0067U
Bladder CARE	0549U

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Procedures address by this guideline	Procedure codes
Bladder EpiCheck	81599
BluePrint Molecular Subtyping Profile	81479
BTG Early Detection of Pancreatic Cancer	0405U
CARDIO inCode Score (CIC SCORE)	0401U
CardioRisk+	0466U
CELLSEARCH CTC Test	86152, 86153
ChemoFX	81535 81536
Chromosome Genome Mapping	0454U
Clarava	0319U
Clarifi ASD	0170U
CNGnome	0209U
Cologuard Plus	0464U
ColonAiQ	0453U
ColonSentry	81479
ColoScape Colorectal Cancer Detection	0368U
ColoScape PLUS	0496U
Colvera	0229U
CyPath Lung	0406U
Cytogenomic (genome-wide) analysis, hematologic malignancy, structural variants and copy number variants, optical genome mapping (OGM)	81195
Decipher Bladder TURBT	0016M
DecisionDx Cutaneous Melanoma	81529
DecisionDx DiffDx - Melanoma	0314U
DecisionDx - SCC	0315U

E/I/U

Procedures address by this guideline	Procedure codes
DEPArray	0009U
DH Optical Genome Mapping/Digital Karyotyping Assay	0413U
Digitization of pathology slides	0760T, 0761T, 0762T, 0763T, 0848T, 0849T, 0850T, 0851T, 0852T, 0853T
EarlyDx MethylScan HCC	0565U
EarlyTect Bladder Cancer Detection (EarlyTect BCD)	0452U
EndoSign Barrett's Esophagus Test	0506U
Envisia Genomic Classifier	81554
Epi+Gen CHD	0439U
Epignostix CNS Tumor Methylation Classifier	0020M
EPISEEK MPE	0566U
EpiSign Complete	0318U
EpiSwitch CiRT	0332U
EpiSwitch Prostate Screening Test	0433U
ERA (Endometrial Receptivity Analysis)	0253U
EsoGuard	0114U
ESOPREDICT Barrett's Esophagus Risk Classifier Assay	0398U
Eurofins TRAC dd-cfDNA	0118U
ExoDx Prostate (IntelliScore)	0005U
FM/a fibromyalgia	81599
GPS Cancer	81479
Guardant Reveal	0569U
Haystack MRD Baseline	0560U
Haystack MRD Monitoring	0561U

E/I/U

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Procedures address by this guideline	Procedure codes
HelioLiver Test	0333U
Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis	81451
HepatoTrack	0575U
HPV-SEQ Test	0470U
Insight TNBCtype	0153U
Invitae PCM MRD Monitoring	0307U
Invitae PCM Tissue Profiling and MRD Baseline Assay	0306U
IriSight CNV Analysis	0469U
IriSight Prenatal Analysis – Proband	0335U
IriSight Prenatal Analysis – Comparator	0336U
KawasakiDx	0389U
KIF6 Genotype	81479
Know error	81479, 81265, 81266
LactoTYPE	81400
Lifetime Genomics Risk Assessment, VTE	0529U
LPA-Aspirin Genotype	81479
LPA-Intron 25 Genotype	81479
LungLB	0317U
LungOI	0414U
Lymph2Cx Lymphoma Molecular Subtyping Assay	0017M
Lymph3Cx Lymphoma Molecular Subtyping Assay	0120U

E/I/U

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Procedures address by this guideline	Procedure codes
Macula Risk	81401, 81479
Mammostrat Breast Cancer Recurrence Assay	S3854
Merlin Test	0578U
Mind.Px	0258U
MindX Blood Test - Longevity	0294U
MindX Blood Test - Memory/Alzheimer's	0289U
MindX Blood Test - Mood	0291U
MindX Blood Test - Pain	0290U
MindX Blood Test - Stress	0292U
MindX Blood Test - Suicidality	0293U
MindX One Blood Test – Anxiety	0437U
miR-31now	0069U
miR Sentinel Prostate Cancer Test	0343U
miR Sentinel Prostate Cancer Test	0424U
MI Tumor Seek Hybrid	81479
Molecular Microscope MMDx—Heart	0087U
Molecular Microscope MMDx—Kidney	0088U
mRNA CancerDetect	0296U
MyHPVscore	81479
myPath Melanoma	0090U
MyProstateScore	81599 or 0113U
MyProstateScore 2.0	0403U
myTAIHEART	0055U
NavDx	0356U
Northstar Response	0486U
OmniGraf Liver	0576U

E/I/U

Procedures address by this guideline	Procedure codes
OncoAssure Prostate	0497U
OncobiotaLUNG	0395U
Oncomap ExTra	0329U
OncoSignal 7 Pathway Signal	0262U
OncoTarget/OncoTreat	0019U
OncotypeDx AR-V7 Nucleus Detect	81479
OptiSeq Colorectal Cancer NGS Panel	0498U
PAI-1 (SERPINE1) Testing for Cardiovascular Disease Risk Assessment	81400, 85415
PancreaSeq Genomic Classifier	0313U
PanGIA Prostate	0228U
Pathway Fit	81291, 81401, 81479
Percepta Genomic Sequencing Classifier	81479
Pharmaco-oncologic Algorithmic Treatment Ranking	0794T
POC (Products of Conception)	0252U
Praxis Optical Genome Mapping	0264U
Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping	0300U
Praxis Somatic Optical Genome Mapping	0299U
Praxis Somatic Transcriptome	0298U
Praxis Somatic Whole Genome Sequencing	0297U
Praxis Transcriptome	0266U
PreciseBreast	0220U
PreciseDx Breast Biopsy Test	0418U
PrecisionCHD	0440U
ProMark Proteomic Prognostic Test	81479

E/I/U

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Procedures address by this guideline	Procedure codes
Prospera	0493U
ProsTAV	0572U
PROSTOX ultra	0534U
PurIST	0510U
QuantiDNA Colorectal Cancer Triage Test	0501U
RadTox cfDNA test	0285U
RetnaGene AMD	81401, 81405, 81408, 81479, 81599
RiskReveal	0288U
RNA Salah Targeted Expression Panel	0586U
ROMA Risk of Ovarian Malignancy Algorithm	81500
Shield	0537U
Signatera	0340U
Single Cell Prenatal Diagnosis (SCPD) Test	0341U
SMART PGT-A (Pre-implantation Genetic Testing - Aneuploidy)	0254U
SMASH	0156U
Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis	81449
Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis	81456
Strata Select	0391U
Stockholm3	0495U

E/I/U

Procedures address by this guideline	Procedure codes
Thyroid GuidePx	0362U
ToxLok	0079U
TruGraf Kidney	81558
Tuteva	0320U
Twin Zygosity, cell free fetal DNA	0060U
UriFind Urothelial Carcinoma Assay	0465U
UroAmp MRD	0467U
Vectra	81490
VeriStrat	81538
VitaGraft Kidney 2.0	0544U
VitaGraft Kidney Baseline + 1st Plasma Test	0508U
VitaGraft Kidney Subsequent	0509U
Vita Risk	0205U
Investigational and experimental tests that make use of molecular and genomic technologies	81479, 84999, 81599, and others

What is E/I/U molecular and genomic testing?

An experimental, investigational, or unproven (E/I/U) procedure is the use of a service, supply, drug, or device that is not recognized as standard medical care for the condition, disease, illness, or injury. Treatment is determined by the health plan based on an independent, peer review of literature and scientific data. E/I/U molecular and genomic tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact.

Experimental, investigational, or unproven determinations

Molecular and genomic tests are routinely released to market that make use of novel technologies or have a novel clinical application. These tests are often available on a

clinical basis long before the required evidence to support clinical validity and clinical utility are established. Typically, there is insufficient data to support that the test

- accurately assesses the outcome of interest, analytical and clinical validity
- significantly improves health outcomes, clinical utility, and
- performs better than an existing standard of care medical management option.

Because these tests are often proprietary, there may be no independent test evaluation data available in the early stages to support the laboratory's claims regarding test performance and utility.

As new molecular and genomic tests become commercially available, the evidence base is reviewed. Tests determined to be E/I/U by the Health Plan are addressed by this guideline or a test-specific guideline and are not eligible for reimbursement.

Food and Drug Administration (FDA) clearance

In the case of laboratory testing, FDA clearance is not a suitable standard given that the clearance assessment does not require evidence to support clinical utility. In addition, while the FDA has stated that it has the discretion to regulate laboratory developed tests (LDTs), it is currently only selectively exercising that discretion to take action against egregious practices.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's Experimental, Investigational, or Unproven Laboratory Testing criteria will ensure that members will not receive testing for which there is not a body of evidence demonstrating analytical validity, clinical validity, and/or clinical utility. Use of a test that does not have evidence to support analytical validity, clinical validity, and/or clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.* However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).[*Korenstein D, Chimonas S, Barrow B, et al. Development of a conceptual map of negative consequences for patients of overuse of medical tests and treatments. JAMA Inter Med. 2018;178(10):1401-1407.]

Criteria

This section catalogues some, but not all, molecular and genomic tests that have been determined to be experimental, investigational, or unproven (E/I/U). E/I/U tests may also be addressed in test-specific guidelines and the reader is referred to those documents

E/I/U

for additional information. New E/I/U tests may not yet be specifically listed in this guideline, but such decisions will be made using the following criteria.

Criteria: general coverage guidance

Molecular and genomic tests are only eligible for reimbursement when ALL of the following conditions are met:

- Technical and clinical validity: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- Clinical utility: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- Reasonable use: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Experimental, investigational, or unproven molecular and genomic tests

The following tests do not meet the above criteria and are not eligible for reimbursement.

- 9p21 Genotype Test (rs10757278 and rs1333049 alleles) CPT: 81479
- AidaBreast [Oncology (breast), RNA expression profiling of 329 genes by targeted next-generation sequencing and 20 proteins by multiplex immunofluorescence, formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic analyses to determine tumor-recurrence risk score from PreludeDx] CPT: 0597U
- AlloSure [Transplantation medicine, quantification of donor-derived cell-free DNA using next-generation sequencing analysis of plasma, reported as percentage of donor-derived cell-free DNA to determine probability of rejection from CareDx] CPT: 0540U
- Altera [Oncology, whole exome and transcriptome-based tumor profiling, reporting TMB, MSI, and IHC for PD-L1 (22C3) and HER2 from Natera] CPT: 81479
- Apolipoprotein E Genotype (APOE) CPT: 81401
- Apolipoprotein L1 (APOL1) Renal Risk Variant Genotyping [APOL1 (apolipoprotein L1) (eg, chronic kidney disease), risk variants (G1, G2) from Quest Diagnostics] CPT: 0355U
- ARISk Autism Risk Assessment Test [Proprietary test from IntegraGen] CPT: 81479
- AssureMDx [Proprietary non-invasive assay that analyzes tumor markers in the urine of individuals with hematuria to identify those at low risk and high risk for bladder cancer by MDx Health] CPT: 81479
- Augusta Optical Genome Mapping [Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping from Bionano Genomics, Inc] CPT: 0260U

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- Augusta Hematology Optical Genome Mapping [Oncology (hematolymphoid neoplasia), optical genome mapping for copy number alterations and gene rearrangements utilizing DNA from blood or bone marrow, report of clinically significant alternations from Georgia Esoteric and Molecular Labs] CPT: 0331U
- Avantect Ovarian Cancer Test [Oncology (ovarian), DNA, whole-genome sequencing with 5-hydroxymethylcytosine (5hmC) enrichment, using whole blood or plasma, algorithm reported as cancer detected or not detected from ClearNote Health] CPT: 0507U
- Avantect Pancreatic Cancer Test[Oncology (pancreatic), DNA, whole genome sequencing with 5-hydroxymethylcytosine enrichment, whole blood or plasma, algorithm reported as cancer detected or not detected from ClearNote Health] CPT: 0410U
- BarreGEN [Oncology (esophageal) risk assessment, quantification of mutational load by multiplex amplification and next-generation sequencing of tumor suppressor genes associated with progression from Barrett's esophagus to high-grade dysplasia and esophageal cancer, algorithm reported as risk score by Interpace Diagnostics] CPT: 81599
- BBDRisk Dx [Oncology (breast), immunohistochemistry, protein expression profiling of 4 biomarkers (matrix metalloproteinase-1 [MMP-1], carcinoembryonic antigen-related cell adhesion molecule 6 [CEACAM6], hyaluronoglucosaminidase [HYAL1], highly expressed in cancer protein [HEC1]), formalin-fixed paraffin-embedded precancerous breast tissue, algorithm reported as carcinoma risk score from Silbiotech, Inc] CPT: 0067U
- Bladder CARE [Oncology (urothelial), DNA, quantitative methylated real-time PCR of TRNA-Cys, SIM2, and NKX1-1, using urine, diagnostic algorithm reported as a probability index for bladder cancer and/or upper tract urothelial carcinoma (UTUC) from Pangea Laboratory LLC] CPT: 0549U
- Bladder EpiCheck [Proprietary non-invasive assay that analyzes methylation biomarkers in the urine of individuals with hematuria to identify those at low risk and high risk for bladder cancer or to monitor tumor recurrence from Nucleix Ltd] CPT: 81599
- BluePrint Molecular Subtyping Profile [Proprietary 80-gene expression signature to classify Basal-type, Luminal-type and ERBB2-type breast cancers from Agendia] CPT: 81479
- BTG Early Detection of Pancreatic Cancer [Oncology (pancreatic), 59 methylation haplotype block markers, next generation sequencing, plasma, reported as cancer signal detected or not detected from Breakthrough Genomics] CPT: 0405U
- CARDIO inCode Score (CIC SCORE) [Cardiology (coronary heart disease [CHD]), 9 genes (12 variants), targeted variant genotyping, blood, saliva, or buccal swab, algorithm reported as a genetic risk score for a coronary event from GENinCode U.S. Inc] CPT: 0401U

E/I/U

- CardioRisk+ [Cardiology (coronary artery disease [CAD]), DNA, genome-wide association studies (564856 single-nucleotide polymorphisms [SNPs], targeted variant genotyping), patient lifestyle and clinical data, buccal swab, algorithm reported as polygenic risk to acquired heart disease from Gene by Gene, Ltd] CPT: 0466U
- CELLSEARCH CTC Test [Immunologic selection of circulating tumor cells in individuals with metastatic breast, prostate, or colorectal cancer for purposes of assessing prognosis from Menarini Silicon Biosystems] CPT: 86152, 86153
- ChemoFX [Proprietary test from Helomics to assess chemosensitivity] CPT: 81535, 81536
- Chromosome Genome Mapping [Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping from Bionano Genomics, Inc] CPT: 0454U
- Clarava [Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood from Verici Dx, Inc] CPT: 0319U
- Clarifi ASD [Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis from Quadrant Biosciences] CPT: 0170U
- CNGnome [Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities from PerkinElmer Genomics] CPT: 0209U
- Cologuard Plus [Oncology (colorectal) screening, quantitative real-time target and signal amplification, methylated DNA markers, including LASS4, LRRC4 and PPP2R5C, a reference marker ZDHHC1, and a protein marker (fecal hemoglobin), utilizing stool, algorithm reported as a positive or negative result from Exact Sciences Laboratories, LLC] CPT: 0464U
- ColonAiQ [Oncology (colorectal cancer), cell-free DNA (cfDNA), methylation-based quantitative PCR assay (SEPTIN9, IKZF1, BCAT1, Septin9-2, VAV3, BCAN), plasma, reported as presence or absence of circulating tumor DNA (ctDNA) from Breakthrough Genomics/ Singlera Genomics, Inc] CPT: 0453U
- ColonSentry [Proprietary 7-gene signature to detect colorectal cancer from StageZero Life Sciences] CPT: 81479
- ColoScape Colorectal Cancer Detection [Oncology (colorectal cancer), evaluation for mutations of APC, BRAF, CTNNB1, KRAS, NRAS, PIK3CA, SMAD4, and TP53, and methylation markers (MYO1G, KCNQ5, C9ORF50, FLI1, CLIP4, ZNF132, and TWIST1), multiplex quantitative polymerase chain reaction (qPCR), circulating cell-free DNA (cfDNA), plasma, report of risk score for advanced adenoma or colorectal cancer from DiaCarta Clinical Lab] CPT: 0368U
- ColoScape PLUS [Oncology (colorectal), cell-free DNA, 8 genes for mutations, 7 genes for methylation by real-time RT-PCR, and 4 proteins by enzyme-linked

E/I/U

immunosorbent assay, blood, reported positive or negative for colorectal cancer or advanced adenoma risk from DiaCarta, Inc] CPT: 0496U
- Colvera [BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis from Colvera] CPT: 0229U
- CyPath Lung [Oncology (lung), flow cytometry, sputum, 5 markers (meso-tetra [4-carboxyphenyl] porphyrin [TCPP], CD206, CD66b, CD3, CD19), algorithm reported as likelihood of lung cancer from Precision Pathology Services, bioAffinity Technologies, Inc] CPT: 0406U
- Cytogenomic (genome-wide) analysis, hematologic malignancy, structural variants and copy number variants, optical genome mapping (OGM) CPT: 81195
- Decipher Bladder TURBT [Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)] CPT: 0016M
- DecisionDx - Cutaneous Melanoma assay [Proprietary 31-gene signature to assess melanoma metastatic risk from Castle Biosciences] CPT: 81529
- DecisionDx DiffDx - Melanoma [Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (ie, benign, intermediate, malignant) from Castle Biosciences, Inc] CPT: 0314U
- DecisionDx - SCC [Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (ie, Class 1, Class 2A, Class 2B) from Castle Biosciences, Inc] CPT: 0315U
- DEPArray [Oncology (breast cancer), ERBB2 (HER2) copy number by FISH, tumor cells from formalin fixed paraffin embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as ERBB2 gene amplified or non-amplified from PacificDx] CPT: 0009U
- DH Optical Genome Mapping/Digital Karyotyping Assay [Oncology (hematolymphoid neoplasm), optical genome mapping for copy number alterations, aneuploidy, and balanced/complex structural rearrangements, DNA from blood or bone marrow, report of clinically significant alterations from The Clinical Genomics and Advanced Technology (CGAT) Laboratory at Dartmouth Health] CPT: 0413U
- Digitization of pathology slides CPT: 0760T, 0761T, 0762T, 0763T, 0848T, 0849T, 0850T, 0851T, 0852T, 0853T
- EarlyDx MethylScan HCC [Oncology (hepatocellular carcinoma), next-generation sequencing methylation pattern assay to detect 6626 epigenetic alterations, cell-

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free DNA, plasma, algorithm reported as cancer signal detected or not detected from EarlyDiagnostics Laboratory] CPT: 0565U

- EarlyTect Bladder Cancer Detection (EarlyTect BCD) [Oncology (bladder), methylated PENK DNA detection by linear target enrichment-quantitative methylation-specific real-time PCR (LTE-qMSP), urine, reported as likelihood of bladder cancer from Promis Diagnostics, Inc] CPT: 0452U
- EndoSign Barrett's Esophagus Test [Gastroenterology (Barrett's esophagus), esophageal cells, DNA methylation analysis by next-generation sequencing of at least 89 differentially methylated genomic regions, algorithm reported as likelihood for Barrett's esophagus from Cyted Health Inc] CPT: 0506U
- Envisia Genomic Classifier [Proprietary gene expression assay designed to aid in the diagnosis of idiopathic pulmonary fibrosis from Veracyte] CPT: 81554
- Epi+Gen CHD [Cardiology (coronary heart disease [CHD]), DNA, analysis of 5 single-nucleotide polymorphisms (SNPs) (rs11716050 [LOC105376934], rs6560711 [WDR37], rs3735222 [SCIN/LOC107986769], rs6820447 intergenic], and rs9638144 [ESYT2]) and 3 DNA methylation markers (cg00300879 [transcription start site {TSS200} of CNKSR1], cg09552548 [intergenic], and cg14789911 [body of SPATC1L]), qPCR and digital PCR, whole blood, algorithm reported as a 4-tiered risk score for a 3-year risk of symptomatic CHD from Cardio Diagnostics, Inc] CPT: 0439U
- Epignostix CNS Tumor Methylation Classifier [Oncology (central nervous system), analysis of 30000 DNA methylation loci by methylation array, utilizing DNA extracted from tumor tissue, diagnostic algorithm reported as probability of matching a reference tumor subclass from Heidelberg Epignostix] CPT: 0020M
- EPISEEK MPE (Malignant Pleural Effusion Detection Test) [Oncology (lung), qPCR-based analysis of 13 differentially methylated regions (CCDC181, HOXA7, LRRC8A, MARCHF11, MIR129-2, NCOR2, PANTR1, PRKCB, SLC9A3, TBR1_2, TRAP1, VWC2, ZNF781), pleural fluid, algorithm reported as a qualitative result from Precision Epigenomics Inc.] CPT: 0566U
- EpiSign Complete [Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood from Greenwood Genetic Center] CPT: 0318U
- EpiSwitch CiRT (Checkpoint-inhibitor Response Test) [Oncology (pan-tumor), genetic profiling of 8 DNA-regulatory (epigenetic) markers by quantitative polymerase chain reaction (qPCR), whole blood, reported as a high or low probability of responding to immune checkpoint–inhibitor therapy from Next Bio-Research Services, LLC] CPT: 0332U
- EpiSwitch Prostate Screening Test [Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer from Oxford BioDynamics, Inc] CPT: 0433U
- ERA (Endometrial Receptivity Analysis) [Reproductive medicine (endometrial receptivity analysis), RNA gene expression profile, 238 genes by next-generation

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sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation (eg, pre-receptive, receptive, post-receptive) from Igenomix] CPT: 0253U

- EsoGuard [Gastroenterology (Barrett's esophagus), VIM and CCNA1 methylation analysis, esophageal cells, algorithm reported as likelihood for Barrett's esophagus from Lucid Diagnostics] CPT: 0114U
- ESOPREDICT Barrett's Esophagus Risk Classifier Assay [Gastroenterology (Barrett esophagus), P16, RUNX3, HPP1, and FBN1 DNA methylation analysis using PCR, formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as risk score for progression to high-grade dysplasia or cancer from Capsulomics, Inc d/b/a Previse] CPT: 0398U
- Eurofins TRAC dd-cfDNA [Transplantation medicine, quantification of donor-derived cell-free DNA using whole genome next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA in the total cell-free DNA from Transplant Genomics, Inc] CPT: 0118U
- ExoDx Prostate (IntelliScore) [Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score from Exosome Diagnostics, Inc.] CPT: 0005U
- FM/a fibromyalgia [interleukin-6, interleukin-8, macrophage inflammatory protein-1 alpha and macrophage inflammatory protein-beta (IL-6, IL-8, MIP-1a and MIP-1b, supernatant of stimulated cell culture, immunoassay, multianalyte assay with algorithmic analysis, reported as a score from EpicGenetics, Inc] CPT: 81599
- GPS Cancer [Proprietary test using a tissue block sample of the highest carcinoma grade of a tumor and a sample of blood to compare an individual's normal DNA to the tumor DNA to be used as part of a precision medicine approach for individuals with cancer from NantHealth] CPT: 81479
- Guardant Reveal [Oncology (solid tumor), next-generation sequencing analysis of tumor methylation markers (>20000 differentially methylated regions) present in cell-free circulating tumor DNA (ctDNA), whole blood, algorithm reported as presence or absence of ctDNA with tumor fraction, if appropriate from Guardant Health, Inc.] CPT: 0569U
- Haystack MRD Baseline [Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood and tumor tissue, baseline assessment for design and construction of a personalized variant panel to evaluate current MRD and for comparison to subsequent MRD assessments from Quest Diagnostics] CPT: 0560U
- Haystack MRD Monitoring [Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood, subsequent assessment with comparison to initial assessment to evaluate for MRD from Quest Diagnostics] CPT: 0561U

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- HelioLiver Test [Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in high-risk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein des-gamma-carboxy prothrombin (DCP), algorithm reported as normal or abnormal result from Helio Genomics] CPT: 0333U
- Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis CPT: 81451
- HepatoTrack [Transplantation medicine (liver allograft rejection), miRNA gene expression profiling by RT-PCR of 4 genes (miR-122, miR-885, miR-23a housekeeping, spike-in control), serum, algorithm reported as risk of liver allograft rejection from LuminoDx Laboratory] CPT: 0575U
- HPV-SEQ Test [Oncology (oropharyngeal), detection of minimal residual disease by next-generation sequencing (NGS) based quantitative evaluation of 8 DNA targets, cell-free HPV 16 and 18 DNA from plasma from Sysmex Inostics, Inc] CPT: 0470U
- Insight TNBCtype [Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement from Insight Molecular Labs] CPT: 0153U
- Invitae PCM MRD Monitoring [Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD from Invitae Corporation] CPT: 0307U
- Invitae PCM Tissue Profiling and MRD Baseline Assay [Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient specific panel for future comparisons to evaluate for MRD from Invitae Corporation] CPT: 0306U
- IriSight CNV Analysis [Rare diseases (constitutional/heritable disorders), whole genome sequence analysis for chromosomal abnormalities, copy number variants, duplications/deletions, inversions, unbalanced translocations, regions of homozygosity (ROH), inheritance pattern that indicate uniparental disomy (UPD), and aneuploidy, fetal sample (amniotic fluid, chorionic villus sample, or products of conception), identification and categorization of genetic variants, diagnostic report of fetal results based on phenotype with maternal sample and paternal sample, if performed, as comparators and/or maternal cell contamination from Variantyx Inc] CPT: 0469U
- IriSight Prenatal Analysis – Proband [Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, fetal

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sample, identification and categorization of genetic variants from Variantyx, Inc] CPT: 0335U
- IriSight Prenatal Analysis – Comparator [Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent) from Variantyx, Inc] CPT: 0336U
- KawasakiDx [Pediatric febrile illness (Kawasaki disease [KD]), interferon alpha-inducible protein 27 (IFI27) and mast cell-expressed membrane protein 1 (MCEMP1), RNA, using quantitative reverse transcription polymerase chain reaction (RT-qPCR), blood, reported as a risk score for KD from OncoOmicsDx Laboratory, mProbe] CPT: 0389U
- KIF6 Genotype Test CPT: 81479
- Know error [Proprietary test for DNA based specimen provenance confirmation from Strand Diagnostics] CPT: 81479, 81265, 81266
- LactoTYPE [Proprietary test from Prometheus that assesses the hypolactasia C/T genetic variant] CPT: 81400
- Lifetime Genomics Risk Assessment, VTE [Hematology (venous thromboembolism [VTE]), genome-wide single-nucleotide polymorphism variants, including F2 and F5 gene analysis, and Leiden variant, by microarray analysis, saliva, report as risk score for VTE from GenomicMD, Inc] CPT: 0529U
- LPA-Aspirin Genotype Test (4399Met allele) CPT: 81479
- LPA-Intron 25 Genotype Test CPT: 81479
- LungLB [Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm generated evaluation reported as decreased or increased risk for lung cancer from LungLife AI] CPT: 0317U
- LungOI [Oncology (lung), augmentative algorithmic analysis of digitized whole slide imaging for 8 genes (ALK, BRAF, EGFR, ERBB2, MET, NTRK1-3, RET, ROS1), and KRAS G12C and PD-L1, if performed, formalinfixed paraffin-embedded (FFPE) tissue, reported as positive or negative for each biomarker from Imagene] CPT: 0414U
- Lymph2Cx Lymphoma Molecular Subtyping Assay, [Oncology (diffuse large B-cell lymphoma [DLBCL]), mRNA, gene expression profiling by fluorescent probe hybridization of 20 genes, formalin-fixed paraffin embedded tissue, algorithm reported as cell of origin from Mayo Clinic] CPT: 0017M
- Lymph3Cx Lymphoma Molecular Subtyping Assay, [Oncology (B-cell lymphoma classification), mRNA, gene expression profiling by fluorescent probe hybridization of 58 genes (45 content and 13 housekeeping genes), formalin-fixed paraffin-embedded tissue, algorithm reported as likelihood for primary mediastinal B-cell lymphoma

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(PMBCL) and diffuse large B-cell lymphoma (DLBCL) with cell of origin subtyping in the latter from Mayo Clinic] CPT: 0120U
- Macula Risk [SNP-based assay to assist in the selection of eye supplement formulations for individuals diagnosed with intermediate dry age-related macular degeneration from ArcticDx, Inc] CPT: 81401, 81479
- Mammostrat Breast Cancer Recurrence Assay [Proprietary immunohistochemical (IHC) assay of 5 proteins in individuals with early stage breast cancer to assess recurrence risk from Clarient, Inc.] CPT: S3854
- Merlin Test [Oncology (cutaneous melanoma), RNA, gene expression profiling by real-time qPCR of 10 genes (8 content and 2 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reports a binary result, either low-risk or high-risk for sentinel lymph node metastasis and recurrence from SkylineDx USA, Inc] CPT: 0578U
- MethylDetox Profile [The MethylDetox Profile test is a testing panel that assesses genes in the methylation pathway to provide "more actionable information than MTHFR testing alone" and provides "suggestions for specific nutrient needs" based on test findings from Cell Science Systems] CPT: none; no insurance billing
- Mind.Px [Autoimmune (psoriasis), mRNA, next-generation sequencing, gene expression profiling of 50-100 genes, skin-surface collection using adhesive patch, algorithm reported as likelihood of response to psoriasis biologics from Mindera Corporation] CPT: 0258U
- MindX Blood Test - Longevity [Longevity and mortality risk, mRNA, gene expression profiling by RNA sequencing of 18 genes, whole blood, algorithm reported as predictive risk score from MindX Sciences Inc] CPT: 0294U
- MindX Blood Test - Memory/Alzheimer's [Neurology (Alzheimer disease), mRNA, gene expression profiling by RNA sequencing of 24 genes, whole blood, algorithm reported as predictive risk score from MindX Sciences Inc] CPT: 0289U
- MindX Blood Test - Mood [Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score from MindX Sciences Inc] CPT: 0291U
- MindX Blood Test - Pain [Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score from MindX Sciences Inc] CPT: 0290U
- MindX Blood Test - Stress [Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score from MindX Sciences Inc] CPT: 0292U
- MindX Blood Test - Suicidality [Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score from MindX Sciences Inc] CPT: 0293U

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- MindX One Blood Test – Anxiety [Psychiatry (anxiety disorders), mRNA, gene expression profiling by RNA sequencing of 15 biomarkers, whole blood, algorithm reported as predictive risk score from MindX Sciences] CPT: 0437U
- miR-31now [Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin fixed paraffin-embedded tissue, algorithm reported as an expression score from GoPath Laboratories] CPT: 0069U
- miR Sentinel Prostate Cancer Test [Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chainreaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer from miR Scientific, LLC] CPT: 0343U
- miR Sentinel Prostate Cancer Test [Oncology (prostate), exosome-based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cance from miR Scientific, LLC] CPT: 0424U
- Mitomic Prostate Test [Proprietary test using mitochondrial DNA to detect prostate cancer not identified by standard biopsy pathology from MDNA Life Sciences] CPT: none; research use only
- MI Tumor Seek Hybrid [Oncology (pan-tumor), DNA by next-generation sequencing and whole transcriptome sequencing of RNA specimen, utilizing fresh or formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, gene fusions, tumor mutational burden, microsatellite instability, homologous recombination deficiency status, HLA genotyping, with therapy association, artificial intelligence assessment of genome and transcriptome data reported as a probability score for tissue of origin and a prediction of chemotherapy efficacy in metastatic colorectal cancer patients from Caris Life Sciences] CPT: 81479
- Molecular Microscope MMDx—Heart [Transplantation medicine (heart allograft rejection), microarray gene expression profiling of 1283 genes, utilizing transplant biopsy tissue, algorithm reported as a probability score for rejection from Kashi Clinical Laboratories] CPT: 0087U
- Molecular Microscope MMDx—Kidney [Transplantation medicine (kidney allograft rejection), microarray gene expression profiling of 1494 genes, utilizing transplant biopsy tissue, algorithm reported as a probability score for rejection from Kashi Clinical Laboratories] CPT: 0088U
- mRNA CancerDetect [Oncology (oral and/or oropharyngeal cancer), gene expression profiling by RNA sequencing at least 20 molecular features (eg, human and/or microbial mRNA), saliva, algorithm reported as positive or negative for signature associated with malignancy from Viome Life Sciences, Inc] CPT: 0296U
- MyHPVscore [Oncology (head and neck) ctDNA-based assay for HPV detection in individuals at risk for HPV-related cancers, used to detect, confirm HPV genotype,

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monitor treatment response, or detect biochemical recurrence of disease from University of Michigan Health] CPT: 81479

- myPath Melanoma [Proprietary 23-gene expression assay to assess the risk of malignant melanoma when a result cannot be obtained by clinical assessment and/or histopathology alone from Castle Biosciences, Inc] CPT: 0090U
- MyProstateScore [urine analysis of TMPRSS2:ERG and PCA3 genes combined with blood PSA levels for early detection of prostate cancer from Lynx Dx] CPT: 81599 or 0113U
- MyProstateScore 2.0, [Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch urine, algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer from LynxDX] CPT: 0403U
- myTAIHEART CPT: 0055U
- NavDx [Oncology (oropharyngeal or anal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence from Naveris] CPT: 0356U
- Northstar Response [Oncology (pan-solid tumor), next-generation sequencing analysis of tumor methylation markers present in cell-free circulating tumor DNA, algorithm reported as quantitative measurement of methylation as a correlate of tumor fraction from BillionToOne Laboratory] CPT: 0486U
- OmniGraf Liver [Transplantation medicine (liver allograft rejection), quantitative donor-derived cell-free DNA (cfDNA) by whole genome next-generation sequencing, plasma and mRNA gene expression profiling by multiplex real-time PCR of 56 genes, whole blood, combined algorithm reported as a rejection risk score from Eurofins Transplant Genomics] CPT: 0576U
- OncoAssure Prostate [Oncology (prostate), mRNA gene-expression profiling by real-time RT-PCR of 6 genes (FOXM1, MCM3, MTUS1, TTC21B, ALAS1, and PPP2CA), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a risk score for prostate cancer from DiaCarta, Inc] CPT: 0497U
- OncobiotaLUNG [Oncology (lung), multi-omics (microbial DNA by shotgun next-generation sequencing and carcinoembryonic antigen and osteopontin by immunoassay), plasma, algorithm reported as malignancy risk for lung nodules in early-stage disease from Micronoma] CPT: 0395U
- Oncomap ExTra [Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations from Exact Sciences] CPT: 0329U
- OncoSignal 7 Pathway Signal [Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch),

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formalin-fixed paraffin-embedded (FFPE), algorithm reported as gene pathway activity score from Protean BioDiagnostics] CPT: 0262U

- OncoTarget/OncoTreat [Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents from Columbia University Department of Pathology and Cell Biology, Darwin Health] CPT: 0019U
- OncotypeDx AR-V7 Nucleus Detect [Proprietary test designed to detect AR-V7 proteins in the nucleus of CTCs to determine response to AR-targeted therapies from Genomic Health] CPT: 81479
- OptiSeq Colorectal Cancer NGS Panel [Oncology (colorectal), next-generation sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with interpretation from DiaCarta, Inc] CPT: 0498U
- PAI-1 (SERPINE1) Testing for Cardiovascular Disease Risk Assessment CPT: 81400, 85415
- PancreaSeq Genomic Classifier [Oncology (pancreas), DNA and mRNA next-generation sequencing analysis of 74 genes and analysis of CEA (CEACAM5) gene expression, pancreatic cyst fluid, algorithm reported as a categorical result (ie, negative, low probability of neoplasia or positive, high probability of neoplasia) from Molecular and Genomic Pathology Laboratory, University of Pittsburgh Medical Center] CPT: 0313U
- PanGIA Prostate [Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanosponge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer from Genetics Institute of America] CPT: 0228U
- Pathway Fit [Proprietary test from Pathway Genomics that focuses on metabolism, diet, and exercise traits] CPT: 81291, 81401, 81479
- PAULA [Proprietary panel of four proteins designed to detect lung cancer in asymptomatic individuals at high risk from Genesys Biolabs] CPT: none; no insurance billing
- Percepta Genomic Sequencing Classifier [Proprietary gene expression assay designed to assess the risk of malignancy of lung nodules from Veracyte] CPT: 81479
- Pharmaco-oncologic Algorithmic Treatment Ranking [Patient-specific, assistive, rules-based algorithm for ranking pharmaco-oncologic treatment options based on the patient's tumor-specific cancer marker information obtained from prior molecular pathology, immunohistochemical, or other pathology results which have been previously interpreted and reported separately from CureMatch] CPT: 0794T
- POC (Products of Conception) [Fetal aneuploidy short tandem–repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploidy from Igenomix] CPT: 0252U

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- Praxis Optical Genome Mapping [Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping from Praxis Genomics, LLC] CPT: 0264U
- Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping [Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification from Praxis Genomics LLC] CPT: 0300U
- Praxis Somatic Optical Genome Mapping [Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification from Praxis Genomics LLC] CPT: 0299U
- Praxis Somatic Transcriptome [Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification from Praxis Genomics LLC] CPT: 0298U
- Praxis Somatic Whole Genome Sequencing [Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification from Praxis Genomics LLC] CPT: 0297U
- Praxis Transcriptome [Unexplained constitutional or other heritable disorders or syndromes, tissue-specific gene expression by whole-transcriptome and next-generation sequencing, blood, formalin-fixed paraffin-embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression changes from Praxis Genomics, LLC] CPT: 0266U
- PreciseBreast [Oncology (breast cancer), image analysis with artificial intelligence assessment of 12 histologic and immunohistochemical features, reported as a recurrence score from PreciseDx] CPT: 0220U
- PreciseDx Breast Biopsy Test [Oncology (breast), augmentative algorithmic analysis of digitized whole slide imaging of 8 histologic and immunohistochemical features, reported as a recurrence score from PreciseDx, Inc] CPT: 0418U
- PrecisionCHD [Cardiology (coronary heart disease [CHD]), DNA, analysis of 10 single-nucleotide polymorphisms (SNPs) rs710987 [LINC010019], rs1333048 [CDKN2B-AS1], rs12129789 [KCND3], rs942317 [KTN1-AS1], rs1441433 [PPP3CA], rs2869675 [PREX1], rs4639796 [ZBTB41], rs4376434 [LINC00972], rs12714414 [TMEM18], and rs7585056 [TMEM18]) and 6 DNA methylation markers (cg03725309 [SARS1], cg12586707 [CXCL1], cg04988978 [MPO], cg17901584 [DHCR24-DT], cg21161138 [AHRR], and cg12655112 [EHD4]), qPCR and digital PCR, whole blood, algorithm reported as detected or not detected for CHD from Cardio Diagnostics, Inc] CPT: 0440U

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- ProMark Proteomic Prognostic Test [Proprietary proteomic assay designed to assess the risk of aggressive prostate cancer from Metamark] CPT: 81479
- Prospera [Transplantation medicine, quantification of donor-derived cell-free DNA (cfDNA) using next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA from Natera] CPT: 0493U
- ProsTAV [Oncology (prostate), high-throughput telomere length quantification by FISH, whole blood, diagnostic algorithm reported as risk of prostate cancer from Life Length S.L.] CPT: 0572U
- PROSTOX ultra [Oncology (prostate), microRNA, single-nucleotide polymorphisms (SNPs) analysis by RT-PCR of 32 variants, using buccal swab, algorithm reported as a risk score from MiraDx, Inc] CPT: 0534U
- PurIST [Oncology (pancreatic cancer), augmentative algorithmic analysis of 16 genes from previously sequenced RNA whole-transcriptome data, reported as probability of predicted molecular subtype from Tempus AI, Inc] CPT: 0510U
- QuantiDNA Colorectal Cancer Triage Test [Oncology (colorectal), blood, quantitative measurement of cell-free DNA (cfDNA) from DiaCarta, Inc] CPT: 0501U
- RadTox cfDNA test [Oncology, disease progression and response monitoring to radiation, chemotherapy, or other systematic treatments, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported in ng/mL from DiaCarta Inc] CPT: 0285U
- RetnaGene AMD [Proprietary test from Sequenom CMM to predict risk of wet AMD progression] CPT: 81401, 81405, 81408, 81479, 81599
- RiskReveal [Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score from Razor Genomics] CPT: 0288U
- RNA Salah Targeted Expression Panel [Oncology, mRNA, gene expression profiling of 216 genes (204 targeted and 12 housekeeping genes), RNA expression analysis, formalin-fixed paraffin-embedded (FFPE) tissue, quantitative, reported as log2 ratio per gene from Moffitt Cancer Center Advanced Diagnostics Laboratory] CPT: 0586U
- ROMA Risk of Ovarian Malignancy Algorithm [Proprietary test using the combination of CA125 + HE4 antigens to assess the likelihood of malignancy before surgery; test kit from Fujirebio Diagnostics, Inc. and offered by several reference laboratories] CPT: 81500
- Shield [Oncology (colorectal cancer), analysis of cell-free DNA for epigenomic patterns, next-generation sequencing, >2500 differentially methylated regions (DMRs), plasma, algorithm reported as positive or negative from Guardant Health, Inc] CPT: 0537U
- Signatera [Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next generation

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sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate from Natera, Inc] CPT: 0340U

- Single Cell Prenatal Diagnosis (SCPD) Test [Fetal aneuploidy DNA sequencing comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploid from Luna Genetics, Inc] CPT: 0341U
- SMART PGT-A (Pre-implantation Genetic Testing - Aneuploidy) [Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploidy, per embryo tested from Igenomix] CPT: 0254U
- SMASH [Copy number (eg, intellectual disability, dysmorphology), sequence analysis from Marvel Genomics] CPT: 0156U
- Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis CPT: 81449
- Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis CPT: 81456
- Stockholm3 [Oncology (prostate), analysis of circulating plasma proteins (tPSA, fPSA, KLK2, PSP94, and GDF15), germline polygenic risk score (60 variants), clinical information (age, family history of prostate cancer, prior negative prostate biopsy), algorithm reported as risk of likelihood of detecting clinically significant prostate cancer from BioAgilytix Diagnostics] CPT: 0495U
- Strata Select [Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice-site variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score from Strata Oncology, Inc] CPT: 0391U
- Thyroid GuidePx [Oncology (papillary thyroid cancer), gene-expression profiling via targeted hybrid capture-enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, fine needle aspirate or formalin-fixed paraffin embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes from Protean BioDiagnostics] CPT: 0362U
- ToxLok [Comparative DNA analysis using multiple selected single-nucleotide polymorphisms (SNPs), urine and buccal DNA, for specimen identity verification from InSource Diagnostics] CPT: 0079U

E/I/U

- TruGraf Kidney [Transplantation medicine (allograft rejection, kidney), mRNA, gene expression profiling by quantitative polymerase chain reaction (qPCR) of 139 genes, utilizing whole blood, algorithm reported as a binary categorization as transplant excellence, which indicates immune quiescence, or not transplant excellence, indicating subclinical rejection from Eurofins Transplant Genomics, Inc] CPT: 81558
- Tuteva [Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using posttransplant peripheral blood, algorithm reported as a risk score for acute cellular rejection from Verici Dx, Inc] CPT: 0320U
- Twin zygosity [genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood from Natera] CPT: 0060U
- UriFind Urothelial Carcinoma Assay [Oncology (urothelial carcinoma), DNA, quantitative methylation-specific PCR of 2 genes (ONECUT2, VIM), algorithmic analysis reported as positive or negative from DiaCarta, Inc, AnchorDx] CPT: 0465U
- UroAmp MRD [Oncology (bladder), DNA, next-generation sequencing (NGS) of 60 genes and whole genome aneuploidy, urine, algorithms reported as minimal residual disease (MRD) status positive or negative and quantitative disease burden from Convergent Genomics, Inc] CPT: 0467U
- Vectra [Proprietary panel of 12 biomarkers that yields a rheumatoid arthritis disease activity score from LabCorp] CPT: 81490
- VeriStrat [Oncology (lung) mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival from Biodesix, Inc] CPT: 81538
- VitaGraft Kidney 2.0 [Nephrology (transplant monitoring), 48 variants by digital PCR, using cell-free DNA from plasma, donor- derived cell-free DNA, percentage reported as risk for rejection from Oncocyte Corporation] CPT: 0544U
- VitaGraft Kidney Baseline + 1st Plasma Test [Transplantation medicine, quantification of donor-derived cell-free DNA using 40 single-nucleotide polymorphisms (SNPs), plasma, and urine, initial evaluation reported as percentage of donor-derived cell-free DNA with risk for active rejection from Oncocyte Corporation] CPT: 0508U
- VitaGraft Kidney Subsequent [Transplantation medicine, quantification of donor-derived cell-free DNA using up to 12 single-nucleotide polymorphisms (SNPs) previously identified, plasma, reported as percentage of donor-derived cell-free DNA with risk for active rejection from Oncocyte Corporation] CPT: 0509U
- Vita Risk [Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular age-related macular-degeneration risk associated with zinc supplements from Arctic Medical Laboratories] CPT: 0205U

E/I/U

Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes

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Description

Genetic testing for cancer susceptibility and hereditary cancer syndromes is performed in people with known risk factors for an inherited form of cancer. Testing may be used in people diagnosed with cancer when there are "red flags" in the individual's personal medical and/or family history for a hereditary form. Predictive genetic testing may also be performed for this group of conditions, in people known to be at increased risk of developing an inherited condition based on their family history. This testing is generally limited to adult individuals; however, it may be considered for minors if the results will be of medical and/or psychosocial benefit.[1-3] A positive genetic test result increases the risk for cancer (types vary by the gene involved) and, therefore, impacts medical management decisions around screening, prevention, and treatment.

- For information on tests used to screen for or make a diagnosis of cancer, please refer to the guideline *Genetic Testing for the Screening, Diagnosis, and Monitoring of Cancer,* as this testing is not addressed here.
- For information on diagnostic or predictive testing for conditions other than hereditary cancer, please refer to the guideline *Genetic Testing to Diagnose Non-Cancer Conditions* and *Genetic Testing to Predict Disease Risk* as this testing is not addressed here.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for genetic testing for cancer susceptibility and hereditary cancer syndromes will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

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Criteria

Introduction

Genetic testing for cancer susceptibility and hereditary cancer syndromes are reviewed using the following criteria.

Criteria: General Coverage Guidance

Genetic testing for hereditary cancer syndromes is medically necessary when **ALL** of the following conditions are met:

- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will be considered only for the number of genes or tests necessary to establish carrier status. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Genetic testing is medically necessary once per lifetime per condition. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

Criteria: Special Circumstances

The following policies address a group of tests that are used for similar purposes. Because a variety of tests may be used, but the circumstances that justify testing are the same, individual test-specific policies are not necessary.

Predictive testing for at-risk people with known familial mutations

The genetic mutation(s) associated with a hereditary cancer syndrome can often be defined in an affected family member, allowing for testing of at-risk relatives for those specific mutations. Testing for known familial mutations is medically necessary when **ALL** of the following conditions are met:

- The mutation(s) in the family have been **clearly defined** by previous genetic testing and **information about those mutations can be provided** to the testing lab.
- **Technical and clinical validity**: The test must be accurate, sensitive and specific to the familial mutation(s).

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- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will be considered only for the known familial mutations when clinically possible.
- Predictive genetic testing is reimbursable once per lifetime per condition.
- Predictive genetic testing will be considered only for adult individuals (age 18 and over). Exceptions may be considered if there are medical management and/or significant psychosocial benefits to testing prior to adulthood.

Criteria: Test-specific Guidelines

Test-specific guidelines are available for some hereditary cancer syndrome tests. For tests without a specific guideline, use the General Coverage Guidance above.

References

1. Ross LF, Saal HM, David KL, Anderson RR. Technical report: ethical and policy issues in genetic testing and screening of children. *Genet Med.* 2013;15:234–245. Available at: **http://www.nature.com/gim/journal/v15/n3/pdf/gim2012176a.pdf**
2. National Society of Genetic Counselors Position Statement. Genetic testing of minors for adult-onset conditions. Adopted 2012. Updated April 2018. Available at: **https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/genetic-testing-of-minors-for-adult-onset-conditions**
3. Botkin, JR, Belmont JW, Berg JS, et al. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *Am J Hum Genet*. 2015;97:6-21. Available at: **https://www.cell.com/ajhg/fulltext/S0002-9297(15)00236-0?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0002929715002360%3Fshowall%3Dtrue**

Genetic Testing for Carrier Status

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Genetic testing for carrier status is performed to identify genetic risks that could impact reproductive decision-making for parents or prospective parents. Carriers are generally not affected but have an increased risk to have a child with a genetic condition. Carrier testing may be performed when there is a known elevated risk for a condition based on an individual's family history or ancestry or as a means of screening for reproductive risks in the general population.

Availability of genetic testing for carrier status

Carrier testing may be available for autosomal recessive conditions, X-linked conditions, and certain chromosome abnormalities. Ideally, carrier screening is performed prior to pregnancy so that a full range of reproductive options are available to an at-risk couple. However, in practice, it is often performed early in pregnancy when prenatal care is established.

Other applications of carrier testing

For information on prenatal screening and diagnostic testing, please refer to the guideline *Genetic Testing for Prenatal Screening and Diagnostic Testing,* as this testing is not addressed here.

For information on preimplantation genetic screening, please refer to the guideline *Preimplantation Genetic Screening and Diagnosis,* as this testing is not addressed here.

For information on non-invasive prenatal testing, please refer to the guideline *Non-invasive Prenatal Screening*, as this testing is not addressed here.

This guideline does not include testing that may identify carriers who have clinical signs and symptoms, such as cystic fibrosis testing for men with congenital absence of the vas deferens or fragile X genetic testing for women with premature ovarian failure. For information on this, please refer to the test specific guideline or *Genetic Testing to Diagnose Non-Cancer Conditions.*

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for genetic testing for carrier status will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are

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considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

Criteria

Requests for genetic testing for carrier status are reviewed using these criteria.

Criteria for general coverage guidance

Genetic testing for carrier status is medically necessary when ALL of the following conditions are met:

Technical and clinical validity	The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
Clinical utility	Healthcare providers can use the test results to provide significantly better medical care and/or assist individuals with reproductive planning.
Reasonable use	The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits

- Testing is only medically necessary for the number of genes or tests necessary to establish carrier status. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Carrier testing will be allowed once per lifetime. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.
- Carrier testing is only medically necessary in adults. Carrier screening in minor children is not medically necessary, except in the case of a pregnancy of the minor child.

Carrier testing based on family history

Carrier testing based on a family history of a genetic condition is medically necessary when ALL of the following conditions are met in addition to the general criteria above:

- The diagnosis of a genetic condition in a family member is known.
- The parent(s) or prospective parent(s) are at-risk to be carriers of that condition based on the pattern of inheritance.

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- The genetic condition is associated with potentially severe disability or has a lethal natural history.

Partner testing of known carrier or affected individuals

Carrier screening is medically necessary in individuals whose partners are known carriers or affected individuals when all of the following conditions are met in addition to the general criteria above:

- The diagnosis of a genetic condition or carrier status in the partner is known.
- The genetic condition is associated with potentially severe disability or has a lethal natural history.

Test-specific guidelines

Test-specific guidelines are available for some tests designed to predict carrier status. For tests without a specific guideline, use the General Coverage Guidance above.

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Genetic Testing for Known Familial Mutations

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Genetic Testing for Known Familial Mutations is addressed by this guideline.

Description

When genetic testing reveals the cause of an inherited disease in an affected family member, the genetic change is called a 'known familial mutation' (KFM). Relatives of the affected individual should generally have genetic testing that targets this disease-causing KFM rather than full sequencing of a gene or a multi-gene panel.

KFM testing is less expensive, less complex, and avoids finding variants of uncertain clinical significance (VUS) that have unclear medical management implications.

Presymptomatic or diagnostic testing for known familial mutations should only be offered when the variant is considered disease-causing, or classified as pathogenic or likely pathogenic per American College of Medical Genetics and Genomics (ACMG) variant classification guidelines.[1]

If there is a KFM in the family, testing for this mutation should be performed prior to any other genetic testing for the disease in an individual.[2,3]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for genetic testing for known familial mutations will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

Criteria

Requests for genetic testing for Known Familial Mutations (KFM) are reviewed using the following criteria.

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Criteria: General Coverage Guidance

- Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- No previous genetic testing of the requested gene that would have included the KFM, AND
- Member is a 1st, 2nd, or 3rd degree biological relative of the family member with the KFM, AND
- KFM is disease-causing (classified as pathogenic or likely pathogenic), AND
- Member is at risk based on the inheritance pattern of the disorder in question, AND
- Diagnostic Testing in Symptomatic Individuals:
  - Member exhibits symptoms consistent with the disease caused by the KFM, OR
- Presymptomatic or Predictive Testing in Asymptomatic Adults:
  - Member is 18 years of age or older, AND
- Healthcare providers can use the test results to provide significantly better medical care for the individual, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Limits:

- Diagnostic or presymptomatic/predictive KFM testing will be allowed once per lifetime per condition.

Note:

For medical necessity criteria for presymptomatic/predictive testing of a known familial mutation in individuals younger than 18 years, see the guideline: *Genetic Testing to Predict Disease Risk*.

Billing and Reimbursement Considerations

- Once the mutation(s) that cause disease in the family have been identified, KFM testing is generally the only testing needed for that particular gene. As a result, if broad gene testing (for example, full gene sequencing or deletion/duplication analysis) is requested and a KFM has been identified in a family member, testing will be redirected to KFM testing.
- In rare circumstances, additional gene testing may be indicated following KFM testing, which will be assessed on a case-by-case basis.
- CPT codes specific for KFM testing (generally including language such as “known familial variant” in the code description) may not be used to bill for any other types of testing. There must be a documented KFM in the family. For example, the use of a KFM CPT code when billing part of a panel of genes, which is generally used as the initial step in identifying a disease-causing mutation in an individual, is not a correct use of these codes and is therefore not eligible for reimbursement.

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Criteria: Test-specific Guidelines

Test-specific guidelines are available for some tests designed to assess known familial mutations. For tests without a specific guideline, use the General Coverage Guidance above.

References

This guideline cites the following references.

1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015; 17(5):405-24. doi: 10.1038/gim.2015.30.
2. U.S. Preventative Services Task Force. Final recommendation Statement BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing. August 20, 2019. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing
3. Gupta A, Weiss JM, Axell L, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2024 – October 31, 2024. Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric, available at: **https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal V3.2024 – October 31, 2024. ©2024 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines®, go online to **NCCN.org** .

Genetic Testing for Non-Medical Purposes

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Description

While most traditional genetic tests are used for clear medical purposes, advances in gene discovery and genetic testing technology allow laboratories to offer genetic testing for other uses. Testing for paternity, ancestry, general wellness, and non-disease traits such as baldness and eye color may be accurate or interesting; however, because these kinds of tests are not useful for medical management in the vast majority of cases, they are typically excluded from consideration.

Non-medical tests are usually offered as direct-to-consumer products and do not require a clinical evaluation or order from a healthcare provider. Common providers of such tests may include:

- 23andMe
- Ancestry.com
- everlywell
- Invitae
- HomeDNA
- Affinity DNA

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for genetic testing for non-medical purposes will ensure that members will not receive testing that does not contribute to medical management decisions. However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

Criteria

Criteria: General Coverage Guidance

Any genetic test that **DOES NOT** meet the following criteria is excluded from consideration:

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- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- **Reasonable use:** The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Criteria:

The following types of testing are not considered medically necessary and therefore, not eligible for reimbursement:

- Genome-wide association studies (GWAS): testing a large number of genetic variations spread across the whole genome for disease associations, generally done for information outside of a specific clinical need or context
- Paternity testing: testing to establish biological relationships, often between a father and child(ren) but sometimes to determine other kinds of relationships (siblings, grandparents, etc.)
- Ancestry testing: testing that helps people discover more about the genetic make-up of their ancestors, generally used by genealogists and those interested in family history
- Nutritional testing: for variations in metabolism pathways that may suggest vitamin or other nutritional supplements
- Athletic ability or fitness: Testing to predict athletic performance types
- Genetic testing related to dating services
- Beauty care: testing for genetic variants to optimize beauty products, skin care ingredients or supplement selection

Genetic Testing for Non-Medical Purposes

Genetic Testing for Prenatal Screening and Diagnostic Testing

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Description

Prenatal screening and diagnostic testing is performed during pregnancy to identify fetuses at increased risk for or affected with genetic conditions and birth defects. Screening with ultrasound and maternal serum markers is routinely offered. Prenatal diagnosis by chorionic villus sampling or amniocentesis for chromosome abnormalities is available to all women; however, it is usually offered specifically to those at higher risk because of maternal age, a positive screen result, abnormal ultrasound findings, or known risk of a genetic condition based on family history. Investigations for fetal infection and blood antigen incompatibility may also be performed in the prenatal period. Results of testing are used to guide reproductive decision-making, pregnancy management and anticipatory management of the infant at birth.

- For information on prenatal or preconception carrier screening or preimplantation genetic testing, please refer to the guidelines *Genetic Testing for Carrier Status* and *Preimplantation Genetic Screening and Diagnosis,* as this testing is not addressed here.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for genetic testing for prenatal screening and diagnostic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

Criteria

Criteria: General Coverage Guidance

Genetic testing for prenatal screening and diagnostic testing is medically necessary when **ALL** of the following conditions are met:

- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.

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- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care and/or assist patients with reproductive planning.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will only be covered for the number of genes or tests necessary to establish a prenatal diagnosis. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Prenatal diagnostic testing is medically necessary once per pregnancy. Exceptions may be considered if ambiguous results require retesting for clarification.
- If prenatal samples are studied concurrently with a maternal DNA sample to rule out prenatal analytic errors due to maternal cell contamination, a single unit of CPT code 81265 is reimbursable.

Criteria: Special Prenatal Diagnosis Circumstances

Each of the following sections addresses a group of tests that are used for similar purposes in pregnancy. Because a variety of tests may be used, but the circumstances that justify testing are the same, individual test-specific policies are not necessary.

Prenatal diagnostic testing based on family history

Prenatal genetic testing, generally by amniocentesis or CVS, for the diagnosis of a genetic condition is medically necessary when the following conditions are met:

- The pregnancy is at an increased risk for a genetic disease based on the inheritance pattern of the disorder in question and ANY of the following:
  - At least one parent is known or suspected to be a carrier of a genetic condition based on the family history and/or previous carrier testing results; or
  - One or both parent(s) are affected with a genetic condition; or
  - A sibling is affected with a genetic condition; AND
- The genetic condition is associated with potentially severe disability or has a lethal natural history.

Fetal infectious disease testing

Genetic testing may be used for the diagnosis of an infectious disease (e.g., cytomegalovirus, toxoplasmosis, parvovirus B19, and varicella zoster) in a fetus according to current guidelines from the American College of Obstetricians and Gynecologists (ACOG).[1] Prenatal testing, generally by amniocentesis or CVS, is medically necessary when ANY of the following conditions are met:

- Clinical signs and symptoms of a current infection in the mother; OR
- Serologic evidence of a current or recent infection in the mother (with or without clinical signs); OR

- Fetal abnormalities identified on ultrasound indicating an increased risk for a congenital infection

Criteria: Test-specific Guidelines

- Test-specific guidelines are available for some prenatal screening tests and diagnostic tests. For tests without a specific guideline, use the General Coverage Guidance above.

References

1. ACOG Practice Bulletin. Cytomegalovirus, Parvovirus B19, Varicella Zoster, and Toxoplasmosis in Pregnancy. Number 151, June 2015 (reaffirmed 2024). *Obstet Gynecol.* 2015;125(6):1510-1525.

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Genetic Testing for Variants of Uncertain Clinical Significance

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Genetic testing for variants of uncertain clinical significance is addressed by this guideline.

Description

Genetic testing of an affected individual by gene sequencing or multi-gene panel testing can reveal genetic variants that have an unknown effect. These variants of uncertain clinical significance (VUS) may or may not cause disease in the individual; there is simply not enough known at the time of the report to call the variant disease-causing or benign.[1]

The accumulation of sufficient data to reclassify a VUS may take many years and require identification of the variant in multiple individuals. Pathogenicity of a variant is determined by labs through assessing:

- Disease-specific or gene-specific mutation databases
- Large population variant frequency databases
- In silico prediction tools
- Multi-species conservation assessment
- Peer reviewed literature
- Functional studies
- Family assortment studies

Family studies may be offered by the laboratory at no charge to the family, as the result may assist the lab in future classification of the variant. Testing relatives for a VUS may not always lead to reclassification of a variant to either disease-causing or benign, but it can be helpful in certain clinical scenarios, potentially contributing evidence that it is more or less likely to be disease-causing.

Targeted VUS Testing

Testing the parents of an affected child who has a VUS may be helpful in determining the clinical significance of that variant in some situations. For instance, if the condition is dominant and the VUS is not inherited from either parent (de novo), it is more likely to be disease-causing. If it is inherited from a healthy parent, it may be more likely to be benign.

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Similarly, for an autosomal recessive condition, one or both of two potential disease-causing variants in a child may be called VUS. Testing parents should confirm whether one of the variants was inherited from each parent, and therefore fits the recessive pattern of inheritance.

If a VUS is identified in apparent homozygosity (2 copies), testing parents should determine copy number. A VUS that is inherited in two copies, one from each parent, would be consistent with the expected pattern of inheritance for recessive disease. If the VUS is only inherited from one parent, other mechanisms for pathogenicity (such as gene deletion or uniparental disomy) should be investigated.

Simply testing a relative for a VUS will not determine if that variant is disease causing or benign. This is especially true for adult onset conditions (e.g., hereditary cancer syndromes) or conditions for which there is reduced or non-penetrance or highly variable expressivity. After targeted testing for a VUS, careful clinical and family history evaluation and correlation with the result are essential.

Genes of Uncertain Clinical Significance

Broader tests, such as whole exome sequencing or whole genome sequencing, may identify variants in genes that have an unknown effect. For a gene of uncertain clinical significance (GUS), there is not enough known about the gene and its function to say whether it can cause the disease in question.[1]

Potential Outcomes of Targeted VUS testing

Results of testing and possible significance of testing.

Result of VUS testing	Possible significance
VUS is not inherited (de novo)	Increased likelihood of causing disease
VUS is inherited from affected parent	Increased likelihood of causing disease
VUS is inherited from unaffected parent	Decreased likelihood of causing disease
VUS is inherited with a disease-causing variant or VUS from the same parent	Decreased likelihood of causing disease
VUS that is apparently homozygous is not inherited from both parents	Alternate mechanisms should be investigated

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for genetic testing for variants of uncertain clinical significance will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not

meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

Criteria

Requests for genetic testing for variants of uncertain clinical significance are reviewed using these criteria.

Criteria: General Coverage Guidance

- Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- No previous genetic testing of the requested gene that would detect the VUS, AND
- No known alternate genetic cause for the diagnosis in the family, AND
- Member is the biological parent of a child in whom a VUS was identified, AND
- VUS is in a gene that is
  - Known to be disease-associated, and
  - Consistent with the child's clinical diagnosis, AND
- Purpose of testing is to determine
  - Whether the VUS is inherited or de novo, or
  - Whether the VUS is present in homozygosity, AND
- Determination of the inheritance or copy number of the VUS will lead to treatment changes for the member or the member's child, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Limitations and Exclusions

- Testing of multiple affected and unaffected relatives to determine if a VUS assorts with symptoms in the family is not considered medically necessary; therefore, it is not reimbursable.
- Testing for variants in genes of uncertain clinical significance (GUS) is not considered medically necessary; therefore, it is not reimbursable.
- Each test request for VUS testing should be reviewed based on the medical information available for the member and the clinical utility and technical and clinical validity of the service requested.

Criteria: Test-specific Guidelines

Test-specific guidelines may be available for tests that could target a VUS. For tests without a specific guideline, use the General Coverage Guidance above.

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References

This guideline cites the following references.

1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015; 17(5):405-24. doi: 10.1038/gim.2015.30.

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Genetic Testing for the Screening, Diagnosis, and Monitoring of Cancer

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Description

Genetic testing for screening, diagnosis and monitoring of cancer refers to molecular diagnostic tests whose purposes include identifying the possible presence of cancer in asymptomatic, average risk individuals; confirming the absence or presence of cancer; and monitoring the absence or presence of cancer after a prior diagnosis and treatment.

Screening

The goal of cancer screening is to identify the possible presence of cancer before symptoms appear. Screening tests cannot diagnose cancer, but typically determine if there is an increased chance cancer is present, and triages individuals for more invasive, diagnostic testing. Most cancer screening does not include genetic testing, but instead relies on physical exam, radiological exams, or non-genetic laboratory tests. Advances in human genetics, however, have identified several molecular diagnostic tests that may provide clues for early cancer detection.

Diagnosis

When cancer is suspected because of an abnormal screening test or symptoms, blood tests for tumor markers or molecular testing on tissue samples can aid in confirming a diagnosis of cancer. These tests may contribute information to helping the clinician understand prognosis and treatment options.

Monitoring

During treatment, or after an apparently successful treatment, active monitoring is often recommended to identify if the cancer is responding to treatment or has returned or spread, before any symptoms appear. Monitoring may include increased surveillance or routine blood tests for tumor markers, and increasingly, molecular genetic tests.

- For information on tests used to determine hereditary cancer risk, please refer to the guideline *Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes*, as this testing is not addressed here.
- For information on drug response to cancer or testing to determine which therapies to use, please refer to the guideline *Pharmacogenomic Testing for Drug Toxicity and Response*, as this testing is not addressed here.

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- For information on molecular tumor marker testing in solid tumors, please refer to the guideline *Somatic Mutation Testing* and *Liquid Biopsy Testing,* as this testing is not addressed here.
- For information on diagnostic or predictive testing for conditions other than non-inherited cancer, please refer to the guideline *Genetic Testing to Diagnose Non-Cancer Conditions* and *Genetic Testing to Predict Disease Risk*, as this testing is not addressed here.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for genetic testing for the screening, diagnosis, and monitoring of cancer will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

Criteria

Criteria: General Coverage Guidance

Genetic testing for screening, diagnosing, or monitoring cancer is medically necessary when **ALL** of the following conditions are met:

- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will be considered only for the number of genes or tests necessary. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- For tests that look for changes in germline DNA (i.e., not tumor DNA or viral DNA), testing is medically necessary once per lifetime per gene. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

Criteria: Test-specific Guidelines

Test-specific guidelines are available for some tests designed to screen for, diagnose, or monitor cancer. For tests without a specific guideline, use the General Coverage Guidance above.

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Genetic Testing to Diagnose Non-Cancer Conditions

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Description

Diagnostic testing is performed in patients with clinical signs or symptoms of a non-cancer genetic condition. The genetic test may confirm or rule out a clinical diagnosis. In some cases, genetic testing is the gold standard for making a diagnosis based on evidence- or consensus-based guidelines. In others, it may be used to confirm a clinical diagnosis, offer prognostic information that impacts management, rule out a diagnosis in the differential, or confirm a positive newborn screening result. Often, diagnostic testing of an affected individual will offer results that are relevant to the testing of other family members.

- This guideline does not include risk assessment or predictive testing for at-risk, asymptomatic individuals. Please refer to *Genetic Testing to Predict Disease Risk* for that purpose.
- Diagnostic testing of a pregnancy or an embryo is addressed by guidelines on *Genetic Testing for Prenatal Screening and Diagnostic Testing* and *Preimplantation Genetic Screening and Diagnosis*, respectively.
- In addition, testing for hereditary cancer syndromes is addressed separately under *Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes*.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for genetic testing to diagnose non-cancer conditions will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

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Criteria

Criteria: General Coverage Guidance

Diagnostic genetic testing is medically necessary when **ALL** of the following conditions are met:

- **Clinical signs and symptoms** in the individual are consistent with the diagnosis in question.
- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will be considered only for the number of genes or tests necessary to establish mutation status. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Diagnostic genetic testing is medically necessary once per lifetime per condition. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

Criteria: Special Circumstances

Diagnostic testing of an individual to inform reproductive planning and testing for parents or testing for siblings

Diagnostic genetic testing may be requested in a symptomatic individual with a known genetic condition. While diagnostic testing may not impact management of the affected individual, the information gained from genetic testing may be needed to perform accurate carrier testing in the parent(s), genetic diagnosis in a pregnancy, or genetic diagnosis in a sibling.*

In these circumstances, diagnostic genetic testing in a symptomatic individual is medically necessary when **ALL** of the following conditions are met:

- The diagnosis of the disease in the affected individual is **certain or highly probable** based on clinical signs and symptoms, history, imaging, and/or results of other laboratory testing.
- The results of the genetic test in the symptomatic individual must be **required** in order to perform accurate carrier testing in the parent(s), genetic diagnosis in a pregnancy, or genetic diagnosis in a sibling.

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- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility**: Healthcare providers can use the test results to provide informative genetic testing for the sibling, parents, or for a current or future at-risk pregnancy.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Limits:

- Testing will be indicated only for the number of genes or tests necessary to establish the familial mutation(s). A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Diagnostic genetic testing is medically necessary once per lifetime per condition. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

*Parent or sibling must also be a covered member under the same health plan.

Diagnostic testing of an individual to confirm newborn screening results

Newborn Screening (NBS) is state-mandated testing performed in the first days of life, using blood spots obtained from a heel stick. Biochemical studies are used, and often supplemented with molecular analysis, in order to screen for a number of different disorders. The goal of NBS is to identify affected infants before they become symptomatic, since these disorders may cause significant morbidity or mortality unless treatment is initiated in the neonatal period. Diagnostic genetic testing may be requested for infants with positive, borderline, or inconclusive results. The American College of Medical Genetics and Genomics (ACMG) ACT Algorithms contain an overview of the steps involved in determining a final diagnosis, and can be found **here** .

Diagnostic genetic testing in an individual for the purposes of confirming newborn screening results is medically necessary when the following conditions are met:

- The individual has had a newborn screening result that is positive, borderline, or inconclusive for a specific disorder for which confirmatory genetic testing is required, AND
- The requested testing has not been previously performed, AND
- The member will benefit from information provided by the requested gene testing based on at least one of the following:
  - All criteria are met from a test-specific guideline, if one is available, or
  - The ACMG ACT Algorithm associated with the suspected disorder includes genetic testing, and all preliminary studies recommended in the algorithm have been completed (however, the genetic test must not simply be listed as "optional", or as an intervention that may be considered), or
  - There is uncertainty in the diagnosis, despite further evaluation by an appropriate provider, and genetic testing is needed to clarify the diagnosis, or

- An individual has a confirmed biochemical diagnosis of the disorder for which testing is requested, but healthcare providers can use the genetic test results to directly impact medical care for the individual (e.g. change in surveillance or treatment plan).

Limits:

- Testing will be indicated only for the number of genes or tests necessary to establish the diagnosis. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Diagnostic genetic testing is medically necessary once per lifetime per condition. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

Criteria: Test-specific Guidelines

Test-specific guidelines are available for some tests designed to diagnosis non-cancer conditions. For tests without a specific guideline, use the General Coverage Guidance above.

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Genetic Testing to Predict Disease Risk

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Description

Predictive genetic testing is performed in people known to be at increased risk of developing an inherited non-cancer condition (for the purposes of this guideline) based on their family history. According to the Genetics Home Reference, presymptomatic testing "can determine whether a person will develop a genetic disorder," while predictive testing "can identify mutations that increase a person's risk of developing disorders with a genetic basis."[1] Predictive testing should be limited to disorders for which the genetic contribution is strong. A positive test result may improve medical management through improved screening, preventive measures, prophylactic medication, and other means. A negative result may rule out a condition, or lower the risk significantly, and may also lead to changes in recommended medical management.

Predictive testing is often performed only in adult individuals (age 18 and over).[2-4] Some adult-onset conditions have surveillance or medical intervention recommendations that are initiated in childhood, while for others there is no change in medical management. The National Society of Genetic Counselors (NSGC) states that individuals should be able to make the decision to have testing for themselves, after understanding and assessing the risks, benefits, and limitations of the test. In their 2018 position statement entitled "Genetic Testing of Minors for Adult-Onset Conditions," NSGC "encourages deferring predictive genetic testing of minors for adult-onset conditions when results will not impact childhood medical management or significantly benefit the child."[3]

- For information on testing a symptomatic individual, please refer to the guideline *Genetic Testing to Diagnose Non-Cancer Conditions* or the appropriate EviCore test-specific guideline.
- For information on predictive testing for hereditary cancer syndromes, please refer to the guideline *Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes* or the appropriate EviCore test-specific guideline.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for genetic testing to predict disease risk will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible

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that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

Criteria

Criteria: General Coverage Guidance

Predictive genetic testing is medically necessary when **ALL** of the following conditions are met:

- The individual is **known to be at-risk** for developing inherited condition because a parent, sibling, or child is affected by or known to be a carrier of a genetic disease.
- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test.
- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care for the individual.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

Criteria: Special circumstances

Testing for Known Familial Mutations

The genetic mutation(s) associated with a genetic disease can often be defined in an affected family member, allowing for testing of at-risk relatives for those specific mutations. Testing for known familial mutations (KFM) is medically necessary when the following conditions are met:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing of the requested gene that would have included the KFM, and
  - KFM is disease-causing (classified as pathogenic or likely pathogenic), AND
- Predictive Testing for Asymptomatic Individuals:
  - Member is a 1st, 2nd, or 3rd degree biological relative of the family member with the KFM, and
  - Member is at risk based on the inheritance pattern of the disorder in question, and
  - Member is 18 years of age or older (see Predictive Testing in Minors for specific exceptions), and

  - Healthcare providers can use the test results to provide significantly better medical care for the individual, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Predictive Testing in Minors

Predictive molecular testing of minors (members under the age of 18 years) for X-linked or autosomal dominant disorders is medically necessary when the following criteria have been met:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous testing for the condition, and
  - A familial disease-causing mutation has been identified in a 1st or 2nd degree biological relative who is affected with an adult-onset autosomal dominant or X-linked condition, AND
- Predictive Testing for Asymptomatic Individuals:
  - The minor is at risk for inheriting the familial disease-causing mutation, and
  - The condition may have either symptom onset or recommendations for medical management that begin in childhood, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Note:

Testing of any minor who is symptomatic for a condition, regardless of typical circumstances of onset, is considered diagnostic testing and should be reviewed using *Genetic Testing to Diagnose Non-Cancer Conditions* or the appropriate EviCore test-specific guideline, when available. Certain circumstances not related to medical management (such as consideration of a minor for organ/tissue donation or pregnancy in a minor with a family history of adult-onset disease) may present sufficient clinical utility to outweigh the criteria presented in this guideline. Such rare cases should be carefully considered on an individual basis

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Criteria: Test-specific Guidelines

EviCore test-specific guidelines are available for some tests designed to predict disease risk. For tests without a specific guideline, use the General Coverage Guidance above.

Limitations and Exclusions

- Testing will be considered only for known familial mutations when clinically possible.

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- Testing will be considered only for the number of genes or tests necessary to establish carrier status. A tiered approach to testing, with reflex to more detailed testing and/or different genes, will be required when clinically possible.
- Predictive genetic testing is medically necessary once per lifetime per condition. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.
- Testing for genetic variants that are not causative of inherited disease is not medically necessary; and therefore, is not reimbursable. Examples of mutations or variants that are not causative include:
  - Variants assessed by a testing laboratory to be of uncertain clinical significance, except as addressed in the guideline *Genetic Testing for Variants of Uncertain Clinical Significance*
  - Variants in genes of uncertain clinical significance
  - Variants deemed to be associated with but not causative of a disorder (e.g.: variants identified in genome-wide association studies (GWAS) or risk alleles for common disorders)

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Genetic Testing by Multigene Panels

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Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Genomic Sequencing Procedures	81410-81471
Molecular Proprietary Laboratory Analyses (PLA)	Various Molecular* PLA codes (ending in U)
Tier 1 Molecular Pathology Procedures	81161-81383
Tier 2 Molecular Pathology Procedures	81400-81408
Unlisted Molecular Pathology Procedure	81479

What are multigene panels?

Various methodologies can be used to identify potential disease-causing gene mutations. Gene sequencing involves evaluating each DNA nucleotide along the length of a gene. Full gene sequencing is the best approach when many different mutations in the same gene can cause the disorder.

- There are two main ways to sequence a gene:
  - Sanger sequencing methodology, originally developed in the 1970s, sequences DNA from one gene at a time in several independent assays. Sanger sequencing is labor intensive and did not lend itself to high-throughput applications.[1]
  - Next generation sequencing (NGS), also called massively parallel sequencing, was developed to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence.[1]
- The efficiency of NGS has led to an increasing number of large, multigene testing panels.

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  - NGS panels are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes.
  - Panels including genes associated with a high risk of a condition are of greatest value since these mutation-positive results often lead to changes in medical management.
  - Panels may also include genes believed to be associated with a particular condition, but with a more modest impact on risk. Results for such genes are of less clear value because there often are not clear management recommendation for mutation-positive individuals.
- Laboratories offer panel testing for multiple genes at the same time in an effort to increase the likelihood of finding a causative gene mutation in a more efficient manner. Such testing may be performed for diagnostic or predictive purposes.
  - Diagnostic testing is performed in patients with clinical signs or symptoms of a genetic condition. The genetic test may confirm or rule out a clinical diagnosis. However, many genetic conditions have overlapping features, which can make determining appropriate genetic testing difficult. The use of clinical and family history information may not always lead to a likely diagnosis for an individual. In some cases, many genes may be candidates for an individual's symptoms. In these cases, testing one gene at a time may be time-consuming and costly.
  - Predictive genetic testing is performed in people known to be at increased risk of developing an inherited condition based on their family history. For some conditions, a positive genetic test predicts with certainty that the individual will eventually develop signs and symptoms of a condition. For other conditions, a positive genetic test result indicates an increased risk (susceptibility) for a condition. Without a specific known mutation running in the family, a negative result rarely rules out a condition. Having test results may improve medical management through improved screening, preventive measures (e.g., prophylactic medication, surgery) and other means. In order to better define an individual's risk, it is preferable to first test someone in the family who is affected.

Test information

- Multigene panel tests, even for similar clinical scenarios, vary considerably in the genes that are included and in technical specifications (e.g., depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis). Therefore, technologies used in multigene testing may fail to identify mutations that might be identifiable through single-gene testing.

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- If high clinical suspicion remains for a particular syndrome after negative multigene test results, consultation with the testing lab and/or additional targeted genetic testing may be warranted.
- Results may be obtained that cannot be adequately interpreted based on the current knowledgebase. When a sequence variation is identified that has not been previously characterized or shown to cause the disorder in question, it is called a variant of uncertain clinical significance (VUS). VUSs are relatively common findings when sequencing large amounts of DNA with NGS.[2]
- Since genes can be added or removed from multigene tests over time by a given lab, medical records must document which genes were included in the specific multigene test used for each patient, and in which labs they were performed.
- Tests should be chosen to:
  - maximize the likelihood of identifying mutations in the genes of interest
  - contribute to alterations in patient management
  - minimize the chance of finding variants of uncertain significance.

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2021) revised technical standard for clinical NGS stated:[3]

- "Choosing an appropriate NGS-based test is the responsibility of the ordering health-care provider. Given the large number of tests (https://www.ncbi.nlm.nih.gov/gtr/) available to the clinician, the clinical laboratory often provides critical advice in test selection. Ordering providers must weigh considerations of sensitivity, specificity, cost, and turnaround time for each clinical situation."
- "Diagnostic gene panels are optimal for well-defined clinical presentations that are genetically heterogeneous (e.g., congenital hearing loss), for which pathogenic variants in disease-associated genes account for a significant fraction of cases. Secondary/ incidental findings should not be encountered, although broad panels (e.g., epilepsy, or pan-cancer panels) may identify clinically significant findings unrelated to the test indication. By limiting the test to those genes relevant to a given disease, the panel can be optimized to maximize coverage of relevant regions of the gene(s).[Bean et al. 2020]"
- "Test development must consider the variant types that will be detected in the genes or regions of the genome interrogated."

The ACMG (2020) technical standard on diagnostic gene panels stated:[4]

- "Gene panels developed by clinical molecular laboratories assess multiple potential genetic causes of a suspected disorder(s) simultaneously and reduce the cost and time of diagnostic testing. Gene panels are useful to diagnose disorders with genetic

and clinical heterogeneity. Panels for phenotypically related disorders can increase the likelihood of identifying an underlying genetic cause and may be preferred to exome or genome sequencing to maximize target coverage and avoid secondary findings."

- "The goal of a diagnostic gene panel is to maximize clinical sensitivity and minimize the clinical burden from analysis of inappropriate or unnecessary genes that may result in variants of uncertain clinical significance (VUS)."
- "While it may be technically possible to sequence all genes related to a phenotype, the power of a gene panel is the ability to match a patient's specific clinical features to genes associated with that phenotype, thereby increasing clinical specificity and limiting the number of VUS."
- "While it is technically feasible to include genes with low-penetrance pathogenic variants on gene panels, the penetrance and the factors affecting penetrance are generally not known, thus limiting clinical utility. "

In an earlier Points to Consider document, ACMG (2012) offered general guidance on the clinical application of large-scale sequencing focusing primarily on whole exome and whole genome testing. However, some of the recommendations regarding counseling around unexpected results and variants of unknown significance and minimum requirements for reporting apply to many applications of NGS sequencing applications.[5]

National Society of Genetic Counselors

The National Society of Genetic Counselors position statement on the use of multigene panels (NSGC, 2023) stated:[6]

- "The National Society of Genetic Counselors (NSGC) endorses the use of multi-gene panel tests when clinically warranted and appropriately applied. These tests can provide a comprehensive and efficient route to identifying the genetic causes of disease. Before ordering a multi-gene panel test, providers should thoroughly evaluate the analytic and clinical validity of the test, as well as its clinical utility. Additional factors to consider include, but are not limited to: clinical and family history information, gene content of the panel, limitations of the sequencing and informatics technologies, and variant interpretation and reporting practices."
- "Panels magnify the complexities of genetic testing and underscore the value of experts, such as genetic counselors, who can educate stakeholders about appropriate utilization of the technology to mitigate risks of patient harm and unnecessary costs to the healthcare system. NSGC supports straightforward and transparent pricing so that patients, providers, laboratories, and health plans can easily weigh the value of genetic testing in light of its cost."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the policy, following EviCore's criteria for genetic testing by multigene panels will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

Criteria

This guideline applies to multigene panel testing, which is defined as any assay that simultaneously tests for more than one gene associated with a condition. The testing may focus on sequence variants and/or deletions/duplications of those genes. Panels vary in scope, and may include:

- Multiple genes that are associated with one specific genetic condition (e.g., Noonan syndrome, Stickler syndrome, etc.)
- Multiple genes that are associated with a symptom or non-specific presentation (e.g., epilepsy, intellectual disability, hearing loss, retinal disorders, etc.)
- Coverage determinations generally rely on the medical necessity of the components of a panel. A panel approach to testing is most compelling when:
  - Multiple genes are known to cause the same condition and a limited subset of genes does not account for the majority of disease-causing mutations.
  - The clinical presentation is highly suspicious for a genetic disorder, but the constellation of findings in the personal or family history does not suggest a specific diagnosis or limited set of conditions.
- The following general principles apply:
  - Broad symptom-based panels (e.g., comprehensive ataxia panel) are not medically necessary when a narrower panel is available and more appropriate based on the clinical findings (e.g., autosomal dominant ataxia panel).
  - More than one multigene panel should not be necessary at the same time. Multigene panel testing should be performed in a tiered fashion with independent justification for each panel requested.
  - If more than ten units of any combination of procedure codes will be billed as part of a panel with no stated differential, the panel will be deemed excessive and not medically necessary.
  - Germline genetic testing is only medically necessary once per lifetime. Therefore, a single gene included in a panel or a multigene panel may not be reimbursed if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

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- This guideline may not apply to multigene panel testing for indications that are addressed in test-specific guidelines.

Other Considerations

- All requested procedures must follow correct coding practices. Any procedure codes that do not meet these standards will not be reimbursable, even if medical necessity criteria for the associated test(s) are met. For general coding requirements, please refer to the guideline *Laboratory Billing and Reimbursement*.
- Multiple guidelines may apply to multigene panel testing, including test-specific guidelines, where they exist, or the clinical use guidelines *Genetic Testing to Diagnose Non-Cancer Conditions* or *Genetic Testing to Predict Disease Risk*.

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Hereditary (Germline) Testing After Tumor (Somatic) Testing

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Introduction

Germline hereditary cancer testing following somatic tumor testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
APC deletion/duplication analysis	81203
APC known familial variants	81202
APC sequencing	81201
ATM sequencing	81408
BRCA1 deletion/duplication analysis	81166
BRCA1 sequencing	81165
BRCA2 deletion/duplication analysis	81167
BRCA2 dequencing	81216
BRCA1/2 185delAG, 5385insC, 617delT variants	81212
BRCA1/2 deletion/duplication analysis	81164
BRCA1/2 known familial variants	81215

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Procedures addressed by this guideline	Procedure codes
BRCA1/2 sequencing	81163
Chromosomal microarray [BAC], constitutional	81228
Chromosomal microarray [SNP], constitutional	81229
Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis	81349
Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer, hereditary pancreatic cancer, hereditary prostate cancer), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants	81432
Hereditary cancer syndrome gene tests	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479

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Procedures addressed by this guideline	Procedure codes
Hereditary colon cancer-related disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants	81435
Hereditary neuroendocrine tumor-related disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants	81437
MLH1 deletion/duplication analysis	81294
MLH1 known familial variants	81293
MLH1 sequencing	81292
MSH2 deletion/duplication analysis	81297
MSH2 sequencing	81295
MSH2 known familial variants	81296
MSH6 deletion/duplication analysis	81300
MSH6 known familial variants	81299
MSH6 sequencing	81298
PMS2 deletion/duplication analysis	81319
PMS2 known familial variants	81318
PMS2 sequencing	81317

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Procedures addressed by this guideline	Procedure codes
PTEN deletion/duplication analysis	81323
PTEN known familial variants	81322
PTEN sequencing	81321

What is germline hereditary cancer testing following somatic tumor testing?

Most cancer is sporadic and due to the acquisition of somatic mutations (also known as variants). About 5-10% of cancer has a hereditary etiology due to constitutional germline mutations.[1]

- In oncology, next generation sequencing (NGS) technology makes it feasible to catalog the DNA sequence mutations within a person's cancer (i.e., somatic mutation profiling). This helps define therapeutic targets which might improve outcomes through the use of specific medications directed at those mutations.[2] These genomic mutations can also serve as biomarkers of an individual's prognosis and aid in diagnosis.[3,4]
- Germline mutations can also be identified as an ancillary finding during primary tumor profiling to identify somatic mutations. "In the course of analyzing tumor DNA (without matched normal DNA), sequencing can identify potential constitutional (germline) DNA variations that are associated with disease or susceptibility to disease as well as carrier states for Mendelian disorders.[4] Centers may use matched tumor-normal sequencing to facilitate more accurate calling of somatic mutations by using the normal DNA to exclude germline variants from the tumor cells."[3,4]
    - In a study by Schrader et al, "Targeted tumor sequencing with a panel of 341 genes and matched normal DNA in 1566 individuals with advanced malignant neoplasms revealed presumed pathogenic germline variants (PPGVs) in about 16% of individuals. Most PPGVs (80.5%, 95% CI, 75.1%-85.0%) were in genes related to cancer susceptibility. The PPGVs in genes previously designated as clinically actionable cancer targets were seen in 5.0% (95% CI, 4.1%-6.2%) of individuals. Most cancer-susceptibility PPGVs were retained in the tumor (91.9%; 95% CI, 87.3%-95.0%).[5] This study is in line with other published studies investigating the prevalence of incidental findings with somatic tumor profiling."[5-7]
- The debate continues regarding whether there is an obligation to test for and report these germline findings, which are secondary to the original purpose of somatic tumor profiling. In making this determination, pre-test informed consent is of utmost importance. "Honoring patient preferences requires oncology providers to

communicate the potential for incidental and secondary germline information specific to the test being offered, the relevance and potential benefits of this information for patients and their relatives, and the limitations and risks of receiving incidental and secondary germline information"[2]

Test information

Introduction

Mutations detected on somatic testing may be indicative of a hereditary cancer syndrome due to a germline mutation. Thus, germline hereditary cancer testing following somatic tumor testing may be indicated in certain situations.

- Testing to investigate somatic and germline DNA mutations has become more common as sequencing technology has evolved from the more labor intensive Sanger sequencing to next generation sequencing (NGS). "NGS is a powerful technology that permits the characterization of large amounts of DNA sequence much quicker and at lower cost than traditional Sanger sequencing."[2]
- Laboratories performing somatic mutation profiling may include paired germline testing, not in an effort to identify hereditary etiologies, but to report pure somatic alterations, clarify interpretation, and identify mutations that are genetic "drivers" of the individual's malignancy.[4,5,8]
- Laboratories may also use bioinformatics to subtract the inherited mutations from the somatic tumor profiling findings. Germline mutations may be missed during this process without performing further analysis.[8-11]

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2020) stated the following regarding germline mutations in individuals undergoing somatic tumor testing:[12]

- "Individuals undergoing tumor testing should undergo informed consent of the possibility that a PGPV [presumed germline pathogenic variant] might be discovered. However, if there is clinical indicator for germline cancer predisposition, then dedicated germline testing should be ordered."
- "Patient choice and autonomy (opt-out of PGPV result return) should be respected."
- "When automated methods are used for pre- and post-testing education and counseling, clinicians with experience in cancer genetics should be available to answer specific questions."

- “Patients should be informed that discovery of a PGPV would prompt referral for genetic consultation and the possibility of confirmatory germline testing."
- “Confirmatory germline testing should be performed in a clinical laboratory that has adequate resources and expertise in conducting germline testing and interpreting and reporting the test results."
- “Positive germline test results should be returned by qualified and experienced clinicians (e.g., oncologists with genetics expertise, geneticists, and genetic counselors)."

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO, 2024) published the following recommendations regarding genes for which mutations identified with somatic testing should prompt consideration of germline genetic testing:

- All patients with tumor pathogenic variants in the following genes should be offered germline testing:[13]
  - BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, RAD51C, RAD51D, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TSC2, VHL. Test only if patient <30 years of age: APC, PTEN, RB1, TP53.
    - For MUTYH: "germline follow-up testing should only be performed when two (biallelic) pathogenic variants are detected in the tumor."
    - For VHL: "renal cell carcinoma may be excluded from testing."
    - For TP53: "brain tumors may be excluded from testing."
- Any patient with tumor pathogenic variants in these genes may also be offered germline testing:
  - ATM, BAP1, BARD1, CHEK2, DICER1, FH, FLCN, NF1, POLD1, POLE, SDHA. Test only if patient <30 years of age: CDKN2A, SMARCA4
    - For CHEK2: "CHEK2 variants c.1283C>T (S428F) and c.470T>C (I157T) are low-penetrant variants with relative risk of 1.5 for cancer and do not affect screening recommendations the same way other CHEK2 variants do."
- However, if a conservative testing approach is preferred, testing for these genes may be limited to patients who have a mutation in a relevant tumor (ie, only test if a mutation is found in certain cancers):
  - ATM (breast, gastric, epithelia ovarian, pancreatic, or prostate cancers), BAP1 (melanoma, renal cell carcinoma, or malignant mesothelioma), BARD1 (breast cancer), CDKN2A (melanoma or pancreatic adenocarcinoma), CHEK2 ((breast, colon, prostate, or thyroid cancers. CHEK2 c.1100del testing should occur regardless of tumor type), DICER1 (pleuropulmonary blastoma, cystic nephroma, embryonal rhabdomyosarcoma, ovarian Sertoli-Leydig cell tumors, ovarian sarcoma, neuroblastoma, or thyroid cancer), FH (paraganglioma, pheochromocytoma, or renal cell carcinoma), FLCN (renal cell carcinoma), NF1 (breast cancer, GIST, paraganglioma, or pheochromocytoma), POLD1 (colorectal

cancer), POLE (colorectal cancer), SDHA (GIST, paraganglioma, or renal cell carcinoma), SMARCA4 (small cell carcinoma of the ovary, hypercalcemic type or malignant rhabdoid tumors).
    - "Do not test if a conservative testing approach is preferred: PTCH1, SMAD3, SMARCB1, SUFU"
        - Regarding SMAD3: "Germline SMAD3 causes Loeys-Dietz syndrome 3 and nonsyndromic thoracic aortic aneurysms and dissections. It is highly actionable although it is not associated with cancer risk."
- "If there is uncertainty around whether a variant identified through tumor genetic testing is pathogenic, oncologists may want to confer with genetics experts. The germline variant database ClinVar is another useful resource to help with this determination."
- "Variant allele frequency (VAF) is not sufficient in and of itself to confirm or exclude a germline origin. While a VAF <30% for a variant identified from tumor genomic profiling is unlikely to be germline, other factors (eg, tumor purity) must be considered and some laboratories do not report VAF. VAF identified from circulating tumor DNA testing is not informative with respect to germline origin."
- "Founder mutations are almost always germline and confirmatory germline testing is indicated, regardless of the patient's ancestry or tumor type."
- ""Patients who meet criteria for germline genetic testing should be offered germline testing regardless of results from tumor testing."

European Society of Medical Oncology

The European Society for Medical Oncology (ESMO, 2019) published recommendations for germline analysis of tumor-only sequencing data.[14,15] Factors considered include the gene, tumor type, the age of the affected individual, and VAF to determine if germline testing is recommended. These guidelines were recently updated (ESMO, 2023) and stated:[16]

- "We analysed an expanded dataset including 49 264 paired tumour-normal samples. We applied filters to tumour-detected variants based on variant allele frequency, predicted pathogenicity and population variant frequency. For 58 cancer-susceptibility genes, we then examined the proportion of filtered tumour-detected variants of true germline origin [germline conversion rate (GCR)]. We conducted subanalyses based on the age of cancer diagnosis, specific tumour types and 'on-tumour' status (established tumour-gene association)."
- Forty genes were identified for potential germline follow-up testing.
- Four different approaches were provided for germline follow-up of tumor-only sequencing results:
    - "Permissive: germline follow-up for all 40 genes in all tumour types
    - Intermediate-permissive: germline follow-up for all 23 MA-CSGs/HA-CSGs [most-actionability cancer-susceptibility gene/high-actionability cancer-susceptibility

gene] in all tumour types but germline follow-up only in 'associated' tumour types for 17 SA-CSGs [standard-actionability cancer-susceptibility gene].
    - Intermediate-conservative: germline follow-up in all tumour types for the 7 MA-CSGs but germline follow-up only in 'associated' tumour types for the other 33 HA-CSGs/SA-CSGs.
    - Conservative: germline follow-up only in 'associated' tumour types for all 40 genes"
- "Strategic filtering improves the GCR with minimal loss of true germline variants present in the tumour."
- "GCR of filtered tumour-detected variants is very high (>80%) for genes such as BRCA1, BRCA2 and PALB2."
- "GCR of filtered tumour-detected variants is very low (<2%) for genes such as APC, TP53 and STK11."
- "Germline follow-up should involve multidisciplinary expertise and follow expert guidance regarding tumour context."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2024) stated the following regarding germline testing following somatic tumor testing:[17]

- "Tumor profiling can be considered complementary to germline testing. However, the absence of a P/LP [pathogenic/likely pathogenic] variant for a given gene from tumor profiling does not rule out the possibility of a germline P/LP variant in that gene. … Therefore, a variant interpreted as P/LP in the germline may be interpreted as normal or as a VUS in the tumor, if that variant has no clear clinical implications. In addition, the sensitivity of most tumor testing is lower (particularly for intermediate-sized deletions and duplications) than that for most dedicated germline tests, sometimes due to filtering out of germline findings reported in tumor sequencing results."
- “If a mutation is detected through tumor profiling that has clinical implications if identified in the germline, then germline testing for this variant is indicated."
- "Somatic P/LP variants seen in tumor specimens are common in some genes with germline implications (eg, TP53, STK11, PTEN) and may not indicate the need for germline testing unless the clinical/family history is consistent with a P/LP variant in the germline."
- "If a patient meets testing criteria for germline testing for a given gene, then confirmatory germline testing should be considered through a CLIA-approved lab despite tumor profiling results."

The National Comprehensive Cancer Network (NCCN, 2024) stated the following regarding interpreting information obtained from tumor-only profiling:[18]

- "Because tumor genomic testing is designed to address treatment actionability, not germline status, a variant that may be considered as P/ LP in the germline may not be reported at all, or reported as normal in the tumor if it lacks clinical implications."

- "The filtering of raw sequencing data may differ between tumor and germline testing labs so that variants reported out with one analysis may not be reported with the other."
- "Somatic P/LP variants seen in tumor specimens are common in some genes with germline implications (eg, TP53, STK11, PTEN, APC) and may not indicate the need for germline testing unless the clinical/family history is consistent with a P/LP variant in the germline."
- "Tumor-only sequencing may not detect about 10% of clinically actionable P/LP germline variants (eg, deletion, duplication, and splicing variants)"
- "The fraction of PVs in cancer susceptibility genes identified through tumor-only testing, and also present in the germline, is highly variable between genes."
- "Regardless of findings in the tumor, when germline testing is clinically indicated, it should be performed in a CLIA-approved lab with established experience in germline testing…"

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC, 2022) provided a "Somatic Research Task Force Incidental Findings Worksheet" which gave guidance for making decisions regarding the indications for germline testing after somatic testing. This stated the following:[19]

- First, determine if the gene with the mutation has an associated germline risk. If not, no further testing is indicated based on the somatic results. If so, then determine if the testing performed on the tumor was tumor paired with a normal sample such as blood or saliva. If it was paired testing, then determine if the mutation is a founder mutation or if the mutation is present in a relative to determine if confirmatory germline testing is necessary. Additionally, following-up with the testing laboratory to determine their germline confirmation policy may be necessary.
- If the testing was on tumor only, the following was stated:
  - If the following apply, then the mutation is likely somatic and no further testing may be indicated based on the somatic results:
    - The variant allele frequency is less 30%
    - The gene mutation(s) is/are associated with the tumor type
    - There is a lacking phenotype consistent with the gene mutation
    - The individual's age of diagnosis is not consistent with the gene mutation
  - If any of the following apply and the mutation is classified as pathogenic/likely pathogenic when present in the germline, then confirmatory genetic testing is appropriate:
    - The variant allele frequency is 30% or greater
    - The phenotype matches the gene mutation
    - The individual's age at diagnosis is consistent with the gene mutation

        - Of note, if a mutation is not found in databases to confirm pathogenicity, confirmatory testing may still be indicated.
    - If the gene change is classified as a variant of uncertain significance when present in the germline, confirmatory germline testing is generally not indicated however could be considered if:
        - Germline testing may be of benefit to the individual/family in the future
        - The individual/family are eligible for family or follow-up studies
        - There is clinical suspicion about the gene change
    - If the gene change is classified as benign/likely benign when present in the germline, no further testing in indicated based on the somatic results.

Additionally points noted were:

- "Consider multigene panel testing rather than targeted variant testing based on personal/family history of cancer AND/OR other NCCN criteria met for germline testing."
- "Germline testing may be necessary despite paired tumor-normal report. Some somatic testing labs are not validated for germline analysis."

Selected Relevant Publications

There have been various peer-reviewed publications that reviewed pre- and post-test considerations for germline testing following somatic tumor testing.

- Pre-test considerations:
    - Somatic tumor-only NGS testing is used to guide treatment for an affected person. The testing is not designed to elucidate a hereditary etiology. A germline variant may not be detected (due to differences in coverage in the testing, cellularity of the sample, allelic loss of the germline mutation) or may not be reported by the somatic testing laboratory.[2,3,20,21]
    - Directed germline genetic testing can be ordered to identify a potential hereditary etiology for the person's tumor. Referrals to oncology genetic counselors or other specialized healthcare providers should occur if the individual's personal and/or family history meets established criteria to warrant a more detailed discussion.[14,15,20,22]
    - Ancillary findings from somatic or germline testing may include variants in genes that cause a hereditary cancer syndrome, a non-oncologic hereditary syndrome, or identify carrier status for Mendelian disease. Specific findings are dependent on specific testing performed by the laboratory.[2,3,10,11,20]
    - Many individuals undergoing somatic tumor profiling have advanced stage disease. Centers performing somatic tumor profiling should consider obtaining a surrogate individual to receive results in the event that the proband has passed away or is otherwise unable to receive the results.[2,3,23]
- Post-test considerations:

- Clinicians must determine the technical specifications of the laboratory used for somatic tumor profiling and determine if this includes paired germline testing. Some laboratories may not report germline variants, include certain known germline variants on a panel, or be able to detect certain types of variants (such as copy number variants) depending on the assay methodology used.[2,3,23]
- Somatic variant interpretation differs from the variant interpretation and classification process for germline variants. For example, a laboratory profiling a somatic tumor may classify a certain variant as pathogenic whereas a laboratory testing a germline mutation may classify that same variant as a variant of uncertain significance (VUS), or vice versa.[2,3,23] Resources, such as ClinVar, should be used by the provider to determine if a pathogenic variant classification provided by germline testing laboratories is consistent with independent assessments of that variant.[24]
- Referrals to oncology genetic counselors or other specialized healthcare providers should occur if the individual's personal and/or family history meets established criteria to warrant a more detailed discussion, regardless of somatic tumor profiling results.[10,18,20] In individuals meeting criteria for germline DNA testing, analysis of the entire gene, as opposed to single site testing for the identified somatic variant, is recommended.[6]
- Germline testing may also be considered in individuals when any of the following apply:
  - The individual does not meet published criteria for germline testing, but variant(s) within genes known to play a role in tumor biology and to cause an inherited cancer syndrome (including but not limited to TP53, APC, CDH1) are identified and the variant allele frequency in the tumor is at least 30%.[19,25-27]
  - One of the identified variants on tumor testing is a highly-recurrent or founder mutation (i.e., BRCA1 c185delAG, the recurrent inversion of MSH2 seen in some families with Lynch syndrome, the p.R337H TP53 mutation).[3,28]
  - The tumor profile shows thousands of somatic variants, suggesting a germline mutation in a DNA mismatch repair gene or in the POLE proofreading domain.[3,29]
  - Two separate primary tumors are sequenced and both harbor the same genetic variant.[9]
  - The individual's tumor harbors a mutation in BRCA1 or BRCA2.[17]

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for hereditary (germline) testing after tumor (somatic) testing will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that

some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

Criteria

Introduction

Requests for germline hereditary cancer testing following somatic tumor testing are reviewed using the following criteria.

- Requests for single-site or full-gene sequence germline testing following somatic tumor analysis will be considered medically necessary when at least one of the following criteria is met:
  - The individual's personal or family history is suggestive of a germline mutation, a specific germline variation is identified by somatic tumor testing, and the individual meets the published test-specific criteria to test for that variant, OR
  - One of the identified variants is a highly-recurrent or founder mutation (i.e., BRCA1 c185delAG or the recurrent inversion of MSH2 seen in some families with Lynch syndrome, the p.R337H TP53 mutation), OR
  - The tumor profile shows thousands of somatic variants, suggesting a germline mutation in a DNA mismatch repair gene or in the POLE proofreading domain, OR
  - Two separate primary tumors are sequenced and both harbor the same genetic variant, OR
  - The individual's tumor harbors a mutation in BRCA1/2, OR
  - The individual does not meet published criteria for germline testing, but variant(s) within genes known to play a role in tumor biology and to cause an inherited cancer syndrome (including but not limited to TP53, APC, CDH1) are identified and the variant allele frequency in the tumor is at least 30%.

Exclusions and Other Considerations

- Germline testing of somatic variants of uncertain significance (VUS) is not considered medically necessary.
- Germline testing for asymptomatic individuals based solely on a family member's somatic testing result is not considered medically necessary.
- In individuals meeting criteria for germline DNA testing, analysis of the entire gene, as opposed to single site testing for the identified somatic variant, is recommended.
- Clinically indicated germline testing is still appropriate for individuals meeting testing guidelines regardless of tumor profiling results.

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- Resources, such as ClinVar, should be used by the provider to determine if a pathogenic variant classification provided by germline testing laboratories is consistent with independent assessments of that variant.

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Medically Necessary Laboratory Testing

MOL.CU.333.B
v1.0.2026

Description

All delegated lab service procedure codes are subject to this guideline. Refer to the specific Health Plan's procedure code list for management requirements.

Background

Laboratory testing represents approximately 4% of healthcare expenditures.[1] While a relatively small contributor to overall healthcare expense, laboratory testing is a high volume service commonly performed during healthcare encounters with a critical role in informing downstream medical decisions.[2,3] Therefore, inappropriate over- or under-utilization of laboratory tests presumably also influences the medical costs associated with those medical services informed by test results.[1]

Laboratory tests are imperfect due to the overlap between disease and health as well as the fact that laboratory errors can occur in any phase of the laboratory process from specimen collection through specimen reporting and interpretation.[4] Even under ideal testing conditions, approximately 5% of healthy patients will have results outside of the reference range simply due to the method used to calculate most reference ranges for laboratory tests. Most reference ranges represent the central 95% of the results (e.g. the mean +/- two standard deviations) for a population of reasonably healthy individuals.[5] The individuals used for a reference range calculation are often people who are accepted as blood donors. When a result occurs outside the reference range in a healthy individual, that result is a setup for an erroneous interpretation, such as a false positive, which can lead to a false diagnosis. False diagnoses can lead to low value healthcare in the form of unnecessary interventions that can be dangerous and expensive.

Excessive testing

Testing that is unfocused, not indicated for routine prevention, and not specific to a patient's symptoms has an increased likelihood of false positives. As the number of tests ordered increases, so does the likelihood that at least one result will fall outside the reference range in a healthy individual. Therefore, large wellness panels in asymptomatic individuals or individuals with nonspecific signs and symptoms

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associated with daily life will nearly always lead to false positive tests and a potentially expensive medical diagnostic odyssey.

Appropriate test use

Laboratory tests are routinely used to screen for common disease, diagnose disorders in patients with signs or symptoms, inform effective treatment plans, and monitor therapies. Thus, correct test choice and interpretation is critical.

For individuals with suspected or diagnosed disease, appropriate laboratory testing may be defined in guidelines issued by the professional societies that guide care for those individuals. However, a substantial number of tests and indications will not be addressed in clear evidence-based guidelines, therefore requiring ongoing evaluation of the primary literature.

Laboratory testing is considered medically necessary when proven to be clinically useful for routine preventive screening or to diagnose, treat, monitor, or otherwise manage significant illness, infirmity, disability, or suffering.

Guidelines and Evidence

This section includes relevant guidelines and evidence pertaining to medically necessary laboratory testing.

U.S Preventive Task Force (USPSTF)

The U.S. Preventive Services Task Force, with the support of the Agency for Healthcare Research and Quality, develops evidence-based preventive service recommendations, including laboratory screening tests, that are generally accepted as the standard of care in screening otherwise healthy individuals. USPSTF describes its scope as follows:[6]

- “The recommendations apply only to people who have no signs or symptoms of the specific disease or condition under evaluation, and the recommendations address only services offered in the primary care setting or services referred by a primary care clinician.”

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for medically necessary laboratory testing will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/ management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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Criteria

Introduction

Requests for medically necessary laboratory testing are reviewed using these criteria.

Criteria: General Coverage Guidance

In order for a test to be considered medically necessary, the following criteria must be met:

- Be a preventive service as defined by the U.S. Preventive Services Task Force, Centers for Disease Control and Prevention, or other widely recognized preventive service guideline authors, OR
- Be necessary for the member's indication based on strong evidence-based professional society practice guidelines, OR
- Meet ALL of the following criteria:
  - Clinical signs, symptoms, treatment or monitoring needs are consistent with the test being performed, and
  - Technical and clinical validity: The test must be accurate, precise, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test, and
  - Clinical utility: Healthcare providers can use the test results to provide significantly better medical care for the individual, and
  - Reasonable use: The test is cost-effective when compared with equally acceptable alternatives and its usefulness is not significantly offset by negative factors, AND
- Testing must be ordered by a qualified healthcare provider who is actively managing the member's medical care, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other considerations

- Tests should not be duplicative or overlap in clinical intent with other performed services.
- Tests should not be repeated more often than is recommended and necessary.
- Direct-to-consumer lab testing is not eligible for reimbursement. This includes laboratory services supported by physicians serving in the role of ordering provider without having an active role in managing the member's healthcare.
- Expanded health and wellness panels that exceed routine preventive care services are not eligible for reimbursement.

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Medically Necessary Lab Testing

Pharmacogenomic Testing for Drug Toxicity and Response

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v1.0.2026

Pharmacogenomic testing for drug toxicity and response is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
5HT2C Serotonin Receptor (HTR2C) Gene Variants	81479
5-Fluorouracil (5-FU) Toxicity and Chemotherapeutic Response	81232 81346
ADRB2 Gene Variants	81479
AvertD	81599
BRACAnalysis CDx Germline Companion Diagnostic Test	81162 81479
Catechol-O-Methyltransferase (COMT) Genotype	0032U
CNT (CEP72, TPMT and NUDT15) genotyping panel	0286U
COMT (Catechol Methyl Transferase) Gene Variants	81479
CYP1A2 Genotyping	81479
CYP2B6 Genotyping	81479
CYP2C9 Genotyping	81227
CYP2C19 Genotyping	81225
CYP2C8 Genotyping	81479

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Procedures addressed by this guideline	Procedure codes
CYP2D6 Genotyping for Drug Response	81226
CYP2D6 Common Variants and Copy Number	0070U
CYP2D6 Full Gene Sequencing	0071U
CYP2D6-2D7 Hybrid Gene Targeted Sequence Analysis	0072U
CYP2D7-2D6 Hybrid Gene Targeted Sequence Analysis	0073U
CYP2D6 trans-duplication/ multiplication nonduplicated gene targeted sequence analysis	0074U
CYP2D6 5’ gene duplication/ multiplication targeted sequence analysis	0075U
CYP2D6 3’ gene duplication/ multiplication targeted sequence analysis	0076U
CYP3A4 Gene Analysis	81230
CYP3A5 Gene Analysis	81231
CYP4F2 Genotyping	81479
Cytochrome P450 1A2 (CYP1A2) Genotype	0031U
DPYD Genotyping	81232
Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis	81418
EffectiveRX Comprehensive Panel	0438U
Focused Pharmacogenomics Panel	0029U
G6PD Common Variants	81247
G6PD Full Gene Sequencing	81249
GeneSight Psychotropic	0345U

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Procedures addressed by this guideline	Procedure codes
Genomind Pharmacogenetics Report - Full	0423U
Genomind Professional PGx Express	0175U
HLA-B*1502 Genotyping	81381
HLA-B*5701 Genotyping	81381
IDgenetix	0411U
IFNL3 (IL28B) rs12979860 Gene Variant	81283
Medication Management Neuropsychiatric Panel (EffectiveRX Neuropsychiatric Panel)	0392U
Mental Health DNA Insight	81225 81226 81479
MTHFR Gene Variants	81291
MyGenVar Pharmacogenomics Test	0516U
NT (NUDT15 and TPMT) Genotyping Panel	0169U
NUDT15 Genotyping	81306
OPRM1 Gene Variants	81479
Pain Medication DNA Insight	81225 81226 81227 81291 81479
Psych HealthPGx Panel	0173U
RightMed Comprehensive Test	0349U
RightMed Comprehensive Test Exclude F2 and F5	0348U
RightMed Gene Report	0350U

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Procedures addressed by this guideline	Procedure codes
RightMed Gene Test Exclude F2 and F5	0434U
RightMed Mental Health Gene Report	0476U
RightMed Mental Health Medication Report	0477U
RightMed Oncology Gene Report	0460U
RightMed Oncology Medication Report	0461U
RightMed PGx16 Test	0347U
Serotonin Receptor Genotype (HTR2A and HTR2C)	0033U
Statin Induced Myopathy Genotype (SLCO1B1)	81328
Tempus nP	0419U
Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping	0034U
TPMT Genotyping	81335
TYMS Genotyping	81346
UCSF Pharmacogenomics Panel	0533U
UGT1A1 Targeted Variant Analysis	81350
VEGF Gene Variants	81479
VKORC1 Genotyping	81355
Warfarin Response Genotype	0030U
Warfarin responsiveness testing by genetic technique using any method	G9143
Pharmacogenomic tests that make use of molecular and genomic technologies	81479, 81599, and others

What are pharmacogenomic tests?

For the purposes of this guideline, pharmacogenomic tests are those germline tests performed to predict or assess an individual's response to therapy as well as the risk of toxicity from drug treatment.

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Testing may be performed prior to treatment in order to determine if the individual has genetic variants that could affect drug response and/or increase the risk for adverse drug reactions. Testing may also be performed during treatment to assess whether an individual is having an adequate response or investigate the cause of an unexpected or adverse reaction.

Companion Diagnostics

Companion diagnostics are assays that help determine whether a drug may be safe or effective for a particular individual. Companion assays are evaluated as part of the Food & Drug Administration's (FDA's) development and approval process for the new drug. According to the FDA, "A companion diagnostic is a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional determine whether a particular therapeutic product's benefits to patients will outweigh any potential serious side effects or risks." [1] Although specific companion diagnostic tests may be identified in the FDA label for a new drug approval, similar laboratory-developed tests (LDTs) performed by a CLIA-certified laboratory are generally accepted as alternatives that can typically provide the required information.

Complementary Diagnostics

Complementary diagnostics are assays that were developed and in use prior to the FDA's approval of a new drug. They are not evaluated through the FDA's development and approval process for new drugs. Complementary diagnostics are used to help provide additional information about how a drug might be used, or whether someone should receive a certain class of drugs. These tests are not specifically required for the safe and effective use of a drug, which is part of what differentiates them from companion diagnostics. As with companion diagnostics, LDTs that are similar to the defined complementary diagnostic, when performed by a CLIA-certified laboratory, are able to provide the same information.[2]

The FDA website includes a table of drugs that have information about gene variants and other biomarkers on their labels (may not be all-inclusive): **https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling** . While some drug labels provide specific actions to take based on the results of genetic testing, other labels merely describe a gene's role in the drug's metabolism (i.e. pharmacokinetics).

An international consortium called the Clinical Pharmacogenetics Implementation Consortium (CPIC) also develops and maintains detailed gene/drug practice guidelines to assist healthcare providers in the interpretation of pharmacogenomic test results when they are available; however, the consortium does not make specific recommendations about whether these tests should be performed.[3]

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Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for pharmacogenomic testing for drug toxicity and response will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate management/diagnostic strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

Test information

Introduction

Pharmacogenomic testing involves testing single nucleotide polymorphisms (SNPs) within genes that affect an individual's metabolism and response to certain medications.

Test Methods

For pharmacogenomic testing, one of the following testing strategies is typically employed:

- **Targeted testing:** assesses SNPs in a single gene or narrow subset of genes focused on response to one particular medication that is currently prescribed or under consideration for an individual.
- **Multi-gene panels:** assess SNPs in multiple genes to determine general drug response or response to a broad category of medications (e.g., psychotherapeutic, cardiovascular, etc.). Some laboratories apply a proprietary algorithm in order to classify the suitability of various medications based on the results. In contrast to targeted testing, multi-gene panels do not require that a particular medication be prescribed or under consideration, and the test may identify variants in many genes with no current impact on the individual's clinical care.

Criteria

Criteria: General Coverage Guidance

Pharmacogenomic tests are considered medically necessary when ALL of the following conditions are met:

- The individual is currently taking or considering treatment with a drug potentially affected by a known mutation that can be detected by a corresponding test.
- Technical and clinical validity: The test must be accurate, sensitive, and specific, based on sufficient, quality scientific evidence to support the claims of the test.

- Clinical utility: Healthcare providers can use the test results to guide changes in drug therapy management that will improve patient outcomes.
- Reasonable use: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social, or ethical challenges.

Criteria: Targeted Pharmacogenomic Tests

Testing of variants in a single gene or narrow subset of genes (e.g., a targeted panel consisting solely of TPMT and NUDT15) associated with response to a specific medication will be considered medically necessary when the following criteria are met:

- Requested testing is performed in a CLIA-certified laboratory, AND
- Testing of the requested gene(s) has not been previously performed, AND
- Healthcare providers can use the test results to directly impact medical care for the individual, AND
- At least one of the following criteria is met:
  - Documentation is provided that the requested testing is required to obtain health plan coverage for the medication being considered for treatment, or
  - A medication's FDA label requires results from the genetic test to effectively or safely use the therapy in question, with specific actions recommended based on the tested genotype (e.g., the label states the drug is contraindicated, recommends consideration of an alternative therapy, and/or requires dosage adjustments), or
  - The member meets criteria for one of the following tests covered without FDA label requirements:
    - DPYD testing for genetic variants DPYD*2A (rs3918290), DPYD*13 (rs55886062), and rs67376798 A (on the positive chromosomal strand) is requested for an individual considering or currently on therapy with any 5-FU containing drug including, but not limited to: 5-fluorouracil (Fluorouracil®, Adrucil®), capecitabine (Xeloda®), or fluorouracil topical formulations (Carac®, Efudex®, Fluoroplex®).

Targeted testing will be covered only for the number of genes or tests necessary to establish drug response.

- When available and cost-efficient, a tiered approach to testing, with reflex to more detailed testing and/or different genes, is recommended.
- When requested with a single procedure code, all components of the test must individually meet the above medical necessity criteria in order to be considered for reimbursement (e.g., CYP2D6 tests denoted by CPT codes 0071U–0076U, which test for other CYP2D6 findings in addition to the common gene variants, are typically not medically necessary).

Testing of any pharmacogenomic gene variants for general drug response or response to broad categories of drugs (e.g., psychotherapeutic, cardiovascular, etc.) would

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not meet the above criteria for targeted testing, and is therefore not eligible for reimbursement.

Targeted Pharmacogenomic Tests Considered Not Medically Necessary

The following tests and indications (i.e. gene/drug interactions) have not demonstrated clinical utility at the time this guideline was updated.[4-44] These tests are considered not medically necessary for these specific indications. This list is not intended to be all-inclusive.*

- CNT (CEP72, TPMT and NUDT15) genotyping panel from RPRD Diagnostics for response to thiopurines and/or vincristine CPT: 0286U
- CYP2C19 gene variants for the management of H. pylori CPT: 81225
- CYP2C9 gene variants for warfarin response CPT: 81227
- CYP2D6 gene variants for tamoxifen response CPT: 81226
- Warfarin Response Genotype from Mayo Clinic CPT: 0030U

Note:

*Please note that some targeted tests and procedure codes in this list may be coverable for other indications. When a test is requested for the purposes of assessing response to a drug not listed here, please see Criteria: Targeted Pharmacogenomic Tests above.

Criteria: Single-Gene Pharmacogenomic Tests Considered Experimental, Investigational, or Unproven

The following single-gene pharmacogenomic tests have not demonstrated clinical utility for any indication at the time this guideline was updated and are considered experimental, investigational, or unproven, and therefore not eligible for reimbursement. This list is not intended to be all-inclusive.†

- 5HT2C (Serotonin Receptor; HTR2C) gene variants CPT: 81479
- ADRB2 (Beta-2-Adrenergic Receptor) gene variants CPT: 81479
- COMT (Catechol Methyl Transferase) gene variants CPT: 81479
- Catechol-O-Methyltransferase (COMT) Genotype from Mayo Clinic CPT: 0032U
- CYP1A2 (Cytochrome P450 1A2) (CYP1A2) gene variants CPT: 81479
- Cytochrome P450 1A2 (CYP1A2) Genotype from Mayo Clinic CPT: 0031U
- CYP2B6 (Cytochrome P450 2B6) gene variants CPT: 81479
- CYP2C8 (Cytochrome P450 2C8) gene variants CPT: 81479
- CYP3A4 (Cytochrome P450 3A4) gene variants CPT: 81230
- CYP3A5 (Cytochrome P450 3A5) gene variants CPT: 81231
- CYP4F2 (Cytochrome P450 4F2) gene variants CPT: 81479
- IFNL3 (IL28B) rs12979860 gene variant CPT: 81283

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- MTHFR (5,10-Methylenetetrahydrofolate Reductase) gene variants CPT: 81291
- OPRM1 (Opioid Receptor, Mu-1) gene variants CPT: 81479
- Serotonin Receptor Genotype (HTR2A and HTR2C) from Mayo Clinic CPT: 0033U
- Statin Induced Myopathy Genotype (SLCO1B1) CPT: 81328
- TYMS (Thymidylate Synthetase) gene variants CPT: 81346
- VEGF (Vascular Endothelial Growth Factor) gene variants CPT: 81479
- VKORC1 (Vitamin K Epoxide Reductase Complex, Subunit 1) gene variants CPT: 81355

Note:

†Please note that some tests in this list may be coverable at the time of request due to an update in the FDA drug label. When a test is requested for the purposes of assessing response to a specific drug, please see Criteria: Targeted Pharmacogenomic Tests above.

Criteria: Pharmacogenomic Panels Considered Experimental, Investigational, or Unproven

Multi-gene pharmacogenomic panels that assess general drug response or response to broad categories of medications (e.g., psychotherapeutic, cardiovascular, etc.), regardless of the number of genes included or how they are billed, are considered experimental, investigational, or unproven (E/I/U) and therefore not eligible for reimbursement. The following are examples of panels that are considered E/I/U. This list is not intended to be all-inclusive.

- AvertD [Opioid use disorder risk assessment, genotyping of 15 single nucleotide polymorphisms (SNPs) by microarray analysis, buccal swab, algorithm reported as risk score for developing opioid use disorder in individuals not previously treated with opioid drugs and considering a 4-30 day prescription by AutoGenomics/SOLVD Health] CPT: 81599
- Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis CPT 81418
- EffectiveRX Comprehensive Panel [Drug metabolism (adverse drug reactions and drug response), buccal specimen, gene-drug interactions, variant analysis of 33 genes, including deletion/duplication analysis of CYP2D6, including reported phenotypes and impacted gene-drug interactions from RCA Laboratory Services] CPT: 0438U
- Focused Pharmacogenomics Panel from Mayo Clinic CPT: 0029U
- GeneSight Psychotropic [Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 from Myriad Genetics] CPT: 0345U

- Genomind Pharmacogenetics Report – Full [Psychiatry (eg, depression, anxiety), genomic analysis panel, including variant analysis of 26 genes, buccal swab, report including metabolizer status and risk of drug toxicity by condition from Genomind, Inc] CPT: 0423U
- Genomind Professional PGx Express CPT: 0175U
- IDgenetix [Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 from Castle Biosciences, Inc] CPT: 0411U
- Medication Management Neuropsychiatric Panel (EffectiveRX Neuropsychiatric Panel) [Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes, including deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug from RCA Laboratory Services LLC d/b/a GENETWORx] CPT: 0392U
- Mental Health DNA Insight [Proprietary test from Pathway Genomics] CPT: 81225, 81226, 81479
- MyGenVar Pharmacogenomics Test [Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status from Geisinger Medical Laboratories] CPT: 0516U
- Pain Medication DNA Insight [Proprietary test from Pathway Genomics] CPT: 81225, 81226, 81227, 81291, 81479
- RightMed Comprehensive Test [Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis including reported phenotypes and impacted gene-drug interactions from OneOme, LLC] CPT: 0349U
- RightMed Comprehensive Test Exclude F2 and F5 [Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes from OneOme, LLC] CPT: 0348U
- RightMed Gene Report [Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes from OneOme, LLC] CPT: 0350U
- RightMed Gene Test Exclude F2 and F5 [Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes from OneOme LLC] CPT: 0434U
- RightMed Mental Health Gene Report [Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis and reported phenotypes from OneOme, LLC] CPT: 0476U
- RightMed Mental Health Medication Report [Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity

disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis, including impacted gene-drug interactions and reported phenotypes from OneOme, LLC] CPT: 0477U
- RightMed Oncology Gene Report [Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes from OneOme LLC] CPT: 0460U
- RightMed Oncology Medication Report [Oncology, pharmacogenomic analysis of single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, whole blood or buccal swab, with variant analysis, including impacted gene-drug interactions and reported phenotypes from OneOme LLC] CPT: 0461U
- RightMed PGx16 Test [Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes from OneOme, LLC] CPT: 0347U
- Tempus nP [Neuropsychiatry (eg, depression, anxiety), genomic sequence analysis panel, variant analysis of 13 genes, saliva or buccal swab, report of each gene phenotype from Tempus Labs, Inc] CPT: 0419U
- UCSF Pharmacogenomics Panel [Drug metabolism (adverse drug reactions and drug response), genotyping of 16 genes (ie, ABCG2, CYP2B6, CYP2C9, CYP2C19, CYP2C, CYP2D6, CYP3A5, CYP4F2, DPYD, G6PD, GGCX, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1), reported as metabolizer status and transporter function from University of California San Francisco Genomic Medicine Laboratory] CPT: 0533U

Other Considerations

For pharmacogenomic tests that look for changes in germline DNA (i.e., not tumor DNA or viral DNA), testing will be allowed once per lifetime per gene. Exceptions may be considered if technical advances in testing or the discovery of novel genetic variants demonstrate significant advantages that would support a medical need to retest.

Testing performed in a CLIA-certified laboratory will be considered for coverage. The use of a specific FDA approved companion diagnostic is not necessary for coverage to be considered.

Test-specific guidelines may be available for some pharmacogenomic tests. Please refer to the guidelines manual for a list of test-specific guidelines. For tests without a specific guideline, use the above criteria.

For information on somatic mutation testing in solid tumor tissue or hematological malignancies, please refer to the guideline, *Somatic Mutation Testing*, as this testing is not addressed here.

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Preimplantation Genetic Testing

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Introduction

Preimplantation genetic testing (PGT) is addressed by this guideline.

Definition

Preimplantation genetic testing (PGT) is used to detect genetic conditions, chromosome abnormalities, and fetal sex during assisted reproduction with in vitro fertilization (IVF). Genetic testing is performed on cells from the developing embryo prior to implantation. Only those embryos not affected with a genetic condition are implanted. PGT may allow at-risk couples to avoid a pregnancy affected with a genetic condition. The Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine have published joint practice committee opinions to address the safety, accuracy, and overall efficacy of PGT.[1,2]

The following terminology for PGT has been established to differentiate various clinical testing indications:

- PGT-M: testing performed when the embryo is at an increased risk for a monogenic disorder[3]
- PGT-SR: testing performed when the embryo is at increased risk for a structural chromosome rearrangement[3]
- PGT-A: testing performed to screen an embryo for aneuploidy when both parents are chromosomally normal[3]
- PGT-P: testing performed to screen an embryo for polygenic disorders using polygenic risk score analyses[4]

For information on prenatal and preconception carrier screening, please refer to the guideline *Genetic Testing for Carrier Status,* as this testing is not addressed here.

For information on prenatal genetic testing, please refer to the guideline *Genetic Testing for Prenatal Screening and Diagnostic Testing,* as this testing is not addressed here.

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2023) published a points to consider statement providing several general considerations regarding

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polygenic risk score (PRS) testing for healthcare providers.[5] Regarding the clinical application of preimplantation PRS testing, ACMG stated:[5]

- "The ACMG's position is that preimplantation PRS testing is not yet appropriate for clinical use and should not be offered at this time."
- "Owing to the complexity of PRS testing and the interpretation and applicability of its results, the ACMG considers preimplantation genetic testing for disorders that exhibit multigenic or polygenic inheritance is not appropriate for clinical use and should not be offered as direct-to-consumer testing at this time."

American College of Obstetrics and Gynecology

The American College of Obstetrics and Gynecology (ACOG, 2020; Reaffirmed 2023) stated the following:[6]

- Confirmation of results from PGT-M and PGT-SR should be offered. This confirmation is completed through chorionic villus sampling or amniocentesis.
- For PGT-A, "traditional diagnostic testing or screening for aneuploidy should be offered to all patients who have had preimplantation genetic testing-aneuploidy, in accordance with recommendations for all pregnant patients."

American Society of Reproductive Medicine

The American Society of Reproductive Medicine (ASRM, 2023) published a committee opinion for the indications and management of preimplantation genetic testing for monogenic conditions.[7]

Initially, PGT-M was utilized for "severe, untreatable, or life-threatening childhood-onset conditions". However, the technology can be used for a variety of conditions with a broad range of symptoms including a mild to moderate phenotype, later age of onset, and/or reduced penetrance. Testing for some conditions is controversial. Additionally, there are also some conditions for which PGT-M is "not technically feasible". The committee opinion of ASRM stratified PGT-M indications into four categories on the "basis of age of onset, condition severity, penetrance, and the expected impact of PGT-M on overall risk reduction".

- "Traditional/Pediatric Indications: childhood-onset, lethal, and/or severe conditions that lack effective treatment. Most providers agree that PGT-M should be available for these conditions."
- "Serious Adult-Onset Conditions: ... [ASRM] has issued a statement generally supporting the use of the technology for such conditions "when the conditions are serious and when there are no known interventions...or the available interventions are either inadequately effective or significantly burdensome."
- "Mild Conditions or Indications of Limited/Questionable Risk Reduction: ... These include cases in which the risk of offspring is very low or not increased above that of the general population, conditions of very low penetrance or mild severity, and

variants of uncertain significance (VUSs). ... Whether or not to offer PGT for a VUS may depend on a variety of factors including how the VUS was identified, supporting classification evidence, whether it tracks with the condition in the patient and family, associated recurrence risks, supporting clinical documentation, and the patient's risk tolerance."

- "Indications for Which PGT-M is not Recommended: ... Autosomal recessive carrier status without manifestations of symptoms; combination of variants not associated with disease; pseudodeficiency alleles; somatic only variants."

The committee also stated PGT-M should be optional, individuals should have access to genetic counseling to discuss all reproductive options and individuals may benefit from genetic counseling to discuss PGT-M results. Additionally, there are technical limitations with PGT-M and thus, prenatal testing should be offered for pregnancies conceived using PGT-M. Prenatal testing may include confirmation of the PGT-M results and also testing for other fetal conditions unrelated to the reason for PGT-M.

The Ethics Committee of the American Society of Reproductive Medicine (ASRM, 2024) published a committee opinion for the use of preimplantation genetic testing for monogenic adult-onset conditions.[8] They stated:

- PGT-M for adult-onset conditions that are often fully penetrant and have a predisposition for disease manifestations is "ethically justifiable". Individual autonomy should be respected and nondirective counseling should be utilized. The likelihood of a successful pregnancy with in vitro fertilization along with PGT-M are important discussion points.
- "Patients considering PGT-M should be carefully and thoroughly counseled by a genetic counselor with expertise in preimplantation genetic testing to understand the risks, benefits, and limitations of PGT-M, as well as to discuss the potential manifestations of the hereditary condition. Consulting medical professionals with expertise in the condition to be tested should be considered in addition to help patients make decisions regarding using PGT-M in these situations."

Society for Assisted Reproductive Technology and American Society for Reproductive Medicine

In a joint practice committee opinion, the Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine (SART and ASRM, 2008) stated the following:[1]

- "PGD is indicated for couples at risk for transmitting a specific genetic disease or abnormality to their offspring."
- "Due to the risk for conceiving a child with a genetic disease or other abnormality, counseling for couples considering PGD is required..."
- Suggested key points of genetic counseling include IVF and embryo biopsy-related risks, natural history of the tested condition, other reproductive options, limitations of preimplantation testing, and prenatal follow-up options.

In a joint practice committee opinion, the Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine (SART and ASRM, 2024) stated the following:[2]

- "The value of PGT-A as a universal screening test for all patients undergoing IVF has not been demonstrated. … The value of PGT-A to lower the risk of clinical miscarriage is also unclear. However, these studies have important limitations and there remain questions about appropriate patient selection and testing platforms."
- "A broader selection of patients with randomization at cycle start rather than blastulation would more appropriately address the applicability of wider use of this technology. Furthermore, the randomized trials were performed in centers with broad and deep experience in embryo biopsy and specimen preparation. The ability to expand reliably these techniques to centers with less experience has yet to be established."
- "Other important considerations about PGT-A that must be addressed by further research include cost-effectiveness, use of mosaic embryos, false-positive results, risk of embryo damage, the role and effect of cryopreservation, time to pregnancy, utility in specific subgroups (such as RPL [recurrent pregnancy loss], prior implantation failure, advanced maternal age, and so on), use of sex selection, and total reproductive potential per intervention."
- "Large, prospective, well-controlled studies evaluating the combination of multiple approaches (genomics, time-lapse imaging, transcriptomics, proteomics, metabolomics, artificial intelligence, and so on) for enhanced embryo selection applicable in a more inclusive patient population are needed to determine not only the effectiveness, but also the safety and potential risks of these technologies."
- "At present, however, the routine use of blastocyst biopsy with aneuploidy testing in all infertile patients undergoing IVF treatment cannot be recommended."

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for preimplantation genetic screening and diagnosis will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate management/diagnostic strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

Criteria

Introduction

Requests for preimplantation genetic testing (PGT) are reviewed using the following criteria. This guideline ONLY addresses the genetic testing component of PGT. Coverage of any procedures, services, or tests related to assisted reproduction is subject to any applicable plan benefit limitations.

Criteria: General Coverage Guidance

Preimplantation genetic testing is medically necessary when **ALL** of the following conditions are met:

- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test. In the case of PGT, the mutation(s) or translocation(s) to be tested in the embryo should first be well-characterized in the parent(s) AND the embryonic test results must be demonstrated to be highly accurate.
- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care and/or assist individuals with reproductive planning.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

AND, one of the following tests is being performed and the corresponding criteria are met:

PGT-M

Medically Necessary Indications

- The couple is known to be at-risk to have a child with a genetic condition because of ANY of the following:
  - Both parents are known carriers of a recessive genetic condition and the specific gene mutation has been identified in each parent; OR
  - One parent is affected by or known to be a carrier of a dominant condition and the specific gene mutation has been identified; OR
  - The individual contributing the egg is known to be a carrier of an X-linked condition and the specific gene mutation has been identified; OR
  - One or both parents have a known chromosome microdeletion (e.g. 22q11 deletion – DiGeorge syndrome, 7q11.23 deletion – Williams syndrome), OR
  - PGT-M for human leukocyte antigen (HLA) typing for transplant donation is medically necessary only if:

    - A couple has a child with a bone marrow disorder needing a stem cell transplant, and
    - The only potential source of a compatible donor is an HLA-matched sibling, AND
- The genetic condition is associated with potentially severe disability or has a lethal natural history.

Not Medically Necessary Indications
- PGT-M for variants of unknown significance is not medically necessary.

OR

PGT-A

Medically Necessary Indications
- PGT-A for sex (X and Y chromosome testing) is medically necessary only for identification of potentially affected embryos for sex-related conditions.

Not Medically Necessary Indications
- PGT-A for de novo chromosome abnormalities is not medically necessary. This includes the following indications:
    - Maternal age alone
    - To improve in vitro success rates
    - For recurrent unexplained miscarriage and/or recurrent implantation failures

OR

PGT-SR

Medically Necessary Indications
- The couple is known to be at-risk to have a child with a structural rearrangement because of the following:
    - One or both parents are carriers of a structural chromosome rearrangement (e.g., translocation or inversion), AND
- The genetic condition is associated with potentially severe disability or has a lethal natural history.

PGT-P

PGT-P for polygenic disorders is experimental, investigational, or unproven.

Select PGT Assays Considered Not Medically Necessary for Any Indication

The following PGT assays are considered not medically necessary:

- Smart PGT-A Plus [Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from embryonic trophectoderm for structural rearrangements, aneuploidy, and a mitochondrial DNA score, results reported as normal/balanced (euploidy/balanced), unbalanced structural rearrangement, monosomy, trisomy, segmental aneuploidy, or mosaic, per embryo tested] CPT 0553U
- Smart PGT-SR [Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from trophectoderm biopsy for aneuploidy, ploidy, a mitochondrial DNA score, and embryo quality control, results reported as normal (euploidy), monosomy, trisomy, segmental aneuploidy, triploid, haploid, or mosaic, with quality control results reported as contamination detected or inconsistent cohort when applicable, per embryo tested] CPT 0554U
- Smart PGT-SR Plus [Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from embryonic trophectoderm for structural rearrangements, aneuploidy, ploidy, a mitochondrial DNA score, and embryo quality control, results reported as normal/balanced (euploidy/balanced), unbalanced structural rearrangement, monosomy, trisomy, segmental aneuploidy, triploid, haploid, or mosaic, with quality control results reported as contamination detected or inconsistent cohort when applicable, per embryo tested] CPT 0555U

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Test Specific Guidelines

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AlloSure for Kidney Transplant Rejection

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AlloSure for kidney transplant rejection (AlloSure Kidney) is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
AlloSure Kidney	0540U

Criteria

Requests for AlloSure Kidney testing for allograft kidney transplant rejection are reviewed using the following criteria.

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

What Is Kidney Transplant Rejection?

Kidney disease is a loss of renal function which, without treatment, leads to eventual build-up of waste and other toxic substances in the blood.[1] Treatment of advanced kidney disease, called end-stage kidney disease, consists of dialysis or renal transplant. Transplant rejection can be acute or chronic.

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Incidence and Prevalence

According to the National Kidney Foundation, 97% of kidney transplants are functioning 1 year after transplant.[2] Between 10 and 20% of kidney transplant recipients experience at least one episode of organ rejection.[3] Organ rejection after kidney transplant is more likely in younger recipients (9.1% in recipients 18-34) than older recipients (5.9% over age 65).[2] Recipients are most likely to experience organ rejection within 6 months of transplant, but can occur at any time.[3]

Symptoms

Kidney transplant rejection can be acute (occurring suddenly and progressing quickly) or chronic (occurring slowly over time), and is typically immune system mediated. Symptoms of transplant rejection include fever and flu-like symptoms, decreased urinary output, weight gain, fatigue, and pain over the transplanted organ.[3]

Acute rejection of the donated kidney is thought to lead to tissue injury, including increased cell death in the allograft, which then leads to increased donor-derived cell free DNA (dd-cfDNA) in the bloodstream. Other investigators have reported that the fraction of cell-free DNA (cfDNA) originating from the organ grafts is approximately less than 1% and during rejection, level of dd-cfDNA increase.[4-6]

Cause

Transplanted kidneys can fail for multiple reasons:[7]

- Blood clot in the vessels leading to the kidney
- Infection
- Medication side effects
- Non-compliance with post-transplant medications and other post-surgical care
- Recurrence of the original medical problem that necessitated the kidney transplant
- Acute or chronic rejection caused by immune-mediated donor kidney damage

Diagnosis

Rise in creatinine levels is currently used to initially diagnose graft rejection, and the gold standard for initial diagnosis is histological analysis based on needle biopsy of the organ.[4-5] However, organ biopsy is invasive and often associated with complications, patient discomfort, and inconvenience. Biopsy is also prone to sampling error. Serum creatinine is one of the main markers used to monitor allograft functioning, but has been shown to lack sensitivity and specificity for graft injury and may change too late to allow prompt clinical management decisions.[8,9]

Alternatively, donor-derived cell-free DNA (dd-cfDNA) (as a fraction of the total cell-free DNA [cfDNA]) has been proposed as a noninvasive marker for detecting graft rejection and measuring allograft damage among recent kidney transplant patients.

Treatment

Rejection episodes are typically managed on an inpatient basis by altering medication dosage.[3]

Survival

The 5-year survival in individuals who have living donor transplants is over 80%.[2] Survival rates are lower with deceased donor transplants.[2] If the kidneys fail completely, survival is a few months without treatment.[1] After transplant, long-term survival is still limited, and acute rejection is a frequent complication and associated with reduced graft survival.[1]

Test Information

AlloSure Kidney is an assay designed to detect allograft rejection in kidney transplant recipients.

Description and Purpose

According to the manufacturer of AlloSure Kidney (Care Dx), the test is intended to non-invasively measure donor DNA in the blood for early detection of allograft injury and rejection.[10] AlloSure Kidney can detect antibody mediated rejection (ABMR), T cell mediated rejection (TCMR), graft injury, and de novo donor-specific antibodies (dnDSA).[10]

Test Targets

AlloSure Kidney is a targeted next-generation sequencing assay that uses 266 single-nucleotide polymorphisms (SNPs) to quantify dd-cfDNA in transplant patients.[10]

Result

The test reports an AlloSure Score (percent of donor derived DNA in the patient's blood sample) along with quality control cut-off values.[10]

Interpretation of test results:[10]

- Low risk of rejection: less than 0.5%
- Likely graft injury: 0.5-1.0%
- High risk of rejection: 1.0-2.9%

In addition, the relative change (RCV) of dd-cfDNA over time can provide additional information:[10]

- RCV less than 61%: biological variation
- RCV 149% or greater: high likelihood of graft injury.

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Guidelines and evidence

American Society of Transplant Surgeons

The American Society of Transplant Surgeons (ASTS, 2024) issued a position statement on the use of dd-cfDNA in transplant recipients that stated:[11]

- "We recommend that clinicians measure dd-cfDNA levels in kidney transplant recipients with acute allograft dysfunction to exclude the presence of rejection, particularly antibody-mediated rejection (ABMR)."
- "We strongly recommend ongoing further clinical studies to clarify the scenarios and frequency in which molecular diagnostic studies should be utilized."
- "We specifically recommend that studies be carried out to evaluate the potential role of dd-cfDNA surveillance in kidney transplant recipients to improve long term allograft survival."

The Renal Association

The Renal Association Clinical Practice Guideline Post-Operative Care in the Kidney Transplant Recipient (RA, 2017, Reviewed 2022) was endorsed by the British Transplantation Society and the National Institute for Health and Care Excellence. The guideline stated:[12]

- "We recommend that a transplant renal biopsy should be carried out before treating an acute rejection episode unless this will substantially delay treatment or pose a significant risk to the patient. (1C)"
- "We suggest that two cores of renal tissue should be obtained at transplant biopsy since this will increase the sensitivity of the investigation. (2C)"
- "We recommend that a protocol transplant renal biopsy, defined as a biopsy performed in a stable graft without clinical evidence of acute rejection, be considered in the setting of persisting delayed graft function. (1C)"

The Transplantation Society

The Transplantation Society, via the Kidney Disease: Improving Global Outcomes (KDIGO, 2009) Transplant Work Group, states the following regarding acute rejection, renal allograft function, and renal allograft biopsy:[13]

Treatment of Acute Rejection

- "6.1: We recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. (1C)"
- "6.2: We suggest treating subclinical and borderline acute rejection. (2D)"

Kidney Allograft Biopsy

- “9.1: We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine. (1C)"
- “9.2: We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection. (2D)"
- “9.3: We suggest kidney allograft biopsy every 7–10 days during delayed function. (2C)”
- “9.4: We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1–2 months after transplantation. (2D)"
- “9.5: We suggest kidney allograft biopsy when there is"
  - "new onset proteinuria (2C)"
  - "unexplained proteinuria ≥3.0 g/g creatinine or ≥3.0g per 24 hours. (2C)"

Selected Relevant Publications

The available studies evaluating AlloSure Kidney provide limited evidence regarding the validity of the test for detecting renal graft rejection.[14-25] Several studies have shown an association between levels of donor derived cell-free DNA (dd-cfDNA) and kidney function, donor specific antibodies, non-immune injury, and rejection. However, these studies were hampered by several limitations including observational study designs, small sample sizes, lack of blinding, and overlapping patient populations. Additionally, the diagnostic threshold has not been definitively established, nor has the importance of absolute percentage of dd-cfDNA compared to relative changes in dd-cfDNA over time. Evidence of clinical utility for AlloSure Kidney is lacking, thus the impact of testing on clinically relevant outcomes and clinical decision-making remains unclear. Further studies are needed that demonstrate the safety of forgoing biopsies based on AlloSure Kidney results, or that demonstrate the use of AlloSure Kidney ultimately leads to improved survival or patient outcomes.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for AlloSure for kidney transplant rejection will ensure that members will not receive testing for which there is not a body of evidence demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[26] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

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AlloSure Kidney

Alpha-1 Antitrypsin Deficiency Testing

MOL.TS.124.A
v1.0.2026

Alpha-1 antitrypsin deficiency (AATD) testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Protease inhibitor (PI) typing	82104
SERPINA1 sequencing	81479
SERPINA1 targeted mutation analysis	81332

Criteria

Requests for alpha-1 antitrypsin deficiency (AATD) testing are reviewed using the following criteria.

Protease Inhibitor Typing or SERPINA1 Targeted Mutation Analysis

Protease inhibitor (PI) typing or SERPINA1 targeted mutation analysis (*S, *Z) is considered medically necessary in individuals who meet the following criteria:

- Abnormally low (less than 120mg/dL) or borderline (90-140mg/dL) alpha-1 antitrypsin (AAT) levels; AND
- At least one of the following:
  - Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators; or
  - Individuals of any age with unexplained liver disease (including obstructive liver disease in infancy); or
  - Asymptomatic individuals with persistent obstruction on pulmonary function tests who have identifiable risk factors (e.g., cigarette smoking, occupational exposure); or

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  - C-ANCA positive vasculitis; or
  - Adults with necrotizing panniculitis; or
  - Siblings of an individual with AATD, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

SERPINA1 Sequence Analysis

Sequencing of the SERPINA1 gene is considered medically necessary in individuals who meet the following criteria:

- There are discrepancies between clinical presentation, serum alpha-1 antitrypsin quantification, targeted mutation analysis, and/or PI typing; OR
- The presence of rare variants or null alleles (which cannot be identified by other methods) is suspected, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

What is alpha-1 antitrypsin deficiency?

Alpha-1 antitrypsin deficiency (AATD) is an inherited condition which can affect the lungs, liver, and rarely, skin. This condition is also referred to as AAT Deficiency and A1AT Deficiency.

Prevalence

It is estimated that 1 in 5000 to 1 in 7000 people in North America have AATD. AATD commonly affects individuals of Northern European heritage. This disorder is most common in Scandinavia, occurring in approximately 1 in 1500 to 1 in 3000 individuals there.[1] However, AATD is an under-recognized condition, with estimates that only 10% of those affected are actually diagnosed.[2]

Symptoms

The most common clinical manifestation is COPD, particularly emphysema and/or bronchiectasis.[1-3] The age of onset for COPD is generally older than 30 years.[1] Lung disease in children with AATD is rare.[1] Smoking is a major environmental risk factor for lung disease in AATD.[1,3]

AATD also increases the risk for neonatal or childhood liver disease, manifested by obstructive jaundice (cholestasis) and hyperbilirubinemia, and early onset adult liver disease, usually cirrhosis and fibrosis.[1] The prevalence of liver disease increases with age.[1] The lifetime risk of hepatocellular carcinoma (HCC) may also be increased.[1] In more rare cases, individuals with AATD are also at increased risk for panniculitis (tender skin nodules which may be inflammatory and may ulcerate) and C-ANCA positive vasculitis, specifically granulomatosis with polyangiitis.[1]

Genotype-phenotype correlations for AATD exist (i.e., certain types of mutations in the SERPINA1 gene are expected to be associated with a more severe presentation).[1]

Cause

AATD results from mutations in the SERPINA1 gene, which codes for the enzyme alpha-1 antitrypsin (AAT).[1]

Inheritance

AATD is inherited in an autosomal codominant pattern.[1] Codominance means that two different versions (alleles) of the gene may be active, with both versions contributing to the expression of features. The most common version of the SERPINA1 gene, called PI*M, produces normal levels of AAT.[1] Most people in the general population will have two copies of the PI*M allele (MM).[1] Other alleles of the SERPINA1 gene are anticipated to lead to reduced levels of the AAT enzyme.

For example, the PI*Z allele is the most common pathogenic (disease-causing) allele producing very small amounts of AAT.[1] Individuals who are homozygous (or have two copies) of the PI*Z allele tend to have severe features of AATD.[1] The PI*S pathogenic allele of SERPINA1 produces moderately low levels of AAT.[1] The PI*I allele of SERPINA1 is associated with mildly reduced levels of AAT.[1]

Additional alleles include the PI*F allele ("a pathogenic allele that is distinctive because the resulting protein is functionally impaired in binding neutrophil elastase but quantitatively normal") as well as null alleles ("sometimes designated as PI*QO").[1] Individuals with a PI*QO genotype have no measurable serum AAT secondary to complete lack of synthesis of AAT.[1]

Disease risks will depend on the combination of SERPINA1 alleles from biological parents. For example, if both biological parents are heterozygous (carriers) for one SERPINA1 PI*Z pathogenic variant, but also have a copy of the normal PI*M allele (denoted MZ), there will be a 25% risk that their offspring are homozygous PI*Z (ZZ).

Diagnosis

AATD may first be suspected based on reduced serum concentration levels of AAT.[1] Confirmatory testing includes either protease inhibitor typing or genetic testing for common mutations.[1] Targeted analysis for the PI*Z, PI*S, PI*I, and PI*F alleles may be performed first.[1] Sequence analysis may be indicated in certain situations.[1]

Management

Individuals with COPD are treated with standard therapy.[1] Individuals with emphysema may be treated with periodic human serum AAT by intravenous infusion.[1] For individuals with end-stage lung disease, lung transplantation may be considered. "Liver

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transplantation is the definitive treatment for those with severe disease" as it will restore AAT levels.[1] “Dapsone or doxycycline therapy is used for panniculitis; if refractory to this, high-dose intravenous AAT augmentation therapy is indicated.”[1] Individuals are strongly encouraged to avoid exposure to active and passive smoking, environmental pollutants, and excessive alcohol use.[1] Surveillance includes periodic pulmonary and liver function tests.[1]

Survival

The prognosis for individuals with AATD is dependent on the severity of the disease and lifestyle factors. Individuals with AATD may have a normal lifespan; however, those with exposure to cigarette smoke may experience earlier and faster progression of lung disease.[1]

Test information

Testing for AATD may include protease inhibitor typing, targeted mutation analysis, and/or next generation sequencing.

Protease Inhibitor Typing

Protease Inhibitor (PI) typing is performed with isoelectric focusing of serum to determine phenotype.[1] PI typing can detect normal as well as variant alleles, but cannot detect null alleles[1,2]

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

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Guidelines and evidence

American Thoracic Society and European Respiratory Society

The American Thoracic Society and the European Respiratory Society stated that testing for AATD is recommended for the following indications:[3]

- "symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators"
- "individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly
- asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors, (e.g., cigarette smoking, occupational exposure)
- adults with necrotizing panniculitis", and
- "siblings of an individual with AATD."

Selected Relevant Publications

Multiple publications outlined recommendations for the diagnosis of AATD.[4-7]

One study provided recommendations for the diagnosis of AATD based on systematic review and expert scientist and clinician appraisal.[6] They recommended testing for:

- "All individuals with COPD, regardless of age or ethnicity"
- "All individuals with unexplained chronic liver disease"
- "All individuals with necrotizing panniculitis, granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), or unexplained bronchiectasis"

In addition, the authors recommended that "adult siblings of individuals identified with an abnormal gene for AAT, whether heterozygote or homozygote, should be provided with genetic counseling and offered testing for AATD".

For diagnostic testing of symptomatic individuals, the authors recommended "genotyping for at least the S and Z alleles. Advanced or confirmatory testing should include Pi-typing, AAT level testing, and/or expanded genotyping."

Pathogenic mutations have been detected after negative PI and/or targeted mutation testing.[4,5] One study detected pathogenic mutations in 22% of individuals with negative PI and targeted mutation analysis and recommended direct sequencing of the coding regions of the SERPINA1 gene with suspected AATD due to a serum AAT concentration of ≤1.0 g/L.[4] When ambiguous results are obtained between quantification, genotype or phenotype assays, gene sequencing can identify rare variants or null alleles that would otherwise be missed.[4,5]

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Another study recommended inclusion of C-reactive protein levels, a marker of inflammation reported to impact observed AAT levels, to decrease the rate of false negative results in individuals with intermediate deficiency.[7] They found the highest sensitivity by using an approach that evaluated all individuals for AAT levels, serum CRP levels, and genotyping of the S and Z alleles.[7]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Alpha-1 Antitrypsin Deficiency testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Amyotrophic Lateral Sclerosis (ALS) Genetic Testing

MOL.TS.125.A
v1.0.2026

Amyotrophic lateral sclerosis (ALS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
ALS gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
ALS known familial mutation analysis	81403
Genetic testing for ALS	S3800
ALS multigene panel	81479

Criteria

Requests for amyotrophic lateral sclerosis (ALS) genetic testing are reviewed using the following criteria.

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Known Familial Mutation Testing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for ALS that would detect the familial mutation, AND
- Diagnostic Testing for Symptomatic or Presymptomatic Individuals:
  - Genetic ALS known familial mutation identified in a 1st, 2nd, or 3rd degree biological relative(s), and
  - Age 18 years or older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Sequencing and Deletion/Duplication Analysis of C9orf72, SOD1, FUS, TARDBP

Individual testing of these genes for the purpose of diagnosing ALS is not medically necessary.

Multigene Panel Testing for ALS

When a multi-gene panel is being requested and will be billed with an appropriate CPT panel code, (e.g. 81479), the panel will be considered medically necessary when the following criteria are met:

- Previous Genetic Testing:
  - No previous ALS multi-gene panel testing, and
  - No previous C9orf72 or SOD1 testing performed, and
  - No known ALS-related mutation in the member's family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Family history of ALS in a first degree relative (i.e., parent, sibling, child), and
  - Evidence of lower motor neuron degeneration (e.g., clinical exam, electrophysiological, muscle or nerve biopsy), and
  - Evidence of upper motor neuron degeneration (e.g., clinical exam, imaging), and
  - Progressive spread of signs within a region or to other regions, and
  - Lower and upper motor neuron disease cannot be explained by another condition, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

For information on ALS genetic testing to determine eligibility for targeted treatment, please refer to the guideline *Pharmacogenomic Testing for Drug Toxicity and Response*, as this testing is not addressed here.

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Gene panels that are specific to ALS will be considered for medical necessity according to the criteria outlined in this guideline. Panels must include, at minimum, analysis of all of the following genes: C9orf72, SOD1, FUS, TARDBP.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81479*).
    - Gene panels that are specific to ALS and include all of the following genes will be eligible for reimbursement according to the criteria outlined in this guideline: C9orf72, SOD1, FUS, TARDBP.
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
  - When an ALS multi-gene panel is billed with multiple stacked codes, only the following genes may be considered for reimbursement:
    - C9orf72
    - SOD1

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

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What is amyotrophic lateral sclerosis?

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disease that involves the brain and spinal cord.[1]

Prevalence

Between 4 and 8 out every 100,000 people develop ALS.[2] About 10% of individuals with ALS have at least one other family member affected with ALS.[1] About 85% of ALS occurs in individuals with no family history of ALS.[1]

Symptoms

While ALS historically has been described as primarily affecting motor neurons, additional areas within the frontal and temporal lobes are involved to varying degrees in a subset of individuals.[1] Systems outside the nervous system may also be involved, such as bone (Paget disease of the bone) and muscle (inclusion body myopathy). The clinical picture includes motor decline, and may also include cognitive and behavioral symptoms, based on the location and extent of the degeneration in an individual.[1]

The average age of ALS onset is 55 years in males, and mid 60s in females.[1] Earlier onset of symptoms is seen in individuals with genetic forms of ALS.[1] There are infantile and juvenile onset forms that should also prompt consideration of a genetic etiology.[1]

Cause

Traditionally, a diagnosis of "familial ALS" indicated that two or more close relatives were known to be affected with ALS and "sporadic ALS" indicated that no other relatives are known to have ALS. However, evolving genetic research in ALS and an increase in the clinical use of genetic testing has resulted in new terminology. "Genetic ALS" refers to ALS caused by a pathogenic mutation in a known ALS gene, regardless of family history and "ALS of unknown cause" refers to ALS in which a pathogenic mutation in a known ALS gene has not been identified, also regardless of family history.[1]

Thirty genes have been implicated with varying degrees of certainty to cause genetic ALS and the condition demonstrates genetic overlap with frontotemporal dementia (FTD). Genetic testing for many of the genes is clinically available.[1,4-7]

A pathogenic mutation can be identified in 50-60% of cases of ALS when there is a family history of ALS or dementia, and in approximately 10% of simplex cases (no family history).[8-10] Mutations in SOD1, C9orf72 (39-45%)[1], TARDBP (TDP-43), and FUS account for the greatest number of cases, while the remaining genes are relatively rare causes of the disorder.[1,4-13] The majority of combined ALS/FTD cases with a family history of either disorder are caused by C9orf72 repeat expansions, particularly in Caucasian populations, while the percentage of cases attributed to this gene is

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somewhat lower in China.[5,11] Many other candidate genes have been identified and are still pending further validation studies.[7]

Inheritance

Genetic ALS can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner although autosomal dominant is the most common inheritance mode.[1] The mode of inheritance is based on family history and molecular genetic testing.

Genes commonly associated with genetic ALS

Some of the most common genetic causes of genetic ALS are summarized below. The remaining genes are relatively rare causes of the disorder. Genetic testing for many of the genes is available clinically.[1,4-13]

Gene symbol	% of ALS with family history	% of simplex ALS	Inheritance
C9orf72	39%-45%	3%-7%	Autosomal dominant
SOD1	15%-20%	3%	Autosomal dominant, Autosomal recessive
FUS	~4%-8%	Very Rare	Autosomal dominant
TARDBP/TDP43	1%-4%	Unknown	Autosomal dominant

Diagnosis

Most cases of suspected ALS are diagnosed based on a unique combination of symptoms and the exclusion of similar disorders. The Escorial Criteria were developed in 2000 to standardize the clinical diagnosis of ALS.[3] These criteria include:

- the presence of upper and lower motor neuron deterioration
- the progressive spread of symptoms, and
- no clinical evidence of other diseases with similar symptoms.

Management

Treatment for individuals with ALS is palliative. There are three FDA-approved drugs available, including a gene-specific treatment for individuals with ALS due to a SOD1 mutation.[1] "Many individuals benefit from care by a multidisciplinary team that includes a neurologist, specially trained nurses, pulmonologist, speech therapist, physical therapist, occupational therapist, respiratory therapist, nutritionist, psychologist, social worker, and genetic counselor."[1]

Survival

ALS is fatal. Disease duration is variable and can range from months to several decades. Approximately half of affected individuals die within five years of symptom onset.[1] Treatment focuses on slowing progression with medication and therapy, and optimizing quality of life.[1]

Test information

Testing for genetic forms of ALS may include known familial mutation testing, targeted expansion analysis of C9orf72, or next generation sequencing of a single gene or in multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Known familial mutation analysis can provide predictive information about the risk to develop genetic ALS. It can also be used to diagnose ALS when the individual does not yet meet the full ALS diagnostic criteria.[14]

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Expansions of the hexanucleotide repeat non-coding region of the open reading frame C9orf72 (a protein as yet uncharacterized) are the most frequent cause of genetic ALS and can be assessed through targeted analysis.[1,8] Although estimation of the repeat size is typically accurate, there is disagreement as to the normal and pathogenic repeat size ranges.[15] In general, more than 30 hexanucleotide repeats are considered pathogenic and Southern blot is considered the gold standard for clinical testing.[9]

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA

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simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and evidence

European Federation of Neurological Societies

A European Federation of Neurological Societies Task Force (EFNS, 2012) addressed presymptomatic testing in its diagnosis and management guidelines: "Presymptomatic genetic testing should only be performed in first-degree adult blood relatives of patients with a known gene mutation. Testing should only be performed on a strictly voluntary basis as outlined (see Table 7 in the original guideline document) and should follow accepted ethical principles."[16]

The EFNS (2012) stated the following regarding molecular testing for ALS:[16]

- "Clinical DNA analysis for gene mutations should only be performed in cases with a known family history of ALS, and in sporadic ALS cases with the characteristic phenotype of the recessive D90A mutation."
- "In familial or sporadic cases where the diagnosis is uncertain, SMN, androgen receptor, or TARDBP, FUS, ANG, or SOD1 DNA analysis may accelerate the diagnostic process."
- "Before blood is drawn for DNA analysis, the patient should receive genetic counseling. Give the patient time for consideration. DNA analysis should be performed only with the patient's informed consent."

The EFNS (2011) addressed the molecular diagnosis of ALS and other neurogenetic disorders:[17]

- "Currently molecular diagnosis mainly has implications for genetic counseling rather than for therapy. However, when more directed causal therapies become available in the future, establishing a correct genetic diagnosis in a given patient will be essential.

Despite the rather low prevalence, sequencing of the small SOD1 gene should be considered in patients with ALS with dominant inheritance to offer presymptomatic or prenatal diagnosis, if this is requested by the family (Level B)."

World Federation of Neurology Research Group on Motor Neuron Diseases

The World Federation of Neurology Research Group on Motor Neuron Diseases (WFNALS, 2015) revised the El Escorial criteria:[18]

- These revised criteria did not specify when genetic testing should be done, but stated "If a pathogenic mutation in a disease-causing gene is found in the patient and segregates with the disease the term hereditary or primary genetic ALS (HALS/GALS) should be used. The finding of a pathogenic mutation in a known gene can substitute for either lower or upper motor neuron signs, so that diagnosis of ALS can be made on the basis of UMN or LMN signs in one body region, associated with a positive genetic test."
- "ALS can be defined as Mendelian in inheritance if a disease-causing gene variant can be shown to segregate within a family. In such cases the genetic variant can serve as a substitute for upper motor neuron deficits or a second limb or region (rule of two)."

Consensus guidelines from the WFNALS (2000) revised the El Escorial criteria to improve ALS diagnostic sensitivity.[3] This group didn't specify when genetic testing should be done, but stated, "The demonstration of the presence of a pathogenetically relevant gene mutation can assist in the diagnosis of ALS (such as SOD1)".

These criteria set a lower threshold for diagnosis when an ALS-causing mutation is known in the family. For example, an individual may be diagnosed as "Clinically Definite Familial ALS — Laboratory-supported" with evidence of only upper or lower motor neuron disease in one region; whereas a definite diagnosis without genetic test results requires upper and lower motor neuron disease in three regions.

Selected Relevant Publications

An ALS Expert Panel (2023) developed evidence-based, consensus guidelines for care of individuals with ALS that stated:[19]

- "...all persons with ALS should be offered single-step genetic testing, consisting of a C9orf72 assay, along with sequencing of SOD1, FUS, and TARDBP at a minimum."
- In addition, gene panels should include "Any gene for which the Food and Drug Administration (FDA) approves a targeted therapy" and "Genes rated as 'strong' or 'definitively' associated with ALS by ClinGen".
- The guideline stated that pretest genetic counseling should be provided. This should include pedigree analysis, risk assessment, discussion of genetic heterogeneity, penetrance, and inheritance patterns, and a review of the possible test results such as positive, negative, and variant of uncertain significance. Furthermore,

pretest genetic counseling should also "prepare individuals for possible personal, psychological, and economic impacts of testing on themselves and their family members."
- "All persons with ALS who have genetic testing should receive posttest counseling." The points to review in the posttest counseling sessions are outlined in the consensus guideline.
- The consensus guideline also provided information for commercial laboratories on testing methods and reporting of the C9orf72 mutation and other genes.

An expert recommendation (2016) for predictive genetic counseling and testing for genetic ALS stated: [20]
- Testing should be voluntary and include informed consent.
- Psychosocial readiness to undergo presymptomatic testing should be assessed.
- Genetic counseling should be provided and at least two counseling sessions should be performed. "These may include predecision counseling as well as pretest and posttest counseling." Specific points to review during each of these sessions were discussed in detail.
- Individuals have the option "not to take the test at all, to undergo testing but not to learn the results, or simply to provide a DNA sample for future research."
- The rendering laboratory should be a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Amyotrophic Lateral Sclerosis (ALS) testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Angelman Syndrome Genetic Testing

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Angelman syndrome (AS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Chromosomal microarray [BAC], constitutional	81228
Chromosomal microarray [CGH], constitutional	S3870
Chromosomal microarray [SNP], constitutional	81229
Chromosome 15 uniparental disomy	81402
Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis	81349
FISH analysis for 15q11-q13 deletion	88271
Imprinting center defect analysis	81479
Imprinting center known familial mutation analysis	81403
SNRPN/UBE3A methylation analysis	81331
UBE3A deletion/duplication analysis	81479

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Procedures addressed by this guideline	Procedure codes
UBE3A known familial mutation analysis	81403
UBE3A sequencing	81406

Criteria

Requests for Angelman syndrome (AS) genetic testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous UBE3A sequencing or imprinting center defect analysis testing that would detect the familial mutation, AND
- Family History:
  - Known familial UBE3A mutation in a blood relative, or
  - Known familial imprinting center defect mutation in a blood relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

SNRPN/UBE3A Methylation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous SNRPN/UBE3A methylation analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Developmental delay by age 6-12 months, typically severe to profound, without loss of milestones, and
  - Some combination of the following:
    - Movement or balance disorder, typically with ataxia, or

        - Frequent laughter/smiling, apparent happy demeanor; easily excitable personality (often with uplifted hand-flapping, or waving movements),or hypermotoric behavior, or
        - Speech impairment with no or minimal number of words, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Deletion Analysis (FISH for 15q11-q13 Deletion or Chromosomal Microarray)

- Genetic Counseling:
    - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
    - No previous chromosomal microarray, and
    - No previous 15q11-q13 deletion analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
    - Developmental delay by age 6-12 months, typically severe to profound, without loss of milestones, and
    - Some combination of the following:
        - Movement or balance disorder, typically with ataxia, or
        - Frequent laughter/smiling, apparent happy demeanor; easily excitable personality (often with uplifted hand-flapping, or waving movements),or hypermotoric behavior, or
        - Speech impairment with no or minimal number of words, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Chromosome 15 Uniparental Disomy (UPD)

- Genetic Counseling:
    - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
    - SNRPN/UBE3A methylation analysis results are abnormal, and
    - 15q11-q13 deletion analysis is negative, and
    - No previous chromosome 15 UPD studies, AND
- Diagnostic Testing for Symptomatic Individuals:
    - Meets clinical criteria for SNRPN/UBE3A methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Imprinting Center Defect Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - SNRPN/UBE3A methylation analysis results are abnormal, and
  - 15q11-q13 deletion analysis is negative, and
  - Previous chromosome 15 UPD testing is negative, and
  - No previous imprinting center (IC) analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Meets clinical criteria for SNRPN/UBE3A methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

UBE3A Sequencing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - SNRPN/UBE3A methylation analysis results are normal, and
  - No previous sequencing of UBE3A, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Meets clinical criteria for SNRPN/UBE3A methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

UBE3A Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - SNRPN/UBE3A methylation analysis results are normal, and
  - Normal UBE3A sequencing, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Meets clinical criteria for SNRPN/UBE3A methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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What is Angelman syndrome?

Angelman syndrome (AS) is a genetic disorder that can cause intellectual disability, severe speech impairment, tremors, seizures, microcephaly, and decreased need for sleep.

Prevalence

The prevalence of AS in the population is one in 12,000-24,000.[1]

Symptoms

Clinical features of AS (quoted directly):[2]

A. Consistent (100%)

- Developmental delay, functionally severe
- Movement or balance disorder, usually ataxia of gait, and/or tremulous movement of limbs. Movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions
- Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping, or waving movements; hypermotoric behavior
- Speech impairment, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones

B. Frequent (more than 80%)

- Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (2 SD of normal OFC) by age 2 years. Microcephaly is more pronounced in those with 15q11.2-q13 deletions
- Seizures, onset usually <3 years of age. Seizure severity usually decreases with age but the seizure disorder lasts throughout adulthood
- Abnormal EEG, with a characteristic pattern, as mentioned in the text. The EEG abnormalities can occur in the first 2 years of life and can precede clinical features, and are often not correlated to clinical seizure events

C. Associated (20%-80%)

- Flat occiput
- Occipital groove
- Protruding tongue
- Tongue thrusting; suck/swallowing disorders
- Feeding problems and/or truncal hypotonia during infancy
- Prognathia
- Wide mouth, wide-spaced teeth
- Frequent drooling

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- Excessive chewing/mouthing behaviors
- Strabismus
- Hypopigmented skin, light hair, and eye color compared to family, seen only in deletion cases
- Hyperactive lower extremity deep tendon reflexes
- Uplifted, flexed arm position especially during ambulation
- Wide-based gait with pronated or valgus-position ankles
- Increased sensitivity to heat
- Abnormal sleep-wake cycles and diminished need for sleep
- Attraction to/fascination with water, fascination with crinkly items such as certain papers and plastics
- Abnormal food related behaviors
- Obesity (in older child)
- Scoliosis
- Constipation

Causes

Angelman syndrome is caused by a missing or defective UBE3A gene inherited from the individual's mother.[3]

A missing or defective UBE3A gene can be caused by a gene deletion, gene mutation, uniparental disomy (two copies of the paternal chromosome), imprinting defect, or a chromosome rearrangement.[3,4]

Molecular genetic testing will identify an etiology in approximately 90% of individuals. A portion of individuals (around 10%) with a clinical diagnosis of AS will not have a molecular cause identified.[1]

Diagnosis

The diagnosis of AS is established in an individual who has findings on molecular genetic testing that are consistent with deficient expression or function of the maternally inherited UBE3A allele.[1,2,5,6]

Genetic testing is recommended when an individual has all of the clinical findings in sub-bullets A and B listed above under "symptoms" and whose developmental history is as follows:[2]

- Unremarkable prenatal and birth history. The neonate does not present with an abnormal head circumference or major birth defects although feeding difficulties may be evident.

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- At 6-12 months of age, developmental delays become evident and there may be low muscle tone of the trunk. Differences in limb movements and/or increased smiling may be noticed.
- There is no regression but there is delayed development in progression of skills.
- Metabolic, hematologic, and chemistry profiles are normal.
- Overall normal brain MRI or CT although there may be "mild cortical atrophy or dysmyelination".
- The authors note that "these findings are useful as inclusion criteria but deviations should not exclude diagnosis"

Determination of recurrence risk following a diagnosis of AS may require genetic testing of one or both parents depending on the identified molecular cause.[5,6]

Management

“Anti-seizure medication for seizures. Accommodation for hypermotoric behaviors and disruptive nighttime wakefulness. Behavior modification can be effective for disruptive or self-injurious behaviors. Physical therapy, occupational therapy, and speech therapy with an emphasis on nonverbal methods of communication, including augmentative communication aids (e.g., picture cards, communication boards) and signing. Individualization and flexibility in school settings. Routine management of gastroesophageal reflux, feeding difficulties, constipation, and strabismus. Thoraco-lumbar jackets and/or surgical intervention for scoliosis. Bracing or surgery as needed for subluxed or pronated ankles or tight Achilles tendons."[1]

Other recommendations include the following:

- Sleep disturbance: Sleep concerns may require consideration of effect on other aspects of the individual's health, etiological investigations, behavioral interventions, medication trials, and evaluation by a sleep specialist.[6]
- "Surveillance: Evaluation of older children for obesity associated with an excessive appetite. Annual clinical examination for scoliosis; ophthalmology examination in the first year if strabismus is present; ophthalmology exam at age two years with follow up per ophthalmologist; clinical examination for scoliosis annually."[1]
- "Agents/circumstances to avoid: Overtreatment with sedating medications in order to reduce hyperexcitable and hypermotoric behavior. Overtreatment with antiepileptic drugs when movement abnormalities are mistaken for seizures and/or when EEG abnormalities persist even as seizures are controlled."[1]

Test information

Testing for AS may include known familial mutation analysis, SNRPN/UBE3A methylation analysis, chromosomal microarray, FISH analysis for 15q11-q13 deletion,

chromosome 15 uniparental disomy (UPD), imprinting center defect analysis, or UBE3A sequencing and deletion testing.

Known Familial Mutation Analysis: Known familial mutation analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing. Analysis for known familial mutations typically includes only the specific mutation identified in the family, but if available, a targeted mutation panel that includes the familial mutation(s) may be performed.

SNRPN/UBE3A Methylation Analysis: This test is typically the first test in the evaluation of both Angelman syndrome (AS) and Prader-Willi syndrome (PWS). It will detect about 80% of individuals with AS and greater than 99% of individuals with PWS. However, DNA methylation analysis does not identify the underlying cause, which is important for determining the risk to future siblings. This risk ranges from less than 1% to up to 50%, depending on the genetic mechanism. Follow-up testing for these causes may be appropriate.

Chromosomal Microarray or FISH Analysis for 15q11-q13 Deletion: If DNA methylation analysis for AS or PWS is abnormal, deletion analysis is typically the next step. Approximately 70% of cases of both AS and PWS have a deletion in one copy of chromosome 15 involving the 15q11.2-q13 region. FISH (fluorescence in situ hybridization) analysis and chromosomal microarray (CMA, array CGH) can detect such deletions. If CMA has already been done, FISH is not likely to be necessary.

Chromosome 15 Uniparental Disomy (UPD): If DNA methylation analysis is abnormal but deletion analysis is normal, UPD analysis may be an appropriate next step for evaluation of both AS and PWS. About 28% of PWS cases are due to maternal UPD (both chromosome 15s are inherited from the mother). About 7% of cases of AS are due to paternal UPD (both chromosome 15s are inherited from the father). Both parents must be tested to diagnose UPD.

Imprinting Center Defect Analysis: This test may be considered in the evaluation of AS and PWS when methylation is abnormal, but FISH (or array CGH) and UPD studies are normal. Individuals with such results are presumed to have an imprinting defect. An abnormality in the imprinting process has been described in a minority of cases. However, imprinting center deletions may be familial, and if familial, the recurrence risk can be up to 50%.

UBE3A Sequencing

If DNA methylation analysis is normal, UBE3A gene mutations should be suspected. Such mutations are found in 11% of individuals with AS and can only be detected by sequencing the entire gene.[1] These mutations can be carried by the mother of an affected individual and pose up to a 50% risk of recurrence in her other children, and an increased risk to other family members.

UBE3A Gene-Targeted Deletion/Duplication Analysis

"Gene-targeted deletion/duplication analysis detects deletions or duplications in intragenic or other targeted regions. … CMA usually detects large 15q11.2-q13 deletions, but in rare instances has detected UBE3A multiexon or whole-gene deletions."[1]

Guidelines and evidence

The Angelman Syndrome Foundation

The Angelman Syndrome Foundation (ASF, 2024) recommended the following genetic testing strategy:[4,7]

- UBE3A methylation analysis
  - If normal, consider UBE3A gene sequencing.
  - If abnormal (only paternal alleles are present), a diagnosis of AS is confirmed. Consider the following to identify the underlying molecular cause for recurrence risk counseling.
- Deletion analysis (chromosomal microarray or FISH for 15q11-q13)
  - If deletion testing is abnormal, FISH testing on the mother should be done to rule out an inherited chromosome abnormality (rare).
  - If deletion testing is normal, consider UPD analysis.
- Uniparental Disomy (UPD) analysis of chromosome 15 to determine whether the proband inherited both copies of chromosome 15 from the father.
- If deletion analysis and UPD analysis are normal, an imprinting center mutation is a likely cause and should be evaluated (which may carry a higher recurrence risk than other causes).

Selected Relevant Publications

An expert-authored review (2021) commented on the appropriate diagnostic testing strategy and the utility of familial testing analysis:[1]

Diagnostic Testing:

- DNA methylation testing is usually the first-tier test. If methylation analysis is abnormal, additional analysis is needed to identify the molecular cause.
- If methylation analysis is normal, UBE3A sequencing should be considered, followed by deletion/duplication analysis.

Familial Testing:

- Individuals with an imprinting center (IC) deletion can have a phenotypically normal mother who also has an IC deletion. If a proband's mother has a known IC deletion, the risk to the sibs is 50%.

- UBE3A pathogenic variants can be inherited or de novo. Cases of somatic and germline mosaicism for a UBE3A pathogenic variant have been noted. If a proband's mother has a UBE3A pathogenic variant, the risk to the sibs is 50%.
- "If a proband's mother is heterozygous for a known imprinting center deletion or UBE3A pathogenic variant, the mother's sibs are also at risk of having the imprinting center deletion or the UBE3A pathogenic variant. Each child of the unaffected heterozygous sister is at a 50% risk of having AS. Unaffected maternal uncles of the proband who are heterozygous are not at risk of having affected children, but are at risk of having affected grandchildren through their unaffected daughters who inherited the imprinting center deletion or UBE3A pathogenic variant from them."

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Angelman Syndrome testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Ashkenazi Jewish Carrier Screening

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Ashkenazi Jewish carrier screening is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Ashkenazi Jewish genetic disorders gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Ashkenazi Jewish genetic disorders sequencing	81412
ASPA targeted mutation analysis	81200
BCKDHB targeted mutation analysis	81205
BLM targeted mutation analysis	81209
CFTR targeted mutation analysis	81220
FANCC targeted mutation analysis	81242

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Procedures addressed by this guideline	Procedure codes
G6PC targeted mutation analysis	81250
GBA targeted mutation analysis	81251
HEXA targeted mutation analysis	81255
IKBKAP targeted mutation analysis	81260
MCOLN1 targeted mutation analysis	81290
SMPD1 targeted mutation analysis	81330

Criteria

Requests for Ashkenazi Jewish carrier screening are reviewed using the following criteria.

Single Ashkenazi Jewish Genetic Diseases Carrier Screening Tests

Carrier screening is medically necessary for a single Ashkenazi Jewish disease if any of the following are met:

- The individual is of Ashkenazi Jewish ancestry, OR
- The individual has a family history of the condition for which testing is being requested, OR
- The individual's partner is a known carrier or affected with the condition for which testing is being requested, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

Ashkenazi Jewish Genetic Diseases Carrier Screening Panels

Carrier screening is medically necessary for all or any desired subset of the Ashkenazi Jewish genetic diseases eligible for coverage per the Coverage Guidance table when the following criteria are met:

- The individual is planning a pregnancy or currently pregnant, AND
- At least one partner of a couple is Ashkenazi Jewish (NOTE: Detection rates for testing are higher in people with Ashkenazi Jewish ancestry. If only one partner of a couple is Ashkenazi Jewish, testing should start in that person when possible.), AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

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Other Considerations

For information on the diagnostic testing of symptomatic individuals for the genetic conditions included in this guideline, please refer to the *Genetic Testing to Diagnose Non-Cancer Conditions* guideline or EviCore test-specific guidelines, as this testing is not addressed here.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

When testing is otherwise reimbursable, the following limitations apply:

- If an Ashkenazi Jewish carrier screening panel was previously performed and an updated, larger panel is being requested, only testing of previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.
- If testing will be billed using procedure code 81412 to represent all tests performed for the assessment of carrier status based on Ashkenazi Jewish ancestry, no additional tests for this purpose will be reimbursed for the same date of service.
- If testing will be billed for separate genes because the panel code is not more appropriate (e.g., fewer than the 9 stated genes will be assessed or a different methodology is used), reimbursement for individual gene tests will be assessed based on the guidance provided in the Criteria section above and in the Table: *Coverage Guidance for Genes Included in Ashkenazi Jewish Carrier Screening Tests*.
- Carrier screening panels are reimbursable once per lifetime.
  - If an Ashkenazi Jewish carrier screening panel was previously billed, an additional carrier screening panel will not be reimbursable.
  - If a non-Ashkenazi Jewish carrier screening panel was previously billed, subsequent carrier screening of any type will not be reimbursable (e.g. individual genes, Ashkenazi Jewish carrier screening panels).

Table: Coverage Guidance for Genes Included in Ashkenazi Jewish Carrier Screening Tests

Condition, Gene, CPT Code, Required Claim Code

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Condition	Gene	CPT	Required Claim Code
Bloom syndrome	BLM	81209	NONE
Canavan disease	ASPA	81200	NONE
Cystic fibrosis	CFTR	81220	NONE
Dihydrolipoamide dehydrogenase deficiency	DLD	81406	DLD
Familial dysautonomia	ELP1	81260	NONE
Familial hyperinsulinism	ABCC8	81401	ABCC8
Fanconi anemia, type C	FANCC	81242	NONE
Gaucher disease, type 1	GBA	81251	NONE
Glycogen storage disease, type 1A	G6PC	81250	NONE
Joubert syndrome, type 2	TMEM216	81479	TMEM216
Maple syrup urine disease, type 1b	BCKDHB	81205	NONE
Mucolipidosis, type IV	MCOLN1	81290	NONE
Nemaline myopathy, type 2	NEB	81400	NEB

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Condition	Gene	CPT	Required Claim Code
Niemann-Pick disease, type A	SMPD1	81330	NONE
Tay-Sachs disease	HEXA	81255	NONE
Usher syndrome, type 1F	PCDH15	81400	PCDH15
Usher syndrome, type 3	CLRN1	81400	CLRN1

Note:

Other tests may be eligible for coverage under the above criteria if the condition is associated with significant morbidity and mortality, the allele frequency is >1% in the Ashkenazi Jewish population, and the selected test method has >90% detection rate for disease-causing mutations.

What is Ashkenazi Jewish carrier screening?

Ashkenazi Jewish carrier screening is available for certain genetic conditions that are either more common or for which there are higher mutation detection rates in the Ashkenazi Jewish population. "Ashkenazi" refers to someone whose Jewish ancestors originally came from Central or Eastern Europe, such as Russia, Poland, Germany, Hungary, Lithuania. Most Jewish people in the US are of Ashkenazi descent. There are regional differences in the number and types of tests commonly offered. Individuals and providers may choose all or a subset of these conditions.[1-3]

Inheritance

The genetic diseases that are more common in the Ashkenazi Jewish population are typically inherited in an autosomal recessive manner. An affected individual must inherit a gene mutation from both biological parents.[1,2]

- Individuals who inherit only one mutation are called carriers. Carriers usually do not show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children.
- Two carriers of the same disease have a 25% chance, with each pregnancy, of having a child with the disorder.

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Prevalence

While these genetic diseases are individually rare, the overall chance for an individual of Ashkenazi Jewish descent to be a carrier for one of these genetic diseases is 1 in 4 to 1 in 5.[3] An individual can also be a carrier of more than one condition.

People from other ethnic backgrounds can be carriers of these conditions, but it is generally less common. The test is typically not as effective at identifying carrier status in individuals of non-Ashkenazi Jewish descent.

Test information

Ashkenazi Jewish carrier screening can be offered to couples or individuals of Ashkenazi Jewish descent when they are planning a pregnancy (preconceptional) or during a pregnancy (prenatal).[1-3]

One member of couple is Jewish

If only one member of the couple is Ashkenazi Jewish, carrier screening should start with the Ashkenazi Jewish partner. In general, both parents must be carriers to have an affected child, so reproductive partners of known carriers should also be offered testing even if not Jewish. In some cases, full gene sequencing would be most appropriate for testing of a non-Jewish partner.

Purpose of test

Carrier screening generally looks for a small number of gene mutations that are particularly common in the Ashkenazi Jewish population, although an increasing number of full gene sequencing panels are becoming available.

In addition, enzyme analysis is a particularly effective screening test for Tay-Sachs disease and can be preferred to mutation testing.

Detection rate

The carrier detection rate is greater than 95% in the Ashkenazi Jewish population for most of these genetic diseases.[3]

The detection rate for these tests in the non-Ashkenazi Jewish population is unknown for most conditions, but generally low. Exceptions include cystic fibrosis and Tay-Sachs enzyme analysis, which each generally have good detection rates in non- Ashkenazi Jewish populations.

A negative test result in one or both partners significantly lowers the chance of an affected child but does not eliminate it.[2]

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Commonly tested conditions

The genes included in carrier screening panels vary widely between laboratories. The following table includes the most commonly tested conditions.

Ashkenazi Jewish genetic disease	Ashkenazi carrier frequency	What the test looks for	Chance of correctly finding an Ashkenazi Jewish carrier
Bloom syndrome[3]	1/107	1 mutation (2281del6ins7)	>99%
Canavan disease[3]	1/41	2 mutations (E285A, Y231X)	97.4%
Cystic fibrosis[2]	1/24	23 most common mutations in several ethnic groups	94%
Dihydrolipoamide dehydrogenase deficiency[4]	1/107	2 mutations (G229C and Y35X)	>95%
Familial dysautonomia[3]	1/31	2 mutations (2507+6TtoC, R696P)	>99%
Familial hyperinsulinism[4]	1/68	2 mutations (c.3989-9G>A and F1387del)	90%
Fanconi anemia group C[3]	1/89	1 mutation (IVS4+4AtoT)	>99%
Gaucher disease Type 1[3]	1/18	4 mutations (N370S, 84GG, L444P, IVS2+1GtoA)	Up to 94.6%
Glycogen storage disease type 1A (GSD1A)[5]	1/71	1 mutation (R83C)	93% to 100%

Ashkenazi Jewish genetic disease	Ashkenazi carrier frequency	What the test looks for	Chance of correctly finding an Ashkenazi Jewish carrier
Joubert syndrome 2[6,7]	1/92	1 mutation (R12L)	99%
Maple syrup urine disease (MSUD)[8,9]	1/80	3 mutations (R183P, G278S, E372X)	About 99%
Mucolipidosis type IV[3]	1/127	2 mutations (IVS3–2AtoG, Del6.4kb)	95%
Nemaline myopathy[4]	1/168	1 mutation (R2478_D2512del)	>95%
Niemann-Pick disease type A[3]	1/90	3 mutations (R496L, L302P, fsP330)	97%
Tay-Sachs disease[2,3]	1/31	Mutation analysis: 3 mutations (1278insTATC, 1421+1GtoC, G269S) OR	>92-99%
		Hexosaminidase A enzyme analysis	About 98%
Usher syndrome III[4]	1/120	1 mutation (N48K)	>95%

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2008) guidelines outlined criteria for adding disorders to carrier screening in the Ashkenazi Jewish population:[3]

- the natural history must be well understood
- people affected with the disorder must have significant morbidity and/or mortality, and

- the test must have greater than 90% detection OR the allele frequency must be at least 1%.

Conditions that meet ACMG criteria

The following conditions meet these criteria:

- cystic fibrosis
- Canavan disease
- familial dysautonomia
- Tay-Sachs disease
- Fanconi anemia (group C)
- Niemann-Pick (type A)
- Bloom syndrome
- mucolipidosis type IV
- Gaucher disease
- dilipoamide dehydrogenase deficiency[4]
- familial hyperinsulinism[4]
- glycogen storage disease type 1a[5]
- Joubert syndrome 2[6,7]
- maple syrup urine disease [8,9]
- nemaline myopathy,[4] and
- Usher syndrome type III.[4]

ACMG (2021) released an educational practice resource on carrier screening.[10] This consensus statement asserted that general population carrier screening should be ethnicity and family history agnostic. To accomplish this, screening all individuals in the prenatal/preconception period for autosomal recessive and X-linked conditions with a carrier frequency of ≥1/200 was suggested. ACMG generated a list of 113 genes meeting these criteria.

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2017; reaffirmed 2023) Committee on Genetics issued an opinion that "ethnic-specific [e.g. Ashkenazi Jewish], panethnic, and expanded carrier screening are acceptable strategies for pre-pregnancy and prenatal carrier screening."[11]

If providers choose to offer ethnic-specific screening to individuals of Ashkenazi Jewish ancestry, ACOG recommended that screening include Canavan disease, cystic fibrosis, familial dysautonomia, Tay-Sachs disease, Bloom syndrome, familial hyperinsulinism, Fanconi anemia, Gaucher disease, glycogen storage disease type I, Joubert syndrome, maple syrup urine disease, mucolipidosis type IV, Niemann-Pick disease, and Usher syndrome.[2]

Regardless of screening strategy chosen by the provider and regardless of the individual's ethnicity, ACOG recommended that all individuals who are considering pregnancy or are already pregnant be "...offered carrier screening for cystic fibrosis and spinal muscular atrophy, as well as a complete blood count and screening for thalassemias and hemoglobinopathies. Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome, or women with a personal history of ovarian insufficiency."[11]

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC, 2023) issued a practice guideline on carrier screening in support of an expanded panel approach that is ethnicity and family history agnostic. They recommended expanded carrier screening be made available for all individuals considering reproduction and all pregnant reproductive pairs. "The final decision to pursue carrier screening should be directed by shared decision-making, which takes into account specific features of patients as well as their preferences and values."[12]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for Ashkenazi Jewish carrier screening will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

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Hereditary Ataxia Genetic Testing

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Hereditary ataxia genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Ataxia gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
ATN1 expansion analysis	81177
ATXN1 gene analysis, evaluation to detect abnormal (eg,expanded) allele	81178
ATXN2 gene analysis, evaluation to detect abnormal (eg,expanded) allele	81179
ATXN3 gene analysis, evaluation to detect abnormal (eg,expanded) allele	81180
ATXN7 gene analysis, evaluation to detect abnormal (eg,expanded) allele	81181

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Procedures addressed by this guideline	Procedure codes
ATXN8 gene analysis, evaluation to detect abnormal (eg, expanded) alleles	81182
ATXN10 gene analysis, evaluation to detect abnormal (eg, expanded) alleles	81183
CACNA1A gene analysis; evaluation to detect abnormal (eg, expanded) alleles	81184
CACNA1A gene analysis; full gene sequence	81185
CACNA1A gene analysis; known familial variant	81186
FXN gene analysis; evaluation to detect abnormal (expanded alleles)	81284
FXN gene analysis; characterization of alleles (e.g. expanded size)	81285
FXN gene analysis; full gene sequence	81286
FXN gene analysis; known familial variant(s)	81289
FXN gene analysis, deletion/duplication	81479
Genomic Unity Ataxia Repeat Expansion and Sequence Analysis	0216U
Genomic Unity Comprehensive Ataxia Repeat Expansion and Sequence Analysis	0217U
Hereditary ataxia multigene panel	81479
Hereditary ataxia multigene panel (including sequencing of at least 15 genes)	81443
PPP2R2B gene analysis, evaluation to detect abnormal (eg, expanded) alleles	81343
TBP gene analysis, evaluation to detect abnormal (eg, expanded) alleles	81344

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Criteria

Requests for hereditary ataxia genetic testing are reviewed using the following criteria.

Hereditary Ataxia Known Familial Mutation Testing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing inclusive of the known familial mutation(s), and
  - Disease-causing mutation(s) identified in biological relative with the following degree of relationship to the member:
    - 1st or 2nd degree biological relative for an autosomal dominant disorder, or
    - 1st, 2nd, or 3rd degree biological relative for an autosomal recessive or X-linked disorder, and
  - Member is at risk to have the familial mutation based on the inheritance pattern of the disorder in question, AND
- Predictive Testing for Asymptomatic Individuals:
  - 18 years of age or older, or
  - Under the age of 18 years, and
    - Test results are needed for treatment or medical screening, OR
- Diagnostic Testing for Symptomatic Individuals:
  - Clinical examination and/or biochemical results are suggestive, but not confirmatory, of the familial diagnosis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Hereditary Ataxia Single-Gene Testing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No known ataxia-related mutation in the member or the member's family that would explain the member's clinical symptoms, AND
  - No previous testing that would have included the requested gene, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Test methodology is appropriate to the disease-causing mutations that are commonly reported for the disorder in question and any recommended previous testing has already been performed (e.g. FRDA trinucleotide repeat testing is completed before sequencing and/or deletion/duplication analysis), and

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- Clinical examination is remarkable for ataxia and other clinical features and/or biochemical results are suggestive, but not confirmatory, of the targeted disorder (see Table: *Select Hereditary Ataxias*), and
- The member does not have an underlying non-genetic cause for their ataxia (e.g. alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors, etc) or the clinical suspicion for a gene mutation remains high even in the presence of a non-genetic cause, and
- When family history is present, inheritance pattern is consistent with the targeted ataxia disorder, and
- Genetic diagnosis would result in changes to the member's medical management, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Multigene Panel Testing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous testing of the requested genes, and
  - No known ataxia-related mutation in the member or the member's family that would explain the member's clinical symptoms, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Test methodology is appropriate to the disease-causing mutations that are commonly reported for the disorder in question (e.g., sequencing-only panels will not detect triplet repeat or large deletion/duplication mutations), and
  - Individual has been diagnosed with cerebellar ataxia, regardless of age of onset, and
  - The member does not have an underlying non-genetic cause for their ataxia (e.g. alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors, etc) or the clinical suspicion for a gene mutation remains high even in the presence of a non-genetic cause, and
  - Family and medical histories do not point to a specific genetic diagnosis (see Table: *Select Hereditary Ataxias* for specific examples) or pattern of inheritance for which a more focused test would be appropriate, and
  - The requested hereditary ataxia multigene panel and genetic diagnosis would result in changes to the member's medical management, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Exclusions and Other Considerations

- This guideline may not apply to genetic testing for indications that are specifically addressed elsewhere. Please refer to test-specific guidelines when available (see Table: *Select Hereditary Ataxias*).
- Gene panels that are specific to hereditary ataxias will be considered for medical necessity according to the criteria outlined in this guideline.
- Broad hereditary ataxia panels may not be medically necessary when a narrower panel (e.g., a single-syndrome panel) is available and more appropriate based on the clinical findings.
- Germline genetic testing is only medically reimbursable once per lifetime. Therefore, a single gene included in a multigene panel may not be medically necessary if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81443, 81479, 0216U, or 0217U)*.
  - Analysis of individual genes will not be reimbursed separately when performed as part of a multi-gene panel (i.e. multiple stacked codes are not eligible for reimbursement of panels).

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What are hereditary ataxias?

The hereditary ataxias are a group of genetic disorders characterized by slowly progressive uncoordinated, unsteady movement and gait, and often poor coordination of hands, abnormal eye movements, and slurred speech. Cerebellar atrophy is also frequently seen via brain imaging.[1] Hereditary ataxias include, but are not limited to, ataxia telangiectasia (A-T), dentatorubral-pallidoluysian atrophy (DRPLA), fragile X-associated tremor/ataxia syndrome (FXTAS), Friedreich ataxia (FRDA), and spinocerebellar ataxias (SCAs). Specific features may vary with each subtype of hereditary ataxia.[1-19]

Prevalence

Prevalence estimates vary. The prevalence is approximately 2.7/100,000 and 3.3/100,000 for autosomal dominant and autosomal recessive hereditary ataxias, respectively.[20] One study in Norway estimated the prevalence of hereditary ataxia at 6.5 per 100,000 people.[21] Founder mutations may account for a higher prevalence of certain hereditary ataxias in specific regions.[2,17,18,22-24]

Symptoms

The hereditary ataxias are made up of multiple different conditions. Common symptoms include slowly progressive uncoordinated, unsteady movement and gait, and poor coordination of hands, abnormal eye movements, and slurred speech. Brain imaging is often remarkable for cerebellar atrophy.[1] The table below summarizes some of the clinical features of the more common hereditary ataxias.

Table: Select Hereditary Ataxias

This table is not intended to be all-inclusive; other conditions not listed here may have coverage under this guideline.

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Syndrome Name	Clinical Features	Cause	Inheritance
Ataxia-telangiectasia (A-T)[*16,27,28]	Age of onset for classic A-T: early childhood, usually between 1 and 4 years of age. Signs and symptoms of classic A-T include: • cerebellar ataxia; • extrapyramidal movement disorders such as chorea, myoclonus, dystonia and tremor; • peripheral neuropathy; • dysarthria; • dysphagia; • eye movement disorders such as gaze-evoked nystagmus and oculomotor apraxia; • telangiectasias, particularly of conjunctiva and sun-exposed skin; • immunodeficiencies and frequent non-opportunistic infections; • pulmonary disease; • respiratory infections;	Biallelic mutations in the ATM gene.	AR

Syndrome Name	Clinical Features	Cause	Inheritance
	• malignancies, especially leukemias and lymphomas in children or solid tumors in adults; • endocrine abnormalities such as growth impairment, gonadal dysfunction, and insulin resistance, and • radiation sensitivity. Variant A-T has a less progressive disease course and may present in childhood to adulthood; most individuals have first manifestations by age 10 years. Immunodeficiency, respiratory infections, and pulmonary disease are typically absent.		

Syndrome Name	Clinical Features	Cause	Inheritance
Dentatorubral-pallidoluysian atrophy (DRPLA)[18,28,29]	Age of onset: ranges from one year of age to 72 years of age; the mean age of onset is 31.5 years of age. Signs and symptoms of the juvenile onset form (under ~age 20 years) include: • progressive intellectual deterioration; • behavior changes; ◦ ataxia; ◦ chorea; ◦ myoclonus, and ◦ seizures. Signs and symptoms of the juvenile onset form (over ~age 20 years) include: • ataxia; • choreoathetosis; • dementia, and • psychiatric disturbance.	Monoallelic expansion of a CAG trinucleotide repeat in the ATN1 gene.	AD

Syndrome Name	Clinical Features	Cause	Inheritance
Fragile X-associated tremor/ ataxia syndrome (FXTAS)**[19]	Age of onset: typically, older than 50 years. Signs and symptoms of FXTAS include: • progressive cerebellar ataxia; • intention tremor; • psychiatric disturbances; • short term memory loss; • executive function deficits; • cognitive decline; • dementia; • parkinsonism; • autonomic dysfunction, and • neuropathy in lower extremities.	Monoallelic expansion of a CGG trinucleotide repeat in the premutation range (55-200 CGG repeats) in the FMR1 gene.	X-linked

Syndrome Name	Clinical Features	Cause	Inheritance
Friedreich ataxia (FRDA)[17,30]	Age of onset for typical FRDA: typically, before age 25 years with the mean age of onset between 10 and 15 years. Signs and symptoms of typical FRDA include: • progressive ataxia of the limbs and gait; • dysarthria; • dysphagia; • absent lower limb reflexes; • peripheral motor and sensory neuropathy; • spasticity; • autonomic disturbance; • abnormal eye movements; • optic atrophy; • muscle weakness; • cardiomyopathy; • diabetes mellitus; • scoliosis; • pes cavus, and • sensorineural hearing loss. Approximately 25% of affected individuals have an atypical form that includes late-onset	Most often due to biallelic expansions of a GAA trinucleotide repeat in the FXN gene. Approximately 4% of affected individuals have a trinucleotide repeat expansion in one allele and a sequence variant or large deletion in the other allele.	AR

Syndrome Name	Clinical Features	Cause	Inheritance
	FRDA, very-late onset FRDA, and FRDA with retained reflexes.		

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Syndrome Name	Clinical Features	Cause	Inheritance
Spinocerebellar ataxia (SCA)[3-15] The most common subtypes are 1, 2, 3, 6, and 7.***	Age of onset: typically, adult onset. Common signs and symptoms for SCAs include progressive cerebellar ataxia, dysarthia, ophthalmologic involvement (depending on the subtype of SCA, this may include nystagmus, slow saccadic eye movements, ophthalmoparesis, dysconjugate eye movements, diplopia, and lid retraction). Subtype-specific features include: SCA1: deterioration of bulbar functions, pyramidal signs, cognitive dysfunction, and peripheral neuropathy. SCA2: peripheral neuropathy, decreased deep tendon reflexes, and dementia. SCA3: vestibular dysfunction, pyramidal and extrapyramidal	SCA1: Monoallelic expansion of a CAG trinucleotide repeat in the ATNX1 gene. SCA2: Monoallelic expansion of a CAG trinucleotide repeat in the ATNX2 gene. SCA3: Monoallelic expansion of a CAG trinucleotide repeat in the ATNX3 gene. SCA6: Monoallelic expansion of a CAG trinucleotide repeat in the CACNA1A gene. SCA7: Monoallelic expansion of a CAG trinucleotide repeat in the ATNX7 gene.	AD

Syndrome Name	Clinical Features	Cause	Inheritance
	signs, amyotrophy, fasciculations, and sensory loss. SCA6: sometimes episodic ataxia and very slow progression. SCA7: Onset may be infantile, early-childhood, or adult. • Infantile or early-childhood onset: Failure to thrive, loss of motor milestones, multiorgan failure, rapid deterioration, and early death. • Adult onset: progressive cerebellar ataxia, dysarthria, dysphagia, dysmetria, dysdiadochokinesia, cone-rod and retinal dystrophy with progressive central visual loss resulting in blindness.		

AD: autosomal dominant inheritance; **AR**: autosomal recessive inheritance; **XL**: X-linked inheritance

*If testing of this gene is requested for hereditary cancer risk assessment due to a monoallelic mutation, please refer to the guideline, *Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes,* or *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

**For information on fragile X-associated tremor/ataxia syndrome testing, please refer to the guideline *FMR1-Related Disorders (Fragile X) Genetic Testing*, as this testing is not addressed here.

***SCAs are due to mutations in numerous genes. This table in not all inclusive and includes information on the most common subtypes of SCAs.

Cause

Pathogenic mutations in one of numerous genes cause hereditary ataxias [1-19] Several of the ataxias are caused by nucleotide repeat expansions. Testing for these conditions is performed by expansion analysis to identify the number of repeats. Anticipation is observed for some hereditary ataxias due to nucleotide repeat expansion. This means that as the disease passes through generations, the severity can increase and the age of onset can decrease. Other hereditary ataxias are due to single nucleotide substitutions or small deletions and duplications. Next generation sequencing is used to identify these pathogenic mutations.[1-19]

Inheritance

Hereditary ataxias may be inherited in an autosomal dominant (AD), autosomal recessive (AR), or X-linked (XL) manner, depending on the gene involved.[1-19]

Diagnosis

The diagnosis and classification of a hereditary ataxia may include a combination of clinical assessment, family history, laboratory testing, and physical examination in addition to specialized testing, such as molecular diagnostics.[1] Molecular genetic testing can be used to establish a specific diagnosis. In the absence of a family history, it can be difficult to differentiate the type or subtype of hereditary ataxia based on clinical features.[1] One study found that in approximately 13% of apparently sporadic ataxias, a causative genetic change was identified.[25]

Acquired causes of ataxia — including alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, and tumors — should be ruled out.[1] Timely genetic testing may help establish a diagnosis in the individual and guide appropriate management. Genetic testing can allow not only for diagnostic testing but also presymptomatic testing and prenatal testing.[1]

Management

Individuals with a hereditary ataxia are best cared for by a multidisciplinary team. Care is largely supportive and may include speech therapy, occupational therapy, physical therapy, and the use of mobility aids and other assistive devices.[1-19,26] Some pharmacologic treatments may be effective in decreasing the presence of associated

symptoms. Certain hereditary ataxias may require disease specific interventions (e.g. immunodeficiency and increased risk for malignancy seen with ataxia-telangiectasia).[1,16]

Survival

The survival range of the hereditary ataxias varies across the multiple conditions included in this group. Specific symptoms and a genetically determined diagnosis can assist with determining predicted survival and prognosis.[1]

Test Information

Testing for hereditary ataxias may include known familial mutation analysis, trinucleotide repeat testing, next generation sequencing, deletion/duplication analysis and/or multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Trinucleotide Repeat Testing

Repeat expansion genetic testing allows for the determination of the size of a repeated DNA sequence. This testing may involve more than one test methodology. Smaller repeat expansions are typically identified using certain types of polymerase chain reaction (PCR), while larger expansions may require Southern blot. More comprehensive repeat expansion testing that utilizes next generation sequencing and exome sequencing methods is under development.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

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Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and Evidence

American College of Medical Genetics and Genomics

An overview published by the American College of Medical Genetics (ACMG, 2013) stated the following regarding testing for hereditary ataxias:[2]

"Establishing the diagnosis of hereditary ataxia requires:

- Detection on neurological examination of typical clinical signs including poorly coordinated gait and finger/hand movements, dysarthria (incoordination of speech), and eye movement abnormalities such as nystagmus, abnormal saccade movements, and ophthalmoplegia.
- Exclusion of nongenetic causes of ataxia (see Differential Diagnosis below).
- Documentation of the hereditary nature of the disease by finding a positive family history of ataxia, identifying an ataxia-causing mutation, or recognizing a clinical phenotype characteristic of a genetic form of ataxia."

"Differential diagnosis of hereditary ataxia includes acquired, nongenetic causes of ataxia, such as alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, primary or metastatic tumors, and paraneoplastic diseases associated with occult carcinoma of the ovary, breast, or lung, and the idiopathic degenerative disease multiple system atrophy (spinal muscular atrophy). The possibility of an acquired cause of ataxia needs to be considered in each individual with ataxia because a specific treatment may be available."

"Testing strategy when the family history suggests autosomal recessive inheritance:

- A family history in which only sibs are affected and/or when the parents are consanguineous suggests autosomal recessive inheritance. Because of their frequency and/or treatment potential, FRDA, A-T, AOA1, AOA2, AVED, and metabolic or lipid storage disorders such as Refsum disease and mitochondrial diseases should be considered."

"Testing simplex cases. A simplex case is a single occurrence of a disorder in a family, sometimes incorrectly referred to as a 'sporadic' case.

- If no acquired cause of the ataxia is identified, the probability is ~13% that the affected individual has SCA1, SCA2, SCA3, SCA6, SCA8, SCA17, or FRDA, and mutations in rare ataxia genes are even less common.
- Other possibilities to consider are a de novo mutation in a different autosomal dominant ataxia, decreased penetrance, alternative paternity, or a single occurrence of an autosomal recessive or X-linked disorder in a family such as fragile X-associated tremor/ataxia syndrome.
- Although the probability of a positive result from molecular genetic testing is low in an individual with ataxia who has no family history of ataxia, such testing is usually justified to establish a specific diagnosis for the individual's medical evaluation and for genetic counseling.
- Always consider a possible nongenetic cause such as multiple system atrophy, cerebellar type in simplex cases."

European Federation of Neurological Sciences

The European Federation of Neurological Sciences (EFNS, 2014) stated the following regarding testing for hereditary ataxias:[31]

- “In the case of a family history that is compatible with an autosomal dominant cerebellar ataxia, screening for SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17 is recommended (Level B). In Asian patients, DRPLA should also be tested for.”
- “If mutation analysis is negative, we recommend contact with or referral to a specialized clinic for reviewing the phenotype and further genetic testing (good practice point).”
- “In the case of sporadic ataxia and independent from onset age, we recommend routine testing for SCA1, SCA2, SCA3, SCA6, and DRPLA (in Asian patients) (level B), the step one panel of the recessive ataxia workup, i.e. mutation analysis of the FRDA gene (level B), and biochemical testing that includes cholestanol, vitamin E, cholesterol, albumin, CK, and alpha-fetoprotein.”

Selected Relevant Publications

Peer-reviewed publications stated that diagnostic evaluations for ataxia may include assessments for acquired, other nongenetic, and genetic etiologies. [2,26] Establishing the diagnosis of a hereditary ataxia may include demonstration of typical clinical signs

on neurological examination and exclusion of acquired or other nongenetic causes. Additionally, a positive family history, documentation of a hereditary ataxia disease causing mutation, and/or the presence of a characteristic clinical phenotype of a specific hereditary ataxia may solidify the diagnosis.[26]

The results of additional evaluations, such as brain imaging, may increase the suspicion of a hereditary etiology. These additional studies may indicate that an ataxia is slowly progressive and long standing which may signify early onset.[25] Furthermore, findings on MR spectroscopy may indicate that a hereditary etiology is more likely compared to an immune-mediated ataxia.[25]

The likelihood of a hereditary etiology is higher in those with early age of onset (81%) compared to late onset (55%) idiopathic ataxia.[25] The presence of other clinical features also increases the likelihood of detecting a mutation.[25] In those with a family history consistent with autosomal dominant inheritance, a mutation was detected in 50-60% with testing for SCA1, 2, 3, 6, 7, 8, 10, 12, 17 and dentatorubral-pallidoluysian atrophy (DRPLA).[2] In a simplex case with no known acquired cause, according to one study, the likelihood an individual has SCA1, 2, 3, 6, 8, 17, or Friedreich ataxia (FRDA) is approximately 13% and the likelihood of a mutation in a different hereditary ataxia gene is more rare.[2] In another study utilizing targeted exome analysis of 441 genes in individuals with ataxia of unknown etiology, a positive result was detected in 52% of individuals. Forty percent of the positive cases were due to mutations in SPG7, SYNE1, ADCK3, CACNA1A, ATP1A3, and SPTBN2.[32] Even in those with an unremarkable family history, genetic testing may aid in their medical evaluation and in genetic counseling.[2]

It was suggested that genetic testing for progressive ataxias should include evaluation of the genes for FRDA, SCA 1, 2, 3, 6, 7 (12, 17) and fragile X-associated tremor/ataxia syndrome.[26] Testing may proceed in a sequential fashion. For those with a family history suggestive of autosomal dominant inheritance, first round testing for the most common hereditary ataxias (SCA1, SCA2, SCA3, SCA6, and SCA7) may be completed followed by testing for less common hereditary etiologies, which may be guided by ethnic background and/or specific clinical features.[2] In those with a family history suggestive of autosomal recessive inheritance, the following may be tested due to "frequency and/or treatment potential": FRDA, ataxia telangiectasia, ataxia with oculomotor apraxia type 1, ataxia with oculomotor apraxia type 2, ataxia with vitamin E deficiency, and metabolic or lipid storage disorders.[2] Single-gene testing may be pursued if the clinical examination is consistent with a specific diagnosis or if a specific type is known in the family.[2]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for hereditary ataxia multigene panel testing will ensure that testing will be available to those members most likely to benefit from a genetic

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diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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Autism, Intellectual Disability, and Developmental Delay Genetic Testing

MOL.TS.269.A
v1.0.2026

Introduction

Autism, intellectual disability, and developmental delay genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures covered by this guideline	Procedure codes
AFF2 gene analysis; evaluation to detect abnormal (eg, expanded) alleles	81171
AFF2 gene analysis; characterization of alleles (eg, expanded size and methylation status)	81172
Autism Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479

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Procedures covered by this guideline	Procedure codes
Autism Known Familial Mutation Analysis	81403
Developmental Delay Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Developmental Delay Known Familial Mutation Analysis	81403
Intellectual Disability Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Intellectual Disability Known Familial Mutation Analysis	81403
X-linked Intellectual Disability Duplication/ Deletion Analysis Panel	81471

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Procedures covered by this guideline	Procedure codes
X-linked Intellectual Disability Sequence Analysis Panel	81470

Criteria

Introduction

Requests for Autism Spectrum Disorder (ASD), Intellectual Disability (ID), and Developmental Delay testing are reviewed using the following clinical criteria.

Known Familial Mutation Testing

- Genetic counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for the known familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Known family mutation in a causative gene in 1st, 2nd, or 3rd degree biological relative, OR
- Prenatal Testing for At-Risk Pregnancies:
  - Known familial disease-causing mutation identified in both biological parents (if recessive), or a single biological parent or an affected sibling of the pregnancy (if dominant), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Autism, Intellectual Disability and Developmental Delay Single Gene Diagnostic Tests (Sequencing and Deletion/Duplication)

- The member has a formal diagnosis of ASD/autism, intellectual disability, and/or developmental delay as made by an appropriate health care professional, AND
- The member has a condition that will benefit from information provided by the requested gene testing based on the following:
  - The member displays at least one clinical feature (in addition to autism, intellectual disability, and/or developmental delay) of the suspected condition for which testing is being requested, AND
    - The member's medical management would be significantly altered by the genetic diagnosis, or

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        - A particular treatment is being considered for the member that requires a genetic diagnosis, OR
    - The member meets all criteria in a test-specific guideline, if available (see the Table below for a list of genes, associated conditions, and applicable guidelines), AND
- The member does not have a known underlying cause for their symptoms (e.g. known genetic condition), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Autism, Intellectual Disability, and Developmental Delay Multi-Gene Panels

X-Linked Intellectual Disability Panels

Targeted panels consisting solely of genes associated with X-linked intellectual disability (XLID) are medically necessary when all of the following criteria are met:

- Individual assigned male at birth, AND
- The member has a formal diagnosis of ASD/autism, intellectual disability, and/or developmental delay as made by an appropriate health care professional, AND
- The member has a family history of ASD/autism, intellectual disability, and/or developmental delay of unknown etiology consistent with X-linked inheritance, AND
    - The member's medical management would be significantly altered by the genetic diagnosis, or
    - A particular treatment is being considered for the member that requires a genetic diagnosis, AND
- The member does not have a known underlying cause for their symptoms (e.g. known genetic condition), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Comprehensive Autism, Intellectual Disability, and/or Developmental Delay Panels

Multi-gene panels for individuals with a primary medical diagnosis of ASD, ID, and/or GDD (global developmental delay) have not demonstrated a high diagnostic yield and are not likely to lead to a change in treatment. Comprehensive ASD and/or ID/GDD panels, regardless of panel size, are experimental, investigational, or unproven (E/I/U).

Separate clinical guidelines may apply to other panel testing and exome sequencing for members who have findings in addition to ASD/ID/GDD, such as seizures or multiple congenital anomalies (see Other Considerations and Table: *Common neurodevelopmental disorder genes, associated conditions, and applicable guidelines*).

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Other Considerations

- ASD, ID, and/or GDD testing may be performed as part of a chromosomal microarray, exome sequence, or genome sequence. For information on these tests, please refer to the guidelines *Chromosomal Microarray Testing For Developmental Disorders (Prenatal and Postnatal)*, *Exome Sequencing*, or *Genome Sequencing*, as these tests are not addressed here.
- Genetic testing is only medically necessary once per lifetime. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.
- This guideline may not apply to genetic testing for indications that are addressed in test-specific guidelines. Please see the test-specific list of guidelines for a complete list of test-specific panel guidelines.

Table: Common neurodevelopmental disorder genes, associated conditions, and applicable guidelines

This list is not all-inclusive.

Gene	CPT	Condition	Applicable guideline name	Applicable guideline number
15q11.2	81331	Prader-Willi Syndrome, Angelman Syndrome	Prader-Willi Syndrome testing; Angelman Syndrome Testing	MOL.TS.217; MOL.TS.126
AFF2	81171 81172	Fragile X Syndrome 2 (FRAXE)	Autism, Intellectual Disability, and Developmental Delay Genetic Testing	MOL.TS.269
BRAF	81406	Noonan Syndrome, Cardiofaciocutaneous Syndrome	Noonan Spectrum Disorder Genetic Testing	MOL.TS.371
CHD7	81407	CHARGE Syndrome	CHARGE Syndrome and CHD7 Disorder Genetic Testing	MOL.TS.324
FMR1	81243 81244	Fragile X Syndrome	FMR1-Related Disorders (Fragile X) Genetic Testing	MOL.TS.172

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Gene	CPT	Condition	Applicable guideline name	Applicable guideline number
MECP2	81302	Classic Rett Syndrome, Preserved Speech Variant Rett Syndrome, MECP2-Related Epileptic Encephalopathy (males), X-Linked ID	Rett Syndrome Genetic Testing	MOL.TS.224
NF1	81408	Neurofibromatosis 1	Neurofibromatosis Type 1 Genetic Testing	MOL.TS.301
PTEN	81321	PTEN Hamartoma Tumor Syndromes	PTEN Hamartoma Tumor Syndrome Genetic Testing	MOL.TS.223
PTPN11	81406	Noonan Syndrome	Noonan Spectrum Disorder Genetic Testing	MOL.TS.371
UBE3A	81406	Angelman Syndrome	Angelman Syndrome Genetic Testing	MOL.TS.126

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Comprehensive Autism Spectrum Disorder panels, Intellectual Disability/ Developmental Delay panels, and Neurodevelopmental Disorder panels, regardless of how they are billed, are not reimbursable.
- When otherwise reimbursable, the following limitations apply:
  - Any individual gene or multi-gene panel is only reimbursable once per lifetime.

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- When an X-linked intellectual disability panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81470/81471*).
- When use of a panel code is not possible, each billed component procedure will be assessed independently.
- In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What are Autism Spectrum Disorders, Intellectual Disability, and Global Developmental Delay?

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in communication and social interaction, as well as restricted, repetitive patterns of behavior, interests, or activities. Intellectual disability (ID, formerly referred to as mental retardation) is "a disability characterized by significant limitations in both intellectual functioning and in adaptive behavior as expressed in conceptual, social and practical adaptive skills."[1] Global developmental delay (GDD) categorizes younger children (typically less than 5 years of age) who have significant delay (characterized as performance two standard deviations or more below the mean on age-appropriate, standardized, normal-referenced testing) in two or more developmental domains, including gross or fine motor, speech and language, cognitive, social and personal, and activities of daily living.[2]

Incidence

ASD affects approximately 1/54 children.[3] ID affects 1-3% of the population worldwide.[2] The incidence of GDD is estimated to be comparable to ID.[1,4] All three neurodevelopmental disorders are more common in males.[2,4-7]

Symptoms

ASD was previously divided into categories that included autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder- not otherwise specified (PDD-NOS). With current diagnostic criteria, these categories were subsumed under the diagnosis of ASD.

Symptom onset is in early childhood (typically before 3 years of age).[6,7] ASD is often accompanied by intellectual disability, behavioral difficulties, and/or sensory abnormalities.

ID and GDD may present in infancy or early childhood. ID is assessed in three domains: intelligence (IQ), adaptive behavior, and systems of supports the individual requires.[1] Children with GDD have significant delay in two or more developmental domains. Young children with GDD may later be diagnosed with ID and/or ASD.[2,4] There are both syndromic and non-syndromic forms of inherited ASD, ID, and GDD. The constellation of associated findings is highly dependent on the underlying etiology. Clinical information (e.g. presence of specific congenital malformations, dysmorphic features, and other symptoms) may be used in some cases to help narrow down the suspected cause. In these cases, it may be possible to identify a narrow subset of genes that may be responsible for an individual's neurodevelopmental concerns.

Cause

ASD, ID, and GDD can develop secondary to head injury, birth complication, endocrine disorder (e.g., hypothyroidism), toxic exposure (e.g., fetal alcohol syndrome), inborn error of metabolism (e.g., phenylketonuria), and central nervous system infection.[2,6,7]

There are also many known genetic conditions that are associated with an increased risk for ASD, ID, and GDD. A thorough clinical genetics evaluation is estimated to result in an identified cause in 30–40% of affected individuals with ASD.[6] Chromosome microarray analysis was previously thought to have the highest diagnostic yield of any single test for these disorders, with an estimated detection rate of at least 10-20% for ASD, ID, and GDD (often grouped together as neurodevelopmental disorders, or NDDs).[4,6,8,9] Whole exome and genome sequencing have more recently been demonstrated to have diagnostic yields of up to 35% for those with NDDs and potentially higher for those with other comorbidities such as epilepsy or congenital anomalies.[9]

Inheritance

Inheritance patterns differ between the various syndromes associated with ASD, ID, GDD. Inherited forms of these disorders can show autosomal dominant, autosomal recessive, X-linked, or mitochondrial patterns of inheritance.

Diagnosis

ASD, ID, and GDD are diagnosed through the evaluation of an individual's development and behaviors by an appropriate specialist (such as neurodevelopmental pediatrician or developmental-behavioral pediatrician). Medical tests such as hearing screening, vision screening, and neurological evaluations may also be performed.[2,5] A diagnosis of ASD and/or ID is often difficult to establish in infants and very young children, as the standardized methods used for diagnosis are less reliable in children under the

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age of 5 years; the term "global developmental delay" is thus used to categorize these individuals.[2] Identifying an underlying genetic etiology for an individual's NDD cannot provide a diagnosis of ASD versus ID versus a specific learning disability.

Management

Management for ASD includes behavioral interventions such as applied behavioral analysis (ABA) therapy, structured educational interventions, and in some cases, pharmacotherapy.[6,7] NDDs are also managed with therapies and educational intervention plans tailored to the individual's needs. In a limited number of cases (mostly metabolic disorders), knowing the genetic mutation that is responsible for a neurodevelopmental disorder can help to guide management. Identifying a genetic syndrome may also alert the healthcare team to potential comorbidities for which evaluation and surveillance may be needed.

Survival

While life expectancy in autism may be reported as reduced, this is often secondary to accidents such as drowning.[3] With the exception of individuals with multiple disabilities (such as Down syndrome), the life expectancy of individuals with intellectual disability is now similar to that of the general population.[10] Comorbid conditions can also affect survival in these disorders.

Test information

Introduction

Testing for ASD, ID, and GDD may include known familial mutation analysis, single gene sequence analysis, single gene deletion/duplication analysis, or multi-gene panels of various sizes.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA

simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

ASD, ID and GDD multi-gene panels include a wide variety of genes: from a few to hundreds or even thousands. These disorders may also be grouped together in broad "neurodevelopmental" panels. Multi-gene panels may also include genes believed to be associated with disease (e.g. "susceptibility" genes), but with a lower impact on risk than recognized syndromes. Results for such genes are of less clear value because there often are not clear management recommendations for mutation-positive individuals.

Guidelines and evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to testing for ASD, ID, and GDD.

American Academy of Child and Adolescent Psychiatry

The American Academy of Child and Adolescent Psychiatry (AACAP, 2014) stated that as a clinical standard, clinicians should coordinate an appropriate multidisciplinary assessment of children with ASD to include:[5]

- "All children with ASD should have a medical assessment, which typically includes physical examination, a hearing screen, a Wood's lamp examination for signs of tuberous sclerosis, and genetic testing, which may include G-banded karyotype, fragile X testing, or chromosomal microarray."
- "Unusual features in the child (e.g., history of regression, dysmorphology, staring spells, family history) should prompt additional evaluations… Genetic or neurologic consultation, neuroimaging, EEG, and additional laboratory tests should be obtained when relevant, based on examination or history (e.g., testing for the MECP2 gene in cases of possible Rett's disorder)."

American Academy of Child and Adolescent Psychiatry

The American Academy of Child and Adolescent Psychiatry (AACAP, 2020) recommended a diagnostic genetic testing algorithm for youth with developmental disorders (autism spectrum disorder, intellectual disability, or global developmental delay):[11]

- If there is a recognized genetic syndrome, targeted testing is recommended first. This could include a karyotype if Down syndrome is suspected.
- In the absence of a recognized syndrome, or if testing is unrevealing, then chromosomal microarray and Fragile X testing are recommended as the next step.
- "Microarray is currently the genetic test with the highest diagnostic yield in children with unexplained ID/IDD, with an abnormal result reported in 7.8% of subjects with GDD/ID/IDD and in 10.6% of those with syndromic features, on average."

American Academy of Pediatrics

The American Academy of Pediatrics (AAP, 2014, Reaffirmed 2019) recommended a clinical genetics evaluation for all individuals with ID, regardless of degree of severity.[4]

- "If a specific diagnosis is suspected, arrange for the appropriate diagnostic studies to confirm including single-gene tests or chromosomal microarray test."
- "If diagnosis is unknown and no clinical diagnosis is strongly suspected, begin the stepwise evaluation process:
  - Chromosomal microarray should be performed in all.
  - Specific metabolic testing should be considered and should include serum total homocysteine, acyl-carnitine profile, amino acids; and urine organic acids, glycosaminoglycans, oligosaccharides, purines, pyrimidines, GAA/creatine metabolites.
  - Fragile X genetic testing should be performed in all."
- "If no diagnosis is established:
  - Male gender and family history suggestive X-linkage, complete XLID panel that contains genes causal of nonsyndromic XLID and complete high-density X-CMA. Consider X-inactivation skewing in the mother of the proband.

- Female gender: complete MECP2 deletion, duplication, and sequencing study."

The American Academy of Pediatrics (AAP, 2020) recommended the following for the evaluation of children with ASD:[7]

- "Families should be offered genetic evaluation, including chromosomal microarray and fragile X testing, with consideration of other cytogenetic and molecular testing, as indicated. Consultation with a pediatric geneticist may be warranted."

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2013) recommended a genetic evaluation, with a tiered approach, for all individuals with diagnosed ASD:[6]

- "Several well-described single-gene disorders have been reported for which ASDs can be seen as part of the expanded phenotype associated with changes in that gene...For a selected few of such conditions, there is adequate evidence to suggest testing for changes in these genes in patients with ASDs with no other identifiable etiology. These would include fragile X syndrome, methyl-CPG-binding protein 2 (MECP2) spectrum disorders, and phosphatase and tensin homolog (PTEN)–related conditions."
- First tier:
  - Three-generation family history with pedigree analysis.
  - Initial evaluation to identify known syndromes or associated conditions:
    - Examination with special attention to dysmorphic features
    - If specific syndromic diagnosis is suspected, proceed with targeted testing
    - If appropriate clinical indicators present, perform metabolic and/ or mitochondrial testing (alternatively, consider a referral to a metabolic specialist)
  - Chromosomal microarray: oligonucleotide array-comparative genomic hybridization or single-nucleotide polymorphism array.
  - DNA testing for fragile X (to be performed routinely for males and in females if indicators are present - e.g., family history and phenotype).
- Second tier:
  - MECP2 sequencing to be performed for all females with ASDs
  - MECP2 duplication testing in males, if phenotype is suggestive
  - PTEN testing only if the head circumference is >2.5 SD above the mean
  - Brain magnetic resonance imaging only in the presence of specific indicators (e.g., microcephaly, regression, seizures, and history of stupor/coma)
- “When a family history is consistent with X-linked inheritance and the patient has cognitive impairments, an “X-linked intellectual disability gene panel” is a consideration. Several X-linked genes are known to present as either ASD or intellectual disability. Another disorder to consider is the X-linked creatine transporter defect (SCL6A8 gene). Patients with this condition have been reported with neurobehavioral changes in the ASD spectrum, along with hypotonia and seizures.

Currently, no studies have been reported on the diagnostic yield of such panels in persons with ASDs."
- The following are genetic tests “that have been suggested in the etiologic evaluation of ASDs, but currently with insufficient evidence to recommend routine testing:” CDKL5 testing, NSD1 testing, chromosome 15 methylation/UBE3A gene testing, methylation/epigenetic testing, mitochondrial gene sequencing/oligoarray, and metabolic studies.

The American College of Medical Genetics and Genomics (ACMG, 2021) developed an evidence-based clinical practice guideline for the use of exome and genome sequencing (ES/GS) in the care of children with one or more congenital anomalies (CA) with onset prior to age one year, or development delay (DD) or ID with onset prior to 18 years.[12]

- ES/GS is strongly recommended as a first- or second-tier test for children with CA/DD/ID.
- "Consistent with existing guidelines/recommendations/position statements, patients with clinical presentations highly suggestive of a specific genetic diagnosis should undergo targeted testing first. This may include patients with suspicion of a chromosomal disorder, known family history of a disorder, or strong clinical suspicion of a diagnosis in which sequencing may not be diagnostic, such as Prader–Willi/Angelman related methylation abnormality or fragile X syndrome."
- "Isolated autism without ID or congenital malformation is formally out of scope for this recommendation."

The National Institute for Health and Clinical Excellence

The National Institute for Health and Clinical Excellence (NICE, 2017) stated the following regarding medical investigations following diagnosis of an ASD: “Do not routinely perform any medical investigations as part of an autism diagnostic assessment, but consider the following in individual circumstances and based on physical examination, clinical judgment, and the child or young person's profile:[13]

- Genetic tests, as recommended by your regional genetics center, if there are specific dysmorphic features, congenital anomalies and/or evidence of intellectual disability.
- Electroencephalography if there is suspicion of epilepsy."

Selected Relevant Publications

A 2017 peer reviewed article assessed the clinical utility of a targeted gene panel (101-237 genes) in 100 well-phenotyped individuals with ASD, and found:[14]

- 12% diagnostic yield for chromosomal microarray
- 0% diagnostic yield for targeted gene panel (11 pathogenic variants identified; all assessed as non-causative by clinicians based on clinical evaluation of the individuals, allele frequency in the study population, or conflicting data in the literature on causation)

- If the individual does not fit a syndromic diagnosis, the authors suggested ACMG recommended tests followed by whole exome sequencing in individuals with ASD plus
  - Severe disability
  - Congenital abnormalities
  - Comorbid conditions (eg: seizure disorder)
  - Abnormal head size

A 2019 meta-analysis published the diagnostic yield of exome sequencing compared to chromosomal microarray for neurodevelopmental disorder (NDD, defined as GDD, ID, and/or ASD) and found: [8]

- The yield of exome sequencing overall was 36%, markedly greater than previous studies of chromosomal microarray (15-20%).
- The diagnostic yield in individuals with isolated NDD was 31% and 53% for individuals with NDD plus associated conditions (such as Rett-like features).

A 2021 systematic review published results of clinical sequencing studies utilizing targeted gene panel sequencing and exome sequencing in individuals with epilepsy, ASD, or ID.[15] Of the 103 studies included, 73 utilized targeted gene panels and 36 used exome sequencing.

- The overall diagnostic yield was 23.7% (17.1% for ASD, 24% for epilepsy, and 28.2% for ID).
- Although not statistically significant, the diagnostic yield for exome sequencing was higher than for panel sequencing (27.2% vs 22.6%, P = .071).

A 2022 peer-reviewed article assessed different genetic testing strategies for individuals with ID and/or NDD.[9] Three cohorts of individuals underwent testing. The three strategies included chromosomal microarray with or without FMR1 analysis (421 individuals), genome sequencing as a secondary testing (129 individuals), and genome sequencing first (100 individuals).

- The diagnostic yield was 11% for individuals who underwent chromosomal microarray / FMR1 analysis, 26% for individuals who underwent genome sequencing as a secondary test, and 35% for individuals who underwent genome sequencing as a first test.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for autism, intellectual disability, and developmental delay genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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References

Introduction

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BRCA Analysis

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Germline BRCA analysis is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
BRCA1 full duplication/deletion analysis	81166
BRCA1 full sequencing	81165
BRCA1 known familial mutation analysis	81215
BRCA2 full duplication/deletion analysis	81167
BRCA2 full sequencing	81216
BRCA2 known familial mutation analysis	81217
BRCA1/2 full duplication/deletion analysis	81164
BRCA1/2 full sequence analysis	81163
BRCA1/2 full sequencing and duplication/ deletion analysis (combined)	81162
BRCA1 and BRCA2 Ashkenazi Jewish founder mutation analysis	81212

Criteria

Requests for BRCA analysis are reviewed using the following criteria.

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Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, and
  - Known family mutation in BRCA1/2 identified in 1st, 2nd, or 3rd degree relative(s), AND
- Age 18 years or older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Ashkenazi Jewish Founder Mutation Testing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous full sequence testing, and
  - No previous deletion/duplication analysis, and
  - No previous Ashkenazi founder mutation testing, AND
- Age 18 years or older, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Ashkenazi Jewish descent, and
    - Epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosis at any age, or
    - Male or female breast cancer diagnosis at any age, or
    - Personal history of exocrine pancreatic cancer, or
    - Personal history of a confirmed diagnosis of prostate cancer at any age, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Ashkenazi Jewish descent, and
  - A first or second degree relative who is Ashkenazi Jewish and meets at least one of the following:
    - Epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosis at any age, or
    - Male or female breast cancer diagnosis at any age, or
    - Exocrine pancreatic cancer, or
    - A confirmed diagnosis of prostate cancer at any age, and
    - The affected relative is deceased, unable, or unwilling to be tested[†], or

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        - Close blood relative (1st, 2nd, or 3rd degree) with a known Ashkenazi Jewish founder mutation in BRCA 1/2 gene, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

†Testing of unaffected individuals should only be considered when an affected family member is unavailable for testing due to the significant limitations in interpreting a negative result.

Full Sequence Analysis

- Genetic Counseling:
    - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
    - No previous full sequencing of BRCA1/2, and
    - No mutation identified by alternate methods of BRCA analysis, if previously performed, and
    - If there is a known familial mutation in the family, that mutation does not sufficiently explain the indication for testing, AND
- Age 18 years or older, AND
- Diagnostic Testing for Symptomatic Individuals:
    - Member meets "Diagnostic Testing for Symptomatic Individuals" criteria for AJ Founder mutation testing and had no previous founder mutation testing, and/or
    - Female with breast cancer diagnosis 50 years of age or younger, and/or
    - Diagnosed with two or more primary breast cancers at any age, and/or
    - Diagnosed at any age with triple negative breast cancer (i.e., estrogen receptor negative (ER-), progesterone receptor negative (PR-), and human epidermal growth factor receptor negative (HER2-) breast cancer), and/or
    - Male with breast cancer at any age, and/or
    - Epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosis at any age, and/or
    - Prostate cancer at any age with metastatic (radiographic evidence of or biopsy-proven disease), intraductal/cribriform histology, high-risk, or very-high-risk group per the National Comprehensive Cancer Network (NCCN), and/or
    - Exocrine pancreatic cancer, OR
- Personal & Family History Combination
    - Initial breast cancer diagnosis at any age and one or more of the following:
        - Breast cancer in at least 1 close blood relative (first-, second-, or third- degree) occurring at 50 years of age or younger, and/or
        - Epithelial ovarian, fallopian tube, or primary peritoneal cancer in at least 1 close blood relative (first-, second-, or third- degree) at any age, and/or

        - Male close blood relative (first- or second-degree) with breast cancer, and/or
        - Metastatic (radiographic evidence of or biopsy proven disease) or intraductal/ cribriform histology, high- or very-high risk prostate cancer per the NCCN in at least 1 close blood relative (first-, second-, or third- degree) at any age, and/or
        - Pancreatic cancer in at least 1 close blood relative (first-, second-, or third-degree), and/or
        - A close blood relative (first- or second-degree) with a triple negative breast cancer (ER-, PR-, HER2-) at any age, and/or
        - At least two close blood relatives (on the same side of the family) with either breast cancer or a confirmed diagnosis of prostate cancer at any age, and/or
    - Personal history of a confirmed diagnosis of prostate cancer at any age with ≥1 close blood relatives (on the same side of the family) with ovarian cancer at any age, pancreatic cancer at any age, metastatic (radiographic evidence of or biopsy proven disease) or intraductal/cribriform prostate cancer at any age, high- or very-high risk group prostate cancer per the NCCN at any age, breast cancer occurring at 50 years of age or younger, triple-negative breast cancer at any age, or male breast cancer, and/or
    - Personal history of a confirmed diagnosis of prostate cancer at any age with two or more close blood relatives (on the same side of the family) with breast or prostate cancer (any grade) at any age, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals
    - The member has a first-degree relative who meets any of the "Diagnostic Testing for Symptomatic Individuals" or "Personal & Family History Combination" criteria above, or
    - The member has a second-degree relative who meets any of the "Diagnostic Testing for Symptomatic Individuals" or "Personal & Family History Combination" criteria above, excluding those who meet solely based on one of the following:
        - A single affected relative with pancreatic cancer, or
        - A single affected relative with prostate cancer (metastatic, intraductal/cribriform, or high- or very-high risk group per the NCCN), or
        - A single affected relative who meets AJ Founder Mutation "Diagnostic Testing for Symptomatic Individuals" criteria, AND
    - Unaffected member is the most informative person to test and an affected family member cannot proceed with testing. If the member is not the most informative person to test, documentation must be provided by the ordering physician's office clearly documenting that it is impossible to test the most informative family member and describing the reason the unaffected member is being tested at this time, OR
- BRCA 1/2 mutation detected by tumor profiling in the absence of a germline mutation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous BRCA deletion/duplication analysis, and
  - Meets criteria for full sequence analysis of BRCA1/2, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

- Family history terminology used in the above criteria is defined as follows:
  - First-degree relatives: parents, siblings, children
  - Second-degree relatives: aunts, uncles, grandparents, grandchildren, nieces, nephews and half-siblings
  - Third-degree relatives: great-grandparents, great-aunts, great-uncles, and first cousins
  - Relatives "on the same side of the family" are defined as individuals who share a common ancestor and are thus related to each other by blood (e.g., a member's maternal grandmother and maternal grandfather are not considered to be on the same side of the family if they are only related by marriage).
- For information on BRCA genetic testing to determine eligibility for targeted treatment (e.g., BRCAnalysis CDx), please refer to the guidelines *Pharmacogenomic Testing for Drug Toxicity and Response* or *Somatic Mutation Testing*, as this testing is not addressed here.
- BRCA1/2 testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:

- If BRCA1/2 deletion/duplication analysis will be performed concurrently with BRCA1/2 gene sequencing, CPT code 81162 is likely most appropriate.

What is hereditary breast and ovarian cancer?

Hereditary breast and ovarian cancer (HBOC) is an inherited form of cancer.

Prevalence

About 1 in 100-200 people in the general population has a BRCA1 or BRCA2 mutation. The prevalence of mutations is higher in people of West African, Norwegian, Dutch, Inuit from Ammassalik (Greenland), or Icelandic ethnicity due to the presence of founder mutations.[1,2]

Ashkenazi Jewish ancestry

About 1 in 40 people of Ashkenazi Jewish ancestry has a BRCA1 or BRCA2 mutation. The majority of the risk in the Ashkenazi Jewish population is associated with three common founder mutations, two of which are in the BRCA1 gene and one in the BRCA2 gene.[1,3,4] These three mutations account for up to 99% of identified mutations in the Ashkenazi Jewish population.[1]

Signs of HBOC

Individuals and/or families with HBOC may have the following histories of cancer or other characteristics:[1,3,5]

- breast cancer at a young age, typically under age 50
- multiple breast primaries in one individual and/or family members (on the same side of the family)
- triple negative breast cancer (ER-, PR-, HER2-)
- ovarian, fallopian tube, or primary peritoneal cancer
- metastatic (radiographic evidence of or biopsy-proven disease), intraductal/cribriform histology, high-risk, or very-high-risk group prostate cancer as defined by NCCN
- male breast cancer
- exocrine pancreatic cancer
- multiple cases of breast and/or ovarian cancer in a family or one individual with breast and ovarian cancer
- a confirmed diagnosis of prostate cancer and a family history of ovarian, breast, prostate, or pancreatic cancer
- previously identified germline BRCA1 or BRCA2 mutation in the family, or
- any of the above with Ashkenazi Jewish ancestry.

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Cancer Risks

People with a BRCA mutation have an increased risk of various types of cancer.[1] These risks vary based on whether the mutation is in the BRCA1 or BRCA2 gene.

Type of cancer	Risk for malignancy with a BRCA1 mutation	Risk for malignancy with a BRCA2 mutation
Breast cancer	55-72% by age 70	45-69%
Ovarian cancer	39-44%	11-17%
Male breast cancer	1-2%	6-8%
Prostate cancer	21% by age 75	27% by age 70
Pancreatic cancer	1-3%	3-5% by age 70
Melanoma	N/A	Elevated

Note:

The risk for breast and ovarian cancer varies among family members and between families.

Cause

Up to 10% of all breast cancer and 15% of all ovarian cancer is associated with an inherited gene mutation, with BRCA1 and BRCA2 accounting for about 50% of pathogenic mutations in hereditary breast cases and 80% of hereditary ovarian cases.[1,2,6]

Inheritance

HBOC due to a mutation in BRCA1 or BRCA2 is an autosomal dominant disorder.[1]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

BRCA2 mutations inherited in an autosomal recessive manner (mutations in both copies of the gene) cause Fanconi Anemia. BRCA1 mutations inherited in an autosomal recessive manner usually end in miscarriage, however, rare reports of individuals with Fanconi Anemia due to biallelic mutations in BRCA1 have been reported. For more information on testing for Fanconi Anemia, please refer to the

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guideline *Inherited Bone Marrow Failure Syndrome (IBMFS) Testing*, as this testing is not addressed here.

Diagnosis

The diagnosis is established by the identification of a pathogenic mutation in a gene associated with HBOC.

Management

Screening and prevention options are available to specifically address the increased risk of these cancers in a person with a BRCA mutation.[1]

Special Considerations

Other inherited cancer syndromes that can include breast cancer are Li-Fraumeni syndrome (TP53), Cowden syndrome (PTEN), Hereditary Diffuse Gastric Cancer (CDH1), and Peutz-Jeghers syndrome (STK11). Additionally, other genes that can increase the risk for breast cancer are ATM, BARD1, CHEK2, NF1, and PALB2.[1,3,7,8,9]

Test information

BRCA testing may include known familial mutation analysis, Ashkenazi Jewish founder mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

This test is appropriate for those who have a known BRCA mutation in the family and are not Ashkenazi Jewish.[3,4]

Ashkenazi Jewish Founder Mutation Testing

Ashkenazi Jewish founder mutation testing includes the three mutations most commonly found in the Ashkenazi Jewish population:

- 185delAG and 5382insC in BRCA1, and
- 6174delT in BRCA2

Testing for these mutations detects up to 99% of mutations in those with Ashkenazi Jewish ancestry.

Founder mutation testing may be appropriate for those with Ashkenazi Jewish ancestry, even with a known familial mutation, since these mutations are common enough that multiple mutations can be found in the same Ashkenazi Jewish individual or family. If the familial mutation is not one of the three Ashkenazi Jewish mutations, the known familial mutation analysis for that mutation should be performed in addition to the founder mutation panel.[1,3]

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2019) issued a statement regarding BRCA1/2 testing in all individuals with breast cancer:[10]

- "With the advances in sequencing technologies and increasing access to and expanding indications for genetic testing, it remains critical to ensure that implementation of testing is based on evidence. Currently, there is insufficient evidence to recommend genetic testing for BRCA1/2 alone or in combination with multi-gene panels for all breast cancer patients."

American Society of Breast Surgeons

The American Society of Breast Surgeons (ASBrS, 2019) published a consensus guideline on genetic testing for hereditary breast cancer. They stated the following:[11]

- "Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling

and make recommendations to their patients regarding genetic testing and arrange testing. When the patient's history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful. Genetic testing is increasingly provided through multi-gene panels. There are a wide variety of panels available, with different genes on different panels. There is a lack of consensus among experts regarding which genes should be tested in different clinical scenarios. There is also variation in the degree of consensus regarding the understanding of risk and appropriate clinical management of mutations in some genes."

- "Genetic testing should be made available to all patients with a personal history of breast cancer. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies."
- "Patients who had genetic testing previously may benefit from updated testing. Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. In particular, a patient who had negative germline BRCA1 and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing. Genetic testing performed prior to 2014 most likely would not have had PALB2 or other potentially relevant genes included and may not have included testing for large genomic rearrangements in BRCA1 or BRCA2."
- "Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines. Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves. When it is not feasible to test the affected relative first, then the unaffected family member should be considered for testing if they are interested, with careful pre-test counseling to explain the limited value of "uninformative negative" results. It is also reasonable to order a multi-gene panel if the family history is incomplete (i.e., a case of adoption, patient is uncertain of exact type of cancer affecting family members, among others) or other cancers are found in the family history, as described above."

American Society of Clinical Oncology

A 2025 American Society of Clinical Oncology (ASCO, 2025) guideline update on neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer stated the following:[12]

- "All patients with EOC [epithelial ovarian cancer] should be offered germline and somatic testing for BRCA1 and BRCA2. Germline testing for other ovarian cancer susceptibility genes is recommended."

A 2025 American Society of Clinical Oncology (ASCO, 2025) guideline on germline and somatic genomic testing for metastatic prostate cancer stated the following:[13]

- "Patients with metastatic prostate cancer should undergo both germline and somatic DNA sequencing using panel-based assays. These tests can guide the use of poly(ADP-ribose) polymerase inhibitors, which have a survival benefit in metastatic castration-resistant prostate cancer. In addition, germline testing may have screening implications for additional cancers for patients and cascade testing implications for family members."

American Society of Clinical Oncology and Society of Surgical Oncology

A 2024 American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) joint guideline for germline testing in individuals with breast cancer stated the following:[7]

- "All patients newly diagnosed with breast cancer with stage I-III or de novo stage IV/metastatic disease who are 65 years or younger at diagnosis should be offered BRCA1/2 testing"
- "All patients newly diagnosed with breast cancer with stage I-III or de novo stage IV/ metastatic disease who are older than age 65 should be offered BRCA1/2 testing if:
  - they are candidates for poly(ADP-ribose) polymerase (PARP) inhibitor therapy for early-stage or metastatic disease,
  - they have triple-negative breast cancer,
  - their personal or family history suggests the possibility of a pathogenic variant,
  - they were assigned male sex at birth,
  - they are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations"

  "BRCA1/2 testing should be offered to patients with a second primary cancer either in the contralateral or ipsilateral breast"

American Urological Association and American Society for Radiation Oncology

A 2022 American Urological Association (AUA) and American Society for Radiation Oncology (ASTRO) joint guideline for clinically localized prostate cancer stated the following:[14]

- "Clinicians should perform an assessment of patient and tumor risk factors to guide the decision to offer germline testing that includes mutations known to be associated with aggressive prostate cancer and/or known to have implications for treatment."

- Indications for germline testing for individuals with clinically localized prostate cancer included: a strong personal or family history of related cancers, a known familial mutation, and adverse tumor characteristics. Genes associated with prostate cancer risk included: "ATM, BRCA1, BRCA2, CHEK2, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, TP53."

American Urological Association and Society of Urological Oncology

A 2023 American Urological Association (AUA) and Society of Urological Oncology (SUO) joint guideline for advanced prostate cancer stated the following:[15]

- "In patients with mHSPC [metastatic hormone-sensitive prostate cancer], clinicians should offer germline testing, and consider somatic testing and genetic counseling."
- "In patients with mCRPC [metastatic castrate-resistant prostate cancer], clinicians should offer germline (if not already performed) and somatic genetic testing to identify DNA repair deficiency, MSI status, tumor mutational burden, and other potential mutations that may inform prognosis and familial cancer risk as well as direct potential targeted therapies."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) evidence and consensus-based guidelines addressed test indications for BRCA testing. These guidelines included recommendations related to unaffected individuals with a family history of cancer, those with a known mutation in the family, those with a personal history of breast cancer, exocrine pancreatic cancer, ovarian cancer, a confirmed diagnosis of prostate cancer, and men with breast cancer. They take into consideration age of diagnosis, tumor pathology, degree of relationship, and Ashkenazi Jewish ancestry.[3]

These recommendations are Category 2A, defined as "lower-level evidence" with "uniform NCCN consensus that the intervention is appropriate" and are frequently updated.[3]

Testing unaffected individuals

NCCN stated "[t]he testing of the unaffected individual (or of unaffected family members) is reasonable when no affected family member is available for testing." They cautioned that the significant limitations in interpreting results from unaffected relatives must be discussed.[3]

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC, 2021) guidelines stated: "[f]or families with a known P/LPV, cascade testing refers to the process of counseling and testing at-risk family members. Relatives who do not carry the variation can avoid

unnecessary medical interventions, whereas those who do can pursue surveillance and prevention measures aimed at reducing morbidity and mortality."[8]

U.S. Preventive Services Task Force

The U.S. Preventive Services Task Force (USPSTF, 2019) recommendations addressed women with a personal and/or family history of breast cancer and/or ovarian, tubal, or primary peritoneal cancer. The USPSTF guideline recommended:[16]

- When a woman's personal or family history of cancer is consistent with a BRCA1/2 mutation: "that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (BRCA1/2) gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing." (Evidence grade: B)
- When a woman's personal or family history is not consistent with a BRCA1/2 mutation: "recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful BRCA1/2 gene mutations." (Evidence grade: D)
- "Genetic risk assessment and BRCA1/2 mutation testing is a multistep process that begins with identifying patients with family or personal histories of breast, ovarian, tubal, or peritoneal cancer; family members with known harmful BRCA1/2 mutations; or ancestry associated with harmful BRCA1/2 mutations. Risk for clinically significant BRCA1/2 mutations can be further evaluated with genetic counseling by suitably trained health care clinicians, followed by genetic testing of selected high-risk individuals and post-test counseling about results."
- "The type of mutation analysis required depends on family history. Individuals from families with known mutations or from ancestry groups in which certain mutations are more common (eg, Ashkenazi Jewish founder mutations) can be tested for these specific mutations."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for BRCA analysis will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Breast Cancer Index for Breast Cancer Prognosis

MOL.TS.248.A
v1.0.2026

Breast Cancer Index (BCI) for breast cancer prognosis is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
Breast Cancer Index	81518

Criteria

Requests for Breast Cancer Index (BCI) testing are reviewed using the following criteria.

Criteria

- For prognostic testing for adjuvant chemotherapy decision making
  - No previous gene expression assay on the same tumor when a prognostic result was previously successfully obtained, AND
  - Required Clinical Characteristics at Initial Diagnosis:
    - Primary invasive breast cancer meeting all of the following criteria:
    - Unilateral tumor
      - Tumor size >0.5cm (5mm) in greatest dimension (T1b-T3), and
      - Hormone receptor positive (ER+ or PR+), and
      - Human epidermal growth factor receptor 2 (HER2) negative, AND
  - Individual has no regional lymph node metastasis (pN0) or only micrometastases (pN1mi, malignant cells in regional lymph node(s) not greater than 2.0 mm), and
  - Adjuvant endocrine systemic chemotherapy is a planned treatment option for the individual or results from this Breast Cancer Index test will be used in making adjuvant chemotherapy treatment decision, AND
  - Rendering laboratory is a qualified provider of service per the Health Plan policy.
- For predictive testing for extended endocrine therapy decision making

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- No previous gene expression assay on the same tumor when a predictive result was previously successfully obtained, AND
- Required Clinical Characteristics at Initial Diagnosis:
  - Primary invasive breast cancer meeting all of the following criteria:
  - Unilateral tumor:
    - Hormone receptor positive (ER+ or PR+), and
    - Human epidermal growth factor receptor 2 (HER2) negative, AND
- Individual has involvement of 0-3 ipsilateral axillary lymph nodes, and
- Extended endocrine therapy beyond five years is a treatment option for the individual and results from this Breast Cancer Index test will be used in making extended endocrine therapy treatment decisions, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

Testing Multiple Samples:

- When more than one ipsilateral breast cancer primary is diagnosed, testing should be performed on the tumor with the most aggressive histologic characteristics. If an exception is requested, the following criteria will apply:
  - There should be reasonable evidence that the tumors are distinct (e.g., different quadrants, different histopathologic features, etc.), AND
  - There should be no evidence from either tumor that chemotherapy is indicated (e.g., histopathologic features or previous Breast Cancer Index result of one tumor suggest chemotherapy is indicated), AND
  - If both tumors are to be tested, both tumors must independently meet the required clinical characteristics.

What is Breast Cancer Index for breast cancer prognosis?

Breast Cancer Index® (BCI) is a commercial multigene expression profiling assay designed to assess prognosis in individuals with early-stage breast cancer.[1]

Breast Cancer Recurrence

A large percentage of individuals with breast cancer (ER+ [estrogen receptor positive]/ LN- [lymph node-negative]) treated with endocrine therapy alone are free of disease 10+ years after initial diagnosis, and could forgo chemotherapy and its toxic side effects. Furthermore, a meta-analysis (n=~35,000 individuals) reported a rate of recurrence of ~2% per year for individuals with breast cancer (ER+/LN-) receiving only tamoxifen.[2] Consequently, accurate prediction of the risk of breast cancer recurrence is important

for establishing the most optimal course of treatment with endocrine therapy, adjuvant chemotherapy, or both for individuals with early-stage breast cancer.

Risk Assessment

Conventional methods of risk assessment include using the following clinicopathologic factors

- tumor size
- involvement of regional lymph nodes
- histologic grade
- expression of hormone receptors (estrogen and progesterone), and
- human epidermal growth factor receptor 2 (HER2) amplification.

These may not be sufficiently accurate to identify those subgroups of individuals who are at low risk of recurrence and who are unlikely to benefit from extended endocrine therapy or adjuvant chemotherapy.[3]

As a result, alternative biomarker prognostic tests have been developed to more accurately predict individual risk of cancer recurrence and to better inform clinicians making treatment decisions for individuals with early-stage breast cancer, including

- determining appropriate chemotherapy regimens
- decreasing treatment-associated complications, and
- avoiding unnecessary treatment.[4]

Intended Use

According to the manufacturer, "The Breast Cancer Index (BCI) Risk of Recurrence & Extended Endocrine Benefit Test is indicated for use in women diagnosed with hormone receptor-positive (HR+), lymph node-negative (LN-) or lymph node-positive (LN+; with 1-3 positive nodes) early-stage, invasive breast cancer, who are distant recurrence-free. The BCI test provides: 1) a quantitative estimate of the risk for both late (post-5 years from diagnosis) distant recurrence and of the cumulative distant recurrence risk over 10 years (0-10y) in patients treated with adjuvant endocrine therapy (LN- patients) or adjuvant chemoendocrine therapy (LN+ patients), and 2) prediction of the likelihood of benefit from extended (>5 year) endocrine therapy. BCI results are adjunctive to the ordering physician's workup; treatment decisions require correlation with all other clinical findings."[1]

Test information

The test is intended to provide risk information beyond standard predictive and prognostic factors and identify those individuals unlikely to benefit from extended endocrine therapy or adjuvant chemotherapy.[1]

Breast Cancer Index

The BCI assay is an algorithmic gene expression-based signature, which combines 2 independent biomarkers (HOXB13:IL17BR [H:I or H/I] and the 5-gene molecular grade index (MGI) to evaluate estrogen-mediated signaling and tumor grade.[2]

As a risk stratification tool, BCI attempts to stratify individuals with early-stage ER+/LN- into three different risk groups, as well offer a continuous evaluation of an individual's risk of distant recurrence.[2]

Guidelines and evidence

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO, 2022) published a clinical practice guideline regarding the use of biomarkers to guide clinical decision-making on adjuvant systemic therapy among individuals with early-stage invasive breast cancer. Based on a review of the peer-reviewed scientific evidence, the following recommendations were published:[5]

- "If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)."
- "If a patient has node-positive breast cancer with 4 or more positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong)."
- "If a patient has HER2-positive breast cancer or TNBC [triple negative breast cancer], the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4) to guide decisions for adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong)."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) Clinical Practice Guidelines for Breast Cancer provided evaluations of various multigene assays used to determine whether adjuvant systemic chemotherapy should be added to adjuvant

endocrine therapy.[6] With regard to prognostic use of the BCI assay, the NCCN stated the following (with evidence level of category 2A):[6]

- BCI is listed as predictive of benefit of extended adjuvant endocrine therapy and as prognostic.
- "For patients with T1 and T2 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) in the low-risk range (0-5), regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0. Patients with BCI (H/I) low demonstrated a lower risk of distant recurrence (compared to BCI [H/I] high) and no significant improvement in disease free survival (DFS) or OS [overall survival] compared to control arm in terms of extending endocrine therapy duration."
- "For patients with T1 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) high (5.1-10) demonstrated significant rates of late distant recurrence. In secondary analyses of the MA.17, Trans-aTTom, and IDEAL trials, patients with HR-positive, T1-T3, pN0 or pN+ who had a BCI (H/I) high demonstrated significant improvements in DFS when adjuvant endocrine therapy was extended, compared to the control arm."
- "The benefit of testing BCI (H/I) for extended adjuvant endocrine therapy is unknown in patients who had ovarian function suppression, CDK4/6 inhibitors, or olaparib in addition to adjuvant endocrine therapy."

Ontario Health (Cancer Care Ontario) Program in Evidence-Based Care

The Ontario Health (Cancer Care Ontario) Program in Evidence-Based Care (PEBC, 2022) conducted a systematic review of the literature to serve as the basis of their clinical practice guideline. The clinical practice guideline for the clinical utility of multigene profiling assays in early-stage invasive breast cancer stated the following regarding BCI:[7]

- For early stage ER-positive and HER2-negative breast cancer, consider using multigene profiling assays, such as BCI, to assist with guiding the decision regarding systemic therapy.
- For early stage node-negative, ER-positive, HER2-negative breast cancer, a low-risk result from multigene profiling assays, such as BCI, may support a decision to not use adjuvant chemotherapy.
- "The evidence to support the use of molecular profiling to select the duration of endocrine therapy is evolving. In patients with ER-positive disease, clinicians may consider using a Breast Cancer Index (H/I) high assay result to support a decision to extend adjuvant endocrine therapy if the decision is supported by other clinical, pathological, or patient-related factors."

St. Gallen International Expert Consensus

The St. Gallen International Expert Consensus (2017) stated the following:

- "The Panel did not recommend the use of gene expression signatures for choosing whether to recommend extended adjuvant endocrine treatment, as no prospective data exist and the retrospective data were not considered sufficient to justify the routine use of genomic assays in this setting."[8]

Selected Relevant Publications

Several retrospective and prospective-retrospective studies, published by the manufacturer, have assessed the clinical validity of the BCI test for individuals with early stage breast cancer (ER+/LN-) to guide clinical decision making regarding adjuvant therapy (prognostic) or regarding treatment response (predictive).[2,9-17] Results of clinical validity are generally consistent across these studies, reporting that individuals classified by the BCI test into higher risk categories tend to have worse rates of distant recurrence, and individuals in lower risk categories have better rates of distant recurrence.

There is evidence that the BCI test is predictive of extended endocrine therapy benefit. Two retrospective studies evaluating subsets of individuals from the IDEAL and ATAC trials found that BCI was significantly associated with extended letrozole benefit.[10,15] Two retrospective analyses of individuals from the Trans-aTTom trial, both by the same author, assessed BCI for predicting extended tamoxifen benefit.[14,17] The first study of a small subset of individuals who were node-positive and postmenopausal found that the test was associated with individuals who experienced a benefit from extended therapy. The second study included individuals with varying nodal (32% node-positive) and menopausal statuses (86% postmenopausal). Notably, the overall and node-negative cohorts were underpowered due to low even rates. In the node-positive group, BCI results were significantly associated with a benefit from extended therapy. Several individual study limitations were identified across the evidence for the predictive use of the test including: limited numbers of premenopausal individuals, wide confidence intervals, potential selection bias, and retrospective study designs. A systematic review evaluated the clinical validity and clinical utility of five breast cancer GEP assays, including BCI. Study authors indicated that BCI may identify individuals likely to benefit from extended endocrine therapy. This review was hampered by several limitations, including a non-comprehensive literature search and an insufficient assessment of individual study bias and heterogeneity.[18]

The evidence for the use of BCI as a prognostic test in node-positive individuals is sparse and of low quality. Additional well-designed clinical trials are needed that evaluate the prognostic performance of BCI in large populations of node positive individuals currently receiving endocrine therapy and adjuvant chemotherapy.[19,20]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Breast Cancer Index will ensure that testing will be

available to those members most likely to benefit from the information provided by the assay. For those not meeting criteria, it ensures alternate management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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CADASIL Genetic Testing

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CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
NOTCH3 deletion/duplication analysis	81479
NOTCH3 known familial mutation analysis	81403
NOTCH3 targeted sequencing	81406

Criteria

Requests for CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) genetic testing are reviewed using the following criteria.

Known Familial Mutation Testing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for NOTCH3 mutations that would detect the familial mutation, AND
- Predictive Testing:
  - Member has a first-degree relative (i.e. parent, sibling, child) with an identified NOTCH3 gene mutation, and
  - Member is at least 18 years of age, OR

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- Diagnostic Testing for Symptomatic Individuals:
  - Member has a first-degree relative (i.e. parent, sibling, child) with an identified NOTCH3 gene mutation, and
  - High index of suspicion for CADASIL diagnosis based on clinical findings, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

NOTCH3 Targeted Sequencing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic sequencing for NOTCH3 mutations, AND
- Diagnostic Testing for Symptomatic Individuals:
  - High index of suspicion for CADASIL diagnosis based on clinical findings, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

NOTCH3 Deletion/Duplication Analysis

- Member meets the above criteria for NOTCH3 targeted sequencing, AND
- NOTCH3 targeted sequencing performed and detected no mutations, AND
- No previous NOTCH3 deletion/duplication analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

What is CADASIL?

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is an adult-onset form of cerebrovascular disease. There are no generally accepted clinical diagnostic criteria for CADASIL and symptoms vary among affected individuals.

Prevalence

CADASIL is a rare disease.[1-3] The exact prevalence is unknown. CADASIL is probably still underdiagnosed. The minimum prevalence is estimated to be between 2-5 per 100,000 based on multiple small and national registries.[1,3] More recent "reports suggest that the prevalence of NOTCH3 cysteine-altering pathogenic variants is substantially higher, and may be as high as 1 in 300 worldwide."[2] A founder effect has been reported for Finnish individuals and individuals in the Marche region of Italy.[1]

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CADASIL is the most prevalent inherited cause of cerebral small-vessel disease.[4]

Symptoms

Typical signs and symptoms include[1,3,5]

- transient ischemic attacks and ischemic stroke, occurs at a mean age of 47 years (age range 20-70 years), in most cases without conventional vascular risk factors
- cognitive disturbance, primarily affecting executive function, may start as early as age 35 years
- psychiatric or behavioral abnormalities
- migraine with aura, occurs with a mean age of onset of 30 years (age range 6-48 years), and

Less common symptoms include:

- recurrent seizures with onset in middle age, usually secondary to stroke
- acute encephalopathy, with a mean age of onset of 42 years

Cause

CADASIL is caused by mutations in the NOTCH3 gene.

To date, NOTCH3 is the only gene in which mutations are known to cause CADASIL.[1] NOTCH3 has 33 exons. CADASIL pathogenic variants occur in exons 2–24, which encode the 34 epidermal growth factor repeats (EGFR).[1,6] The majority of pathogenic variants occur in exons 2-6.[3] NOTCH3 encodes a transmembrane receptor that is primarily expressed in vascular smooth-muscle cells, preferentially in small arteries.[1] "In CADASIL, the extracellular domain of the Notch3 receptor accumulates within blood vessels. Accumulation takes place at the cytoplasmic membrane of VSMCs [vascular smooth muscle cells] and pericytes in close vicinity to the granular osmiophilic deposits (GOM) that characterize the disease. NOTCH3 recruits other proteins into the extracellular deposits, among them vitronectin and tissue inhibitor of metalloproteinase-3 (TIMP3), which may be relevant for disease pathogenesis."[3] There is a hypothesis that structural abnormalities in the vascular smooth-muscle protein NOTCH3 trigger arterial degeneration, vascular protein accumulation, and cerebrovascular failure.[4,6]

No clear genotype-phenotype correlations exist for individuals with CADASIL.[7,8] Some studies describe phenotype-genotype correlations. "There is reasonably strong evidence that pathogenic variants in the first six epidermal growth factor-like repeat domains (EGFR 1 to 6) of the Notch3 protein are associated with an earlier age of stroke onset, a more severe phenotype, and lower survival compared with pathogenic variants in EGFR 7 to 34."[3] However, there can be significant intrafamilial variability with the age of onset, disease severity, and disease progression. The genotype cannot be used to predict the phenotype.[1,4] NOTCH3 cysteine-altering pathogenic variants are associated with a broad phenotypic spectrum which includes classic CADASIL, mild small vessel

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disease, and non-penetrance.[3] A recent meta-analysis that surveyed clinical studies and genomic databases from 1996-2023 reported the six most common NOTCH3 mutations causative for CADASIL, and summarized genotype-phenotype correlations for four of these mutations.[9]

Inheritance

CADASIL is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

Brain Magnetic Resonance Imaging (MRI) findings include T2-signal-abnormalities in the white matter of the temporal pole and T2-signal-abnormalities in the external capsule and corpus callosum.[3]

CADASIL is suspected in an individual with the clinical signs and MRI findings. A positive family history for stroke or dementia is also indicative of disease in symptomatic individuals. However, a negative family history should not exclude the diagnosis, as de novo mutations have been reported, and affected family members are frequently misdiagnosed.[1,7]

Sequencing of all NOTCH3 exons encoding EGF–like domains fails to identify a mutation in some individuals with CADASIL. Therefore, skin biopsy with histopathologic evaluation for characteristic GOM deposits is appropriate for individuals with a high index of clinical suspicion for CADASIL and negative genetic testing.[2,3]

For a firm diagnosis of CADASIL, at least one of the following is required:

- Documentation of a typical NOTCH3 mutation by genetic analysis.[1,3,7]
  - NOTCH3 mutation detection may reach >95% in individuals with strong clinical suspicion of CADASIL[1].
- Documentation of characteristic GOM deposits within small blood vessels by skin biopsy.[1,3,7]

Management

A correct diagnosis of CADASIL is important because the clinical course of disease is different from individuals with other types of cerebral small-vessel disease and proven therapies for stroke have not been validated in individuals with CADASIL.[7] However, no

specific disease-modifying treatments for CADASIL exist. Management and treatment of individuals is generally symptomatic and supportive.[1,3,5,7,10]

Patients with CADASIL should avoid anticoagulants, angiography, and smoking to avoid disease-related complications, so clinical utility is represented.[1,7] Because of the risk for cerebral hemorrhage, use of antiplatelets rather than anticoagulants is considered for prevention of ischemic attacks. Evidence against the use of intravenous tissue plasminogen activator (IV tPA) has been suggested due to the possibility of hemorrhage; however, this is not conclusive.[11] A two-center cohort study found that blood pressure and hemoglobin A1c levels were associated with cerebral mini bleeds in individuals with CADASIL.[5] Therefore, controlling blood pressure and glucose levels may improve the clinical course of the disease. It is also reasonable to control for high cholesterol and high blood pressure given the high rate of ischemic stroke seen in CADASIL.[5]

Statins are used for treatment of hypercholesterolemia and antihypertensive drugs are used for hypertension and hypertension treatment may have an additional benefit.[3] Management of neurologic events (migraines, depression, psychiatric manifestations) by a neurologist or neuropsychiatrist can be beneficial; pregnancy and postpartum periods are potential risk factors.[1] The American Heart Association issued a scientific statement summarizing the current recommendations for the diagnosis and management of CADASIL.[12]

Survival

"In a retrospective analysis of 411 patients with CADASIL, the median age at death was 65 years in men and 71 years in women."[2]

Test information

Testing for CADASIL may include genetic testing (known familial mutation analysis, sequence analysis, or deletion/duplication analysis) and/or skin biopsy.

Skin biopsy

A pathognomonic characteristic of CADASIL is the finding of characteristic GOM within the vascular media and increased NOTCH3 staining of the arterial wall, which can be evaluated in a skin biopsy.[1] Specificity of skin biopsy findings is high, as the characteristic deposits have not been documented in any other disorder. Sensitivity has been reported to range from 45%-100%. Sensitivity and specificity can be maximized to >90% by immunostaining for NOTCH3 protein.[7] When interpreted by an experienced (neuro) pathologist, combined analysis by electron microscopy and immunohistochemistry usually allows for a conclusive CADASIL diagnosis.

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Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Sequence analysis

To date, all mutations in NOTCH3 causing CADASIL have been in exons 2-24, including intron-exon boundaries.[1] In the United States, laboratories offering CADASIL testing appear to perform, at minimum, next-generation sequencing (NGS) of exons 2-24 at the time of this review.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Large deletions and duplications in the NOTCH3 gene have not been reported.[3] Molecular testing approaches can include deletion/duplication analysis if sequencing analysis of NOTCH3 is unrevealing.[1]

Guidelines and evidence

American Heart Association

The American Heart Association (AHA, 2023) published a scientific statement with information on the management of inherited cerebral small vessel disease (CSVD), including CADASIL.[12] They stated the following regarding genetic testing for CADASIL.

- "Several approaches have been developed to help clinicians prioritize gene testing. For at least two decades, it has been recognized that anterior temporal polar WMH [white matter hyperintensities] on brain MRI is a marker of CADASIL with good sensitivity and specificity. The Pescini scale ranges from 0 to 25 (>14 points suspicious of CADASIL) and uses clinical features like stroke or transient ischemic attack onset before 50 years of age."
- "Strong consideration should be given to genetic counseling to allow discussion of the ramifications of obtaining genetic test results on the individual patient and their family." The authors provided additional considerations of pre-test genetic counseling

including addressing possible discrimination, the possible "negative psychological consequences", and the general consensus against predictive testing for minors.
- "Post-test counseling can help with interpretation, especially of variants of unclear significance, and navigating grief or guilt from positive, negative, or equivocal results."
- "A known pathogenic NOTCH3 mutation within a family simplifies testing because only a single mutation needs to be investigated. When the mutation is unknown or unavailable, the laboratory must undertake a more complex analysis." The genetic analysis outlined when a known familial mutation has not been identified may include targeted sequencing or full gene sequencing. If multiple inherited CVSDs are in the differential, a multigene panel may be considered.
- "Although used less frequently, there is still a role for skin biopsy to look for pathognomonic granular osmophilic material on electron microscopy that may clarify the clinical significance of a mutation of uncertain or unknown significance. The accuracy of skin biopsy is enhanced by the use of immunohistochemistry."

European Academy of Neurology

The European Academy of Neurology (EAN, 2020) consensus panel stated:[10]
- "CADASIL can only be definitively confirmed by genetic testing, revealing a NOTCH3 mutation altering the number of cysteines in one of the 34 EGFr domains of the NOTCH3 protein."
- A diagnosis of CADASIL can be established by skin biopsy with electron microscopy showing GOM, but genetic testing should be the first diagnostic line of investigation.
- "In the case of a NOTCH3 variant of unknown significance, CADASIL can be confirmed using a skin biopsy for electron microscopy and/or NOTCH3 immunostaining."
- "All or almost all variants leading to CADASIL result in a loss or gain of a cysteine in EGFr repeats. Some non-cysteine-changing variants have been reported but the consensus was that the vast majority of these variants are not pathogenic. In such cases, electron microscopy revealing GOM can be a useful diagnostic tool."
- "The diagnosis of CADASIL should be considered in any patient with unexplained symmetrical periventricular WMHs and a positive family history of migraine with aura, stroke, mood disorders or dementia."

Selected Relevant Publications

Various publications have addressed CADASIL testing.[13-15] A retrospective cohort study suggested that an adequate skin biopsy for analysis of GOM is a cost effective way to determine a diagnosis of CADASIL in symptomatic individuals.[13] The biopsy results can then be used to guide the decision regarding who should have genetic testing, particularly in individuals with no known familial mutation or from ethnic populations with no evidence of founder mutations.[13] Additionally, a clinical scale has been published to

assist with determining which individuals would have a high probability of a pathogenic mutation with genetic testing with a sensitivity of 96.7% and specificity of 74.2%.[14] At the time of publication, the results needed to be confirmed with further validation.[14] Other authors suggested that a multigene panel may be the preferred test for a symptomatic individual.[15] This is due to the overlap between CADASIL and other hereditary small vessel diseases and the lack of specific or sensitive clinical features for CADASIL.[15]

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for CADASIL testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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CHARGE Syndrome and CHD7 Disorder Genetic Testing

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CHARGE Syndrome and CHD7 disorder genetic testing are addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
CHD7 deletion/duplication analysis	81479
CHD7 known familial mutation analysis	81403
CHD7 sequencing	81407

Criteria

Requests for CHD7 genetic testing are reviewed using the following criteria.

CHD7 Known Familial Mutation Analysis

- Genetic Counseling
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing
  - No previous genetic testing of CHD7 that would detect the familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals
  - Known family mutation in CHD7 in 1st degree biological relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CHD7 Sequencing

- Genetic Counseling

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  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing
  - No previous CHD7 sequencing, and
  - No known CHD7 mutation in the family, and
  - Chromosomal microarray, if performed, was negative, AND
- Diagnostic Testing for Symptomatic Individuals
  - The member is suspected to have CHARGE syndrome, but the diagnosis is in question because member meets ONLY ONE of the following using the Blake or Verloes criteria (see Table: *Clinical Diagnostic Criteria for Typical CHARGE Syndrome*, below)
    - 2 major criteria and 1 minor criterion, or
    - 2 major criteria and 0 minor criteria, or
    - 1 major criterion and 3 minor criteria, AND
- Molecular test results will impact medical management, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CHD7 Deletion/Duplication Analysis

- Genetic Counseling
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing
  - No previous CHD7 deletion/duplication testing, and
  - Previous CHD7 sequencing was performed and was negative, and
  - No known CHD7 mutation in the family, and
- Diagnostic Testing for Symptomatic Individuals
  - The member meets the above criteria for CHD7 sequencing, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

What is CHARGE Syndrome/CHD7 disorder?

CHARGE syndrome is a clinically variable syndrome involving multiple congenital anomalies of diverse organ systems.[1] The phenotype has been expanded to CHD7 disorder, which encompasses the full spectrum of clinical findings in individuals with pathogenic CHD7 mutations. This guideline focuses on CHARGE syndrome, as the majority of individuals found to have CHD7 mutations have clinical findings typical of CHARGE syndrome.[2]

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Incidence

CHARGE syndrome occurs in approximately 1/10,000 newborns with an estimated range of 1/8,500 – 1/15,000.[1-3] The disorder is pan-ethnic.[3]

Symptoms

CHARGE was the acronym initially used to describe an association of eye colobomas, heart defects, choanal atresia, growth retardation, genital anomalies, and ear malformations.[1] Following the discovery that heterozygous CHD7 variants cause CHARGE syndrome, molecular genetic testing of family members of probands with CHARGE syndrome expanded the phenotypic spectrum to include phenotypes that do not fulfill the previously proposed CHARGE syndrome clinical diagnostic criteria.[1,2] Additional symptoms associated with CHD7-related disorder phenotype include cleft lip and/or palate, developmental delay, hearing loss, cranial nerve anomalies, vestibular defects, hypothyroidism, hypogonadotropic hypogonadism, tracheoesophageal anomalies, brain anomalies, seizures, renal anomalies, and characteristic dysmorphic facial features.[1,2] Thus, CHD7 disorder exhibits a high degree of clinical variability even among individuals in the same family and among individuals from different families with the same pathogenic variant.[1,2] Given this variability, the presence of a CHD7 mutation is "not equivalent to a diagnosis of CHARGE syndrome."[2]

Cause

CHARGE syndrome and CHD7 disorder are caused by mutations in the CHD7 gene. This gene plays a role in guidance of neural crest cell migration.[4] Sequencing the CHD7 gene will find a causative mutation in 98% of affected individuals.[2] Approximately 2% of mutations identified in CHD7 are whole or partial gene deletions.[2]

Inheritance

CHARGE syndrome and CHD7 disorder are considered autosomal dominant disorders. Although some cases of parent to child transmission of CHARGE syndrome have been reported, most cases are simplex (the only case in the family) and CHD7 mutations, if identified, are typically de novo.[1,2]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

If neither parent is affected, there is a 1-2% risk of recurrence, most likely due to germline mosaicism.[2]

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Diagnosis

Two common sets of clinical diagnostic criteria for CHARGE syndrome have been described.[1] The Blake criteria (first published in 1998 and updated in 2009) set out major and minor diagnostic criteria to be used in diagnosing typical CHARGE syndrome.[5,6] The Verloes criteria provide a means of diagnosing typical CHARGE syndrome (see Table), as well as minor presentations termed partial CHARGE (criteria: 2 major and 1 minor) and atypical CHARGE (criteria: 2 major and 0 minor or 1 major and 3 minor).[7] There are no clinical diagnostic criteria for the phenotypic spectrum associated with CHD7 disorder.

Clinical Diagnostic Criteria for Typical CHARGE Syndrome (Adapted from Bergman et al 2011)[1]

Criteria Set	Major Criteria	Minor Criteria
Blake[5,6] (4 Major or 3 Major and 3 Minor)	Coloboma or microphthalmia Choanal atresia or stenosis External ear anomaly/ middle ear malformation/ mixed sensorineural deafness Cranial nerve dysfunction	Cardiac defect Tracheo-esophageal defects Genital hypoplasia or delayed puberty Cleft lip and/or palate Developmental delay Growth retardation Characteristic facial features
Verloes[7] (3 Major or 2 Major and 2 Minor)	Ocular coloboma Choanal atresia Hypoplastic semicircular canals of the inner ear	Cardiac or esophageal malformation Malformation of the middle or external ear Rhombencephalic dysfunction including sensorineural deafness Hypothalamo-hypophyseal dysfunction (gonadotropin or growth hormone deficiency) Intellectual disability

Management

Management of CHARGE syndrome and CHD7 disorder is based on the variable clinical manifestations. Airway management and cardiac assessment are essential in the newborn period, as is addressing feeding and growth difficulties.[2] Other recommended evaluations and surveillance include the following:[2]

- Ophthalmologic assessment
- Audiologic assessment
- ENT assessment, including imaging to assess middle and inner ear defects
- Genitourinary assessment, including renal ultrasound
- Endocrine evaluation if puberty is delayed or if there is presence of genital anomalies
- Cranial nerve assessment / swallowing studies
- Gastrointestinal assessment for esophageal atresia or trachea-esophageal fistula
- Developmental assessment

Survival

"Life expectancy highly depends on the severity of manifestations; mortality can be high in the first few years when severe birth defects (particularly complex heart defects) are present and often complicated by airway and feeding issues. In childhood, adolescence, and adulthood, decreased life expectancy is likely related to a combination of residual heart defects, infections, aspiration or choking, respiratory issues including obstructive and central apnea, and possibly seizures. Despite these complications, the life expectancy for many individuals can be normal."[2]

Test Information

Testing for CHARGE syndrome and CHD7 disorder may include known familial mutation analysis, next generation sequencing, or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA

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simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and Evidence

Selected Relevant Publications

van Ravenswaaij-Arts et al., 2022

An expert authored review updated in 2022 stated:[2]

- “With the current widespread use of multigene panels and comprehensive genomic testing, it has become apparent that the phenotypic spectrum of heterozygous CHD7 pathogenic variants has broadened to encompass CHARGE syndrome as well as subsets of features that comprise the CHARGE syndrome phenotype ."
- “CHD7 disorder, refers to the entire phenotypic spectrum that can be associated with heterozygous CHD7 pathogenic variants and emphasizes both the need to evaluate an individual found to have a CHD7 pathogenic variant for medically actionable manifestations in the entire phenotypic spectrum (regardless of clinical findings that prompted molecular genetic testing) and the importance of counseling families that the finding of a CHD7 pathogenic variant is not equivalent to a diagnosis of CHARGE syndrome."
- “The diagnosis of CHD7 disorder is established in a proband with suggestive clinical and imaging findings and a heterozygous pathogenic variant in or deletion of CHD7 identified by molecular genetic testing."
- "Sequence analysis of CHD7 is performed to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications and/or chromosomal microarray (CMA) to detect whole-gene deletions."

- “Because CHD7 disorder typically includes multiple congenital anomalies, it is also reasonable to pursue chromosomal microarray testing first, unless classic features of CHD7 disorder (e.g., the CHARGE syndrome phenotype) are apparent."
- “Management of the manifestations of CHD7 disorder can be complex and require a multidisciplinary approach involving clinicians, therapists, and educators."
- “Requires routine follow up of manifestations identified in infancy/childhood, as well as ongoing monitoring of growth, development, educational progress, behavior, and possible endocrine issues."
- “Because of the increased risk of post-anesthesia airway complications, procedures requiring anesthesia should be minimized and combined whenever possible."

van Ravenswaaij-Arts and Martin, 2017

In a review of the etiology and diagnosis, van Ravenswaaij-Arts and Martin stated:[8]

- "In clinically typical individuals with CHARGE syndrome, the tests of first choice are CHD7 Sanger sequencing and chromosomal microarray to screen for deletions and/or MLPA to test for exonic-deletions."
- "CHD7 pathogenic variants have been described in very mildly affected individuals, for example, individuals with isolated hypogonadotropic hypogonadism [HH] due to CHD7 missense variants."
- "It is recommended that individuals with HH and a CHD7 variant be clinically screened for CHARGE syndrome features such as balance problems and deafness, amongst [sic] others."
- "One to two percent of individuals who test positive have an intragenic or whole CHD7 gene deletion that can be detected by microarray analysis, although for small exonic deletions, MLPA is preferred."
- "Most individuals with CHARGE syndrome are sporadic, but recurrence has been documented. ... Parent-child transmission with a recurrence risk of 50% is predominantly seen in milder presentations of the syndrome, although intrafamilial variability is high and a mildly affected parent does not exclude a more severely affected child. If the pathogenic CHD7 variant of a proband cannot be detected in leukocyte DNA of the parents, there remains a 1-2% recurrence risk due to germline mosaicism."

Hefner and Fassi, 2017

In a review of genetic counseling issues in CHARGE syndrome, Hefner and Fassi stated:[9]

- "[Genetic counseling] is particularly important in CS [CHARGE syndrome], as it is extremely complex and variable in its presentation and in its natural history."

- "Despite the identification of pathogenic CHD7 variants in the majority of cases, the diagnosis of CS remains clinical...with genetic testing being particularly helpful in borderline clinical cases."
- "As CS can affect any organ system in the body, the features overlap with countless other syndromes. The top candidates in the differential diagnosis of CS are 22q11.2 deletion syndrome (22q) and Kabuki syndrome (KS). VACTERL association also has a good deal of overlap, but typically does not have significant dysmorphic features."
- "CMA is often performed initially for fetuses or infants with multiple anomalies. This is reasonable as 22q is far more common than CS and CMA can identify other rare microdeletions or microduplications with overlapping features."
- "If CMA is nondiagnostic, CHD7 genetic testing (sequencing and deletion/duplication analysis) is recommended in the presence of any major feature of CS with multiple anomalies. If CHD7 analysis is nondiagnostic, whole exome sequencing (WES) may be considered."
- "Every individual with CS has his or her own unique set of medical and developmental issues. Medical management of CS involves comprehensive monitoring of multiple organ systems by a multitude of specialists."
- "Appropriate therapies will involve not only traditional therapies (occupational, physical, speech, and language therapies, etc.) but require the expertise of DB [deafblind] specialists. DB specialists are professionals expert in the unique needs of children with multiple sensory impairments."
- Genetic counseling should include information on prognosis including mortality, morbidity, and sensory, motor and intellectual expectations.

Bergman et al., 2011

In addressing molecular testing for CHARGE syndrome, Bergman and colleagues suggested that CHD7 testing, including sequencing and deletion analysis, should be considered in individuals with:[1]

- 3 cardinal features
- 2 cardinal features and 1 supportive feature
- 2 cardinal features if imaging shows semicircular canal abnormalities
- 1 cardinal feature and 1 supportive feature if imaging shows semicircular canal abnormalities

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for CHARGE syndrome and CHD7 disorder testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the

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condition, but have non-standard features, will not receive an immediate approval for testing.

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Cardiomyopathy and Arrhythmia Genetic Testing

MOL.TS.410.A
v1.0.2026

Genetic testing for non-syndromic cardiomyopathy and arrhythmia is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
4q25-AF Risk Genotype	81479
Arrhythmia Single Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Arrhythmia Known Familial Mutation Analysis	81403
Brugada Syndrome Genetic Testing (SCN5A and Variants)	S3861

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Procedures addressed by this guideline	Procedure codes
Cardiomyopathy Single Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Cardiomyopathy Known Familial Mutation Analysis	81403
Cardiac Ion Channelopathies Sequencing Panel (at least 10 channelopathy-related genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A)	81413
Cardiac Ion Channelopathies Deletion/Duplication Panel (at least 2 channelopathy-related genes, including KCNH2 and KCNQ1)	81414
Genomic Unity Cardiac Ion Channelopathies Analysis	0237U
Hereditary Cardiomyopathy Sequencing Panel (at least 5 cardiomyopathy-related genes)	81439
Hypertrophic Cardiomyopathy Comprehensive Gene Sequence Analysis	S3865
Hypertrophic Cardiomyopathy Known Familial Mutation Analysis	S3866

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Criteria

Requests for cardiomyopathy and arrhythmia genetic testing are reviewed using these criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic or Predisposition Testing:*
  - Known familial mutation in a 1st or 2nd degree biological relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Note:

Since symptoms may occur in childhood, testing of children who are at-risk for a pathogenic mutation may be appropriate, but requires genetic counseling and careful consideration of ethical issues related to genetic testing in minors.

Single Gene Tests (Sequencing and Deletion/Duplication Analysis)

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous analysis of the requested gene, and
  - No known mutation in the family that would explain the member's clinical features, AND
- Diagnostic Testing in Symptomatic Individuals:
  - Clinical history points to the specific gene requested, and
  - Single gene analysis is appropriate due to one or more of the following:
    - The requested gene is the only gene that has a confirmed association with the member's cardiac subtype (e.g., SCN5A for individuals with an established or suspected diagnosis of Brugada syndrome), or
    - Analysis of other genes associated with the member's cardiac subtype was previously completed and was not diagnostic, and
  - Non-genetic causes have been ruled out (e.g., hypokalemia for arrhythmia; sarcoidosis, endomyocardial fibrosis, infection, or toxin exposure for

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cardiomyopathy), or clinical suspicion for a gene mutation remains high even in the presence of a potential non-genetic cause, and
    - The results of the test will directly impact the diagnostic and treatment options that are recommended for the individual, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Multi-Gene Sequencing Panels

Subtype-specific panels or comprehensive panels with multiple cardiomyopathy and/or arrhythmia subtypes are considered medically necessary when the criteria below are met.

- Genetic Counseling:
    - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
    - No previous gene sequencing for the suspected condition, and
    - No known pathogenic or likely pathogenic mutation in the family that would explain the member's clinical features, AND
- Diagnostic Testing for Symptomatic Individuals:
    - The member meets subtype-specific criteria (see below) for one or more of the following cardiac subtypes:
        - Arrhythmogenic cardiomyopathy (ACM), or
        - Catecholaminergic polymorphic ventricular tachycardia (CPVT), or
        - Dilated cardiomyopathy (DCM), or
        - Hypertrophic cardiomyopathy (HCM), or
        - Long QT syndrome (LQTS) with or without signs of Jervell and Lange-Nielson Syndrome (JLNS), or
        - Progressive cardiac conduction disease or cardiac conduction disease (PCCD/CCD), or
        - Restrictive cardiomyopathy (RCM), or
        - Short QT syndrome (SQTS), and
    - No personal or family history of extra-cardiac features that are highly suggestive of an underlying multi-systemic syndrome for which syndrome-specific genetic testing is available and appropriate (see table titled *Select Cardiac Syndromes, Associated Genes, and Applicable Guidelines*), and
    - Non-genetic causes have been ruled out (e.g., hypokalemia for arrhythmia; sarcoidosis, endomyocardial fibrosis, infection, or toxin exposure for cardiomyopathy), or clinical suspicion for a gene mutation remains high even in the presence of a potential non-genetic cause, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Arrhythmogenic Cardiomyopathy (ACM) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: DSC2, DSG2, DSP, JUP, PKP2 (plus FLNC if the left ventricle is affected), AND
- The member meets at least one of the following:
  - Arrhythmogenic right ventricular cardiomyopathy (ARVC) Task Force criteria are met for at least possible ARVC (defined as having at least one major or two minor criteria) based on electrocardiogram, echocardiogram, MRI, and/or angiogram findings, or
  - Clinical documentation is provided supporting a diagnosis or clinical suspicion of ARVC, arrhythmogenic left ventricular cardiomyopathy (ALVC), or bi-ventricular arrhythmogenic cardiomyopathy (BiVACM) and the presence of one or more of the following:
    - One or more first- or second-degree relatives with a diagnosis of cardiomyopathy, or
    - A suspicious family history including a first- or second-degree relative with sudden death or cardiac event at <50 years of age.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: RYR2 and CASQ2, AND
- The member has an established or suspected diagnosis of CPVT based on at least one of the following:
  - A CPVT diagnostic score ≥3.5, or
  - All of the following features are present:
    - A structurally normal heart, and
    - Normal resting ECG, and
    - Exercise- or emotion-induced bidirectional or polymorphic ventricular tachycardia (VT).

Dilated Cardiomyopathy (DCM) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: BAG3, FLNC, LMNA, MYH7, RBM20, SCN5A, TNNT2, and TTN, AND
- The member meets at least one of the following:

- Diagnosis of idiopathic DCM (IDCM) based on the following findings from appropriate imaging and/or electrophysiology modality (e.g. echocardiogram, electrocardiogram, MRI, angiogram):
  - Left ventricular (LV) enlargement with end-diastolic dimensions or volumes >2 z-scores above population mean values corrected for body size, sex, and/or age (i.e. in adults, LV end-diastolic diameter >58mm in males and >52 mm in females and an LVEDV index of ≥75 mL/m2 in males and ≥62 mL/m2 in females), and
  - Left ventricular systolic dysfunction, (defined as an ejection fraction of less than 50%), and
  - Absence of abnormal loading conditions (severe hypertension and valve disease) or coronary artery disease sufficient to cause the above features, or
- Clinical documentation is provided supporting a diagnosis of DCM (with or without abnormal loading conditions or coronary artery disease) and at least one of the following:
  - One or more first- or second-degree relatives with a diagnosis of DCM, peripartum cardiomyopathy, or alcoholic cardiomyopathy, or
  - A suspicious family history including a first- or second-degree relative with sudden death or cardiac/thromboembolic event at <50 years of age, or
- Mildly affected individual (defined as having dilated left ventricle but normal ejection fraction, or left ventricular systolic dysfunction without dilatation) with a known diagnosis of IDCM in a first- or second-degree relative who is deceased or otherwise unavailable for testing.

Hypertrophic Cardiomyopathy (HCM) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: ACTC1, MYBPC3, MYH7, MYL2, MYL3, PLN, TNNI3, TNNT2, and TPM1, AND
- The member meets at least one of the following:
  - Diagnosis of HCM based on the following findings from appropriate imaging (e.g., echocardiogram or MRI):
    - Left ventricular hypertrophy without obvious cause (valvular disease, hypertension, infiltrative or neuromuscular disorder), and
    - Maximum myocardial wall thickness meeting one of the following parameters:
      - ≥15mm (1.5cm) in adults without a family history of HCM, or
      - ≥13mm (1.3 cm) in adults with a first- or second-degree relative with a known diagnosis of HCM who is deceased or otherwise unavailable for testing, or
      - >2 standard deviations for age in children, or

- Pathognomonic histopathologic features of HCM on endomyocardial biopsy (e.g. myocyte disarray, hypertrophy, increased myocardial fibrosis).

Long QT Syndrome (LQTS) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: KCNQ1, KCNH2, and SCN5A (or KCNQ1 and KCNE1 if Jervell and Lange-Nielson syndrome is suspected), AND
- The member has an established or suspected diagnosis of LQTS based on at least one of the following:
  - Schwartz criteria score ≥1.5, or
  - Confirmation of prolonged QTc or T-wave abnormalities [>460ms (prepuberty) or >480ms (adults) on serial 12-lead ECGs] on exercise or ambulatory ECG, or during pharmacologic provocation testing, or
  - A prolonged or borderline prolonged QT interval on ECG or Holter monitor, or
  - Profound congenital bilateral sensorineural hearing loss and prolonged QTc.

Progressive Cardiac Conduction Disease (PCCD/CCD) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: SCN5A and TRPM4, AND
- Clinical documentation is provided supporting a diagnosis of PCCD/CCD (e.g., complete right bundle branch block, complete left bundle branch block, left anterior fascicular block/hemiblock or left posterior hemiblock, prolonged PR interval or complete atrioventricular block with broad QRS complexes), AND
- The member has one or more of the following:
  - PCCD/CCD diagnosed at <50 years of age, or
  - A first- or second-degree relative with PCCD/CCD.

Restrictive Cardiomyopathy (RCM) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: ACTC1, MYBPC3, MYH7, MYL2, MYL3, TNNI3, TNNT2, TPM1, and TTR, AND
- Clinical documentation is provided supporting a diagnosis of RCM, AND
- The member has one or more of the following:
  - Left ventricular hypertrophy and/or hypertrophic cardiomyopathy (HCM), or

- A first- or second-degree relative with cardiomyopathy (e.g., RCM, HCM) and/or left ventricular hypertrophy.

Short QT Syndrome (SQTS) Specific Criteria

- The member meets the above general criteria for multi-gene panel sequencing, AND
- The panel includes, at minimum, the following genes: KCNH2 and KCNQ1, AND
- The member has an established or suspected diagnosis of SQTS based on at least one of the following:
  - An SQTS diagnostic score ≥4, or
  - A QTc ≤330ms, or
  - A QTc <360ms with survival of a ventricular tachycardia/fibrillation episode in the absence of heart disease, or
  - A QTc <360ms with family history of SQTS or sudden death at age ≤40.

Diagnostic criteria, scoring systems, and their associated references are summarized in the background section of this guideline, under "Diagnosis".

Multi-Gene Deletion/Duplication Panels

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous gene deletion/duplication testing for the suspected condition, and
  - A multi-gene sequencing panel was previously performed for the suspected condition, with one of the following results:
    - No pathogenic or likely pathogenic mutation identified, or
    - One pathogenic or likely pathogenic mutation identified in a gene associated with an autosomal recessive condition (e.g., Jervell and Lange-Nielson Syndrome), AND
- Diagnostic Testing for Symptomatic Individuals:
  - Meets clinical criteria for multi-gene sequencing panels, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Exclusions and Other Considerations

- Genetic testing (including single-gene or multi-gene panels) for the following conditions, in isolation, is considered experimental, investigational, or unproven:
  - Left ventricular non-compaction (LVNC)

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  - The following types of arrhythmia: atrial fibrillation, early repolarization syndrome, sinus node dysfunction ('sick sinus syndrome') and Wolff-Parkinson-White syndrome
- Testing the 4q25 atrial fibrillation risk genotype is considered experimental, investigational, or unproven.
- Due to low diagnostic yield and lack of clinical utility for genes other than SCN5A, multi-gene panel testing for Brugada syndrome (BrS) is considered experimental, investigational, or unproven.
- This guideline may not apply to genetic testing for indications that are addressed in other test-specific guidelines (e.g., testing for multi-system syndromes that may include cardiomyopathy or arrhythmia as a feature). For these indications, please refer to applicable test-specific guidelines in the table titled *Select Cardiac Syndromes, Associated Genes, and Applicable Guidelines*, or the general guideline, *Genetic Testing to Diagnose Non-Cancer Conditions*.
- Genetic testing for cardiomyopathies and/or arrhythmias is only medically necessary once per lifetime. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest (e.g., additional genes are being tested that account for >1% of cases of the member's cardiac subtype and have a definitive association with the subtype according to the **ClinGen Gene-Disease Validity Curation**).

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Multi-gene panel testing for Brugada syndrome (e.g., S3861) is not reimbursable.
- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
  - A single gene included in a multi-gene panel may not be reimbursed if testing has been performed previously.
  - If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.
- When otherwise reimbursable, the following limitations apply:

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- When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81439, 81413/81414 or 81479)*.
- When use of a panel code is not possible, each billed component procedure will be assessed independently.
- In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
- When the test is billed with multiple stacked procedure codes, only the following genes may be considered for reimbursement, based on the cardiac subtype:
  - Arrhythmogenic right ventricular cardiomyopathy: DSC2, DSG2, DSP, JUP, PKP2, TMEM43
  - Catecholaminergic polymorphic ventricular tachycardia: RYR2, CASQ2
  - Dilated cardiomyopathy: TTN, TNNT2, MYH7, SCN5A, MYBPC3, LMNA
  - Hypertrophic cardiomyopathy: MYH7, MYBPC3, TNNT2, TNNI3
  - Long QT syndrome: KCNQ1, KCNH2, SCN5A (if Jervell and Lange-Nielson syndrome is suspected: KCNQ1 and KCNE1)
  - Progressive cardiac conduction disease: SCN5A, LMNA, TRPM4
  - Restrictive cardiomyopathy: ACTC1, MYH7, TNNI3, TTN, TTR
  - Short QT syndrome: KCNH2, KCNQ1

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What are Cardiomyopathy and Arrhythmia?

Cardiomyopathy is a disease of the heart muscle that compromises heart function. The most relevant subtypes for genetic testing include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ACM), and restrictive cardiomyopathy (RCM). ACM is further divided into the following, based on which ventricles are involved: arrhythmogenic right ventricular cardiomyopathy (ARVC), arrhythmogenic left ventricular cardiomyopathy (ALVC), and bi-ventricular arrhythmogenic cardiomyopathy (BiVAC). Left ventricular non-compaction (LVNC) is now more often considered a phenotypic trait rather than a primary cardiomyopathy; it may occur alongside other cardiac subtypes or as an isolated finding seen in athletes, pregnant individuals, and healthy adult populations.[1-4]

In addition to non-syndromic forms of cardiomyopathy, more than 100 syndromes have cardiomyopathy as a feature, including various muscular dystrophies and storage

disorders.[1,3,4] It is beyond the scope of this guideline to provide detailed descriptions of these syndromes (see table titled *Select Cardiac Syndromes, Associated Genes, and Applicable Guidelines* for eviCore guidelines that address some of them more specifically).

Arrhythmias (sometimes called channelopathies) are heart rhythm disturbances that may be detected on electrocardiogram (ECG). Genetic arrhythmias are primarily ventricular arrhythmias that occur due to abnormalities in the ion currents that drive the electrical activity of the heart.[5] Subtypes of arrhythmia that are most likely to prompt a genetic evaluation include long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), short QT syndrome (SQTS) and progressive cardiac conduction disease (PCCD). Extra-cardiac features may be present, particularly with certain types of LQTS. Syndromic forms of arrhythmia are included in the table titled *Select Cardiac Syndromes, Associated Genes, and Applicable Guidelines*. Other more common arrhythmias include atrial fibrillation, early repolarization syndrome (ERS), sinus node dysfunction (SND; also called 'sick sinus syndrome') and Wolff-Parkinson-White (WPW) syndrome. These arrhythmias may occur in conjunction with some of the cardiac subtypes listed above; however, isolated cases are generally acquired.[1]

Table: Select Cardiac Syndromes, Associated Genes, and Applicable Guidelines

Syndromes that may include cardiomyopathy and/or arrhythmia, along with their associated clinical features, genes, and eviCore guidelines. Note: Some genes may be associated with both syndromic and non-syndromic forms of disease. .

Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
Anderson-Tawil Syndrome (ATS or LQTS type 7)[6]	Prominent U waves, prolonged QTc or QUc interval, or bidirectional and/or polymorphic PVCs/ VT; characteristic dysmorphic features; periodic paralysis	KCNJ2	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
Barth syndrome[1,7]	DCM; LVNC; neutropenia; muscle weakness; growth delay; infantile/early-childhood onset	TAFAZZIN (TAZ)	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114
Danon disease[1,7,8]	In males: HCM; DCM; LVNC; CCD; skeletal myopathy; retinal dystrophy; learning disability. Females may present with isolated cardiac features.	LAMP2	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114
Duchenne & Becker muscular dystrophy[1,7]	In males: DCM; CCD; muscle weakness, increased serum creatine kinase (CK); loss of ambulation. Females may present with isolated cardiac features.	DMD	Duchenne and Becker Muscular Dystrophy Testing	MOL.TS.161
Emery-Dreifuss muscular dystrophy[1,7,8]	DCM; HCM; conduction system disease, and/or arrhythmias; joint contractures; increased serum CK; muscle weakness	EMD FHL1 LMNA	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
Fabry disease[1,8]	HCM; RCM; CCD; periodic pain crises; angiokeratomas; hypohidrosis; ocular abnormalities (cornea verticillatata); hearing loss; proteinuria and renal dysfunction	GLA	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114
Friedreich ataxia[1,8]	HCM; slowly progressive ataxia at <25 years; dysarthria; muscle weakness	FXN	Friedreich Ataxia Genetic Testing	MOL.TS.309
Glycogen storage disease of the heart, lethal congenital[1,8]	HCM; conduction system disease (e.g., sinus node disease, atrial fibrillation, etc.); neonatal hypoglycemia; vacuolar myopathy; facial dysmorphism and/or macroglossia	PRKAG2	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
Hereditary transthyretin amyloidosis[1,8]	HCM; RCM; heart failure and/or aortic stenosis at ≥65 years; peripheral sensorimotor neuropathy and autonomic neuropathy; vitreous opacities, central nervous system amyloidosis	TTR	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114
HFE hemochromatosis[1,7]	DCM; non-dilated and/or infiltrative cardiomyopathy; cirrhosis; diabetes; hypermelanotic pigmentation; increased serum iron & ferritin	HFE	HFE Hemochromatosis Genetic Testing	MOL.TS.183
Laing distal myopathy[7,8]	DCM; HCM; facial weakness; childhood-onset weakness of ankles, great toes, finger extensors, & neck flexors	MYH7	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

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Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
Mitochondrial disorders[1,7]	Complex phenotypes including DCM and/or CCD; focal segmental glomerulosclerosis; Kearns-Sayre syndrome (KSS); ptosis; progressive external ophthalmoplegia; ataxia	mtDNA	Mitochondrial Disorders Genetic Testing	MOL.TS.266
Myotonic dystrophy type 1[1,7]	DCM; CCD; adults may present with muscle weakness (especially distal leg, hand, neck & face); myotonia; posterior subcapsular cataracts. Neonates: hypotonia; facial muscle weakness; generalized weakness; clubfoot; respiratory insufficiency.	DMPK	Myotonic Dystrophy Type 1 Genetic Testing	MOL.TS.312
Pompe disease[8]	HCM with onset in first few months of life; poor feeding; macroglossia; motor delay; hypotonia; muscle weakness; respiratory difficulty	GAA	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

Syndrome	Clinical Features	Genes	Applicable Guideline Name	Applicable Guideline Number
RASopathies (Noonan syndrome, cardiofacio-cutaneous syndrome, Costello syndrome, Noonan syndrome with multiple lentigines)[8]	HCM with infant or childhood onset; congenital heart defects; characteristic facies; short stature; developmental delay; broad, webbed neck; unusual chest shape	BRAF HRAS KRAS LZTR1 MAP2K1 MAP2K2 NRAS PTPN11 RAF1 RASA2 RRAS2 RIT1 SOS1 SOS2	Noonan Spectrum Disorder Genetic Testing	MOL.TS.371
Timothy Syndrome (LQTS type 8)[9]	Prolonged QT interval (QTc >480 ms); cardiovascular malformations; cutaneous syndactyly of the fingers/toes; neurological findings (autism, seizures, intellectual disability, and/or hypotonia); facial anomalies	CACNA1C	Genetic Testing to Diagnose Non-Cancer Conditions	MOL.CU.114

Prevalence

Prevalence of cardiomyopathy varies by subtype, and is estimated to be 0.2% for HCM, 0.036-0.400% for DCM, and 0.078% for ARVC in adult populations.[4] Childhood prevalence for these cardiomyopathies is 0.029% for HCM, 0.026% for DCM, and unknown for ARVC.[4] The true prevalence of RCM is unknown; it is considered the rarest cardiomyopathy subtype.[4,10]

Genetic arrhythmias have a prevalence of 1:2,500 for LQTS, 1:1000 to 1:10,000 for BrS (more common in Southeast Asia than in other regions) and 1:10,000 for CPVT.[1,11-15]

Symptoms

The severity of cardiomyopathy ranges from a lifelong asymptomatic course to thromboembolism, arrhythmia, progressive heart failure, and sudden cardiac death (SCD).[5,16] Affected individuals may present with signs and symptoms of heart failure, including peripheral edema, fatigue, orthopnea, dyspnea, syncope, and cardiac ischemia.[16] Sometimes the symptoms may suggest a particular subtype of cardiomyopathy.[4,16]

Cardiac channelopathies can be largely asymptomatic. Symptoms of ventricular arrhythmias may include palpitations, either skipped or extra beats or sustained palpitations, shortness of breath, chest pain, dizziness, near syncope, and syncope.[12] Consideration of a channelopathy is warranted when there is recurrent syncope, aborted cardiac arrest, ventricular fibrillation, or sudden death in a child or young adult.[11]

Variable expressivity and reduced penetrance have been reported for cardiomyopathy and arrhythmia syndromes, and disease onset can span all ages, from the prenatal period to late adulthood.[3,4,11,17] SCD can be the presenting symptom in some cases.[8,13,15,18]

Cause

Cardiomyopathies and arrhythmias may be inherited or acquired disorders.

Non-syndromic cardiomyopathies are "mainly caused by pathogenic variants in genes encoding the structural components of cardiomyocytes."[5] Acquired causes of cardiomyopathy can include myocarditis, stress, and/or tachycardia. Cardiomyopathy may also be associated with pregnancy and delivery.[16,19] Secondary systemic etiologies are extensive in variety, and include but are not limited to, sarcoidosis, endomyocardial fibrosis, autoimmune disease, toxin exposure, and underlying cardiac diseases such as hypertension.[3,16,19] While the percentage varies by subtype, cardiomyopathy is thought to have a genetic etiology in up to 60% of cases.[1,4,5,7,8,20] The presence of an acquired cause does not always preclude the possibility of a genetic etiology; for example, 10-15% of individuals with chemotherapy-induced, alcoholic, or peripartum DCM will have a causative gene variant.[4.]

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Genetic arrhythmias are "generally caused by defects in genes encoding cardiac ion channel macromolecular complexes and associated regulatory proteins."[5] Inherited cardiac channelopathies may present with similar clinical and ECG features to other causes for these cardiac symptoms, including heart-rhythm altering drugs, hypokalemia, syndromic genetic disorders, stroke, and structural heart disease. When a genetic etiology is suspected based on initial investigations, but a clear diagnosis cannot be established, molecular testing may help to clarify a cause.[11,14] The yield of genetic testing is highest for LQTS (70-85%) and somewhat lower for other subtypes.[1,11,14]

Inheritance

Non-syndromic cardiomyopathies and arrhythmias most commonly follow an autosomal dominant inheritance pattern.[3-5] Autosomal recessive inheritance is often associated with childhood onset, more severe cardiac disease and/or extra-cardiac manifestations.[3,7,11,20] X-linked and mitochondrial inheritance are rare and typically seen only in syndromic cases.[3,7]

Diagnosis

Diagnosis of a cardiomyopathy or arrhythmia can often be confirmed with cardiac imaging (e.g., echocardiography, cardiac magnetic resonance imaging [CMR]) and/or electrocardiogram (ECG). Cases of arrhythmia may be further evaluated with the use of exercise testing, toxicology, and blood testing.[13,21] Endomyocardial biopsy (EMB) may aid in the diagnosis of a cardiomyopathy in some cases.[4,10] A detailed clinical history and evaluation should aim to exclude acquired and secondary causes when an isolated genetic etiology is under consideration.

Consensus clinical diagnostic criteria have been developed for most recognized subtypes of cardiomyopathy and arrhythmia.

- **Arrhythmogenic cardiomyopathy (ACM):** Task force diagnostic criteria for ARVC were most recently proposed by Corrado et al in 2024 to refine the "Padua criteria" proposed in 2020, which in turn were an update to the criteria by Marcus et al in 2010.[18,22,23] As summarized in an expert-authored review, these criteria use findings from cardiac imaging, EMB, ECG, family history, and/or genetic testing to classify individuals as having a definite, borderline, or possible diagnosis of ARVC.[20] The updated criteria seek to improve the diagnostic sensitivity for ALVC and BiVAC, but have not yet been validated in larger studies.[20,22]
- **Brugada syndrome (BrS):** A clinical diagnosis of BrS is suspected in an individual with a type 1, type 2, or type 3 ECG pattern and at least one of the following: recurrent syncope, ventricular fibrillation, self-termination polymorphic ventricular tachycardia, cardiac arrest, or family history of SCD. The diagnosis is established clinically in the majority of cases, although genetic testing may help confirm it.[14]

- **Catecholaminergic polymorphic ventricular tachycardia (CPVT):** CPVT can be diagnosed clinically based on cardiac findings and/or the presence of a pathogenic or likely pathogenic mutation.[15,24] A scoring system has also been developed to categorize the pretest probability of CPVT, with a score of 3.5 or greater indicating a high probability of having the condition.[1]
- **Dilated cardiomyopathy (DCM):** The diagnosis of DCM is established in individuals having the following findings on echocardiogram or cardiac MRI: left ventricular enlargement and systolic dysfunction.[7]
- **Hypertrophic cardiomyopathy (HCM):** The diagnosis of HCM is typically established with cardiac imaging (echocardiogram and/or cardiac MRI), and is defined by the presence of unexplained left ventricular hypertrophy (LVH) with a maximum wall thickness ≥15 mm in adults or a z-score >3 in children. In individuals with a family history of HCM, a maximum left ventricular wall thickness of ≥13 mm supports the diagnosis.[8]
- **Long QT syndrome (LQTS):** Schwartz et al developed a clinical diagnostic scoring system for this condition, which was last updated in 2011.[25] As described in an expert-authored review, this score is used to calculate the risk of having LQTS, with a score of 1.5-3 indicating an intermediate risk, and a score of ≥3.5 indicating a high risk.[11] A diagnosis of LQTS can be made with a Schwartz diagnostic score ≥3.5, a pathogenic mutation in an LQTS gene, or specific ECG findings.[24]
- **Progressive cardiac conduction disease (PCCD):** A diagnosis of PCCD can be made in individuals with unexplained progressive conduction abnormalities at a young age (<50 years), structurally normal hearts, and absence of skeletal myopathies, especially when there is a family history of PCCD.[24]
- **Restrictive cardiomyopathy (RCM):** Consensus diagnostic criteria for RCM are currently lacking.[10,26] A 2022 expert-authored review proposed an updated strategy for the diagnosis of this condition, which includes identification of a restrictive pathophysiology confirmed in repeated evaluations, absence of ventricular dilatation, and investigation of red flags for specific conditions among clinical, ECG, and imaging findings.[26]
- **Short QT syndrome (SQTS):** A diagnosis of SQTS can be made in the presence of a QTc <330 ms or with a QTc <360 ms when at least one of the following is present: a pathogenic mutation, family history of SQTS, family history of sudden death at age ≤40, or survival of a ventricular tachycardia/fibrillation episode in the absence of heart disease.[24]

The yield of genetic testing varies by subtype, and the presence of a family history usually increases the likelihood of identifying a causative mutation.[1,3-5,27] Genetic testing can be useful to confirm a diagnosis of inherited cardiomyopathy or arrhythmia in persons with cardiac symptoms and has been incorporated into the diagnostic criteria for ARVC, CPVT, LQTS, and SQTS.[1,4,11,15,20,24] Post-mortem genetic testing may be

performed after a sudden death when an inherited cardiomyopathy or arrhythmia is suspected in order to aid in the risk assessment of family members.[1,5,13,21]

Once a disease-causing mutation is identified, at-risk relatives can have reliable genetic testing to define their risk and screening needs. Identifying a gene mutation significantly changes medical management in symptomatic individuals without a clinical diagnosis and may improve life expectancy.[3,4,7,13,17] For relatives who are not found to have the familial pathogenic mutation, it may be possible to eliminate the need for ongoing clinical surveillance and other medical expenditures.[1,3,4,17] Clinical screening is recommended for family members when genetic testing was not performed in the affected individual or failed to identify a causative mutation.[1,12]

Management

Treatment of cardiomyopathies and arrhythmias is focused on controlling and preventing symptoms. Management may include therapy and/or screening for heart failure, activity restriction, pharmacologic therapy (including beta blockers), catheter ablation, consideration of a pacemaker or implantable cardioverter defibrillator (ICD), and heart transplantation.[4,13,19] The identification of a genetic variant may provide prognostic information, guide treatment strategies, and allow for earlier intervention.[1,3,5,13] Genotype-phenotype correlation exists for a subset of genes, and management recommendations have been developed for certain genes/mutations.[1,13,17,20,28] Identification of a syndromic form may also facilitate surveillance and treatment for associated extra-cardiac manifestations.[3,4,13]

Survival

Cardiomyopathy and arrhythmia are both associated with a higher mortality rate than is seen in the general population.[13,19] Some factors that may affect the survival rate include age at diagnosis, presence of symptoms, etiology, and cardiac subtype.[13,19] Diagnosis and appropriate treatment has led to a decrease in the mortality rate for some of these disorders.[3,11]

A significant proportion of SCD is attributed to genetic arrhythmias and, to a lesser extent, cardiomyopathies, especially in individuals under the age of 50 years.[1,13] SCD can occur in all subtypes of cardiomyopathy and arrhythmia.[13] The overall risk, age distribution, and triggering factors vary by subtype.[13]

Test information

Testing for cardiomyopathies may include known familial mutation analysis, single gene sequencing or deletion/duplication analysis, or multigene panel testing.

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Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Panels may be subtype-specific (e.g., long QT syndrome panel, hypertrophic cardiomyopathy panel, etc.) or broad panels that address multiple cardiomyopathy and/or arrhythmia subtypes. Due to overlapping clinical features and associated genes, panels that include genes for multiple cardiac subtypes are increasingly employed, and often include syndromes with important medical management implications.[3]

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Guidelines and evidence

The following section includes relevant guidelines and evidence pertaining to cardiomyopathy and arrhythmia genetic testing.

American College of Cardiology, American Heart Association Task Force, and Heart Rhythm Society

A guideline from the American College of Cardiology, the American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society (ACC/AHA/HRS, 2017) on the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (SCD) made the following recommendations regarding genetic testing for these indications:[12]

- "In young patients (<40 years of age) with unexplained SCA [sudden cardiac arrest], unexplained near drowning, or recurrent exertional syncope, who do not have ischemic or other structural heart disease, further evaluation for genetic arrhythmia syndromes is recommended." (Class I, Level B)
- "In first-degree relatives of SCD victims who were 40 years of age or younger, cardiac evaluation is recommended, with genetic counseling and genetic testing performed as indicated by clinical findings." (Class I, Level B)
- "In patients and family members in whom genetic testing for risk stratification for SCA or SCD is recommended, genetic counseling is beneficial." (Class I, Level C)

The ACC/AHA/HRS 2017 guideline also made the following recommendations regarding genetic testing for specific cardiomyopathies and arrhythmias:[12]

- Nonischemic Cardiomyopathy (NICM):
  - "In patients with NICM [nonischemic cardiomyopathy] who develop conduction disease or LV dysfunction at less than 40 years of age, or who have a family history of NICM or SCD in a first-degree relative (<50 years of age), genetic counseling and genetic testing are reasonable to detect a heritable disease that may clarify prognosis and facilitate cascade screening of relatives." (Class IIa, Level C)
- Arrhythmogenic Right Ventricular Cardiomyopathy:
  - "In selected first-degree relatives of patients with arrhythmogenic right ventricular cardiomyopathy, clinical screening for the disease is recommended along with genetic counseling and genetic testing, if the proband has a disease causing mutation." (Class I, Level B)
  - "In patients with clinically diagnosed or suspected arrhythmogenic right ventricular cardiomyopathy, genetic counseling and genetic testing can be useful for diagnosis and for gene-specific targeted family screening." (Class IIa, Level B)
- Hypertrophic Cardiomyopathy (HCM):

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  - "In first-degree relatives of patients with HCM due to a known causative mutation, genetic counseling and mutation-specific genetic testing are recommended." (Class I, Level B).
  - "In patients with clinically suspected or diagnosed HCM, genetic counseling and genetic testing are reasonable." (Class IIa, Level B)
- Long QT Syndrome (LQTS):
  - The authors highlighted the ability to stratify risk based on genotype in LQTS and stated, "In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended." (Class I, Level B)
- Catecholaminergic Polymorphic Ventricular Tachycardia:
  - "In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable." (Class IIa, Level B)
- Brugada Syndrome:
  - "In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives." (Class IIb, Level C)
- Short QT Syndrome:
  - "In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives." (Class IIb, Level C)
- Early Repolarization Syndrome:
  - "In patients with early repolarization pattern on ECG, genetic testing is not recommended." (Class III: No Benefit, Level B)

In a guideline for the evaluation and management of patients with bradycardia (including sinus node disease) and cardiac conduction delay authored by the American College of Cardiology, the American Heart Association Task Force, and the Heart Rhythm Society (ACC/AHA/HRS, 2018), genetic testing was not included in the diagnostic algorithms for these conditions, and the authors acknowledged that these disorders are usually acquired. However, they made the following recommendations:[29]

- "In patients in whom a conduction disorder-causative mutation has been identified, genetic counseling and mutation-specific genetic testing of first-degree relatives is recommended to identify similarly affected individuals." (Class I, Level C)
- "In patients with inherited conduction disease, genetic counseling and targeted testing may be considered to facilitate cascade screening of relatives as part of the diagnostic evaluation." (Class IIb, Level C)

American College of Cardiology, American Heart Association Task Force, American College of Clinical Pharmacy, and Heart Rhythm Society

In a guideline for the management of patients with atrial fibrillation (AF), the American College of Cardiology, American Heart Association Task Force, American College of

Clinical Pharmacy and Heart Rhythm Society (ACC/AHA/ACCP/HRS, 2023) stated the following regarding genetic testing for this condition:[30]

- "In patents with an onset of AF before 45 years of age without obvious risk factors for AF, referral for genetic counseling, genetic testing for rare pathogenic variants, and surveillance for cardiomyopathy or arrhythmia syndromes may be reasonable." (Class IIb, Level B)

American College of Cardiology and American Heart Association

A joint committee guideline from the American College of Cardiology and American Heart Association (ACC/AHA, 2020) made the following class 1 recommendations for HCM:[31]

- "When performing genetic testing in an HCM proband, the initial tier of genes tested should include genes with strong evidence to be disease-causing in HCM."
- "In first-degree relatives of patients with HCM, both clinical screening (ECG and 2D echocardiogram) and cascade genetic testing (when a pathogenic/likely pathogenic variant has been identified in the proband) should be offered."
- "In patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause, a work-up including genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy ('HCM phenocopies') is recommended."

Asia Pacific Heart Rhythm Society and Heart Rhythm Society

The Asia Pacific Heart Rhythm Society and the Heart Rhythm Society (APHRS/HRS, 2020) made the following recommendations in regards to sudden cardiac arrest (SCA) and sudden unexplained death (SUD):[21]

- "Genetic evaluation of SCA survivors is recommended for those with a diagnosed or suspected genetic cardiac disease phenotype when the results are likely to influence diagnosis, management, or family screening." (Class 1, Level B)
- "When genetic evaluation is performed in an SCA survivor with a suspected or diagnosed genetic cardiac disease phenotype, it is recommended that evaluations include only genes where there is robust gene–disease association." (Class 1, Level B)
- "Genetic testing in SCA survivors with a well-established nongenetic cause of SCA is not recommended." (Class 3: No benefit, Level C)
- "Family screening should include genetic testing and clinical evaluation when genetic testing of a proband with SUD detects a pathogenic or likely pathogenic variant." (Class 1, Level B)
- "If a pathogenic or likely pathogenic variant that fits the phenotype has been identified in an SUD proband, first-degree relatives should be offered DNA testing, with ongoing clinical evaluation for those testing positive." (Class 1, Level C)

- "It is recommended that genetic testing in families where an SUD or resuscitated SCA due to a heritable cause is suspected is performed only with appropriate genetic counseling." (Class 1, Level C)

European Heart Rhythm Association, Asia Pacific Heart Rhythm Society, Heart Rhythm Society, and Latin American Heart Rhythm Society

An expert consensus statement from the European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, and Latin American Heart Rhythm Society (EHRA/HRS/APHRS/LAHRS, 2022) addressed the utility and appropriateness of genetic testing for inherited cardiovascular conditions.[1] The consensus statements were categorized as follows:

- Supported by strong observational evidence and author's consensus
- Some evidence and general agreement favor the usefulness/ efficacy of a test
- There is evidence or general agreement not to recommend a test

Regarding the choice of genetic testing, EHRA/HRS/APHRS/LAHRS (2022) stated the following:[1]

- Genetic testing should occur with genetic counseling. [Supported by strong observational evidence and authors' consensus]
- If an individual has a clear phenotype, it is appropriate to analyze genes with definite/ strong evidence support disease causation [Supported by strong observational evidence and author's consensus] and may be appropriate to analyze genes with moderate evidence for disease causation. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
- In some cases with a clear phenotype and negative genetic testing of genes with definite/strong evidence for disease causation, broader genetic testing may be considered. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
- "Genetic testing for genes with (i) limited, (ii) disputed, or (iii) refuted evidence should not be performed in patients with a weak (non-definite) phenotype in the clinical setting." [There is evidence or general agreement not to recommend a test]
- When a likely pathogenic or pathogenic variant has been identified, genetic counseling should be offered. The inheritance pattern, penetrance, and associated risks can be discussed. Additionally, cascade testing for relatives should be facilitated. [Supported by strong observational evidence and author's consensus]
- Some affected individuals may have had previous genetic testing that was not a comprehensive, such as prior to the use of next generation sequencing or with an incomplete testing panel. Repeat testing should be considered in these cases. [Supported by strong observational evidence and author's consensus]

Regarding genetic testing for specific cardiomyopathies and arrhythmias, EHRA/HRS/APHRS/LAHRS (2022) stated the following:[1]

- Long QT Syndrome (LQTS):
  - Genetic testing for genes with a definitive disease association was recommended for all patients with a high probability of LQTS (Schwartz Score ≥ 3.5) [Supported by strong observational evidence and author's consensus]. Testing of less definitive genes could also be considered in these individuals [Some evidence and general agreement favor the usefulness/ efficacy of a test].
  - Genetic testing of definitive disease-associated genes should also be offered to "all patients with acquired LQTS who experienced drug-induced TdP [torsades de pointes], are aged below 40 years and have a QTc >440 ms (males) and >450 ms (females) in the absence of culprit drug" [Supported by strong observational evidence and author's consensus].
  - Targeted gene analysis was recommended in patients with Jervell and Lange-Nielsen syndrome, Timothy syndrome, Andersen–Tawil syndrome, and suspected triadin knockout syndrome [Supported by strong observational evidence and author's consensus].
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT):
  - Genetic testing for genes with definite/strong evidence of disease association is recommended for individuals meeting diagnostic criteria for CPVT ("Class 1 clinical diagnosis or CPVT diagnostic score >3.5") [Supported by strong observational evidence and author's consensus].
  - Genetic testing can also be considered for individuals with a modest CPVT phenotype ("i.e. CPVT diagnostic score ≥ 2 but < 3.5") [Some evidence and general agreement favor the usefulness/ efficacy of a test].
  - For individuals meeting CPVT diagnostic criteria, genetic testing could also be considered for CPVT phenocopies (e.g., pathogenic variants in the KCNJ2, SCN5A, and PKP2 genes) [Some evidence and general agreement favor the usefulness/ efficacy of a test].
- Short QT Syndrome (SQTS):
  - Genetic testing for genes with definite/strong evidence of disease association was recommended for individuals meeting diagnostic criteria for SQTS ("Class 1 clinical diagnosis or SQTS diagnostic score >4") [Supported by strong observational evidence and author's consensus].
  - Testing of the KCNJ2 and SLC4A3 genes could be considered in individuals with an SQTS diagnostic score ≥4. [Some evidence and general agreement favor the usefulness/ efficacy of a test].
- Brugada Syndrome (BrS):
  - "Genetic testing with sequencing of SCN5A is recommended for an index case diagnosed with BrS with a type I ECG in standard or high precordial leads occurring either (i) spontaneously, or (ii) induced by sodium-channel blockade in presence of supporting clinical features or family history" [Supported by strong observational evidence and author's consensus].

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  - "Rare variants in genes with a disputed or refuted gene-disease clinical validity should not be reported routinely for BrS genetic testing in a diagnostic setting" [There is evidence or general agreement not to recommend a test].
- Progressive Cardiac Conduction Disease (PCCD/CCD):
  - "Targeted genetic testing is recommended as part of the diagnostic evaluation for index patients with isolated cardiac conduction disease (CCD/PCCD) or with concomitant structural heart disease or extracardiac disease, when there is early age of diagnosis or a suspicion of laminopathy, especially when there is documentation of a positive family history of CCD/PCCD" [Supported by strong observational evidence and author's consensus]. Such testing could also be considered for individuals "with isolated cardiac conduction disease (CCD/PCCD) or with concomitant structural heart disease or extracardiac disease, especially in the setting of a positive family history" [Some evidence and general agreement favor the usefulness/ efficacy of a test].
- Other Arrhythmias:
  - The authors stated that targeted genetic testing could be considered for individuals with familial atrial fibrillation (AF at age <60), unexplained cardiac arrest survivors with a clinical diagnosis of early repolarization syndrome (ERS), and for individuals "with familial or isolated, but otherwise unexplained sinus node dysfunction (SND)" [Some evidence and general agreement favor the usefulness/ efficacy of a test].
  - No recommendations were made regarding genetic testing for Wolff-Parkinson-White (WPW) syndrome, as the authors concluded "only in the presence of the combination of pre-excitation and HCM and/or progressive CCD is genetic testing pertinent."
- Hypertrophic cardiomyopathy (HCM):
  - Comprehensive genetic testing was recommended for all individuals with HCM, using a first tier of genes with a definitive/strong disease association [Supported by strong observational evidence and author's consensus]. According to the authors, the inclusion of genes with moderate evidence of pathogenicity should also be considered [Some evidence and general agreement favor the usefulness/ efficacy of a test].
  - The authors also recommended genetic testing in "patients with atypical clinical presentation of HCM, or when another genetic condition associated with unexplained hypertrophy is suspected (e.g. HCM phenocopy)." [Supported by strong observational evidence and author's consensus]
- Dilated cardiomyopathy (DCM):
  - Comprehensive genetic testing was recommended for all individuals with DCM with a family history of DCM, using a first tier of genes with a definitive/strong disease association [Supported by strong observational evidence and author's consensus]. The authors stated that the inclusion of genes with moderate evidence

of pathogenicity could also be considered in these individuals [Some evidence and general agreement favor the usefulness/ efficacy of a test].
    - Genetic testing could be considered in individuals with apparently sporadic DCM, or "patients with DCM related to an acquired or environmental cause that may overlap with a genetic cause (such as peripartum or alcoholic cardiomyopathy)." [Some evidence and general agreement favor the usefulness/ efficacy of a test].
- Arrhythmogenic cardiomyopathy (ACM):
    - Comprehensive testing of definitive disease-associated genes was recommended for all individuals with features of ACM [Supported by strong observational evidence and author's consensus].
    - Genetic testing could also be considered in individuals with a borderline ACM phenotype [Some evidence and general agreement favor the usefulness/ efficacy of a test].
- Left Ventricular Non-compaction (LVNC):
    - Genetic testing could be considered for individuals with LVNC in whom a cardiologist has established a diagnosis based on clinical history, family history, and electrocardiographic/echocardiographic/MRI phenotype. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
    - "Genetic testing should not be performed in isolated (incidental) LVNC with normal LV function, no associated syndromic features and no family history." [There is evidence or general agreement not to recommend a test]
- Restrictive Cardiomyopathy (RCM):
    - Genetic testing could be considered for individuals with RCM in whom a cardiologist has established a diagnosis based on clinical history, family history, and electrocardiographic/echocardiographic/MRI phenotype. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
    - Genetic testing of the TTR gene was specifically recommended for patients with RCM and a clinical diagnosis of cardiac TTR amyloidosis. [Supported by strong observational evidence and author's consensus]

Lastly, EHRA/HRS/APHRS/LAHRS (2022) made recommendations regarding genetic testing in survivors of unexplained cardiac arrest (UCA) or relatives of individuals with sudden cardiac death (SCD):[1]

- "In selected UCA survivors with idiopathic VF [ventricular fibrillation], genetic testing for founder variants, where relevant, should be considered." [Supported by strong observational evidence and authors' consensus]
- "In relatives of UCA survivors or SCD decedents, clinical evaluation of 1st degree family members should be performed, and targeted to the index case's phenotype if present."
- "In decedents with SCD or survivors with cardiac arrest in whom a non-genetic cause has been identified, genetic testing of the index case and clinical evaluation of

relatives should not be performed." [There is evidence or general agreement not to recommend a test]

European Society of Cardiology

In their 2023 guidelines for the management of cardiomyopathies, the European Society for Cardiology (ESC, 2023) made the following genetic testing recommendations:[4]

- "Genetic counselling, provided by an appropriately trained healthcare professional and including genetic education to inform decision-making and psychosocial support, is recommended for families with an inherited or suspected inherited cardiomyopathy, regardless of whether genetic testing is being considered." (Class I, Level B)
- "It is recommended that genetic testing for cardiomyopathy is performed with access to a multidisciplinary team, including those with expertise in genetic testing methodology, sequence variant interpretation, and clinical application of genetic testing, typically in a specialized cardiomyopathy service or in a network model with access to equivalent expertise." Also, "pre- and post-test genetic counselling is recommended in all individuals undergoing genetic testing for cardiomyopathy." (Class I, Level B)
- "Genetic testing is recommended in patients fulfilling diagnostic criteria for cardiomyopathy in cases where it enables diagnosis, prognostication, therapeutic stratification, or reproductive management of the patient, or where it enables cascade genetic evaluation of their relatives who would otherwise be enrolled into long-term surveillance." (Class I, Level B)
- "Genetic testing may be considered in patients fulfilling diagnostic criteria for cardiomyopathy when it will have a net benefit to the patient, considering the psychological impact and preference, even if it does not enable diagnosis, prognostication, or therapeutic stratification, or cascade genetic screening of their relatives." (Class IIb, Level C)
- "Genetic testing in patients with a borderline phenotype not fulfilling diagnostic criteria for a cardiomyopathy may be considered only after detailed assessment by specialist teams." (Class IIb, Level C)
- "It is recommended that cascade genetic testing, with pre- and post-test counselling, is offered to adult at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives if available, and cascading out sequentially)." (Class I, Level B)
- "Cascade genetic testing with pre- and post-test counselling should be considered in paediatric at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives, if available, and cascading out sequentially), considering the underlying cardiomyopathy, expected age of onset, presentation in the family, and clinical/legal consequences." (Class IIa, Level B)

- "Testing for the presence of a familial variant of unknown significance, typically in parents and/or affected relatives, to determine if the variant segregates with the cardiomyopathy phenotype should be considered if this might allow the variant to be interpreted with confidence." (Class IIa, Level C)
- "Diagnostic genetic testing is not recommended in a phenotype-negative relative of a patient with cardiomyopathy in the absence of a confident genetic diagnosis (i.e. a P/LP variant) in the family." (Class III, Level C)

2022 European Society of Cardiology guidelines (ESC, 2022), which were endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC, 2022), addressed the management of individuals with ventricular arrhythmias [VA] and the prevention of sudden cardiac death [SCD]. They stated the following regarding genetic testing for these indications:[13]

- "Genetic testing is recommended when a condition is diagnosed in a living or deceased individual with a likely genetic basis and a risk of VA and SCD." (Class I, Level B)
- "When a putative causative variant is first identified, evaluation for pathogenicity is recommended using an internationally accepted framework." (Class I, Level C)
- "When a Class IV or Class V variant has been identified in a living or deceased individual with a condition that carries a risk of VA and SCD, genetic testing of first-degree and symptomatic relatives and obligate carriers is recommended." (Class I, Level C)
- "It is recommended that genetic testing and counselling on its potential consequences should be undertaken by an expert multidisciplinary team." (Class I, Level C)
- "It is recommended that Class III (variants of uncertain significance) and Class IV variants should be evaluated for segregation in families where possible, and the variant re-evaluated periodically." (Class I, Level C)
- "It is not recommended to undertake genetic testing in index patients with insufficient evidence of a genetic disease." (Class III, Level C)

The 2022 ESC guidelines also included the following recommendations regarding testing for specific arrhythmias and cardiomyopathies:[13]

- Long QT Syndrome (LQTS):
  - "In patients with clinically diagnosed LQTS, genetic testing, and genetic counselling are recommended." (Class I, Level C)
  - "It is recommended that LQTS is diagnosed in the presence of a pathogenic mutation, irrespective of the QT duration." (Class I, Level C) The guideline also noted that genetic testing is useful in providing genotype-specific risks and, in some cases, genotype-specific treatment.
  - "Genetic testing is recommended in patients with suspected Anderson-Tawil syndrome." (Class I, Level C)
- Brugada Syndrome (BrS):

  - "Genetic testing for SCN5A gene is recommended for probands with BrS." (Class I, Level C)
  - The authors also noted: "The yield of genetic testing in BrS patients is approximately 20%, with the SCN5A gene the only gene with evidence of association for clinical testing purposes."
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT):
  - "Genetic testing and genetic counselling are indicated in patients with clinical suspicion or clinical diagnosis of CPVT." (Class I, Level C)
  - "It is recommended that CPVT is diagnosed in patients who are carriers of a mutation in disease-causing genes." (Class I, Level C)
- Short QT Syndrome (SQTS):
  - "Genetic testing is indicated in patients diagnosed with SQTS." (Class I, Level C)
  - "It is recommended that SQTS is diagnosed in the presence of a QTc ≤360ms and one or more of the following: (a) a pathogenic mutation, (b) a family history of SQTS, (c) survival from a VT/VF episode in the absence of heart disease." (Class I, Level C)
- Early repolarization syndrome (ERS):
  - "Genetic testing in ERS patients may be considered." (Class IIb, Level C)
- Dilated Cardiomyopathy (DCM):
  - "Genetic testing (including at least LMNA, PLN, RBM20, and FLNC genes) is recommended in patients with DCM/HNDCM [hypokinetic non-dilated cardiomyopathy] and AV [atrioventricular] conduction delay at <50 years, or who have a family history of DCM/HNDCM or SCD in a first-degree relative (at age <50 years)." (Class I, Level B)
  - "Genetic testing (including at least LMNA, PLN, RBM20, and FLNC genes) should be considered for risk stratification in patients with apparently sporadic DCM/HNDCM, who present at young age, or with signs suspicious for an inherited aetiology." (Class IIa, Level C)
- Arrhythmogenic right ventricular cardiomyopathy (ARVC):
  - "In patients with a suspected or definite diagnosis of ARVC, genetic counselling and testing are recommended." (Class I, Level B)
- Hypertrophic cardiomyopathy (HCM):
  - "Genetic counselling and testing are recommended in HCM patients." (Class I, Level B)

Heart Failure Society of America and American College of Medical Genetics and Genomics

The Heart Failure Society of America in collaboration with the American College of Medical Genetics and Genomics (HFSA/ACMG, 2018) stated the following regarding cardiomyopathy genetic testing:[3]

- "Guideline 4: Genetic testing is recommended for patients with cardiomyopathy" (Level of evidence A for HCM, DCM, ARVC, and cardiomyopathies associated with extracardiac manifestations; evidence level B for RCM)
  - "4a: Genetic testing is recommended for the most clearly affected family member."
  - "4b: Cascade genetic testing of at-risk family members if recommended for pathogenic and likely pathogenic variants."
  - "4c: In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered."
- "Genetic testing is recommended to determine if a pathogenic variant can be identified to facilitate patient management and family screening."
- "Testing should ideally be initiated on the person in a family with the most definitive diagnosis and most severe manifestations. This approach would maximize the likelihood of obtaining diagnostic results and detecting whether multiple pathogenic variants may be present and contributing to variable disease expression or severity."
- "Molecular genetic testing for multiple genes with the use of a multigene panel is now the standard of practice for cardio-vascular genetic medicine. Furthermore, multigene panel genetic testing is recommended over a serial single-gene testing approach owing to the genetically heterogeneous nature of cardiomyopathy. Genetic testing and cascade screening have been shown to be cost-effective."
- "[T]he LVNC phenotype may be observed in conjunction with all other cardiomyopathy phenotypes, so considerations related to genetic testing should always be directed by findings of a cardiomyopathy (or other cardiovascular) phenotype. Genetic testing is not recommended when the LVNC phenotype is identified serendipitously in asymptomatic individuals with otherwise normal cardiovascular structure and function."

The American College of Medical Genetics and Genomics (ACMG, 2018) published a practice resource on genetic testing for cardiomyopathies.[31] This practice resource was an abbreviated version of the Heart Failure Society of America (HFSA) guideline above, on which the ACMG collaborated.

Heart Rhythm Society

In a consensus statement focused on arrhythmogenic cardiomyopathy (ACM), the Heart Rhythm Society (HRS, 2019) stated the following:[33]

- "For individuals and decedent with either a clinical or necropsy diagnosis of ACM, genetic testing of the established ACM-susceptibility genes is recommended." (Class I, Level C)
- "For genetic testing of the established ACM-susceptibility genes, comprehensive analysis of all established genes with full coverage is recommended." (Class I, Level C)

Heart Rhythm Society, European Heart Rhythm Association, and Asia Pacific Heart Rhythm Society

An expert consensus statement from the Heart Rhythm Society, the European Heart Rhythm Association, and the Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS, 2013) for the diagnosis and management of inherited primary arrhythmia established diagnostic criteria for multiple arrhythmia syndromes and recommended that genetic test results be incorporated into the criteria for LQTS, CPVT, and SQTS.[24] These recommendations were endorsed by the American College of Cardiology Foundation (ACCF, 2013), American Heart Association (AHA, 2013), Pediatric and Congenital Electrophysiology Society (PACES, 2013), and Association for European Paediatric and Congenital Cardiology (AEPC, 2013). No specific recommendations were made for when to perform genetic testing, since this topic was addressed elsewhere.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for cardiomyopathy and arrhythmia genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Charcot-Marie-Tooth Neuropathy Genetic Testing

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Genetic testing for Charcot-Marie-Tooth (CMT) disease is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
CMT gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
CMT known familial mutation analysis	81403
Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)	81448
PMP22 deletion/duplication analysis	81324

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Procedures addressed by this guideline	Procedure codes
PMP22 known familial mutation analysis	81326
PMP22 sequencing	81325

Criteria

Requests for Charcot-Marie-Tooth (CMT) genetic testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, and
  - Pathogenic CMT-related mutation in a 1st or 2nd degree biologic relative, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Distal muscle weakness and atrophy, or
  - Weak ankle dorsiflexion (e.g. foot drop), or
  - Distal sensory loss, or
  - Depressed or absent tendon reflexes, or
  - Foot deformity (e.g. high arches, hammer toes, pes cavus), or
  - Electrodiagnostic studies consistent with a peripheral neuropathy, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Age 18 years or older, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

PMP22 Deletion/Duplication Analysis

- Previous Genetic Testing:
  - No previous PMP22 deletion/duplication analysis, and
  - No known CMT-related mutation in the member or the member's family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Distal muscle weakness and atrophy, or
  - Weak ankle dorsiflexion (e.g. foot drop), or
  - Distal sensory loss, or
  - Depressed or absent tendon reflexes, or
  - Foot deformity (e.g. high arches, hammer toes, pes cavus), AND

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- The member does not have an underlying non-genetic cause for their neuropathy (e.g. diabetic neuropathy, vitamin B12 deficiency, chronic inflammatory demyelinating polyneuropathy), or clinical suspicion for a gene mutation remains high even in the presence of a non-genetic cause, AND
- Member's electrodiagnostic studies are consistent with a primary demyelinating neuropathy, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

CMT Neuropathy Multigene Panel

Multi-gene panels will be considered medically necessary when the following criteria are met:

- Previous Genetic Testing:
  - No previous CMT neuropathy multi-gene panel testing, and
  - No known CMT-related mutation in the member or the member's family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Distal muscle weakness and atrophy, or
  - Weak ankle dorsiflexion (e.g. foot drop), or
  - Distal sensory loss, or
  - Depressed or absent tendon reflexes, or
  - Foot deformity (e.g. high arches, hammer toes, pes cavus), AND
- The member does not have an underlying non-genetic cause for their neuropathy (e.g. diabetic neuropathy, vitamin B12 deficiency, chronic inflammatory demyelinating polyneuropathy), or clinical suspicion for a gene mutation remains high even in the presence of a non-genetic cause, AND
- The panel includes the genes with the highest diagnostic yield for the member's suspected CMT neuropathy subtype, AND
- Member's electrodiagnostic studies are consistent with an axonal neuropathy or combined axonal and demyelinating neuropathy (e.g., CMT1 is NOT the most likely diagnosis), OR
- Member's electrodiagnostic studies are consistent with a primary demyelinating neuropathy (e.g., CMT1 is the most likely diagnosis) and PMP22 deletion/duplication analysis was previously performed and was negative, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

Other Considerations

Broad CMT neuropathy panels are not medically necessary when a narrower panel is available and more appropriate based on the clinical finding.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81448*).
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
  - When the test is billed with multiple stacked codes, only sequencing of the following genes may be considered for reimbursement, based on electrodiagnostic findings and the family history:
    - Primary demyelinating neuropathy with negative PMP22 deletion/duplication analysis (CMT1 suspected): GDAP1, MPZ, and PMP22. If there is no evidence of male-to-male transmission in the family, GJB1 (for CMTX) is also reimbursable.
    - Primary axonal neuropathy (CMT2 suspected): GDAP1, MFN2, MPZ, HINT1, SH3TC2, and SORD. If there is no evidence of male-to-male transmission in the family, GJB1 (for CMTX) is also reimbursable.
    - Combined axonal and demyelinating neuropathy (intermediate CMT suspected): GDAP1, MPZ, and SORD. If there is no evidence of male-to-male transmission in the family, GJB1 (for CMTX) is also reimbursable.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is Charcot-Marie-Tooth Hereditary Neuropathy?

Charcot-Marie-Tooth Hereditary Neuropathy (CMT) is a group of inherited genetic conditions characterized by chronic motor and sensory polyneuropathy.[1]

Prevalence

CMT is the most common inherited neurological disorder. The prevalence of all CMT types is 1 in 2,500.[2]

Symptoms

The key finding in CMT is symmetric, slowly progressive distal motor neuropathy of the arms and legs, usually beginning in the first to third decade and resulting in weakness and atrophy of the muscles in the feet and/or hands. This is expressed as distal muscle weakness and atrophy, weak ankle dorsiflexion, depressed tendon reflexes, and pes cavus foot deformity (e.g. high arched feet).[1]

Cause

The most common cause of CMT is a large chromosome 17 duplication involving the PMP22 gene (CMT1A), but more than 80 different genes have been associated with CMT.[1]

As more genes causing CMT were identified and as the overlap of neuropathy phenotypes and modes of inheritance became apparent, the previous alphanumeric classification system proved unwieldy and inadequate. In 2018, Magy et al proposed a gene-based classification of inherited neuropathies, which includes a comprehensive list of CMT-associated genes and correlation with the alphanumeric classification.[3] An additional advantage of this classification system is that an individual's findings can be described in terms of mode of inheritance, neuropathy type, and gene.

Inheritance

CMT can be inherited in an autosomal dominant, autosomal recessive, or an X-linked manner.[1] De novo cases are reported, but the proportion ranges widely depending on the gene involved.[1]

Diagnosis

"The clinical diagnosis of CMT in a symptomatic person is based on characteristic findings of peripheral neuropathy on medical history and physical examination."[1] "CMT . . . needs to be distinguished from the following entities: systemic disorders with neuropathy, other types of hereditary neuropathy, distal myopathies, hereditary sensory neuropathies (HSN), and acquired disorders."[1]

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Molecular genetic testing can be used to establish a specific diagnosis, which aids in understanding the prognosis and risk assessment for family members.[1]

A 1.5Mb duplication at 17p11.2 that includes the PMP22 gene is the most common cause of CMT, accounting for up to 50% of cases.[1] Therefore, PMP22 deletion/duplication analysis is recommended as a first tier diagnostic test.[1] If negative, a multi-gene testing panel may be indicated.

Management

Management of CMT is symptom-based, and is often accomplished through a multidisciplinary team.[1] Treatment addresses neurological deficits and mobility issues, often including physical and occupational therapies and orthoses to aid in walking.[1]

Survival

Life span is normal in many forms of CMT, but quality of life is often impacted by the degree of physical disability experienced.[1]

Test information

Testing for CMT may include known familial mutation analysis, deletion/duplication analysis, and/or multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally,

tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

CMT multi-gene testing panels include a wide variety of genes associated with CMT neuropathy. The following are points to consider regarding multi-gene panel testing for CMT:[1,4]

- Multi-gene testing panels may include genes without clear management recommendations. A comprehensive panel with simultaneous testing of genes not associated with CMT may not be cost-effective or necessary.
- Multi-gene testing panels may vary in technical specifications (e.g. depth of coverage, large deletion/duplication analysis, etc).
- Given differences in testing methods and sensitivity, single-gene testing after a negative multi-gene testing panel may be warranted if there is a high clinical suspicion for a particular syndrome.
- The genes included on a multi-gene testing panel may vary. The medical record should document the performing laboratory and genes tested.

Guidelines and evidence

American Academy of Neurology

Evidence-based guidelines from the American Academy of Neurology (AAN, 2009; reaffirmed 2025) recommended testing for CMT, but with a tiered approach:[5]

- "Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies."
  - This is considered a level A recommendation which is defined as "established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population."
- "Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype. Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features and should focus on the most common abnormalities which are CMT1A duplication/HNPP deletion, Cx32 (GJB1), and MFN2 mutation screening."
  - This is considered a level C recommendation which is defined as "possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population."
- "There is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype."

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- This is considered a level U recommendation which is defined as "data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven."

Selected Relevant Publications

Roggenbuck et al. [2024] reported outcomes after completing genetic testing (panels ranging from 66-111 genes) for a cohort of 6849 adults with peripheral neuropathy. A molecular diagnosis was identified for 8.4% of the cohort. Variants in PMP22, MFN2, GJB1, MPZ, and TTR accounted for 73.8% of molecular diagnoses. Results had potential clinical actionability for 398 (69.5%) patients. Most notably, their results suggest that 225/573 (39.3%) of molecular diagnoses and 113/398 (28.4%) of clinical interventions would have been missed if the testing approach had been restricted to sequential testing of a few genes.[6]

DiVincenzo et al. [2014] described their experience testing more than 17,000 patients for CMT using a commercially available comprehensive panel of 14 genes.[6] Overall, they identified a mutation in 18.5% of patients. Notably they state that "Among patients with a positive genetic finding in a CMT-related gene, 94.9% were positive in one of four genes (PMP22, GJB1, MPZ, or MFN2). The results of our study in a population in over 17,000 individuals support the initial genetic testing of four genes (PMP22, GJB1, MPZ, and MFN2) followed by an evaluation of rarer genetic causes in the diagnostic evaluation of CMT."[7]

Gemelli et al [2022] examined a cohort of 585 CMT patients (447 index cases), 64.9% of whom had a demyelinating neuropathy and 35.1% of whom had an axonal neuropathy. Combining a gene-by-gene approach or targeted gene panels based on clinical presentation, a genetic diagnosis was achieved in 66% of all patients, with the following distribution: PMP22 duplication (48%), PMP22 deletion (14%), GJB1 (13%), MFN2 (5%), and MPZ (7%), accounting all together for 87% of all the molecularly defined neuropathies.[8]

Record et al [2024] reported on a cohort of 1515 patients with a clinical diagnosis of CMT and related disorders (excluding patients with hereditary ATTR amyloidosis). Genetic testing of the cohort included single-gene and multi-gene NGS panels, research whole exome, and research whole genome sequencing. Overall, a genetic diagnosis was reached in 76.9% (1165/1515). A diagnosis was most likely in the demyelinating form (96.8%, 601/621), followed by CMT with intermediate conduction velocities (81.0%, 166/205) and then HSN (69.9%, 65/93). Diagnostic rates remained less than 50% in the axonal form, hereditary motor neuropathies, and complex neuropathies. The most common genetic diagnosis was PMP22 duplication (505/1165, 43.3%), then GJB1 (151/1165, 13.0%), PMP22 deletion (72/1165, 6.2%) and MFN2 (46/1165, 3.9%).[9]

In a 2025 expert-authored review, the following step-wise genetic testing strategy was recommended:[1]

- Step 1: "Single-gene testing for PMP22 duplication/deletion is recommended as the first test in all probands with CMT. PMP22 duplication (a 1.5-Mb duplication at 17p11.2 that includes PMP22) accounts for as much as 50% of all CMT and, thus, PMP22 deletion/duplication analysis is recommended as the first test for all probands with CMT."
- Step 2: "A multigene panel that includes the eight most commonly involved genes (i.e., GDAP1, GJB1, HINT1, MFN2, MPZ, PMP22, SH3CT2, and SORD) as well as some or all of the other genes listed in Table 4 is most likely to identify the genetic cause of the neuropathy while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype."
- Step 3: "Comprehensive genomic testing - which does not require the clinician to determine which gene(s) are likely involved – may be considered if a genetic cause has not been identified in Step 1 and Step 2. Exome sequencing is most commonly used; genome sequencing is also possible."
- "Given the complexity of interpreting genetic test results and their implications for genetic counseling, health care providers should consider referral to a neurogenetics center or a genetic counselor specializing in neurogenetics."
- "For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Charcot-Marie-Tooth Neuropathy testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Chromosomal Microarray Testing For Developmental Disorders (Prenatal and Postnatal)

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Chromosomal microarray (CMA) testing for developmental disorders in the prenatal or postnatal setting is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Chromosomal microarray [BAC], constitutional	81228
Chromosomal microarray [CGH], constitutional	S3870
Chromosomal microarray [SNP], constitutional	81229
Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis	81349

Criteria

Requests for chromosomal microarray (CMA) testing for developmental disorders in the prenatal and postnatal setting are reviewed using the following criteria.

Criteria

- Genetic Counseling:

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  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Diagnostic Testing for Symptomatic Individuals:
  - No previous CMA testing,* and
  - Testing performed on living child or adult, and
  - Diagnosis cannot be made on clinical evaluation alone, and
  - A more appropriate targeted test is not available (e.g., chromosome analysis, fluorescence in situ hybridization [FISH], single gene sequencing, etc.), and
  - Common aneuploidy (trisomy 13, 18, 21, or sex chromosome) is not a suspected diagnosis, and
  - One of the following presentations:
    - Developmental delay/intellectual disability (DD/ID), or
    - Autism spectrum disorder, or
    - Major congenital cardiac anomaly†, or
    - Multiple congenital anomalies†, OR
- Diagnostic Testing for Pregnancy Loss (including fetal demise, stillbirth, and miscarriage):
  - No previous CMA testing in the same pregnancy, and
  - Testing performed on products of conception, and
  - A more appropriate targeted test is not available (e.g., chromosome analysis, FISH, single gene sequencing, etc.), and
  - Common aneuploidy (trisomy 13, 18, 21, or sex chromosome) is not a suspected diagnosis, and
  - One of the following presentations:
    - Major congenital cardiac anomaly†, or
    - Multiple congenital anomalies†, or
    - Pregnancy loss occurred in the second trimester or later, or
    - Pregnancy loss in the first trimester when there is a parental history of one or more prior pregnancy losses, OR
- Diagnostic Prenatal Testing:
  - No previous CMA testing in the same pregnancy, and
  - The member has sufficient risk of fetal copy number variant (CNV) to justify invasive prenatal diagnosis. [It is important to note that invasive diagnostic procedures such as chorionic villus sampling and amniocentesis are associated with risks; the provider and member must have determined that the associated benefits outweigh the risks.], AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

*Microarray is considered a first-tier test in the evaluation of postnatal developmental disorders. Therefore, it often is not necessary to do chromosome analysis or FISH in

conjunction with microarray. Microarray requests following such testing will require review.

†**Multiple congenital anomalies** defined as 1) two or more major anomalies affecting different organ systems or 2) one major and two or more minor anomalies affecting different organ systems. **Major structural abnormalities** are generally serious enough as to require medical treatment on their own (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder.

Chromosomal Microarray (CMA) Exclusions and Considerations

If routine karyotype and CMA are ordered simultaneously, only the most appropriate test based on clinical history will be considered for coverage. If CMA has been performed, the following tests are often excessive and thus not considered medically necessary. Each test may require medical necessity review.

- Routine karyotype: Full karyotype in addition to CMA is typically considered excessive. However, a limited 5 cell analysis may be approved in addition to CMA if criteria for CMA are met. This approval may be subject to claims review to ensure that the appropriate procedure code for a limited 5 cell analysis is billed (CPT 88261 x1, 88230 x1, 88291 x1).
- FISH Analysis
- Telomere Analysis
- More than one type of microarray analysis (i.e. if 81228 performed, 81229 is not medically necessary)
- CMA is not considered medically necessary in cases of family history of chromosome rearrangement in phenotypically normal individuals.
- CMA is not considered medically necessary in individuals experiencing infertility, structurally normal pregnancy losses that occur at less than 20 weeks, or recurrent pregnancy loss.
- When a multigene deletion/duplication panel is being requested and billed using a microarray procedure code (typically 81228 or 81229), please refer to the *Genetic Testing by Multigene Panels* clinical use guideline; do not apply the criteria in this guideline.
- CMA for delineation of deletion, duplication, or translocation breakpoints will be reviewed on a case by case basis.
- CMA for determination of whether a translocation is balanced or unbalanced with be reviewed on a case by case basis.

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Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- CMA is only reimbursable once per lifetime.
- When CMA is otherwise reimbursable, the following limitations apply:
  - Only one type of microarray analysis (e.g., 81228, 81229 or 81349) will be reimbursed.
  - A limited 5 cell chromosome analysis (88261x1, 88230x1, 88291x1) may be reimbursed in addition to the CMA.
  - FISH or other procedure codes that do not accurately describe the test methodology performed (e.g. 88271) are not eligible for reimbursement of CMA.
- If CMA has been performed, the following tests are not reimbursable:
  - Routine karyotype
  - FISH Analysis
  - Telomere Analysis

What are Copy Number Variants in Developmental Disorders?

Copy number variation is when the number of copies of genetic material differs between individuals. When present, the following developmental disorders often prompt an evaluation for copy number variants: intellectual disability (ID), global developmental delay (GDD), autism spectrum disorders (ASD), and congenital anomalies.

Copy Number Variants (CNVs)

Copy number variants (CNVs) are deletions and duplications of genetic material. CNVs account for a significant proportion of congenital anomalies and developmental disorders without a clear etiology based on clinical findings. CNVs are detected using chromosomal microarray (CMA) testing. CMA is known by several names including array-comparative genomic hybridization (aCGH) and single-nucleotide polymorphism arrays (SNP-array).

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Incidence

ID and congenital anomalies affect approximately 3-4% of the general population.[1] The incidence of GDD is comparable to ID. ASD, which now includes autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and Asperger syndrome, are also of increasing concern, with recent CDC incidence figures estimating 1 in 31 affected children.[2]

Heart defects are the most common congenital anomaly, affecting nearly 1-1.2% of live births.[3] Sixty to eighty percent of major structural anomalies are identified prenatally by ultrasound evaluation.[4]

Cause

The etiology of developmental disorders and congenital anomalies is complex. Some developmental problems may be caused by non-genetic factors, such as injury, birth complications, endocrine disorders, toxic exposures, and infection. However, genetic causes also play a significant role.[5-8]

A clinical genetics evaluation can identify a cause in a portion of individuals with ID, GDD, or ASD. Identifying an underlying genetic cause in these individuals may:[5-8]

- Provide diagnostic and prognostic information
- Improve health screening and prevention for some conditions
- Allow for testing of family members and accurate recurrence risk counseling, and
- Empower the individual and family to acquire needed services and support

CMA on chorionic villi or amniocytes is indicated in any pregnancy in which diagnostic testing for chromosome abnormalities and CNVs is desired.[9-11] Identifying an underlying genetic cause in these individuals may:[6]

- Provide diagnostic and prognostic information
- Guide prenatal management and decision-making, and
- Allow for testing of family members and accurate recurrence risk counseling.

Parental Testing

If a CNV is detected in a child, it may be helpful to test both parents to determine whether the CNV is inherited or a new (de novo) genetic change. This information along with parental findings can be used to weigh the possibilities of a benign vs. pathogenic variant. However, even with parental studies, the clinical outcome may remain unclear.[1,9] A de novo variant is more likely to represent a pathologic abnormality.[1]

Clinical Classification of CNVs

In a joint consensus recommendation, the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome resource (ClinGen) introduced updated

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standards to help reduce discordance in clinical classifications of CNVs, including those detected during postnatal or prenatal testing.[12,13] The standards include a semi-quantitative point-based scoring system metric for CNV classification, including separate scoring metrics for copy number losses and copy number gains. Evaluation of the inheritance pattern, including whether the CNV is inherited or a new (de novo) genetic change, factors into this scoring system.

Test information

Testing for developmental disorders in the prenatal and postnatal setting may include CMA testing.

Chromosomal Microarray

CMA testing generally works by fluorescently tagging DNA from an individual's test sample with one color and combining it with a control sample tagged in a different color. The two samples are mixed and then added to the array chip, where they compete to hybridize with the DNA fragments on the chip. By comparing the test sample versus the control, computer analysis can determine where genetic material has been deleted or duplicated in the individual.

There are a growing number of CMA testing platforms, including non-chip based applications, which differ in approach and resolution. Clinical laboratories may not only differ in the arrays that they utilize but also in their reporting practices. Although testing guidelines do not endorse one CMA over another, it is typically advisable that coverage of an ordered CMA is better than that offered by a standard karyotype and that the minimum resolution of the CMA provided by the laboratory is adequate. The inclusion of analysis of subtelomeric regions and known microdeletion syndromes with CMA testing obviates the need for additional FISH analysis.

CMA testing offers advantages over conventional karyotyping with regard to resolution and yield. However, there are some limitations of CMA testing including:

- the inability to detect
  - balanced chromosomal rearrangements such as translocations or inversions
  - certain forms of polyploidy
  - sex chromosome aneuploidy dependent on the gender control used
  - low level mosaicism
  - some marker chromosomes
- the detection of CNVs of uncertain clinical significance
- the inability to differentiate free trisomies from unbalanced Robertsonian translocations.

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Diagnostic Yield

Diagnostic yield for CMA differs based on clinical presentation.

The diagnostic yield for CMA across various prenatal clinical settings is presented below.

- The diagnostic yield for CMA performed on amniocentesis samples is ~8-9% across indications.[14,15] The diagnostic yield is up to 23% for fetuses with congenital heart disease (CHD).[16,17]
- CMA may also be useful in the workup of non-immune fetal hydrops and fetal ventriculomegaly.[18-20]
- The diagnostic yield for CMA performed on products-of-conception samples ranges from 16.3% to 55%, and may vary by gestational age.[15,21-24]
- Studies have demonstrated that CMA will detect chromosome abnormalities in up to 10% of cases with a normal conventional karyotype.[10,14,17,25] However, some forms of mosaic aneuploidy will only be detected by a cultured sample, as typically required for karyotype, and would not be observed using CMA on a direct sample.[26]

The diagnostic yield for CMA across various postnatal clinical settings is presented below.

- Approximately 10-19% of people with unexplained ID or developmental delay (DD) will have CNVs.[1,7,8,27]
- CMA finds a pathogenic CNV in 5% to 14% of those with ASD who are tested clinically by this method.[28]
- The diagnostic yield in individuals with ASD is higher in those with a syndromic presentation, meaning that they have additional findings.[5]

Guidelines and evidence

American Academy of Pediatrics

The American Academy of Pediatrics (AAP, 2014; reaffirmed 2019) Committee on Genetics recommended genetics evaluation for all individuals following the diagnosis of GDD or ID. They stated:[29]

"[i]f diagnosis is unknown and no clinical diagnosis is strongly suspected, begin the stepwise evaluation process:

- Chromosomal microarray should be performed in all.
- Specific metabolic testing should be considered and should include serum total homocysteine, acyl-carnitine profile, amino acids; and urine organic acids, glycosaminoglycans, oligosaccharides, purines, pyrimidines, GAA/creatine metabolites.

- Fragile X genetic testing should be performed in all."

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2010; reaffirmed 2020) Professional Practice and Guidelines Committee recommended CMA as a first-tier test for the evaluation of individuals who have the following:[6,7]

- "Multiple anomalies not specific to a well-delineated genetic syndrome."
- "Apparently non-syndromic DD [developmental delay]/ID [intellectual disability]."
- "Autism spectrum disorders"

The American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and the Chromosomal Microarray Additional Testing Reaffirmation Workgroup (ACMG, 2024) reaffirmed their 2018 practice guideline on additional genetic testing after chromosomal microarray for diagnosing neurodevelopmental disability and congenital anomalies. The addendum stated:[30]

- "Although the rationale for additional testing remains valid, microarray is no longer the sole first-tier go-to test per ACMG evidence-based clinical guidelines."
- "Additional testing after chromosomal microarray remains clinically relevant for disease-specific testing (eg, testing for an autosomal recessive pathogenic variant or uniparental disomy after detection of homozygosity), as well as more general testing recommendations (eg, balanced translocations and insertions)."
- "Genome sequencing, long-read sequencing, and optical genome mapping can detect balanced [structural variations] typically cryptic by chromosomal microarray."

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2024) released a clinical expert series on recurrent pregnancy loss that stated:[31]

- "We recommend that genetic testing of the products of conception with single-nucleotide polymorphism (SNP) microarray be offered by the obstetrician-gynecologist to all patients as soon as pregnancy loss is confirmed, including with the first occurrence for second-trimester losses and the second occurrence or beyond for first-trimester losses."

American College of Obstetricians and Gynecologists and Society for Maternal Fetal Medicine

The American College of Obstetricians and Gynecologists (ACOG, 2016; reaffirmed 2023) and Society for Maternal Fetal Medicine (SMFM, 2016; reaffirmed 2023) joint committee opinion on chromosomal microarray stated:[32]

- "Chromosomal microarray analysis of fetal tissue (i.e. amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine death or

stillbirth when further cytogenetic analysis is desired because of the test's increased likelihood of obtaining results and improved detection of causative abnormalities."
- "Additional information is needed regarding the clinical use and cost-effectiveness in cases of recurrent miscarriage and structurally normal pregnancy losses at less than 20 weeks of gestation."
- "The routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published."
- "Prenatal chromosomal microarray analysis is recommended for a patient with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. This test typically can replace the need for fetal karyotype."
- "In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either fetal karyotyping or chromosomal microarray analysis can be performed."

The American College of Obstetricians and Gynecologists (ACOG, 2016) and Society for Maternal Fetal Medicine (SMFM, 2016) practice bulletin on prenatal diagnostic testing stated:[33]

- CMA is recommended "as the primary test (replacing conventional karyotype) for patients undergoing prenatal diagnosis for the indication of a fetal structural abnormality detected by ultrasound examination."
- "It is recommended that chromosomal microarray analysis be made available to any patient choosing to undergoing invasive diagnostic testing."

In a joint Obstetric Care Consensus statement, the American College of Obstetricians and Gynecologists (ACOG, 2020) and Society for Maternal Fetal Medicine (SMFM, 2020) stated the following:[34]

- "We recommend that prenatal genetic screening (serum screening with or without nuchal translucency ultrasonography or cell-free DNA screening) and diagnostic testing (chorionic villus sampling or amniocentesis) options be discussed and offered to all pregnant individuals regardless of age or risk of chromosomal abnormality. After review and discussion, every patient has the right to pursue or decline prenatal genetic screening and diagnostic testing. (GRADE 1A. Strong recommendation, high-quality evidence.)"

European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, and Latin American Heart Rhythm Society

The European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, and Latin American Heart Rhythm Society (EHRA/HRS/APHRS/LAHRS, 2022) issued consensus statements regarding genetic testing for cardiac conditions.[35] The consensus statements were categorized as follows:

- Supported by strong observational evidence and author's consensus

- Some evidence and general agreement favor the usefulness/ efficacy of a test
- There is evidence or general agreement not to recommend a test

The following recommendations were made for chromosomal microarray:[35]

- Regarding antenatal testing: "When foetal congenital heart disease (CHD) is identified on antenatal ultrasound examinations, a chromosomal microarray (CMA) or CNV sequencing (CNV seq) of foetal tissue [amniocentesis or chorionic villous sample (CVS)] should be offered." [Supported by strong observational evidence and author's consensus]
- Regarding neonates and infants requiring investigation or procedures for complex CHD: "CMA or CNV seq is indicated in infants with CHD to identify pathogenic CNVs." [Supported by strong observational evidence and author's consensus]
- Regarding individuals with CHD and extracardiac anomalies: "CMA or CNV seq is indicated in patients with CHD and extracardiac anomalies to identify pathogenic CNVs." [Supported by strong observational evidence and author's consensus]
- Regarding sporadic non-syndromic CHD (excluding neonates or infants): "CMA or CNV seq for pathogenic CNVs may be performed in older individuals with sporadic non-syndromic CHD." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

International Standard Cytogenomic Array Consortium

The International Standard Cytogenomic Array Consortium (ISCA, 2010) recommended offering CMA as a first-tier genetic test, in place of karyotype, for individuals with unexplained developmental delay/intellectual disability, autism spectrum disorders, or birth defects.[1]

Society for Maternal Fetal Medicine

The Society for Maternal Fetal Medicine (SMFM, 2016) published a consult series that stated:[36]

- We recommend that CMA "be offered when genetic analysis is performed in cases with fetal structural anomalies and/or stillbirth and replaces the need for fetal karyotype in these cases." (GRADE 1A).

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for chromosomal microarray testing for developmental disorders (prenatal and postnatal) will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that

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some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

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Chromosomal Microarray for Solid Tumors

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Chromosomal microarray analysis (CMA) of solid tumors is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure code(s)
Cytogenomic neoplasia microarray analysis	81277

Criteria

Chromosomal microarray analysis (CMA) on solid tumor tissue is medically necessary in individuals who meet the following criteria:

- Member has been diagnosed with:
  - Cancer of the central nervous system, or
  - Soft tissue sarcoma, AND
- Rendering laboratory is a qualified provider of service per Health Plan policy.

What are chromosome abnormalities in cancer?

Chromosomal aberrations are known to contribute to tumorigenesis.[1]

Chromosome Abnormalities in Cancer

A chromosome abnormality is any difference in the structure, arrangement, or amount of genetic material packaged into the chromosomes. Chromosome abnormalities have been identified in many types of cancer, including leukemias, lymphomas, and solid tumors. Chromosome abnormalities can include deletions, duplications, balanced or unbalanced rearrangements, and gain or loss of whole or partial chromosomes. These abnormalities can play a key role in the development, diagnosis, and monitoring of

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cancer. The cytogenetics of a cancer can also change over time or in response to treatment. Therefore, chromosome analysis can be used to monitor disease progression and treatment response.

"[C]ancer is thought to be a consequence of genomic alteration accumulation, such as single-nucleotide variants (SNVs) and copy number variants (CNVs), and structural rearrangements, which encompass deletions, duplications, inversions, insertions, and translocations that could lead to novel fusion genes."[2]

Some chromosome abnormalities are characteristic of certain types of malignancy, and can be used to classify a type or subtype of cancer. For example, codeletion of 1p and 19q along with IDH1/2 mutations indicate oligodendroglioma.[3]

"The presence of specific chromosomal and genetic alterations exclusively observed in malignant cells helps in cancer diagnosis and prognosis, allowing also to quantify residual disease. Several different types and sizes of chromosomal abnormalities can be found in human cancers, being the products of these dysregulated genes and cellular pathways specific targets for new drugs."[2]

Test information

Chromosome analysis of solid tumors can be done through traditional cytogenetic testing (karyotype), fluorescence in situ hybridization (FISH), or CMA. This guideline addresses only CMA on solid tumors.

Chromosomal Microarray

CMA testing generally works by fluorescently tagging DNA from an individual's test sample with one color and combining it with a control sample tagged in a different color. The two samples are mixed and then added to the array chip, where they compete to hybridize with the DNA fragments on the chip. By comparing the test sample versus the control, computer analysis can determine where genetic material has been deleted or duplicated in the individual.

There are a growing number of CMA testing platforms, including non-chip based applications, which differ in approach and resolution. Clinical laboratories may not only differ in the arrays that they utilize but also in their reporting practices. Although testing guidelines do not endorse one CMA over another, it is typically advisable that coverage of an ordered CMA is better than that offered by a standard karyotype and that the minimum resolution of the CMA provided by the laboratory is adequate. The inclusion of analysis of subtelomeric regions and known microdeletion syndromes with CMA testing obviates the need for additional FISH analysis.

CMA testing offers advantages over conventional karyotyping with regard to resolution and yield. However, there are some limitations of CMA testing including:

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- the inability to detect
  - balanced chromosomal rearrangements such as translocations or inversions
  - certain forms of polyploidy
  - sex chromosome aneuploidy dependent on the gender control used
  - low level mosaicism
  - some marker chromosomes
- the detection of CNVs of uncertain clinical significance
- the inability to differentiate free trisomies from unbalanced Robertsonian translocations.

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2019) provided technical standards and guidelines for interpretation and reporting of acquired copy number abnormalities and loss of heterozygosity in neoplastic disorders:[4]

- "Genomic testing of hematologic malignancies and solid tumors at the time of disease presentation provides information that is crucial for diagnosis and management. This evaluation may include G-banded chromosome analysis, fluorescence in situ hybridization (FISH) analysis, chromosomal microarray analysis (CMA), gene expression and fusion studies, targeted gene sequencing, as well as gene sequencing panels."
- "[A] unified approach for the clinical interpretation, classification, and reporting of all somatic variants will become a necessity."
- Tier 1 variants are those with a strong clinical significance, and several cytogenetic abnormalities in CNS cancers are classified as Tier 1. Additionally, select cytogenetic abnormalities are classified as Tier 1 in the following cancers:
  - Renal cell carcinoma
  - Pediatric embryonal cancers
  - Breast cancer
  - Bone cancer
  - Gastrointestinal stromal tumors
  - Mesothelioma
- "The laboratory must ensure that the clinical report accurately describes the findings and clearly communicates their clinical significance."

The American College of Medical Genetics and Genomics (ACMG, 2024) provided technical standards and guidelines for chromosome analysis in solid tumor-acquired chromosome abnormalities:[5]

- "Clinical cytogenomic studies of solid tumor samples are critical to the diagnosis, prognostication, and treatment selection for cancer patients."
- "Cytogenomic analysis of solid tumors is performed to detect and characterize chromosome alterations to support clinical care. This analysis may provide critical information for diagnosis, prognostication, and selection of therapy. Cytogenomic studies of tumor tissues may be accomplished by G-banded chromosome analysis, FISH, CMA, OGM [optical genome mapping], sequencing, or a combination of these methodologies."
- "CMA can provide valuable information to supplement that of G-banded chromosome and FISH analyses. ... Isolated tumor DNA hybridized to whole-genome copy number and/or single nucleotide polymorphism microarrays allows detection of loss, gain, and amplification of regions of DNA, which may not otherwise be detected by conventional cytogenetic methods."
- "Cytogenomic studies may reveal germline and/or secondary findings. It is recommended that laboratories refer to their policies and procedures to address these situations."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2024) guideline on soft tissue sarcoma stated:[6]

- "Morphologic diagnosis based on microscopic examination of histologic sections remains the gold standard for sarcoma diagnosis. However, several ancillary techniques are useful in support of morphologic diagnosis, including IHC [immunohistochemistry], classical cytogenetics, electron microscopy, and molecular genetic testing. Molecular genetic testing has emerged as an ancillary testing approach since many sarcoma types harbor characteristic gene aberrations, including single base pair substitutions, deletions and amplifications, and translocations. Molecular testing utilizes multiple techniques such as fluorescence in situ hybridization (FISH), or polymerase chain reaction (PCR)-based methods and next-generation sequencing (NGS)-based methods (including DNA and RNA sequencing)."

The National Comprehensive Cancer Network (NCCN, 2024) guideline on central nervous system (CNS) cancers stated:[7]

- "With the use of genetic and molecular testing, histologically similar CNS neoplasms can be differentiated more accurately in terms of prognosis and, in some instances, response to different therapies."
- "Molecular characterization of primary CNS tumors has substantially impacted clinical trial eligibility and risk stratification in the past 10 years, thereby evolving the standard of care towards an integrated tumor diagnosis in neuro-oncology".

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- "Molecular/genetic characterization does not replace standard histologic assessment, but serves as a complementary approach to provide additional diagnostic and prognostic information that often enhances treatment selection."
- "Some diffusely infiltrative astrocytomas lack the histologic features of glioblastoma (necrosis and/or microvascular proliferation) but have the molecular hallmarks of glioblastoma, including one or more of the following: IDH wild-type; EGFR amplification; gain of chromosome 7 and loss of chromosome 10; and TERT promoter mutation. In such cases, the tumor can now be diagnosed as "Glioblastoma, IDH-wild-type, WHO grade 4". Because these tumors have similar clinical outcomes as typical grade 4 glioblastomas, they may be treated as such."
- "Recommendation: 1p/19q testing is an essential part of molecular diagnostics for oligodendroglioma."
- "Detection: The codeletion of 1p and 19q is detectable by array-based genomic copy number testing (preferable), or fluorescence in situ hybridization (FISH)."

World Health Organization

The World Health Organization (WHO, 2021) classification of tumors of the central nervous system stated:[3]

- "Because of the growing importance of molecular information in CNS tumor classification, diagnoses and diagnostic reports need to combine different data types in a single "integrated" diagnosis. Such integrated diagnoses are implicit in the use of WHO CNS5…Thus, to display the full range of diagnostic information available the use of layered (or tiered) diagnostic reports is strongly encouraged…Such reports feature an integrated diagnosis at the top, followed by layers that display histological, molecular, and other key types of information."
- "In the updated fourth edition CNS classification from 2016, the common diffuse gliomas of adults were divided into 15 entities, largely because different grades were assigned to different entities (eg, Anaplastic oligodendroglioma was considered a different type from Oligodendroglioma) and because NOS designations were assigned to distinct entities (eg, Diffuse astrocytoma, NOS). WHO CNS5, on the other hand, includes only 3 types: Astrocytoma, IDH-mutant; Oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and Glioblastoma, IDH-wildtype."
- "...[A]ll IDH-mutant diffuse astrocytic tumors are considered a single type (Astrocytoma, IDH-mutant) and are then graded as CNS WHO grade 2, 3, or 4. Moreover, grading is no longer entirely histological, since the presence of CDKN2A/B homozygous deletion results in a CNS WHO grade of 4, even in the absence of microvascular proliferation or necrosis."
- "For IDH-wildtype diffuse astrocytic (NB: diffuse and astrocytic) tumors in adults, a number of papers have shown that the presence of 1 or more of 3 genetic parameters (TERT promoter mutation, EGFR gene amplification, combined gain of entire chromosome 7 and loss of entire chromosome 10 [+7/−10]) appears sufficient

to assign the highest WHO grade. WHO CNS5 therefore incorporates these 3 genetic parameters as criteria for a diagnosis of Glioblastoma, IDH-wildtype. As a result, Glioblastoma, IDH-wildtype should be diagnosed in the setting of an IDH-wildtype diffuse and astrocytic glioma in adults if there is microvascular proliferation or necrosis or TERT promoter mutation or EGFR gene amplification or +7/−10 chromosome copy number changes."

- "Several molecular biomarkers are also associated with classification and grading of meningiomas, including SMARCE1 (clear cell subtype), BAP1 (rhabdoid and papillary subtypes), and KLF4/TRAF7 (secretory subtype) mutations, TERT promoter mutation and/or homozygous deletion of CDKN2A/B (CNS WHO grade 3), H3K27me3 loss of nuclear expression (potentially worse prognosis), and methylome profiling (prognostic subtyping."

Selected Relevant Publication

Ribeiro and colleagues stated in an expert-authored review (2019):[2]

- "Chromosome translocations, inversions, and insertions are frequently found in solid tumors…" however, "only few biomarkers have been approved for clinical practice that could change clinical decision making, helping in the therapeutic choices and patient management, showing the complexity of cancer and the lack of a strong bridge between the laboratory and clinicians."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for chromosomal microarray for solid tumors will ensure that testing will be available to those members most likely to benefit from the information provided by the assay. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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Cystic Fibrosis Genetic Testing

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Cystic fibrosis testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
CFTR targeted mutation analysis	81220
CFTR known familial mutation analysis	81221
CFTR full gene sequencing	81223
CFTR deletion/duplication analysis	81222
CFTR Poly T Tract (5T) Genotyping	81224

Criteria

Requests for cystic fibrosis (CF) genetic testing are reviewed using the following criteria.

CFTR Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing that would identify the familial mutation(s), AND
- Diagnostic Testing for Symptomatic Individuals:
  - Individuals who have a suspected diagnosis of cystic fibrosis and the familial mutations to be tested were identified in 1st degree biological relative(s), OR
- Mutation Identification to Guide Pharmacologic Therapy Selection

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  - Individuals who meet diagnostic criteria for CF and are eligible for FDA-approved CFTR mutation-specific therapies, OR
- Carrier Screening:
  - Be of reproductive age and have potential and intention to reproduce, and
  - Familial CFTR mutation(s) in known biological relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CFTR Targeted Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for CFTR mutation(s), AND
- Diagnostic Testing for Symptomatic Individuals:
  - Individuals with an intermediate range/equivocal sweat chloride test (30-59mmol/L), or
  - Individuals with a negative sweat chloride test when symptoms of CF are present, or
  - Infants with meconium ileus or other symptoms indicative of CF and are too young to produce adequate volumes of sweat for sweat chloride test, or
  - Infants with an elevated IRT value on newborn screening, or
  - Fetus with finding of echogenic bowel on ultrasound, or
  - Males with oligospermia/azoospermia/congenital absence of vas deferens (CAVD), OR
- Mutation Identification to Guide Pharmacologic Therapy Selection
  - Individuals who meet diagnostic criteria for CF and are eligible for FDA-approved CFTR mutation-specific therapies, OR
- Carrier Screening:
  - Individuals of reproductive age and have potential and intention to reproduce, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CFTR Sequencing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Diagnostic Testing for Symptomatic Individuals:
  - Previous CFTR standard panel, if performed, was non-diagnostic (fewer than 2 pathogenic mutations detected), and

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  - Individuals with a negative or equivocal sweat chloride test, and unexplained chronic obstructive pulmonary disease (COPD) or bronchiectasis with unexplained chronic or recurrent sinusitis and abnormal pulmonary function tests (PFTs), or
  - Infants with meconium ileus or other symptoms indicative of CF and are too young to produce adequate volumes of sweat for sweat chloride test, or
  - Infants with an elevated immunoreactive trypsinogen (IRT) value on newborn screening and fewer than 2 pathogenic mutations identified on standard panel testing, OR
- Mutation Identification to Guide Pharmacologic Therapy Selection
  - Individuals who meet diagnostic criteria for CF and are eligible for CFTR FDA-approved genotype-based therapies, OR
- Carrier Screening:
  - General Population Screening (e.g., no family history of CF):
    - No previous CFTR testing, and
    - Be of reproductive age and have potential and intention to reproduce, OR
  - High-risk Screening (e.g., family history of CF):
    - Previous CFTR standard panel, if performed, was negative, and
    - An individual with a family history of CF with an unknown mutation(s), or
    - An individual whose reproductive partner is a known CF carrier, has a diagnosis of CF, or has a diagnosis of CFTR-related CAVD, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CFTR Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous CFTR deletion/duplication testing, and
  - Previous CFTR gene sequencing was non-diagnostic (fewer than 2 pathogenic mutations detected), and
  - No known familial mutation, AND
- Member meets criteria for CFTR sequencing in symptomatic or high-risk carrier individuals, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CFTR Intron 9 Poly T Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - No previous CFTR intron 9 poly T testing, AND
- Diagnostic Testing:
  - CFTR mutation analysis performed and R117H mutation detected, or
  - Diagnosis of male infertility (congenital absence of vas deferens [CAVD], obstructive azoospermia), or
  - Diagnosis of non-classic CF, OR
- Carrier Testing:
  - CFTR mutation analysis performed and R117H mutation detected, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

- For information regarding CFTR testing for individuals with pancreatitis, please refer to the guideline *Hereditary Pancreatitis Genetic Testing*, as this testing is not addressed here.
- For information regarding carrier screening for Cystic Fibrosis performed as part of a large carrier screening panel, please see the guideline *Carrier Screening Panels, Including Targeted, Pan-Ethnic, Universal, and Expanded*, as this testing is not addressed here.

What is cystic fibrosis?

Cystic fibrosis (CF) is a genetic disorder that can cause chronic lung disease, pancreatic insufficiency, and male infertility.[1,2]

Prevalence

CF affects at least 100,000 individuals worldwide.[1] While CF is most common in individuals with northern European ancestry, it can occur in any ethnic group.[2]

Symptoms

Symptoms associated with CF may include:[1]

- Frequent respiratory infections
- Bronchiectasis
- Pancreatic exocrine insufficiency
- Elevated sweat chloride levels
- Meconium ileus in newborns
- Congenital absence of the vas deferens (CAVD; can be unilateral or bilateral).

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Pulmonary disease is the major cause of morbidity and mortality in individuals with CF.[1]

CFTR-Related Disorders

Several other conditions that share some clinical similarities to CF, are also caused by mutations in the CFTR gene, but do not meet the diagnostic criteria for CF. These are called "CFTR-related disorders" and include congenital bilateral absence of vas deferens (CBAVD/CAVD), acute recurrent or chronic pancreatitis, and some respiratory tract conditions such as bronchiectasis, sinusitis, and nasal polyps.[1,3]

CAVD is frequently identified after semen analysis shows absent sperm (azoospermia). CAVD is often caused by one severe CFTR mutation and one non-CF causing mutation or 2 non-CF causing mutations.[1]

CFTR-Related Metabolic Syndrome / CF Screen Positive, Inconclusive Diagnosis

CFTR-related metabolic syndrome/CF screen-positive, inconclusive diagnosis (CRMS/CF-SPID) is defined as "[a]n asymptomatic infant with a positive NBS result for CF and either a sweat chloride value <30 mmol/L and two CFTR variants at least one of which has unclear phenotypic consequences OR an intermediate sweat chloride value (30–59 mmol/L) and one or zero CF causing variants".[4] The majority of infants with CRMS/CF-SPID remain healthy. Some will convert to a CF diagnosis, and there is potential for developing a CFTR-Related Disorder (CFTR-RD) later in life.[4]

Cause

CF is caused by mutations in the CFTR gene.

Inheritance

CF is an autosomal recessive condition.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

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Diagnosis

The diagnosis of CF can be made based on clinical symptoms and evidence of CFTR dysfunction, which may include elevated sweat chloride or nasal potential difference, or the identification of 2 CFTR mutations.[1] In newborns, the diagnosis is made based on elevated trypsinogen on newborn screening and the presence of 2 CFTR mutations.[1]

Most signs of CF cannot be identified on prenatal ultrasound examination. However, pregnancies in which fetal echogenic bowel is identified on ultrasound are at an increased risk to be affected with CF.[1]

Prenatal diagnosis for CF can be performed on a sample from chorionic villus sampling (CVS) or amniocentesis:[1]

- If both parents are known carriers, a mutation panel that includes both parental mutations is typically the test of choice.
- If only one parent is a carrier, or if testing is indicated because of echogenic bowel, testing with a large mutation panel or sequencing and deletion/duplication analysis offers greater sensitivity.

Newborn screening (NBS) programs include screening for CF, though the screening protocol may vary by state.[5]

The American College of Medical Genetics has defined a panel of 23 common, pan-ethnic mutations that occur at a frequency of at least 0.1% in patients with cystic fibrosis.[6,7] While this panel was created for carrier screening purposes, the CF diagnostic guidelines also endorse its use in that setting for most patients.[2] In 2023, the ACMG-recommended mutation list was updated to 100 variants.[8] Laboratories performing mutation panel testing routinely include all of these mutations. Many laboratories expand their panels with more mutations intended to increase the detection rate, particularly in non-Caucasian populations. Expanded mutation panels generally test for 70 or more CFTR mutations. The detection rates of targeted mutation panels vary by laboratory and depend on the mutations included and the patient's ethnicity.[1]

CFTR-sequencing detects more than 97% of mutations.[1] The frequency of deletions and duplications is estimated to be less than 5% of all detected CFTR variants, but this may be an underestimate.[7]

Management

Management of CF addresses respiratory and digestive issues through inhaled medications and replacement of pancreatic enzymes.

There are several FDA-approved mutation-specific therapies.[9]

Survival

CF Foundation Patient registry data from 2023 indicate that the median predicted survival for people with CF is about 61 years.[10]

Test information

Testing for cystic fibrosis tests may include known familial mutation analysis, targeted mutation analysis, NGS sequencing, deletion/duplication analysis, and intron 9 poly-T and TG analysis (previously called intron 8 or IVS8 poly-T analysis).

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

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Intron 9 poly-T and TG analysis

Intron 9 (formerly intron 8 or IVS 8) poly-T analysis identifies the number of thymidine bases in intron 9 of the CFTR gene. The three common variants are 5T, 7T, and 9T, with 7T and 9T being considered normal variants.[1]

"The 5T allele by itself is associated with variable penetrance for CF and CAVD based on the status of an adjacent poly TG tract, which usually contains 11, 12, or 13 repeats (c.1210–34TG[11], c.1210–34TG[12], c.1210–34TG [13]). When paired with a known CF-causing variant, 5T and 11TG variants in cis rarely confer an increased risk for CAVD in males while 5T in cis with 12TG or 13TG confers risk for CAVD and rarely for nonclassic CF. Given the commonness of the 5T allele (one in ten individuals carry a 5T variant), interpretation of its disease liability should ideally be performed in the context of the number of associated TG repeats."[7]

Guidelines and evidence

The American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2020) technical standard for CFTR variant testing stated:[7]

- "As a way to ensure that CFTR variant testing for carrier screening and diagnostic testing purposes remains comprehensive, pan-ethnic, and up-to-date, the ACMG recommends either a classification-based reporting approach or a classification-based (targeted) testing approach (which has historically been used for CFTR carrier screening."
- "For those laboratories who wish to continue using a targeted testing approach, the ACMG-23 variant panel remains as the minimum list of CFTR variants that should be included. Laboratories may want to consider adding additional variants to their panel depending on the ethnic composition of their expected test population. However, the minimum list of CFTR variants recommended for pan-ethnic carrier screening has not been increased at this time."
- "Targeted and comprehensive approaches are both acceptable for the testing of individuals regardless of race, ethnicity, or test indication."
- "The ACMG recommends that laboratories performing initial CFTR variant testing on an individual can use either targeted or comprehensive methods to evaluate the gene…If pathogenic or likely pathogenic CFTR variants have been confirmed in both biological parents, or an affected full sibling, only targeted methods should be used."
- "For all prenatal, postnatal, and adult diagnostic testing indications for CFTR, the ACMG recommends the reporting of R117H status as well as the results from at least the associated polyT tract. For all adult carrier screening indications for CFTR, polyT status should be reported when the R117H variant is detected; laboratories may also

want to consider reporting the results from the associated polyT tract in the partner of an individual who had a pathogenic or likely pathogenic variant detected during screening."

ACMG (2023) issued a position statement updating the minimum set of CFTR variants to be included for CF carrier screening that stated:[8]

- "The new set of 100 variants represents an updated minimum CFTR carrier screening variant set, but it does not represent a limit on the total number of variants that a laboratory can choose to assess, and it is likely that laboratories may already have many (but likely not all) of these variants included as a part of their tests."
- "The workgroup is also aware that there are not likely any existing targeted CF tests available that contain all of the newly recommended variants. However, some laboratories may have previously chosen to offer CF carrier screening using either Sanger or NGS of CFTR, and these methods should encompass all of the genomic regions containing the recommended variants."

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2017; Reaffirmed 2023) issued a committee opinion on carrier screening for genetic conditions that stated:[11]

- "Cystic fibrosis carrier screening should be offered to all women who are considering pregnancy or are currently pregnant."
- "Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening."
- "For couples in which both partners are unaffected but one or both has a family history of cystic fibrosis, genetic counseling and medical record review should be performed to determine if CFTR mutation analysis in the affected family member is available."
- "If a woman's reproductive partner has cystic fibrosis or apparently isolated congenital bilateral absence of the vas deferens, the couple should be provided follow-up genetic counseling by an obstetrician–gynecologist or other health care provider with expertise in genetics for mutation analysis and consultation."
- "If both partners are found to be carriers of a genetic condition, genetic counseling should be offered. Prenatal diagnosis and advanced reproductive technologies to decrease the risk of an affected offspring should be discussed."
- "Carrier screening for a particular condition generally should be performed only once in a person's lifetime, and the results should be documented in the patient's health record. Because of the rapid evolution of genetic testing, additional mutations may be included in newer screening panels. The decision to rescreen a patient should be undertaken only with the guidance of a genetics professional who can best assess the incremental benefit of repeat testing for additional mutations."

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American Urological Association in partnership with the American Society for Reproductive Medicine

The American Urological Association in partnership with the American Society for Reproductive Medicine (2020) published guidelines on the diagnosis and treatment of infertility in males that stated:[12]

- "Clinicians should recommend Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutation carrier testing (including assessment of the 5T allele) in men with vasal agenesis or idiopathic obstructive azoospermia. (Expert Opinion)"
- "For men who harbor a CFTR mutation, genetic evaluation of the female partner should be recommended. (Expert Opinion)"
- "Specifically, studies suggest that mutations in the CFTR gene are present in up to 80% of men with congenital bilateral absence of the vas deferens (CBAVD), 20% of men with CUAVD and 21% of men with idiopathic epididymal obstruction."
- "As the goal of genetic testing is to help identify the etiology as well as provide counseling on potential offspring transmission, expanded carrier screening or gene sequencing should be considered. In addition to classic mutations, the 5-thymidine (5T) variant of the polythymidine tract in the splice site of intron 8 (which regulates exon 9 splicing efficiency) is also commonly found in men with obstructive azoospermia due to CFTR abnormalities."

Cystic Fibrosis Foundation

Consensus-based guidelines from the Cystic Fibrosis Foundation (2017) outline the ways in which a CF diagnosis can be established (see below). Characteristic features of CF include chronic sinopulmonary disease (such as persistent infection with characteristic CF pathogens, chronic productive cough, bronchiectasis, airway obstruction, nasal polyps, and digital clubbing), gastrointestinal/nutritional abnormalities (including meconium ileus, pancreatic insufficiency, chronic pancreatitis, liver disease, and failure to thrive), salt loss syndromes, and obstructive azoospermia in males (due to CAVD).[2]

When at least one characteristic feature is present, a diagnosis of CF can be established by:

- Two abnormal sweat chloride values; or
- Identification of two CF-causing CFTR gene mutations; or
- Characteristic transepithelial nasal potential difference (NPD)

In the absence of symptoms, a CF diagnosis can be established in:

- A newborn with two CF-causing CFTR gene mutations identified via newborn screening

"Individuals who are screen-positive and meet sweat chloride criteria for CF diagnosis should undergo CFTR genetic testing if the CFTR genotype was not

available through the screening process or is incomplete." "Even in the presence of a positive sweat test, the identification of 2 CF-causing mutations should be confirmed in a clinical genetics laboratory capable of performing in-depth genetic analysis when required to further define CF risk (eg, the length of polyT tracts with the c.350G>A [legacy:R117H] CFTR mutation). Confirmation of genetic testing results with an FDA-approved companion diagnostic test also has additional value in therapy selection and access."[2]

These guidelines further state that, “Individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30- 59 mmol/L) on 2 separate occasions may have CF. They should be considered for extended CFTR gene analysis and/ or CFTR functional analysis."[2]

A CFF evidence-based guideline (2024) on management of CRMS/CFSPID stated:[13]

- "The CFF recommends that people with CRMS/CFSPID who have <2 disease-causing variants identified by NBS, should undergo sequencing of the coding and flanking regions and del/dup analysis of the coding and exon flanking regions of CFTR." Grade B; Certainty: Moderate
- "The CFF recommends CFTR genetic evaluation for parents of people with CRMS/CFSPID when phasing of the CFTR variants (ie, in cis or trans) would inform the diagnostic status of the individual by confirming the inheritance pattern." Grade A; Certainty: High

A CFF Consensus Guideline (2025) addressing newborn screening stated:[14]

- "The Cystic Fibrosis Foundation recommends that CF newborn screening programs screen for all CF-causing CFTR variants in CFTR2."
- "The Cystic Fibrosis Foundation recommends the inclusion of a CFTR sequencing tier following IRT and CFTR variant panel testing to improve the specificity and positive predictive value of CF newborn screening."

Society for Maternal-Fetal Medicine

The Society for Maternal Fetal Medicine (SMFM, 2021) statement on the evaluation of soft ultrasound markers such as fetal echogenic bowel identified during ultrasound stated:[15]

- "...for fetuses with isolated echogenic bowel, we recommend an evaluation for cystic fibrosis and fetal cytomegalovirus infection and a third-trimester ultrasound examination for reassessment and evaluation of growth (GRADE 1C)".

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for cystic fibrosis testing will ensure that testing will be

available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Decipher Prostate Genomic Classifier

MOL.TS.294.A
v1.0.2026

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Decipher Prostate Genomic Classifier	81542

Criteria

Decipher Prostate for Radical Prostatectomy (RP)

- No previous gene expression profile testing performed for this diagnosis of cancer, AND
- Member is post-radical prostatectomy, AND
- Post-surgical PSA is undetectable (below 0.2mg/dl), AND
- No evidence of lymph node metastasis identified, AND
- One or more of the following adverse features identified in the surgical specimen:
  - positive surgical margin(s), or
  - extracapsular extension, or
  - seminal vesicle invasion, AND
- Test is being requested to inform adjuvant treatment decisions.

Decipher Prostate for Biopsy

Decipher Prostate for biopsy is not medically necessary.

What are gene expression profiling tests for prostate cancer?

Prostate cancer (PC) is the most common cancer in men, and metastatic prostate cancer is a leading cause of cancer-related deaths worldwide. It is considered a heterogeneous disease with highly variable prognosis.[1]

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- At the time of diagnosis of localized PC, patients typically undergo a prognostic risk assessment with routine clinical and pathological tests to assess the probability of subsequent progression or metastasis. These prognostic assessments help to identify lower risk patients with indolent disease who may opt for active surveillance (AS), or higher risk patients with more aggressive disease who may benefit from a treatment intervention.
- High-risk prostate cancer (PC) patients treated with radical prostatectomy (RP) also undergo risk assessment to assess future disease prognosis and determine optimal treatment strategies. Post-RP pathology findings, such as disease stage, baseline Gleason score, time of biochemical recurrence (BCR) after RP, and PSA doubling-time, are considered strong predictors of disease-associated metastasis and mortality. Following RP, up to 50% of patients have pathology or clinical features that are considered at high risk of recurrence and these patients usually undergo post-RP treatments, including adjuvant or salvage therapy or radiation therapy, which can have serious risks and complications. According to clinical practice guideline recommendations, high risk patients should undergo 6 to 8 weeks of radiation therapy (RT) following RP. However, approximately 90% of high-risk patients do not develop metastases or die of prostate cancer, and instead may be appropriate candidates for alternative treatment approaches, including AS. As such, many patients may be subjected to unnecessary follow-up procedures and their associated complications, highlighting the need for improved methods of prognostic risk assessment.[2,3]
- Several genomic biomarkers have been commercially developed to augment the prognostic ability of currently available routine clinical and pathological tests and identify those patients either at the time of diagnosis of localized PC or after radical prostatectomy (RP) most and least likely to benefit from a specific treatment strategy. Prognostic genomic tests, including gene expression profiling tests, may help to avoid overtreatment by reclassifying those men originally identified as high risk, but who are unlikely to develop metastatic disease. Genomic biomarkers may also play a role in assisting clinicians to tailor personalized and more appropriate treatments for subgroups of PC patients, and improve overall health outcomes.[2,3]

Test information

- Gene expression profiles (GEPs) evaluate the expression of several genes using one sample. Gene expression is determined through RNA analysis, using either reverse transcriptase (RT) polymerase chain reaction (PCR) or DNA microarrays.[4]
- Decipher Prostate Genomic Classifier predicts risk of metastasis to assist with treatment plan and/or intensity.[5]
- "Decipher uses an oligonucleotide microarray to measure the expression of 22 content genes to derive a Decipher score (ranging from 0 to 1.0) and corresponding calibrated probabilities for the following clinical endpoints:"[6,7]

  - "Risk of adverse pathology at RP (i.e., Grade Group 3-5, pT3b-T4, or lymph node involvement)."
  - "5-year and 10-year risk of clinical metastasis and 15-year risk of prostate cancer specific mortality (PCSM) after standard therapy."
- A Decipher score of 0.60 – 1.0 is considered high risk.[5]
- Decipher Prostate for Biopsy
  - “Decipher Prostate Biopsy is intended for use in patients who are diagnosed with localized or regional prostate cancer who have not received pelvic radiation or hormone therapy prior to the biopsy. Decipher results are intended for use as an adjunct to conventional clinical risk factors for determining the metastatic potential of the tumor and patient prognosis.”[6]
- Decipher Prostate for Radical Prostatectomy (RP)
  - "Decipher Prostate RP is intended for use in patients with localized prostate cancer after radical prostatectomy (RP) with undetectable, persistent, or rising prostate-specific antigen (PSA) who are being considered for treatment and have not received pelvic radiation or hormone therapy prior to RP. Decipher results are intended for use as an adjunct to conventional clinical risk factors for determining the metastatic potential of the tumor and patient prognosis.”[7]

Guidelines and evidence

American Association of Clinical Urologists

The American Association of Clinical Urologists (AACU, 2022) has issued a position statement on genomic testing in prostate cancer that states the following:[8]

- “The AACU supports the use of tissue-based molecular testing as a component of risk stratification in prostate cancer treatment decision making.”

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO, 2020) issued a guideline on molecular biomarkers in prostate cancer. This guideline states:[9]

- "Are there molecular biomarkers to diagnose clinically significant prostate cancer?"
  - "Recommendation 2.1. Commercially available molecular biomarkers (ie, Oncotype Dx Prostate [now Genomic Prostate Score], Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate)."
  - "Recommendation 2.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and

thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate)."

- "Are there molecular biomarkers to guide the decision of postprostatectomy adjuvant versus salvage radiation?"
  - "Recommendation 3.1. The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate)."
  - "Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate)."

American Urological Association and American Society of Radiation Oncology

The American Urological Association and American Society for Radiation Oncology (AUA/ASTRO, 2022) published an evidence-based guideline on localized prostate cancer endorsed by the Society of Urologic Oncology (SUO) that stated:[10]

- "Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)"
- "Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)"
- "Regarding tissue-based genomic biomarkers, several currently available commercial tests, including Prolaris, Oncotype Dx [now Genomic Prostate Score], and Decipher, variously offer prediction of adverse pathology as well as the risks of biochemical recurrence, metastasis, and prostate cancer death. However, most of the reported studies to date that evaluated the prognostic ability of these genomic tests did not meet inclusion criteria for the systematic review as the studies used surgical (ie, prostatectomy) rather than biopsy specimens."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) Clinical Practice Guidelines on Prostate Cancer stated the following regarding molecular assays:[11]

- "Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN or CAPRA risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or EBRT [external beam radiation therapy], likelihood of

adverse pathologic features after radical prostatectomy, and likelihood of developing metastasis after operation, definitive EBRT, or post-recurrence EBRT."

- "These molecular biomarker tests have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathways for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that men with low or favorable intermediate disease and life expectancy greater than or equal to 10 years may consider the use of Decipher, Oncotype DX Prostate [now Genomic Prostate Score], or Prolaris during initial risk stratification. Patients with unfavorable intermediate- and high-risk disease and life expectancy greater than or equal to 10 years may consider the use of Decipher or Prolaris."
- Decipher is included in the Principles of Risk Stratification table as an advanced tool providing prognostic information in individuals with localized prostate cancer or post RP.

With regard to the use of Decipher post-radical prostatectomy (RP), NCCN stated:[11]

- "The panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, PSADT, and Decipher molecular assays to individualize treatment discussion."
- "The Decipher molecular assay is recommended to inform adjuvant treatment if adverse features are found post-radical prostatectomy, and can be considered as part of counseling for risk stratification in patients with PSA resistance/recurrence after radical prostatectomy (category 2B)."
- "Adverse laboratory/pathologic features include: positive margin(s); seminal vesicle invasion; extracapsular extension; or detectable PSA."

Selected Relevant Publications

The majority of the evidence for Decipher retrospectively evaluates the association between the Decipher score and adverse pathology, biochemical recurrence, or metastasis in men post-RP.[12-37] Low quality evidence suggests Decipher results are associated with metastasis and adverse pathology at initial biopsy. However, these findings are weakened by several limitations, including: overlapping patient populations, retrospective study designs, small sample sizes, and reporting of surrogate outcomes. Several decision impact studies suggest Decipher results may influence clinical decision-making; however, it remains unclear if Decipher-based decision-making ultimately leads to improvements in patient health outcomes. Future trials should prospectively evaluate the impact of Decipher testing on clinical decision-making in large independent cohorts of men and include sufficient follow-up to capture patient-relevant outcomes (e.g., mortality, recurrence, and metastasis). This conclusion is echoed by several systematic reviews.[38-41]

Clinical trials may be ongoing. Additional information can be found at **https://clinicaltrials.gov** .

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Decipher Prostate Genomic Classifier will ensure that testing will be available to those members most likely to benefit from the information provided by the assay. For those not meeting criteria, it ensures alternate management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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DecisionDx Uveal Melanoma

MOL.TS.254.A
v1.0.2026

Introduction

DecisionDX testing for uveal melanoma is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
DecisionDx-PRAME	81401
DecisionDx Uveal Melanoma Gene Expression Profile	81552

Criteria

Introduction

Requests for DecisionDX testing for uveal melanoma are reviewed using the following criteria.

DecisionDX-UM

DecisionDx-UM testing is medically necessary when the following criteria are met:
- No previous DecisionDx-UM testing performed after current diagnosis when a result was successfully obtained, AND
- Member has primary, localized uveal melanoma, AND
- No evidence of metastatic disease, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

DecisionDx-PRAME

This test is considered Experimental, Investigational, or Unproven.

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- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

DecisionDx-UMSeq

For information on DecisionDX-UMSeq testing, please refer to the guideline *Somatic Mutation Testing*, as this testing is not addressed here.

What is Uveal Melanoma?

Uveal melanoma (UM) is a rare cancer of the eye, arising in the choroid, ciliary body or iris of the eye, with about 1500 new cases per year in the US. It accounts for about 5% of all melanomas in the US.[1]

- The diagnosis is usually established by clinical assessment combined with ancillary diagnostic testing, using fluorescein angiography and ultrasonography.[2]
- Despite relatively high cure rates of the primary tumor following treatment,[3] metastatic disease to the liver occurs in 20 to 50% of individuals with UM. Median survival after metastasis detection has been reported to be approximately 9 months.[4]
- As a result, accurate prognostic assessment for metastatic risk is considered crucial for an individual's survival. Conventional prognostic evaluation of UM involves clinical and pathologic criteria, such as age, tumor diameter, tumor thickness, ciliary body involvement, tumor cell morphology, extracellular matrix patterning, and extraocular tumor extension.[4,5]
- Some experts have questioned the accuracy of these methods to predict metastasis.[6,7] As such, new molecular techniques examining the genetic composition of tumor cells have been introduced to improve prognostic evaluations potentially allowing for more targeted surveillance and treatment options for UM. Additionally, it may also facilitate referral of high-risk individuals to clinical trials.[7,8]

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Test information

Introduction

DecisionDx-UM is a 15 gene panel that measures gene expression of 12 genes present in ocular melanoma (CDH1, ECM1, EIF1B, FXR1, HTR2B, ID2, LMCD1, LTA4H, MTUS1, RAB31, ROBO1, and SATB1) and 3 control genes (MRPS21, RBM23, and SAP130). This test is designed to assess the risk of metastasis within 5 years.[9]

- DecisionDx-UM test results are reported as follows:[9,10]
  - Class 1A – very low risk (2%) of metastasis within 5 years
  - Class 1B – intermediate risk (21%) of metastasis within 5 years
  - Class 2 – high risk (72%) of metastasis within 5 years
- DecisionDx-PRAME is a test that can be added on to the DecisionDx-UM assay for additional information regarding prognosis. According to Castle Biosciences,"PRAME [preferentially expressed antigen in melanoma] is usually not expressed in normal adult tissues, but in some cancers, PRAME expression is elevated. Studies have suggested that elevated PRAME expression (“PRAME positive”) in a Class 1 uveal melanoma tumor may be associated with an increased risk of metastasis compared to a Class 1 tumor that does not express PRAME (“PRAME negative”)."[11]
- The manufacturer also offers the DecisionDX-UMSeq test.[12,13]

Guidelines and evidence

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2024) stated the following regarding gene expression for uveal melanoma.[8]

- "Biopsy of the primary tumor may provide prognostic information that can help inform frequency of follow-up and may be needed for eligibility for clinical trials. Biopsy is typically performed before the tumor is irradiated and can often be performed at the time of primary treatment depending on the procedure modality. If biopsy is performed, molecular/chromosomal testing for prognostication is preferred over cytology alone. The risk/benefits of biopsy for prognostic analysis should be carefully considered and discussed."
- "For patients who had a biopsy of their primary tumor, certain molecular features have been shown to be prognostic for risk of distant spread and should be used for risk stratification."
- Gene expression profiling as described by Onken et al[14] was recommended as part of the stratification in determining the class of the tumor [Class 1A (low risk), Class 1B (medium risk), or Class 2 (high risk)] to inform frequency of follow-up.

  - "It has been shown that class 2 was associated with a 5-fold to 20-fold higher risk of metastasis than class 1."
- "PRAME expression, present in about a third of uveal melanomas has also been associated with increased risk of metastasis. … PRAME expression is also an indicator of high risk to be used to inform frequency of follow-up."

Selected Relevant Publications

Based on the review of the available peer-reviewed published literature, the DecisionDx-UM 15-gene assay has sufficient evidence for use as a prognostic test in individuals diagnosed with primary, localized uveal melanoma to assist clinicians with predicting disease severity and improving disease management strategies.[3,14-28]

DecisionDX-PRAME

There is currently insufficient evidence regarding use of DecisionDX-PRAME.[29-34] Clinical validity and clinical utility studies are lacking. Additional studies are needed to determine whether DecisionDX-PRAME improves clinical outcomes more than DecisionDX-UM alone. As a result, no conclusions can be drawn regarding the value and usefulness of this test.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for DecisionDX Uveal Melanoma will ensure that testing will be available to those members most likely to benefit from the information provided by the assay. For those not meeting criteria, it ensures alternate management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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DecisionDx Uveal Melanoma

DermTech Melanoma Test

MOL.TS.282.A
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Introduction

Pigmented Lesion Assay (DermTech Melanoma Test) is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure code
Pigmented Lesion Assay (DermTech Melanoma Test)	0089U

Criteria

Requests for Pigmented Lesion Assay (DermTech Melanoma Test) are reviewed using the following criteria.

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

What is melanoma?

According to the American Cancer Society (ACS), the incidence of primary cutaneous melanoma varies by age and sex. The incidence of melanoma has been reported to be increasing at a rate of 3% annually among women ages 50 and older.[1]

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Melanoma accounts for the majority of skin cancer related deaths, but treatment is nearly always curative with early detection of disease. Minimal depth (thin) melanomas have a cure rate of nearly 100%, while tumors with a Breslow depth of greater than 4mm have a 10-year survival rate of less than 50%.[2]

Standard of care for the assessment of clinically suspicious pigmented skin lesions is surgical biopsy with pathologic evaluation. However, histopathology is believed to have inherent limitations. Some lesions that are likely to be true melanomas based on clinical behavior do not meet the complete set of histologic criteria to establish a melanoma diagnosis.[2] There is also considerable interrater variability with visual image and pattern recognition of skin lesions.[3] In an effort to improve patient survival, a number of novel noninvasive techniques have been developed to classify pigmented skin lesions at an earlier stage.[4]

Test information

The DermTech Melanoma Test is a non-invasive method for the biopsy of clinically atypical pigmented lesions or moles using an adhesive patch to obtain mRNA from the surface of the suspicious lesion.

According to the manufacturer, this test assesses gene expression consistent with melanoma and is intended as a decision making aid for the clinician to determine whether or not to biopsy a pigmented skin lesion, clinically suspicious for melanoma.[5] The test is intended for use on pigmented lesions suspicious for melanoma that meet at least one of the A (asymmetry) B (border) C (color) D (diameter) E (evolving) criteria for which the clinician would like additional information prior to surgical biopsy. Uses include the following: lesions being followed for change; lesions in cosmetically sensitive areas of the body; lesions on individuals with possible risks for complications during surgical biopsy; or lesions among individuals who refuse biopsy.[5]

The DermTech Melanoma Test is a non-invasive method for the assessment of clinically atypical pigmented lesions or moles using an adhesive patch to obtain mRNA from the surface of the suspicious lesion. The method of adhesive tape stripping has been used to obtain RNA from the stratum corneum for gene expression of other disorders, such as allergic and irritant skin reactions and psoriasis.[6] This test detects the expression of 2 specific genes, PRAME and LINC00518, both of which are believed to play key roles in oncogenesis and both of which have been shown to be elevated in melanoma. If sufficient material is available, a DNA-based TERT Add-On Assay can be performed to detect TERT promoter mutations as well. If one or more of these biomarkers is detected, the test is considered positive. The positive lesions generally undergo surgical biopsy to definitively establish a melanoma diagnosis. The test manufacturer notes that this assay cannot be used on mucous membranes, palms of the hands, or soles of the feet.[3,5]

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Guidelines and evidence

American Academy of Dermatology

The American Academy of Dermatology (AAD) acknowledged that the clinical and prognostic significance of the use of biomarkers and mutational analysis is still unclear and there are gaps regarding their clinical usefulness that have yet to be addressed. The 2019 guideline stated:[4]

- "Ancillary diagnostic molecular techniques (eg, CGH, FISH, GEP) may be used for equivocal melanocytic neoplasms."
- "Routine molecular testing, including GEP [gene expression profiling], for prognostication is discouraged until better use criteria are defined. The application of molecular information for clinical management (eg, sentinel lymph node eligibility, follow-up, and/or therapeutic choice) is not recommended outside of a clinical study or trial."
- "Once a lesion has been identified as clinically concerning, dermoscopy can improve diagnostic accuracy and/or help direct optimal and adequate tissue sampling in the case of very large lesions or those in cosmetically or functionally sensitive areas. Newer noninvasive techniques (eg, reflectance confocal microscopy [RCM], as well as electrical impedance spectroscopy, gene expression analysis, optical coherence tomography, and others can also be considered as these become more readily available."
- "Lingering questions remain regarding the degree to which the selected gene sets represent genes associated with tumor progression, how they compare with current well-characterized prognostic factors and AJCC eighth edition survival data, and whether they improve prognostic models enough to affect patient management and outcomes. As such, the WG discourages routine baseline GEP for prognostication."
- "There is insufficient evidence to recommend routine molecular profiling assessment for baseline prognostication. Evidence is lacking that molecular classification should be used to alter patient management outside of current guidelines (eg, NCCN and AAD). The criteria for and the utility of prognostic molecular testing, including GEP, in aiding clinical decision making (eg, SLNB eligibility, surveillance intensity, and/or therapeutic choice) needs to be evaluated in the context of clinical study or trial."
- "Noninvasive genomic methods (eg, adhesive patch ‘‘biopsy’’) are being investigated to further classify melanocytic lesions as either benign or malignant to guide the need for further biopsy. The uptake of 1 or more of these technologies will eventually depend on cumulative evidence regarding their effectiveness, clinical utility, cost versus benefit, and competing strategies."

DermTech Melanoma Test

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) made no recommendation to use the DermTech Melanoma Test in the evaluation of skin lesions suspicious for melanoma. With regard to the evaluation of melanocytic lesions for the possibility of melanoma, the NCCN offered the following guidance relevant to the DermTech Melanoma Test:[7]

- "Melanocytic neoplasms of uncertain biologic potential present a unique challenge to pathologists and treating clinicians. Ancillary tests to differentiate benign from malignant melanocytic neoplasms include immunohistochemistry (IHC), and molecular testing via comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), single-nucleotide polymorphism (SNP) array, and next-generation sequencing (NGS). These tests may facilitate a more definitive diagnosis and guide therapy in cases that are diagnostically uncertain or controversial by histopathology. Ancillary tests should be used as adjuncts to clinical and expert dermatopathologic examination and therefore be interpreted within the context of these findings."

In the discussion of follow-up recommendations following a melanoma diagnosis, the NCCN stated the following:

- "Prediagnostic clinical modalities (ie, dermoscopy, total-body photography, sequential digital dermoscopy), noninvasive imaging and other technologies (eg, reflectance confocal microscopy, electrical impedance spectroscopy) may aid in surveillance for new primary melanoma, particularly in patients with high mole count and/or presence of clinically atypical nevi. For melanocytic neoplasms that are clinically/dermoscopically suspicious for melanoma, pre-diagnostic noninvasive patch testing may also be helpful to guide biopsy decisions."

Selected Relevant Publications

There is insufficient evidence to support the use of the DermTech Melanoma Test to accurately discriminate between early melanoma and non-melanoma in individuals with clinically suspicious lesions.[2,3,8-23] A recurring limitation within the evidence base is the assumption that non-biopsied lesions with negative results are true negatives without follow up assessment for confirmation. Additional limitations include retrospective study designs, small individual study populations, overlapping patient populations, short follow up times, and a lack of reported health outcomes.

Based on the current evidence, the DermTech Melanoma Test may have a high negative predictive value and influence clinical management decisions regarding biopsy but it remains unclear if these decisions result in meaningful clinical outcomes. Well-designed studies that report the impact on clinical management decisions together with the health outcomes that result from those decisions are needed to confirm the utility of the DermTech Melanoma Test.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for DermTech will ensure that members will not receive testing for which there is not a body of evidence demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[24] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

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Early Onset Familial Alzheimer Disease Genetic Testing

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Introduction

Early onset familial Alzheimer disease (EOFAD) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
APP deletion/duplication	81479
APP known familial mutation	81403
APP sequencing	81406
EOFAD multigene panel	81479
PSEN1 deletion/duplication	81479
PSEN1 known familial mutation	81403
PSEN1 sequencing	81405
PSEN2 known familial mutation	81403
PSEN2 sequencing	81406

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Criteria

Introduction

Requests for early onset familial Alzheimer disease (EOFAD) testing are reviewed using the following criteria.

PSEN1, PSEN2, or APP Known Familial Mutation Testing

- Clinical Consultation:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, and
  - PSEN1, PSEN2, or APP mutation identified in a 1st or 2nd degree biological relative, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Dementia diagnosed ≤65 years of age, OR
- Predictive Testing:
  - Age 18 years or older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

PSEN1 Full Sequence and Deletion/Duplication Analysis

- Clinical Consultation:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous PSEN1 sequencing or deletion/duplication analysis, and
  - No known PSEN1, PSEN2, or APP mutation in the family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Dementia diagnosed ≤65 years of age, and
  - Family history of dementia in 1st or 2nd degree relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

APP Full Sequence and Deletion/Duplication Analysis

- Criteria for PSEN1 analysis are met, AND
- No previous APP sequencing or deletion/duplication analysis, AND
- PSEN1 sequencing and deletion/duplication analysis were performed, and no mutations were detected, AND

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- No mutations detected in PSEN2 sequencing, if performed.

PSEN2 Full Sequence Analysis

- Criteria for PSEN1 analysis are met, AND
- No previous PSEN2 sequencing analysis, AND
- PSEN1 sequencing and deletion/duplication analysis were performed, and no mutations were detected, AND
- No mutations detected in APP sequencing, if performed.

Multigene Panel (PSEN1, APP, and PSEN2 ONLY)

- Clinical Consultation:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous testing for EOFAD, and
  - No known PSEN1, PSEN2, or APP mutation in the family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Dementia diagnosed less than or equal to 65 years of age, and
  - Family history of dementia in 1st or 2nd degree relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

When otherwise reimbursable, the following limitations apply:

- When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81479*).
- When use of a panel code is not possible, each billed component procedure will be assessed independently.

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- In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
- When the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement in a tiered fashion:
  - PSEN1
  - APP
  - PSEN2

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is early onset familial Alzheimer disease?

Alzheimer disease (AD) is characterized by adult onset, progressive dementia with cerebral cortical atrophy, beta amyloid plaque formation, and intraneuronal neurofibrillary tangles.[1] Approximately 95% of all AD is late-onset (age >60-65 years), and 5% is early-onset (age <60-65 years).[1]

Prevalence

The general population lifetime risk of AD is about 10%.

Familial AD

Familial AD (3 or more affected individuals in a family) accounts for about 25% of all AD, including late and early onset.[1]

Most familial AD is late-onset, but in less than 2% of cases, symptoms start at an unusually young age (called "early onset familial Alzheimer disease" or EOFAD).[1]

Symptoms

Common findings include memory loss, confusion, speech issues, hallucinations, and personality and behavioral changes such as poor judgment, agitation, and withdrawal.[1,2] Symptoms of AD usually start after 60-65 years old; however, symptoms of EOFAD begin at 65 years or younger.[1]

EOFAD is suspected when:[1]

- More than one family member has AD; and
- Symptoms occur before the age of 65.

Cause

There are three subtypes of EOFAD.[1]

- While not clinically distinguishable, the underlying genetic cause differs. Among families with EOFAD, 60-80% will have a detectable mutation in the APP, PSEN1, or PSEN2 gene.[1] Therefore, some families with EOFAD will not have an identifiable mutation by current testing. There may be other disease-causing genes that have not been identified to date.
- Most people with EOFAD have an affected parent. In cases where there appears to be no parent affected, most people have a second degree relative with the condition. De novo (new) mutations are possible. However, they have not been reported in EOFAD.[1,2]
- Reduced penetrance of EOFAD-associated mutations has been described.

Table 1: Subtypes of EOFAD[1]

Gene	Proportion of EOFAD cases	Average age of onset
APP	10-15%	40s to 50s (occasionally 60s)
PSEN1	20-70%	40s to early 50s
PSEN2	~5%	40 to 75

Inheritance

EOFAD is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

The diagnosis of AD relies on clinical assessment, which may include mental status testing, neurological examinations, diagnostic tests (such as biomarker testing), and brain imaging. [1]Genetic testing of APP, PSEN1, or PSEN2 is another tool to establish the diagnosis in individuals with early onset AD and a positive family history. In asymptomatic individuals with a mutation in one of these genes, there is an

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increased likelihood they will develop EOFAD however reduced penetrance has been documented.[1]

Because of the implications of predictive testing, pretest genetic counseling should include limitations of predictive testing and potential consequences with regard to health, life, and disability insurance coverage; employment and educational discrimination; reproductive decision-making; and changes in social and family dynamics.[1] Predictive testing is considered inappropriate for asymptomatic minors who are at risk for adult-onset conditions if there is not an early treatment option expected to have a beneficial effect on the disease morbidity and mortality.[1]

Management

There is no cure for AD however some medications may help with symptoms such as memory loss and confusion. There are also non-drug treatments for Alzheimer's disease that are used with the goals of maintaining or improving cognitive function, overall quality of life and engagement, and the ability to perform activities of daily living.[3] Non-drug treatments include physical activity, memory and orientation exercises, and music- and art-based therapies.

Survival

The survival for individuals with EOFAD is unknown due to the rarity of the condition and a paucity of longitudinal studies. In individuals with late-onset AD diagnosed at age 65 or older, the average survival is four to eight years after the diagnosis is made but can be as long as 20 years.[3] EOFAD is believed to have a more aggressive disease course than late-onset AD with faster progression.[1]

Test information

Introduction

Testing for EOFAD may include known familial mutation analysis, next generation sequencing, deletion/duplication analysis, and/or multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

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Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Given the significant overlap in clinical manifestations and age of onset in AD, a multigene panel that includes PSEN 1/2 and APP, rather than single gene testing, is most likely to identify the genetic cause but also limit identification of variants of uncertain significance.[1]

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and evidence

American College of Medical Genetics and Genomics and National Society of Genetic Counselors

The American College of Medical Genetics and Genomics (ACMG, 2011; reaffirmed 2018) and The National Society of Genetic Counselors (NSGC, 2011; reaffirmed 2016) stated:[4]

- "Testing for genes associated with early-onset autosomal dominant AD should be offered in the following situations:"

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- "A symptomatic individual with EOAD in the setting of a family history of dementia or in the setting of an unknown family history (e.g., adoption)".
- "Autosomal dominant family history of dementia with one or more cases of EOAD."
- "A relative with a pathogenic variant consistent with EOAD (currently PSEN 1/2 or APP)."

Amyloid Imaging Taskforce, Society of Nuclear Medicine and Molecular Imaging, and Alzheimer's Association

The Amyloid Imaging Taskforce (AIT, 2013), Society of Nuclear Medicine and Molecular Imaging (SNMMI, 2013), and the Alzheimer's Association referenced genetic testing in their recommendations:[5]

- "The use of amyloid PET in lieu of genotyping for suspected autosomal dominant mutation carriers is considered inappropriate. The optimal clinical evaluation in these cases is careful collection of a family history, followed (if appropriate) by genetic counseling prior to and after genetic testing for known mutations. Future use of amyloid PET in autosomal dominant mutation carriers could include determination of whether the amyloid deposition phase of their illness has begun. In the setting of a complete clinical evaluation, including serial neuropsychological testing, this information may be useful in identifying one disease-related milestone that, along with the genetic information, aids decision making."

European Federation of Neurological Societies

The European Federation of Neurological Societies (EFNS, 2010) Alzheimer's diagnosis and management guidelines addressed genetic testing:[6]

- "Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia." (No evidence level assigned.) They add, "Testing of patients with familial dementia and of unaffected at-risk-relatives should be accompanied by neurogenetic counseling and undertaken only after full consent and by specialist centers. Pre-symptomatic testing may be performed in at risk member of family-carrying mutation. It is recommended that the Huntington's disease protocol is followed for pre-symptomatic testing."

Selected Relevant Publications

A 2018 expert-authored review stated:[1]

- "Establishing a specific genetic cause of Alzheimer disease (AD): Can aid in discussions of prognosis (which are beyond the scope of this GeneReview) and genetic counseling (Section 4); Usually involves a medical history, physical examination, and laboratory testing to exclude disorders included in the differential diagnosis (see Section 1), family history, and genomic/genetic testing."

- "Because familial AD and nonfamilial AD appear to have the same clinical and pathologic phenotypes, they can only be distinguished by family history and/or by molecular genetic testing."
- "Because of the significant overlap in clinical manifestations and age of onset in AD, single-gene testing (i.e., sequence analysis, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended."
- "Predictive testing for asymptomatic adults at risk for APP-, PSEN1-, or PSEN2-related EOFAD is possible if the pathogenic variant has been identified in an affected family member."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for early onset familial Alzheimer disease testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Epilepsy Genetic Testing

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Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures covered by this guideline	Procedure codes
CACNA1A full gene sequence	81185
CSTB full gene sequence	81189
CSTB gene analysis; evaluation to detect abnormal alleles	81188
Epilepsy gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Epilepsy gene known familial mutation analysis	81403

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Procedures covered by this guideline	Procedure codes
Epilepsy gene panel (must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2)	81419
Genomic Unity CACNA1A Analysis	0231U
Genomic Unity CSTB Analysis	0232U

Criteria

This guideline applies to all epilepsy testing, including single gene analysis and multi-gene panels, which are defined as assays that simultaneously test for more than one epilepsy gene. Coverage criteria differ based on the type of testing being performed (i.e., individual epilepsy genes separately chosen versus pre-defined panels of epilepsy genes).

Epilepsy single gene tests

Epilepsy single gene tests are considered medically necessary when the following criteria are met:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing inclusive of the gene(s) requested, AND
- Diagnostic Testing in Symptomatic Individuals:
  - The member has a condition that will benefit from information provided by the requested epilepsy gene testing based on at least one of the following criteria:
    - The member displays clinical features of the condition for which testing is being requested and a particular treatment is being considered for the member that requires a genetic diagnosis, OR
    - A particular antiepileptic drug (AED) is being considered for the member and the AED is contraindicated for individuals with mutations in the requested gene, defined by ONE of the following criteria:

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- A neurology therapy FDA label requires results from the genetic test to effectively or safely use or avoidance of the therapy for the member's epilepsy type, and the member has not previously had a trial of the therapy, or
- An American neurological society specifically recommends the testing for the safe and effective use or avoidance of a therapy, and the member has not previously had a trial of the therapy, OR

▪ The member meets all criteria in a test-specific guideline, if available (see Table: *Select Epilepsy Conditions, Associated Genes, and Applicable Guidelines*), AND

◦ The member does not have a known underlying cause for their seizures (e.g. tumor, head trauma, known genetic condition), AND
◦ Rendering laboratory is a qualified provider of service per the Health Plan policy

Epilepsy multi-gene panels

Epilepsy multigene panels are considered medically necessary when all of the following criteria are met:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous epilepsy multigene panel testing, AND
- Diagnostic Testing in Symptomatic Individuals:
  - The member has a diagnosis of early infantile epileptic encephalopathy, OR
  - The member has a diagnosis of infantile spasms, OR
  - The member has a diagnosis of intractable, neonatal seizures, OR
  - The member has drug-resistant focal epilepsy, OR
  - The member has focal epilepsy with a positive family history suggestive of monogenic inheritance, OR
  - The member has a diagnosis of febrile seizures with at least one episode of status epilepticus, OR
  - The member has a progressive neurological disease defined by the following:
    - Member has epilepsy with persistent loss of developmental milestones, and
    - Member's seizures are worsening in severity and/or frequency despite treatment, OR
  - A particular antiepileptic drug (AED) is being considered for the member and there are 2 or more genes on the panel for which the AED is contraindicated for individuals with mutations in that gene by ONE of the following:

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        - A neurology therapy FDA label requires results from the genetic test to effectively or safely use or avoidance of the therapy for the member's epilepsy type and the member has not previously had a trial of the therapy, or
        - An American neurological society specifically recommends the testing for the safe and effective use or avoidance of a therapy and the member has not previously had a trial of the therapy, AND
    - The member does not display clinical features of a specific condition for which testing is available (e.g. Tuberous Sclerosis, Angelman Syndrome, Rett Syndrome, etc.), AND
    - The member does not have a known underlying cause for their seizures (e.g. tumor, head trauma, known genetic condition), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other considerations

This guideline may not apply to genetic testing for indications that are addressed in test-specific guidelines. Please see the test-specific list of guidelines for a complete list of test-specific panel guidelines.

Genetic testing for a specific gene is medically necessary only once per lifetime. Therefore, a single gene included in a panel or a multi-gene panel may not be reimbursed if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest. Further, given rapidly advancing knowledge regarding genetic variations in epilepsy and in normal or healthy populations, re-analysis of genetic tests may be warranted at regular intervals.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
    - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81419*).

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- When use of a panel code is not possible, each billed component procedure will be assessed independently.
- In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is epilepsy?

Epilepsy is a neurological condition that causes seizures.

Prevalence

Epilepsy is one of the most common disorders, with an estimated prevalence of 6 in 1000 people worldwide.[1]

Symptoms

Epilepsy can manifest in different ways, including different types of seizures or with multiple neurodevelopmental and medical complications besides seizures. Seizure types include generalized seizures (absence seizures, tonic-clonic seizures, myoclonic seizures), focal seizures (simple focal seizures, complex focal seizures, secondary generalized seizures, among others), and seizures for which the type is unknown.

Epilepsy syndromes can be associated with generalized, focal, or combined generalized and focal seizures, and can have onset in childhood or adulthood.[2] Epilepsy syndromes may be associated with developmental and/or epileptic encephalopathy (childhood onset) or progressive neurological deterioration (later onset).[2]

Cause

Epilepsy has multiple causes, including central nervous system infection, autoimmune disease, structural brain abnormalities, brain tumors, and head trauma.[3] There are also numerous genetic conditions associated with epilepsy. It is estimated that approximately 40% of individuals with seizures have an underlying genetic basis for their condition (see Table for a list of common genetic causes).[4] Factors that contribute to the likelihood of a genetic basis includes type of seizures (focal or generalized) or epilepsy syndromes (such as epileptic encephalopathy), age of onset, family history, and presence of other clinical features.

Through Next Generation Sequencing (NGS)-based testing, including multi-gene panels, whole exome and genome sequencing as well as whole-genome screening for CNVs, pathogenic sequence variants have been identified in about 30-40% and deletions or duplications in ~5-10% of patients with a range of epilepsy phenotypes, including focal epilepsy, generalized epilepsies, epileptic encephalopathies, fever-associated epilepsy syndromes, other epilepsy syndromes, and patients with neurodevelopmental disorders and epilepsy.[5,6]

There are many different epilepsy syndromes, including generalized epilepsy syndromes, focal epilepsy syndromes, combined generalized and focal epilepsy syndromes, epilepsy syndromes with developmental and/or epileptic encephalopathy (DEE). These syndromes can present at variable ages ranging from neonatal to adulthood.[2,7]

DEE is a group of disorders in which seizures are accompanied by developmental delays, cognitive impairment, or a host of other neurological issues such as feeding difficulties, sleep dysregulation, and behavioral problems.[8] Knowledge regarding the genetic basis of these disorders has increased significantly in the last decade due to the advent of high throughput NGS methods, resulting in a growing list of known associated genes and wider availability of multi-gene panel testing. The following are examples of epileptic encephalopathies:

- Ohtahara Syndrome (Early Infantile Epileptic Encephalopathy)
  - "Characterized by early onset intractable tonic spasms, suppression-burst pattern on interictal EEG, and poor prognosis."[9]
  - "To date various genes, which have essential roles in the brain's neuronal and interneuronal functions, have been reported to be associated with Ohtahara syndrome. For instance, syntaxin binding protein 1 (STXBP1) regulates synaptic vesicle release; aristaless-related homeobox (ARX) acts as a regulator of proliferation and differentiation of neuronal progenitors; solute carrier family 25 member 22 (SLC25A22) encodes a mitochondrial glutamate transporter13; and potassium voltage-gated channel, KQT-like subfamily, member 2 (KCNQ2) plays a key role in a cell's ability to generate and transmit electrical signals."[10]
- Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy)
  - "Clinical cardinal features include febrile or afebrile generalized or hemiconvulsions starting in the first year of life, seizure evolution to a mixture of intractable generalized (myoclonic or atonic seizures, atypical absences) and focal seizures, normal early development, subsequent psychomotor retardation, and normal brain imaging at onset."[9]
  - "In most of the cases with Dravet syndrome, one single gene has been involved, in contrast to other epileptic encephalopathy syndromes. SCN1A mutations have been shown in at least 80% of patients with Dravet syndrome."[10]
- Infantile Spasms (West Syndrome and X-linked Infantile Spasms)

  - "West syndrome is characterized by a specific seizure type, i.e., epileptic spasms, a unique interictal EEG pattern termed hypsarrhythmia, and psychomotor retardation. Spasms start within the first year of life, mainly between 4 and 6 months of age."[9]
  - "There are multiple genetic determinants of infantile spasms, which are usually explained by mutations in distinct genes. Genetic analysis of children with unexplained infantile spasms have demonstrated mutations on the X chromosome in genes such as ARX, cyclin-dependent kinase-like 5 (CDKL5), and UDP-N-acetylglucosaminyltransferase subunit (ALG13) as well as de novo mutations in autosomal genes, including membrane-associated guanylate kinase, WW and PDZ domain containing protein 2 (MAGI2), STXBP1, sodium channel alpha 1 subunit (SCN1A), sodium channel protein type 2 subunit alpha (SCN2A), g-aminobutyric acid (GABA) A receptor, beta 3 (GABRB3), and dynamin 1 (DNM1)."[10]
- Epilepsy and Intellectual Disability Limited to Females
  - "Epilepsy and intellectual disability limited to females (EFMR) is an underrecognized disorder with X-linked inheritance but surprisingly only affecting females while sparing transmitting males. Seizure, cognitive, and psychiatric phenotypes show heterogeneity. Seizures start from the age of 6 to 36 months and may be precipitated by fever. Seizure types include GTCS, myoclonic and tonic seizures, absences, and focal."[9]
  - "Different mutations of PCDH19 (protocadherin 19), including missense, nonsense, and frameshift mutations, have been reported as the cause of EFMR."[9]

Table: Select Epilepsy Conditions, Associated Genes, and Applicable Guidelines

Condition*	Associated genes*	Applicable guideline	Guideline number
Angelman syndrome	UBE3A	Angelman Syndrome Genetic Testing	MOL.TS.126
Biotin-thiamine-responsive basal ganglia disease	SLC19A3	Epilepsy Genetic Testing	MOL.TS.257
Cerebral folate transport deficiency	FOLR1	Epilepsy Genetic Testing	MOL.TS.257

Condition*	Associated genes*	Applicable guideline	Guideline number
Classic Rett syndrome (females); MECP2-Related Epileptic Encephalopathy (males)	MECP2	Rett Syndrome Genetic Testing	MOL.TS.224
Creatine deficiency syndromes	GAMT, GATM, SLC6A8	Epilepsy Genetic Testing	MOL.TS.257
Developmental and epileptic encephalopathy (DEE)	ARGHEF9, ARX, CDKL5, CHD2, PCDH19, GABRA1, GABR2, GABRB3, GRIN2A, KCNQ2, KCNT1, PNKP, SCN1A, SCN1B, SCN2A, SCN8A, SLC25A22, SPTAN1, STXBP1, TBC1D24	Epilepsy Genetic Testing	MOL.TS.257
Familial hemiplegic migraine	ATP1A2, CACNA1A, PRRT2	Epilepsy Genetic Testing	MOL.TS.257
GLUT1 Deficiency	SLC2A1	Epilepsy Genetic Testing	MOL.TS.257
POLG-related disorders	POLG	Polymerase Gamma (POLG) Related Disorders Genetic Testing	MOL.TS.276
Progressive myoclonic epilepsy	CSTB, EPM2A, GOSR2, KCNC1, KCTD7, NHLRC1, PRICKLE1, SCARB2	Epilepsy Genetic Testing	MOL.TS.257
Pyridoxine-dependent epilepsy	ALDH7A1, PNPO	Epilepsy Genetic Testing	MOL.TS.257

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Condition*	Associated genes*	Applicable guideline	Guideline number
Tuberous sclerosis	TSC1, TSC2	Epilepsy Genetic Testing	MOL.TS.257

*This list of conditions and their associated genes is not all-inclusive. Many genes can be associated with multiple types of seizure disorders, including some milder disorders not listed here (e.g., generalized epilepsy with febrile seizures or self-limited familial neonatal/infantile epilepsy).

Inheritance

Inheritance patterns differ between various epilepsy syndromes, and include monogenic inheritance patterns such as dominant, X-linked, recessive, and mitochondrial, in addition to epilepsy caused by de novo (i.e. new) genetic mutations. Clinical heterogeneity is also seen in these conditions.

Diagnosis

An electroencephalograph (EEG) can be used to help diagnose epilepsy and possibly give information as to the seizure type. A brain magnetic resonance imaging (MRI) scan can further help define whether epilepsy is caused by a structural brain abnormality or help determine the origin of epilepsy.

Genetic testing for epilepsy is complicated by many factors. Epilepsy syndromes frequently have overlapping features, such as the types of seizures involved, ages of onset, and/or additional clinical findings. Reduced penetrance, with not all individuals carrying a pathogenic genetic change developing seizures, also complicates the family history assessment. Many (if not most) epilepsy syndromes, including epileptic encephalopathy, are genetically heterogeneous, and can be caused by mutations in a number of different genes. Sometimes, the inheritance pattern or the presence of pathognomonic features makes the underlying syndrome clear. However, in many cases, it can be difficult to reliably diagnose a genetic epilepsy syndrome based on clinical and family history alone.

NGS-based testing has been shown to dramatically improve the diagnostic rate for children and adults with epilepsy, as well as significantly shorten the time from assessment to diagnosis.[11-13] The diagnostic yield of NGS in patients with epilepsy is estimated to be 20-40%.[6,14,15]

Clinical information (e.g. age of onset, seizure type, EEG results, etc.) or family history may be used in some cases to help narrow down the suspected cause. In these cases, it may be possible to identify a narrow subset of genes that may be responsible for an individual's epilepsy.[9,10]

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Management

Treatment for epilepsy ranges from antiepileptic drugs (AEDs) to the ketogenic diet to vagal nerve stimulation to epilepsy surgery in the most severe situations. Not all treatments will work for everyone and often, it takes multiple treatment trials to find a regimen that is successful. Refractory epilepsy is diagnosed after two or more AEDs have failed to control seizures. Drug-resistant epilepsy is defined as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".[16]

In a rapidly growing number of epilepsy disorders, knowing the genetic mutation that is responsible for the epilepsy has been shown to help guide management and provide more disease-specific treatment.[17,18]

Survival

Lifespan is dependent upon seizure control and the underlying cause of the individual's epilepsy.

Test information

Introduction

Genetic testing for epilepsy may consist of next-generation sequencing or multigene panels.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes

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of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and evidence

International League Against Epilepsy

A Task Force for the International League Against Epilepsy (ILAE, 2015) Commission of Pediatrics published recommendations for the management of infantile seizures that stated:[19]

- "[F]or Dravet syndrome, strong evidence supports that stiripentol is effective (in combination with valproate and clobazam), whereas weak evidence supports that topiramate, zonisamide, valproate, bromide, and the ketogenic diet are possibly effective; and for Ohtahara syndrome, there is weak evidence that most antiepileptic drugs are poorly effective."
- "Genetic evaluation for Dravet syndrome and other infantile-onset epileptic encephalopathies should be available at tertiary and quaternary levels of care (optimal intervention would permit an extended genetic evaluation) (level of evidence—weak recommendation, level C)."
- "Early diagnosis of some mitochondrial conditions may alter long-term outcome, but whether screening at quaternary level is beneficial is unknown (level of evidence U)."

The ILAE (2022) Task Force on Clinical Genetic Testing in the Epilepsies provided an updated review of the role of genetic testing for those with epilepsy that stated:[20]

- "A precise epilepsy genetic diagnosis is important for individuals and their families as it has both clinical and personal utility."
- "Testing should be considered in epilepsy types with a reasonably high pre-test probability of a genetic cause being identified and, especially, if the results may lead to improved care for the individual."
- "Overall, the likelihood of identifying a genetic cause decreases with increasing age at onset of the epilepsy; the greatest proportion of genetic epilepsies manifests in the neonatal period, followed by infancy. In this age period, the diagnostic yield of genetic testing may reach up to 60%. However, age at testing (as opposed to the age at onset of epilepsy) should not influence the decision to test or the type of test chosen. Individuals who are now adults who had early-onset epilepsy likely presented in the era before genetic testing was widely available, and should be considered candidates for testing."
- "Clinical utility of genetic testing is highest in the more severe, drug-resistant epilepsies. Overall, the most obvious indication, in terms of clinical utility and diagnostic yield, is for people with early-onset DEE or neurodevelopmental disorders with epilepsy. The presence of comorbid conditions, such as intellectual disability, autism, dysmorphic features or multi-system symptoms increases the likelihood of

a genetic finding. Testing of individuals with drug-resistant non-acquired epilepsy without such comorbidities could be useful as identification of an underlying genetic cause might lead to a more targeted treatment."

National Society of Genetic Counselors

The National Society of Genetic Counselors practice guideline on epilepsy (2022), which was endorsed by the American Epilepsy Society (AES), stated:[7]

- "We strongly recommend that individuals with unexplained epilepsy be offered genetic testing, without limitation of age."
- "We strongly recommend comprehensive, multi-gene testing, such as ES/GS [exome sequencing/genome sequencing] or MGP [multigene panels] as a first-tier test. We conditionally recommend ES/GS over MGP as the first-tier test."
- "The MGP panel should have a minimum of 25 genes and include copy number analysis."
- "MGPs are valuable clinical tools that can be employed in a number of clinical scenarios, for example, when an individual presents with a defined epilepsy syndrome for which a subset of genes should be interrogated more robustly than through ES when GS is unavailable. Additionally, if urgent results are required and rapid ES/GS is unavailable, a targeted MGP may be considered. MGPs may also be utilized as a first-tier test when access to ES/GS, or the additional genetic counseling required to implement such testing, may be limited."

Selected Relevant Publications

Peer reviewed and expert authored articles are presented below.

- In 2016, a peer reviewed article on genetic testing for epileptic encephalopathy stated the following:
  - "Second line investigations: Targeted next generation sequencing panels of epileptic encephalopathy genes for individuals with epileptic encephalopathy." [8]
- In 2016, a peer reviewed article on genetic causes of early-onset epileptic encephalopathy stated the following:[10]
  - "Molecular-based studies on early-onset epileptic encephalopathies should be performed, necessitating programmed genetical algorithms. If the phenotype could be determined with clinical findings, specific gene testing would be helpful in diagnosis. However, if the phenotype could not be determined because of overlapping phenotypes of different syndromes and the spectrum of phenotypes seen in different mutations, the use of gene panels for epilepsy would increase the probability of correct diagnosis. In a recent study, the rate of diagnosis with targeted single gene sequencing has been reported as 15.4%, whereas the rate has increased to 46.2% with the utility of epilepsy gene panels."

- A systematic evidence review and meta-analyses of the diagnostic yield of genetic tests commonly utilized for patients with epilepsy was conducted in 2022.[6] Studies that utilized genome sequencing, exome sequencing, multigene panel, and/or genome-wide comparative genomic hybridization/chromosomal microarray (CGH/CMA) in cohorts (n ≥ 10) ascertained for epilepsy were included.
  - Overall diagnostic yield across all test modalities was 17%, with the highest yield for GS (48%), followed by ES (24%), MGP (19%), and CGH/CMA (9%).
  - The number of genes included on MGP increases the diagnostic yield. Panels with 26-500 genes had a yield of 20-25% and >500 genes had a yield of about 35% (26-45%).
  - Phenotypic factors that were significantly associated with increased diagnostic yield included the presence of:
    - developmental and epileptic encephalopathy, and/or
    - neurodevelopmental comorbidities.
- Multiple peer-reviewed articles have shown that epilepsy multi-gene panels have a significant diagnostic yield when seizure onset is in infancy or early childhood.[13,21-23] The diagnostic yields in adults with epilepsy tend to be lower.[24,25]
- A 2023 peer reviewed article on the genetics of nonlesional focal epilepsy stated:[26]
  - "Genetic testing should be performed on individuals with a family history suggestive of monogenic inheritance, patients with defined syndromes (e.g., epilepsy with auditory features), and individuals with additive symptoms (intellectual impairment, autism, dysmorphic features)."
  - "Genetic testing should be considered during presurgical evaluation of patients with drug-resistant focal epilepsy."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for epilepsy genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Exome Sequencing

MOL.TS.235.C
v1.0.2026

Introduction

Exome sequencing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Exome sequencing (e.g., unexplained constitutional or heritable disorder or syndrome)	81415
Exome sequencing, comparator (e.g., parent(s), sibling(s))	81416
Exome sequencing re-evaluation (e.g., updated knowledge or unrelated condition/ syndrome)	81417
Genomic Unity Exome Plus Analysis - Comparator	0215U
Genomic Unity Exome Plus Analysis - Proband	0214U

Criteria

Introduction

Requests for exome sequencing are reviewed using the following criteria.

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Exome Sequencing

- Exome sequencing (ES) is considered medically necessary when ALL of the following criteria are met:
  - The member has not had previous exome sequencing performed, AND
  - The member has not had previous genome sequencing performed, AND
  - The member has had appropriate genetic and family history evaluation, and a clinical letter detailing the evaluation is provided which includes ALL of the following information:
    - Differential diagnoses, and
    - Testing algorithm, and
    - Previous tests performed and results, and
    - A genetic etiology is the most likely explanation, and
    - Recommendation that exome sequencing is the most appropriate test, and
    - Predicted impact on member's plan of care, AND
  - Member is <21 years of age, AND
  - A genetic etiology is considered the most likely explanation for the phenotype, based on ONE of the following:
    - Unexplained epileptic encephalopathy (onset before three years of age) and no prior epilepsy multigene panel testing performed, OR
    - Global developmental delay (significant delay in younger children, under age 5 years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living) following formal assessment by a developmental pediatrician or neurologist, OR
    - Moderate/severe/profound intellectual disability (defined by Diagnostic and Statistical Manual of Mental Disorders [DSM-5] criteria, diagnosed by 18 years of age) following formal assessment by a developmental pediatrician or neurologist, OR
    - Multiple congenital abnormalities defined by ONE of the following:
      - Two or more major anomalies affecting different organ systems*, or
      - One major and two or more minor anomalies affecting different organ systems*, OR
    - TWO of the following criteria are met:
      - major abnormality affecting at minimum a single organ system*, and/or
      - formal diagnosis of autism, and/or
      - symptoms of a complex neurodevelopmental disorder (e.g., epilepsy, self-injurious behavior, reverse sleep-wake cycles, dystonia, ataxia, alternating hemiplegia, neuromuscular disorder, cerebral palsy), and/or

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    - severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome), and/or
    - period of unexplained developmental regression, and/or
    - laboratory findings suggestive of an inherited metabolic disorder, AND
  - Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), AND
  - Clinical presentation does not fit a well-described syndrome for which more appropriate targeted testing (e.g., single gene testing, comparative genomic hybridization [CGH]/chromosomal microarray analysis [CMA]) is available, AND
  - There is a predicted impact on health outcomes including:
    - Application of specific treatments, or
    - Withholding of contraindicated treatments, or
    - Surveillance for later-onset comorbidities, or
    - Initiation of palliative care, or
    - Withdrawal of care, AND
  - A diagnosis cannot be made by standard clinical work-up, excluding invasive procedures such as muscle biopsy, AND
  - Rendering laboratory is a qualified provider of service per the Health Plan policy.

* Major structural abnormalities are generally serious enough to require medical treatment on their own (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder.

Prenatal Exome

Testing of a fetus using exome sequencing is considered medically necessary when ALL of the following criteria are met:

- Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested
- Standard diagnostic genetic testing (CMA and/or karyotype) of the fetus has been performed and is uninformative
- Testing is performed on direct amniotic fluid/chorionic villi, cultured cells from amniotic fluid/chorionic villi or DNA extracted from fetal blood or tissue
- At least one of the following is present:
  - Multiple fetal structural anomalies affecting unrelated organ systems
  - Fetal hydrops of unknown etiology
  - A fetal structural anomaly affecting a single organ system and family history strongly suggests a genetic etiology

Genomic Unity Exome Plus Analysis (CPT: 0214U and 0215U)

The member meets the above criteria for exome sequencing, AND

The member meets criteria for whole mitochondrial DNA (mtDNA) sequencing based on current EviCore guideline *Mitochondrial Disorders Genetic Testing* AND

The member has not had previous whole mtDNA sequencing analysis performed

Other considerations

- ES on tissue from a pregnancy loss is considered not medically necessary.
- Exome deletion/duplication analysis (typically billed with 81228 or 81229) is considered experimental, investigational, or unproven (E/I/U).
- ES is considered E/I/U for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- ES on tissue from a pregnancy loss is not reimbursable.
- ES is not reimbursable for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.
- Exome deletion/duplication analysis (typically billed with 81228 or 81229) is not reimbursable.
- ES will be considered for reimbursement only when billed with an appropriate CPT code:
  - 81415 should be billed for the proband. 81415 should only be billed when analyzing the entire exome sequence, rather than a targeted set of genes.
  - 81416 should be billed when a comparator exome is performed. A trio of the proband and both parents is generally preferred, although other family members may be more informative based on the clinical presentation. A maximum of two units of 81416 will be considered for reimbursement.

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  - Re-evaluation of a previously obtained exome due to updated clinical information or expanded scientific knowledge or for the purpose of evaluating an individual for an unrelated condition/syndrome on a different date of service will be considered for reimbursement only when billed using 81417. 81417 is not reimbursable for reflex from targeted to full exome.
- 81415 is not reimbursable for a targeted exome analysis (e.g. XomeDxSlice custom gene panel completed on a single exome platform). The appropriate GSP panel code, unlisted code (e.g. 81479), or Tier 1 or Tier 2 code(s) must be billed.
- 81415 will be reimbursable once per lifetime.

What is exome sequencing?

Exome sequencing (ES/WES) utilizes DNA-enrichment methods and massively parallel nucleotide sequencing to identify disease-associated variants throughout the human genome.

- ES has been proposed for diagnostic use in individuals who present with complex genetic phenotypes suspected of having a rare genetic condition, who cannot be diagnosed by standard clinical workup, or when features suggest a broad differential diagnosis that would require evaluation by multiple genetic tests.
- The standard diagnostic evaluation of an individual suspected of having a rare genetic condition may include combinations of radiographic, biochemical, electrophysiological, and genetic testing such as a chromosomal microarray, single-gene analysis, targeted gene panel, and/or broad genomic sequencing, including exome/genome sequencing.[1]
- ES may be appropriate if any prior testing is unrevealing, there is no single-gene or panel test available for the particular condition, or a rapid diagnosis for a critically ill child is indicated.[2-5]
- Identifying a molecularly confirmed diagnosis in a timely manner for an individual with a rare genetic condition can have a variety of health outcomes,[2-12] including:
  - guiding prognosis and improving clinical decision-making, which can improve clinical outcome by
    - application of specific treatments as well as withholding of contraindicated treatments for certain rare genetic conditions
    - surveillance for later-onset comorbidities
    - initiation of palliative care
    - withdrawal of care
  - reducing the financial and psychological impact of diagnostic uncertainty and the diagnostic odyssey (e.g., eliminating lower-yield testing and additional screening testing that may later be proven unnecessary once a diagnosis is achieved)

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- informing genetic counseling related to recurrence risk and prenatal or preconception (utilizing in-vitro fertilization with preimplantation genetic diagnosis) diagnosis options
- allowing for more rapid molecular diagnosis than a sequential genetic testing approach

Test information

Introduction

Exome sequencing is limited to the DNA sequence of coding regions (exons) and flanking intronic regions of the genome, which is estimated to contain 85% of heritable disease-causing variants. Results of testing with ES include known pathogenic variants definitely associated with disease or a variant of uncertain significance (VUS).[13,14]

- Pathogenic variants that can be identified by ES include missense, nonsense, splice-site, and small deletions or insertions.
- At the present time, ES can fail to detect certain classes of disease-causing variants, such as structural variants (e.g., translocations, inversions), abnormal chromosome imprinting or methylation, some mid-size insertions and deletions (ca. 10-500 bp), trinucleotide repeat expansion mutations, deeper intronic mutations, and low-level mosaicism. The current evidence base evaluating ES to specifically identify deletions/duplications is limited but suggests improved detection in recent years.[15]
- ES has the advantage of decreased turnaround time and increased efficiency relative to Sanger sequencing of multiple genes.
- ES is associated with technical and analytical variability, including uneven sequencing coverage, gaps in exon capture before sequencing, as well as variability in variant classification based on proprietary filtering algorithms and potential lack of critical clinical history or family samples.[16]

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics (ACMG, 2012) stated the following regarding the clinical application of exome and genome testing:[17]

- "WGS [whole genome sequencing]/WES should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:"
  - "The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis."

  - "A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach."
  - "A patient presents with a likely genetic disorder, but specific genetic tests available for that phenotype have failed to arrive at a diagnosis."
  - "A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis."
  - "Prenatal diagnosis by genomic (i.e., next-generation whole-exome or whole-genome) sequencing has significant limitations. The current technology does not support short turnaround times, which are often expected in the prenatal setting. There are high rates of false positives, false negatives, and variants of unknown clinical significance. These can be expected to be significantly higher than seen when array CGH is used in prenatal diagnosis."
- The following were recommended pretest considerations:
  - "Pretest counseling should be done by a medical geneticist or an affiliated genetic counselor and should include a formal consent process."
  - "Before initiating WGS/WES, participants should be counseled regarding the expected outcomes of testing, the likelihood and type of incidental results that could be generated, and what results will or will not be disclosed."
  - "As part of the pretest counseling, a clear distinction should be made between clinical and research-based testing. In many cases, findings will include variants of unknown significance that might be the subject for research; in such instances a protocol approved by an institutional review board must be in place and appropriate prior informed consent obtained from the participant."

The American College of Medical Genetics (ACMG, 2013) stated the following regarding informed consent for exome and genome testing:[18]

- "Before initiating GS/ES, counseling should be performed by a medical geneticist or an affiliated genetic counselor and should include written documentation of consent from the patient."
- "Incidental/secondary findings revealed in either children or adults may have high clinical significance for which interventions exist to prevent or ameliorate disease severity. Patients should be informed of this possibility as a part of the informed consent process."
- "Pretest counseling should include a discussion of the expected outcomes of testing, the likelihood and type of incidental results that may be generated, and the types of results that will or will not be returned. Patients should know if and what type of incidental findings may be returned to their referring physician by the laboratory performing the test."

- "Patients should be counseled regarding the potential benefits and risks of GS/ES, the limitations of such testing, potential implications for family members, and alternatives to such testing."
- "GS/ES is not recommended before the legal age of majority except for
  - Phenotype-driven clinical diagnostic uses;
  - Circumstances in which early monitoring or interventions are available and effective; or
  - Institutional review board-approved research."
- "As part of the pretest counseling, a clear distinction should be made between clinical and research-based testing."
- "Patients should be informed as to whether individually identifiable results may be provided to databases, and they should be permitted to opt out of such disclosure."
- "Patients should be informed of policies regarding re-contact of referring physicians as new knowledge is gained about the significance of particular results."

The American College of Medical Genetics (ACMG, 2021) published an updated guideline for the reporting of secondary findings (SF) in clinical exome and genome sequencing. They stated:[19]

- "The overall goal of the SFWG [Secondary Findings Working Group] is to recommend a minimum list of genes that places limited excess burden on patients and clinical laboratories while maximizing the potential to reduce morbidity and mortality when ES/GS is being performed."
- "Variants of uncertain significance should not be reported in any gene."
- “It is important to reiterate here that use of the SF results should not be a replacement for indication-based diagnostic clinical genetic testing.”
- A table of “ACMG SF v3.0 gene and associated phenotypes recommended for return as secondary findings from clinical exome and genome sequencing” was provided. ACMG has published updates to this list to expand upon the recommended genes.[20,21,22]

The American College of Medical Genetics and Genomics (ACMG, 2020) issued an educational Points to Consider Statement addressing good process, benefits, and limitations of using exome sequencing in the prenatal setting.[23]

A 2020 systematic evidence-based review by the ACMG on genome-wide sequencing for pediatric patients with congenital anomalies (CA), developmental delay (DD), or intellectual disability (ID) stated:[24]

- "There is evidence that ES/GS for patients with CA/DD/ID informs clinical and reproductive decision-making, which could lead to improved outcomes for patients and their family members. Further research is needed to generate evidence regarding health outcomes to inform robust guidelines regarding ES/GS in the care of patients with CA/DD/ID."

ACMG (2021) published a clinical guideline on the use of exome and genome sequencing in the pediatric population that stated:[25]

- "We strongly recommend ES and GS as a first-tier or second-tier test (guided by clinical judgment and often clinician–patient/family shared decision making after CMA or focused testing) for patients with one or more CAs prior to one year of age or for patients with DD/ID with onset prior to 18 years of age."
- "Consistent with existing guidelines/recommendations/position statements, patients with clinical presentations highly suggestive of a specific genetic diagnosis should undergo targeted testing first."
- "Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing."
- Diagnostic yield of genome-wide sequencing was determined to be outside the scope of the systematic evidence review.

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2018; reaffirmed 2023) stated the following in a technology assessment for modern genetics in obstetrics and gynecology:[26]

- “The American College of Medical Genetics and Genomics recommends considering whole-exome sequencing when specific genetic tests available for a phenotype, including targeted sequencing tests, have failed to arrive at a diagnosis in a fetus with multiple congenital anomalies suggestive of a genetic disorder."

The 2020 guidelines for management of stillbirth stated:[27]

- “Microarray is the preferred method of evaluation for these reasons but, due to cost and logistic concerns, karyotype may be the only method readily available for some patients. In the future, whole exome sequencing or whole genome sequencing may be part of the stillbirth workup, but it is not currently part of the standard evaluation."

American College Obstetricians and Gynecologists and Society for Maternal Fetal Medicine

In a joint statement, the American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine (ACOG/SMFM, 2016; reaffirmed 2023) stated the following regarding prenatal ES.[28]

- "The routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published."

International Society for Prenatal Diagnosis

The International Society for Prenatal Diagnosis (2022) updated position statement on the use of prenatal genome-wide sequencing stated:[29]

- "Although wider integration of genome-wide sequencing into prenatal care is now considered appropriate for specific indications, it remains a complex test, particularly when used clinically for prenatal diagnosis of fetuses with suspected genetic disorders."
- "There is currently still limited genotype-phenotype correlation for the genetic disorders identified in the fetal period since ultrasound and/or MRI imaging is frequently limited, the fetal phenotypes of many conditions have not been well described and new fetal phenotypes for conditions recognized postnatally are now being described."
- "There is no universal consensus on the management of IF [incidental findings] and SF [secondary findings] and each center should convey their policy detailing whether they are or are not reported, and if reported what is included for parents and fetus."
- Data support benefit of prenatal genomic analysis for clinical indications such as multiple congenital anomalies with a negative microarray and previous undiagnosed fetus with major or multiple anomalies. Routine prenatal genomic testing (by parental request) is not supported by the current body of evidence.

International Society for Prenatal Diagnosis, Society for Maternal Fetal Medicine, and Perinatal Quality Foundation

A joint statement from the International Society for Prenatal Diagnosis (ISPD, 2018), the Society for Maternal Fetal Medicine (SMFM, 2018), and the Perinatal Quality Foundation (PQF, 2018) on prenatal ES stated:[30]

- "The routine use of prenatal [genome wide] sequencing as a diagnostic test cannot currently be supported due to insufficient validation data and knowledge about its benefits and pitfalls. Prospective studies with adequate population numbers for validation are needed…. Currently, it is ideally done in the setting of a research protocol. Alternatively, sequencing may be performed outside a research setting on a case-by-case basis when a genetic disorder is suspected for which a confirmatory genetic diagnosis can be obtained more quickly and accurately by sequencing. Such cases should be managed after consultation with and under the expert guidance of genetic professionals working in multidisciplinary teams with expertise in the clinical diagnostic application of sequencing, including interpretation of genomic sequencing results and how they translate to the prenatal setting, as well as expertise in prenatal imaging and counseling."
- "There is currently limited genotype-phenotype correlation for the genetic disorders identified in the fetal period because ultrasound imaging is frequently limited, and the fetal phenotypes of many conditions have not been well described."

Selected Relevant Publications

Evidence for the clinical utility of ES in individuals with multiple congenital anomalies and/or a neurodevelopmental phenotype includes numerous large case series. Relevant

outcomes include improved clinical decision making (e.g., application of specific treatments, withholding of contraindicated treatments, changes to surveillance), changes in reproductive decision making, and resource utilization. ES serves as a powerful diagnostic tool for individuals with rare genetic conditions in which the specific genetic etiology is unclear or unidentified by standard clinical workup.[10,15,31-33]

- The average diagnostic yield of ES is 20-40% depending on the individual's age, phenotype, previous workup, and number of comparator samples analyzed.[8,11,31,34,35] Among individuals with a pathogenic or likely pathogenic findings by ES, 5-7% received a dual molecular diagnosis (i.e., two significant findings associated with non-overlapping clinical presentations).[31,34]
- The use of family trio ES reduces the rate of uncertain findings, adds to the clinical sensitivity with regard to the interpretation of clinically novel genes, and increases the diagnostic utility of ES. For example, in three publications the positive rate ranges from 31-37% in individuals undergoing trio analysis compared to 20-23% positive rate among proband-only ES.[5,31,36,37]
- Re-evaluation of previously obtained exome sequence has the potential for additional diagnostic yield because of constant expansions of existing variant databases, as well as periodic novel gene discovery.[38-40]

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Expanded Carrier Screening Panels

MOL.TS.428.C
v1.0.2026

Please see Cigna policy 0514: *Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis* for criteria related to the use of expanded carrier screening panels. The current Health Plan policy can be found **here**.

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Facioscapulohumeral Muscular Dystrophy Genetic Testing

MOL.TS.290.A
v1.0.2026

Facioscapulohumeral muscular dystrophy (FSHD) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
D4Z4 region (FSHMD1A) deletion analysis	81404
D4Z4 region (FSHMD1A) methylation analysis	81479
FSHMD1 characterization of 4qA/4qB haplotypes	81404
SMCHD1 sequencing	81479
SMCHD1 deletion/duplication analysis	81479

Criteria

Requests for facioscapulohumeral muscular dystrophy (FSHD) testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, AND

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- Diagnostic Testing for Symptomatic Individuals:
  - D4Z4 deletion and permissive 4A haplotype in a 1st, 2nd, or 3rd degree biologic relative with a clinical diagnosis of FSHD, or
  - Abnormal D4Z4 methylation or disease-causing SMCHD1 mutation and permissive 4A haplotype in a 1st, 2nd, or 3rd degree biologic relative with a clinical diagnosis of FSHD, OR
- Presymptomatic Testing for Asymptomatic Individuals:
  - Member is 18 years of age or older, AND
  - One of the following has been identified in a 1st, 2nd, or 3rd degree biologic relative:
    - D4Z4 deletion and permissive 4A haplotype in a 1st, 2nd, or 3rd degree biologic relative with a clinical diagnosis of FSHD, or
    - Abnormal D4Z4 methylation or disease-causing SMCHD1 mutation and permissive 4A haplotype in a 1st, 2nd, or 3rd degree biologic relative with a clinical diagnosis of FSHD, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

D4Z4 Targeted Analysis and Haplotyping

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No redundant previous FSHD related testing, AND
- Diagnostic Testing for Symptomatic Individuals:
  - The member has a probable clinical diagnosis of FSHD based on the following:
    - Weakness of facial muscles, scapular stabilizers, hamstrings, and/or foot dorsiflexors, or
    - Wasting of humeral muscles or atrophy of calves, or
    - Poly-hill or Beevor sign, and
  - An alternative diagnosis is unlikely based on the following:
    - No involvement of the extrinsic ocular muscles (responsible for eyeball movement), and
    - Muscle biopsy, if available, is not consistent with another diagnosis, and
    - EMG, if available, does not show myotonia or neurogenic changes, and
    - Creatine kinase, if performed, is less than 1500 IU/L, and
  - The member does not have a known underlying cause for their symptoms, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

D4Z4 Methylation Analysis

- Previous Genetic Testing:

    - No redundant previous FSHD related testing, AND
- Diagnostic Testing for Symptomatic Individuals:
    - The member meets the above criteria for D4Z4 targeted analysis and haplotyping, and
    - The member has previously had negative D4Z4 deletion testing, and
    - The member has a permissive 4A haplotype, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

SMCHD1 Analysis

- Previous Genetic Testing:
    - No redundant previous FSHD related testing, AND
- Diagnostic Testing for Symptomatic Individuals:
    - The member meets the above criteria for D4Z4 methylation analysis, and
    - The member has low D4Z4 methylation analysis results (less than 25%), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

What is Facioscapulohumeral Muscular Dystrophy?

Facioscapulohumeral muscular dystrophy (FSHD) is both a genetic and epigenetic condition characterized by progressive, asymmetrical muscle weakness involving facial, scapular, and humeral muscle groups early followed by distal then proximal lower extremities.[1,2] There is significant variability in phenotype even for affected individuals within the same family. There are two types of FSHD (FSHD1 and FSHD2) that are clinically identical, but distinguished by their different genetic causes.

Prevalence

Prevalence is estimated between 12 or more per 100,000.[3] Approximately 95% of FSHD cases are FSHD1; the remaining cases are FSHD2.[2]

Symptoms

Signs and symptoms can begin anytime between childhood and adulthood. More than 50% of individuals with FSHD demonstrate findings by age 20 years, but some individuals remain asymptomatic throughout their lives.[4] Around 5% of affected individuals show symptoms before age 5.[1] There is a severe infantile form of FSHD in which muscle weakness is present from birth.[4]

Symptoms of FSHD include:[1-5]

- Progressive facial muscle weakness (seen by difficulty closing the eyes, raising the eyebrows, whistling, frowning, puffing the cheeks, or showing teeth)

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- Progressive shoulder girdle muscle weakness and atrophy
- Upper arm weakness and atrophy (“Popeye arms”), often asymmetric
- Pelvic muscle weakness and atrophy develop later
- Gait weakness, foot drop, calf hypertrophy
- Scapular winging
- Exercise intolerance
- Pain
- Extra-muscular manifestations include hearing loss (common) and vision deterioration (rare)

Severity ranges from almost asymptomatic weakness to severe restrictions of activities of daily living with approximately 20% of individuals requiring a wheelchair. Initial presentation is most often with facial and shoulder weakness, but can be variable including bent spine and less specific limb girdle patterns.[2]

Cause

FSHD is caused by inappropriate expression of the DUX4 gene in muscle cells. The DUX4 gene is located within a microsatellite region called D4Z4, and relaxation of the chromatin in this region is believed to cause the aberrant expression.[4]

In FSHD1, the chromatin relaxation is caused by a deletion or contraction of a repeated stretch of DNA (called the D4Z4 repeat). Symptoms arise when this deletion occurs in the context of a permissive nearby haplotype (called 4A). Inheritance with another haplotype results in non-penetrance of the deletion, and FSHD1 is not likely.

In FSHD2, the chromatin relaxation is caused by the loss of methylation at D4Z4. This is commonly caused by a mutation in the SMCHD1 gene or, very rarely, the DNMT3B gene.[2,4]

Inheritance

The pattern of inheritance differs between FSHD1 and FSHD2.

FSHD1 is inherited in an autosomal dominant pattern, with symptoms only occurring when the D4Z4 deletion occurs in the presence of the permissive haplotype. Without the presence of a specific chromosome 4A haplotype, a D4Z4 region deletion will not lead to the FSHD1 disorder.

FSHD2 inheritance is digenic, with symptoms only occurring when a mutation in SMCHD1 or DNMT3B occurs with the permissive 4A haplotype. The inheritance is not simply autosomal dominant, as SMCHD1 and DNMT3B sort independently from the permissive 4A haplotype locus: they are not always inherited together or from the same parent, as is the case with FSHD1.

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Between 10 and 30% of individuals diagnosed with FSHD have no family history. In these putative non-familial cases the genetic change occurred either de novo or the parents may be mosaic for the causative genetic change.

Diagnosis

Diagnosis of FSHD is suggested by clinical phenotype and inheritance pattern, and confirmed by molecular testing. Because of the complex inheritance, careful correlation between clinical presentation and molecular result is essential.

- Diagnostic features should include a facial, scapular, humeral, and/or peroneal distribution of weakness and atrophy. Presence of a clinical phenotype more consistent with FSHD than other myopathies is an important diagnostic consideration. Note, myotonic dystrophy type 1 and 2 are very similar to FSHD and may only be distinguished by molecular testing.
- Biochemical abnormalities are nonspecific but point in the direction of muscle damage. Creatine kinase (CK) is normal to elevated, but it is not typically greater than 1500 IU/L.[4]
- EMG shows mild myopathic changes.
- Muscle biopsy is usually reserved for cases in which molecular testing is inconclusive. If a muscle biopsy is performed, results typically show nonspecific, chronic myopathic changes and dystrophy. Occasionally there can be inflammatory changes present significant enough to suggest an inflammatory myopathy.

The University of Rochester's National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy defines definite FSHD diagnosis as:[6]

- Weakness of facial muscles, and
- Either of the following
  - Scapular weakness, or
  - Foot dorsiflexor weakness, AND
- Absence of eye involvement (ptosis or extraocular muscle weakness), and
- Absence of an alternative diagnosis on muscle biopsy, and
- EMG results that do not demonstrate myotonia or neurogenic changes

Probable FSHD diagnosis is defined as either:[5]

- Weakness of facial muscles, or
- Either of the following
  - Scapular weakness, or
  - Foot dorsiflexor weakness, and
- Absence of eye involvement (ptosis or extraocular muscle weakness), and
- Absence of an alternative diagnosis on muscle biopsy, and
- EMG results that do not demonstrate myotonia or neurogenic change

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OR
- Weakness of facial muscles, and
- Either of the following
  - Scapular weakness, or
  - Foot dorsiflexor weakness, and muscle biopsy and/or EMG results are not available

A molecular diagnosis of FSHD1 is achieved with the detection of a heterozygous pathogenic contraction of D4Z4 on the permissive 4A haplotype. A molecular diagnosis of FSHD2 is established when hypomethylation of the D4Z4 repeat is detected on the permissive 4A haplotype.[4]

Treatment

There are no disease-modifying treatments currently available for FSHD. Management is symptom driven and primarily consists of support needed to address loss of strength. Hearing loss and rarer sequelae such as vision impairment or decreased lung function should be assessed and addressed as needed.

Standard of care and management guidelines for confirmed FSHD diagnosis include:[7]
- Evaluation by physical therapy to address functional limitations
- Help determining standard follow-up schedules to monitor for complications (such as pulmonary function testing and ophthalmologic screenings), and the need for assistive devices
- Assessments for hearing and vision loss and other orthopedic interventions
- Pain management to avoid compounding existing mechanical limitations

Survival

FSHD is not typically life shortening, but does lead to increased morbidity.

Test information

Testing for FSHD may include known familial mutation analysis, targeted analysis with haplotyping, methylation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

FSHD1 Testing: Targeted Analysis and Haplotyping

Molecular testing for FSHD starts with assessment for the more common FSHD1. This testing consists of detecting contractions of the D4Z4 locus (reported as a number of D4Z4 repeats) and determination of the associated haplotype, using Southern blot analysis and optical genome mapping or molecular combing.[3,8]

- The normal range is defined as 12-100 repeat units.
- The FSHD-associated repeat range is defined as 1-10; however, to be pathogenic, the contraction needs to occur in the context of the permissive 4A haplotype.
- Borderline repeat lengths between 8 and 11 can display reduced penetrance and may require consideration of clinical phenotype and additional molecular testing to confirm a diagnosis as they may or may not be associated with FSHD1 in a given individual, even in the presence of the 4A haplotype.[9]

This analysis will detect causative variants in 95% of clinically affected individuals.[4]

FSHD2 Testing: Methylation Analysis and SMCHD1 Sequencing

Molecular testing for FSHD2 consists of determining the methylation status of the D4Z4 region.

- D4Z4 methylation (methylation-sensitive restriction enzyme and Southern blot): methylation levels below 25% are consistent with an FSHD2 diagnosis. Again, to be pathogenic, the hypomethylation needs to occur in the context of the permissive 4A haplotype.
- If hypomethylation is identified, SMCHD1 next generation sequencing may be performed to determine the causative mutation.
- SMCHD1 deletion/duplication analysis will find gene rearrangements that are too large to be detected by sequencing. Large deletions in SMCHD1 are infrequently reported; therefore, deletion/duplication analysis is done as second tier testing in FSHD2.
- DNMT3B gene sequencing may detect rare causative mutations.

This analysis will detect causative variants in less than 5% of clinically affected individuals.[4]

Guidelines and evidence

American Academy of Neurology

The American Academy of Neurology Evidenced-based Guideline for Clinicians (AAN, 2015; reaffirmed 2021) considered the following to be Level B practice recommendations:[7]

- "Clinicians should obtain genetic confirmation of FSHD1 in patients with atypical presentations and no first-degree relatives with genetic confirmation of the disease."

- "Large D4Z4 deletion sizes (contracted D4Z4 allele of 10-20 kb) should alert the clinician that the patient is more likely to develop more significant disability and at an earlier age. Patients with large deletions are also more likely to develop symptomatic extramuscular manifestations."

European Neuromuscular Center

The 268th European Neuromuscular Center (ENMC, 2023) International Workshop: Genetic diagnosis, clinical classification, outcome measures, and biomarkers in Facioscapulohumeral Muscular Dystrophy stated the following:[9]

- "Genetic testing is the preferred tool to confirm a diagnosis of FSHD in a patient with suggestive clinical features."
- This workshop provided expert opinion on the complexities of FSHD genetic testing, including: the advantages and disadvantages of the different genetic testing modalities, the variability in penetrance and expression for repeat sizes in an intermediate range, and opportunities for biomarker use in FSHD detection and management.

The European Neuromuscular Center (ENMC, 2024) workshop participants of the FSHD European Trial Network and invited global genetic and clinical experts published an update to the 2012 guidelines which included information on the following:[10]

- The pros and cons of established and new technologies
- The possibilities and challenges of prenatal testing, including preimplantation genetic testing
- The minimal requirements and recommendations for genetic confirmation of FSHD1 and FSHD2
- The typical signs of an FSHD phenotype including weakness of facial muscles, winging and overriding scapula which can lead to scapular weakness, weakness of hamstrings, or foot dorsiflexors, wasting of humeral muscles, atrophy of calves, poly-hill sign, Beevor sign, and other signs.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for facioscapulohumeral muscular dystrophy testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Familial Adenomatous Polyposis Genetic Testing

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Introduction

Genetic testing for familial adenomatous polyposis (FAP) is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
APC deletion/duplication analysis	81203
APC known familial mutation analysis	81202
APC sequencing	81201

Criteria

Introduction

Requests for genetic testing for familial adenomatous polyposis (FAP) are reviewed using the following criteria.

APC Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic APC mutation testing that would detect the familial mutation, AND
- Diagnostic or Predisposition Testing:
  - Family History:

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        - Known family mutation in APC identified in 1st degree relative(s). (Note: 2nd or 3rd degree relatives may be considered when 1st degree relatives are unavailable or unwilling to be tested), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

APC Sequencing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous APC mutation testing, and
  - No known familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Personal history:
    - At least 10 cumulative adenomas (known or suspected diagnosis of FAP – 100 or more adenomas or attenuated FAP [AFAP] – 10 to 100 adenomas), or
    - A desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal/bilateral congenital hypertrophy of retinal epithelium (CHRPE), OR
    - At least two adenomas, AND
      - At least 5 serrated polyps proximal to the sigmoid colon (2 or more of >10mm), or
      - > 20 serrated polyps of any size, but distributed throughout the colon, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Family history:
    - First-degree relative of an individual in whom FAP has been clinically diagnosed or AFAP is considered (at least 10 but less than 100 polyps). (Note: Whenever possible, an affected family member should be tested first), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

APC Duplication/Deletion Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous large rearrangement testing, and
  - Previous APC sequencing performed and no mutations found, and
  - No known familial mutation, and
  - Meets criteria for APC full sequencing, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy

Other Considerations

Due to the risk of mosaicism, requests for testing capable of detecting low-level mosaicism (<10% VAF) after negative APC testing may be considered on a case-by-case basis when there is a high clinical suspicion for FAP/AFAP.

APC testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

What is Familial Adenomatous Polyposis?

Familial adenomatous polyposis (FAP) is an inherited colorectal cancer syndrome characterized by the development of numerous colorectal adenomatous polyps and an increased risk for colon cancer if left untreated. Affected individuals also have an increased risk for gastrointestinal polyps outside the colon, extracolonic malignancies, and non-malignant extracolonic manifestations.[1]

Prevalence

The prevalence of FAP varies and has been reported as 1/6,850 to 1/31,250.[1] Males and females are equally affected.

Symptoms

FAP is considered in an individual with 100 or more colorectal adenomatous polyps or in an individual with fewer than 100 polyps and a family member with FAP. Polyposis typically begins before age 35. Virtually all people with classic FAP will develop colorectal cancer without intervention.[1] Other clinical manifestations include:[1]

- Modestly increased risk for other malignancies including cancers of the thyroid, small bowel, stomach, liver (hepatoblastoma, typically seen in children under 5), pancreas, brain (medulloblastoma), and bile duct.
- Additional gastrointestinal manifestations including adenomatous polyps of the duodenum and stomach and gastric fundic gland polyps.
- Non-gastrointestinal manifestations including osteomas (often of the mandible or skull), dental abnormalities (supernumerary teeth, odontomas), desmoid tumors, soft tissue tumors (epidermoid cysts, fibromas), adrenal masses (adenomas), and congenital hypertrophy of retinal epithelium (CHRPE).[1] Isolated CHRPE may be found in the general population, but multiple or bilateral CHRPE in an at-risk family member may be suspicious for FAP.
- Attenuated FAP (AFAP) is a milder form of FAP characterized by a later onset of disease and fewer cumulative lifetime adenomas (ranging from 10 to <100).[2]

Phenotypic expression of classic versus attenuated FAP is often variable within families. Colorectal cancer (CRC) onset is typically delayed by 10 to 20 years compared with individuals with FAP. Currently, there is no consensus regarding precise clinical diagnostic criteria for AFAP.[1,3,4]

Cause

Almost all cases of FAP are due to mutations in the adenomatous polyposis coli (APC) gene, a tumor suppressor gene.

- Most people inherit an APC mutation from an affected parent.
- Up to 1 in 4 people with FAP have a de novo mutation with no known affected family members.
- About 20% of simplex cases of FAP are caused by somatic mosaicism for APC mutations.[1]
- The parents of someone with FAP may also be unaffected or mildly affected due to germline and/or somatic mosaicism.[1]

Some genotype-phenotype correlations have been established. Surveillance and management should be focused on an "affected individual's phenotype and not based solely on genotype."[1]

Inheritance

FAP is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

The diagnosis is established when a mutation is identified in the adenomatous polyposis coli (APC) gene in an individual with characteristic clinical findings.

- APC sequence analysis is used to identify disease-causing mutations in those clinically diagnosed with FAP/AFAP.[4-7] This testing will detect a mutation in up to 90% of individuals with clinically diagnosed FAP.[1] The mutation rate is lower for those with AFAP.[6] Testing may be considered for close relatives of someone with FAP when an affected relative is unavailable for testing. [6]
- APC deletion/duplication testing is typically performed in reflex to negative sequence analysis. Deletion/duplication testing detects an additional 8-12% of mutations in those with clinical suspicion of FAP.[1]

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Surveillance

Management and prevention strategies for those affected with or at-risk for FAP/AFAP include annual colon screening (colonoscopy is preferred over flexible sigmoidoscopy) beginning at 10-15 years for FAP and every 1-2 years beginning in the late teens for AFAP in those with a small adenoma burden (..."defined somewhat arbitrarily as fewer than 20 adenomas, all less than 1 cm and none with advanced histology...".[4] Other guidelines state to begin colonoscopy screening at 10-12 years in individuals suspected to have FAP and at 18-20 years for individuals suspected to have AFAP and repeat every 1-2 years in both cases.[8] Prophylactic colectomy is generally recommended when sufficient polyps emerge such that polyposis cannot be managed endoscopically.[4] Annual physical examinations are recommended to include thyroid palpation, neurological examination, and abdominal examination.[1] Surveillance may also include upper endoscopy screening, thyroid ultrasounds, imaging for abdominal symptoms suggestive of a desmoid tumor, and screening for hepatoblastomas in children up to five years of age.[4]

Test information

Introduction

Testing for FAP may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

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Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Special Considerations

The following special considerations apply to genetic testing for APC.

- Molecular genetic testing of MUTYH should be considered if no APC mutation is found.[1]
- Single gene testing for APC may be completed or multigene panel testing may be performed. Some multigene panels include all polyposis and colorectal cancer genes.[1,4]
- A common variant in the APC gene, called I1307K, may mildly increase the risk for colorectal cancer, but **does not cause FAP**.

Guidelines and evidence

American College of Gastroenterology

The American College of Gastroenterology (ACG, 2015) clinical guidelines stated:[7]

- "Individuals who have a personal history of >10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndrome."

American Gastroenterological Association

Consensus guidelines from the American Gastroenterological Association (AGA, 2001) recommended:[5,6]

- APC gene testing in individuals aged 10 years or older to confirm the diagnosis of FAP or AFAP, or to provide presymptomatic screening in individuals aged 10 or older with a first-degree relative with FAP or AFAP.
- First testing an affected family member to establish if a detectable causative variant is present in the family.

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American Society of Gastrointestinal Endoscopy

Consensus guidelines from the American Society of Gastrointestinal Endoscopy (ASGE, 2020) recommended:[8]

- "...genetic counseling and testing in patients with clinical polyposis defined as 10 or more adenomas found on a single endoscopy and 20 or more adenomas during their lifetime" [low quality]
- "...genetic counseling and testing in all first-degree relatives of confirmed polyposis syndrome patients. Suspected FAP individuals should be tested at ages 10 to 12 years, whereas suspected AFAP and MAP should be tested at ages 18 to 20 years" [low quality]
- "...screening sigmoidoscopy or colonoscopy in children with or suspected to have FAP starting at ages 10 to 12 years [and] follow-up colonoscopy for patients found to have rectosigmoid polyps if sigmoidoscopy was the initial screening test. In patients with negative sigmoidoscopy findings, colonoscopy screening should be offered starting in late teen years" [moderate quality]
- "...surveillance colonoscopy at 1- to 2-year intervals in FAP" [moderate quality]
- "...screening colonoscopy in patients with or suspected to have AFAP starting at ages 18 to 20 years" [low quality]
- "...surveillance colonoscopy at 1- to 2-year intervals in AFAP" [low quality]

National Comprehensive Cancer Network

Evidence- and consensus-based guidelines from the National Comprehensive Cancer Network (NCCN, 2025) stated:[4]

- "APC genetic testing is recommended in a proband to confirm a diagnosis of FAP and allow for PV [pathogenic variant]-specific testing in other family members. Additionally, knowing the location of the pathogenic variant in the APC gene can be helpful for predicting severity of polyposis, rectal involvement and desmoid tumors."
- "When a familial P/LP [pathogenic/likely pathogenic] variant is known (ie, deleterious APC pathogenic variant, monoallelic or biallelic MUTYH pathogenic variant, other known pathogenic variant in another polyposis gene), genetic testing can be considered for at-risk family members. A family member at risk can be defined as a sibling of an affected individual and/or proband."
- "If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known PV in the family."
- "FAP genetic testing in children should be done by age 10-15 y when colon screening would be initiated. If there is intent to do hepatoblastoma screening, FAP genetic testing should be considered in infancy."
- NCCN guidelines provided criteria for adenomatous polyposis testing. These include an individual with one or more of the following: known pathogenic or likely pathogenic variant in APC in the family, at least 20 adenomas (consider testing if ≥10 adenomas),

multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE), a desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or an individual meeting criteria for serrated polyposis syndrome (SPS) with at least some adenomas.
  - SPS clinical diagnostic criteria are stated as:
    - "≥5 serrated lesions/polyps proximal to the rectum, all being ≥5 mm in size, with ≥2 being ≥10mm in size."
    - ">20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum."
    - Note: "The polyp count is cumulative over multiple colonoscopies, and includes any histologic subtype of serrated lesion/polyp"
- These recommendations are Category 2A, defined as "lower-level evidence" with "uniform NCCN consensus."
- Individuals with the APC I1307K mutation should have colonoscopy screening as determined by family history. For individuals not affected by colorectal cancer, colonoscopy screening should occur every 5 years, beginning at age 40 years (or 10 years prior to the age at diagnosis for the affected first-degree relative).

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for familial adenomatous polyposis testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Familial Hypercholesterolemia Genetic Testing

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Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
APOB common variants	81401
APOB sequence analysis	81407
FH known familial mutation analysis	81403
FH multigene panel	81479
LDLR sequence analysis	81406
LDLR deletion/duplication analysis	81405
PCSK9 sequence analysis	81406

Criteria

Introduction

Requests for familial hypercholesterolemia (FH) genetic testing are reviewed using these criteria.

Known Familial Mutation Testing for Familial Hypercholesterolemia

- Clinical Consultation:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:

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  - No previous genetic testing of LDLR, APOB, or PCSK9 that would detect the familial mutation, and
  - LDLR, APOB, or PCSK9 mutation identified in 1st, 2nd or 3rd degree biological relative, AND
- Diagnostic Testing:
  - LDL cholesterol of >120 mg/dL in the absence of treatment, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

LDLR Full Sequence and Deletion/Duplication Analysis

- Clinical Consultation:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous LDLR sequencing or deletion/duplication testing, and
  - No known LDLR, APOB, or PCSK9 mutation in the family, AND
- Diagnostic Testing:
  - Member meets either the Dutch criteria or the Simon Broome criteria for possible or probable FH, and
  - Genetic testing is necessary because there is uncertainty in the clinical diagnosis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

APOB Targeted Mutation Analysis or Full Sequence Analysis

- Criteria for LDLR sequencing and deletion/duplication analysis is met, AND
- No previous full sequence analysis of APOB, AND
- No mutations detected in full sequencing or deletion/duplication testing of LDLR or PCSK9 sequencing, if previously performed, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

PCSK9 Full Sequence Analysis

- Criteria for LDLR sequencing and deletion/duplication analysis is met, AND
- No previous genetic testing for PCSK9, AND
- No mutations detected in full sequencing or deletion/duplication analysis of LDLR or APOB sequencing, if previously performed, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

LDLR, APOB, PCSK9 Multigene Panels

FH multi-gene panels, limited to testing for LDLR, APOB, and PCSK9, will be reimbursed when the following criteria are met:

- Clinical Consultation:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous LDLR, APOB, or PCSK9 sequencing or deletion/duplication testing, and
  - No known LDLR, APOB, or PCSK9 mutation in the family, AND
- Diagnostic Testing:
  - Member meets the Dutch criteria or the Simon Broome criteria for possible or probable FH, and
  - Genetic testing is necessary because there is uncertainty in the clinical diagnosis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Exclusions

Genetic testing for the sole purpose of treatment decisions (i.e. PCSK9 inhibitors) in the absence of a clinical suspicion supported by either the Dutch or Simon Broome criteria is not medically necessary.

What is familial hypercholesterolemia?

Familial hypercholesterolemia (FH) is a genetic disorder characterized by very high levels of low-density lipoprotein (LDL) cholesterol.

Prevalence

About 1 in 200-250 individuals worldwide have heterozygous FH (they have 1 FH-causing mutation), but may be higher in certain ethnicities.[1]

Approximately one in 160,000-400,000 individuals have homozygous FH (they have 2 FH-causing mutations). This is much more severe than heterozygous FH.[2] Individuals with this type of FH typically have severe coronary heart disease by their mid-20s; the rate of death or the need for surgical treatment of heart problems by the teenage years is high.[1]

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Symptoms

FH is a genetic disorder characterized by very high levels of low-density lipoprotein (LDL) cholesterol: usually >190 mg/dL in untreated adults and >130 mg/dl in untreated children/adolescents.[1] This leads to an increased risk for coronary heart disease (CHD), including heart attacks, at an early age.[1,3,4]

- Men with untreated FH have a 50% risk for a coronary event by age 50.[1,2]
- Women with untreated FH have a 30% risk for a coronary event by age 60.[1,2]

Individuals with untreated FH have about a 22 fold increased risk for coronary artery disease.[1]

Cause

Most cases of FH are caused by mutations in one of three genes: LDLR, APOB, PCSK9.[1] However, mutations in these genes only account for approximately 60%-80% of FH.[1]

There are likely other genes that are not known at the present time that make up the remaining 20%-40% of cases of FH; therefore, a negative genetic test does not rule out a diagnosis of FH.[1]

Inheritance

FH is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Although not included in this guideline, it is important to note that there is an autosomal recessive form of hypercholesterolemia which is caused by mutations in the LDLRAP1 gene.

Diagnosis

A clinical diagnosis of FH is suspected based on some combination of personal and family history of very high cholesterol, premature CHD, and cholesterol deposits, such as tendon xanthomas and corneal arcus.[4] Several organizations have attempted to define clinical diagnostic criteria for FH with the Dutch Lipid Clinic Network and Simon Broom criteria being most widely used, but all criteria have recognized limitations.[5-8]

Genetic testing for FH can confirm a diagnosis of FH, particularly in borderline clinical cases.[4,9,10]

MEDPED criteria[6]

Table gives required cholesterol levels and family history for diagnosing FH.

Total Cholesterol (LDL), mg/dL

Patient's age	Patient has 1st degree relative with FH	Patient has 2nd degree relative with FH	Patient has 3rd degree relative with FH	General population
<20	220 (155)	230 (165)	240 (170)	270 (200)
20-29	240 (170)	250 (180)	260 (185)	290 (220)
30-39	270 (190)	280 (200)	290 (210)	340 (240)
40 or older	290 (205)	300 (215)	310 (225)	360 (260)

Dutch criteria[6]

Definitive FH: Greater than 8 points; Probable FH: 6-8 points; Possible FH: 3-5 points; Unlikely FH <3 points

Points	Description
1 point	First-degree relative with premature* cardiovascular disease or LDL >95th percentile, or personal history of premature peripheral or cerebrovascular disease or LDL 155-189 mg/dL**
2 points	First-degree relative with tendinous xanthoma and/or corneal arcus, or first-degree relative age <18 with LDL >95th percentile, or personal history of coronary artery disease
3 points	LDL 190-249 mg/dL**
4 points	Corneal arcus in patient age <45 years
5 points	LDL 250-329 mg/dL**

Points	Description
6 points	Tendon xanthoma
8 points	LDL ≥330 mg/dL**

Note:

* Premature: less than 55 years in men; less than 60 years in women

** Please note that these are LDL level cut offs for untreated individuals.

Simon Broome criteria[5]

Definitive FH

- Total cholesterol (LDL cholesterol): 290 (190) mg/dL or higher in adults or 260 (155) mg/dL or higher in pediatric patients and tendon xanthoma in patient or in first-or second-degree relative, or
- DNA mutation

Probable FH

- Total cholesterol (LDL): 290 (190) mg/dL in adults or 260 (155) mg/dL in pediatric patients, and
- Family history of myocardial infarction (MI) at age <50 in second-degree relative or at age <60 in first-degree relative or family history of total cholesterol >290 mg/dL in first- or second-degree relative

Management

Early and aggressive LDL-lowering with high doses of potent statins or statin combination therapy significantly lowers CHD morbidity and mortality for individuals with FH.[11,12] Statins are contraindicated during pregnancy due to concerns for teratogenicity and should be discontinued prior to conception.[1] Due to considerable overlap between the LDL levels of those with FH and common multifactorial hypercholesterolemia, FH often goes undiagnosed until middle age, when much of the preventive value of cholesterol-lowering therapy is lost.[13]

The US Food and Drug Administration (FDA) has approved several medications for FH homozygous and heterozygous mutation carriers.[14] However, there have been no guidelines recommending that genetic testing should be performed for the sole purpose of treatment decisions in the absence of a clinical suspicion of FH.

Only 10% of individuals with FH have been identified, and more than 80% of those are not adequately treated.[4]

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Once a mutation is found in an affected person, single-site testing should be offered to at-risk family members to allow for appropriately early intervention.[4, 15-18]

Survival

Individuals with untreated FH have a much higher risk of dying from a coronary event than those in the general population.[2]

Adequate treatment with statins and other medications significantly decreases morbidity and mortality.[1] In one study, survival to age 39 in those treated since childhood was 100%, while in their affected parents, the survival rate was 93%.[19]

Test information

Introduction

Testing for FH may include known familial mutation analysis, targeted or full single gene sequence analysis, deletion/duplication analysis, and/or multigene panels.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon

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boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Over 1000 LDLR mutations have been characterized so sequence analysis is required. Major gene deletions and rearrangements account for an estimated 15% of mutations and require specialized deletion testing to detect them.[1]

APOB mutations are primarily found in a limited region of the gene, with the R3500Q mutation being most common.[1] Laboratory testing may be done by targeted mutation analysis for a limited number of APOB mutations or sequencing of the gene region where these mutations are generally found.[1] Deletions and duplications of APOB are not commonly reported in individuals with FH.[1]

Mutations in PCSK9 are the least common genetic cause of FH with less than 5% of cases being attributed.[20] Whole-gene duplications have been reported to cause FH in 2 families.[1]

The proportion of FH attributed to each gene and recommended testing differs. See the Table: Molecular Genetic Testing for FH.

Molecular Genetic Testing for FH

Gene	Proportion of FH Attributed to Mutations in Gene[1]	Test Method[1]
LDLR	>50%	Sequence Analysis Deletion/Duplication
APOB	~5-10%	Targeted Analysis Sequencing Analysis

Gene	Proportion of FH Attributed to Mutations in Gene[1]	Test Method[1]
PCSK9	<1%	Targeted Analysis Sequencing Analysis Deletion/Duplication
Unknown	20%-40%	NA

Guidelines and evidence

Canadian Cardiovascular Society

The Canadian Cardiovascular Society (CCS, 2018) published an updated position statement that stated the following:[21]

- "We recommend that genetic testing be offered, when available, to complement a diagnosis of FH and enable cascade screening (Strong Recommendation, High-Quality Evidence)."
- "The decision to request genetic screening should be made by the treating physician after discussion with the patient."
- "We suggest that if available, genetic testing should be used to stratify the ASCVD risk in patients with FH (Weak Recommendation, Moderate-Quality Evidence)."
- "We recommend that patients with HoFH be referred to a specialized lipid clinic and undergo complete evaluation for genetic analysis, presence of ASCVD, and aggressive lipid-lowering therapies, including consideration for extracorporeal LDL-C removal, lomitapide, and PCSK9 inhibitors (Strong Recommendation, Moderate-Quality Evidence)."

Cardiac Society of Australia and New Zealand

Consensus-based guidelines from The Cardiac Society of Australia and New Zealand (CSANZ, 2016) stated:[9]

- "Although the clinical picture of FH will be clear-cut in many instances, the diagnostic criteria suggest that genetic testing can provide certainty of diagnosis in some cases where confounding factors such as borderline cholesterol levels, inconclusive family histories or tendon injuries have resulted in a diagnostic dilemma."

European Atherosclerosis Society

The European Atherosclerosis Society Consensus Panel (2015) stated the following: [22]

- "Given the proven atherogenicity of LDL-C in experimental models and in humans with FH, with evidence that exposure to even moderate hypercholesterolaemia increases the long-term risk of a new CHD event, and given the lifelong benefit of genetically determined low LDL-C concentrations, there is an urgent need to identify and treat FH early to maximize therapeutic benefit…. Detection of a pathogenic mutation, usually in the LDLR gene, is the gold standard for diagnosis of FH."

International Atherosclerosis Society

The International Atherosclerosis Society (2023) evidence-based guidelines stated the following with regard to diagnosis of FH:[4]

- "A diagnosis of HeFH [heterozygous FH] or HoFH [homozygous FH] should be made, whenever possible, using genetic testing that identifies pathogenic variants (such as in LDLR, APOB, PCSK9 or LDLRAP1) that impair the LDL-receptor pathway; such testing is particularly important when phenotypic features are less obvious, such as in children, and for planning long-term care and cascade testing of family members. Conversely, if the phenotype strongly suggests FH and a pathogenic or likely pathogenic variant is not detected, FH should not be excluded."
- "The value of early detection derives from the premise that the burden of ASCVD [atherosclerotic cardiovascular disease] owing to genetically elevated plasma LDL-cholesterol concentrations in FH begins at birth and accumulates over time and that initiation of treatment in childhood can cost-effectively prevent coronary events, improve quality of life and reduce mortality."

National Institute for Health and Care Excellence

Evidence-based guidelines by the National Institute for Health and Care Excellence (NICE, 2019) supported genetic testing for FH as follows:[16]

- "Use the Simon Broome or Dutch Lipid Clinic Network (DLCL) criteria to make a clinical diagnosis of FH in primary care settings. This should be done by a healthcare professional competent in using the criteria."
- "Refer the person to an FH specialist service for DNA testing if they meet the Simon Broome criteria for possible or definite FH, or they have a DLCN score greater than 5."
- "Healthcare professionals should offer all people with FH a referral to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing."
- "Inform all people who have an identified mutation diagnostic of FH that they have an unequivocal diagnosis of FH even if their LDL-C concentration does not meet the diagnostic criteria ..."

- "In a family where a DNA mutation is identified, not all family members may have inherited the mutation. When DNA testing has excluded FH in a member of a family, healthcare professionals should manage the person's coronary heart disease risk as in the general population."
- "In children aged 0–10 years at risk of FH because of 1 affected parent, offer a DNA test at the earliest opportunity. If testing of a child at risk has not been undertaken by the age of 10 years, offer an additional opportunity for a DNA test."

National Lipid Association

The National Lipid Association expert panel on Familial Hypercholesterolemia (NLA, 2011) made the following recommendations regarding genetic testing:[20]

- "Genetic screening for FH is generally not needed for diagnosis or clinical management but may be useful when the diagnosis is uncertain."
- "Identification of a causal mutation may provide additional motivation for some patients to implement appropriate treatment."
- "Importantly, a negative genetic test does not exclude FH, since approximately 20% of clinically definite FH patients will not be found to have a mutation despite an exhaustive search using current methods."

In a statement on genetic testing in dyslipidemia (2020), the NLA stated:[10]

- "Patients with severe primary hypercholesterolemia, and suspected to have FH, are at high risk of ASCVD; the precise genotype is not predictive in an individual patient."
- "Intensity of treatment should be guided by LDL-C elevation rather than the underlying genotype."
- "Prospective studies are needed to determine whether genetic testing for FH in addition to routine lipid profile testing will alter cardiovascular outcomes by identifying the appropriate LDL-C–lowering therapy based on a patient’s gene mutations."

Selected Relevant Publication

A Journal of the American College of Cardiology Scientific Expert Panel (2018) statement on clinical genetic testing for FH stated:[17]

- "Because FH is common yet underdiagnosed, it is expected that genetic testing will facilitate the diagnosis of FH, the initiation and intensity of recommended lipid-lowering therapy (LLT), and the identification of affected relatives, thus reducing the burden of cardiovascular disease in families with FH."

A Journal of the American Heart Association expert authored review (2019) stated:[23]

- "Depending on the setting, a substantial percentage of patients with a definitive clinical diagnosis of FH may not have an identifiable mutation, even with next#generation whole#gene sequencing. In mutation#negative patients, hypercholesterolemia may be secondary to an unidentified mutation or may be

polygenic in nature. However, polygenic hypercholesterolemia would not typically be associated with the autosomal dominant pattern of inheritance seen in many families with a clinical diagnosis of FH."

- "The results of genetic testing should complement clinical and nongenetic laboratory diagnoses."
- "Diagnosing FH in a child or parent provides the opportunity for cascade screening, which involves testing all first#degree relatives for elevated LDL#C or a known genetic mutation."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for familial hypercholesterolemia testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Familial Malignant Melanoma Genetic Testing

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Introduction

Familial malignant melanoma (FMM) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
CDKN2A deletion/duplication analysis	81479
CDKN2A known familial mutation analysis	81403
CDKN2A sequencing	81404
CDK4 known familial mutation analysis	81403
CDK4 sequencing	81479

Criteria

Introduction

Requests for familial malignant melanoma (FMM) genetic testing are reviewed using the following criteria.

Single Gene Sequencing and Deletion/Duplication Analysis

Due to the low diagnostic yield of single gene sequencing and deletion/duplication analysis, testing of a single gene is not considered medically necessary.

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Other Considerations

FMM testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

What is familial malignant melanoma?

Familial malignant melanoma (FMM) is a strongly inherited form of melanoma.

Prevalence

The lifetime risk for a cutaneous melanoma for someone born in the U.S is 1 in 34 women and 1 in 53 men. [1] The incidence continues to rise dramatically.[1] Most melanoma is sporadic. It is usually the result of a combination of genetic susceptibility (probably from several relatively low risk gene variants such as those involved with pigment) and environmental risk factors such as sun exposure.[1-4]

Approximately 3-15% of people with melanoma have a family history of melanoma.[3] "The proportion of all cutaneous melanomas that is attributable to the inheritance of autosomal dominantly inherited mutations in melanoma susceptibility genes is unknown, but it is estimated by the Consortium to be less than 1% to 2%."[2]

Symptoms

People who inherit an FMM mutation do not always develop melanoma. Studies have found a 28%-76% risk for melanoma. The likelihood of developing melanoma can be influenced by other factors such as demographic location, family history, and genetic modifiers.[1,5] The risk for pancreatic cancer is 15% or higher and smoking may increase this risk.[1]

Cause

Several genes have been linked to a higher risk of melanoma in families. CDNK2A gene mutations account for most of the currently identifiable FMM mutations, followed by CDK4 mutations.[6]

Inheritance

FMM is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each

offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

FMM is most likely in a family when there are three or more close relatives diagnosed with melanoma.[2] Other factors that may also suggest FMM include:[2,4]

- Melanoma diagnosed younger than usual (average diagnosis age 30s versus 50s in people without FMM)
- More than one melanoma primary in the same individual
- Melanoma and pancreatic cancer in the same family
- Multiple, atypical moles, called dysplastic nevi that are often larger than 5mm in diameter with irregular borders. Melanoma with multiple nevi has also been called familial atypical mole-malignant melanoma syndrome. However, the presence or absence of such moles is no longer viewed as a reliable predictor of FMM in a family.

CDKN2A next generation sequencing identifies the majority of FMM-causing mutations and, in the absence of a known familial mutation, is usually the first step in testing. The likelihood that genetic testing will identify an FMM mutation varies with the personal and family history. The chance of finding a CDKN2A mutation is:

- 20-40% of people with melanoma from a family with at least 3 affected first-degree relatives.[2,6]
- Less than 5% of those with only 2 affected first-degree relatives[2]
- 15% in someone with multiple melanoma primaries and no known family history[2]
- 25-40% in people diagnosed with familial atypical mole-malignant melanoma syndrome - a subset of FMM characterized by >50 atypical nevi with characteristic microscopy features[7]
- 74% of families with FMM and pancreatic cancer[6]

CDK4 next generation sequencing, sometimes of only exon 2, is also available, but mutations are uncommon, accounting for only 2-3% of FMM cases.[6]

Management

For all individuals with a pathogenic mutation in CDKN2A, "consider pancreatic cancer screening beginning at age 40 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier)".[8] NCCN does not comment on pancreatic cancer screening for individuals with CDK4 mutations.

For individuals with a mutation in a hereditary melanoma gene such as CDKN2A or CDK4, "[t]hese individuals should be instructed on photoprotection and monthly self-skin screening examinations and should receive a regular skin screening examination by a medical professional. The frequency of examination by a health care provider should be tailored to account for the melanoma status and the difficulty of the examination, with

higher-risk individuals receiving more frequent examinations ranging from every 3 to 12 months. If the individual has a personal history of melanoma, examinations should be in accordance with NCCN guidelines."[9]

Survival

The increased risk for malignant tumors is the largest factor impacting survival.

Special Considerations

Familial melanoma is also associated with other inherited cancer syndromes such as Li Fraumeni syndrome, hereditary breast and ovarian cancer syndrome, PTEN hamartoma tumor syndrome, inherited retinoblastoma, BAP1 tumor predisposition syndrome, and xeroderma pigmentosum.[2,9,10]

Test information

Introduction

FMM testing may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

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Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and evidence

American Cancer Society

The American Cancer Society (ACS, 2023) stated the following:[11]

The likelihood an individual has a melanoma-associated gene mutation is higher when any of these characteristics are present:

- multiple family members (usually at least three) on the same side of the family with melanoma
- an individual has had three or more melanomas
- an individual is diagnosed with melanoma before 45 years of age
- an individual has a personal and/or family history of other cancers that are part of an inherited cancer syndrome

"The most common gene changes in families with high rates of melanoma are mutations in the CDKN2A gene (also known as p16). Genetic tests for changes in this gene have been available for several years, although it hasn't always been clear how useful they are. In part, this is because people with any of the factors above are already known to have a higher risk of melanoma whether they carry a mutated CDKN2A gene or not, so it's not always clear how genetic testing results would change what a person does (or what a doctor would recommend). … With advances in technology in recent years, the costs of genetic testing have come down, and testing can now be done to look for changes in several different genes at the same time. Still, most melanoma experts don't recommend genetic testing for all people with a personal or family history of melanoma. Testing is more likely to be helpful if you have any of the factors in the list above, or if your family history includes some of the cancer types listed above."

Melanoma Genetics Consortium

The Melanoma Genetics Consortium (GenoMEL), an international research collaborative group, published guidances which stated:[2,12]

- "GenoMEL, the International Genetics Consortium, supports a qualitative framework to identify candidate individuals for CDKN2A mutation testing based on population-based melanoma incidence rates, diagnosis of multiple primary melanomas, and a verified family history of melanoma and/or pancreatic cancer."[12]

- "Individuals who choose to undergo genetic testing [in a research setting] should have a second independent diagnostic (as distinct from research) DNA test performed in an accredited genetic testing laboratory."[2]
- For at-risk relatives with a known familial mutation, test sensitivity is virtually 100%. However, the likelihood of developing melanoma in mutation-positive individuals is largely unknown and there is "lack of proved efficacy of prevention and surveillance strategies based on DNA testing, even for mutation carriers."[2]
- "Rapid identification of familial melanoma patients with low probability of a germline mutation in CDKN2A could aid to direct patients toward risk counseling and away from inappropriate genetic testing."[12]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) evidence and consensus based guidelines stated:[1]

- "Consider genetic counseling referral for p16/CDKN2A mutation testing in the presence of 3 or more invasive cutaneous melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnosis in an individual or family."
- "Multigene panel testing that includes CDKN2A is recommended for patients with invasive cutaneous melanoma who have a first degree relative diagnosed with pancreatic cancer."
- "Testing for other genes that can harbor melanoma-predisposing mutations may be warranted."

Special Considerations

- FMM genetic testing outside of the research setting is not currently recommended for several reasons, including:
  - Currently available testing does not detect a mutation in a significant number of people who appear to have FMM. Therefore, a negative result cannot rule out FMM and should not change the prevention and screening plan for at-risk people.[2]
  - Individuals with FMM mutations need essentially the same prevention and screening as anyone at high risk for melanoma (family history, pigmentation, multiple moles, history of blistering sunburn).[2] Therefore, identifying an FMM-causing mutation is also not expected to change screening or treatment for melanoma.[5,13,14]
  - When a family FMM mutation has been found, other relatives who test negative for that mutation at best only return to the background risk for melanoma (which may be as high as 1 in 25) and still need regular skin screening.[2]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for familial malignant melanoma genetic testing will ensure that members will not receive testing for which there is not a body of evidence demonstrating medical necessity. Use of a test that does not have evidence to support medical necessity can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[15] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

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Genome Sequencing

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Introduction

Genome sequencing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis	81425
Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (list separately in addition to code for primary procedure)	81426
Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)	81427
Genomic Unity Whole Genome Analysis - Comparator	0213U
Genomic Unity Whole Genome Analysis - Proband	0212U
Genomic Unity 2.0	0567U
Praxis Combined Whole Genome Sequencing and Optical Genome Mapping	0267U
Praxis Whole Genome	0265U

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Procedures addressed by this guideline	Procedure codes
Rapid Genome Sequencing Test (UCSF)	0532U
Rapid Whole Genome Sequencing	0582U
Rapid Genome Sequencing Family Member Comparator	0583U
RCIGM Rapid Whole Genome Sequencing	0094U
RCIGM Rapid Whole Genome Sequencing, Comparator Genome	0425U
RCIGM Ultra-Rapid Whole Genome Sequencing	0426U

Criteria

Requests for genome sequencing (GS) are reviewed using the following criteria.

Genome Sequencing

Genome sequencing (GS) is considered medically necessary when ALL of the following criteria are met:

- The member has not had previous exome sequencing performed, AND
- The member has not had previous genome sequencing performed, AND
- The member has had appropriate genetic and family history evaluation, and a clinical letter detailing the evaluation is provided which includes ALL of the following information:
  - Differential diagnoses, and
  - Testing algorithm, and
  - Previous tests performed and results, and
  - A genetic etiology is the most likely explanation, and
  - Recommendation that genome sequencing is the most appropriate test, and
  - Predicted impact on member's plan of care, AND
- Member is <21 years of age, AND
- A genetic etiology is considered the most likely explanation for the phenotype, based on ONE of the following:
  - Unexplained epileptic encephalopathy (onset before three years of age) and no prior epilepsy multigene panel testing performed, OR

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  - Global developmental delay (significant delay in younger children, under age 5 years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living) following formal assessment by a developmental pediatrician or neurologist, OR
  - Moderate/severe/profound intellectual disability (defined by Diagnostic and Statistical Manual of Mental Disorders [DSM-5] criteria, diagnosed by 18 years of age) following formal assessment by a developmental pediatrician or neurologist, OR
  - Multiple congenital abnormalities defined by ONE of the following:
    - Two or more major anomalies affecting different organ systems*, or
    - One major and two or more minor anomalies affecting different organ systems*, OR
  - TWO of the following criteria are met:
    - major abnormality affecting at minimum a single organ system*, and/or
    - formal diagnosis of autism, and/or
    - symptoms of a complex neurodevelopmental disorder (e.g., epilepsy, self-injurious behavior, reverse sleep-wake cycles, dystonia, ataxia, alternating hemiplegia, neuromuscular disorder, cerebral palsy), and/or
    - severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome), and/or
    - period of unexplained developmental regression, and/or
    - laboratory findings suggestive of an inherited metabolic disorder, AND
- Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), AND
- Clinical presentation does not fit a well-described syndrome for which more appropriate targeted testing (e.g., single gene testing, comparative genomic hybridization [CGH]/chromosomal microarray analysis [CMA]) is available, AND
- There is a predicted impact on health outcomes including:
  - Application of specific treatments, or
  - Withholding of contraindicated treatments, or
  - Surveillance for later-onset comorbidities, or
  - Initiation of palliative care, or
  - Withdrawal of care, AND
- A diagnosis cannot be made by standard clinical work-up, excluding invasive procedures such as muscle biopsy, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

*Major structural abnormalities are generally serious enough to require medical treatment on their own (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder.

CPT: 0212U, 0213U, 0265U, 0567U

- The member meets the above criteria for genome sequencing, AND
- The member meets criteria for whole mitochondrial DNA (mtDNA) sequencing based on current EviCore guideline, *Mitochondrial Disorders Genetic Testing,* AND
- The member has not had previous whole mtDNA sequencing analysis performed, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Rapid Whole Genome Sequencing (rWGS)

The following criteria apply for individuals who are **inpatient** at the time of testing.

rWGS is considered medically necessary for the evaluation of acutely ill infants 12 months of age or younger when ALL of the following criteria are met:

- The member has not had previous exome sequencing performed, AND
- The member has not had previous genome sequencing performed, AND
- The member has had appropriate genetic and family history evaluation, AND
- The etiology of the infant's features is not known and a genetic etiology is considered a likely explanation for the phenotype, based on EITHER of the following:
  - Multiple congenital abnormalities affecting unrelated organ systems, or
  - TWO of the following criteria are met:
    - abnormality affecting at minimum a single organ system
    - encephalopathy
    - symptoms of a complex neurodevelopmental disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia)
    - family history strongly suggestive of a genetic etiology, including consanguinity
    - laboratory findings suggestive of an inborn error of metabolism
    - abnormal response to therapy, AND
- Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), AND
- Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted panel testing is available, AND
- A diagnosis cannot be made in a timely manner by standard clinical evaluation or laboratory testing, excluding invasive procedures such as muscle biopsy, AND
- Predicted impact on health outcomes, including immediate impact on medical management based on the molecular results, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Exclusions and Other Considerations:

- Trio samples are preferred.

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- rWGS is considered not medically necessary in individuals with the following diagnoses:
  - Isolated transient neonatal tachypnea
  - Isolated unconjugated hyperbilirubinemia
  - Isolated hypoxic ischemic encephalopathy with clear precipitating event
  - Isolated meconium aspiration
  - Isolated prematurity
  - Infection/sepsis with normal response to therapy
- GS or rWGS used for prenatal diagnosis is considered not medically necessary.
- GS on tissue from a pregnancy loss is considered not medically necessary.
- GS and rWGS are considered E/I/U for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.
- GS combined with Optical Genome Mapping (e.g. 0267U) is considered experimental, investigational, or unproven (E/I/U).

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Prenatal diagnosis by genome sequencing (GS) is not reimbursable.
- GS on tissue from a pregnancy loss is not reimbursable.
- GS is not reimbursable for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.
- Genome deletion/duplication analysis (typically billed with 81228 or 81229) is not separately reimbursable.
- GS will be considered for reimbursement only when billed with an appropriate CPT code:
  - 81425 should be billed for the proband. 81425 should only be billed when analyzing the entire genome sequence, rather than a targeted set of genes.
  - 81426 should be billed when a comparator genome is performed. A trio of the proband and both parents is generally preferred, although other family members may be more informative based on the clinical presentation. A maximum of two units of 81426 will be considered for reimbursement.

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  - 81427 should be billed for re-evaluation of a previously obtained genome due to updated clinical information or expanded scientific knowledge or for the purpose of evaluating a patient for an unrelated condition/syndrome on a different date of service. 81427 is not reimbursable for reflex from targeted to full genome.
- 81425 is not reimbursable for a targeted genome analysis. If targeted analysis is performed, the appropriate GSP panel code, unlisted code (e.g. 81479), or Tier 1 or Tier 2 code(s) must be billed instead.
- 81425 will be reimbursable once per lifetime.

What is genome sequencing?

Genome sequencing (WGS or GS) utilizes DNA-enrichment methods and massively parallel nucleotide sequencing to identify disease-associated variants throughout the human genome.

- GS has been proposed for diagnostic use in individuals who present with complex genetic phenotypes suspected of having a rare genetic condition, who cannot be diagnosed by standard clinical workup, or when features suggest a broad differential diagnosis that would require evaluation by multiple genetic tests.[1]
- The standard diagnostic evaluation of an individual suspected of having a rare genetic condition may include combinations of radiographic, biochemical, electrophysiologic, and targeted genetic testing such as a chromosomal microarray, single-gene analysis, a targeted gene panel, and/or broad genomic sequencing, including exome/genome sequencing.[2]
- GS may be an appropriate first- or second-tier test if initial testing is unrevealing, or if there is no single-gene or panel test available for the particular condition.[3]
- Identifying a molecularly confirmed diagnosis in a timely manner for an individual with a rare genetic condition can have a variety of health outcomes,[3-9] including:
  - guiding prognosis and improving clinical decision-making, which can improve clinical outcome by
    - application of specific treatments as well as withholding of contraindicated treatments for certain rare genetic conditions
    - surveillance for later-onset comorbidities
    - initiation of palliative care
    - withdrawal of care
  - reducing the financial and psychological impact of diagnostic uncertainty and the diagnostic odyssey (e.g., eliminating lower-yield testing and additional screening testing that may later be proven unnecessary once a diagnosis is achieved)
  - informing genetic counseling related to recurrence risk and prenatal or preconceptional (utilizing in-vitro fertilization with preimplantation genetic diagnosis) diagnosis options

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- allowing for more rapid molecular diagnosis than a sequential genetic testing approach

Test information

Introduction

Both coding (exons) and noncoding (introns) regions are analyzed by GS.[10] Often, coding regions are first analyzed by GS. If no pathogenic mutations are found, the noncoding regions are then analyzed.[10]

Pathogenic variants that can be identified by GS include missense, nonsense, splice-site, and small deletions or insertions. "Data can also be examined for copy-number variant (CNVs) or structural variants that may either be outside of the coding regions or more easily detected using GS due to increased quantitative accuracy."[10]

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2021) published a guideline on the use of exome and genome sequencing in the pediatric population that stated:[11]

- "We strongly recommend ES [exome sequencing] and GS as a first-tier or second-tier test (guided by clinical judgment and often clinician–patient/family shared decision making after CMA or focused testing) for patients with one or more CAs [congenital anomalies] prior to one year of age or for patients with DD/ID with onset prior to 18 years of age."
- "Consistent with existing guidelines/recommendations/position statements, patients with clinical presentations highly suggestive of a specific genetic diagnosis should undergo targeted testing first."
- "Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing."
- Diagnostic yield of genome-wide sequencing was determined to be outside the scope of the systematic evidence review.

ACMG (2013) stated the following regarding informed consent for exome and genome testing:[12]

- "Before initiating GS/ES, counseling should be performed by a medical geneticist or an affiliated genetic counselor and should include written documentation of consent from the patient."

- "Incidental/secondary findings revealed in either children or adults may have high clinical significance for which interventions exist to prevent or ameliorate disease severity. Patients should be informed of this possibility as a part of the informed consent process."
- "Pretest counseling should include a discussion of the expected outcomes of testing, the likelihood and type of incidental results that may be generated, and the types of results that will or will not be returned. Patients should know if and what type of incidental findings may be returned to their referring physician by the laboratory performing the test."
- "GS/ES is not recommended before the legal age of majority except for:
  - Phenotype-driven clinical diagnostic uses
  - Circumstances in which early monitoring or interventions are available and effective; or
  - Institutional review board–approved research."
- "As part of the pretest counseling, a clear distinction should be made between clinical and research-based testing."
- "Patients should be informed as to whether individually identifiable results may be provided to databases, and they should be permitted to opt out of such disclosure."
- "Patients should be informed of policies regarding re-contact of referring physicians as new knowledge is gained about the significance of particular results."

ACMG (2021) published guidelines for the reporting of secondary findings (SF) in clinical exome and genome sequencing that stated:[13,14]

- "Variants classified as likely pathogenic and pathogenic variants should be reported. Variants of uncertain significance, likely benign, and benign variants should not be reported as a secondary finding."
- This guideline includes a table of "ACMG SF v3.0 genes and associated phenotypes recommended for return from clinical exome and genome sequencing." ACMG has published updates to this list to expand upon the recommended genes.[15,16]

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2018; reaffirmed 2023) stated the following in a technology assessment for modern genetics in obstetrics and gynecology:[17]

- "The American College of Medical Genetics and Genomics recommends considering whole-exome sequencing when specific genetic tests available for a phenotype, including targeted sequencing tests, have failed to arrive at a diagnosis in a fetus with multiple congenital anomalies suggestive of a genetic disorder."

The 2020 guidelines for management of stillbirth stated:[18]

- "Microarray is the preferred method of evaluation for these reasons but, due to cost and logistic concerns, karyotype may be the only method readily available for some

patients. In the future, whole exome sequencing or whole genome sequencing may be part of the stillbirth workup, but it is not currently part of the standard evaluation."

American College Obstetricians and Gynecologists and Society for Maternal Fetal Medicine

A joint statement, the American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine (ACOG/SMFM, 2016; reaffirmed 2023) stated the following regarding prenatal GS.[19]

- "The routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published."

International Society for Prenatal Diagnosis

The International Society for Prenatal Diagnosis (2022) updated position statement on the use of prenatal genome-wide sequencing stated:[20]

- "Although wider integration of genome-wide sequencing into prenatal care is now considered appropriate for specific indications, it remains a complex test, particularly when used clinically for prenatal diagnosis of fetuses with suspected genetic disorders."
- "There is currently still limited genotype-phenotype correlation for the genetic disorders identified in the fetal period since ultrasound and/or MRI imaging is frequently limited, the fetal phenotypes of many conditions have not been well described and new fetal phenotypes for conditions recognized postnatally are now being described."
- "There is no universal consensus on the management of IF [incidental findings] and SF and each center should convey their policy detailing whether they are or are not reported, and if reported what is included for parents and fetus."
- Data support benefit of prenatal genomic analysis for clinical indications such as multiple congenital anomalies with a negative microarray and previous undiagnosed fetus with major or multiple anomalies. Routine prenatal genomic testing (by parental request) is not supported by the current body of evidence.

International Society for Prenatal Diagnosis, Society for Maternal Fetal Medicine, and Perinatal Quality Foundation

A joint statement from the International Society for Prenatal Diagnosis (ISPD, 2018), the Society for Maternal Fetal Medicine (SMFM, 2018), and the Perinatal Quality Foundation (PQF, 2018) on prenatal ES stated:[21]

- "The routine use of prenatal [genome wide] sequencing as a diagnostic test cannot currently be supported due to insufficient validation data and knowledge about its benefits and pitfalls. Prospective studies with adequate population numbers for

validation are needed…. Currently, it is ideally done in the setting of a research protocol. Alternatively, sequencing may be performed outside a research setting on a case-by-case basis when a genetic disorder is suspected for which a confirmatory genetic diagnosis can be obtained more quickly and accurately by sequencing. Such cases should be managed after consultation with and under the expert guidance of genetic professionals working in multidisciplinary teams with expertise in the clinical diagnostic application of sequencing, including interpretation of genomic sequencing results and how they translate to the prenatal setting, as well as expertise in prenatal imaging and counseling."

- "There is currently limited genotype-phenotype correlation for the genetic disorders identified in the fetal period because ultrasound imaging is frequently limited, and the fetal phenotypes of many conditions have not been well described."

Selected Relevant Publications

GS is a useful diagnostic tool for individuals with rare genetic conditions in which the specific genetic etiology is unclear or unidentified by standard clinical evaluation. While the diagnostic yield of GS varies depending upon the individual's age, phenotype, previous workup, and inclusion of comparators, the efficacy is well established. A meta-analysis including probands with diverse clinical indications showed diagnostic yield for GS of 34%.[22] The 100,000 Genomes Project demonstrated that GS had an overall diagnostic yield of 25% in 2183 probands—many of whom were heavily pre-tested.[23] Notably, diagnostic yields for intellectual disability, hearing disorders, and vision disorders ranged from 40 to 55%; diagnostic yield for individuals with dysmorphic or congenital anomalies was 21%.

The use of family trio samples in genomic sequencing analysis helps reduces the time to diagnosis, the rate of uncertain findings, and improves the clinical sensitivity and efficiency with regard to the interpretation of clinically novel genes, and increases the diagnostic yield of GS.[24,25]

Evidence for the clinical utility of GS in individuals suspected of having rare genetic disease includes numerous retrospective and prospective case series, and randomized controlled trials. Relevant outcomes include improved clinical decision-making (e.g., initiation of specific treatments, withholding of contraindicated treatments, changes to surveillance, changes in reproductive decision making, and resource utilization.[26,27,28]

The clinical utility of prenatal genomic sequencing is currently lacking. Multiple recent reviews cite a need for further research to better understand the impact of testing in the clinical setting.[29-33] Future studies are needed to "better understand which pregnancies benefit most and how to prioritise cases in a way that maximizes benefit" and to "determine the extent to which prenatal genomic sequencing results actually alter perinatal care."[32,33]

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Prenatal genomic sequencing aims to improve reproductive decision-making, allow for more informed pregnancy and perinatal management options, and reduce morbidity and mortality.[31,32] However, there is a paucity of well-designed studies examining the use of prenatal WGS, and routine usage cannot be recommended due to insufficient data and a need to address several complex clinical scenarios that may arise during clinical use.[30,32,33]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for genome sequencing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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Genomic Prostate Score

MOL.TS.295.A
v1.0.2026

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Genomic Prostate Score (formerly OncotypeDX Genomic Prostate Score)	0047U

Criteria

Introduction

Requests for Genomic Prostate Score testing are reviewed using the following criteria.

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

What are gene expression profiling tests for prostate cancer?

Prostate cancer (PC) is the most common cancer in men, and metastatic prostate cancer is a leading cause of cancer-related deaths worldwide. It is considered a heterogeneous disease with highly variable prognosis.[1]

- At the time of diagnosis of localized PC, patients typically undergo a prognostic risk assessment with routine clinical and pathological tests to assess the probability of

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subsequent progression or metastasis. These prognostic assessments help to identify lower risk patients with indolent disease who may opt for active surveillance (AS), or higher risk patients with more aggressive disease who may benefit from a treatment intervention.

- High-risk prostate cancer (PC) patients treated with radical prostatectomy (RP) also undergo risk assessment to assess future disease prognosis and determine optimal treatment strategies. Post-RP pathology findings, such as disease stage, baseline Gleason score, time of biochemical recurrence (BCR) after RP, and PSA doubling-time, are considered strong predictors of disease-associated metastasis and mortality. Following RP, up to 50% of patients have pathology or clinical features that are considered at high risk of recurrence and these patients usually undergo post-RP treatments, including adjuvant or salvage therapy or radiation therapy, which can have serious risks and complications. According to clinical practice guideline recommendations, high risk patients should undergo 6 to 8 weeks of radiation therapy (RT) following RP. However, approximately 90% of high-risk patients do not develop metastases or die of prostate cancer, and instead may be appropriate candidates for alternative treatment approaches, including AS. As such, many patients may be subjected to unnecessary follow-up procedures and their associated complications, highlighting the need for improved methods of prognostic risk assessment.[2,3]
- Several genomic biomarkers have been commercially developed to augment the prognostic ability of currently available routine clinical and pathological tests and identify those patients either at the time of diagnosis of localized PC or after radical prostatectomy (RP) most and least likely to benefit from a specific treatment strategy. Prognostic genomic tests, including gene expression profiling tests, may help to avoid overtreatment by reclassifying those men originally identified as high risk, but who are unlikely to develop metastatic disease. Genomic biomarkers may also play a role in assisting clinicians to tailor personalized and more appropriate treatments for subgroups of PC patients, and improve overall health outcomes.[2,3]

Test information

- Gene expression profiles (GEPs) evaluate the expression of several genes using one sample. Gene expression is determined through RNA analysis, using either reverse transcriptase (RT) polymerase chain reaction (PCR) or DNA microarrays.[4]
- The Genomic Prostate Score test (GPS; formerly Oncotype DX GPS) is intended for "men with low-, intermediate-, and high-risk localized prostate cancer to help guide treatment decisions at the time of diagnosis. The test analyzes prostate cancer gene activity to predict disease aggressiveness and provide clinically meaningful endpoints."[5]

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- The GPS test uses quantitative RT-PCR for 12 prostate cancer-related genes and 5 control genes (total of 17 genes). It was developed for use with formalin fixed paraffin-embedded (FFPE) diagnostic prostate needle biopsies (≥1 mm prostate tumor).[5]
- Results are expressed as a genomic prostate score, ranging from 0-100, representing tumor aggressiveness. The GPS test provides risk stratification to properly classify patients with regard to their risk of metastasis and death from prostate cancer. This test is designed to help patients with newly diagnosed, early-stage PC make informed treatment decisions, including active surveillance.[5]
- The GPS test reports the following endpoints:
  - "Risk of high-grade (>Grade Group 3) disease
  - Risk of pT3a+ disease
  - Risk of metastasis within 10 years
  - Risk of PCa-specific death within 10 years"

Guidelines and evidence

American Association of Clinical Urologists

The American Association of Clinical Urologists (AACU, 2018) has issued a position statement on genomic testing in prostate cancer that states the following:[6]

- “The AACU supports the use of tissue-based molecular testing as a component of risk stratification in prostate cancer treatment decision making.”

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO, 2020) issued a guideline in molecular biomarkers in prostate cancer. This guideline states:[7]

- "Are there molecular biomarkers to diagnose clinically significant prostate cancer?"
  - "Recommendation 2.1. Commercially available molecular biomarkers (ie, Oncotype Dx Prostate [now GPS], Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate)."
  - "Recommendation 2.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate)."
- "Are there molecular biomarkers to guide the decision of postprostatectomy adjuvant versus salvage radiation?"

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- "Recommendation 3.1. The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate)."
- "Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate)."

American Urological Association and American Society of Radiation Oncology

The American Urological Association and American Society for Radiation Oncology (AUA/ASTRO, 2022) published an evidence-based guideline on localized prostate cancer endorsed by the Society of Urologic Oncology (SGO) that stated:[8]

- "Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)"
- "Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)"
- "Regarding tissue-based genomic biomarkers, several currently available commercial tests, including Prolaris, Oncotype Dx [now Genomic Prostate Score], and Decipher, variously offer prediction of adverse pathology as well as the risks of biochemical recurrence, metastasis, and prostate cancer death. However, most of the reported studies to date that evaluated the prognostic ability of these genomic tests did not meet inclusion criteria for the systematic review as the studies used surgical (ie, prostatectomy) rather than biopsy specimens."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) Clinical Practice Guidelines on Prostate Cancer state the following regarding molecular assays:[9]

- "Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN or CAPRA risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or EBRT [external beam radiation therapy], likelihood of adverse pathologic features after radical prostatectomy, and likelihood of developing metastasis after operation, definitive EBRT, or post-recurrence EBRT."
- "These molecular biomarker tests have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous

FDA regulatory pathways for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that men with low or favorable intermediate disease and life expectancy greater than or equal to 10 years may consider the use of Decipher, Oncotype DX Prostate [now Genomic Prostate Score], or Prolaris during initial risk stratification. Patients with unfavorable intermediate- and high-risk disease and life expectancy greater than or equal to 10 years may consider the use of Decipher or Prolaris."

- NCCN does not include Genomic Prostate Score in its table of advanced molecular tools with evidence to support clinical use.

Selected Relevant Publications

Overall, the evidence base for the GPS test is large and of low quality.[10-54] Several studies reported that GPS improved prediction of adverse pathology beyond currently used clinical parameters and nomograms; however, these studies did not consistently report precision estimates, and when reported, wide confidence intervals suggested inadequate precision. Direct evidence of clinical utility for GPS is lacking. Indirect clinical utility studies suggest that GPS has an impact on physician and patient decision-making; however, there is limited evidence regarding whether these changes lead to relevant improvements in overall health. This conclusion is echoed by several systematic reviews.[55-59] Additional well-designed studies are needed that evaluate health outcomes in patients whose clinical management decisions were determined by GPS test results.

Clinical trials may be ongoing. Additional information can be found at **www.clinicaltrials.gov** .

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Genomic Prostate Score will ensure that testing will be available to those members most likely to benefit from the information provided by evidence-supported assays. For members or assays not meeting criteria for coverage, it ensures alternate management strategies are considered. However, it is possible that some members who would benefit from the testing will not receive an immediate approval or will experience a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

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Hereditary Connective Tissue and Thoracic Aortic Disease Genetic Testing

MOL.TS.427.A
v1.0.2026

Introduction

Hereditary connective tissue and thoracic aortic disease genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Aortic dysfunction or dilation duplication/ deletion analysis panel	81411
Aortic dysfunction or dilation genomic sequencing analysis panel	81410
Hereditary connective tissue and thoracic aortic disease gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479

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Procedures addressed by this guideline	Procedure codes
Hereditary connective tissue and thoracic aortic disease known familial mutation analysis	81403

Criteria

Introduction

Requests for hereditary connective tissue disorder (HCTD) genetic testing, including testing for thoracic aortic aneurysms and dissections (TAAD), are reviewed using the following criteria.

HCTD Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic or Predisposition Testing for an Autosomal Dominant HCTD:
  - Known familial mutation in a 1st or 2nd degree biological relative, OR
- Diagnostic or Predisposition Testing for an Autosomal Recessive HCTD:
  - Known familial mutation in a 1st, 2nd, or 3rd degree biological relative, OR
- Diagnostic or Predisposition Testing for an X-linked HCTD:
  - Known familial mutation in a 1st, 2nd, or 3rd degree biological relative and the individual is at risk for inheriting the familial mutation based on an X-linked inheritance pattern, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HCTD Single-Gene Testing

Sequencing and/or duplication/deletion analysis of a single gene is considered medically necessary when the following criteria are met:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous testing that would have included the requested gene, and

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    - The member does not have a family history of a known gene mutation that would explain their clinical symptoms, AND
- Diagnostic Testing in Symptomatic Individuals:
    - The member has multiple clinical features consistent with the condition for which testing is requested (see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases* for specific examples), and
    - The member does not have a known underlying cause for their symptoms (e.g. pathogenic or likely pathogenic mutation, clinical diagnosis of hypermobile Ehlers-Danlos syndrome or hypermobility spectrum disorder), and
    - A genetic diagnosis would result in changes to the member's medical management, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HCTD Multigene Sequencing Panels

Multigene sequencing panels, including syndrome-specific panels (e.g., Ehlers-Danlos syndrome panels, Stickler syndrome panels) or multi-syndrome panels (e.g., combined Marfan/Loeys-Dietz/TAAD panels, Connective Tissue Disorder panels), are considered medically necessary when the following criteria are met:

- Genetic Counseling:
    - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
    - No previous multigene sequencing for the suspected condition(s), and
    - The member does not have a family history of a known gene mutation that would explain their clinical symptoms, AND
- Diagnostic Testing in Symptomatic Individuals:
    - The member has, or is suspected of having, a condition that will benefit from information provided by the requested panel based on one of the following:
        - Documentation from the ordering provider indicating clinical suspicion for Ehlers-Danlos syndrome (EDS), and
            - The member meets 2017 International Criteria for at least one type of EDS included on the panel (excluding hypermobile type), and/or
        - Documentation from the ordering provider indicating clinical suspicion for at least one non-EDS HCTD included on the panel, and
            - The member has multiple clinical features consistent with the suspected condition(s) (see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases* for specific examples), and/or
        - Member's cardiovascular examination consistent with TAAD (e.g., aortic root or ascending aortic diameter ≥4.0 cm, Z score ≥2, or dissection), and
            - Absence of known ectopia lentis, and

    - The panel includes, at minimum, the FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK genes, and
  - The member does not have a known underlying cause for their symptoms (e.g. pathogenic/likely pathogenic mutation, clinical diagnosis of hypermobile Ehlers-Danlos syndrome or hypermobility spectrum disorder), and
  - A genetic diagnosis would result in changes to the member's medical management, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HCTD Multigene Deletion/Duplication Analysis Panels

- Member meets criteria for HCTD Multigene Sequencing Panels, AND
- Previous HCTD multigene sequencing panel performed with one of the following results:
  - No pathogenic or likely pathogenic mutation identified, or
  - One pathogenic or likely pathogenic mutation identified in a gene associated with an autosomal recessive condition, AND
- No previous multigene deletion/duplication panel for the suspected condition, AND
- Rendering laboratory is a qualified provider for service per Health Plan policy.

Exclusions and Other Considerations

- This guideline may not apply to genetic testing for indications that are specifically addressed elsewhere. HCTDs that commonly present with joint, cutaneous, cardiovascular, and/or ocular features are the focus of this guideline.
- Germline genetic testing is only medically necessary once per lifetime. Therefore, a single gene included in a panel may not be medically necessary if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest (e.g., testing a single new gene, or a panel with multiple new genes, that have a definitive association with TAAD according to the **ClinGen Gene-Disease Validity Curation**).
- Genetic testing is not medically necessary for the following indications:
  - Personal and/or family history consistent with hypermobile EDS (formerly EDS type III), hypermobility spectrum disorders (formerly "joint hypermobility syndromes"), or isolated joint hypermobility
  - Definitive clinical diagnosis of Marfan syndrome due to having both aortic root dilation and ectopia lentis, without features suggesting an alternative disorder.
    - Exceptions for single-gene (FBN1) testing may be considered on a case-by-case basis (e.g., when required for clinically appropriate treatment or surveillance of the member).

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- If genetic testing is requested for the purpose of facilitating diagnosis of at-risk family members, including at-risk pregnancies, please refer to the guideline, *Genetic Testing to Diagnose Non-Cancer Conditions*, as this indication is not addressed here.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - Both the sequencing and deletion/duplication components of genetic testing for clinically indicated gene(s) will be reimbursed.
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81410 or 81479*).
    - When deletion/duplication testing is not part of a single panel CPT code being billed, it is separately reimbursable when billed with a single CPT code specific to the performed deletion/duplication analysis panel (e.g., 81411*).
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

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What are hereditary connective tissue and thoracic aortic diseases?

Hereditary connective tissue disorders (HCTDs) are a group of disorders that affect the connective tissues that support the skin, bones, joints, heart, blood vessels, eyes, and other organs.[1] There are more than 200 connective tissue disorders.[2]

HCTDs that primarily affect bone development (e.g., skeletal dysplasia, osteogenesis imperfecta, and other rare bone disorders) are not addressed by this guideline.

Prevalence

Although connective tissue disorders as a whole are common, individual hereditary connective tissue disorders are relatively uncommon:

- Familial thoracic aortic aneurysms and dissections (TAAD) is estimated to account for approximately 20% of all cases of TAAD.[3]
- Ehlers-Danlos syndrome (EDS) is estimated to occur in approximately 1 in 5,000 individuals.[1,4] Hypermobile EDS and the related "hypermobility spectrum disorders" are by far the most common types, and their combined prevalence may be as high as 1 in 500.[5] Other EDS types are much rarer.[1,4]
- Marfan syndrome is estimated to occur in 1 to 5 per 10,000 individuals.[1,6]
- The exact prevalence is unknown for Loeys-Dietz syndrome, Stickler syndrome, and other rare HCTDs.[7-13]

Symptoms

While specific features vary by type, the following are present in many HCTDs:

• **Joint hypermobility**	Joint hypermobility is an unusually large range of joint movement, which may be asymptomatic or associated with musculoskeletal complications such as chronic pain and disturbed proprioception.[14,15]
• **Thoracic aortic aneurysms and aortic dissections (TAAD)**	TAAD typically involves aneurysms (bulges) in the aortic root and ascending aorta.[16] Most aneurysms are asymptomatic; however, if undetected and untreated, they can lead to aortic dissection (a tear within the aortic wall), which is a life-threatening condition.[16] TAAD may occur as part of a syndromic HCTD (e.g., Marfan syndrome or Loeys-Dietz syndrome) involving multiple organ systems or as an isolated finding (referred to as "nonsyndromic TAAD").[16,17]

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A detailed description of all HCTDs is beyond the scope of this guideline. Please see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases* for a summary of some of the most common types.

Cause and Inheritance

Associated genes have been identified for many HCTDs, and medical management may differ based on the underlying genetic etiology.[1] Inheritance patterns vary by type and include autosomal dominant, autosomal recessive, and X-linked inheritance.

Some of the most common types of HCTDs and associated genes are summarized below:

Table: Select Hereditary Connective Tissue and Thoracic Aortic Diseases

This table is not intended to be all-inclusive; other genes/disorders not listed here may have coverage under this guideline. Many genes in this table are also associated with other disorders that are not described here (e.g., osteogenesis imperfecta, skeletal dysplasia, etc.). Genetic testing should be reviewed for the appropriate condition/indication.

Disorder	Clinical Features	Genes & Inheritance
ACTA2-related disorders (including smooth muscle dysfunction syndrome)[16,18]	TAAD; patent ductus arteriosus; moyamoya-like cerebrovascular disease; early-onset coronary artery disease; iris flocculi; livedo reticularis; pulmonary disease; congenital mydriasis (fixed, dilated pupils); hypoperistalsis of the gut; and/or hypotonic bladder	ACTA2 (AD)
Arterial tortuosity syndrome[9]	Severe and widespread elongation and tortuosity of the aorta and mid-sized arteries along with any of the following: characteristic facial features; evidence of a generalized connective tissue disorder (e.g., joint hypermobility, skin involvement, and/or hernias); skeletal findings (e.g., pectus deformities, arachnodactyly, scoliosis, contractures, and/or camptodactyly)	SLC2A10 (AR)

Disorder	Clinical Features	Genes & Inheritance
Congenital contractural arachnodactyly (CCA or Beals syndrome)[10]	Arachnodactyly with positive wrist and thumb sign; flexion contractures of multiple joints (elbows, knees, hips, ankles, and/or fingers); kyphoscoliosis; abnormal ears ("crumpled" outer helices); and/or a marfanoid habitus. A clinical diagnostic scoring system is also available.	FBN2 (AD)
Cutis laxa[11,19]	Lax, sagging skin causing a droopy appearance to the face and other parts of the body; wrinkled skin that is particularly noticeable on the neck and in the armpits and groin; TAAD; emphysema; and/or inguinal or umbilical hernia	ELN, FBLN5, ALDH18A1 (AD) ATP6V0A2, EFEMP2, LTBP4, PYCR1 (AR) ATP7A (XL)
Ehlers-Danlos Syndrome (EDS)[4,5,20]	Generalized joint hypermobility, subluxations/ dislocations; characteristic skin findings (e.g., hyperextensibility, fragility, poor healing, atrophic scars); organ or vascular rupture; severe cardiac valvular disease; and/or marked muscular, skeletal or ocular findings seen in rare EDS types (see "Diagnosis" section for 2017 International Criteria).*	COL5A1, COL5A2, COL3A1, COL1A1 (AD) TNXB, AEBP1, ADAMTS2 (AR) COL1A2 (AD or AR)
FLNA deficiency[12]	A family history consistent with X-linked inheritance (which may include male lethality), and any combination of the following: neuroimaging features (especially periventricular nodular heterotopia [PVNH]); seizures; cardiovascular findings (e.g., TAAD, valvular heart disease, structural heart disease); pulmonary findings; gastrointestinal manifestations; and/or joint hypermobility	FLNA (XL)

Disorder	Clinical Features	Genes & Inheritance
Loeys-Dietz syndrome (LDS)[7]	Vascular findings (TAAD, other arterial aneurysms or tortuosity); skeletal findings (e.g., pectus deformities, scoliosis, joint laxity or contracture, arachnodactyly, talipes equinovarus, cervical spine malformation or instability, early-onset osteoarthritis); characteristic craniofacial features (hypertelorism, bifid uvula / cleft palate, craniosynostosis); cutaneous involvement (e.g., translucent skin with easily visible underlying veins, atrophic scarring, easy bruising); dural ectasia (stretching of the dural sac); allergic / inflammatory disease; and/or blue sclerae	TGFBR2, TGFBR1, SMAD3, TGFB2, TGFB3, SMAD2 (AD) IPO8 (AR)
Marfan syndrome (MFS)[6]	TAAD; ectopia lentis (dislocated lens of the eye); and/or a combination of features including specific skeletal, ocular, cardiovascular, cutaneous and/or craniofacial findings (see "Diagnosis" section for Ghent clinical diagnostic criteria)	FBN1 (AD)
Nonsyndromic thoracic aortic aneurysm and dissection (nsTAAD; also called familial TAAD)[3,16,17]	TAAD, with or without other cardiovascular findings (e.g., patent ductus arteriosus, bicuspid aortic valve), in the absence of systemic features. The genes to the right have been classified as having a definitive association with nsTAAD.**	ACTA2, COL3A1, FBN1, MYH11, MYLK, SMAD3, TGFB2, TGFBR1, TGFBR2 (AD)
NOTCH1-related cardiovascular disorders[16,18]	Bicuspid aortic valve with an associated risk for TAAD and/or other congenital cardiac malformations involving the left ventricular outflow tract (LVOT)	NOTCH1 (AD)
Shprintzen-Goldberg syndrome (SGS)[13]	Developmental delay or intellectual disability; characteristic craniofacial features; craniosynostosis involving the coronal, sagittal, or lambdoid sutures; and/or musculoskeletal findings (C1-C2 spine malformation, joint contractures, clubfeet)	SKI (AD)

Disorder	Clinical Features	Genes & Inheritance
Stickler syndrome[8,21]	Ocular findings (myopia, cataract, retinal detachment, and/or vitreous abnormalities); hearing loss; craniofacial findings*** (midfacial underdevelopment and/or cleft palate, which may occur as part of Pierre Robin sequence); mild spondyloepiphyseal dysplasia; and/or early-onset arthritis	COL2A1, COL11A1, COL11A2 (AD) COL9A1, COL9A2, COL9A3 (AR)

Note:

AD: autosomal dominant inheritance; **AR:** autosomal recessive inheritance; **XL:** X-linked inheritance; *Gene list for EDS is not all-inclusive. Additional genes associated with rare types are listed in the "Diagnosis" section of this guideline. The genetic etiology of hypermobile EDS is unknown.[20] **Gene list for nsTAAD is not all-inclusive. Genes with a strong or moderate association include LOX, PRKG1, EFEMP2, FOXE3, MFAP5, and SMAD2, while other, unlisted genes have a limited association.[16,17] ***Pierre Robin sequence is a group of related malformations that includes micrognathia (small mouth), glossoptosis (tongue displaced towards the back of the oral cavity), and cleft palate; cleft lip is NOT a feature of Stickler syndrome.[21]

Diagnosis

HCTDs may be diagnosed through a combination of clinical evaluation, cardiac imaging, and/or molecular testing (when the causative genes for the suspected disorder are known).[1] Clinical diagnostic criteria are available for a few HCTDs, including Marfan syndrome and Ehlers-Danlos syndrome.[6,10,19,22,23] Since it can sometimes be difficult to reliably identify a specific condition based on clinical and family history alone, many diagnostic criteria have also incorporated genetic testing.

Clinical evaluation by a specialist familiar with HCTDs may help narrow the differential to one condition or group of conditions.[1] An ophthalmology examination may be performed to identify eye findings associated with HCTDs, such as ectopia lentis characteristic of Marfan syndrome.[6] Physical examination may identify craniofacial, cutaneous, and musculoskeletal features. Joint hypermobility can be evaluated with calculation of a 9-point Beighton score, a 5-point questionnaire, and assessment for comorbidities.[14,15,20] The Beighton scoring system assesses the flexibility of multiple joints and is scored as follows:[15,20]

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- Adults ≤ 50 years of age with a Beighton score of ≥5, adults >50 years of age with a Beighton score ≥4, and pre-pubertal children and adolescents with a Beighton score ≥6, are considered to have generalized joint hypermobility.
- In individuals with a Beighton score 1 point below the age-specific cut-off, a positive 5-point questionnaire result can be taken as evidence of generalized joint hypermobility.
- Assessment for generalized joint hypermobility is considered inaccurate in children under the age of 5 years.

Cardiac imaging is important for the evaluation of HCTDs and may utilize echocardiography, CT, or MRI to detect associated cardiovascular features, including TAAD.[16] An aortic diameter ≥4.0 cm to 4.4 cm is defined as aortic dilation, while a diameter ≥4.5 cm is defined as an aortic aneurysm.[18] However, these thresholds may be less accurate in individuals whose height and/or body surface area are not within 1 to 2 standard deviations of the mean. A Z score is used to normalize aortic root and ascending aorta diameters for body size, particularly in the pediatric population.[16,18]

Clinical genetic testing is available for many HCTDs and may be used to confirm the diagnosis when clinically suspected.[1] Hypermobile EDS and the related hypermobility spectrum disorders (formerly "joint hypermobility syndrome") continue to require a clinical diagnosis, as their genetic etiologies are not yet known.[1,5,24] While the diagnostic yield of genetic testing is high in individuals with features of a syndromic TAAD, individuals with familial, nonsyndromic TAAD will only have an identifiable mutation in ~20-30% of cases.[16]

Diagnostic Criteria for Heritable Thoracic Aortic Disease

A diagnosis of heritable thoracic aortic disease (HTAD, which includes TAAD) can be established in an individual with any of the following:[16]

- Highly penetrant pathogenic mutation(s) in a known HTAD gene, and/or
- Thoracic aortic disease and one or more additional family member(s) with thoracic aortic disease, and/or
- Thoracic aortic disease with specific clinical features of a syndrome associated with thoracic aortic disease (e.g., Marfan syndrome, Loeys-Dietz syndrome)

Ghent Criteria for Marfan Syndrome

A clinical diagnosis of Marfan syndrome is made according to Ghent Criteria.[6,22,23]

With no known family history, a Marfan syndrome diagnosis is confirmed if any ONE of the following is met:[6,22,23]

- Significant aortic dilation (Z-score ≥2)/dissection + ectopia lentis**
- Significant aortic dilation (Z-score ≥2)/dissection + FBN1 mutation
- Aortic dilation/dissection + sufficient points from other system findings**
- Ectopia lentis + FBN1 mutation known to be associated with aortic disease

With a known family history, the presence of any ONE of the following is diagnostic:[6,22,23]

- Ectopia lentis
- Significant aortic root enlargement (Z-score ≥2 in those >20 years of age or ≥3 in those <20 years of age)**
- Sufficient points (≥7) from other system findings**

** Marfan syndrome can be clinically diagnosed in these cases, provided there are not other findings that more strongly suggest conditions with clinical overlap, such as Sphrintzen-Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome, or these conditions are unlikely based on genetic or collagen testing.

Systemic scoring system[6,22,23]

- Wrist and thumb sign - 3 points
- Wrist or thumb sign - 1 point
- Pectus carinatum deformity - 2 points
- Pectus excavatum or chest asymmetry -1 point
- Hindfoot deformity - 2 points
- Plan pes planus -1 point
- Pneumothorax - 2 points
- Dural ectasia - 2 points
- Protrusio acetabulae - 2 points
- Reduced upper seg/lower seg and inc. arm span/height ratios - 1 point
- Scoliosis or thoracolumbar kyphosis - 1 point
- Reduced elbow extension - 1 point
- 3 of 5 facial features: Dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia - 1 point
- Skin striae - 1 point
- Myopia - 1 point
- Mitral valve prolapse - 1 point

According to the Ghent criteria, many of the manifestations of Marfan syndrome can emerge with age. Therefore, it is not advisable to establish definitive alternative diagnosis in individuals younger than age 20 years who have some physical manifestations of Marfan syndrome but not enough for a clinical diagnosis. In this circumstance, the following is suggested:[22]

- "If the systemic score is <7 and/or borderline aortic root measurements (Z-score <3) are present (without an FBN1 pathogenic variant), use of the term "nonspecific connective tissue disorder" is suggested until follow-up echocardiographic evaluation shows aortic root dilation (Z-score ≥3)."

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- "If an FBN1 pathogenic variant is identified in simplex or familial cases but aortic root Z-score is below 3.0, the term 'potential Marfan syndrome' should be used until the aorta reaches this threshold."

2017 International Criteria for EDS

As defined in the sections below, an International Consortium developed clinical criteria for EDS.[20]

Classical EDS

Molecular basis: Heterozygous mutations in either COL5A1 or COL5A2 for >90% of cases; rarely, specific heterozygous COL1A1 mutations or biallelic COL1A2 mutations

Minimal criteria suggestive for Classical EDS (cEDS) are met when the following are present:

- Skin hyperextensibility and atrophic scarring, PLUS either of the following:
  - Generalized joint hypermobility
  - Three or more of the following features:
    - Easy bruising
    - Soft, doughy skin
    - Skin fragility (or traumatic splitting)
    - Molluscoid pseudotumors
    - Subcutaneous spheroids
    - Hernia (or history thereof)
    - Epicanthal folds
    - Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot)
    - Family history of a first-degree relative who meets clinical criteria

Classical-like EDS

Molecular basis: Biallelic TNXB mutations/deletions or AEBP1 mutations*

Minimal criteria suggestive for Classical-like EDS (clEDS) are met when ALL of the following are present:

- Skin hyperextensibility, with velvety skin texture and absence of atrophic scarring
- Generalized joint hypermobility with or without recurrent dislocations (most commonly shoulder and ankle)
- Easy bruisable skin/spontaneous ecchymoses
- A family history compatible with autosomal recessive transmission

Minor criteria for clEDS include:

- Foot deformities: broad/plump forefoot, brachydactyly with excessive skin; pes planus; hallux valgus; piezogenic papules
- Edema in the legs in absence of cardiac failure
- Mild proximal and distal muscle weakness
- Axonal polyneuropathy
- Atrophy of muscles in hands and feet
- Acrogeric hands, mallet finger(s), clinodactyly, brachydactyly
- Vaginal/uterus/rectal prolapse

Note:

*TNXB was the only gene known to be associated with clEDS when the 2017 International Criteria were published.[20] AEBP1 was later identified as an EDS gene associated with a clinical presentation resembling clEDS.[25] This gene and its associated phenotype have not yet been classified by the International Consortium.

Cardiac-Valvular EDS

Molecular basis: Specific types of biallelic COL1A2 mutations

Minimal criteria suggestive for Cardiac-Valvular EDS (cvEDS) are met when BOTH of the following are present:

- Severe progressive cardiac-valvular problems (aortic valve, mitral valve)
- A family history compatible with autosomal recessive inheritance, PLUS either of the following:
  - One or more of the following features:
    - Skin involvement: skin hyperextensibility, atrophic scars, thin skin, easy bruising
    - Joint hypermobility (generalized or restricted to small joints)
  - Two or more of the following features:
    - Inguinal hernia
    - Pectus deformity (especially pectus excavatum)
    - Joint dislocations
    - Foot deformities: pes planus, pes planovalgus, hallux valgus

Vascular EDS

Molecular basis: Heterozygous mutations in COL3A1 or (rarely) specific heterozygous mutations in COL1A1

Minimal criteria suggestive for Vascular EDS (vEDS) are met when AT LEAST ONE of the following is present:

- A family history of the disorder

- Arterial rupture or dissection in individuals less than 40 years of age
- Unexplained sigmoid colon rupture (i.e. in the absence of known diverticular disease or other bowel pathology)
- Spontaneous pneumothorax in the presence of other features consistent with vEDS
- Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears
- Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma
- A combination of the following features:
  - Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back
  - Thin, translucent skin with increased venous visibility
  - Characteristic facial appearance
  - Spontaneous pneumothorax
  - Acrogeria
  - Talipes equinovarus
  - Congenital hip dislocation
  - Hypermobility of small joints
  - Tendon and muscle rupture
  - Keratoconus
  - Gingival recession and gingival fragility
  - Early onset varicose veins (under 30 and nulliparous if female)

Hypermobile EDS

Molecular basis: Unknown; clinical diagnosis required

Diagnosis of Hypermobile EDS (hEDS) requires all of the following criteria (1 AND 2 AND 3) to be met:

- Criteria 1: Generalized joint hypermobility
- Criterion 2: Two or more among the features (A-C) listed in the table below must be present (for example: A and B; A and C; B and C; A and B and C)
- Criterion 3: All of the following prerequisites are met:
  - Absence of unusual skin fragility
  - Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions
  - Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity.

Feature A (a total of 5 must be present):

- Unusually soft or velvety skin
- Mild skin hyperextensibility

- Unexplained striae
- Bilateral piezogenic papules of the heel
- Recurrent or multiple abdominal hernia(s)
- Atrophic scarring involving at least two sites
- Pelvic floor, rectal, and/or uterine prolapes in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
- Dental crowding and high or narrow palate
- Arachnodactyly
- Arm span-to-height ≥ 1.05
- Mitral valve prolapse (MVP)
- Aortic root dilatation with Z-score > +2

Feature B: Positive family history, with one or more first degree relatives independently meeting the current diagnostic criteria for hEDS

Feature C (must have at least one):
- Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months.
- Chronic, widespread pain for ≥ 3 months
- Recurrent joint dislocations or frank joint instability, in the absence of trauma, based on at least one of the following:
  - Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times
  - Medical confirmation of joint instability at two or more sites not related to trauma

Arthrochalasia EDS

Molecular basis: Specific types of heterozygous mutations in either COL1A1 or COL1A2

Minimal criteria suggestive for Arthrochalasia EDS (aEDS) are met when the following are present:
- Congenital bilateral hip dislocation, PLUS either of the following:
  - Skin hyperextensibility
  - Severe generalized joint hypermobility, with multiple dislocations/ subluxations, and two or more of the following features:
    - Muscle hypotonia
    - Kyphoscoliosis
    - Radiologically mild osteopenia
    - Tissue fragility, including atrophic scars
    - Easy bruisable skin

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Dermatosparaxis EDS

Molecular basis: Biallelic mutations in ADAMTS2

Minimal criteria suggestive for Dermatosparaxis EDS (dEDS) are met when BOTH of the following are present:

- Extreme skin fragility with congenital or postnatal skin tears
- Characteristic craniofacial features, which are evident at birth or early infancy, or evolve later in childhood, PLUS either of the following:
  - One or more of the following features:
    - Redundant, almost lax skin, with excessive skin folds at the wrist and ankles
    - Increased palmar wrinkling
    - Severe bruisability with a risk of subcutaneous hematomas and hemorrhage
    - Umbilical hernia
    - Postnatal growth retardation
    - Short limbs, hands and feet
    - Perinatal complications due to connective tissue fragility
  - Three or more of the following features:
    - Soft and doughy skin texture
    - Skin hyperextensibility
    - Atrophic scars
    - Generalized joint hypermobility
    - Complications of visceral fragility (e.g., bladder rupture, diaphragmatic rupture, rectal prolapse)
    - Delayed motor development
    - Osteopenia
    - Hirsutism
    - Tooth abnormalities
    - Refractive errors (myopia, astigmatism)
    - Strabismus

Kyphoscoliotic EDS

Molecular basis: Biallelic mutations in either PLOD1 or FKBP14

Minimal criteria suggestive for Kyphoscoliotic EDS (kEDS) are met when BOTH of the following are present:

- Congenital muscle hypotonia
- Congenital or early onset kyphoscoliosis (progressive or non-progressive), PLUS either of the following:

- Generalized joint hypermobility with dislocations/subluxations (shoulders, hips, and knees in particular)
- Three or more of the following features (either general or gene-specific):
  - General:
    - Skin hyperextensibility
    - Easy bruisable skin
    - Rupture/aneurysm of a medium-sized artery
    - Osteopenia/osteoporosis
    - Blue sclerae
    - Hernia (umbilical or inguinal)
    - Pectus deformity
    - Marfanoid habitus
    - Talipes equinovarus
    - Refractive errors (myopia, hypermetropia)
  - PLOD1-specific:
    - Skin fragility (easy bruising, friable skin, poor wound healing), widened atrophic scarring
    - Scleral and ocular fragility/rupture
    - Microcornea
    - Facial dysmorphology
  - FKBP14-specific:
    - Congenital hearing impairment (any type)
    - Follicular hyperkeratosis
    - Muscle atrophy
    - Bladder diverticula

Brittle Cornea Syndrome (BCS)

Molecular basis: Biallelic mutations in either ZNF469 or PRDM5

Minimal criteria suggestive for Brittle Cornea Syndrome (BCS) are met when the following are present:

- Thin cornea, with or without rupture (central corneal thickness often <400 µm), PLUS either of the following:
  - One or more of the following features:
    - Early onset progressive keratoconus
    - Early onset progressive keratoglobus
    - Blue sclerae
  - Three or more of the following features:
    - Enucleation or corneal scarring as a result of previous rupture
    - Progressive loss of corneal stromal depth, especially in central cornea

        - High myopia, with normal or moderately increased axial length
        - Retinal detachment
        - Deafness (often mixed, progressive, higher frequencies often more severely affected)
        - Hypercompliant tympanic membranes
        - Developmental dysplasia of the hip
        - Hypotonia in infancy, usually mild if present
        - Scoliosis
        - Arachnodactyly
        - Hypermobility of distal joints
        - Pes planus, hallux valgus
        - Mild contractures of fingers (especially fifth)
        - Soft, velvety skin, translucent skin

Spondylodysplastic EDS

Molecular basis: Biallelic mutations in B4GALT7, SLC39A13, or B3GALT6

Minimal criteria suggestive for Spondylodysplastic EDS (spEDS) are met when ALL of the following are present:

- Short stature (progressive in childhood)
- Muscle hypotonia (ranging from severe congenital, to mild later-onset)
- Characteristic radiographic findings (e.g. bowing of limbs)
- Three or more of the following features (general or gene-specific):
    - General:
        - Skin hyperextensibility, soft, doughy skin, thin translucent skin
        - Pes planus
        - Delayed motor development
        - Osteopenia
        - Delayed cognitive development
    - B4GALT7-specific:
        - Radioulnar synostosis
        - Bilateral elbow contractures or limited elbow movement
        - Generalized joint hypermobility
        - Single transverse palmar curve
        - Characteristic craniofacial features
        - Characteristic radiographic findings
        - Severe hypermetropia
        - Clouded cornea
    - SLC39A13-specific:

        - Protuberant eyes with bluish sclerae
        - Hands with finely wrinkled palms
        - Atrophy of the thenar muscles, tapering fingers
        - Hypermobility of distal joints
        - Characteristic radiologic findings
    - B3GALT6-specific:
        - Kyphoscoliosis (congenital or early onset, progressive)
        - Joint hypermobility, generalized or restricted to distal joints, with joint dislocations
        - Joint contractures (congenital or progressive) (especially hands)
        - Peculiar fingers (slender, tapered, arachnodactyly, spatulate, with broad distal phalanges)
        - Talipes equinovarus
        - Characteristic craniofacial features
        - Tooth discoloration, dysplastic teeth
        - Characteristic radiographic findings
        - Osteoporosis with multiple spontaneous fractures Ascending aortic aneurysm
        - Lung hypoplasia, restrictive lung disease

Musculocontractural EDS

Molecular basis: Biallelic mutations in CHST14 or (rarely) DSE

Minimal criteria suggestive for Musculocontractural EDS (mcEDS) are met with EITHER of the following:

- At birth or in early childhood when both of the following are present:
    - Congenital multiple contractures, characteristically adduction-flexion contractures, and/or talipes equinovarus (clubfoot)
    - Characteristic craniofacial features, which are evident at birth or in early infancy
- In adolescence and in adulthood when both of the following are present:
    - Congenital multiple contractures, characteristically adduction-flexion contractures, and/or talipes equinovarus (clubfoot)
    - Characteristic cutaneous features including skin hyperextensibility, easy bruisability, skin fragility with atrophic scars, increased palmar wrinkling

Minor criteria for mcEDS include:

- Recurrent/chronic dislocations
- Pectus deformities (flat, excavated)
- Spinal deformities (scoliosis, kyphoscoliosis)
- Peculiar fingers (tapering, slender, cylindrical)

- Progressive talipes deformities (valgus, planus, cavum)
- Large subcutaneous hematomas
- Chronic constipation
- Colonic diverticula
- Pneumothorax/pneumohemothorax
- Nephrolithiasis/cystolithiasis
- Hydronephrosis
- Cryptorchidism in males
- Strabismus
- Refractive errors (myopia, astigmatism)
- Glaucoma/elevated intraocular pressure

Myopathic EDS

Molecular basis: Heterozygous or biallelic mutations in COL12A1

Minimal criteria suggestive for Myopathic EDS (mEDS) are met when the following are present:

- Congenital muscle hypotonia, and/or muscle atrophy, that improves with age, PLUS either of the following:
  - One or more of the following features:
    - Proximal joint contractures (knee, hip, and elbow)
    - Hypermobility of distal joints
  - Three or more of the following features:
    - Soft, doughy skin
    - Atrophic scarring
    - Motor developmental delay
    - Myopathy on muscle biopsy

Periodontal EDS

Molecular basis: Heterozygous gain-of-function mutations in either C1R or C1S

Minimal criteria suggestive for Periodontal EDS (pEDS) are met when BOTH of the following are present:

- Either of the following combinations of features:
  - Severe and intractable periodontitis of early onset (childhood or adolescence), and two or more of the following features:
    - Lack of attached gingiva
    - Pretibial plaques
    - Family history of a first-degree relative who meets clinical criteria
  - Lack of attached gingiva, and both of the following features:
    - Pretibial plaques

        - Family history of a first-degree relative who meets clinical criteria
    - One or more of the following features:
        - Easy bruising
        - Joint hypermobility, mostly distal joints
        - Skin hyperextensibility and fragility, abnormal scarring (wide or atrophic)
        - Increased rate of infections
        - Hernias
        - Marfanoid facial features
        - Acrogeria
        - Prominent vasculature

Joint Hypermobility and Hypermobility Spectrum Disorders

In a 2017 diagnostic framework proposed by Castori and colleagues, the authors noted that while most cases of joint hypermobility are asymptomatic, some are associated with musculoskeletal symptoms/complications including dislocations, subluxations, chronic pain, and disturbed proprioception. For individuals with symptomatic joint hypermobility not having a well-defined syndrome such as hEDS, they proposed that the term "hypermobility spectrum disorder(s) (HSDs)" be used.[14]

In 2023, the International Consortium on EDS and HSD proposed that the 2017 International Criteria for hEDS not be used to establish the diagnosis in children. Instead, they recommended that children over the age of 5 be classified as having joint hypermobility when musculoskeletal complications are absent, or HSD when musculoskeletal complications are present. They developed a pediatric diagnostic framework that further categorizes hypermobile children based on their phenotypic and symptomatic presentation. This framework includes four components:[15]

- Generalized joint hypermobility (GJH)
- Skin and tissue abnormalities
- Musculoskeletal complications
- Core comorbidities (other features causing disability or distress, including chronic primary pain, chronic fatigue, functional gastrointestinal/bladder disorders, primary dysautonomia, and anxiety)

The above pediatric diagnostic framework was intended to be used after exclusion of other EDS types, HCTDs, genetic syndromes or neuromuscular disorders, until adulthood or biological maturity, at which point the 2017 International Criteria for hEDS should be used. Genetic testing was not recommended for all children with GJH, HSD, or hEDS.[15]

Test information

Clinical genetic testing is available for many HCTDs. Testing may include known familial mutation testing, next-generation sequencing, deletion/duplication analysis, or multigene panels.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

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Guidelines and evidence

Marfan Syndrome, Loeys-Dietz Syndrome, and TAAD

American College of Medical Genetics and Genomics

According to the American College of Medical Genetics and Genomics (ACMG, 2012) practice guidelines for the evaluation of Marfan syndrome (MFS):[26]

- "There is no case of classic, bona fide MFS due to mutations in a gene other than FBN1. However, current clinical molecular testing of FBN1 successfully detects mutations in such unequivocal patients in only about 90-95% of cases. For all of these reasons, searching for mutations in FBN1 continues to have a circumscribed role in the diagnosis of equivocal cases. Said differently, MFS remains, by and large, a clinical diagnosis."

American Heart Association

The American Heart Association (AHA, 2024) published a scientific statement on management of aortopathy in children and stated the following: [27]

- "The role of genetic testing for aortopathy has expanded with greater recognition of the importance of a specific genetic diagnosis in risk assessment as well as medical and surgical management. Genetic testing should be targeted to those with the highest likelihood of confirming a diagnosis and those for whom a genetic diagnosis would affect clinical management."
- "Multigene panels that include genes associated with HTAD [heritable thoracic aortic disease] are most commonly used; however, the genes included vary widely by laboratory. When there is a known familial pathogenic variant or when the clinical presentation strongly suggests a specific diagnosis, single gene testing can be used; for example, in the presence of ectopia lentis (lens dislocation), MFS [Marfan syndrome] associated with a variant in FBN1 is most likely. An HTAD panel may be considered for nonsyndromic presentations or in those with predominant systemic connective tissue findings. Broader testing (eg, whole exome sequencing) may be considered for early-onset and severe clinical presentations with features that are atypical for defined HTADs. Genetic testing should be initiated in the family member with the most severe and typical presentation."
- "Clinical diagnostic criteria for classic MFS have limitations in children. The MFS systemic score is a useful screening tool for historical and physical findings suggestive of MFS, but should not be relied upon in isolation."
- "Genetic testing should be performed in children suspected to have MFS; variants in FBN1 are found in >95% of children with MFS."

- "Absence of a positive genetic test result should not be assumed to rule out HTAD if clinical suspicion is otherwise high. Reclassification of uncertain variants, discovery of new genes, and addition of these genes to aortopathy panels occur on an ongoing basis. Thus, continued follow-up with genetics should be considered."

Indications for genetic testing in children with suspected HTAD included the following in the absence of bicuspid aortic valve (BAV):[27]

- "Personal history of aortic or arterial dissection/rupture, spontaneous bowel perforation
- Aortic root or ascending aortic Z score ≥2 and <3 and 1 or more features seen in syndrome HTAD without another non HTAD explanation
- Aortic root or ascending aortic Z score ≥3 OR dimension ≥4 cm without another non HTAD explanation
- Aortic root or ascending aorta ≥5 cm
- Multiple clinical features of syndromic HTAD (does not have to meet full clinical criteria)
- First degree family member with a (likely) pathogenic variant in HTAD gene
- First degree family member with history of aortic or arterial dissection/rupture, aortic aneurysm, bowel perforation"

Indications for genetic testing in children with BAV included:[27]

- "Personal history of aortic or arterial dissection/rupture, spontaneous bowel perforation
- Features seen in syndromic HTAD
- First degree family member with a (likely) pathogenic variant in HTAD gene
- First degree family member with history of aortic or arterial dissection/rupture, aortic aneurysm, bowel perforation

Consider when patient has BAV without the above but one of the following:

- Ascending aortic Z score ≥5.0
- Aortic root Z score ≥3.5
- Aortic root or ascending aorta ≥4 cm
- Aortic root phenotype (aortic root Z score > ascending aortic Z score)
- Family history of BAV, coarctation, HLHS (hypoplastic left heart syndrome)"

"Common non-HTAD associations with aortic root or ascending aortic Zscore ≥2 include congenital heart block; chronic renal disease and hypertension; certain congenital heart defects (ie, truncus arteriosus, dextro-transposition of the great arteries, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, single

ventricle status post Fontan); very low weight for height or age; or single or erroneous measurement."[27]

American Heart Association and American College of Cardiology

The American Heart Association (AHA, 2022) and American College of Cardiology (ACC, 2022) published clinical practice guidelines for the diagnosis and management of aortic disease. They stated the following regarding genetic evaluation and family screening:[18]

- Risk factors for familial thoracic aortic disease (TAD), also known as heritable thoracic aortic disease (HTAD), were outlined as:
  - "TAD and syndromic features of Marfan syndrome, Loeys-Dietz syndrome, or vascular EDS syndrome
  - TAD presenting at <60 years
  - A family history of either TAD or peripheral/intracranial aneurysms in a first- or second-degree relative
  - A history of unexplained sudden death at a relatively young age in a first- or second-degree relative"
- "In patients with aortic root/ascending aortic aneurysms or aortic dissection, obtaining a multigenerational family history of TAD, unexplained sudden deaths, and peripheral and intracranial aneurysms is recommended."
- "In patients with aortic root/ascending aortic aneurysms or aortic dissection and risk factors for HTAD, genetic testing to identify pathogenic/likely pathogenic variants (ie, mutations) is recommended."
- "In patients with an established pathogenic or likely pathogenic variant in a gene predisposing to HTAD, it is recommended that genetic counseling be provided and the patient's clinical management be informed by the specific gene and variant in the gene."
- "In patients with TAD who have a pathogenic/likely pathogenic variant, genetic testing of at-risk biological relatives (ie, cascade testing) is recommended. In family members who are found by genetic screening to have inherited the pathogenic/likely pathogenic variant, aortic imaging with TTE [transthoracic echocardiography] (if aortic root and ascending aorta are adequately visualized, otherwise with CT or MRI) is recommended."
- "In a family with aortic root/ascending aortic aneurysms or aortic dissection, if the disease-causing variant is not identified with genetic testing, screening aortic imaging of at-risk biological relatives (ie, cascade testing) is recommended."
- "In patients with aortic root/ascending aortic aneurysms or aortic dissection, in the absence of either a known family history of TAD or pathogenic/likely pathogenic variant, screening aortic imaging of first-degree relatives is recommended."

- "In patients with acute type A aortic dissection, the diameter of the aortic root and ascending aorta should be recorded in the operative note and medical record to inform the management of affected relatives."
- "The HTAD genetic testing panels include (at the time of this writing) 11 genes that are confirmed to confer a highly penetrant risk for TAD: FBN1, LOX, COL3A1, TGFBR1, TGFBR2, SMAD3, TGFB2, ACTA2, MYH11, MYLK, and PRKG1. These panels also include genes that increase the risk for TAD and/or lead to systemic features that overlap with Marfan syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome. Clinical genetic testing is integral to the diagnostic evaluation of patients with TAD who have clinical indicators suggestive of an underlying single gene disorder. In patients who meet the clinical diagnostic criteria for Marfan syndrome but do not have ectopia lentis (ie, dislocated lens), genetic testing is reasonable to exclude an alternative diagnosis of Loeys-Dietz syndrome."

Canadian Cardiovascular Society

The Canadian Cardiovascular Society (2014) stated the following:[28]

- "We recommend that surgical intervention be considered for thoracic aortic aneurysms according to the disease etiology and anatomic region affected… (Strong Recommendation, Moderate-Quality Evidence)."
- "We recommend clinical and genetic screening for suspected Marfan syndrome to clarify the nature of the disease and provide a basis for individual counseling (Strong recommendation, High quality evidence)"

"For non-Marfan, genetic forms of aortic disease:

- We recommend aortic imaging for first-degree relatives of patients with genetic forms of TAD to identify asymptomatic carriers (Strong Recommendation, Moderate-Quality Evidence).
- We recommend cardiac imaging in adult first-degree relatives of patients with BAV to identify asymptomatic carriers (Strong Recommendation, Moderate-Quality Evidence).
- We recommend screening for TAD-associated genes in non-BAV [bicuspid aortic valve] aortopathy index cases to clarify the origin of disease and improve clinical and genetic counseling (Strong Recommendation, Moderate Quality Evidence).
- We recommend that genetic counselling and testing be offered to first-degree relatives of patients in whom a causal mutation of a TAD-associated gene is identified. We recommend that aortic imaging be offered only to mutation carriers (Strong Recommendation, Low-Quality Evidence).
- We recommend complete aortic imaging at initial diagnosis and at 6 months for patients with LDS or a confirmed genetic aortopathy (e.g., TGFBR1/2, TGFB,

SMAD3, ACTA2, or MYH11) to establish if enlargement is occurring (Strong Recommendation, Moderate-Quality Evidence)."[28]

Cardiac Society of Australia and New Zealand

The Cardiac Society of Australia and New Zealand Cardiovascular Genetic Disease Council (CSANZ, 2017) stated:[29]

- "Molecular confirmation of a suspected clinical diagnosis is increasingly important for guiding patient management. As an example, an individual who looks marfanoid will have more extensive arterial imaging screening if identified to have a SMAD3 mutation as opposed to an FBN1 mutation."
- "A definitive molecular genetic diagnosis can clarify an equivocal clinical picture or result in a diagnosis in an apparently phenotypically normal individual. It is unknown at this stage what proportion of patients with these different genetic mutations will develop aortic dilatation or dissection. Identification of a causal mutation allows for the provision of accurate genetic counseling, the screening of at-risk family members and offers the possibility of accurate prenatal or preimplantation genetic diagnosis."
- "Sanger sequencing may be considered when there is no doubt about the clinical diagnosis. Despite clinical certainty however, a pathogenic mutation may not be found. Typically, exonic or whole-gene deletions and/or duplications are not detected by this method and require alternative technology e.g. quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes the relevant gene/chromosome segment."
- "Many clinical laboratories offer a multi-gene MFS/LDS/ familial TAAD panel that includes FBN1 and numerous other genes associated with aortic aneurysm and dissection disorders. This approach may be advantageous, given the known clinical and genetic heterogeneity of these disorders."
- "The clinical picture of non-syndromic aortopathies remains to be fully elucidated, and therefore the optimal extent and frequency of vascular imaging is unclear. We would err on the side of caution and suggest imaging the entire vasculature, at least at baseline, in non-syndromic individuals with a genetic mutation."
- "If there is a clear genetic diagnosis, then first-degree relatives should be offered predictive testing. If the screened relative does not have the familial mutation they can be released from screening. We advocate erring on the side of caution with respect to screening echocardiography of at-risk relatives." Screening was advised in the following relatives:
  1. "All family members who share the familial mutation and who therefore should be under clinical care, not screening"
  2. "At-risk family members where a clinical genetic diagnosis exists"

3. "At-risk family members where no clinical genetic diagnosis is made but the dissection occurred in a young individual without an apparent risk factor e.g. long standing hypertension"

European Reference Network on Rare Multisystemic Cardiovascular Diseases

The HTAD [heritable thoracic aortic disease] Rare Disease Working Group of the European Reference Network on Rare Multisystemic Cardiovascular Diseases (VASCERN, 2023) stated the following regarding genetic testing:[30]

"Genetic testing should be proposed when there is a high suspicion of an underlying genetic aortopathy and includes:

- patients with a familial form with or without hypertension (2 first or second-degree affected relatives) of thoracic aortic dissection or aneurysm (TAA/TAD),
- sporadic [defined as only one family member affected], TAA/TAD at
  - any age, in the absence of arterial hypertension, or
  - <70 years of age in presence of hypertension
- patients with non-traumatic ectopia lentis compatible with MFS
- patients with a combination of TAAD and syndromic features of Marfan or LDS."

"Nowadays, multiple genes are tested within panels dedicated to specific diseases. The genes tested may vary from one center to another but should include the following:

- ectopia lentis: FBN1
- TAA or TAD or systemic features: genes with a definitive or strong association with HTAD: ACTA2, COL3A1, FBN1, LOX, MYH11, MYLK, PRKG1, SMAD3, TGFB2, TGFBR1, TGFBR2. This list is dynamic and will be updated regularly. The list of genes presently used in the various centers is available on the website of VASCERN."

"The technical capacity to detect small intragenic copy number variants using NGS data is suboptimal, though algorithms have improved considerably over the last few years.Additional high-resolution copy number variant analysis should be considered in case of negative panels in patients with a high suspicion. Furthermore, after multidisciplinary discussion, in some specific cases, it may be necessary to consider whole exome or genome sequencing for diagnosis since deep intronic variants can be present, or other syndromes, like Alagille syndrome, Noonan syndrome and neurofibromatosis type 1, can have TAA as a rare manifestation. Despite this, a causative variant remains unidentified in many (roughly 80%) non-syndromic HTAD patients."[30]

"In cases where the pathogenic variant is known, it is proposed that family members undergo genetic cascade screening. Thereafter, only patients carrying the pathogenic variant will need serial aortic imaging. When the disease-causing pathogenic variant

in the index patient is not known, follow-up by imaging (mainly TTE) of first-degree relatives depends on how many first or second-degree relatives have a dilated aorta."

- "In familial TAAs (at least 2 affected relatives), aortic imaging should be performed yearly when the aorta is dilated and every 5 years when aorta is not dilated in first-degree relatives."
- "In sporadic TAAs (only one family member affected), only the affected patient requires follow-up, and a single screening echocardiogram is deemed sufficient in adult relatives unless the first test is performed before the age of 40 years, in which case a further test after the age of 40 years could be considered. In case the measured aortic diameter is borderline, a second echocardiography after 5 years appears wise."[30]

European Society of Cardiology

The European Society of Cardiology (ESC, 2024) provided guidelines for the management of peripheral arterial and aortic diseases. Risk factors for HTAD were defined as the following:[31]

- In individuals with TAD ≤60 years of age:
  - Aortic dissection
  - Aortic dilatation in the absence of hypertension
  - Aortic dilatation with any additional risk feature (syndromic features of MFS, LDS, or vEDS and/or family history of TAD, peripheral/intracranial artery aneurysm, or unexplained sudden death at <60 years)
  - Aortic root/ascending z-score ≥3
- In individuals with TAD >60 years of age:
  - Aortic root/ascending z-score ≥3 or aortic dissection in the absence of hypertension
  - Aortic root/ascending z-score ≥3 or aortic dissection with any additional risk feature (syndromic features of MFS, LDS, or vEDS and/or family history of TAD, peripheral/intracranial artery aneurysm, or unexplained sudden death at <60 years)

The ESC provided the following recommendations regarding genetic testing and aortic imaging:[31]

- "In patients with aortic root/ascending aneurysms or thoracic aortic dissection and risk factors for HTAD, genetic counselling at an expert centre and subsequent testing, if indicated, is recommended." (Class I, Level B)
- "In patients with HTAD who have a pathogenic/likely pathogenic variant, genetic testing of at-risk biological relatives (i.e. cascade testing) is recommended, irrespective of age." (Class I, Level C)
- "In patients with HTAD, guidance of clinical management by the underlying gene/variant, when known, should be considered." (Class IIa, Level B)

- "In patients with TAD with risk factors for HTAD, with a negative family history of TAD and in whom no (likely) pathogenic variant is identified, TTE screening aortic imaging of FDRs [first-degree relatives] is recommended." (Class I, Level B)
- "Imaging screening of family members of patients with TAD with risk factors for HTAD in whom no (likely) pathogenic variant is identified should be considered starting at age 25, or 10 years below the youngest case, whichever is younger. If the initial screening is normal continued screening every 5 years until the age of 60 should be considered." (Class IIa, Level C)

European Society of Cardiology and European Society of Human Genetics

A consensus document for genetic counseling and testing in adults with congenital heart disease, published by the European Society of Cardiology (ESC, 2019) and European Society of Human Genetics (ESHG, 2019), recommended that genetic testing for HTAD include at least the genes known to have a "definitive" or "strong" association with the condition according to the Clinical Genome Resource (ClinGen) framework. Regarding when to test, the authors stated:[32]

- "…genetic testing may be considered after proper counselling and evaluation when at least two members of a family present HTAD or in isolated cases when (a) children (<18 years) present with aortic dissection or an aortic root diameter Z-score ≥3 or (b) adults present with aortic dissection or an aortic root diameter Z-score >3.5 or with a Z-score between 2.5–3.5 and <60 years or >60 years, and no arterial hypertension."

The ESC/ESHG, 2019 consensus document also addressed the relationship between BAV and TAAD:[32]

- "Familial occurrence of BAV has clearly been established with rates of 5–10% in first-degree relatives in various studies. Interestingly, the incidence of TAA in first-degree relatives is even higher in family members with TAV [tricuspid aortic valve] or BAV. The genetic basis of BAV is unclear. Rare pathogenic variants have been identified in a number of genes (SMAD6, NOTCH1, ROBO4, TBX20); however, these variants account for <5% of all BAV/TAA cases."
- "Echocardiographic screening in first-degree relatives of BAV patients is recommended and may be appropriate, particularly in boys, athletes and if hypertension is present. Genetic screening may be considered in familial cases with associated TAA."

National Working Group on Bicuspid Aortic Valve and Thoracic Aortic Aneurysm

A 2018 expert consensus recommendation published on behalf of the National Working Group on Bicuspid Aortic Valve (BAV) and Thoracic Aortic Aneurysm (TAA) stated the following regarding cardiogenetic care for individuals with thoracic aortic disease and their first-degree relatives:[33]

- High-risk groups for genetic predisposition are defined as thoracic aneurysm (equal to or greater than 45 mm) or dissection:
  - Age at diagnosis <50 years, or
  - Age at diagnosis 50-60 years, no hypertension, or
  - Positive family history, or
  - Syndromic features
- Due to the small size of modern families and reduced penetrance of hereditary thoracic aortic disease, the authors recommended the following:
  - "We suggest to define a positive family history as having at least one first- or second-degree relative with (1) a thoracic aortic aneurysm or dissection, (2) an aneurysm or dissection elsewhere in the arterial tree, diagnosed below 60#years of age, (3) a left-sided congenital heart defect (e.g. congenital aortic valve stenosis or bicuspid aortic valve) or patent ductus arteriosus, or (4) sudden death below 45#years of age."
- "In patients fulfilling the revised Ghent criteria for Marfan syndrome (e.g. combination of thoracic aortic disease with ectopia lentis), the probability of finding FBN1 mutation is high, between 66% and 91%. Therefore, targeted FBN1 analysis can be considered in these cases. If no specific syndromic features are present, next-generation sequencing (NGS) of multiple genes is the most efficient and cost-effective method."
- "If a disease-causing mutation has been identified in the proband, the working group recommends offering presymptomatic genetic testing to relatives. This is best undertaken using a stepwise approach called "cascade screening."
- Screening of first-degree relatives for familial TAA:
  - "Cardiovascular screening of mutation carriers should take place at or in close collaboration with an academic center, according to gene-specific management guidelines."
  - If no disease-causing mutation has been identified in the proband, screening should be offered to all first-degree relatives (parents, siblings, and children) starting at age 25 years or 10 years before the youngest case in the family using transthoracic echocardiography (TTE), baseline computed tomography (CT), or magnetic resonance imaging (MRI). If normal, repeat every 5 years. Discontinue at age 65 years or if first screening >60 years.

Selected Relevant Publications

In 1996, an international group of Marfan syndrome experts initially proposed clinical diagnostic criteria for Marfan syndrome called the Ghent nosology that gained wide acceptance.[34] The Ghent criteria were updated in 2010 and now address the role of FBN1 genetic testing in the diagnosis of Marfan syndrome.[22] While the authors did not make specific recommendations regarding when to perform genetic testing for Marfan syndrome, they did make the following statements:[22]

- "In practice, this does not make FBN1 testing a formal requirement (which imposes financial burden in some countries, and does not yet have 100% sensitivity and specificity), but allows its appropriate use when available."
- "The presence of aortic root dilatation (Z-score ≥2 when standardised to age and body size) or dissection and ectopia lentis allows the unequivocal diagnosis of MFS, irrespective of the presence or absence of systemic features except where these are indicative of SGS, LDS or vEDS."
- "Where aortic root dilatation (Z ≥2) or dissection is present but ectopia lentis is absent and the FBN1 status is either unknown or negative, an MFS diagnosis is confirmed by the presence of sufficient systemic findings (≥7 points, according to a new scoring system). However, features suggestive of SGS, LDS or vEDS must be excluded and appropriate alternative genetic testing (TGFBR1/2, collagen biochemistry, COL3A1, and other relevant genetic testing when indicated and available upon the discovery of other genes) should be performed."
- "In the presence of ectopia lentis but absence of aortic root dilatation/dissection, the identification of an FBN1 mutation previously associated with aortic disease is required before making the diagnosis of MFS. If the FBN1 mutation is not unequivocally associated with cardiovascular disease in either a related or unrelated proband, the patient should be classified as 'ectopia lentis syndrome'."

An expert-authored review for Marfan syndrome in 2022 noted that the condition can be confirmed in an individual meeting the Ghent criteria, and should be suspected in individuals with the following clinical findings:[6]

- Aortic root enlargement (z score ≥2.0)
- Ectopia lentis (diagnosed by slit-lamp examination after maximal pupillary dilation)
- A systemic score ≥7

When the clinical findings suggest the diagnosis of Marfan syndrome, recommended genetic testing approaches included single-gene analysis of FBN1, or a multigene Marfan syndrome / Loeys-Dietz syndrome / familial TAAD panel that includes FBN1.[6]

An expert-authored review in 2024 noted that no clinical diagnostic criteria have been published for Loeys-Dietz syndrome (LDS), but that the condition can be established in individuals with suggestive findings (see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases* for specific examples).[7] The authors also stated, "The molecular diagnosis of LDS can be established in a proband who has a heterozygous pathogenic (or likely pathogenic) variant in SMAD2, SMAD3, TGFB2, TGFB3, TGFBR1, or TGFBR2 or biallelic pathogenic (or likely pathogenic) variants in IPO8 AND any of the following:

- Aortic root enlargement (defined as an aortic root z score ≥2 standard deviations above the mean) or type A dissection
- Other characteristic clinical features of LDS: craniofacial, skeletal, cutaneous, and/or vascular manifestations (especially arterial tortuosity, prominently including the

head and neck vessels, and aneurysms or dissections involving medium-to-large muscular arteries throughout the arterial tree)
- Family history of established diagnosis of LDS"

For genetic testing to confirm a diagnosis of LDS, a multigene Marfan syndrome / Loeys-Dietz syndrome / familial TAAD panel that includes the above LDS genes, as well as other genes associated with TAAD, was recommended.[7]

An expert-authored review for vEDS recommended that genetic testing strategies include either single-gene testing of COL3A1, or a multigene panel including COL3A1 and other genes in the differential diagnosis (i.e. other EDS types, Marfan syndrome, LDS, or nsTAAD). The authors stated:[35]
- "No consensus clinical diagnostic criteria for vascular Ehlers-Danlos syndrome (vEDS) have been published. When the diagnosis is suspected on clinical grounds, molecular diagnostic testing of COL3A1 is indicated due to the presence of clinical phenocopies and variable expression of the vEDS phenotype. Criteria established in 2017 are useful to guide the approach to genetic testing."

EDS and Hypermobility Spectrum Disorders

International Consortium on the Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders

The International Consortium on the Ehlers-Danlos Syndromes (2017) developed clinical criteria for 13 recognized types of EDS as defined above in the "Diagnosis" section. The Consortium stated that genetic testing is needed to confirm the diagnosis when suspected based on clinical criteria (except for hEDS):[20]
- "In view of the vast genetic heterogeneity and phenotypic variability of the EDS subtypes, and the clinical overlap between many of these subtypes, but also with other HCTDs, the definite diagnosis relies for all subtypes, except hEDS, on molecular confirmation with identification of (a) causative variant(s) in the respective gene."
- "Molecular diagnostic strategies should rely on NGS technologies, which offer the potential for parallel sequencing of multiple genes. Targeted resequencing of a panel of genes…is a time- and cost-effective approach for the molecular diagnosis of the genetically heterogeneous EDS. When no mutation (or in case of an autosomal recessive condition only one mutation) is identified, this approach should be complemented with a copy number variant (CNV) detection strategy to identify large deletions or duplications, for example Multiplex Ligation-dependent Probe Amplification (MLPA), qPCR, or targeted array analysis."
- "The diagnosis of hEDS remains clinical as there is yet no reliable or appreciable genetic etiology to test for in the vast majority of patients."

The International Consortium recommended that multigene panel testing include at least the gene(s) associated with the suspected EDS type. Broader panels were specifically suggested for kEDS, BCS, spEDS, and mcEDS due the phenotypic overlap between these types. Similarly, the authors suggested the inclusion of collagen type VI-related myopathies in multigene panel testing for suspected mEDS.[20]

In 2023, the Paediatric Working Group of the International Consortium on EDS and HSD developed a pediatric diagnostic framework that includes four components: generalized joint hypermobility (GJH), skin and tissue abnormalities, musculoskeletal complications, and core comorbidities. The framework supports categorization of hypermobile children into a group describing their phenotypic and symptomatic presentation. Regarding genetic testing, the authors stated:[15]

- "Hypermobility spectrum disorder is reserved for the combination of GJH and musculoskeletal symptoms, with the systemic subtype including those with both musculoskeletal symptoms and comorbidities. This can only be used after exclusion of other Ehlers–Danlos syndrome types, heritable disorders of connective tissue, syndromic conditions, chromosomal microdeletions, skeletal dysplasia, or neuromuscular disorders. This framework would not exclude the abovementioned diagnoses, and individual patients would need to be assessed for risk of alternate diagnosis and investigated appropriately, including, if indicated, next-generation sequencing (NGS) panel-based testing. Currently, we do not recommend genetic testing on all children with GJH, or HSD or hEDS. Medical specialists should remain guided by their clinical reasoning and the healthcare setting in which they practice when deciding if genetic testing is required."

Selected Relevant Publications

An expert-authored review by Zschocke and colleagues in 2024 summarized the genetic diagnosis of EDS. The authors noted that hEDS and HSD account for the majority of "suspected EDS" cases and emphasized that neither condition can be confirmed or excluded with genetic testing. A thorough clinical evaluation was recommended, followed by multigene panel testing for individuals suspected of having monogenic EDS (i.e. one of the 12 types for which the genetic etiology was known, which excluded hEDS/HSD):[5]

- "Diagnostic genetic testing is indicated in individuals with generalized joint hypermobility (with or without recurrent joint subluxations/dislocations) in conjunction with marked, typical skin manifestations (hyperextensibility, fragility, poor wound healing, atrophic scars, hemosiderosis etc.) and possibly arterial vascular events/organ rupture. In the absence of other pathognomonic skeletal, muscular, ocular, or oral manifestations, the genetic analyses may focus on the genes for type V, III and I collagen, TNXB, AEBP1, and ADAMTS2 (THBS2 unconfirmed)."

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- "In the case of marked scoliosis and/or other skeletal deformities, myopathy, and marked neonatal muscular hypotonia, the analyses should cover PLOD1, FKBP14, B4GALT7, B3GALT6, B3GAT3, SLC39A13, CHST14, DSE and COL12A1. ZNF469 and PRDM5 should be targeted if brittle cornea syndrome is a possibility, whereas analysis of C1R and C1S is only necessary in the presence of typical oral manifestations. Special considerations may apply for infants or children in whom the clinical features may not yet be fully developed."
- "A broad massively parallel sequencing 'EDS panel' is sometimes recommended to exclude a genetic diagnosis in individuals with hypermobility even if there is no clear clinical suspicion of a monogenic disease. Although a pathogenic variant in one of the 'EDS genes' is sometimes identified in these cases, this non-specific approach may lead to an excess of expensive genetic investigations with unproven utility. It also has the risk of identifying potentially misleading variants of unknown significance (VUS) that may cause undue uncertainty and sometimes incorrect diagnoses, trigger unnecessary follow-up tests, and may lead to inadequate treatments."
- "Depending on health system resources, it is preferable to avoid genetic tests in suspected hEDS, or provide these to selected individuals that fulfill the strict 2017 hEDS criteria when the indication for testing is made by specialist clinical geneticists or rheumatologists with experience in diagnosing EDS. Vice versa, in the absence of pathognomonic monogenic EDS manifestations in individuals with hEDS/HSD, the latter diagnosis may be made based on the clinical assessment without the need to 'exclude' a monogenic EDS type."

Expert-authored reviews focused on hEDS/HSD likewise recommended that this EDS type be diagnosed clinically with the International Consortium criteria and indicated that genetic testing cannot be used to confirm the diagnosis. Rather, genetic testing should be guided by the presence of clinical history or physical examination findings that are concerning for other HCTDs.[24,36]

Stickler Syndrome

A 2020 review of Stickler syndrome (SS) by Boothe and colleagues noted that clinical diagnostic criteria were previously proposed for the condition but were not validated and may result in underdiagnosis of certain phenotypes. Instead, the authors recommended genetic testing to confirm the diagnosis:[21]

- "Molecular genetic testing should be pursued in any individual for whom SS is suspected. In addition to confirming a diagnosis in the individual, a molecular genetic diagnosis can assist in the testing of at-risk family members, in guiding medical management and screening and in providing accurate recurrence risk for offspring."
- "Many different approaches may be used when pursuing molecular genetic testing for SS. If family history and clinical findings are suggestive of a specific form of SS, one may consider obtaining single-gene testing. Likewise, if suspicion is high for

> AR SS, a gene panel analyzing only the genes associated with AR SS could be considered….[A]dvancements in next-generation gene sequencing technology, which utilizes methods that sequence millions of short-fragment DNA strands rapidly, allows for a cost-effective method for analyzing multiple genes at one time. Thus, one could initiate testing for all genes known to be associated with SS—COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, and COL9A3, rather than choose a sequential approach. This is often preferred because it leads to a more cost-effective and rapid diagnosis. If alternative diagnoses are being considered or if the phenotype is unclear, larger gene panels that include other genes or diagnoses of interest could be considered."

Another expert-authored review for Stickler syndrome in 2023 echoed the need for multigene panel testing to confirm the diagnosis in individuals with characteristic clinical features (see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases*). In addition to the collagen genes related to Stickler syndrome, other genes associated with overlapping clinical phenotypes (e.g., BMP4, GZF1, LOXL3, LRP2, VCAN) may be included in multigene panel testing for this condition.[8]

A 2016 publication of consensus-derived best practices for Pierre Robin sequence (PRS) noted that Stickler syndrome is one of the most common genetic causes of this condition. As part of a comprehensive etiological assessment for PRS, the authors suggested genetic testing targeting the Stickler syndrome-associated collagen genes (COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, COL9A3.[37] A 2024 consensus-based genetic testing algorithm for orofacial clefts similarly recommended that targeted testing for Stickler syndrome be considered for individuals with PRS.[38]

Other Hereditary Connective Tissue Disorders

There were limited clinical practice guidelines available for other HCTDs. A series of expert-authored reviews was published for arterial tortuosity syndrome, congenital contractural arachnodactyly, cutis laxa, FLNA deficiency, and Sphrintzen-Goldberg syndrome. Genetic testing was recommended, preferably via multigene panel, to confirm the diagnosis in individuals with characteristic features of these conditions (see Table: *Select Hereditary Connective Tissue and Thoracic Aortic Diseases*).[9-13] The need for a multigene panel approach (i.e. cutis laxa or arteriopathy panel) was particularly emphasized for cutis laxa, and single-gene testing was described as "rarely useful and typically NOT recommended".[11]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for hereditary connective tissue and thoracic aortic disease genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate

diagnostic strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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HFE Hemochromatosis Genetic Testing

MOL.TS.183.A
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Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
HFE Targeted Mutation Analysis (common variants)	81256
HFE Sequence Analysis	81479
HFE Deletion/Duplication Analysis	81479

Criteria

Introduction

Requests for HFE hemochromatosis genetic testing are reviewed using the following criteria.

HFE known familial mutation testing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing of the HFE gene that would detect the known familial mutation, AND
- Presymptomatic/Asymptomatic Genetic Testing:
  - HFE mutation(s) identified in 1st degree biological relative, OR
- Diagnostic Testing:
  - HFE mutation(s) identified in 1st degree biological relative, and
  - Serologic evidence of iron overload (e.g., a transferrin saturation greater than or equal to 45% and/or elevated ferritin), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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HFE targeted mutation testing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing of the HFE gene, AND
- Presymptomatic/Asymptomatic Genetic Testing:
  - Documented family history of first-degree relative with HFE hemochromatosis, OR
- Diagnostic Testing:
  - Serologic evidence of iron overload (e.g., transferrin saturation greater than or equal to 45% and/or elevated ferritin), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HFE gene sequence analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous sequencing of the HFE gene, and
  - Previous targeted HFE genetic testing performed and zero or one mutation identified, AND
- Diagnostic Testing:
  - Serologic evidence of iron overload (e.g., transferrin saturation greater than or equal to 45% and/or elevated ferritin), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HFE deletion/duplication analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous deletion/duplication analysis of the HFE gene, and
  - Previous HFE sequencing performed and zero or one mutation identified, AND
- Diagnostic Testing:
  - Serologic evidence of iron overload (e.g., transferrin saturation greater than or equal to 45% and/or elevated ferritin), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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What is HFE hemochromatosis?

HFE hemochromatosis is a disorder marked by high absorption of iron by the mucosa of the small intestine.[1]

Prevalence

About 1 in 200 to 1 in 400 non-Hispanic whites in North America are affected with HFE hemochromatosis.[2] The disorder is less common among Blacks, Hispanics and Asians in North America.[1]

Symptoms

There is a phenotypic spectrum of HFE hemochromatosis.[1]

- Clinical HFE hemochromatosis: individuals manifest end-organ damage secondary to iron overload.
- Biochemical HFE hemochromatosis: individuals have increased transferrin-iron saturation and serum ferritin but no clinical features of iron overload.[1]
- Non-expressing C282Y homozygotes: individuals with two copies of the HFE mutation C248Y have neither clinical manifestations of disease nor iron overload.

Individuals who are untreated may experience the following symptoms: abdominal pain, weakness, lethargy, weight loss, arthralgias, diabetes mellitus, and increased risk of cirrhosis when the serum ferritin is higher than 1,000 ng/mL.[1] Other findings may include progressive increase in skin pigmentation, congestive heart failure, and/or arrhythmias, arthritis, and hypogonadism.[1] Clinical HFE hemochromatosis is more common in men than women.[1]

HFE hemochromatosis is typically an adult-onset condition.[1] Juvenile forms of hereditary hemochromatosis exist, but are caused by other genes, and testing for these forms of hemochromatosis is not addressed by this guideline.

Cause

HFE hemochromatosis is caused by pathogenic mutations in the HFE gene that lead to excess iron absorption and storage in the liver, heart, pancreas, and other organs.[1]

There are other, rarer forms of inherited primary iron overload, but testing for these disorders is not addressed by this guideline. Some of these disorders and their associated genes include:[1]

- BMP6-related iron overload (BMP6)
- Aceruloplasminemia (CP)
- Juvenile hemochromatosis (HAMP, HJV)
- SLC40A1-related hemochromatosis (SLC40A1)

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- TFR2-related hemochromatosis (TRF2)

Hemochromatosis may also be caused by pathogenic mutations in 2 different hemochromatosis-related genes.[1]

Inheritance

HFE hemochromatosis is inherited in an autosomal recessive manner.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Diagnosis

When HFE hemochromatosis is suspected, serum iron studies, including transferrin saturation (TS), serum ferritin (SF), and unsaturated iron-binding capacity (UIBC), are the first step in establishing a diagnosis. HFE genetic testing is recommended if TS is greater than or equal to 45%.[3,4]

Current guidelines support HFE genetic testing in individuals with: [2,4,5]

- Serologic evidence of iron overload, considered to be a transferrin saturation greater than or equal to 45% and elevated ferritin
- A known family history of hemochromatosis
- A known family mutation in the HFE gene in a first degree relative

Common changes in the HFE gene associated with HFE hemochromatosis are C282Y, H63D, and S65C.[1] C282Y and H63D are the most common changes associated with HFE-related hemochromatosis in those of northern European ancestry:[1]

- C282Y homozygosity: 60-90%
- H63D homozygosity: 1%
- C282Y/H63D compound heterozygosity: 3-8%

There is controversy over whether the H63D variant causes clinical disease.[2,6] The next most common cause are individually rare mutations.[7] S65C has a lower population frequency and may rarely cause HFE hemochromatosis.[8] The combination of these mutations determines both the chances of symptoms occurring and their severity.

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Management

HFE hemochromatosis can be effectively treated in most people. Phlebotomy therapy can alleviate almost all symptoms of iron overload if initiated before organ damage occurs.[9]

Survival

Untreated HFE hemochromatosis may result in reduced lifespan due to congestive heart failure and other cardiac manifestations, end-stage liver disease, liver cancer, or extrahepatic cancers.[1]

Test information

Introduction

Testing for HFE hemochromatosis may include known familial mutation analysis, targeted mutation analysis, next-generation sequencing, or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon

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boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

HFE sequencing and deletion/duplication analysis may be necessary for individuals who do not have northern European ancestry.[1]

Guidelines and evidence

American Association for the Study of Liver Disease

The American Association for the Study of Liver Diseases (AASLD, 2011) Practice Guidelines stated:[5]

- "In a patient with suggestive symptoms, physical findings, or family history, a combination of transferrin saturation (TS) and ferritin should be obtained rather than relying on a single test. (1B) If either is abnormal (TS ≥45% or ferritin above the upper limit of normal), then HFE mutation analysis should be performed. (1B)"
- "We recommend screening (iron studies and HFE mutation analysis) of first-degree relatives of patients with HFE-related HH to detect early disease and prevent complications."

American College of Gastroenterology

The American College of Gastroenterology (ACG, 2019) Clinical Guideline on Hereditary Hemochromatosis (called HH in this document) stated:[4]

- "We recommend that family members, particularly first-degree relatives, of patients diagnosed with HH should be screened for HH (strong recommendation, moderate quality of evidence)."
- "We recommend that individuals with the H63D or S65C mutation in the absence of C282Y mutation should be counseled that they are not at increased risk of iron overload (conditional recommendation, very low quality of evidence)."
- "We suggest against further genetic testing among patients with iron overload who tested negative for the C282Y and H63D alleles (conditional recommendation, very low quality of evidence)."
- "[G]enotyping for HFE mutations (C282Y) is now a standard part of the evaluation of patients in whom HH is suspected on clinical grounds or based on the finding of elevated iron studies."

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- "We suggest against further genetic testing among patients with iron overload testing negative for the C282Y and H63D alleles (conditional recommendation, very low quality of evidence)."

European Association for the Study of the Liver

The European Association for the Study of the Liver (EASL, 2022) Clinical Practice Guidelines on haemochromatosis stated:[9]

- "Individuals with clinical and biochemical signs of haemochromatosis, elevated transferrin saturation and high serum ferritin concentration, or otherwise unexplained persistently elevated transferrin saturation should be genetically tested for haemochromatosis after informed consent for genetic testing has been obtained (level of evidence 2, strong recommendation, strong consensus)."
- "Adult individuals with a positive family history of first-degree relatives with haemochromatosis should be genetically tested for haemochromatosis after informed consent for genetic testing has been obtained (level of evidence 4, strong recommendation, strong consensus)."
- "Young individuals with biochemical evidence and clinical manifestations of haemochromatosis (liver disease, amenorrhea, hypogonadism, cardiomyopathy) should be tested for rare haemochromatosis gene variants (LoE 4, strong recommendation, strong consensus)."

International Society for the Study of Iron in Biology and Medicine

The International Society for the Study of Iron in Biology and Medicine (BIOIRON Society, 2022) hemochromatosis classification update and recommendations stated:[10]

- "If an appropriately investigated patient has an unequivocal HC [hemochromatosis] phenotype without cofactors but is not a p.Cys282Tyr homozygote (and this includes compound p.Cys282Tyr and p.His63Asp heterozygosity or p.His63Asp homozygosity), a provisional diagnosis of "molecularly undefined" HC can be made, and phlebotomies started."
- "The panelists agree that, whenever possible, an accurate molecular characterization remains important in these patients, especially for cascade screening of asymptomatic siblings or other first-degree relatives. To this end, patients should be referred (or DNA should be sent) to a specialized center. Indeed, second-level genetic tests have limitations that include costs, time delay, and poor availability in certain regions and require a high level of expertise for interpretation."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for HFE hemochromatosis testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For

those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Hereditary Cancer Syndrome Multigene Panels

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Hereditary cancer syndrome multigene panel testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
BRCAplus	0129U
BreastNext	0102U
Chromosomal microarray [BAC], constitutional	81228
Chromosomal microarray [SNP], constitutional	81229
Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis	81349
ColoNext	0101U
CustomNext + RNA: APC	0157U
CustomNext + RNA: MLH1	0158U
CustomNext + RNA: MSH2	0159U
CustomNext + RNA: MSH6	0160U
CustomNext + RNA: PMS2	0161U
CustomNext + RNA: Lynch (MLH1, MSH2, MSH6, PMS2)	0162U

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Procedures addressed by this guideline	Procedure codes
GeneticsNow Comprehensive Germline Panel	0474U
Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer, hereditary pancreatic cancer, hereditary prostate cancer), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants	81432
Hereditary cancer syndrome multigene gene panel	81479
Hereditary colon cancer-related disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants	81435
Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants	81437
OvaNext	0103U
ProstateNow Prostate Germline Panel	0475U
+RNAinsight for ATM	0136U
+RNAinsight for BRCA1/2	0138U
+RNAinsight for BreastNext	0131U
+RNAinsight for CancerNext	0134U
+RNAinsight for ColoNext	0130U

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Procedures addressed by this guideline	Procedure codes
+RNAinsight for GYNPlus	0135U
+RNAinsight for OvaNext	0132U
+RNAinsight for PALB2	0137U
+RNAinsight for ProstateNext	0133U

Criteria

Requests for hereditary cancer syndrome panel testing are reviewed using the following criteria.

Hereditary Cancer Multi-Syndrome Panels

This guideline applies only to testing performed as a multi-syndrome panel for hereditary cancer. For information on single gene or single syndrome requests, please refer to a test-specific policy, if available, as this testing is not addressed here. If none is available, please refer to the clinical use guideline *Genetic Testing for Cancer Susceptibility and Hereditary Cancer Syndromes*.

- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- If there is a known familial mutation in the family, that mutation does not sufficiently explain the indication for testing, AND
- No previous hereditary cancer syndrome multigene panel testing, AND
- No previous hereditary cancer syndrome testing for any gene on the panel, AND
- One of the following is met:
  - Member has a personal diagnosis of cancer consistent with the hereditary cancer syndrome that is suspected in the family, or
  - Member is not affected with cancer but is the most informative person in the family to test and an affected family member cannot proceed with testing. If the member is not the most informative person to test, documentation must be provided by the ordering physician's office clearly documenting that it is impossible to test the most informative family member and describing the reason the unaffected member is being tested at this time, AND
- One of the following is met:
  - Member has a personal history of invasive cutaneous melanoma and a first degree biological relative diagnosed with pancreatic cancer (multi-syndrome panel must include CDKN2A), or

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  - Member meets criteria for BRCA Analysis based on current EviCore guideline *BRCA Analysis*, or
  - Member meets criteria for Lynch Syndrome Genetic Testing based on current EviCore guideline *Lynch Syndrome Genetic Testing*, or
  - Member meets criteria for Familial Adenomatous Polyposis Genetic Testing based on current EviCore guideline *Familial Adenomatous Polyposis Genetic Testing*, or
  - Member meets criteria for MUTYH-Associated Polyposis Genetic Testing based on current EviCore guideline *MUTYH-Associated Polyposis Genetic Testing*, or
  - Member meets criteria for two other separate hereditary cancer syndromes based on EviCore guidelines that are included on the panel, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Deletion/Duplication Analysis

- Member meets criteria for sequencing above, AND
- Previous sequencing panel, if applicable, was performed and no mutations identified.

RNA Testing for Hereditary Cancer Syndromes

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

Hereditary Cancer Testing Reflex or Update Panels

Hereditary cancer testing reflex or update panels (e.g. MyRisk Update) will be reimbursed when the following criteria are met:

- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- No known cancer-causing mutation in the family, AND
- No previous hereditary cancer syndrome multigene panel testing, AND
- Testing for one condition, for which the member meets EviCore criteria, was performed and billed separately. A multigene panel is now being considered and will be billed at a rate comparable to single syndrome pricing, AND

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- Member meets medical necessity criteria for at least one additional condition included in the panel that was not already tested (e.g., hereditary breast and ovarian cancer was already performed, but Lynch syndrome criteria are also met). Please refer to test-specific guidelines for details.
  - Although not a complete list, the following are considered separate conditions:
    - Hereditary breast cancer - this includes both BRCA1/2 and PALB2 (Note that if BRCA1/2 testing was already performed and PALB2 criteria are now met, PALB2 testing alone would be medically necessary and not an update panel.)
    - Lynch syndrome
    - Li-Fraumeni syndrome
    - Familial adenomatous polyposis
    - Cowden syndrome
    - Peutz-Jeghers syndrome
    - MUTYH-associated polyposis

Other Considerations

- Genetic testing is only medically necessary once per lifetime. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multigene panel is only reimbursable once per lifetime.
  - A single gene included in a panel or a multigene panel may not be reimbursed if testing has been performed previously.
  - If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.
- RNA testing is not reimbursable.
- When otherwise reimbursable, the following limitations apply:

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- When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81432 or other DNA-based panel code in the table at the beginning of this policy)*.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What are hereditary cancer syndromes?

When a mutation in a single gene causes a significantly increased risk for certain cancers, it is called a hereditary cancer syndrome. Hereditary cancer syndromes are usually characterized by a pattern of specific cancer types occurring together in the same family, younger cancer diagnosis ages than usual, and/or other co-existing non-cancer conditions.

Prevalence

Most cancer is sporadic and believed to be caused by a mix of behavioral or lifestyle, environmental, and inherited risk factors. However, about 5-10% of cancers are believed to have a major inherited component.[1]

Hereditary cancer syndromes

There are more than 50 hereditary cancer syndromes.[1] Some of the most common are listed below with associated cancers.[2]

- Hereditary breast and ovarian cancer syndrome (HBOC): breast, ovarian/fallopian tube/primary peritoneal cancer, pancreatic, prostate cancers
- Lynch syndrome: colorectal, endometrial, small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain, sebaceous adenoma, and keratoacanthoma tumors
- Familial adenomatous polyposis: colorectal and other gastrointestinal cancers, gastrointestinal tract polyps (adenomas, fundic gland), osteomas, desmoids, thyroid cancer and hepatoblastoma
- MUTYH-associated polyposis: colorectal and other gastrointestinal cancers, adenomas, hyperplastic polyps
- Cowden syndrome: benign and malignant tumors of the breast, endometrium, and thyroid; cancer and polyps (hamartomas) in the colon and rectum

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- Li-Fraumeni syndrome: soft tissue sarcoma, osteosarcoma, leukemia, melanoma, and cancer of the breast, pancreas, colon, adrenal cortex, stomach, esophagus and brain
- Peutz-Jeghers syndrome: polyps (hamartomas) in the stomach, small intestine and colon, and pancreas, lung, breast, uterine and non-epithelial ovarian cancer

Many hereditary cancer syndromes can include the same types of cancer and therefore have overlapping clinical findings. For example, breast cancer is a feature of HBOC, Li-Fraumeni syndrome, Cowden syndrome, and other hereditary cancer syndromes. The pattern of cancers in the family or pathognomonic features may help determine the underlying syndrome. However, in many cases it can be difficult to reliably diagnose hereditary cancer syndromes based on clinical and family history alone.

Genes associated with hereditary cancer syndromes

The National Comprehensive Cancer Network (NCCN) suggested specific genes that may contribute to hereditary cancers.[3-5] Some of these are provided in the table below.

Hereditary cancer type	Associated genes
Breast cancer	ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53
Colon cancer / polyposis	APC, AXIN2, BMPR1A, CHEK2, EPCAM, GREM1, MBD4, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53
Ovarian cancer	BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, PALB2, PMS2, EPCAM, RAD51C, RAD51D, and STK11
Pancreatic cancer	ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53
Prostate cancer	ATM, BRCA1, BRCA2, CHEK2, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2

Test information

Testing for hereditary cancer syndromes may include multigene panel testing.

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Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG) has published several statements or standards that offer general guidance on the clinical application of large-scale sequencing, including recommendations regarding counseling around unexpected results, variants of unknown significance, and minimum requirements for reporting apply to many NGS applications.[6-8]

ACMG (2021) published a technical standard for use of NGS in the clinical laboratories which stated:[7]

- "Choosing an appropriate NGS-based test is the responsibility of the ordering health-care provider. Given the large number of tests (https://www.ncbi.nlm.nih.gov/gtr/) available to the clinician, the clinical laboratory often provides critical advice in test selection. Ordering providers must weigh considerations of sensitivity, specificity, cost, and turnaround time for each clinical situation."
- "Test development must consider the variant types that will be detected in the genes or regions of the genome interrogated."

In a 2020 technical standard on gene sequencing panels, ACMG stated:[8]

- "Gene sequencing panels are a powerful diagnostic tool for many clinical presentations associated with genetic disorders. Advances in DNA sequencing technology have made gene panels more economical, flexible, and efficient."
- "Due to differences in decision-making processes in the absence of clear professional standards, genes included on similar disease-focused panels vary between laboratories. With the ability to sequence multiple genes simultaneously, it is imperative to evaluate critically the validity of gene–disease associations prior to test design."
- "Transparency is imperative when performing a gene sequencing panel so that ordering providers know what the test includes and what it does not."
- Gene panels should:

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- "Maximize clinical specificity by limiting or excluding GUSs [genes of uncertain significance], thereby minimizing detection of VUS [variants of uncertain significance]"
- "Employ auxiliary assays for genes/regions that cannot be interrogated with current sequencing technology to maximize the clinical utility."

In a 2020 statement on whether all individuals with breast cancer should receive BRCA1/2 testing, ACMG stated:[9]

- "With the advances in sequencing technologies and increasing access to and expanding indications for genetic testing, it remains critical to ensure that implementation of testing is based on evidence. Currently, there is insufficient evidence to recommend genetic testing for BRCA1/2 alone or in combination with multi-gene panels for all breast cancer patients."

American College of Obstetricians and Gynecologists

In a Committee Opinion, the American College of Obstetricians and Gynecologists (ACOG, 2019) stated:[10]

- "If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing and tailored cancer screening or risk reduction measures, or both."
- "Genetic testing may be performed using a panel of multiple genes through next-generation sequencing technology. This multigene testing process increases the likelihood of finding variants of unknown significance, and it also allows for testing for pathogenic and likely pathogenic variants in multiple genes that may be associated with a specific cancer syndrome or family cancer phenotype (or multiple phenotypes)."

American Society of Breast Surgeons

The American Society of Breast Surgeons (2019) published a consensus guideline on genetic testing for hereditary breast cancer. They stated the following:[11]

- "Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing. When the patient's history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful. Genetic testing is increasingly provided through multi-gene panels. There are a wide variety of panels available, with different genes on different panels. There is a lack of consensus among experts regarding which genes should be tested in different clinical scenarios.

There is also variation in the degree of consensus regarding the understanding of risk and appropriate clinical management of mutations in some genes."

- "Genetic testing should be made available to all patients with a personal history of breast cancer. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies."
- "Genetic testing should be made available to all patients with a personal history of breast cancer. Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. In particular, a patient who had negative germline BRCA1 and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing. Genetic testing performed prior to 2014 most likely would not have had PALB2 or other potentially relevant genes included and may not have included testing for large genomic rearrangements in BRCA1 or BRCA2."
- "Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines. Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves. When it is not feasible to test the affected relative first, then the unaffected family member should be considered for testing if they are interested, with careful pre-test counseling to explain the limited value of “uninformative negative” results. It is also reasonable to order a multi-gene panel if the family history is incomplete (i.e., a case of adoption, patient is uncertain of exact type of cancer affecting family members, among others) or other cancers are found in the family history, as described above."

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO, 2024) published the following recommendations on germline genetic testing panels in individuals with cancer:[12]

- "Patients should have a family history taken and recorded that includes details of cancers in first- and second-degree relatives and the patient's ethnicity."
- "When more than one gene is relevant based on personal and/or family history, multigene panel testing should be offered."
- ASCO provided information on genes that were more strongly recommended and those that were less strongly recommended based on cancer type. They stated, "[w]hen considering what genes to include in the panel, the minimal panel should

include the more strongly recommended genes … and may include those less strongly recommended."
- "A broader panel may be ordered when the potential benefits are clearly identified, and the potential harms from uncertain results should be mitigated."
- "Patients who meet criteria for germline genetic testing should be offered germline testing regardless of results from tumor testing."

The American Society of Clinical Oncology (ASCO, 2020) published the following recommendations after a consensus conference on germline testing in prostate cancer:[13]

- "For men with metastatic PCA, broader panel testing may be appropriate, particularly if considering treatment or clinical trial options."
  - Recommended priority genes for individuals with metastatic prostate cancer include BRCA1/2 and mismatch repair genes.
  - Recommended priority gene for individuals with nonmetastatic prostate cancer is BRCA2.
  - Additional genes can be considered in either group depending upon personal or family history.
- "Reflex testing may be considered for all patients, but especially for men with nonmetastatic disease considering AS or men without PCA for early detection, which allows for initial testing of genes that inform management."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) made the following general recommendations for using multigene panels in evaluating risk for breast and ovarian cancer and now includes this option in some management algorithms:[3-5]

- "Multi-gene testing is a new and rapidly growing field, but there is currently a lack of evidence regarding proper procedures and risk management strategies that should follow testing, especially when P/LP [pathogenic/likely pathogenic] variants are found for moderate-penetrance genes and when a VUS [variant of uncertain significance] is found. For this reason, the NCCN Panel recommends that multi-gene testing be offered in the context of professional genetic expertise, with pre- and post-test counseling being offered."[4]
- "An individual's personal and/or family history may be explained by more than one inherited cancer syndrome; thus, phenotype-directed testing based on personal and family history through a tailored multi-gene panel test is often more efficient and cost-effective and increases the yield of detecting a P/LP variant in a gene that will impact medical management for the individual or their family members with increased risk."[3]
- "There may also be a role for multi-gene testing in individuals who have tested negative for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility."[3]

- "Because commercially available tests differ in the specific genes analyzed, variant classification, and other factors (eg methods of DNA/RNA analysis or option to reflex from a narrow to a larger panel; provision of financial assistance for cascade testing of relatives), it is important to consider the indication for testing and expertise of the laboratory when choosing the specific laboratory and test panel."[3]
- "Multi-gene testing can include "intermediate" penetrant (moderate-risk) genes. For many of these genes, there are limited data on the degree of cancer risk, and there may currently be no clear guidelines on risk management for carriers of P/LP variants. Not all genes included on available multi-gene tests will change risk management compared to that based on other risk factors such as family history." [3]
- "P/LP variants in many breast, ovarian, pancreatic, and prostate cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions, thus posing risks to offspring to offspring if the partner is also a carrier."[3]
- "As more genes are tested, there is an increased likelihood of finding VUS, mosaicism, and clonal hematopoiesis of indeterminate potential (CHIP)."[3]
- "It may be possible to refine risks associated with both moderate and high-penetrance genes, taking into account the influence of gene/gene or gene/environment interactions. In addition, certain P/LP variants in a gene may pose higher or lower risk than other P/LP variants in that same gene. This information should be taken into consideration when assigning risks and management recommendations for individuals and their relatives who also have increased risk."[3]

NCCN Practice Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (2025) stated the following regarding multigene panel testing:[4]

- "The introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing affected patients who are at increased risk, and their families."
- "Multi-gene testing may be most useful when more than one gene can explain a patient's clinical and family history."
- "PVs in cancer risk genes for which clinical management is uncertain or not informed by well-established evidence will be identified."
- "Multi-gene tests also increase the likelihood of detecting with likelihood rates ranging from 29% to 63% in patients with CRC [colorectal cancer]. The proportion of patients with VUS may be higher among members of racial/ethnic minority groups, particularly with utilization of large multi-gene panels, potentially increasing burden of uncertain results on these populations."
- "Some multi-gene tests may include low- or moderate-penetrance genes, for which there are little available data regarding degree of cancer risk and guidelines for risk management. Further, it is possible that the risks associated with these genes may not be due entirely to that gene only, but may be influenced by gene/gene or gene/environment interactions. It is important to note that a germline multi-gene panel test result alone does not inform treatment decision-making for CRC."

- "The NCCN Panel recommends that MGPT [multigene panel testing] be ideally offered in the context of professional genetic expertise, with pre- and post-test counseling being offered."
- Germline multigene testing that "includes all polyposis and colorectal cancer genes" is preferred for the following individuals when there is no known pathogenic variants in any polyposis gene in the family:
  - "Personal history of 20 or more cumulative adenomas"
  - "Multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)"
  - "Consider testing if a personal history of between 10-19 cumulative adenomas, desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, unilateral CHRPE, if individual meets criteria for SPS [Serrated Polyposis Syndrome] with at least some adenomas, [or] family history of polyposis and family unwilling/unable to have testing."

NCCN Practice Guidelines for Prostate Cancer (2025) stated the following regarding multigene panel testing:[5]

- "If criteria are met, multigene testing is recommended."
- Germline genetic testing is recommended for all men with high-risk, very-high-risk, regional (node positive), or metastatic prostate cancer.[3,5]

NCCN Practice Guidelines for Cutaneous Melanoma (2025) stated the following regarding multigene panel testing:[14]

- "Multigene panel testing that includes CDKN2A is recommended for patients with invasive cutaneous melanoma who have a first degree relative diagnosed with pancreatic cancer."
- "Testing other genes that can harbor melanoma-predisposing mutations may be warranted."

NCCN Practice Guidelines for Kidney Cancer (2025) published criteria for further genetic risk evaluation for hereditary renal cell cancer syndromes. The guideline stated the following regarding multigene panel testing for individuals with no mutation identified in a family member and who have features of a hereditary renal cancer syndrome or who meet criteria as outlined in the guideline:[15]

- "Consider testing of individuals with kidney cancer-focused multi-gene panel or clinically directed single-gene testing."

NCCN Practice Guidelines for Neuroendocrine and Adrenal Tumors (2025) published criteria for genetic testing and stated the following regarding multigene panel testing:[16]

- "The introduction of multigene testing for hereditary endocrine neoplasia syndromes has rapidly altered the clinical approach to genetic testing of patients."
- "Given the possible overlap in clinical presentation amongst hereditary endocrine neoplasias, multigene panel testing may be more efficient and cost-effective in many situations."

- This guideline also addressed the differences that may be present in commercially available tests and the importance of considering the indication for testing and the expertise of the laboratory when considering multigene panel testing.
- Additionally, the guideline stated that testing of unaffected individuals can be considered when an affected family member is unable or unwilling to be tested. Per the guideline, pre-test genetic counseling should include a discussion of the potential difficulties with interpreting test results in this scenario.
- For individuals with likely pathogenic mutations, these are managed similar to pathogenic mutations. For individuals with a VUS, likely benign, or negative results, management is directed based on the cancers/tumors in the individual and family members.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for hereditary cancer syndrome multigene panels will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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Hereditary Pancreatitis Genetic Testing

MOL.TS.287.A
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Genetic testing for hereditary pancreatitis (HP) is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
CFTR deletion/duplication analysis	81222
CFTR known familial mutation analysis	81221
CFTR sequencing	81223
Hereditary pancreatitis gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Hereditary pancreatitis multigene panel	81479

Criteria

Requests for genetic testing for hereditary pancreatitis (HP) are reviewed using the following criteria.

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Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, and
  - Pathogenic pancreatitis-associated mutation(s) in a 1st degree biologic relative, AND
- Diagnostic Testing in Symptomatic Individuals:
  - Member is symptomatic (at least one documented episode of acute pancreatitis or a diagnosis of recurrent acute or chronic pancreatitis), OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Age 16 years or older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

PRSS1 Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous PRSS1 analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
  - An unexplained, documented episode of acute pancreatitis in an individual less than 18 years of age, or
  - Recurrent acute pancreatitis (2 or more documented episodes) or chronic pancreatitis, and
    - Symptom onset prior to age 25 years, and/or
    - A first degree biologic relative with recurrent acute pancreatitis, idiopathic chronic pancreatitis, or childhood pancreatitis (less than 18 years of age) without a known cause, and
  - No known etiology for the member's pancreatitis (e.g. alcoholism, gallstones, known genetic disorder), and
  - Absence of extra-pancreatic features suggestive of a complex genetic syndrome or cystic fibrosis (e.g. chronic sinopulmonary disease, failure-to-thrive, obstructive azoospermia due to congenital absence of the vas deferens, etc.), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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Pancreatitis Multi-Gene Panel

When a multi-gene panel is being requested and will be billed with the appropriate CPT panel code, the panel will be considered medically necessary when the following criteria are met:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous multi-gene analysis, and
  - PRSS1 analysis, if previously performed, was negative, AND
- Diagnostic Testing for Symptomatic Individuals:
  - An unexplained, documented episode of acute pancreatitis in an individual less than 18 years of age, or
  - Recurrent acute pancreatitis (2 or more documented episodes) or chronic pancreatitis, and
    - Symptom onset prior to age 25 years, or
    - A first degree biologic relative with recurrent acute pancreatitis, idiopathic chronic pancreatitis, or childhood pancreatitis (less than 18 years of age) without a known cause, and
  - No known etiology for the member's pancreatitis (e.g., alcoholism, gallstones, known genetic disorder), and
  - Absence of extra-pancreatic features suggestive of a complex genetic syndrome or cystic fibrosis (e.g., chronic sinopulmonary disease, failure-to-thrive, obstructive azoospermia due to congenital absence of the vas deferens, etc.), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CLDN2, PNLIP, and CEL Analysis

Individual testing of these genes for the purpose of diagnosing hereditary pancreatitis is not medically necessary.

Other considerations

Broad gastrointestinal disease panels may not be medically necessary when a narrower panel is available and more appropriate based on the clinical findings.

This guideline addresses testing for non-syndromic hereditary pancreatitis. For information on testing for syndromes that may include pancreatitis as part of a more complex phenotype (e.g. Schwachman-Diamond syndrome, CEL-related MODY, mitochondrial disorders, Johanson-Blizzard syndrome) please refer to appropriate guidelines (e.g. *Maturity-Onset Diabetes of the Young (MODY) Genetic Testing* or *Mitochondrial Disorders Genetic Testing*) or applicable clinical use guidelines, if

available. For information on CFTR analysis for individuals suspected of having Cystic Fibrosis please refer to the guideline *Cystic Fibrosis Testing*, as this is not addressed here.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- CLDN2, PNLIP, and CEL Analysis are not separately reimbursable.
- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81479*).
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
  - When the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement in a tiered fashion:
    - PRSS1
    - SPINK1
    - CFTR
    - CTRC

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is pancreatitis?

Pancreatitis is inflammation of the pancreas that may be acute, recurrent acute, or chronic.[1]

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Prevalence

The prevalence of PRSS1 mutations in individuals with chronic pancreatitis has been reported as 5%-9.6%, depending on the population.[2] In one US study of children, PRSS1 mutations were identified in 46% of those diagnosed with chronic pancreatitis and 17% of those with recurrent acute pancreatitis.[2]

Symptoms

Acute pancreatitis is defined as two of the three following findings:[2]

- Abdominal pain
- Elevated serum amylase or lipase (greater than 3x the upper limit of normal)
- Findings consistent with pancreatic inflammation on abdominal imaging.

Recurrent acute pancreatitis is defined as multiple (2 or more), discrete episodes of acute pancreatitis without any evidence of chronic pancreatitis.[2] There must be complete resolution of clinical and laboratory findings between episodes.

Chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.[3] Common features of established and advanced CP include:

- Pancreatic exocrine dysfunction
- Pancreatic endocrine dysfunction and dysplasia. I individuals with chronic pancreatitis may develop pancreatic cancer.

Individuals with chronic pancreatitis have an increased chance to develop pancreatic cancer.[4,5] Pancreatic cancer screening can be considered in individuals with mutations in PRSS1 or other hereditary pancreatitis (HP) genes when the phenotype is also consistent with HP.[5] Screening is recommended to occur in experienced high-volume centers "after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or indeterminate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening."[5]

Cause

Idiopathic sporadic pancreatitis occurs when a single individual in a family is affected, and the etiology is unknown despite comprehensive investigations.

Familial pancreatitis is pancreatitis of any cause (genetic or non-genetic) that occurs in a family with a greater incidence than would be expected by chance alone.[1]

Hereditary pancreatitis (HP) is a rare cause of acute, recurrent acute, and chronic pancreatitis. It is defined as a personal history of pancreatitis with diagnosis in either two first-degree relatives or three second degree relatives spanning at least two generations. Beginning with the first report of a PRSS1 mutation in a family with HP, it has been shown that multiple genetic risk factors are associated with this disease.[6]

Mutations in the following genes contribute to the development of recurrent acute and chronic pancreatitis:[1]

- PRSS1 mutations are the most common cause of HP.[1,2] Mutations in this gene follow autosomal dominant inheritance and have a penetrance of approximately 40-93%, depending on the specific mutation.[1,2]
  - The mutation detection rate for PRSS1 sequencing is approximately 94%, and deletion/duplication analysis is at least 6%.[2] N29I (p.Asn29Ile) and R122H (p.Arg122His) variants account for approximately 90% of cases of pathogenic variants observed in PRSS1-related HP.[2] Test results particularly for the PRSS1 gene, may offer prognostic information since the risk of pancreatic cancer in those with chronic pancreatitis is significantly increased.
- SPINK1 mutations may increase the severity of recurrent acute and chronic pancreatitis due to mutations in PRSS1, CFTR, CASR, or CTRC.[1,7] The majority of SPINK1 mutations are sequence variants, with deletions having been reported in a very small number of cases.[1]
- CFTR mutations are risk factors for pancreatitis. Individuals with biallelic CFTR mutations may have atypical cystic fibrosis (CF), putting them at risk for additional manifestations such as lung disease, male infertility, and chronic sinusitis.[1] The frequency of CFTR deletions in HP has not been investigated; however, they occur rarely in cystic fibrosis (approximately 1%).[1]
- CTRC mutations have been identified in individuals with recurrent acute and chronic pancreatitis. These variants were initially thought to be modifier genes; however, they have been shown to be sufficient to cause disease without other identifiable genetic or environmental risk factors.[8]
- CASR mutations may be a predisposing genetic factor for pancreatitis either in isolation or as modifying risk when other genetic causes are present.[9]
- CLDN2, CPA1, and GGT1 variants have been implicated as risk factors or modifiers for chronic pancreatitis, but less is known about the utility of screening for these mutations compared to the others mentioned above.[1,9]
- TRPV6 mutations have been reported in individuals with early-onset chronic pancreatitis not associated with alcohol consumption.[1] In a recent study, 20% of individuals with functionally defective TRPV6 variants also had the SPINK1 p.N34S variant.[10]
- CEL and PNLIP variants may result in an increased risk of developing pancreatitis as mutations in these genes are enriched in individuals with chronic pancreatitis. However, current data remains limited and the clinical utility of screening for these genetic variants is uncertain.[1,10]
- Rare disorders that include pancreatitis/pancreatic insufficiency as part of a more complex syndrome include Schwachman-Diamond syndrome (SBDS), mitochondrial DNA deletions, CEL-associated maturity-onset diabetes of the young (MODY), and Johanson-Blizzard syndrome (UBR1).[1]

Genes included on HP multi-gene panels may not be causative or associated with high risk for pancreatitis (e.g. CLDN2).[1]

Inheritance

While single pathogenic variants in SPINK1, CFTR, and CTRC are associated with an increased risk of recurrent acute or chronic pancreatitis, additional unidentified modifying factors may contribute to the disease.[1] These include alcohol use, smoking, chronic kidney disease, autoimmune factors, and anatomic issues.[1] Individuals with multiple risk factors (including multiple gene mutations) have a higher risk for pancreatitis.[1]

Biallelic variants of SPINK1 have been reported to result in early onset pancreatitis, suggesting an autosomal recessive pattern of inheritance with reduced penetrance.[1]

The rare disorders of which pancreatitis is a feature have varying patterns of inheritance.

Diagnosis

Pancreatitis is diagnosed by one of the following:[1-3]

- Abdominal imaging
- Functional studies (e.g. pancreatic exocrine insufficiency or pancreatic endocrine insufficiency with diabetes mellitus)
- Histology

Genetic testing results provide important early information about the etiology of pancreatitis-related disorders.[3] Determining the etiology of a pancreatitis-related disorder may not lead to immediate treatment in some cases, but it often ends exhaustive, invasive, and expensive diagnostic testing for advanced disease. Understanding the genetic etiology also informs decisions about therapy for persistent or severe disease, such as total pancreatectomy with islet autotransplantation.[3] However, genetic testing cannot predict the age of onset or disease severity.[1,4]

Management

Treatment of HP focuses on longitudinal monitoring of endocrine and exocrine pancreatic function, enzyme and nutritional supplementation, pain management and monitoring for complications (such as decreased bone mineral density and fat-soluble vitamin deficiencies). Endoscopic and surgical therapies may be necessary in some cases. Affected individuals are discouraged from smoking and drinking alcohol.[1]

Survival

In a relatively small study of PRSS1 mutation carriers, overall survival did not differ significantly from that of the general US Caucasian population.[11] Pancreatic cancer rates were higher and contributed to mortality.

Test information

Testing for HP may include known familial mutation analysis, next generation sequencing, and/or multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and evidence

American College of Gastroenterology

The American College of Gastroenterology (ACG, 2013) guideline on management of acute pancreatitis stated: "Genetic testing may be considered in young patients (<30 years old) if no cause is evident and a family history of pancreatic disease is present (conditional recommendation, low quality of evidence)."[12]

The ACG (2015) guidelines on genetic testing for hereditary gastrointestinal cancer syndromes stated that having a history of HP is a risk factor for familial pancreatic adenocarcinoma, and genetic testing for pancreatitis-associated genes should be considered for pancreatic cancer in individuals with “a personal history of at least 2 acute attacks of acute pancreatitis of unknown etiology, a family history of pancreatitis, or early-age onset chronic pancreatitis."[13]

The ACG (2020) guideline on chronic pancreatitis recommended genetic testing in individuals with clinical evidence of a pancreatitis-associated disorder or possible chronic pancreatitis in which the etiology is unclear, especially in younger individuals.[3]

American Pancreatic Association

American Pancreatic Association (APA, 2014) guidelines stated: “Several genetic variations have been associated with pancreatitis including PRSS1, PRSS2, SPINK1, CTRC, CASR, and CFTR. The role of these gene mutations in CP [chronic pancreatitis] is becoming increasingly recognized and better understood.” It is also noted that “knowledge of gene, gene-environment interactions may translate into new diagnostic and treatment paradigms” (Strong recommendation, level of evidence – moderate).[14]

Fourth International Symposium of Inherited Diseases of the Pancreas

The Fourth International Symposium of Inherited Diseases of the Pancreas (2007) recommended symptomatic individuals be referred for genetic counseling to consider PRSS1 testing when at least one of the following conditions are met, in order to determine if they may be candidates for pancreatic cancer surveillance:[15]

- "≥2 attacks of acute pancreatitis of unknown aetiology"
- "Idiopathic chronic pancreatitis, particularly if disease onset occurs <25 years of age"
- "One first-degree or second-degree relative with pancreatitis"
- "Unexplained documented episode of childhood pancreatitis that required hospitalization and where there is concern that HP should be excluded."
- "Asymptomatic people should be referred for genetic counseling to consider testing for a PRSS1 mutation when the patient has one first-degree relative with a defined HP gene mutation."

United European Gastroenterology

United European Gastroenterology (UEG, 2018) guidelines on chronic pancreatitis stated:[16]

- "A diagnosis of cystic fibrosis needs to be ruled out in all patients with CP onset before the age of 20 years as well as in patients with so-called ‘idiopathic’ CP (regardless of the age of onset). (GRADE 1B, strong agreement)"
- “All patients with a family history or early onset disease (less than 20 years) should be offered genetic testing for associated variants. (GRADE 2C, strong agreement)”

- "Genetic testing was recommended to include PRSS1, SPINK1, CPA1, CTRC, CEL, and “may include screening for variants in CFTR. (GRADE 2C, strong agreement)"

Select Relevant Publications

2016 Expert Authored Review

A 2016 expert-authored review on HP stated:[17]

- “[…] targeted genetic testing of members of an established HP family may be considered in cases of unexplained [recurrent acute pancreatitis] and/or [chronic pancreatitis], an affected individual with a first or second-degree relative with pancreatitis, unexplained pancreatitis in a child requiring hospitalization and/or when there is a known mutation in the family.”
- “[…] next generation sequencing approaches such as whole exome sequencing or whole genome sequencing should not be used for PRSS1 testing because of challenges in sequence alignment. If a mutation is not identified from sequencing or targeted mutation analysis, deletion/duplication analysis can be considered.”
- “In families where a deleterious variant has been identified, predictive genetic testing may be considered in close family members…Genetic testing of asymptomatic family members in a family without an identifiable mutation is uninformative.”
- “Genetic testing may be indicated in a child with diagnosed or suspected pancreatitis…Predictive genetic testing for asymptomatic patients less than 16 years of age is not recommended and does not have clear benefits.”

2017 Expert Authored Review

A 2017 expert authored review on pediatric acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) concluded:[18]

- “The search for a genetic cause of ARP or CP should include a sweat chloride test (even if newborn screening for cystic fibrosis (CF) is negative) and PRSS1 gene mutation testing. Genetic testing for CF should be considered if a sweat test is unable to be performed.” (Strong consensus, definitely yes, 1A)
- “Mutation analysis of the genes SPINK1, CFTR and CTRC may identify risk factors for ARP or CP.” (Strong consensus, definitely yes, 1B)

2020 Expert Authored Review

A 2020 expert-authored review on pancreatitis recommended molecular genetic testing in a proband with pancreatitis and at least of one of the following:[1]

- “An unexplained documented episode of acute pancreatitis in childhood”
- “Recurrent acute attacks of pancreatitis of unknown cause”
- “Chronic pancreatitis of unknown cause, particularly with onset before age 35 years without a history of heavy alcohol use (>5 drinks per day)”

- "A history of at least one relative with recurrent acute pancreatitis, chronic pancreatitis of unknown cause, or childhood pancreatitis of unknown cause"
- PRSS1 sequencing is recommended, followed by deletion/duplication analysis if sequencing is negative. Alternatively, a multi-gene panel that includes PRSS1, SPINK1, CFTR, and CTRC may be appropriate.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for hereditary pancreatitis genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Human Platelet and Red Blood Cell Antigen Genotyping

MOL.TS.361.A
v1.0.2026

Molecular testing of red blood cell or human platelet antigens in individuals to determine alloimmunization status or risk is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
BLOODchip® ID CORE XT	0084U
Gene analysis (Human Platelet Antigen 1) for common variant	81105
Gene analysis (Human Platelet Antigen 2) for common variant	81106
Gene analysis (Human Platelet Antigen 3) for common variant	81107
Gene analysis (Human Platelet Antigen 4) for common variant	81108
Gene analysis (Human Platelet Antigen 5) for common variant	81109
Gene analysis (Human Platelet Antigen 6) for common variant	81110
Gene analysis (Human Platelet Antigen 9) for common variant	81111
Gene analysis (Human Platelet Antigen 15) for common variant	81112
Fetal RHD genotyping using maternal plasma (e.g. SensiGene)	81403

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Procedure addressed by this guideline	Procedure code
Navigator ABO Blood Group NGS	0221U
Navigator ABO Sequencing	0180U
Navigator CO Sequencing	0181U
Navigator CROM Sequencing	0182U
Navigator DI Sequencing	0183U
Navigator DO Sequencing	0184U
Navigator FUT1 Sequencing	0185U
Navigator FUT2 Sequencing	0186U
Navigator FY Sequencing	0187U
Navigator GE Sequencing	0188U
Navigator GYPA Sequencing	0189U
Navigator GYPB Sequencing	0190U
Navigator IN Sequencing	0191U
Navigator JK Sequencing	0192U
Navigator JR Sequencing	0193U
Navigator KEL Sequencing	0194U
Navigator KLF Sequencing	0195U
Navigator LU Sequencing	0196U
Navigator LW Sequencing	0197U
Navigator Rh Blood Group NGS	0222U
Navigator RHD/C/E Sequencing	0198U
Navigator SC Sequencing	0199U
Navigator XK Sequencing	0200U
Navigator YT Sequencing	0201U
PreciseType HEA Test	0001U
PrecisionBlood Red Cell Antigen Genotyping	0246U
Prenatal Detect RhD	0536U

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Procedure addressed by this guideline	Procedure code
RBC antigen analysis	81479
RHD Deletion analysis	81403
Rh Test (Natera)	0494U
UNITY Fetal Antigen NIPT	0488U
Versiti Red Cell Genotyping Panel	0282U

Criteria

Requests for molecular testing for tissue antigen typing are reviewed using the following criteria.

Human Platelet Antigen (HPA) Genotyping

Testing for human platelet antigens through molecular genotyping is medically necessary for individuals with clinical indications as outlined here.

- Member has at least one of the following:
  - Post-transfusion purpura 5-10 days after a blood transfusion, or
  - Suspected Neonatal Alloimmune Thrombocytopenia (NAIT)/ Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT) based on clinical presentation during pregnancy or neonatal period, or
  - Pregnancy or newborn with suspected or diagnosed NAIT/FNAIT, or
  - Female partner had a previous child with NAIT/FNAIT and is known to be alloimmunized, or
  - Fetus with suspected NAIT/FNAIT based on clinical presentation (ie: intracranial bleeding on ultrasound), and fetal diagnostic testing is medically necessary, or
  - Previous child with NAIT/FNAIT and there is a risk for this disorder in a current pregnancy based on parental HPA genotypes, and prenatal risk assessment is desired, or
  - Platelet refractoriness despite receiving HLA matched platelets, or
  - Platelet refractoriness in the context of being unable to find compatible platelets for transfusion, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other considerations

Targeted HPA genotyping is not medically necessary when assessed as part of a pharmacogenomics or coagulopathy workup.

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The procedure codes billed for HPA genotyping (including, but not limited to ITGB3 and ITGA2B) are not medically necessary outside of those indications outlined above, including for use in pharmacogenomics panels or to assess other cardiovascular disease states.

For information on pharmacogenomics panels, please refer to the guideline *Pharmacogenomic Testing for Drug Toxicity and Response*.

Red Blood Cell (RBC) Antigen Genotyping

Testing for red blood cell antigens through molecular genotyping is considered medically necessary when the member has a documented risk for red blood cell alloimmunization as outlined here.

- One of the following criteria must be met:
  - Member has weak D antigen on serology, or
  - Member is pregnant and has erythrocyte antibodies identified, or
  - Member is the parent of a pregnancy or newborn suspected of having or at risk for Hemolytic Disease of the Fetus and Newborn (HDFN), or
  - Pregnancy or newborn is suspected of having or at risk for Hemolytic Disease of the Fetus and Newborn (HDFN), or
  - Member has warm autoantibodies, or
  - Member is receiving certain monoclonal antibody therapies (such as anti CD38 therapy), or
  - Member has a blood disorder requiring frequent transfusions (such as sickle cell disease, some forms of thalassemia, autoimmune hemolytic anemia, or myelodysplasia), or
  - Member has a result from a traditional serology (hemagglutination) assay that is not consistent with the antibody that they are expressing, or
  - Member has evidence of an antigen that cannot be detected, or is not easily detected, by traditional hemagglutination (including the Dombrock antigen, complex Rh phenotypes, Fy silencing mutations, and MNS system mutations), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other considerations

Although most genotyping tests should only be performed once per lifetime, it may be medically necessary to repeat RBC antigen genotyping in some individuals. These requests will be reviewed on a case by case basis.

Fetal RHD Genotyping Using Maternal Plasma

Fetal RHD genotyping using cell free fetal DNA in maternal plasma is medically necessary when the following criteria are met:

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- Member is currently pregnant and has antibodies to Rh (D) (is alloimmunized), AND
- Genotyping on the father of the current pregnancy, if performed, shows heterozygosity for RHD, AND
- Member has declined amniocentesis for the purpose of genotyping fetal amniocytes for RHD, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

For all other indications, fetal HPA or RBC genotyping using maternal plasma is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

Genotyping is reimbursable once per lifetime.

- When prenatal cell-free DNA testing for RBC antigen genotype is otherwise reimbursable, no more than one prenatal cell-free DNA test is reimbursable per pregnancy, defined as no more than one paid prenatal cell-free RhD procedure code within 10 weeks.

Targeted HPA genotyping (CPT codes 81105-81112) is not reimbursable as part of a pharmacogenomics workup. The following criteria are used to determine if targeted HPA genotyping is being performed as part of a pharmacogenomics workup:

- When billed on the same date of service with any pharmacogenomic testing procedure code (for more details, please refer to the guideline *Pharmacogenomic Testing for Drug Toxicity and Response*).

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What are tissue antigens?

An antigen is a substance (protein, sugar, or lipid) that is on the surface of a cell. Red blood cell antigens are on the surface of red blood cells (RBC), while human platelet antigens (HPA) are on the surface of platelets.

Individuals can be exposed to red blood cell or human platelet antigens that they do not have on their cells through blood transfusion or pregnancy. Once exposed, they may become alloimmunized to these antigens and mount an immune response to them if they are presented again (e.g., during future transfusions).[1,2]

If subsequent antigen exposure occurs during pregnancy, the fetus/newborn is at risk for serious disease.

- Red Blood Cell Antigens: Fetuses and newborns of alloimmunized mothers are at risk for developing Hemolytic Disease of the Fetus and Newborn (HDFN). Symptoms include high output cardiac failure and kernicterus.[3,4]
- Human Platelet Antigens: Fetuses and newborns of alloimmunized mothers are at risk for developing Fetal and Neonatal Alloimmune Thrombocytopenia. (FNAIT). Symptoms include thrombocytopenia and intracranial, gastrointestinal, or genitourinary hemorrhage.[5,6] Unlike HDFN, FNAIT can occur in a first pregnancy.[5,6]

Test information

Laboratory work-up of alloimmunization may include serology (antibody and/or antigen analysis) and molecular analysis.

Human Platelet Antigen (HPA) Genotyping

Molecular testing for human platelet antigens is typically performed in specialized reference laboratories via laboratory developed tests. Testing typically consists of targeted genotyping for specific, well-described gene variants.

Red Blood Cell (RBC) Antigen Genotyping

Molecular testing for red blood cell antigens is typically performed in specialized reference laboratories via laboratory developed tests, but RBC antigen panels may also be performed on FDA-approved instrument platforms. Testing may consist of targeted genotyping for specific gene variants, gene sequencing, or deletion analysis.

Analysis of cell-free placental DNA in maternal plasma (non-invasive prenatal screening, or NIPS) can be used to assess fetal genotype for some red blood cell antigens.

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Table: Selected Red Blood Cell Antigens and Corresponding Genes

RBC antigen names, abbreviations, and genes

Red Blood Cell Blood Group Name	Antigen Abbreviation	Gene
RH	RHD/C/E	RHCE / RHD
ABO	ABO	ABO
Colton	CO	AQP1
Cromer	CROM	CD55
Diego	DI	SLC4A1
Dombrock	DO	ART4
H	FUT1	FUT1
Se	FUT2	FUT2
Duffy	FY	ACKR1
Gerbich	GE	GYPC
MN	GYPA	GYPA
Ss	GYPB	GYPB
Indian	I	CD44
Kidd	JK	SLC14A1
Junior	JR	ABCG2
Kell	KEL	KEL
Lutheran inhibitor	KLF	KLF1

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Red Blood Cell Blood Group Name	Antigen Abbreviation	Gene
Lutheran	LU	BCAM
Landsteiner-Wiener	LW	ICAM4
Scianna	SC	ERMAP
Kell (X-linked)	XK	XK
YT	YT	ACHE
Knops	KN	CR1
Vel	Vel	SMIM1

Guidelines and evidence

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2018) Practice Bulletin 192 Management of Alloimmunization During Pregnancy made the following recommendations after maternal antibodies are identified:[3]

- "The initial management of a pregnancy involving an alloimmunized patient is determination of the paternal erythrocyte antigen status."
- "The fetal genotype should be assessed when the paternal genotype is thought to be heterozygous or is unknown."

A clinical practice update to this bulletin (ACOG, 2024) stated the following regarding recommendations after maternal antibodies are identified:[7]

- "Paternal RHD zygosity testing using genotypic analysis is recommended for Rh-D alloimmunization risk assessment. It may be reasonable to defer or discontinue fetal surveillance for anemia in the setting of paternal genotyping that is RHD homozygous negative."
- "Because cfDNA testing possesses performance characteristics that appear comparable with those of molecular testing, while avoiding the rare complications and costs associated with diagnostic genetic testing, it is reasonable to use it as an alternative tool for fetal RHD testing among alloimmunized patients with potentially at-risk pregnancies who decline amniocentesis."

- "Cell-free DNA for the assessment of selected non–Rh-D red blood cell antigens may be considered for pregnant patients declining amniocentesis, after weighing cost, access, and the encouraging-yet-limited data supporting its use."

An ACOG Practice Advisory (2024) regarding recommendations in settings where triage of Rho(D) immune globulin (RhIg) is required stated:[8]

- "Although current ACOG guidance does not recommend routine use of noninvasive prenatal testing (NIPT) to determine fetal Rh(D) status based on cost-effectiveness analyses, the use of NIPT to prioritize use of RhIg and conserve RhIg supply is a reasonable consideration in the practice setting that is experiencing RhIg shortages."
- "Noninvasive fetal red blood cell antigen genotyping utilizing cell-free DNA (cfDNA) isolated from maternal plasma has demonstrated high sensitivity and specificity for detection of fetal Rh(D) antigen status."
- "If cfDNA testing results confirm an Rh(D)-negative fetus, RhIg would not need to be routinely administered in the antepartum period (for bleeding, abortion, pregnancy loss, or at 28 weeks of gestation)."

ACOG Practice Bulletin 181 Prevention of Rh D Alloimmunization (2017) stated:[4]

- "All pregnant women should be tested at the time of the first prenatal visit for ABO blood group and the Rh D type and screened for the presence of erythrocyte antibodies."
- "If Rh D antibodies are present because of sensitization, anti-D immune globulin is not beneficial, and management should proceed in accordance with protocols for Rh D-alloimmunized pregnancies."
- "If paternity is certain and the father is known to be Rh D negative, antenatal prophylaxis is unnecessary."
- "Despite the improved accuracies noted with noninvasive fetal RHD genotyping, cost comparisons with current routine prophylaxis of anti-D Immunoglobulin at 28 weeks of gestation have not shown a consistent benefit and, thus, this test is not routinely recommended."

Regarding maternal weak D phenotype on serology, ACOG Bulletin 181 (2017) stated:[4]

- "An attractive solution to this problem [maternal weak D phenotype] is to perform molecular genetic RHD typing in weak D phenotype individuals as suggested by the Work Group on RHD Genotyping."
- "Clinicians are advised to administer Rh D immune globulin to patients with weak D blood type in appropriate clinical situations, by the same rationale as that for Rh D typing blood donors, until further scientific and economic studies are available."

In a clinical practice update to Practice Bulletin 181, ACOG (2024) stated:[9]

- "For patients at less than 12 0/7 weeks of gestation who are undergoing abortion (managed with uterine aspiration or medication) or experiencing pregnancy loss (spontaneous or managed with uterine aspiration or medication: ACOG suggests forgoing routine Rh testing and RhIg prophylaxis."

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- ACOG recommends Rh testing in individuals with unknown Rh status and RhIg administration in individuals known to be Rh-negative when pregnancy loss occurs at 12 weeks or later.

American Society of Hematology

The American Society of Hematology (ASH, 2020) stated the following in their guidelines for transfusion support for sickle cell disease:[1]

- "The ASH guideline panel *recommends* prophylactic red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens over only ABO/RhD matching for patients with SCD (all genotypes) receiving transfusions (strong recommendation based on moderate certainty in the evidence about effects)."
- "The ASH guideline panel *suggests* an extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients with SCD (all genotypes) at the earliest opportunity (optimally before the first transfusion) (conditional recommendation based on very low certainty in the evidence about effects)."
- "Extended red cell antigen matching (Jk^a, Jk^b, Fy^a, Fy^b, S/s) may provide further protection from alloimmunization."

In a 2014 Mini Review, the ASH stated:[2]

- "One to two percent of all patients who receive transfusions develop antibodies to RBC antigens."
- Between 10 and 30% of patients receiving chronic transfusions are alloimmunized, typically before the 15^{th} transfusion.
- "Once alloimmunization occurs, the likelihood of additional antibody responses is also relatively high. In surgical, pregnant, and non–hematologic malignancy patients, once RBC antibodies have been induced, 20 percent to 25 percent of patients form additional antibodies after subsequent transfusions and thus become multiply alloimmunized."
- In this review, ASH lists the following scenarios in which red blood cell antigen genotyping may be helpful:
  - Hemoglobinopathy patients at baseline,
  - Alloimmunized patients who are expected to need additional transfusions,
  - Alloimmunized patients with a co-existing autoantibody,
  - Patients who have been recently transfused,
  - Prenatal diagnosis in pregnancies at risk for hemolytic disease of the newborn.

Regarding platelet refractoriness, ASH (2020) recommended ordering HLA/HPA antibody screening tests and either platelet crossmatching or HLA/HPA matched platelets in individuals with thrombocytopenia, repeated poor response to platelet transfusion, and HLA/HPA antibodies.[10]

British Society for Haematology

A British Society for Haematology (BSH, 2025) guideline for the investigation and management of red cell antibodies in pregnancy stated:[11]

- "It is reasonable to omit paternal testing and proceed directly to foetal genotyping using cell-free foetal DNA (cffDNA), where available, in order to avoid issues of non-paternity or donor eggs where indicated."
- "Non-invasive foetal blood grouping using cell-free foetal DNA (cffDNA) from maternal plasma in alloimmunised pregnancies can be performed forRHD(D),RHCE(c and/or E) orKEL*01(K) with a false negative rate of <1%. These tests should be requested at the gestation advised by the reference laboratory used, by obstetricians or foetal medicine specialists who can explain the implications of the test findings having undertaken testing at the appropriate gestation."
- "Fetal RHD typing using a high-throughput methodology in pregnant women who have not formed anti-D, as part of a screening program to target anti-D Ig prophylaxis, is sufficiently accurate for implementation from 11#weeks' gestation."

A BSH (2017; updated 20024) guideline on red cell transfusion in sickle cell disease stated:[12]

- "An extended phenotype (or genotype) including C, c, E, e, K, k, Jka, Jkb, Fya, Fyb, S, s should be performed on all patients at baseline. If the patient is S- s-, then U typing should be performed (Milkins et al, 2013). If the patient has not been transfused within 3 months then this can be undertaken serologically, otherwise the genotype needs determination by molecular techniques (Chou & Westhoff, 2011; Milkins et al, 2013) through an appropriate reference laboratory."
- "Select ABO extended Rh and K matched units negative for the relevant antigen(s) to which there are current or historical antibodies."
- "If the identity of the new alloantibody is in doubt despite further specialist testing, consider providing extended antigen matched blood (if serological phenotyping cannot be used because of the presence of transfused donor red blood cells, the sample should be sent to an appropriate reference laboratory for molecular red cell genotyping)."

A BSH (2017; updated 2022) guideline on the use of platelet transfusions stated:[13]

- Post-transfusion purpura (PTP) is "a rare condition associated with severe thrombocytopenia following blood transfusion and caused by antibodies against platelet-specific antigens. Bleeding can be serious and fatal". The condition usually occurs 5-10 days after transfusion.
- "Management is based on individual case reports and case series."
- "Current practice is to transfuse high dose intravenous immunoglobulin without waiting for the results of laboratory investigations, with random donor platelets reserved to control severe bleeding."

A BSH (2021) guideline on the management of sickle cell disease in pregnancy stated:[14]

- "If transfusion is needed, pregnant women with SCD should be given ABO-compatible, extended Rh- and Kell-matched, CMV-negative units. If there are clinically significant red cell antibodies (current or historical) then the red cells selected should be negative for the corresponding antigens (1C)."

Canadian National Committee Advisory Committee on Blood and Blood Products

The Canadian National Advisory Committee on Blood and Blood Products (NAC, 2022) statement on RHD genotyping in prenatal patients stated:[15]

- "Prenatal patients with discrepant, weak or inconclusive serological RhD test results should be further investigated with RHD genotyping to determine RhIg candidacy and optimal red blood cell RhD type for transfusion."

The NAC (2024) statement on RBC genotyping stated:[16]

- RBC genotyping may be helpful in facilitating optimal RBC matching to avoid alloimmunization, or to select the safest RBC units for transfusion in patients who are already alloimmunized.
- RBC genotyping should be considered in the following scenarios:
  - Individuals with sickle cell disease
  - Complicated antibody investigations: "suspected antibodies against high prevalence or low prevalence antigens, where absence of the antigen from the patient's red cells cannot be confirmed owing to lack of commercially available antisera"
  - Pregnant individuals: "complicated antibody investigations (for example, "private antibodies" i.e., reactivity to paternal red cells but without known specificity"
  - Fetal testing: "complicated prenatal antibody investigations may benefit from fetal and/or paternal genotyping"
- RBC genotyping may be helpful in the following scenarios:
  - Individuals with hemoglobinopathies: "hemoglobinopathy patients who cannot be phenotyped owing to recent RBC transfusion"
  - Individuals in whom alloantibodies cannot be excluded and phenotyping is unavailable or impractical:
    - "Receiving monoclonal antibodies such as daratumumab or isatuximab who demonstrate panreactive screens/panels and in whom treatment of reagent red cells with DTT is unsuccessful or not feasible"
    - "With autoantibodies in whom advanced techniques (autoadsorption/ alloadsorption) are not feasible or are unsuccessful"
  - Individuals at increased risk of forming RBC alloantibodies when phenotyping is unavailable or not /practical
    - "Patients receiving chronic RBC transfusion and patients who have demonstrated a marked propensity to form RBC alloantibodies. In these

patients, provision of antigen-matched RBC units may be used to prevent (further) alloimmunization and genotyping results may facilitate unit selection"
        - "To resolve serologic discrepancies (most often observed in the context of the D antigen), and thus prevent alloimmunozation"
    - Individuals receiving allogeneic stem cell transplantation who have pre-existing antibodies: "for the donor in addition to the patient on a case-by-case basis"
- RBC genotyping is not recommended in the following scenarios:
    - "Uncomplicated antibody investigation"
    - "Post hematopoetic stem cell transplantation without full engraftment"

College of American Pathologists and AABB

A College of American Pathologists (CAP) and AABB Work Group on RHD Genotyping (2015) made the following recommendation regarding genotyping individuals with a weak D phenotype on serology:[17]

- "The Work Group recommends that RHD genotyping be performed whenever a discordant RhD typing result and/or a serological weak D phenotype is detected in patients, including pregnant women, newborns and potential transfusion recipients. It is anticipated that the immediate benefit will be fewer unnecessary injections of RhIG and increased availability of RhD-negative RBCs for transfusion."

The AABB reiterated on their website:[18]

- "RHD genotyping is recommended whenever a weak D phenotype is detected by routine Rh blood typing of pregnant women and other females of childbearing potential. The Work Group rates this as strong recommendation, based on high-quality evidence from observational studies (1A)."

International Collaboration for Transfusion Medicine

The International Collaboration for Transfusion Medicine Guidelines (ICTMG, 2019) guideline on fetal and neonatal alloimmune thrombocytopenia stated:[19]

- "If there is clinical suspicion of fetal and neonatal alloimmune thrombocytopenia (FNAIT), manage as FNAIT without waiting for laboratory confirmation (moderate evidence, strong recommendation)."
- "Fetal HPA typing, preferably using non-invasive methods, if adequately quality assured, should be performed during pregnancy when the father is unknown, unavailable for testing or heterozygous for the implicated antigen (moderate evidence, strong recommendation)."
- "Antenatal IVIG administration to the mother, commencing at 12–16 weeks gestation, should be offered to all women in a subsequent pregnancy with maternal fetal incompatibility who have had a previous fetus or neonate with FNAIT-related ICH (very low evidence, strong recommendation)."

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Newborn Services Clinical Guideline: Auckland District Health Board

The Auckland, New Zealand District Health Board points to the Starship Child Health (2019) clinical management guideline on neonatal alloimmune thrombocytopenia, which stated the following regarding FNAIT:[5]

- "Neonatal Alloimmune Thrombocytopenia (NAIT) results from maternal human platelet antibodies (HPA) against fetal platelet antigens inherited from the father. In contrast to rhesus haemolytic disease, platelet allo-immunization can occur during the first pregnancy."
- "Definitive diagnosis of NAIT depends on parental testing."
- Maternal and paternal genotyping is recommended in this clinical guideline. If paternity is uncertain or no paternal sample is available, fetal genotyping is recommended.

Royal College of Obstetricians and Gynaecologists

The Royal College of Obstetricians and Gynaecologists (RCOG, 2019) guideline addressing pregnancies at risk for alloimmune thrombocytopenia stated:[20]

- There is no evidence to support routine screening for pregnancies at risk of FNAIT (Fetal and Neonatal Alloimmune Thrombocytopenia).
- "IVIg in pregnancy is safe and likely to be effective. It seems reasonable to start therapy at 16–18 weeks of gestation in an at-risk pregnancy."

The RCOG (2024) guideline addressing haemolytic disease of the fetus and newborn (HDFN) and current antenatal screening and testing stated:[21]

- "D negative women are screened for fetal RhD status via non-invasive prenatal testing (NIPT); whereby cell-free fetal DNA present in maternal blood is analysed for the fetal RHD genotype. Accuracy of this test has been validated by numerous studies and approved by NICE."
- "Non-invasive fetal genotyping by cffDNA can be performed on maternal blood to determine the risk of HDFN by assessing for antigens for D, e, E, c, C and K. This test has high sensitivity and specificity. RhD, c, e, C, and E can be detected with good sensitivity after 11#weeks' gestation. Regarding Kell, genotyping can occur after 20 weeks in UK practice due to the risk of false negative results if performed earlier."
- "If cffDNA NIPT is not available it may be useful to undertake paternal genotyping to determine if the father is homozygous or heterozygous; if the father is homozygous then the parents can be informed that all pregnancies will be at risk of HDFN. However this approach is limited by the potential for non-paternity."

Selected Relevant Publications

Multiple review articles have addressed human platelet antigen genotyping, specifically with regard to Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT).

A review by Winklehorst and colleagues (2017) stated:[22]

- "When FNAIT is suspected, or in case of a family member with FNAIT, diagnostic work-up should ideally include HPA genotyping of mother, father, and child to establish possible HPA incompatibilities, as well as serological testing (maternal–paternal serum crossmatch, and a maternal platelet antibody screening)."
- "If, in case of suspicion due to an affected family member, after the HPA-typing, the pregnant woman turns out to be HPA-1a negative, the HPA-1a type of father and, in case of paternal heterozygosity, consequently fetus can be determined."
- "Adequate diagnosis does not only contribute to adequate management in the index cases, but is just as important for taking adequate measures in subsequent pregnancies to prevent bleeding complications."
- "When the father is homozygous, every consecutive pregnancy is incompatible and therefore the fetus is at risk. When the father is heterozygous, fetal genotyping has to be performed."

A review by Mella and colleagues (2015) stated:[23]

- "Approximately 80% of pregnancies affected by NAIT have maternal antibodies that are directed against platelet antigen HPA-1a with the remaining 20% being affected by the other HPA types. Studies have shown that approximately 98% of Caucasian women express HPA-1a (genotype HPA-1a/HPA-1a or HPA1a/HPA1b) and about 2% of Caucasian women are HPA-1a negative (genotype HPA-1b/HPA-1b). The second most common platelet antigen causing NAIT in Caucasians is HPA-5b antigen, followed by HPA-1b and HPA-15."
- "In at-risk pregnancies, mothers are antigen negative (most commonly HPA-1b) and fathers are either antigen-positive homozygous (genotype HPA-1a/1a) or heterozygous (genotype HPA-1a/1b)."
- "If the parental genotypes are different and the mother has specific antibodies to the putative antigen, then the pregnancy is at risk for NAIT and fetal/neonatal antigen typing would then be indicated."

A review by Peterson and colleagues (2013) stated:[24]

- "Some have argued that it may be cost-effective to perform such screening routinely and offer special case management to the 10% of HPA-1a-negative women who produce antibody (Husebekk et al, 2009) but at the present time this is not practiced in the absence of a family history of NAIT, e.g., in a sister."
- "A first affected neonate with NAIT in a family is normally identified when clinical signs of bleeding are evident at or shortly after birth and a platelet count confirms isolated thrombocytopenia."

Platelet Refractoriness

A review by Stanworth et al. (2015) stated the following regarding platelet refractoriness:[25]

- "If there are poor responses to HLA-selected platelet transfusions, the reasons should be sought including poor HLA compatibility of the selected product, non-immune platelet consumption and HPA and ABO incompatibility."
- "Depending on the results of these investigations, the appropriate management could be the use of ABO-identical or HPA-selected platelet concentrates if the specificity of the HPA anti-bodies can be identified."

Fetal Red Blood Cell Antigen Genotyping Using Maternal Plasma

Overall, there is moderate quality evidence that the diagnostic accuracy of fetal RhD genotyping is high after 11 weeks gestation in nonalloimmunized women with singleton pregnancies. There is a paucity of evidence evaluating alloimmunized women and women with multiple pregnancies.[26-30] Moderate quality evidence suggests fetal RhD genotyping may lead to reductions in unnecessary anti-D therapy in nonalloimmunized women. Very low quality evidence suggests fetal RhD genotyping for guiding targeted anti-D therapy may reduce the number of alloimmunization events in nonalloimmunized women. Very low quality evidence suggests fetal RhD genotyping may lead to reductions in unnecessary monitoring and invasive procedures in alloimmunized women. There is a paucity of evidence evaluating the effects of fetal RhD genotyping on patient health outcomes, such as fetal morbidity/mortality or maternal quality of life.

There is low quality, limited evidence that suggests noninvasive fetal RhCE and fetal Kell genotyping have high diagnostic accuracy in alloimmunized and non-alloimmunized women.[29-31] To better understand the use of noninvasive fetal genotyping for non-RhD antigens, clinical utility studies that assess patient-relevant health outcomes and clinical decision making, including assessment of test performance in diverse ethnic groups and multigestational pregnancies, are needed.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for human platelet and red blood cell antigen genotyping will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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Inherited Bone Marrow Failure Syndrome (IBMFS) Testing

MOL.TS.360.A
v1.0.2026

Introduction

Inherited bone marrow failure syndrome (IBMFS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
IBMFS multigene panel [inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2]	81441
IBMFS multigene panel	81479

Criteria

Introduction

This guideline applies to inherited bone marrow failure syndrome (IBMFS) multi-gene panels, which are defined as assays that simultaneously test for more than one inherited bone marrow failure gene. Requests for this testing are reviewed using the following criteria.

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IBMFS Multigene Panel

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous testing of the requested genes, and
  - No known IBMFS pathogenic variant in the family or
  - If there is a known IBMFS pathogenic variant in the family, testing has been performed and is negative, and a diagnosis of IBMFS is still suspected, AND
- The member has or is suspected to have a condition that will benefit from information provided by the requested IBMFS gene testing based on at least one of the following:
  - The member meets all criteria in a test-specific guideline, if available, or
  - The following criteria are met:
    - The member displays clinical features of the condition for which testing is being requested:
      - unexplained chronic cytopenia with or without associated congenital physical anomalies consistent with the condition, or
      - sporadic aplastic anemia, or
      - myelodysplastic syndrome, or
      - lack of cytopenias but classic physical findings, cancer diagnosis, or family history, and
    - Acquired etiologies have been considered and ruled out when possible (e.g., immune-mediated or viral), and
    - Predicted impact on health outcomes, including immediate impact on medical management based on the molecular results, and
    - Family and medical history do not point to a specific genetic diagnosis or pattern of inheritance for which a more focused test or panel would be appropriate, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Note:

An alternative sample, such as DNA from a skin biopsy, may need to be considered in a patient with MDS/AML and/or when there is concern for somatic reversion events.

Other Considerations

This guideline may not apply to genetic testing for indications that are addressed in test-specific guidelines. Please see the test-specific list of guidelines for a complete list of test-specific panel guidelines.

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Table: Select Inherited Bone Marrow Failure Syndromes

Within the broader spectrum of bone marrow failure conditions, myelodysplastic syndrome (MDS) is a heterogeneous group of disorders characterized by dysplastic changes in the bone marrow, cytopenias, and an increased risk of developing acute myeloid leukemia (AML). MDS is primarily a sporadic disease that occurs in older individuals, but inherited forms have been described. Familial MDS disorders are typically inherited in an autosomal dominant manner but all inheritance patterns have been described.[1-3] They may only present with hematologic findings and can be caused by many of the genes listed in the table below (not an all-inclusive list).

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Congenital amegakary-ocytic thrombo-cytopenia (CAMT)[4,5]	Isolated thrombocytopenia due to ineffective megakaryocyto-poiesis at birth, with elevated plasma thrombopoietin (TPO) levels. Progression to pancytopenia/ aplastic anemia will occur in the majority of affected individuals. Individuals are at risk to develop MDS and AML. Genotype-phenotype correlations exist and individuals with type I variants have earlier progression to bone marrow failure than those with type II.	N/A	Identification of mutations in MPL.	AR

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Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Diamond-Blackfan anemia (DBA)[6,7]	Classic: characterized by profound normochromic and typically macrocytic anemia. Elevated erythrocyte adenosine deaminase (eADA) activity levels are elevated in the majority of individuals with DBA. 90% of affected individuals will experience red cell aplasia within the first year of life. Other individuals have very mild anemia, requiring no treatment. There is an increased risk to develop AML, MDS, and solid tumors such as osteosarcoma.	Congenital malformations in up to 50% of individuals with DBA including upper limb and hand malformations, craniofacial anomalies, and congenital heart disease; 30% will have growth retardation.	DBA is suspected in individuals who meet the following diagnostic criteria: • Onset <1 year of age • Macrocytic anemia with no other significant cytopenias • Reticulocytopenia • Normal marrow cellularity with a paucity of erythroid precursors • No evidence of another acquired or inherited disorder of bone marrow function DBA is caused by a mutation in one of the following genes: GATA1, RPL5, RPL9, RPL11, RPL15, RPL18, RPL26, RPL27, RPL31, RPL35, RPL35A, RPS7, RPS10, RPS15A, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS29, TSR2. In up to 20% of affected individuals,	Usually AD GATA1- and TSR2-related DBA are XL

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
			the molecular cause is unknown.	

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Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Dyskeratosis Congenita and Related Telomere Biology Disorders (DC/TBD) 8-12	At increased risk for BMF, MDS, AML, and solid tumors.	Classic DC: Classic triad of nail dysplasia, lacy reticular pigmentation of the upper chest/ and or back, and oral leukoplakia. Phenotypic spectrum of TBD is broad and can also include: IUGR, cerebellar hypoplasia, immunodeficiency, retinopathy, eye abnormalities, dental abnormalities, developmental delay, short stature, microcephaly, gastrointestinal features such as liver fibrosis and genitourinary anomalies. Pulmonary fibrosis is the most common presentation of a telomere biology disorder and may be the only symptom in adults.	Identification of a mutation or mutations in one of the following genes: ACD, CTC1, DKC1, NAF1, NHP2, NOP10, PARN, POT1, RPA1, RTEL1, STN1, TERC, TERT, TINF2, WRAP53, and ZCCHC8. Approximately 80% of individuals with a clinical diagnosis are found to have a mutation in an associated gene.	AD, AR, and XL.

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Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Fanconi Anemia (FA)[13,14]	At increased risk for progressive BMF with pancytopenia, usually in first decade, often initially with thrombocytopenia or leukopenia, increased risk for AML, MDS, and solid tumors (particularly of the head and neck, skin and genitourinary tract). Carriers of a subset of FA-related genes (e.g., BRCA2, PALB2, and BRIP1) have an increased risk for breast and other cancers.	Physical features are present in ~75% of individuals. These include: short stature, abnormal skin pigmentation, skeletal malformations of the upper and/or lower limbs (especially thumbs), microcephaly, ophthalmic anomalies, genitourinary tract anomalies, gastrointestinal anomalies (such as tracheoesopha-geal fistula), heart anomalies, otology anomalies and facial features (such as triangular face micrognathia, mid-face hypoplasia).	Increased chromosome breakage and radial forms on cytogenetic testing of lymphocytes with diepoxybutane (DEB) and mitomycin C (MMC) and/ or molecular diagnosis. Fanconi Anemia is caused by a mutation or mutations in one of the following genes: BRCA1 (FANCS), BRCA2 (FANCD1), BRIP1 (FANCJ), ERCC4 (FANCQ) FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG (XRCC9), FANCI, FANCL, FANCM, PALB2 (FANCN), RAD51 (FANCR), RAD51C (FANCO), REV7 (MAD2L2/FANCV), RFWD3 (FANCW), SLX4 (FANCP), UBE2T (FANCT), XRCC2 (FANCU).	Usually AR AD (RAD51 gene) and XL (FANCB gene) cases have been reported.

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
GATA2 defic-iency[15-17]	Cytopenias, myelodysplasia. Individuals have an increased risk to develop MDS and leukemias, such as AML and chronic myelomonocytic leukemia (CMML). Bone marrow is typically hypocellular with characteristic features including atypical megakaryocytes, ranging from large abnormal forms with separated nuclear lobes (osteoclast-like), to smaller forms with separated nuclear lobes, micromegakary-ocytes, to small hypolobated or mononuclear megakaryocytes. The majority of pediatric individuals who develop MDS will have monosomy 7 on bone marrow karyotype or fluorescence in situ hybridization (FISH).	Viral and bacterial infections, pulmonary alveolar proteinosis and lymphedema.	Identification of a mutation in GATA2. "GATA2 mutations have been found in up to 10% of those with congenital neutropenia and/or aplastic anemia."[15]	AD

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
SAMD9-related MIRAGE and SAMD9L-ATXPC syn-drome[18-21]	SAMD9L: variable hematologic cytopenias, and predisposition to marrow failure, myelodysplasia, and myeloid leukemia, sometimes associated with monosomy 7 in bone marrow specimen biopsy. SAMD9: Myelodysplastic syndrome and/or acute myelogenous leukemia (AML) with monosomy 7. Monosomy 7 may be transient if the clone is small, or it may persist for years before transformation to AML. These syndromes are likely underdiagnosed due to a common occurrence of genetic reversion to restore hematopoiesis.	SAMD9L: cerebellar ataxia SAMD9: MIRAGE (myelodyplasia, infection, restriction of growth, adrenal hyperplasia, genital phenotypes, and enteropathy) syndrome. Moderate-to-severe developmental delay is reported in most affected individuals. Autonomic dysfunction and renal dysfunction are also reported.	Identification of a mutation in SAMD9L or SAMD9.	AD

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Severe congenital neutropenia (SCN) [22-24]	A "chronic state of severe neutropenia associated with a neutrophil count less than 500/uL lasting longer than 3 months, often presenting in the first year of life."[22] At increased risk of MDS and AML.	Severe/recurrent infections, abscesses, omphalitis, oropharyngeal inflammation, cervical adenopathy, and osteopenia. With G6PC3 mutation, developmental anomalies of the cardiac and genitourinary systems are possible.	Identification of a mutation or mutations in one of the following genes: HAX1, ELANE, AK2, GFI1, CSF3R, WAS, JAGN1, G6PC3.	AD, AR, and XL.
Shwachman-diamond syndrome (SDS)[25-27]	Single or multi-lineage cytopenias. At increased risk for MDS and AML.	Exocrine pancreatic dysfunction with gastrointestinal malabsorption, malnutrition, and growth failure.	Diagnosis can be established when exocrine pancreatic dysfunction and bone marrow dysfunction are present. Identification of mutation or mutations in one of the following genes: SBDS, EFL1, DNAJC21, SRP54.	Usually AR. Some AD (SRP54 gene) cases have been reported.

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Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Hematologic neoplasms associated with germline pre-disposition without a constitution-al disorder affecting multiple organs[3,28,29]	Germline mutations in DDX41 and TP53 can predispose to myeloid (AML, MDS) or lymphoid neoplasms. Germline mutations in CEBPA predispose to myeloid neoplasms. Germline mutations in PAX5 or IKZF1 predispose to B-lymphoblastic leukemia (B-ALL).	N/A	Identification of a mutation in DDX41, TP53, CEBPA, PAX5 or IKZF1.	AD

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Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Hematologic neoplasms with germline predis-position associated with constitu-tional platelet dis-order[3,28,29]	Germline RUNX1 alterations can predispose to lymphoid (T-ALL, B-ALL, mature B-cell lymphomas) or myeloid (familial platelet disorder with associated myeloid malignancy – FPDMM) disorders, the latter most commonly MDS, AML, or CMML. Germline mutations in ANKRD26 lead to familial thrombocytopenia and predispose to MDS and AML. Germline alterations in the ETV6 gene predispose to both myeloid and lymphoid neoplasms including B-ALL, MDS, AML, CMML, and plasma cell myeloma. Non-hematologic neoplasms are also reported including colorectal and breast cancers.	N/A	Identification of a mutation in RUNX1, ANKRD26 or ETV6.	AD

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Germline RAS activating mutations[3]	Neurofibromatosis type 1 (germline alterations in NF1 gene), CBL syndrome (germline mutations in CBL), and Noonan syndrome (germline mutations in PTPN11, KRAS, NRAS, or RIT1) are associated with juvenile myelomonocytic leukemia (JMML) or JMML-like neoplasms.	Syndrome-specific features may be present.	Identification of a mutation in NF1, CBL, PTPN11, KRAS, NRAS or RIT1.	AD

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81441*).
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

For general coding requirements, please refer to the guideline *Laboratory Billing and Reimbursement*.

What are inherited bone marrow failure syndromes?

Bone marrow failure (BMF) is the inability of the bone marrow to produce a sufficient quantity of functional blood cells to meet physiologic demands.[22] BMF is typically classified into three categories, based on presumed etiology: inherited, secondary, or idiopathic.[22] Inherited bone marrow failure syndromes (IBMFSs) are a group of genetically defined disorders that are characterized by BMF. Individuals presenting with aplastic anemia (AA), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and chronic unexplained cytopenias should be evaluated for an IBMFS.[22]

Incidence

"The incidence of inherited bone marrow failures accounts for 10% to 15% of marrow aplasia and 30% of pediatric bone marrow failure disorders, with approximately 65 cases per million live births every year."[30] Seventy-five percent of children with an IBMFS have an identifiable cause.[31]

Symptoms

While specific features may vary by each type of IBMFS, features that are present in most IBMFSs include bone marrow failure with single or multi-lineage cytopenia. Many individuals have an increased risk to develop aplastic anemia (AA), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and solid malignancies.[22,31]

IBMFSs typically present with specific patterns of cytopenias, and an individual with an IBMFS may have congenital anomalies and other characteristic physical features or health issues.[22]

Phenotypic overlap between IBMFSs makes it difficult to establish a diagnosis based solely on clinical features.[31]

IBMFSs typically present within the first decade of life; however, delay in diagnosis and variability in phenotypic spectrum may lead to diagnosis into adulthood.[31]

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Cause

"A wide variety of specific syndromes have been described so far with more than 80 different genes associated to IBMFSs. Based on the inheritance patterns of IBMFSs in multiplex families and the segregation of mutated alleles in known IBMFS genes of phenotypically affected family members, the disorders are considered monogenic in the vast majority of patients." [32]

Inheritance

IBMFSs may be inherited in an autosomal dominant (AD), autosomal recessive (AR), or X-linked (XL) manner, depending on the gene involved.

Diagnosis

The diagnosis and classification of an IBMFS requires a combination of clinical, family history, physical examination, laboratory, and bone marrow findings in addition to specialized testing, such as molecular diagnostics. [33]

Timely genetic testing is essential to establish a diagnosis in the individual and to guide appropriate management, treatment, and cancer surveillance.[31] Additionally, knowing the genetic cause in the individual allows for genetic testing in family members. This information is important for their own health and a critical part of their workup if they are being considered as a possible bone marrow transplant donor.

The risk of development of cancers differs greatly between the various IBMFSs, and identification of the underlying etiology of marrow failure is imperative to assess the need for and type of cancer screening.[12]

Treatment

Treatment of IBMFSs varies depending on the specific type, but typically involves supportive care, including blood and/or specific blood cell transfusions, and in severe situations, hematopoietic stem cell transplants (HSCTs).

Survival

The survival range of IBMFSs varies across the multiple conditions included in this group. Survival is impacted by disease severity, response to initial therapy, and the age at the time of initial transplant. The overall survival for individuals with an IBMFS is also significantly impacted by the development of MDS, with disease progression occurring 4.7 months from the time of MDS diagnosis.[34]

Note:

For additional information on specific IBMFSs, their causes and common presentations and symptoms, see the Table: *Select Inherited Bone Marrow Failure Syndromes* in this document.

Test information

Introduction

The investigation and diagnosis of individuals with IBMFSs necessitates a combination of laboratory analyses (including complete blood counts with differential, telomere length studies, exocrine pancreatic function studies, bone marrow analysis, and cytogenetic studies), along with clinical assessment and genetic testing.[22] Clinical genetic testing is available for many IBMFSs, via known familial mutation analysis, single gene analysis and/or multi-gene panels.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to inherited bone marrow failure syndrome genetic testing. Although there are no current U.S. guidelines that address the use of multigene panels in IBMFSs, there are published guidelines for a subset of IBMFSs.

Fanconi Anemia

The Fanconi Anemia Research Fund Inc. (FARF, 2023) established expert guidelines for diagnosis and management of Fanconi Anemia (FA) which stated:[13]

- "The chromosome breakage test is the first test that should be performed for an individual suspected of having FA. This assay is performed in a clinical cytogenetics laboratory, often using a sample of the patient's peripheral blood. Peripheral blood

is treated with diepoxybutane (DEB), a DNA crosslinking agent. Mitomycin C (MMC) is another crosslinking agent commonly used for this assay, although it may lead to a higher rate of false positives than DEB. Following exposure of peripheral blood cells to these DNA damaging agents, the chromosomes are examined for evidence of chromosomal damage. Cells from individuals without FA will have relatively few chromosome breaks or rearrangements. In contrast, cells from patients with FA will exhibit multiple chromosome breaks and rearrangements per cell, including complex rearrangements such as radial figures, which are the hallmark abnormality of this disease."

- "If the results from the chromosome breakage test are positive, genetic testing should be performed to identify the specific FA-causing variants. Genetic testing enables accurate diagnosis and improves clinical care for individuals anticipated with genotype/phenotype manifestations and for relatives who are heterozygous carriers of FA gene variants that confer an increased risk of malignancy."
- Recommendations for follow-up testing are made based on the results of the chromosome breakage studies:
  - Negative: No further testing for FA unless strong clinical suspicion. If the suspicion for FA is high, chromosome breakage studies on fibroblasts should be performed due to the possibility of somatic mosaicism. If negative, patients should undergo evaluation by clinical genetics to identify any additional genetic testing that may be indicated.
  - Positive: Genetic counseling for discussion of targeted FA gene panel and deletion/duplication analysis.
  - Equivocal:
    - Next-generation sequencing for other chromosome instability/DNA repair syndromes
    - Skin fibroblast chromosome breakage study (if not already performed)

Shwachman-Diamond Syndrome

Draft consensus guidelines for the diagnosis and treatment of Shwachman-Diamond Syndrome (SDS, 2011) stated:[35]

- “The clinical diagnosis is established by (a) documenting evidence of characteristic exocrine pancreatic dysfunction and hematological abnormalities and (b) excluding known causes of exocrine pancreatic dysfunction and bone marrow failure. Attention should be given to ruling out cystic fibrosis (the most common cause of pancreatic insufficiency) with a sweat chloride test, Pearson disease (pancreatic insufficiency and cytopenia, marrow ring sideroblasts and vacuolated erythroid and myeloid precursors), cartilage hair hypoplasia (diarrhea and cytopenia, and metaphyseal chondrodysplasia, and more common in certain isolated populations such as the Amish), and other inherited bone marrow failure syndromes (such as dyskeratosis congenita)."

- “As the clinical diagnosis of SDS is usually difficult and patients may present at a stage when no clinical pancreatic insufficiency is evident, it is advisable to test most or all suspected cases for mutations in the SBDS gene. It is noteworthy that about 10% of patients with clinical features of SDS may be negative for mutations, and that de novo SBDS mutations have been identified in some families."

Telomere Biology Disorders

Guidelines for diagnosis and management of telomere biology disorders (TBD) were published by expert authors in consultation with a medical advisory board in 2022:[8]

- "The first step in testing for a suspected TBD is to assess the telomere length in specific subtypes of white blood cells."
- "If all or nearly all of the white blood cells' telomere lengths ... are determined to be very short (less than 1% length for their age), the test result is consistent with diagnosis of TBD. However, it is possible that not all individuals with a TBD will have all very short telomeres."
- "Once an individual has been identified to have clinical features and/or telomere lengths that are consistent with or suggestive of a TBD, genetic testing is recommended for TBD-associated genes to try to identify a causative gene variant."

Selected Relevant Publications

An expert-authored review (2017) stated the following regarding IBMFSs:[22]

- “Genetic testing is an indispensable tool in the diagnostic evaluation of IBMFSs that complements traditional clinical history, examination, and laboratory evaluation, especially in the setting of overlapping or adult presentations. However, clinical use of this powerful tool is currently limited by cost or access in most places."
- "In addition, even when genetic testing is available, it may fail to provide the correct diagnosis." This is because not all genes that cause IBMFS have been identified, many rare variants in known IBMFS genes cannot currently be classified as disease causing, or ... "in the event of somatic reversion, the genetic variant or variants that cause a patient's IBMFS may not be detectable in peripheral blood cells."
- "Now and likely well into the future, the sum of all available tools is greater than any alone, and a modern IBMFS workup should include a focused history and physical examination, screening tests, and genetic evaluation whenever possible."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for inherited bone marrow failure syndrome (IBMFS) testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the

condition, but have non-standard features, will not receive an immediate approval for testing.

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Inflammatory Bowel Disease Biomarker Testing

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Biomarker testing for inflammatory bowel disease (IBD) is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
Crohn's Prognostic	81401, 83520, 86021, 86255
IBD sgi Diagnostic	81479, 82397, 83520, 86140, 86255, 88346, 88350
PredictSURE IBD	0203U

Criteria

Requests for testing of blood or other body fluids in the evaluation and management of inflammatory bowel disease are reviewed using the following criteria. Please note that this guideline does not address anatomic pathology examinations of gastrointestinal biopsies, imaging by any modality, or other assessments of the intestinal tract.

IBD sgi Diagnostic

CPT 81479, 82397, 83520, 86140, 86255, 88346, 88350

Medical necessity requirements

This testing is considered experimental, investigational, or unproven.

Crohn's Prognostic

CPT 81401, 83520, 86021, 86255

Medical necessity requirements

This testing is considered experimental, investigational, or unproven.

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PredictSURE IBD

CPT 0203U

Medical necessity requirements

The clinical utility of PredictSURE IBD in the setting of inflammatory bowel disease (evaluation, diagnosis, monitoring) has not been demonstrated. This testing is considered experimental, investigational, or unproven.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

PredictSURE IBD

CPT 0203U

PredictSURE IBD testing is not reimbursable.

What is inflammatory bowel disease?

Inflammatory bowel disease (IBD) is a chronic, idiopathic, lifelong inflammatory disease of the gastrointestinal tract, characterized by recurrent episodes of abdominal pain, weight loss, diarrhea, and bloody stools.[1]

The two main forms of IBD are Crohn's disease and ulcerative colitis. These two entities are distinguished by their clinical, radiographic, endoscopic, and pathological features. This distinction may, in some cases, be challenging; however, an accurate diagnosis is critical in determining prognosis and therapy. Crohn's disease usually involves the terminal ileum, cecum, perianal region, and colon in a discontinuous pattern, whereas ulcerative colitis involves the rectum and either part of or the entire colon in a continuous fashion.[1] Histologically, these two entities are differentiated by the degree of intestinal involvement. Crohn's disease characteristically displays transmural inflammation with a granulomatous component, fissures, ulceration, and perforation leading to strictures and fibrosis; Ulcerative colitis is typically limited to the mucosa and submucosa, with cryptitis, crypt abscesses, and crypt architectural distortion.

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As many as 50% of individuals with inflammatory bowel disease will experience an extra-intestinal manifestation of their disease, which may occur before the onset of the primary illness.[2] A myriad of extra-intestinal manifestations (EIM) may occur, and includes uveitis, primary sclerosing cholangitis, and ankylosing spondylitis, among others. The risk of developing an EIM is higher in Crohn's disease than in ulcerative colitis, and increases with the duration of the primary disease.

An additional critical relationship of long-standing IBD is the increased risk for colorectal carcinoma, necessitating endoscopic surveillance for the early detection of mucosal dysplasia.[3] The incidence of colorectal cancer is approximately 18% after 30 years of colitis, but studies have demonstrated a decreasing risk with improved therapy and surveillance.[3] Hence, laboratory testing, as a component of care, may be critical in the accurate diagnosis of IBD, therapeutic monitoring, assessment of disease activity, and cancer surveillance.

Endoscopy has played a fundamental role in the diagnosis, management, and treatment of inflammatory bowel disease, and in cancer surveillance of individuals with IBD.[4] Laboratory testing, as a component of care, may also be critical for obtaining an accurate diagnosis of IBD. Many laboratory tests have been developed as potential aids in the diagnosis and management of inflammatory disorders, including inflammatory bowel disease. Non-invasive testing for the evaluation of inflammatory bowel disease has not replaced common parameters derived from endoscopic, radiologic, and histopathologic evaluations. However, research in inflammatory bowel disease has uncovered several potential serologic and genetic markers for clinical use. These include inflammatory biomarkers, mediators of tissue damage, and antibodies to commensal gut organisms.

Advances in endoscopy and therapy have led to an evolution in disease management for both ulcerative colitis and Crohn's disease.[5,6] Clinical guidelines recommend that treatment decisions be based on several levels of care, including patient reported outcomes and inflammatory burden, the latter which may be assessed by endoscopy and markers of inflammation.[5,6] Laboratory testing is used in the therapeutic monitoring, assessment of disease activity, and cancer surveillance for individuals with IBD.

Test Information

Testing for inflammatory bowel disease may include serologic or biomarker testing.

The laboratory tests discussed in this guideline have proposed roles in the diagnosis and management of inflammatory bowel disease. Some of the tests described have established roles in the diagnosis or monitoring of other disorders. This guideline does not address anatomic pathology examinations of gastrointestinal biopsies, imaging by any modality, or other assessments of the intestinal tract.

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

Anti-neutrophil cytoplasmic antibodies are detected by immunofluorescence using ethanol-fixed neutrophils. The cytoplasmic ANCA (cANCA) pattern is represented by a pattern of granular cytoplasmic fluorescence, whereas the peripheral-ANCA (p-ANCA) pattern is perinuclear. ANCA are often detected in individuals with autoimmune vasculitis. P-ANCA may be observed in those with IBD.

Anti-Saccharomyces cerevisiae IgG and IgA (ASCA)

ASCA antibodies are detected by enzyme-linked immunosorbent assay or enzyme immunoassay (EIA). ASCA may be found in individuals with inflammatory bowel disease.

Anti-OmpC Antibody

Anti-OmpC antibody is directed against the outer membrane porin of *Escherichia coli*, and is detected by enzyme-linked immunosorbent assay (ELISA). It may be found in some individuals with IBD.

Cytolethal Distending Toxin B Antibody and Vinculin Antibody

These antibodies, detected by ELISA, may be found in individuals with irritable bowel syndrome (IBS). The tests are proposed as an aid in distinguishing IBS from IBD.

Serum Mannose-Binding Lectin

Mannose-binding lectin is an immune component that binds to mannose residues on a variety of microorganisms, triggering the complement pathway and resulting in opsonization. Mannose-binding protein is also an acute phase reactant. Abnormal mannose-binding protein concentrations have been found in individuals with infectious disorders such as tuberculosis, hepatitis B, and in autoimmune disorders.

Proteinase-3 Antibody

Proteinase-3 is a 29-kD serine protease that exists in neutrophils. Antibodies to proteinase-3 may be detected in individuals with Wegener's Granulomatosis. Proteinase-3 antibody (IgG) is detected by enzyme immunoassay or a multiplex assay using microspheres coated with proteinase-3 antigen, with subsequent antibody detection by laser photometry.

Serum Amyloid A (SAA)

Serum amyloid A has been proposed as a possible biomarker to evaluate mucosal healing in Crohn's disease. SAA may be measured by latex agglutination and ELISA, and has been a component of a multiplex vascular injury panel.

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CBir1 (Flagellin-Like Antigen) Antibody

CBir1 is a flagella component of indigenous bacteria in a mouse colitis model.[7] Anti-CBir1 antibody is detected by ELISA, and may be found in individuals with inflammatory bowel disease, non-IBD colitis, and ankylosing spondylitis.

I2 Antibody

This antibody is directed against *Pseudomonas fluorescens* – associated sequence I2, and may be detected in individuals with IBD and non-IBD colitis. It is detected by ELISA.

Anti-Glycan Antibodies: Anti-Chitobioside Antibody (ACCA), Anti-Laminaribioside Antibody (ALCA), Anti-Mannobioside Antibody (AMCA)

Anti-glycan antibodies are reactive against cell wall components of microorganisms. Anti-glycan antibodies are measured using enzyme immunoassay. They have been proposed as aids in the diagnosis of inflammatory bowel disease, and in the differential diagnosis of Crohn's disease and ulcerative colitis.

Pyruvate Kinase M2 (PKM2)

Serum PKM2 is measured by ELISA. Elevated levels of PKM2 have been detected in individuals with IBD.

IBD sgi Diagnostic™

This commercial proprietary assay combines serologic, genetic, and inflammatory biomarkers in a testing algorithm as an aid in differentiating IBD from IBS, and ulcerative colitis from Crohn's disease. The test includes 9 serological markers including anti-Fla-X, anti-A4-Fla2, anti-CBir1, anti-OMPC, and DNAse-sensitive pANCA, genetic evaluation of ATG16L1, STAT3, NKX2-3, and ECM1. Inflammatory markers include VEGF, ICAM, VCAM, CRP, and SAA.

Crohn's Prognostic™

This commercial proprietary assay combines serologic testing (anti-CBir1, anti-OMPC, DNAse sensitive pANCA) and genetic markers (NOD2 variants SNPs 8,12,13) and employs an algorithm to quantify the probability of disease complications over time.

Crohn's Monitr™

This commercial proprietary assay tests for 13 biomarkers (hsCRP, SAA, carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM 1), vascular cell adhesion molecule 1 (VCAM 1), interleukin-7, transforming growth factor-alpha, angiopoietin 1 and 2, matrix metalloproteinase 1 (MMP 1), MMP 2, MMP 3, MMP 9,

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and extracellular matrix metalloproteinase inducer (EMMPRIN)) and uses a proprietary algorithm to assess the severity of disease.

Fecal Calprotectin

Calprotectin is a calcium and zinc binding protein present in the cytoplasm of granulocytes. There are several commercial, Food and Drug Administration (FDA)-cleared or automated immunoassay assays available to quantify human fecal calprotectin. The methodologies include enzyme linked immunoassays (ELISA), chemiluminescence immunoassays (CLIA), fluoroenzyme immunoassays (FEIA), and particle-enhanced turbidimetric immunoassays (PETIA).[8] Automated immunoassays for measuring fecal calprotectin, and point-of-care tests, are available commercially. Fecal calprotectin's proposed use is as an aid in identifying gastrointestinal disease, assess disease activity, and to monitor treatment.

Fecal Lactoferrin

Fecal lactoferrin is an iron-binding glycoprotein that is a major component of secondary granules in neutrophils. It is detected by ELISA.

PredictSURE IBD

The PredictSURE IBD test is a reverse-transcriptase quantitative polymerase chain reaction performed on whole blood of untreated IBD patients, evaluating expression of 15 informative genes and 2 reference genes. The CD8 T cell gene expression signature generated is analyzed by a proprietary algorithm, which aims to predict which IBD patients will have a more aggressive disease course.

Guidelines and Evidence

General Considerations

American College of Gastroenterology

The American College of Gastroenterology (ACG, 2018), in its guideline for the management of Crohn's disease in adults, stated:[6]

- "Because of the heterogeneous nature of IBD there has been extensive research directed toward finding immunologic markers that would assist in disease diagnosis. These studies have focused on antibodies to microbial antigens and autoantibodies…"
- "Routine use of serologic markers of IBD to establish the diagnosis of Crohn's disease is not indicated."

Similarly, in its guideline for the management of ulcerative colitis (UC), the American College of Gastroenterology (ACG, 2019) recommended against the use of serologic markers for the diagnosis and monitoring of UC:[5]

- "We recommend against serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence)" and "We recommend against serologic antibody testing to determine the prognosis of UC (strong recommendation, very low quality of evidence)."

American Gastroenterological Association

Guidelines on biomarker use in the setting of IBD by the American Gastroenterological Association (AGA, 2023) stated conditional recommendations only for select biomarkers (fecal lactoferrin, fecal calprotectin, C-reactive protein) with a certainty of evidence graded from very low to moderate.[9,10]

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN, 2012) recommended against routine use of serologic assays for diagnosing children with ulcerative colitis (UC) or Crohn's disease (CD):[11]

- "Although a number of serologic assays are commercially available to assist physicians in screening their patients for suspected UC or CD, these commercially available serologic assays may fail to detect CD in at least 30% of children with this disorder and may wrongly suggest a diagnosis of IBD that is not supported by subsequent and more definitive (endoscopic study) testing. As such, it may be most prudent for primary care providers to avoid ordering these tests and instead pursue referral and more conclusive specialty testing."

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

Anti-neutrophil cytoplasmic antibodies are classified according to staining pattern: cytoplasmic (c-ANCA) and perinuclear (p-ANCA). In inflammatory bowel disease, p-ANCA may be detected, and the antigen is thought to be histone 1, and a possible cross-reactant to antigens present in gut flora. p-ANCA is detected in 60-70% of ulcerative colitis cases, 10-15% of Crohn’s disease cases, and less than 5% of non-IBD colitis cases.[7]

American College of Gastroenterology

In its guideline for the management of ulcerative colitis (UC), the American College of Gastroenterology (ACG, 2019) stated:[5]

- "Serologic markers such as perinuclear antineutrophil cytoplasmic antibodies (pANCAs) may be found in up to 70% of patients with UC, and combination of negative anti–Saccharomyces cerevisiae antibodies with elevated pANCA levels has been proposed to facilitate establishing a diagnosis of UC. However,

the pooled sensitivity of antibody testing for diagnosis of UC is low, and such markers are not used for establishing or ruling out a diagnosis of UC. Although pANCA positivity has also been associated with treatment refractory UC, the evidence supporting this is limited, and there is currently no role for such testing to determine the likelihood of disease evolution and prognosis."

Selected Relevant Publications

A 2020 international consensus paper by Moiseev and colleagues assessed the use of ANCA testing for a variety of inflammatory conditions. While the test was considered mandatory for ANCA-associated vasculitis (AAV), anti-glomerular basement membrane disease (Goodpasture's disease), and idiopathic interstitial pneumonia, routine testing was not recommended for IBD:[12]

- "Atypical P-ANCA and ASCA may aid in discriminating UC from CD in case of diagnostic uncertainty. PR3-ANCA, as detected by CLIA, may be a sensitive and specific biomarker for UC. Routine testing of the serological profile for diagnosis or for predicting the course or response to treatment cannot be recommended."

In individuals with an established diagnosis of IBD, an Australian retrospective cross-sectional study demonstrated the presence of ANCA in a high percentage of participants, but ANCA did not add value in disease subtyping.[13] Other retrospective studies demonstrated that p-ANCA may be detected more often in individuals with an established diagnosis of ulcerative colitis than in those with Crohn's disease or indeterminate colitis.[14,15] However, ANCA testing in the evaluation of IBD had low sensitivity.[16]

Proteinase-3 Antibody

Studies demonstrated that proteinase-3 antibodies are more often detected in ulcerative colitis than in Crohn’s disease, however the utility of the test in managing IBD is yet to be established. In a retrospective study using a chemiluminescence assay, antibody to proteinase-3 had a sensitivity of 52.1% for ulcerative colitis.[14] In one study, proteinase-3 antibody levels were higher in individuals with ulcerative colitis, but the test demonstrated moderately poor sensitivity.[17] Similar results were found in other studies.[18,19] In a retrospective cohort study, anti-proteinase 3 was also found to be specific for ulcerative colitis in children, but with similar sensitivity (58%) as in adults.[15]

The utility of proteinase-3 antibody testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Serum Amyloid A (SAA)

Serum amyloid A (SAA) has been proposed to be a more sensitive biomarker of inflammation compared to CRP.[20] In cross-sectional studies of Crohn’s disease, high

SAA levels correlated with a lack of mucosal healing or disease progression.[20,21] In another study, SAA was moderately correlated (r=0.64 and 0.42) with clinical indices of Crohn's disease activity.[22] In studies of individuals with ulcerative colitis in clinical remission, SAA correlated better (r=0.61) with the Mayo Endoscopic Score than CRP (r=0.35), but yielded only marginally better sensitivity, or was found not to be superior to fecal calprotectin.[23,24]

The utility of serum amyloid A testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Anti-Saccharomyces cerevisiae IgG and IgA (ASCA)

The presence of antibodies to the baker's yeast Saccharomyces cerevisiae (ASCA) has been posited as a marker for Crohn's disease and inflammatory bowel disease (IBD).[25]

ASCA may be detected in approximately 60-70% of individuals with Crohn's disease, 10-15% of individuals with ulcerative colitis, and less than 5% of those with non-IBD colitis.[7] However, the ASCA test has not emerged as a recommended test in any clinical presentation. It remains speculative that ASCA antibodies are associated with the development of IBD.[26]

There are reports of ASCA testing being used in conjunction with perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) testing in the context of IBD and Crohn's disease. According to one report, the combination of a positive ASCA test with a negative p-ANCA test had a positive predictive value of 96% and a specificity of 97% for Crohn's disease.[27] It is important to note that both p-ANCA and ASCA antibodies are found in other diseases, such as autoimmune liver disease, primary sclerosing cholangitis and gluten-sensitive enteropathy. Therefore, their role as diagnostic serological markers for IBD is limited.

One frequently cited study concerning ASCA as a marker concluded that ASCA (and p-ANCA) antibodies likely precede the clinical diagnosis of IBD.[25] If true, the presence of ASCA would not be useful in diagnosing IBD or Crohn's disease but would likely only function as a pre-marker for disease, with presumptive utility only with regard to risk of progression. For these reasons ASCA testing has not become commonplace.

Anti-OmpC Antibody

IgA anti-OmpC antibody was present in approximately 55% of individuals with Crohn's disease, 5-10% of individuals with ulcerative colitis, and up to 36% of those with indeterminate colitis.[7] In a retrospective study of 135 children with IBD, anti-OmpC had a low sensitivity for Crohn's disease and ulcerative colitis.[28] In an observational study of 117 individuals with indeterminate colitis and at least of one-year follow-up after serologic testing, anti-OmpC antibody demonstrated low sensitivity and suboptimal specificity for a subsequent diagnosis of Crohn's disease or ulcerative colitis.[29] A

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separate study of indeterminate colitis found that anti-OmpC antibody contributed marginally to serologic testing for IBD.[30]

In a Chinese study, anti-OmpC antibody was detected in individuals with IBD, as well as in those with gastrointestinal tuberculosis and other gastrointestinal disorders.[31] In another study, anti-OmpC was found in over 15% of normal controls.[32] As an isolated test, anti-OmpC did not appear to have value in the diagnosis of IBD. Serologic markers, including OmpC, were also not a reliable predictor of outcome in ulcerative colitis.[33] Prospective studies are also necessary to determine whether use of anti-OmpC in a multi-marker panel can be used to distinguish ulcerative colitis from Crohn's disease.[32]

One potential clinical application for anti-OmpC antibody is as a biomarker for anti-TNF therapy response in ulcerative colitis. In a retrospective study of 230 individuals with ulcerative colitis, anti-OmpC positivity was associated with a lack of response to infliximab.[34] However, additional studies are necessary to support the use of anti-OmpC testing as a therapeutic guide.

Cytolethal Distending Toxin B Antibody and Vinculin Antibody

Historically, the diagnosis of diarrhea-predominant irritable bowel syndrome (IBS-D) has been a clinical one, resting on characteristic clinical findings (e.g. chronic diarrhea) and exclusion of other etiologies such as inflammatory bowel disease (IBD) and celiac disease. Distinguishing between IBS-D and other causes of diarrhea remains a challenge, due to the broad differential diagnosis and lack of specific biomarkers for many entities, and workup may be extensive and costly.[35]

American Gastroenterological Association

The American Gastroenterological Association (AGA) published evidence-based recommendations on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults. Recommendations varied in strength according to the quality of the clinical evidence. With regard to serologic testing for diagnosis of IBD, and specifically anti-CtdB and anti-vinculin, the recommendations stated, "No recommendation; knowledge gap." The authors continued:[36]

- "The available data are sparse but suggest that the contemporary tests lack the diagnostic accuracy needed for routine use. In addition, the case-control design of the studies and the study setting used (secondary and tertiary care) likely inflate the estimates of the test characteristics compared to what is expected in a general population. The specificity in the 2 studies available for the technical review was in the 90% range, meaning that a positive test would indicate a high likelihood of IBS-D. However, the low sensitivity (20%-40%) would not be sufficient to employ

these tests in routine use. More data will be helpful in determining the proper roles of these and similar tests."

Selected Relevant Publications

Some investigations demonstrated that a subset of IBS-D occurs after an episode of acute infectious gastroenteritis. In rat models of post-infectious IBS, antibodies reactive with the Campylobacter jejuni toxin cytolethal distending toxin B (Cdtb) cross react with the cell adhesion protein vinculin, found in the interstitial cells of Cajal and in myenteric ganglia.[37] Anti-CtdB and anti-vinculin antibodies have been investigated as potential biomarkers for IBS-D.[38]

Several case-control studies investigated the utility of anti-CtdB and anti-vinculin in the diagnosis of IBS-D.[38,39] The studies found that mean anti-CtdB titers appeared higher in individuals with IBS-D than in healthy controls, but with substantial overlap in results between the two populations. In a community study, the difference did not reach significance.[40] In the largest study, with 2375 individuals with IBS, the difference was significant, though the effect size was modest for most participants.[38] The area under the receiver-operator curve for anti-CtdB was 0.81, and at an optimized cutoff, the sensitivity was 92% and the specificity 44%.

Studies of anti-vinculin produced conflicting results. In a community study, there was no significant difference between anti-vinculin titers in healthy individuals and those with IBS-D.[40] In another study, the difference was significant.[38] The latter study also investigated whether anti-CtdB and anti-vinculin could distinguish between IBS-D and IBD or celiac disease. It found that mean anti-CtdB and anti-vinculin titers were not significantly elevated in IBD, but were in celiac disease, indicating that elevated anti-CtdB and anti-vinculin did not distinguish between IBS-D and celiac disease.[38]

Other studies demonstrated that anti-CdtB and anti-vinculin lacked the sensitivity and specificity to discriminate functional GI syndromes.[40-42]

The utility of cytolethal distending toxin B antibody and vinculin antibody testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Serum Mannose-Binding Lectin

There were limited studies evaluating the use of serum mannose-binding lectin (MBL) in the clinical setting. In a study of children with IBD, mannose-binding lectin concentrations were lower in both Crohn's disease and ulcerative colitis, compared to controls.[43] In two adult studies, serum MBL did not appear to be beneficial in the diagnosis of IBD.[44,45] In another study, serum MBL was not associated with disease course or therapeutic response.[46]

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The utility of serum mannose-binding lectin testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

CBir1 (Flagellin-Like Antigen) Antibody

Antibody directed against CBir1 was more prevalent in Crohn's disease than in ulcerative colitis, and was found in approximately 8% of non-IBD colitis cases.[7] In one study assessing the performance of anti-CBir1 as a serologic panel component, anti-CBir1 was detected in 39.5% of individuals with Crohn's disease, and 17.4% of individuals with ulcerative colitis.[32] A similar study also demonstrated low sensitivity of anti-CBir1 for Crohn's disease.[31] In a retrospective cohort study, high levels of anti-Cbir1 IgG were associated with a greater likelihood of active Crohn's disease.[47] A study of ankylosing spondylitis demonstrated that those also having IBD had higher levels of CBir1 antibody compared to those without IBD.[48] In children with IBD, CBir1 antibody may be detected in those negative for other serological markers and in younger individuals, and is more likely to be found in individuals with ulcerative colitis that develop pouchitis.[49-51] In a study of 601 adults with ulcerative colitis, anti-CBir1 antibody was not associated with severe disease, proximal disease extension, or colectomy.[33]

I2 Antibody

I2 IgA antibody was detected in approximately 55% of individuals with Crohn's disease,10% of those with ulcerative colitis, and in 20% of non-IBD colitis cases.[7]

Studies assessing the clinical utility of I2 antibody were limited. In a retrospective cohort study of Crohn's disease, individuals with I2 antibody were more likely to have fibrosing Crohn's disease and to require small bowel surgery.[52] In another study, anti-I2 was associated with a clinical response to fecal diversion in individuals with proctocolitis and perianal disease.[53] In the pediatric population, anti-I2 has low sensitivity and specificity for IBD.[53]

The utility of I2 antibody testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Anti-Glycan Antibodies: Anti-Chitobioside Antibody (ACCA), Anti-Laminaribioside Antibody (ALCA), Anti-Mannobioside Antibody (AMCA)

Anti-glycan antibodies were implicated in the pathogenesis of IBD. Anti-glycan antibodies were detected in up to 30.5% of pediatric Crohn's disease cases, and were present in Crohn's disease cases that are negative for other biomarkers.[54,55]

In one cohort study, anti-glycan antibodies had a greater association with Crohn's disease than with ulcerative colitis.[56] In another cohort study, increasing levels of anti-glycan antibodies in Crohn's disease were associated with disease complications and

the need for surgical intervention.[57] However, anti-glycan antibody testing had limited use because of low sensitivity.[6]

The utility of anti-glycan antibody testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Pyruvate Kinase M2 (PKM2)

There were limited studies of the role of serum PKM2 in the evaluation of IBD. In one study, serum PKM2 levels were six times higher in newly diagnosed IBD, but PKM2 values did not correlate with disease activity indices.[58]

There were not any published studies evaluating the clinical utility of serum PKM2 in the diagnosis or management of individuals with IBD.

IBD sgi Diagnostic

There were not any published independent studies evaluating the utility of IBD sgi Diagnostic in the diagnosis or management of individuals with IBD.

Crohn’s Prognostic

There were not any published independent studies evaluating the utility of Crohn’s Prognostic in the diagnosis or management of individuals with IBD.

Crohn’s Monitr

American Gastroenterological Association

In their guidelines on biomarker use in the setting of Crohn's disease, the American Gastroenterological Association (AGA, 2023) stated the following regarding the Crohn's Monitr test (also called the Endoscopic Healing Index [EHI]):[10]

- "In patients with CD, the AGA suggests neither in favor of nor against the use of EHI (Monitr) for monitoring inflammation and treatment decisions. (No recommendation, Knowledge gap)"
- "In arriving at this recommendation, the guideline panel weighed the performance of the test in the reported validation cohorts against the paucity of independent data....The availability of more generalizable data demonstrating high accuracy from independent data sets in sufficiently heterogenous populations, as well as evidence of its feasibility and cost-effectiveness relative to other widely available tests, would merit reconsideration of the recommendation."

Selected Relevant Publications

One study reported on the development and validation of this test.[59] Blood samples from 278 individuals with Crohn's disease were used to develop the test of 13

proteins, the result of which is reported as an endoscopic healing index (EHI). The test was validated using 2 independent cohorts. Test specificity using the two cohorts was 69% and 36.6% using a cutoff EHI of 20 points, and 100% and 87.8% using a cutoff EHI of 50 points. The AUROC for the test did not differ significantly from that of fecal calprotectin.

There were not any published independent studies evaluating the utility of Crohn's Monitr in the diagnosis or management of individuals with IBD.

Fecal Calprotectin

Fecal calprotectin is a non-invasive marker used with the aim of distinguishing IBD from other intestinal disorders, and for the diagnosis of IBD, monitoring therapeutic response, and determining the need for endoscopy.[60,61]

American College of Gastroenterology

For the evaluation of irritable bowel syndrome (IBS), the American College of Gastroenterology (ACG, 2021) recommended fecal calprotectin "in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease".[62]

American Gastroenterological Association

The American Gastroenterological Association (AGA, 2019) clinical practice guidelines provided a conditional recommendation for fecal calprotectin testing in the evaluation of functional diarrhea and diarrhea-predominant IBS in adults:[36]

- "In patients presenting with chronic diarrhea, the AGA suggests the use of either fecal calprotectin or fecal lactoferrin to screen for IBD. Conditional recommendation; low quality evidence."

In a subsequent guideline, the American Gastroenterological Association (AGA, 2023) provided conditional recommendations for fecal calprotectin testing in the setting of ulcerative colitis, albeit with a low or very low level of evidence.[9]

British Society of Gastroenterology

The British Society of Gastroenterology (BSG, 2019) consensus guidelines stated:[63]

- "We recommend that, for patients aged 16–40 presenting in primary care with chronic diarrhoea and symptoms that may be consistent with either IBD or IBS, faecal calprotectin is a useful screening tool with a high negative predictive value. If significantly elevated, patients should have an infective cause excluded and be referred for further investigation (GRADE: strong recommendation, moderate-quality evidence. Agreement: 97.9%)."

Regarding the use of fecal calprotectin in predicting IBD relapse, the British Society of Gastroenterology (BSG, 2019) guidelines further stated:[63]

- "…more evidence is also needed of the role of faecal calprotectin or other biomarkers as non-invasive surrogates for mucosal healing"
- "We suggest that patients in whom anti-TNF therapy is withdrawn should be observed for evidence of relapse. Monitoring of faecal calprotectin may be helpful in this context as levels may rise before clinical relapse occurs (GRADE: weak recommendation, low-quality evidence. Agreement: 97.9%)."
- "We suggest that patients presenting with features of orofacial granulomatosis (OFG) and gastrointestinal symptoms, raised inflammatory markers or raised faecal calprotectin should have the gastrointestinal tract investigated for inflammation (GRADE: weak recommendation, very low-quality evidence. Agreement: 100%)."
- "We suggest that, in the event of symptomatic recurrence following ileocolonic resection for Crohn's disease, an assessment of mucosal inflammation may be performed with ileocolonoscopy. Faecal calprotectin and/or cross-sectional imaging may be used if ileocolonoscopy is not possible or acceptable, but may not be sensitive enough to detect localised inflammation (GRADE: weak recommendation, low-quality evidence. Agreement: 97.4%)."

European Crohn's and Colitis Organisation and European Society of Gastrointestinal and Abdominal Radiology

An expert joint panel of the European Crohn's and Colitis Organisation (ECCO, 2019) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR, 2019) published comprehensive guidelines for the diagnosis and monitoring of IBD in 2019. Calprotectin studies to assess intestinal inflammation in IBD were discussed:[64]

- "Faecal calprotectin [FC], a neutrophil-derived protein, appears to be the most sensitive marker of intestinal inflammation in IBD…An exact cut-off value that distinguishes between IBD and functional bowel diseases does not exist. However, good diagnostic accuracy can potentially be obtained at a cut-off value of 150 µg/g, as recently suggested in a meta-analysis."

European Society for Paediatric Gastroenterology and Nutrition Gastroenterology

The European Society for Paediatric Gastroenterology and Nutrition Gastroenterology Committee (ESPGAN, 2021) stated:[65]

- "Although faecal calprotectin may be considered as a tool to differentiate functional gastrointestinal disorders from organic diseases, it has not proven its value in this respect apart from identifying possible inflammatory bowel disease within these common clinical presentations… Other than inflammatory bowel disease, the

applicability of faecal calprotectin measurement in gastrointestinal inflammatory and immune-mediated conditions remains to be defined."

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN, 2017), in a clinical report on postoperative recurrence (POR) in pediatric Crohn's disease, reviewed the evidence for fecal calprotectin and concluded:[66]

- "FC has been shown to correlate with endoscopic disease in pediatric inflammatory bowel disease but has not yet been systematically evaluated in the postoperative setting in children with CD. Although pediatric studies are still needed, the growing evidence from the adult trials supports that strong consideration can be given to the use of FC to help monitor for POR in children."

Selected Relevant Publications

Some studies found fecal calprotectin to correlate with endoscopic findings or predict relapse. In individuals with Crohn's disease, fecal calprotectin correlated moderately (r=0.45) with a simple endoscopic score.[67] In a meta-analysis of 8 prospective studies, fecal calprotectin essentially excluded IBD in individuals with irritable bowel syndrome (IBS) symptoms when less than 40 ug/g, however it did not reliably distinguish between IBS and healthy controls, and had a maximum predictive value for IBD of 78.7%.[68] There was also significant heterogeneity among the studies. In a second meta-analysis of cohort and case-control studies, fecal calprotectin yielded a pooled sensitivity of 0.88 and specificity of 0.73 when compared to endoscopy.[61] Similar results were obtained in a meta-analysis of eight pediatric IBD studies.[69]

One systematic review was of six prospective studies that evaluated the usefulness of monitoring fecal calprotectin to predict disease relapse. Although two consecutively increased levels appeared to be the best predictor for relapse, the studies demonstrated significant heterogeneity, and poor consistency with regards to the definition of relapse and the reference standard used. Probabilities of relapse and remission were as high as 83% and 33%, respectively; whether therapeutic decisions or health outcomes were affected was not addressed.[70]

A National Institute for Health Research technology assessment concluded that fecal calprotectin could be a highly sensitive test for detecting IBD, concluding that a negative test result could exclude IBD in most cases.[71] The systematic review included studies predominantly of referral populations, limiting generalizability of the study results. A separate meta-analysis assessed the efficacy of fecal calprotectin as a diagnostic marker for IBD in individuals with gastrointestinal symptoms.[72] The authors concluded that individuals with a fecal calprotectin below the cut-off

level would not need to proceed to colonoscopy. In that meta-analysis, the pooled sensitivity and specificity from 19 studies was 0.882 and 0.799, respectively.

Several studies examined the value of fecal calprotectin in predicting IBD relapse. Depending upon the cutoff value chosen, IBD subtype, time to remission, and study endpoint, sensitivity for relapse ranged from 32% to 100%, and specificity from 24% to 91%.[73] In a single center, retrospective cohort study of individuals with IBD in remission, fecal calprotectin levels at baseline were higher in those that experienced disease relapse, however only close to 50% of the participants underwent endoscopy during the 6-month follow-up period.[74] In a multi-center cohort study, fecal calprotectin levels were again found to be a predictor of relapse following therapeutic de-escalation, however cut-off levels for fecal calprotectin were retrospectively determined, and 35 of 98 (35.7%) of individuals with fecal calprotectin levels < 100 µg/g experienced relapse within 12 months.[75] In a prospective study of Crohn's disease treated with infliximab, fecal calprotectin measurement at 14 weeks could not predict relapse at 1 year.[76] In a prospective observational study, fecal calprotectin of 100 µg/g had a sensitivity of 91.7% and specificity of 57.1% for histologic remission of ulcerative colitis.[77]

Randomized controlled trials examining the role of fecal calprotectin with well-defined cutoff values in predicting IBD relapse may clarify the inconsistencies among prior studies.

The CALM study was a multicenter, randomized, open label controlled phase 3 trial comparing endoscopic and clinical outcomes in moderate to severe Crohn's disease managed with a tight control algorithm that included the use of biomarkers versus clinical management.[78] The study revealed better outcomes in individuals managed by symptoms and biomarker results than by symptoms alone. One limitation of this industry-funded study was that 26% of the participants managed by tight-control and 24% managed by symptoms only discontinued the study; statistical analysis did not account for endpoints of participants that discontinued the study. Treatment failure criteria, not including biomarker values, also were different between the two groups. Exclusion criteria utilizing biomarker values contributed selection bias to the study. The study's design of not blinding investigators and participants to treatment did not establish that fecal calprotectin values were independent from other variables in driving medical management or outcomes. Additional study limitations negatively influenced the significance of the investigators' conclusions.

Studies of fecal calprotectin testing in the post-operative setting produced inconsistent results, and its use in the post-operative setting requires further investigation.[79] Studies examining the use of fecal calprotectin in assessing the presence of pouchitis demonstrated moderately good correlation with endoscopic and clinical findings, but did not establish an impact on management.[60]

Fecal Lactoferrin

Like calprotectin, fecal lactoferrin is a non-invasive biomarker used with the aim of distinguishing IBD from IBS and assessing mucosal healing and disease relapse in IBD.

American Gastroenterological Association

The American Gastroenterological Association (AGA, 2019) clinical practice guidelines provided a conditional recommendation for fecal lactoferrin testing in the evaluation of functional diarrhea and diarrhea-predominant IBS in adults:[36]

- "In patients presenting with chronic diarrhea, the AGA suggests the use of either fecal calprotectin or fecal lactoferrin to screen for IBD. Conditional recommendation; low quality evidence."

In a subsequent guideline, the American Gastroenterological Association (AGA, 2022) similarly provided conditional recommendations for fecal lactoferrin testing in the setting of ulcerative colitis, albeit with a low or very low level of evidence.[9]

Selected Relevant Publications

In a meta-analysis involving both fecal biomarkers, pooled sensitivities and specificities for IBD compared to endoscopy were similar.[61] In a tertiary center study, fecal lactoferrin was significantly higher in individuals with IBD compared to those with IBS and healthy controls.[80] Additional studies demonstrated that the accuracy of fecal lactoferrin was similar to that of fecal calprotectin in distinguishing active IBD from inactive IBD and IBS.[81,82]

The utility of fecal lactoferrin testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing was not established.

PredictSURE IBD

National Institute for Health and Care Excellence

In a technology briefing, the National Institute for Health and Care Excellence (NICE, 2023) stated:[83]

- "…PredictSURE IBD may be a helpful test to determine the most appropriate treatment for people with ulcerative colitis; however, there is limited evidence to support that."

Selected Relevant Publications

The benchmark study for this test was a prospective study of a validation cohort of 123 individuals with active IBD recruited from four United Kingdom hospital based IBD specialty clinics over an 8-year period.[84] Disease activity status was confirmed by serum CRP, calprotectin, or endoscopy. The study did not employ a non-diseased comparison population. Participants identified by the algorithm as having a high

probability of aggressive disease were more likely to receive escalated therapy. The data analysis did not stratify the study population by disease history (new diagnosis vs prior diagnosis) or disease activity indicator (CRP, calprotectin, endoscopic findings).

A similar, earlier study examined the likelihood of therapy escalation in a cohort of 77 individuals with IBD, 52% of which had newly diagnosed disease.[85] Subgroups of participants with CD or UC defined by transcriptional signatures of CD8 positive T cells demonstrated differing proportions requiring therapy escalation, however follow-up was inconsistent among and between groups, and there was no subgroup analysis of those with newly diagnosed disease and those with existing disease.

A separate prospective cohort study of 112 treatment-naïve pediatric IBD patients and 19 healthy controls examined the role of CD8 positive T-cell transcription signatures and DNA methylation in disease activity and outcome. Although there was an association between CD8 positive T-cell gene expression and IBD, there was no association with disease outcome.[86]

In the PROFILE trial, the PredictSURE-IBD assay did not demonstrate clinical utility.[87] The utility of PredictSURE IBD testing in altering therapeutic decisions, reducing disease complications, or reducing the need for more invasive testing has not been established.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for inflammatory bowel disease biomarker testing will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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Legius Syndrome Genetic Testing

MOL.TS.302.A
v1.0.2026

Legius syndrome genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
SPRED1 deletion/duplication analysis	81479
SPRED1 known familial mutation analysis	81403
SPRED1 sequencing	81405

Criteria

Requests for Legius syndrome genetic testing are reviewed using the following criteria.

SPRED1 Known Familial Mutation Analysis

Genetic Counseling:
- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Diagnostic Testing for Symptomatic Individuals:
- No previous genetic testing of SPRED1 that would detect the familial mutation, AND
- SPRED1 mutation identified in 1st degree biological relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

SPRED1 Sequence Analysis

Genetic Counseling:
- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:
- No previous sequencing analysis of SPRED1, AND

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- No known pathogenic SPRED1 mutation in the member's close biologic relatives, AND
- No known pathogenic NF1 mutation in the member or the member's close biologic relatives, AND

Diagnostic Testing for Symptomatic Individuals:

- Member has at least one of the following pigmentary findings suggestive of Legius syndrome:
  - Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals, with or without freckling in the axillary or inguinal regions, or
  - Six or more café-au-lait macules over 15 mm in greatest diameter in postpubertal individuals, with or without freckling in the axillary or inguinal regions, AND
- Member's personal and/or family history are not consistent with neurofibromatosis type 1 (e.g., neurofibromas, optic glioma, Lisch nodules, sphenoid dysplasia or tibial pseudoarthrosis are not present), AND
- The results of the test will directly impact the diagnostic and treatment options that are recommended for the member, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

SPRED1 Deletion/Duplication Analysis

- No previous deletion/duplication analysis of SPRED1, AND
- No mutation detected in full sequencing of SPRED1, AND
- Criteria for SPRED1 sequencing are met, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

What is Legius Syndrome?

Legius syndrome is an inherited disorder characterized by multiple café-au-lait macules and axillary or inguinal freckling, without neurofibromas or other tumor symptoms of Neurofibromatosis type 1 (NF1).[1,2]

Prevalence

The prevalence of Legius syndrome is estimated at 1/46,000 to 1/75,000.[3] Studies have shown that approximately 2% of individuals meeting the diagnostic criteria for NF1 have Legius syndrome.[1]

Symptoms

Individuals with Legius syndrome have multiple café-au-lait macules and may have axillary or inguinal freckling. Other clinical features reported in some individuals with Legius syndrome include macrocephaly, Noonan-like facial features, pectus excavatum

or carinatum, developmental concerns, attention deficit hyperactivity disorder (ADHD), and learning difficulties.[2]

Genetic testing may be indicated in an individual with café-au-lait macules to confirm a diagnosis and direct long-term management and surveillance. Approximately 3%-25% of individuals evaluated for NF1 who do not have an identifiable mutation in the NF1 gene are noted to have a SPRED1 pathogenic mutation.[3] Individuals with NF1 require long-term surveillance due to an increased risk of tumor development and other complications. Thus, the diagnosis of Legius syndrome may include molecular testing of the SPRED1 gene, and in some cases the NF1 gene.

Cause

Legius syndrome is caused by mutations in the SPRED1 gene. The protein product of this gene interacts with neurofibromin, the protein product of the NF1 gene.[2]

SPRED1 sequence mutations, such as missense, nonsense, and splice site mutations, account for up to 89% of mutations seen in Legius syndrome.[3] Approximately 10% of the disease-causing mutations in Legius syndrome are multi-exon and whole gene deletions.[4,5]

Inheritance

Legius syndrome is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

The diagnosis of Legius syndrome can be made in an individual without an affected parent if both of the following are present:[6]

- "Six or more café au lait macules ... bilaterally distributed and no other NF1-related diagnostic criteria except for axillary or inguinal freckling"
- "A heterozygous pathogenic variant in SPRED1 with a variant allele fraction of 50% in apparently normal tissue such as white blood cells"

"A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of Legius syndrome if one or more of the criteria [above] are present."

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Management

Management of Legius syndrome includes therapies for developmental delays, learning disorders, and ADHD, if present.[3]

Survival

Lifespan does not appear to be affected by Legius syndrome. Current knowledge is based on the clinical history of fewer than 300 individuals with a confirmed diagnosis of Legius syndrome.[3,4]

Test Information

Testing for Legius syndrome may include known familial mutation analysis, sequence analysis, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

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Guidelines and evidence

Selected Relevant Publication

A 2020 expert-authored review stated:[3]

- "Opinions differ on the appropriate approach when clinical information and family history cannot distinguish between NF1 and Legius syndrome. This is the case in individuals with only cafe au lait macules with or without freckling but no other signs of NF1. The assessment of pros and cons of molecular testing requires consideration of the circumstances unique to each individual, including (but not limited to) the following:
  - Clinical findings and family history
  - Age of the individual
  - Differences in recommended clinical management when the diagnosis of NF1 or Legius syndrome is established with certainty versus when the diagnosis of neither can be established with confidence
  - Psychological burden of a diagnosis or lack thereof
  - Cost of testing and surveillance
  - Odds of identifying a diagnosis of NF1 versus Legius syndrome in those with a phenotype limited to pigmentary findings."

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Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Legius Syndrome testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Limb-Girdle Muscular Dystrophy Genetic Testing

MOL.TS.288.A
v1.0.2026

Genetic testing for limb-girdle muscular dystrophy (LGMD) is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
LGMD gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
LGMD known familial mutation analysis	81403
LGMD multigene panel	81479 81443

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Criteria

Requests for limb-girdle muscular dystrophy (LGMD) genetic testing are reviewed using the following criteria.

LGMD Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Known family mutation(s) in LGMD subtype related gene in 1st or 2nd degree biologic relative, OR
- Presymptomatic Testing for Asymptomatic Individuals:
  - Age 18 years or older, and
  - At increased risk of developing an LGMD phenotype, and
  - Known family mutation(s) in LGMD subtype related gene in 1st or 2nd degree biologic relative, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

LGMD Single Gene Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No redundant previous LGMD related gene sequencing, and
  - No known LGMD related gene mutation in family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Member displays clinical features of LGMD by the following
    - Muscle weakness and atrophy not secondary to a neurogenic cause in a limb-girdle distribution, and
    - Member does not have a congenital myopathy, and
    - Electromyography (EMG) does not show evidence of a nerve etiology as the primary cause, OR
  - Member has had a muscle biopsy and results are consistent with the LGMD subtype for which testing is being requested, AND
- Inheritance pattern is consistent with the LGMD subtype for which testing is being requested, AND

- The results of the test will directly impact the diagnostic and treatment options that are recommended for the individual, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

LGMD Multi-Gene Diagnostic Panels

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No known molecular cause of LGMD (single disease-causing mutation in dominant forms or biallelic disease-causing mutations in recessive forms) in family, and
  - No mutations or one mutation associated with recessive form of LGMD detected by single gene analysis or different mutation panel than being requested, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Muscle weakness and atrophy not secondary to a neurogenic cause in a limb-girdle distribution, and
  - Member does not have a congenital myopathy, and
  - EMG does not show evidence of a nerve etiology as the primary cause, and
  - Muscle biopsy, if available, shows dystrophic changes (degeneration / regeneration of fibers), and immunohistochemical (IHC) staining may reveal aberrant or absent muscle specific proteins, AND
- Inheritance pattern not suggestive of Duchenne muscular dystrophy or other X-linked muscular dystrophies, AND
- The results of the test will directly impact the diagnostic and treatment options that are recommended for the individual, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

Other considerations

Broad neuromuscular panels are not medically necessary.

If the inheritance pattern in the family is evident based on pedigree analysis, only a panel specific to the inheritance pattern is medically necessary.

If a muscle biopsy has been performed with IHC staining, only genes associated with the findings are considered medically necessary.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate.

Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- For a panel code to be considered for reimbursement, it must be limited to LGMD-associated genes. Broad neuromuscular panels are not reimbursable.
- If the inheritance pattern in the family is evident based on pedigree analysis, a panel code specific to the inheritance pattern will be reimbursable; however, panels of all LGMD genes will not.
- If a muscle biopsy has been performed with IHC staining, only procedure codes for genes associated with the findings will be reimbursable.
- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81479 or 81443*).
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is limb-girdle muscular dystrophy?

Limb-girdle muscular dystrophy (LGMD) is a rare, inherited, heterogeneous group of over 30 myopathies with predominant involvement of the proximal musculature, however, other patterns of weakness are not rare and a single genotypic variety may present with varying patterns of weakness. They are typically progressive myopathies characterized by weakness and atrophy of muscle without primary involvement of the nervous system or neurogenic atrophy. The LGMDs are classified into groups, based on inheritance pattern. Historically, these were denoted as LGMD1 (autosomal dominant) and LGMD2 (autosomal recessive). In 2018, the European Neuromuscular Centre published new nomenclature with the types of LGMD denoted as LGMD D (autosomal dominant) and LGMD R (autosomal recessive) with the subtype denoted with a numeral to categorize the order of discovery, and inclusion of the affected protein, if known.

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'LGMD unclassified' refers to individuals with symptoms consistent with LGMD but with negative genetic testing.[2]

Prevalence

Autosomal recessive LGMD is more common, with an overall prevalence of about 1/15,000.[3] Dominant forms are comparatively rare, representing 10% of LGMD cases.[3] The prevalence of specific LGMD subtypes may differ in certain populations:[1]

- LGMD R5 (previously known as LGMD2C) is more common in Roma and Tunisian populations,[1]
- LGMD R1 (previously known as LGMD2A) is more common in Southern European, Eastern European, and British populations[4], and
- LGMD R9 (previously known as LGMD2I) is more common in Northern European populations.[4]

Symptoms

Signs and symptoms typically begin anytime between childhood and adulthood depending on the subtype but are generally not congenital. Symptoms can include the following:

- Upper and lower limb weakness, proximal greater than distal weakness
- Gait weakness
- Foot drop
- Cramps
- Exercise intolerance

LGMDs are most often non-syndromic and usually limited to skeletal muscle, but not always. For example, certain subtypes involve cardiac and respiratory muscles. The clinical course can range from mild, with relatively normal activity and life span, to severe with rapid onset and progression of disease.[3] Serum creatinine kinase (CK) levels may be normal or elevated depending on subtype and individual. Some subtypes of LGMD have distinguishing features including asymmetrical weakness, limb contractures, proximal muscle cramping, scapular winging, and cardiomyopathy.[1,3]

The muscle atrophy in LGMD is greatest at the shoulder girdle (scapulohumeral) and pelvic girdle (pelvifemoral), although it may progress distally. Bulbar muscles (including facial muscles and oropharyngeal muscles innervated by cranial nerves VII-XII) are relatively spared depending on the subtype of LGMD. This general pattern of girdle muscle weakness as well as onset, progression, and distribution help classify LGMD and its genetic subtypes.

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Cause

There are more than 30 genes implicated in LGMD subtypes, which manifest in overlapping and variable clinical presentations.[3] The genes identified so far encode muscle proteins within the sarcomere-sarcolemma-sarcoplasm-extracellular-matrix network.[5]

Inheritance

LGMD inheritance is typically autosomal with updated LGMD subtype nomenclature reflecting autosomal dominant inheritance (LGMD D with subtypes designated by a numeral), and autosomal recessive inheritance (LGMD R with subtypes designated by a numeral). This autosomal inheritance pattern helps distinguish LGMD from the more common X-linked dystrophies (Duchenne, Becker and Emery-Dreifuss).[2,6] Notably, autosomal recessive subtypes of LGMD tend to have a younger age of onset and more rapid progression on average than autosomal dominant subtypes.[3]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Diagnosis

The diagnosis of muscular dystrophies is typically based on clinical phenotype and inheritance pattern.[5] Although classification schema are becoming more reliant on molecular test results, the 2014 American Academy of Neurology guidelines for LGMD still recommend genetic testing that is directed by clinical assessment.[1]

- The phenotype must be more consistent with LGMD than other myopathies
  - Muscle weakness in the proximal limbs and limb girdle (i.e., scapular winging)
  - Myopathic and not neuropathic symptoms
  - Sparing of extra-ocular muscles (although eye anomalies are seen in some severe allelic disorders)[3]

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  - Onset is not congenital
  - Course is progressive
- Biochemical/histological investigation should suggest muscle damage (although findings can be non-specific)[4]
  - Creatine kinase can be elevated or normal
  - EMG typically shows myopathic rather than neuropathic changes
  - Muscle biopsy shows “dystrophic” changes” (degeneration / regeneration of fibers), and immunohistochemical staining may reveal aberrant or absent muscle specific proteins.
- Dystrophinopathy and inflammatory myopathy should be excluded
- Identification of pathogenic variants in an LGMD-associated gene can confirm a clinical diagnosis of LGMD

Given the expanding number of loci involved in LGMD subtypes, a negative molecular test result does not rule out LGMD. There are more than 50 loci implicated in LGMD subtypes.

When a specific LGMD subtype is clinically favored over another, genetic testing specific to that subgroup is supported over large panels. However, given the number of loci, and phenotypic overlap among the limb girdle muscular dystrophies, panel testing grouped by inheritance pattern is acceptable.

Large deletions in autosomal LGMD related genes are infrequently reported. Therefore, deletion/duplication analysis is done as second tier testing or first tier in some cases to help rule out X linked dystrophies if they are a part of the differential.

Management

LGMD management focuses on multidisciplinary treatment of symptoms. This can include weight control, physical therapy, surgery, use of respiratory aids, and cardiology monitoring.[1]

Survival

LGMDs have a broad range of severity. Many are life shortening and debilitating.[3]

Test information

Testing for LGMD disease may include known familial mutation analysis, next generation sequencing, deletion/duplication analysis, and/or multigene panel testing.

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Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and evidence

American Academy of Neurology and American Association of Neuromuscular and Electrodiagnostic Medicine

The Guideline Development Subcommittee of the American Academy of Neurology (AAN, 2014) and the Practice Issues Review Panel of the American Association of

Neuromuscular and Electrodiagnostic Medicine (AANEM, 2014; reaffirmed 2022) issued recommendations for the approach to genetic testing in LGMD:[1]

- Clinically directed genetic testing is recommended (See Table e-2 for reference of clinical features suggestive of LGMD subtypes).
  - Clinicians should use a clinical phenotype, inheritance pattern, and associated manifestations to guide genetic diagnosis (Level B)
  - "In patients with suspected muscular dystrophy in whom initial clinically directed genetic testing does not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole-genome sequencing, or next-generation sequencing to identify the genetic abnormality (Level C)."

Selected Relevant Publications

Studies evaluating diagnostic yield from small and large panels found both number and composition of genes sequenced have a sizeable impact. A 3-fold greater diagnostic pickup rate was seen when the LGMD panel was increased from 11 genes to a more comprehensive panel containing 41 genes (15 - 46%).[7]

Sequencing of 18 LGMD related genes in 35 individuals suspected of having a muscular dystrophy (unknown genetic diagnosis, high CK values and dystrophic changes on muscle biopsy, DMD ruled out prior to study inclusion) was reported.[8] Pathogenic variants confirmed a LGMD-related molecular etiology in 20 individuals (57.1%).

While some panels are getting so large as to overlap with WES, a comprehensive panel approach has been suggested to be similar or superior to WES.[7,9,10] One study analyzed 50 families with an LGMD type distribution of muscle weakness.[9] They showed that after large LGMD panel testing as a first line diagnostic, follow-up WES did not yield further diagnosis. On the other hand, smaller panels would have missed several LGMD related genes.[9] Weaknesses of this study includes the specialized population investigated and the small sample size, albeit somewhat large for this rare disease. The population was suspected to be highly consanguineous (in Saudi Arabia) which authors suggest led in part to their 76% diagnostic yield.

A US study of 4656 individuals with clinically suspected LGMD (no prior molecular testing) underwent genetic testing via a 35-gene NGS panel (included LGMD or LGMD-like genes).[11] A molecular diagnosis was established in 27% (N=1259). There was a high prevalence of individuals with pathogenic variants in more than one LGMD gene (N=31), raising the question of possible synergistic heterozygosity/digenic/multigenic contribution to disease presentation/progression.

A group in Australia performed exome sequencing (ES) on 60 families with LGMDs and achieved a diagnostic success rate of 45%.[12] All had normal dystrophin immunohistochemistry results. In 14 of the 60 families, pathogenic variants were identified in genes typically associated with other forms of inherited myopathy,

highlighting the diagnostic challenge with overlapping clinical presentation among individuals with features of LGMD. An international study including 1001 undiagnosed individuals from Europe and the Middle East performed exome sequencing, evaluating 429 genes involved in muscle conditions.[13] In this cohort of individuals with limb-girdle weakness, they identified pathogenic or likely pathogenic variants in 87 genes, with a diagnostic yield of 52%.

A US study of 55 families affected by LGMD demonstrated pathogenic variants in 22 families using exome sequencing.[5] Most of the probands had clinical muscle biopsies, and none of the muscle biopsies led to a genetic diagnosis prior to enrollment. "Among the pathogenic mutations identified in our cohort, six were found in loci not traditionally classified as being associated with LMGD (e.g., DMD, GAA, SMCHD1, VCP, FLNC, and the D4Z4 region of 4q35)", suggesting that gene panels include a broad array of muscle disease genes, beyond just LGMD, particularly given the decreasing use of muscle biopsy in clinical settings.[5]

Given the degree of phenotypic overlap among LGMD subtypes, atypical presentations of non-LGMD myopathies, and variable expressivity of LGMD, panel testing may be superior to a candidate gene approach when multiple LGMD subtypes are being considered.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for limb-girdle muscular dystrophy testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

References

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Liquid Biopsy Testing

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Introduction

Liquid biopsy testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
ABL1 mutation analysis	81170
APC sequencing	81201
ASXL1 full gene sequencing	81175
ASXL1 mutation analysis	81176
BRAF V600 targeted mutation analysis	81210
BRCA1/2 sequencing	81163
BRCA1 sequencing	81165
BRCA2 sequencing	81216
CALR exon 9 mutation analysis	81219
Caris Assure	0485U
CCND1/IGH (t(11;14)) translocation analysis, major breakpoint	81168
CEBPA full gene sequencing	81218
EGFR targeted mutation analysis	81235
EZH2 common variant(s) (e.g. codon 646)	81237
EZH2 full gene sequencing	81236

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Procedures addressed by this guideline	Procedure codes
FLT3 mutation analysis (internal tandem duplication variants)	81245
FLT3 mutation analysis (tyrosine kinase domain variants)	81246
FoundationOne Liquid CDx	0239U
Guardant360 CDx	0242U
Guardant360 LDT	0326U
Guardant360 Response	0422U
Hematolymphoid neoplasm molecular profiling; 5-50 genes	81450
IDH1 mutation analysis	81120
IDH2 mutation analysis	81121
IGH@/BCL2 (t(14;18)) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints	81278
InVisionFirst-Lung Liquid Biopsy, Inivata, Inc.	0388U
JAK2 targeted mutation analysis (e.g exons 12 and 13)	81279
JAK2 V617F targeted mutation analysis	81270
KIT D816 targeted mutation analysis	81273
KIT targeted sequence analysis	81272
KRAS exon 2 targeted mutation analysis	81275
KRAS targeted mutation analysis, additional variants	81276
Labcorp Plasma Complete	0585U

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Procedures addressed by this guideline	Procedure codes
LiquidHALLMARK (oncology (solid tumor), DNA (80 genes) and RNA (36 genes), by next-generation sequencing from plasma, including single nucleotide variants, insertions/deletions, copy number alterations, microsatellite instability, and fusions, report showing identified mutations with clinical actionability)	0409U
LiquidHALLMARK (oncology (pan-solid tumor), ctDNA, utilizing plasma, next-generation sequencing (NGS) of 77 genes, 8 fusions, microsatellite instability, and tumor mutation burden, interpretative report for single-nucleotide variants, copy number alterations, with therapy association)	0530U
LiquidHALLMARK ctDNA and ctRNA [Oncology (solid tumor), DNA (80 genes) and RNA (10 genes), by next-generation sequencing, plasma, including single-nucleotide variants, insertions/deletions, copy-number alterations, microsatellite instability, and fusions, reported as clinically actionable variants	0571U
MGMT promoter methylation analysis	81287
MLH1 sequencing	81292

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Procedures addressed by this guideline	Procedure codes
Molecular tumor marker test	81400 81401 81402 81403 81405 81406 81407 81408 81479
Molecular tumor marker test	88271
MPL common variants (e.g. W515A, W515K, W515L, W515R)	81338
MPL mutation analysis, exon 10	81339
MSH2 sequencing	81295
MSH6 sequencing	81298
NeoLAB Prostate	0011M
Northstar Select	0487U
NPM1 exon 12 targeted mutation analysis	81310
NRAS exon 2 and exon 3 analysis	81311
NTRK1 translocation analysis	81191
NTRK2 translocation analysis	81192
NTRK3 translocation analysis	81193
NTRK translocation analysis	81194
PDGFRA targeted sequence analysis	81314

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Procedures addressed by this guideline	Procedure codes
PGDx elio plasma focus Dx	0562U
PMS2 sequencing	81317
PredicineCARE Assay	0539U
PTEN sequencing	81321
Resolution ctDx Lung	0179U
RUNX1 mutation analysis	81334
SF3B1 common variants (e.g. A672T, E622D, L833F, R625C, R625L)	81347
Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements	81462
Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability	81463
Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (eg, plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements	81464
SRSF2 common variants (e.g. P95H, P95L)	81348
TERT targeted sequence analysis	81345
therascreen PIK3CA RGQ PCR Kit	0177U
TP53 sequencing	81351
TP53 targeted sequence analysis	81352

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Procedures addressed by this guideline	Procedure codes
U2AF1 common variants (e.g. S34F, S34Y, Q157R, Q157P)	81357
ZRSR2 common variants (e.g. E65fs, E122fs, R448fs)	81360

Criteria

Introduction

Requests for liquid biopsy testing are reviewed using the following criteria.

Companion Diagnostic (CDx) Liquid Biopsy Assay

Liquid biopsy-based companion diagnostic assays are considered medically necessary when the member meets ALL of the following criteria:

- Member has a diagnosis of cancer, AND
- Treatment with a medication for which there is a liquid biopsy-based FDA-approved companion diagnostic is being considered, AND
- FDA approval for the CDx being requested must include the member's specific cancer type as an approved indication, AND
- FDA label for the drug and indication being considered states companion diagnostic testing is necessary for member selection, AND
- Member has not had previous somatic and/or germline testing that would have identified the genetic change required to prescribe the medication under consideration, AND
- Family history:
  - Member does not have a close (1st or 2nd degree) biological relative with a known germline mutation in a gene that is a target of the requested companion diagnostic test (e.g. known familial mutation in BRCA1/2 and requested test is myChoice CDx), or
  - Member has a close (1st or 2nd degree) biological relative with a known germline mutation in a gene that is a target of the requested companion diagnostic test (e.g. known familial mutation in BRCA1/2 and requested test is myChoice CDx), and the member’s germline test was negative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Note:

Not all indications for medications with an FDA-approved companion diagnostic liquid biopsy test require the results of that test prior to prescribing. Testing would not be

considered medically necessary when prescribed for indications that do not require the companion diagnostic.

Guardant360 LDT

When Guardant360 LDT (laboratory developed test) is being requested for indications that are outside the scope of a companion diagnostic (i.e.: non-CDx), the panel will be considered medically necessary when the following criteria are met:

- The member has a diagnosis of metastatic or recurrent non-small cell lung cancer (NSCLC), AND
- NSCLC diagnosis has been confirmed based on a histopathologic assessment of tumor tissue, AND
- No previous multi-gene panel testing has been performed for NSCLC, AND
- Insufficient tumor tissue is available for broad molecular profiling and member is unable to undergo an additional standard tissue biopsy due to documented medical reasons (i.e., invasive tissue sampling is contraindicated due to the member's clinical condition)

ESR1 Liquid Biopsy Test

- The member has a diagnosis of metastatic or recurrent hormone receptor positive (ER+ or PR+) and human epidermal growth factor receptor 2 (HER2) negative breast cancer, AND
- The member's cancer has progressed following endocrine therapy, AND
- Breast cancer diagnosis has been confirmed based on a histopathologic assessment of tumor tissue, AND
- No previous testing has identified a somatic ESR1 mutation*, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Note:

Repeat testing may be warranted for individuals with ESR1 wild-type results from prior somatic testing whose cancer has progressed following treatment.

Other Non-CDx Liquid Biopsy Tests and Tests for Other Indications

These tests are considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.

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- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

When otherwise reimbursable, the following will apply:

- When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81462, 81463, 81464*).

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is liquid biopsy testing?

The use of circulating tumor DNA (ctDNA) to identify genetic mutations present in a tumor is also referred to as a liquid biopsy.

- The National Cancer Institute defines a liquid biopsy as "[a] laboratory test done on a sample of blood, urine, or other body fluid to look for cancer cells from a tumor or small pieces of DNA, RNA, or other molecules released by tumor cells into a person's body fluids. Liquid biopsy allows multiple samples to be taken over time, which may help doctors understand what kind of genetic or molecular changes that are taking place in a tumor."[1]
- Circulating tumor DNA is released into circulation by tumors.[2] It can be found in various substances, including blood, urine, saliva, etc.

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- Analysis of ctDNA can be performed to help identify indicators of disease recurrence or disease progression. It can also help to determine if a specific treatment is indicated.
- Liquid biopsies can be used to more easily obtain serial sampling of a tumor. This is particularly useful since somatic mutations that are used in treatment decisions can change as the tumor progresses.[2] ctDNA is also thought to provide a more representative sample of the entire tumor genome as well as any metastases that may be present.[2]
- Traditional methods of performing biopsies on tumor tissue pose the following problems:[2,3]
  - Biopsies are invasive, involve risks, are typically costly, and are typically difficult to obtain.
  - Treatment decisions often rely on one single biopsy, while tumors are usually heterogeneous in nature, tumor characteristics can evolve, and information regarding metastases may not be known.[2]
- The use of liquid biopsies can help overcome some of the above problems with traditional biopsies since they can be completed in a noninvasive manner.
- This guideline will only address the use of ctDNA as a liquid biopsy in solid tumors and hematologic malignancies. Circulating tumor cells (CTCs) can be used to help obtain information about an individual's cancer prognosis and treatment options. CTC assays are not addressed by this guideline.

Test information

Introduction

Liquid biopsy testing is an assay that utilizes ctDNA to assist with monitoring disease status and potentially determining sensitivity to certain treatments.

Liquid biopsy methodology

Testing methodology relies on the presence of ctDNA in circulation, which is typically analyzed by one of the following methods:

- Standard testing methodologies, such as polymerase chain reaction (PCR) or sequencing, are used to identify targeted mutations commonly present in tumors of a specific type.
- Methodologies such as next-generation sequencing (NGS) or array comparative genomic hybridization (aCGH) are used to identify both novel and recurrent mutations. These include whole genome sequencing or whole exome sequencing. These approaches analyze single genes, panels of genes, exomes, or genomes. Use

of these approaches allows testing with no prior knowledge of genetic mutations that are present in the individual's tumor.
- Several liquid biopsy tests have been designated by the Food and Drug Administration (FDA) as companion diagnostic (CDx) assays deemed necessary for the effective use of a specific medication in the context of a specific clinical indication. Within this guideline, liquid biopsy tests that do not have the designation of companion diagnostics are referred to as non-CDx assays.

Note:

Tests that extract DNA from nucleated cells in the blood or bone marrow for hematologic malignancies are not considered liquid biopsies. For information on these assays, please refer to the guideline *Somatic Mutation Testing*, as this testing is not addressed here.

Guidelines and evidence

American Society of Clinical Oncology

A rapid recommendation on testing to guide therapy for metastatic breast cancer from the American Society of Clinical Oncology (ASCO, 2023) included the following statement:[4]

- "To aid in treatment selection, the Expert Panel recommends routine testing for emergence of ESR1 mutations at recurrence or progression on [endocrine treatment] (given with or without CDK4/6 inhibitor) in patients with ER-positive, HER2-negative MBC. Testing with a Clinical Laboratory Improvement Amendments-certified assay should be performed on blood or tissue obtained at the time of progression, as ESR1 mutations develop in response to selection pressure during treatment and are typically undetectable in the primary tumor. Blood-based ctDNA is preferred owing to greater sensitivity. If not performed earlier, testing for PIK3CA mutations should also be performed to guide further therapy. Patients whose tumor or ctDNA tests remain ESR1 wild-type may warrant retesting at subsequent progression(s) to determine if an ESR1 mutation has arisen (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong)."

A provisional clinical opinion for somatic genomic testing in individuals with metastatic or advanced cancer (ASCO, 2022) stated:[5]

- "There is a growing body of evidence on the clinical utility of genomic testing on cfDNA [cell-free DNA] in the plasma, so-called liquid biopsies. Studies have shown substantial concordance between cfDNA-based testing and tumor testing, with the caveat that copy-number changes may be more difficult to assess in cfDNA, and fusion testing may be more limited in common cfDNA tests used currently. However,

cfDNA has the advantage of being noninvasive and expediting testing because of the lack of need to retrieve archival blocks or arrange for a new biopsy. There are already FDA approvals on the basis of cfDNA-based genomic testing (eg, osimertinib for EGFR T790M mutation in lung cancer). Therefore, in patients without tissue-based genomic test results, treatment may be based on actionable alterations identified in cfDNA. Genomic testing on cfDNA is most helpful when genomic testing is indicated, archival tissue is unavailable, and new tumor biopsies are not feasible. cfDNA is more commonly reported with mutant allelic fractions of individual mutations, compared with solid tumor panels, thus facilitating assessment of clonality. cfDNA testing has the additional advantage of capturing tumor heterogeneity because of pooling in the blood of DNA from throughout the tumor or from multiple tumors and is a promising tool for assessing genomic mechanisms of acquired resistance. Furthermore, cfDNA levels themselves may be prognostic, and early cfDNA dynamics may serve as an early predictor of therapy response or resistance. Ongoing studies are expected to better delineate the clinical utility of serial liquid biopsies."

American Society of Clinical Oncology and College of American Pathologists

Based on a comprehensive systematic review of 77 scientific studies on ctDNA assays for solid tumors, an expert panel assembled by the American Society of Clinical Oncology (ASCO, 2018) and the College of American Pathologists (CAP, 2018) concluded that there is currently insufficient evidence of clinical validity and clinical utility for most ctDNA assays being used in advanced cancer. [6] There are some ctDNA assays that have demonstrated clinical validity and clinical utility with certain types of cancers, such as non-small cell lung cancer. There is no evidence for use in early stage cancer, treatment monitoring, or residual disease detection. They also stated that there is no evidence of clinical value for cancer screening outside of a clinical trial.

To establish clinical validity and clinical utility of ctDNA analyses, the expert panel recommended the following:

- “Future research studies to establish clinical validity and utility of ctDNA assays should include a patient cohort that matches the intended-use population as closely as possible and samples collected from a prospective study with defined entry criteria. Data will most frequently come from a phase II or phase III study in the patient population where it is anticipated the assay would be used in subsequent clinical practice, with the frequency of the variant under study approximately equal to that in an unselected clinical population. In prospective studies of targeted therapies, the entry criteria should allow inclusion of patients in which the variant under study is observed in the plasma, but not in the tissue analysis, to evaluate the treatment response of this population with discordant genotyping results."

European Society for Medical Oncology

The European Society for Medical Oncology (ESMO, 2022) stated the following regarding liquid biopsies (LBs) for testing in individuals with advanced cancer:[7]

- "LB assays with very high analytical and clinical specificity, and therefore positive predictive values, may be used in routine practice when the results will affect standard treatment options. The limitations of ctDNA assays, however, must be taken into account."
- "...the clinical utility of ctDNA is very much context-dependent, contingent on disease types and stages, available treatment that could effectively eradicate MRD [minimal residual disease] and intended use..."
- Tissue-based testing is the most appropriate test for the majority of individuals, while clinical scenarios exist where ctDNA assays are recommended. These include certain aggressive tumors or when tumor tissue is insufficient or not appropriate.

The guidelines also stated that insufficient evidence exists for implementing use of ctDNA assays for cancer screening, monitoring of treatment response, or detection of molecular relapse or MRD.

International Association for the Study of Lung Cancer

A consensus statement from the International Association for the Study of Lung Cancer (IASLC, 2021) on usage of liquid biopsy for advanced NSCLC made the following recommendations:[8]

- For treatment-naive individuals with advanced NSCLC, tumor genotyping with a tissue sample should be performed first if available. If the tumor tissue is of uncertain adequacy or there is concern for incomplete tumor genotyping, ctDNA genotyping can be performed concurrently or as reflex testing. When a tissue sample is unavailable for these individuals, plasma ctDNA genotyping is the recommended test.
- Usage of plasma ctDNA is recommended "[a]t the time of acquired resistance after tyrosine kinase inhibitor (TKI) therapy in an oncogene-driven NSCLC."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) stated the following regarding liquid biopsies for testing in individuals with non-small cell lung cancer:[9]

- "ctDNA testing should not be used in lieu of a histologic tissue diagnosis."
- "ctDNA is not routinely recommended in settings other than advanced/metastatic disease. For stages I-III, tissue-based testing is preferred. Metastatic disease confined to the thorax may have a higher yield with tissue-based testing."
- "Studies have demonstrated ctDNA and tissue testing to have very high specificity. Both ctDNA and tissue testing have appreciable false-negative rates, supporting the complementarity of these approaches, and data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection."

- "…the panel feels that plasma ctDNA testing should not be used to diagnose NSCLC; tissue should be used to diagnose NSCLC. Standards and guidelines for plasma ctDNA testing for somatic variants/mutations have not been published, there is up to a 30% false-negative rate, and variants can be detected that are not related to the tumor….careful consideration is required to determine whether ctDNA findings reflect a true oncogenic driver or an unrelated finding."
- "…plasma ctDNA testing can be used in specific circumstances if 1) the patient is not medically fit for invasive tissue sampling; or 2) there is insufficient tissue for molecular analysis and follow-up tissue-based analysis will be done if an oncogenic driver is not identified. Data suggest that plasma ctDNA testing is a useful minimally invasive test that can be used to identify ALK, BRAF, EGFR, HER2, MET exon 14 skipping, RET, ROS1, and other oncogenic biomarkers that would not otherwise be identified in patients with metastatic NSCLC."
- "The NCCN Guidelines for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories."

The National Comprehensive Cancer Network (NCCN, 2024) guidelines for breast cancer stated that "comprehensive germline and somatic profiling" utilizing tumor tissue or ctDNA assays should be performed in individuals with recurrent or stage IV disease.[10] They also stated that "[t]issue-based assays have greater sensitivity, but ctDNA may reflect tumor heterogeneity more accurately." This guideline does state that liquid biopsy is the preferred methodology for the identification of ESR1 mutations in individuals with hormone receptor positive/HER2 negative recurrent unresectable or stage IV breast cancer.

Selected Relevant Publications

Many laboratories are developing liquid biopsy assays. For many of these assays, analytical validity studies have been performed; however, data regarding the clinical validity and clinical utility of these tests is still emerging.[3,11-51]

The TRACERx study (Tracking Non-small cell lung cancer evolution through therapy (Rx)) is a large, prospective clinical trial being conducted to evaluate "the relationship between intra-tumour heterogeneity and clinical outcome following surgery and adjuvant therapy."[52] Researchers plan to analyze the individual's tumors before surgery and multiple times after surgery during their treatment regimen. Tumor tissue and ctDNA in individual's blood will be examined in approximately 840 individuals with NSCLC. This trial is expected to continue until 2026.[52]

Limited evidence suggests that liquid biopsy with Guardant360, in individuals with advanced NSCLC, may be a reasonable non-invasive alternative to tumor biopsy,

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particularly in individuals unable to undergo standard tissue biopsy or in cases where tumor tissues are lacking or insufficient for proper mutation analysis.[53-68]

Several systematic reviews and meta-analyses have synthesized the findings of multiple studies to evaluate the clinical validity and clinical utility of cell-free circulating tumor DNA (ctDNA) to detect a variety of advanced cancer (excluding non-small cell lung cancer and hematological malignancies).[6,11-15,19-43,69-72] With the exception of FDA-approved ctDNA assays, the majority of assays have limited evidence of clinical validity and very limited-to-no evidence of clinical utility for use in individuals with advanced cancer.[6] Some studies have also reported relatively high rates of discordance between ctDNA assays and tissue-based testing. There is even less evidence regarding the validity of ctDNA testing in early stage disease, during treatment monitoring, or minimal residual disease (MRD) detection.[6] Additional well-designed prospective studies are needed to establish the clinical validity and clinical utility of ctDNA assays before ctDNA assays (liquid biopsy) can be widely adopted in clinical practice.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for liquid biopsy testing will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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Lynch Syndrome Genetic Testing

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Lynch syndrome (LS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
EPCAM deletion/duplication analysis	81403
Genomic Unity Lynch Syndrome Analysis	0238U
Known familial variant not otherwise specified	81403
MLH1 deletion/duplication analysis	81294
MLH1 known familial mutation analysis	81293
MLH1 sequencing	81292
MSH2 deletion/duplication analysis	81297
MSH2 known familial mutation analysis	81296
MSH2 sequencing	81295
MSH6 deletion/duplication analysis	81300
MSH6 known familial mutation analysis	81299
MSH6 sequencing	81298
PMS2 deletion/duplication analysis	81319

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Procedures addressed by this guideline	Procedure codes
PMS2 known familial mutation analysis	81318
PMS2 sequencing	81317

Criteria

Introduction

Requests for Lynch syndrome (LS) genetic testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Family History:
  - Known MLH1, MSH2, MSH6, PMS2, or EPCAM mutation in a close blood relative (1st, 2nd, or 3rd degree), AND
- Age- 18 years and older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Gene Sequencing and/or Deletion/Duplication Analysis of MLH1, MSH2, MSH6, PMS2, or EPCAM

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - Gene requested has not been tested previously by the same methodology (i.e., sequencing or deletion/duplication analysis), and
  - If there is a known familial mutation in the family, that mutation does not sufficiently explain the indication for testing, AND
- Age- 18 years or older, AND
- Familial adenomatous polyposis (FAP) has been ruled out, AND

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- Diagnostic Testing for Symptomatic Individuals
  - Personal history of colorectal cancer (CRC) (or other Lynch syndrome-related tumor[***]), and
    - Colorectal or endometrial cancer diagnosed before 50 years of age, or
    - Colorectal or endometrial cancer diagnosed at any age with abnormal tumor testing indicative of a mutation in a mismatch repair gene (see Figure A), or
    - Presence of synchronous or metachronous Lynch syndrome-associated tumors, regardless of age, or
    - Diagnosed at any age with colorectal or endometrial cancer and there is the following family history:
      - One first-degree or second-degree relative with a Lynch syndrome-related cancer diagnosed before 50 years, or
      - At least two first-degree or second-degree relatives with a Lynch syndrome-related cancer at any age, or
    - Amsterdam II criteria are met:
      - ≥ 3 close blood relatives (1st, 2nd, or 3rd degree) with Lynch syndrome-associated tumor (symptomatic member can be one of the three), and
      - One should be a first-degree relative of the other two, and
      - ≥ 2 successive generations affected, and
      - ≥ 1 diagnosed before age 50, or
    - 5% or greater risk of Lynch syndrome based on one of the following mutations prediction models (MMRPro or MMRPredict), or
    - 2.5% or greater risk of Lynch syndrome based on PREMM[5], OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Immunohistochemistry (IHC) and/or Lynch syndrome genetic testing results from affected family member are unavailable, AND
    - Colorectal or endometrial cancer diagnosed before age 50 in a first-degree relative, or
    - Colorectal or endometrial cancer and another synchronous or metachronous Lynch syndrome-associated tumor in a first-degree or second-degree relative, or
    - ≥ 3 close blood relatives (1st, 2nd, or 3rd degree) with Lynch syndrome-associated tumor, where Amsterdam II criteria are met:
      - One should be a first-degree relative of the other two, and
      - ≥ 2 successive generations affected, and
      - ≥ 1 diagnosed before age 50, OR
  - 5% or greater risk of Lynch syndrome based on one of the following mutations prediction models (MMRPro or MMRPredict), OR
  - 2.5% or greater risk of Lynch syndrome based on PREMM[5], AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy

***Lynch syndrome-associated tumors include colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, biliary tract, brain (usually glioblastomas), and small intestine as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas.

Other Considerations

- Lynch syndrome testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.
- NCCN recommends universal screening for Lynch syndrome for all colorectal and endometrial cancers by MSI [microsatellite instability] and/or IHC regardless of the individual's age. Most people with colorectal or endometrial cancer who are appropriate candidates for Lynch syndrome testing should have access to MSI and/or IHC. Lynch syndrome genetic testing without MSI and/or IHC results will only be considered medically necessary in extenuating circumstances and will require medical necessity review.
- "The [NCCN] Panel also recommends considering tumor screening for MMR [mismatch repair] deficiency in sebaceous neoplasms as well as the following adenocarcinomas: small bowel, ovarian, gastric, pancreatic, biliary tract, brain, bladder/urothelial, and adrenocortical cancers regardless of age at diagnosis."

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

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- For individuals that have had previous tumor testing (MSI and/or IHC), the testing algorithm as outlined in Figure A must be followed for payment of claim.

Figure A [3, 11]

Diagnostic Testing for Individuals with Previous Tumor Testing (MSI and/or IHC)

+ "Studies have shown that 45%–68% of cases with unexplained defective MMR (MSI-H and/or abnormal IHC with no evidence of MLH1 promoter hypermethylation when

indicated) have biallelic somatic MMR gene inactivation (sometimes referred to as double somatic MMR mutations). Biallelic somatic MMR gene inactivation is defined by having either two pathogenic sequence variants or one pathogenic sequence variant and loss of heterozygosity [LOH] in the MMR genes. ... tumor sequencing may be helpful for individuals with tumor testing showing dMMR and no germline pathogenic variant detected. If biallelic somatic MMR gene inactivation is identified, LS is ruled out but there may still be some increased familial risk. If only one somatic pathogenic variant is found, the unidentified pathogenic variant could either be germline or somatic. If no somatic pathogenic variants are found, it is possible that the IHC results were incorrect (especially if the tumor was found to be MSS on tumor sequencing) or that none of the pathogenic variants (germline or somatic) are identifiable. In any of these cases, the individual and their close relatives still need to receive care based on their personal and/or family history."[1]

++"If strong family history (i.e. Amsterdam criteria) or additional features of hereditary cancer syndromes (multiple colon polyps) are present, additional testing may be warranted in the proband, or consider tumor testing in another affected family member due to the possibility of a phenocopy."[1]

+++ Additional testing with MLH1 hypermethylation or BRAF testing may be performed with loss of MLH1 and PMS2 or loss of only MLH1. Per NCCN guidelines, MLH1 promoter mutation analysis, not BRAF testing, is recommended for endometrial tumors when IHC testing has indicated a loss of MLH1 protein.[1]

What is Lynch syndrome?

Lynch syndrome (LS), also called hereditary non-polyposis colorectal cancer (HNPCC), is a hereditary cancer syndrome that is the most common cause of inherited colon and endometrial cancer.[1-3]

Prevalence

Lynch syndrome affects approximately 1 in 35 individuals with colorectal and endometrial cancer and around 1 in 370 individuals in the general population. Lynch syndrome accounts for 3% of all colorectal and endometrial cancer cases.[1-4]

Symptoms

Lynch syndrome is associated with up to a 61% lifetime risk for colorectal cancer and up to a 57% risk for endometrial cancer.[1] The risk is also increased for the development of the following cancers: small bowel, stomach, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, brain, bladder and prostate.[1,5] The average age of diagnosis for these cancers varies based on the gene that harbors the mutation.[1] Individuals may also develop skin lesions such as sebaceous adenomas and keratoacanthomas.[1,5]

Lynch syndrome should be suspected when the personal and family cancer history meets the *Revised Bethesda Guidelines* or the *Amsterdam II Criteria* (see below).[6,7] Risk prediction models, such as PREMM5, MMRpro, and MMRpredict, can be used to gauge the likelihood an individual has a mutation in an LS causative gene.[8]

Cause

Lynch syndrome is caused by mutations in any one of the following five genes: MLH1, MSH2, MSH6, PMS2, or EPCAM.[4,9]

Inheritance

Lynch syndrome is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Lynch syndrome mutations inherited in an autosomal recessive manner cause constitutional MMR deficiency syndrome (CMMR-D). Testing for CMMR-D is not addressed in this summary.[4,5]

Diagnosis

Lynch syndrome is diagnosed with the identification of a constitutional (germline) pathogenic variant in MLH1, MSH2, MSH6, PMS2, or EPCAM.[4]

Management

Management for individuals with LS include more frequent cancer screenings and the option for risk reducing surgeries. The recommended management is dependent on which gene has the mutation. The recommended management guidelines include:[1,10]

- Colonoscopy: begin at 20-25 years for individuals with mutations in MLH1, MSH2, or EPCAM. Begin at 30-35 years in individuals with mutations in MSH6 or PMS2. Colonoscopy screening may begin earlier, 2-5 years earlier than the youngest diagnosis of colon cancer in the family, but not later than the aforementioned ages. Repeat colonoscopy is recommended every 1-2 years in individuals with mutations in MLH1, MSH2, or EPCAM, and every 1-3 years in individuals with mutations in MSH6 or PMS2.
- "[T]he panel suggests that aspirin may be used to reduce the future risk of CRC in patients with LS, but it is emphasized that the optimal dose and duration of therapy should be determined on an individual basis… Discussion of individual risks, benefits,

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adverse effects, and childbearing plans should also be included. The panel also recommends that providers carefully review patient-specific factors that may increase the risk of aspirin therapy, as well as factors that indicate a low future cumulative risk of CRC, as some individuals may be less likely to experience significant benefit."

- Hysterectomy and bilateral salpingo-oophorectomy (BSO) are available risk-reducing surgeries. "...timing of BSO should be individualized based on whether childbearing is complete, menopause status, comorbidities, family history, and LS gene, as risks for ovarian cancer vary by pathogenic variant." For women who decline this risk-reducing surgery, endometrial cancer screening may be an option, although a proven benefit of such screenings has not been documented. Insufficient evidence exists in order to make a specific recommendation for prophylactic bilateral salpingo-oophorectomy for individuals with mutations in MSH6 and PMS2. Individuals with a PMS2 mutation "appear to be at no greater than average risk for ovarian cancer and may consider deferring surveillance and may reasonably elect not to have oophorectomy."
- Annual urinalysis at 30-35 years may be considered to screen for urothelial cancers. This screening may be considered in select individuals (e.g. those with a family history of urothelial cancer or in individuals with a mutation in MSH2).
- "Upper GI surveillance with EGD starting at age 30–40 years and repeat every 2–4 years, preferably performed in conjunction with colonoscopy... Age of initiation prior to 30 years and/or surveillance interval less than 2 years may be considered based on family history of upper GI cancers or high-risk endoscopic findings (such as incomplete or extensive gastric intestinal metaplasia, gastric or duodenal adenomas, or Barrett esophagus with dysplasia). Random biopsy of the proximal and distal stomach should at minimum be performed on the initial procedure to assess for H. pylori (with treatment indicated if H. pylori is detected), autoimmune gastritis, and intestinal metaplasia... Individuals not undergoing upper endoscopic surveillance should have one-time noninvasive testing for H. pylori at the time of LS diagnosis, with treatment indicated if H. pylori is detected. The value of eradication for the prevention of gastric cancer in LS is unknown."
- Screening for pancreatic cancer can be considered at 50 years or 10 years younger than the earliest case of pancreatic cancer diagnosis in the family but not later than 50 years. This screening can be considered in individuals with at least one first- or second-degree relative with exocrine pancreatic cancer and on the same side of the family (or presumed same side) with the mutation in the LS causative gene. Notably, PMS2 mutations have not shown to increase the risk for pancreatic cancer.
- "Patients with LS should consider their risk based on the LS gene and family history of prostate cancer. The NCCN Guidelines for Prostate Cancer Early Detection recommend that it is reasonable for patients with LS to consider beginning shared decision-making about prostate cancer screening at age 40 years and to consider screening at annual intervals rather than every other year."
- "The panel recommends consideration of a skin exam every 1 to 2 years with a health care provider skilled in identifying LS- associated skin manifestations. The age at

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which to begin surveillance cannot be recommended with certainty, and therefore can be individualized."
- "Patients should be educated regarding signs and symptoms of neurologic cancer and the importance of prompt reporting of abnormal symptoms to their physicians."
- Annual physical examination starting at 20-25 years is recommended.

Special Considerations

Historically, LS has included the variants Muir-Torre syndrome (one or more LS-associated cancers and sebaceous neoplasms of the skin) and Turcot syndrome (LS with glioblastoma).[4] These variant designations are considered outdated.

Test information

Testing for LS may include tumor testing, known familial mutation testing, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

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Test Strategy

When the family LS mutation is known, at-risk relatives should be tested for that specific mutation only. Otherwise, genetic testing usually starts either with sequencing and deletion/duplication analysis of the gene identified from tumor IHC results or multigene panel testing. The National Comprehensive Cancer Network has outlined a comprehensive strategy for molecular testing of LS.[1] The first person tested should be the relative most likely to have LS in the family.

Testing those with a suspected LS-related cancer should typically begin with microsatellite instability or immunohistochemistry testing on tumor tissue. The following table lists and describes the various testing scenarios.

When ...	Then ...
tumor tests suggest LS	that individual should be offered genetic testing to look for a mutation that causes LS. IHC studies may suggest which mismatch repair gene is likely to harbor a mutation.[1,9-11]
tumor tests are normal, and there is a young age of diagnosis or a strong family history of LS-associated cancers is present	genetic testing may still be warranted, or tumor testing in another family member with the most suspicious cancer history may be considered.[9]
tumor screening is not possible, and the individual meets the guideline criteria	direct genetic testing may be reasonable.

Guidelines and evidence

Multiple Society Recommendations

The US Multi-Society Task Force (MSTF, 2014), the National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer (NSGC/CGA-ICC, jointly published, 2022), the National Comprehensive Cancer Network (NCCN, 2023), and the American College of Gastroenterology (ACG, 2015) have practice guidelines that addressed LS genetic testing. Generally, these recommendations agreed:[1,9,10,12]

- Test colorectal or endometrial tumors by microsatellite instability and/or immunohistochemistry first when tissue is available.

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- Individuals with abnormal microsatellite instability and/or immunohistochemistry results (and no demonstrated BRAF mutation or hypermethylation of MLH1) should be offered genetic testing to identify a LS disease-causing mutation. Results from tumor testing should guide the genetic testing cascade. When tumor testing is not possible or results are inconclusive, genetic testing for an inherited mutation is indicated if an individual with a suspected LS-related cancer is at increased risk for LS based on tumor type, age at diagnosis, and/or family history. If no affected family member is available for testing, at-risk relatives can consider genetic testing if the family meets certain criteria. However, only a mutation positive result can be clearly interpreted. Mutation-negative results must be interpreted with caution; the chance of inconclusive results is high because the family mutation may not be detectable. Once a LS disease-causing mutation has been identified, at-risk relatives should be offered genetic testing for that specific mutation.

Manchester International Consensus Group

The Manchester International Consensus Group (2019) stated the following regarding germline testing for LS in women with gynecological cancer:[13]

- "The Consensus Group strongly recommends that tumor MMR or MSI status is used to identify women for germline MMR testing. There is no evidence to advocate MSI over MMR immunohistochemistry or vice versa (grade B)."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) guideline for genetic/familial high-risk assessment of colorectal cancer recommended the following:[1]

- "universal screening of all CRCs and endometrial cancers to maximize sensitivity for identifying individuals with LS and to simplify care processes."
- "considering tumor screening for MMR deficiency for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, ovarian, gastric, pancreatic, biliary tract, brain, bladder/urothelial, and adrenocortical cancers regardless of age at diagnosis"

The criteria for LS germline testing include:

- "An individual with an LS-related cancer and any of the following:
  - Diagnosed <50 y
  - A synchronous or metachronous LS-related cancer regardless of age
  - 1 first-degree or second-degree relative with a LS-related cancer diagnosed <50 y
  - ≥2 first-degree or second-degree relatives with a LS-related cancer regardless of age
- Family history of any of the following:
  - ≥1 first-degree relative with a colorectal or endometrial cancer diagnosed <50 y

  - ≥1 first-degree or second-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer regardless of age
  - ≥2 first-degree or second-degree relatives with LS-related cancers, including ≥1 diagnosed <50 y
  - ≥3 first-degree or second-degree relatives with LS-related cancers regardless of age
- Increased model-predicted risk for LS"
- "Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age"

"The germline MGPT [multigene panel testing] strategy is an alternative to tumor- and family history-driven selection of patients with CRC or EC for genetic testing, because it is more sensitive for identifying individuals with LS and other cancer risk genes than a strategy of selecting for germline testing based on family history and tumor-based criteria." NCCN recommended genetic testing start with the most informative person in a family. Other close family members may consider testing if a person affected with a related cancer is not available.

Society of Gynecologic Oncology

The Society of Gynecologic Oncology (SGO, 2023) recommended that all individuals diagnosed with endometrial cancer undergo molecular testing that includes assessment of mismatch repair deficiency status.[14]

Revised Bethesda Guidelines

According to the *Revised Bethesda Guidelines*, consider LS tumor screening when any one of the following criteria are met:[6,15]

- colorectal cancer is diagnosed before the age of 50
- presence of synchronous or metachronous colorectal cancer, or other LS-associated tumor***, regardless of age
- microsatellite unstable (MSI-H) tumor pathology before the age of 60, examples include
  - tumor-infiltrating lymphocytes
  - Crohn's-like lymphocytic reaction
  - mucinous or signet-ring differentiation
  - medullary growth pattern, or
  - other reported features
- colorectal cancer diagnosed in an individual with at least one first-degree relative, including parent, sibling, or child with a LS-related tumor***, one of whom was diagnosed before the age of 50, or
- colorectal cancer diagnosed in an individual with at least two first- or second-degree relatives with LS-related tumors*** at any age.

Amsterdam II Criteria

According to *Amsterdam II Criteria*, LS is likely when all of the following criteria are met:[7]

- there are at least three relatives with LS-associated tumors***
- one affected relative is a first-degree relative (parent, sibling, child) of the other two
- affected relatives are in two or more successive generations
- at least one LS-related tumor was diagnosed before age 50, and
- FAP has been excluded on the basis of no polyposis.

Tumors must be verified by pathology.

***LS-associated tumors include

- colorectal
- endometrial
- small bowel
- stomach
- ovarian
- pancreatic
- ureteral and renal pelvis
- biliary tract
- brain tumors, usually glioblastomas associated with Turcot syndrome variant
- sebaceous adenomas, and
- keratoacanthomas, associated with a Muir-Torre syndrome variant.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Lynch syndrome genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Multi-Cancer Early Detection Screening

MOL.TS.396.A
v1.0.2026

Introduction

Multi-cancer early detection screening tests are addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Multi-Cancer Early Detection (MCED) screening tests	81599 81479

Criteria

Introduction

Requests for multi-cancer early detection screening tests are reviewed using the following criteria. This guideline only addresses liquid biopsy screening tests for early cancer detection. Liquid biopsy testing for other purposes, including monitoring disease status and treatment selection in solid tumors and hematologic malignancies, is not addressed by this guideline. For information on liquid biopsy testing for other purposes, please refer to the guideline *Liquid Biopsy Testing*, as this testing is not addressed here.

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

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What is Multi-Cancer Early Detection Screening?

Multi-cancer early detection (MCED) screening tests analyze biomarkers within blood and urine to predict the presence of cancers. Liquid biopsy to detect circulating free tumor DNA (cfDNA), circulating free tumor proteins, DNA methylation patterns, circulating free immune cell DNA and DNA fragment size is often utilized.[1,2] Multiple biomarkers, including genomic profiles, protein levels, and other analytes, may be combined to provide a comprehensive assessment of individual cancer risk. MCED tests screen for multiple cancer types simultaneously and aim to increase detection rates, particularly at earlier stages when a cancer may be more amenable to treatment.

Incidence

Each year, an estimated 2 million new cancer cases are diagnosed in the United States and over half a million individuals are expected to die from the disease.[3]

Screening and Diagnosis

Population-level screening programs are endorsed for only four cancer types in the United States: breast, cervical, colorectal, and lung cancers.[4] Other cancer types may have individualized screening recommendations, or lack any recognized screening protocols.[4] MCED screening tests are intended to complement existing screening programs and potentially increase rates of cancer detection because patients may be more willing to perform blood-based screening than currently recommended screening methodologies such as mammogram and colonoscopy. Screening for multiple cancer types at once could also allow identification of cancer types that do not have any current screening recommendations, such as pancreatic and stomach cancer.[5]

At this time, the number and type of cancers screened, and the ability to distinguish between cancer types, varies between individual tests. This is partly due to the fact that current MCED screening tests use different biomarkers to identify the presence of cancer.

Positive screening results typically prompt further investigations in an effort to confirm whether cancer is present. Investigations may include gathering of a personal and family medical history, a physical exam, laboratory tests, imaging, and biopsy as needed.[6]

Test information

Introduction

MCED screening tests utilize a variety of techniques for the measuring of biological substances from blood and other body fluids.

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Multi-Cancer Early Detection Testing Methodology

MCED test methodology relies on the presence of individual or a combination of biomarkers in circulation, including cfDNA—which may be analyzed using polymerase chain reaction (PCR), methylation analysis, or next-generation sequencing (NGS). These approaches analyze single genes, panels of genes, exomes, or genomes.

Other biomarkers assessed by MCED screening tests may include routine blood and urine analysis, and levels of certain antibodies, proteins, electrolytes, and other analytes.[5,7] Genomic profiles and the combination of multiple biomarkers are used to distinguish between cancer and non-cancer signals.[7,8]

Guidelines and Evidence

Introduction

While there are no specific guidelines relating to multi-cancer early detection screening tests, the following section includes relevant guidelines and evidence that discuss the use of liquid biopsy for cancer screening.

American Society for Clinical Oncology and the College of American Pathologists

The American Society for Clinical Oncology and the College of American Pathologists (ASCO and CAP, 2018) joint review on the use of clinical circulating tumor DNA (ctDNA) assays in patients with cancer stated "[t]here is no evidence of clinical utility and little evidence of clinical validity of ctDNA assays in early-stage cancer, treatment monitoring, or residual disease detection. There is no evidence of clinical validity and clinical utility to suggest that ctDNA assays are useful for cancer screening, outside of a clinical trial."[9]

European Society for Medical Oncology

The European Society of Medical Oncology (ESMO, 2022) provided recommendations on the use of ctDNA assays for cancer.[10] The guidelines stated that insufficient evidence exists for implementing use of ctDNA assays for cancer screening, monitoring of treatment response, or detection of molecular relapse or minimal residual disease.

United States Preventive Services Task Force

The United States Preventive Services Task Force (USPSTF, 2021) stated the following regarding liquid biopsies for cancer screening:[11,12]

- "more research is needed on the accuracy and effectiveness of emerging screening technologies such as serum- and urine-based colorectal cancer screening tests"[11]

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- For lung cancer, "potential screening modalities that are not recommended because they have not been found to be beneficial include sputum cytology, chest radiography, and measurement of biomarker levels"[12]

Selected Relevant Publications

Current studies have shown variable sensitivity depending on the test product, cancer type, and cancer stage.[13-16] Clinical validation data has also not yet supported the ability of these tests to detect cancers in earlier stages. The average sensitivity for identifying stage I cancers across nine studies of nucleic-acid based MCED tests was 46.2%.[16]

Consistency in detecting early-stage cancers, identifying tissue of origin, and differentiating cancer-related variants from random and age-related variants has not been demonstrated across MCED screening platforms, leading to practical concerns for usage of these tests in standard clinical practice. More well-designed clinical studies are needed to better define the capabilities of individual tests and document changes to clinical outcomes.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for multi-cancer early detection screening (MCED) will ensure that members will not receive testing for which there is not a body of evidence demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[17] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

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Maturity-Onset Diabetes of the Young Genetic Testing

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Introduction

Maturity-onset diabetes of the young (MODY) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
GCK deletion/duplication	81479
GCK sequencing	81406
HNF1A deletion/duplication	81479
HNF1A sequencing	81405
HNF4A deletion/duplication	81479
HNF4A sequencing	81406

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Procedures addressed by this guideline	Procedure codes
MODY gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
MODY multigene panel	81479

Criteria

Introduction

Requests for maturity-onset diabetes of the young (MODY) genetic testing are reviewed using the following criteria.

For gene testing in non-MODY contexts (e.g., neonatal diabetes, familial hyperinsulinism, etc.), refer to the general policies, *Genetic Testing to Diagnose Non-Cancer Conditions* and *Genetic Testing by Multigene Panels*, as appropriate.

HNF1A Sequencing and Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous HNF1A gene sequencing or deletion/duplication analysis, and
  - No known MODY mutation in biologic relative, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Member has a diagnosis of diabetes prior to 35 years of age, and
  - Member has a biological parent with diabetes, and

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  - Member does NOT have symptoms consistent with a specific condition or specific gene mutation, and
  - Member does NOT have any of the following features:
    - Extra-pancreatic manifestations (e.g., congenital malformations and other signs of syndromic diabetes), or
    - Pancreatic autoantibodies suggestive of type 1 diabetes, or
    - Body mass index (BMI) greater than or equal to 35 kg/m^2, or
    - Acanthosis nigricans, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HNF4A Sequencing and Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous HNF4A gene sequencing or deletion/duplication analysis, and
  - No known MODY mutation in biologic relative, and
  - Member has previous HNF1A testing with no deleterious mutation found, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Member meets criteria for HNF1A testing, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

GCK Sequencing and Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous GCK gene sequencing or deletion/duplication analysis, and
  - No known MODY mutation in biologic relative, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Member meets criteria for HNF1A testing and has had previous HNF1A testing with no deleterious mutation found, or
  - Member has a personal history of the following features presenting outside of pregnancy:
    - Persistent, stable elevation of fasting blood glucose (5.5-8 mmol/L), and
    - HbA1C that is no more than mildly elevated (less than or equal to 7.5%), and
    - At least one oral glucose tolerance test demonstrates a small increment (less than 4.6 mmol/L), or

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  - Member has a personal history of the following features in the context of gestational diabetes:
    - Persistent elevation of fasting blood glucose (5.5-8 mmol/L) before, during, and after pregnancy, and
    - At least one oral glucose tolerance test demonstrates a small increment (less than 4.6 mmol/L) either during or after pregnancy, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Sequencing and Deletion/Duplication Analysis of ABCC8, BLK, CEL, HNF1B, INS, KCNJ11, KLF11, NEUROD1, PAX4, and PDX1

Individual testing of these genes for the purpose of diagnosing MODY is not medically necessary.

MODY Multigene Panel Testing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous MODY genetic testing, and
  - No known MODY mutation in biologic relative, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Member has a diagnosis of diabetes prior to 35 years of age, and
  - Member has a family history of diabetes consistent with autosomal dominant inheritance, and
  - Member does NOT have symptoms consistent with a specific condition or specific gene mutation, and
  - Member does NOT have any of the following features:
    - Extra-pancreatic manifestations (e.g., congenital malformations and other signs of syndromic diabetes), or
    - Pancreatic autoantibodies suggestive of type 1 diabetes, or
    - Body mass index (BMI) greater than or equal to 35 kg/m^2, or
    - Acanthosis nigricans, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- ABCC8, BLK, CEL, HNF1B, INS, KCNJ11, KLF11, NEUROD1, PAX4, and PDX1 analysis are not separately reimbursable for the purposes of MODY testing.
- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81479*).
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
  - When the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement:
    - HNF1A
    - GCK
    - HNF4A

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is MODY?

Maturity-onset diabetes of the young (MODY) is a type of monogenic diabetes characterized by non-insulin-dependent diabetes and early onset (usually before age 35 years).[1-3]

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Incidence

As of 2019, approximately 37.3 million people in the United States had diabetes, or 11.3% of the population.[4] The most common types of diabetes are type 1 and type 2. The genetic basis of these types of diabetes is largely unknown. The disease is thought to be the result of a combination of multiple genetic and environmental risk factors.[4] Monogenic forms of diabetes are rare, accounting for approximately 1-4% of all diabetes cases.[1,2]

Symptoms

Diabetes is a disorder that results in elevated blood glucose. Over time, the disorder can cause various health problems, including diseases of the heart, kidneys, eyes, and nervous system.

Cause

Monogenic forms of diabetes are caused by a mutation in a single gene. There are at least 14 known MODY genes. Three genes account for the majority of cases.[1-3]

- MODY3: Mutations in the hepatocyte nuclear factor-1 alpha (HNF1A) gene are the most common cause of MODY, accounting for 30-65% of all cases. This type is characterized by a progressive insulin secretory defect due to beta-cell failure. Laboratory evaluations are negative for pancreatic islet cell antibodies (ruling out type 1) and glycosuria is detectable even at low blood glucose levels (<10 mmol/l). Treatment of choice for people with this type of MODY is sulfonylureas, and a majority of individuals can be transferred from insulin to oral agents.
- MODY2: Mutations in the glucokinase gene (GCK) are the next most common cause of MODY, accounting for approximately 30-50% of cases. GCK encodes the glucokinase enzyme, which acts as the pancreatic glucose sensor. Mutations result in lifelong, stable, mild fasting hyperglycemia. HbA1C values are usually just above the high normal range. People with GCK mutations rarely require treatment. This type of MODY may be detected during pregnancy, when glucose tolerance testing is routinely performed.
- MODY1: Mutations in the hepatocyte nuclear factor-4 alpha (HNF4A) gene cause a clinical presentation similar to HNF1A. However, mutations in this gene are much less common (less than 10% of MODY). Age of onset may be later, and there is not a low renal threshold. HNF4A mutations can also cause high birth weight in newborns and transient neonatal hypoglycemia. These individuals are also more sensitive to sulfonylurea treatment.

The remaining genes are rare causes of MODY, each accounting for less than 5% of cases:[1-3]

- MODY5: Caused by heterozygous mutations in HNF1B. The vast majority of HNF1B mutations cause Renal Cysts and Diabetes Syndrome, which is associated with

diabetes, renal cysts, genitourinary malformations, pancreatic atrophy, hyperuricemia, and abnormal liver function tests.
- MODY8: Caused by heterozygous mutations in CEL. Affected individuals also have pancreatic exocrine dysfunction (diabetes-pancreatic-exocrine dysfunction syndrome).
- Others include: MODY4 (PDX1/IPF-1), MODY6 (NEUROD1), MODY7 (KLF11), MODY9 (PAX4), MODY10 (INS), MODY11 (BLK), MODY12 (ABCC8), MODY13 (KCNJ11), and APPL1 (MODY14).

Other monogenic causes of pediatric diabetes include the following (not meant to be an all-inclusive list):[1,5,6]
- Permanent neonatal diabetes mellitus (PNDM), defined as persistent hyperglycemia in the first 6 months of life. It is most commonly caused by mutations in the ABCC8, KCNJ11, and INS genes. Biallelic mutations in GCK, PDX1, and RFX6 are less common causes.
- Transient neonatal diabetes mellitus (TNDM), which accounts for ~50% of all neonatal diabetes. Affected individuals are at risk for recurrence later in life. 70% of TNDM cases are due to 6q24 methylation defects, while other genetic causes include variants in ABCC8 and KCNJ11.
- Cystic fibrosis, caused by biallelic CFTR mutations (for more information, see test-specific guideline, *Cystic Fibrosis Genetic Testing*)
- Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX syndrome), due to mutations in FOXP3
- Maternally inherited diabetes and deafness (MIDD), caused by mutations in mitochondrial genes: MT-TL1, MT-TK, or MT-TE
- Wolcott-Rallison syndrome, due to mutations in EIF2AK3
- Wolfram syndrome, caused by mutations in WFS1 and less often CISD2
- Other genes associated with PNDM and extra-pancreatic features include GATA6, GLIS3, IER3IP1, NEUROG3, PTF1A, and RFX6.

Inheritance

MODY is typically inherited in an autosomal dominant manner.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Mutations that occur de novo in an affected individual, reduced penetrance, and variable expressivity have been reported.[3] Thus, the absence of a family history does not, by itself, rule out a diagnosis of MODY.

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Diagnosis

Diabetes evaluations may include assessment of pancreatic autoantibodies, plasma glucose levels, hemoglobin A1C assessment (HbA1C), and oral glucose tolerance testing (OGTT). For young individuals in whom a diagnosis of type 1 or type 2 diabetes is considered unlikely, genetic testing for monogenic diabetes may be considered, especially in the presence of a strong family history.[4]

Management

Like other forms of diabetes, monogenic diabetes is treated with diet, oral antidiabetic agents, and/or insulin, as required for blood sugar regulation.[3] Most individuals with MODY are not insulin-dependent. Knowledge of the specific genetic cause of MODY may help guide management.

Survival

Survival of affected individuals was reduced when compared with unaffected relatives, specifically with regard to cardiovascular-related causes of death.[7]

Test information

Introduction

Testing for MODY may include single gene sequence analysis, single gene deletion/duplication analysis, or multigene panels of various sizes.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

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Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

MODY multigene panels include a wide variety of genes associated with MODY and monogenic diabetes in general. Some panels may also include genes associated with other types of monogenic diabetes and glycemic disorders, such as neonatal diabetes, syndromic diabetes, and familial hyperinsulinism.

Guidelines and evidence

American Association of Clinical Chemistry

American Association of Clinical Chemistry (AACL, 2023) stated:[8]

- "Routine determination of genetic markers such as HLA genes or single nucleotide polymorphisms (SNP) is of no value at this time for the diagnosis of management of type 1 diabetes. Typing for genetic markers and the use of genetic risk scores are recommended for individuals who cannot be clearly classified as having type 1 or type 2 diabetes. A (moderate)"
- For selected diabetes syndromes, including neonatal diabetes and MODY (maturity onset diabetes of the young), valuable information including treatment options can be obtained with definition of diabetes-associated mutations. A (moderate)"
- "There is no role for routine genetic testing in people with type 2 diabetes. These studies should be confined to the research setting and evaluation of specific syndromes. A (moderate)"

American Diabetes Association

The American Diabetes Association (ADA, 2025) stated:[9]

- "Children and young adults who do not have typical characteristics of type 1 or type 2 diabetes and family history of diabetes in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young (MODY)." (B)
- "The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:"
  - "Diabetes diagnosed within the first 6 months of life"

- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, no obesity, and lacking other metabolic features, especially strong family of diabetes)
- Stable, mild fasting hyperglycemia (100-150 mg/dL [5.6-8.5 mmol/L]), stable A1C between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially if no obesity"

European Molecular Genetics Quality Network

The European Molecular Genetics Quality Network (EMQN, 2008) made the following recommendations for testing:[2]

- Testing for GCK mutations (presentation outside of pregnancy):
  - Persistent, stable elevation of fasting blood glucose (5.5-8 mmol/l)
  - HbA1c just above the upper limit of normal (rarely exceeds 7.5%)
  - Oral glucose tolerance testing demonstrates a small increment (4.6 mmol/l is often used to prioritize testing)
  - May have a family history consistent with autosomal dominant inheritance
- Testing for GCK mutations (for evaluation of gestational diabetes):
  - Persistent elevation of fasting blood glucose (5.5-8 mmol/l) before, during and after pregnancy
  - At least one oral glucose tolerance test with an increment of <4.6 mmol/l (either during or after pregnancy)
- Testing for HNF1A mutations:
  - Young-onset diabetes (<25 years old)
  - Non-insulin-dependent diabetes
  - Family history of diabetes (at least two generations)
  - Absence of pancreatic islet autoantibodies
  - Glycosuria at blood glucose levels <10 mmol/l
  - Marked sensitivity to sulfonylureas
  - Features suggestive of monogenic diabetes (lack of obesity or evidence of insulin resistance, absence of acanthosis nigricans, etc)
- Testing for HNF4A mutations:
  - Should be considered when HNF1A analysis is normal but the clinical features are strongly suggestive of HNF1A
  - "When diabetic family members have marked macrosomia (>4.4 kg at term) or if diazoxide-responsive neonatal hyperinsulinism has been diagnosed in the context of familial diabetes."
  - "Macrosomic babies with diazoxide-responsive hyperinsulinism and a strong family history of diabetes should be considered for HNF4A mutation screening."

- Syndromic forms of diabetes, including HNF1B and CEL mutations, "are not included in these guidelines since testing is guided by the non-endocrine pancreatic or extra-pancreatic clinical features."

International Society for Pediatric and Adolescent Diabetes

The International Society for Pediatric and Adolescent Diabetes (ISPAD, 2022) made the following recommendations:[1]

- "Testing for GCK-MODY, which is the commonest cause of persistent, incidental hyperglycemia in the pediatric population, is recommended for mild stable fasting hyperglycemia that does not progress." (B)
- "In familial autosomal dominant symptomatic diabetes, mutations in the HNF1A gene (HNF1A-MODY) should be considered as the first diagnostic possibility" (B)
- "Specific features can suggest subtypes of MODY, such as renal developmental disease or renal cysts (HNF1B-MODY), macrosomia and/or neonatal hypoglycemia (HNF4A-MODY), exocrine pancreatic dysfunction or pancreatic cysts (CEL-MODY), or hearing impairment and maternal inheritance of diabetes (mitochondrial diabetes)" (C)
- "Obesity alone should not preclude genetic testing in young persons, especially if:
  - Family history is strongly suggestive of autosomal dominant inheritance of diabetes
  - If some affected family members are NOT obese
  - And/or, there are no other features of metabolic syndrome." (C)
- "Features that suggest monogenic diabetes in children initially thought to have T1D [Type 1 diabetes] are listed below. . . none of these are pathognomonic and should be considered together rather than in isolation:"
  - "Diabetes presenting before 6 months of age (as T1D is extremely rare in this age group), or consider NDM [neonatal diabetes mellitus] if the diagnosis is between 6 and 12 months and there is no evidence of autoimmunity or if the person with diabetes has other features such as congenital defects, or an unusual family history."
  - "Family history of diabetes in one parent and other first-degree relatives of that affected parent."
  - "Absence of islet autoantibodies, especially if checked at diagnosis."
  - "Preserved β-cell function, with low insulin requirements and detectable C-peptide (either in blood or urine) over an extended partial remission phase (at least 5 years after diagnosis)."
- "In young people, T2D [Type 2 diabetes] often presents around puberty and the majority are obese. As there is no diagnostic test for T2D and because obesity has become so common in children, children and adolescents with monogenic diabetes may also be obese and can be very difficult to distinguish from T2D. One recent study found that 3% of obese youth with presumed T2D in fact carried pathogenic

monogenic diabetes variants. Features that suggest monogenic diabetes in young people with suspected T2D are listed below:"

  - "Lack of consistent severe obesity among affected family members."
  - "Lack of consistent acanthosis nigricans and/or other markers of metabolic syndrome (hypertension, low HDL-cholesterol, etc.) among affected family members."
  - "Family history of diabetes in one parent and other first-degree relatives of that affected parent, especially if any affected family member lacks obesity and other markers of metabolic syndrome."
  - "Unusual distribution of fat, such as central fat with thin or muscular extremities."
- "From a clinical perspective, specific clinical scenarios when a diagnosis of monogenic diabetes should be considered include:"
  - "Diabetes presenting before 6 months of age, which is known as NDM."
  - "Autosomal dominant familial mild hyperglycemia or diabetes."
  - "Diabetes associated with extra-pancreatic features (such as, for example, congenital heart or gastrointestinal defects, brain malformations, severe diarrhea, or other autoimmune conditions in a very young child)."
  - "Monogenic IR [insulin resistance] syndromes (see below: characterized by high insulin levels or high insulin requirements; abnormal distribution of fat with a lack of subcutaneous fat, especially in extremities; dyslipidemia, especially high triglycerides; and/or significant acanthosis nigricans)."
- "Three genes are responsible for the majority of MODY cases (GCK, HNF1A, and HNF4A) … At least 14 different genes have been reported to cause diabetes with a MODY-like phenotype, and some panels will include all these genes, or possibly also many other genes associated with exceedingly rare recessive causes. It is reasonable to consider including syndromic causes such as mitochondrial diabetes, as diabetes can often be the first presenting feature and a molecular diagnosis can thereby guide monitoring and treatment of other associated features. In the modern era of expanded testing by many different laboratories, caution must be used when interpreting test results, as often there is very little information available to support the causality of rare variants in uncommon subtypes."

Selected Relevant Publications

A 2018 expert-authored review stated that MODY has an onset in adolescence or young adulthood, typically less than 35 years.[3]

- "Molecular genetic testing approaches to determine the associated MODY gene can include a combination of gene-targeted testing (serial singe[sic]-gene or multigene panel) and comprehensive genomic testing (chromosomal microarray analysis or exome sequencing), depending on the phenotype."

- "Serial single-gene testing. Sequence analysis of the most likely genes is performed first. If no pathogenic variant is found, gene-targeted deletion/duplication analysis to detect exon-sized deletions could be considered, especially for those genes (CEL, GCK, HNF1A, HNF1B, and HNF4A) in which whole-gene or multiexon deletions have been identified."
- "A MODY multigene panel that includes the 14 known MODY-related genes and other genes of interest is most likely to identify the genetic cause of MODY at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype."
  1. "The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time."
  2. "Some custom laboratory-designed multigene panels may include genes not associated with MODY but possibly associated with other types of monogenic diabetes; other custom laboratory-designed panels may not include the genes that rarely cause MODY."
  3. "In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that include genes specified by the clinician."
  4. "Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. Note: Given that whole-gene and/or multiexon deletions have been identified in GCK, HNF1A, HNF1B, and HNF4A, a multigene panel that also includes deletion/duplication analysis is recommended."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for maturity-onset diabetes of the young (MODY) testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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MUTYH-Associated Polyposis Genetic Testing

MOL.TS.206.A
v1.0.2026

Introduction

MUTYH-associated polyposis (MAP) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
MUTYH deletion/duplication analysis	81479
MUTYH known familial mutation analysis	81403
MUTYH sequencing	81406
MUTYH targeted mutation analysis	81401

Criteria

Introduction

Requests for MUTYH-associated polyposis (MAP) testing are reviewed using the following criteria.

MUTYH Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing that would detect the familial mutation(s), AND
- Diagnostic or Predisposition Testing:

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- Two known MUTYH mutations in a sibling, or
- Both parents with one or two known MUTYH mutations, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

MUTYH Targeted Mutation Analysis for p.Y179C and p.G396D Mutations

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous MUTYH testing, and
  - No mutation detected on APC gene testing, if performed, AND
- Individual is of possible Northern European descent, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Clinical findings:
    - At least 10 cumulative adenomas, or
    - At least two adenomas, AND
      - At least 5 serrated polyps proximal to the sigmoid colon (2 or more of >10mm), or
      - > 20 serrated polyps of any size, but distributed throughout the colon, AND
  - Recessive pattern of inheritance (e.g. family history positive for only an affected sibling), OR
- Testing for Presymptomatic/Asymptomatic Individuals:
  - Reproductive partner of a person with MAP-associated mutation(s) (to determine if children at risk), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

MUTYH Sequencing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous MUTYH full sequencing, and
  - Two mutations NOT identified through MUTYH targeted mutation analysis (p.Y179C and p.G396D) if performed, and
  - No mutation detected on APC gene testing, if performed, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Clinical findings:
    - At least 10 cumulative adenomas, or

        - At least two adenomas, AND
            - At least 5 serrated polyps proximal to the sigmoid colon (2 or more of >10mm), or
            - > 20 serrated polyps of any size, but distributed throughout the colon, AND
    - Recessive pattern of inheritance (e.g. family history positive for only an affected sibling), OR
- Testing for Presymptomatic/Asymptomatic Individuals:
    - Reproductive partner of a person with MAP-associated mutation(s) (to determine if children at risk), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

MUTYH Deletion/Duplication Analysis

- Genetic Counseling:
    - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
    - MUTYH full sequencing performed, and
    - No mutations or only one mutation detected in MUTYH through any previous testing (founder mutation panel or full gene sequencing), and
    - Meets criteria for MUTYH full sequencing, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

MUTYH testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

What is MUTYH-associated polyposis?

MUTYH-associated polyposis (MAP) is an inherited colorectal cancer syndrome characterized by the development of multiple colon polyps.[1] Individuals also have an increased chance to develop duodenal adenomas which may cause duodenal cancer.[1-3] Some studies have documented an increased risk for ovarian cancer and bladder cancer.[1] Additionally, there is "some evidence of an increased risk for breast and endometrial cancer. Additional reported features include thyroid nodules, benign adrenal lesions, jawbone cysts, and congenital hypertrophy of the retinal pigment epithelium."[1] At this time, management guidelines are available for colonic and duodenal manifestations.

Prevalence

MAP is estimated to account for 0.7% of all colorectal cancer, and the prevalence of MAP is estimated to be 1/20,000 to 1/60,000.[1] It is estimated that 1-2% of individuals in Northern Europe, Australia, and the United States have a single MUTYH mutation.[1]

MUTYH mutations "account for 10%-20% of classical FAP [Familial Adenomatous Polyposis] cases without an APC mutation and for 30% of AFAP [Attenuated Familial Adenomatous Polyposis] cases."[4]

Symptoms

MAP clinical findings overlap those of FAP and AFAP. Affected individuals most often have fewer than 100 adenomas, but cases of hundreds and occasionally over 1000 polyps have been reported.[1,2] Hyperplastic and sessile serrated, and traditional serrated adenomatous polyps have also been seen individuals with MAP, although adenomas remain the most common polyp type in MAP.[1,3] Duodenal adenomas occur in 17-34% of individuals with MAP and gastric polyps have been reported in about 11%.[1,3,4] Additionally, approximately one third of individuals with MAP have been described with colorectal cancer and no polyposis.[1]

Adenomas and colorectal cancer tend to present later than FAP. MAP is "characterized by a greatly increased lifetime risk of colorectal cancer (CRC) (43%-63% at age 60 years and a lifetime risk of 80%-90% in the absence of timely surveillance)."[1] There is also an estimated 4-5% lifetime risk for duodenal cancer.[1-3]

Cause

MAP is caused by mutations in the MUTYH gene (also called MYH).[1]

Inheritance

MAP is an autosomal recessive disorder.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

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Diagnosis

As MAP is not clinically distinguishable from FAP or AFAP, the identification of two MUTYH mutations is required to make a diagnosis of MAP.[1,5]

Two MUTYH mutations (p.Y165C and p.G382D) are particularly common and account for over 80% of MUTYH mutations in Caucasians of Northern European descent.[6] Some laboratories test for only these two mutations or offer reflex options that begin with these two mutations and proceed to full gene sequencing if two mutations are not found.

If sequencing does not find two mutations, large gene deletion/duplication analysis can be performed. It remains unknown what percentage of MAP is due to large deletions/duplications/rearrangements in the gene and thus are detectable only with this technology. However, large deletions have been reported.[1,7,8]

Surveillance

For individuals with MAP, colonoscopy screening should begin at 25-30 years (earlier colonoscopy may be indicated based on family history). If the colonoscopy is negative, repeat colonoscopy should occur every 1-2 years.[2] For positive colonoscopy findings, the treatment and surveillance is dependent on polyp burden.[2] Additional recommended screening includes upper endoscopy with complete visualization of the ampulla of Vater beginning at 30-35 years.[2] If no duodenal polyps are detected, then repeat endoscopy occurs every 3 to 5 years. If duodenal polyps are detected, repeat endoscopy is dependent on the quantity and size of the polyps.[2]

"Chemoprevention may be considered in select patients, but options have not been studied specifically in MAP. Consider referral to a center with expertise for discussion of chemoprevention and surgical options, particularly for patients with a high polyp burden in the remaining rectum after colectomy."[2]

For individuals with a single MUTYH mutation, the recommended surveillance is dependent on the family history of colon cancer.[2]

- Individuals without a history of colorectal cancer and with a first-degree relative with colorectal cancer: colonoscopy screening every 5 years beginning at 40 years or 10 years prior to the age of the first-degree relative's diagnosis, whichever comes first. Colonoscopy may be repeated at more frequent intervals if indicated based on colonoscopy findings.
- Individuals without a history of colorectal cancer and with a second-degree relative with colorectal cancer or if there is no family history of colorectal cancer: there are no specific screening recommendations.

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Test information

Introduction

Testing for MAP may include known familial mutation analysis, targeted mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutation analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the known mutation(s). However, if available, a targeted mutation panel that includes the familial mutation(s) may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

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Guidelines and evidence

American College of Gastroenterology

Evidence-based guidelines from the American College of Gastroenterology (ACG, 2015) stated:[9]

- "Individuals who have a personal history of >10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors (abdominal>peripheral), papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium (CHRPE), epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes. ... Genetic testing of patients with suspected adenomatous polyposis syndromes should include APC and MUTYH gene mutation analysis."

American Society of Clinical Oncology and European Society for Medical Oncology

The American Society of Clinical Oncology (ASCO, 2015) endorsed the European Society for Medical Oncology (ESMO, 2013) clinical practice guideline on hereditary colorectal cancer syndromes. This guideline stated:[10]

- "Patients with multiple colorectal adenomas (>10), should be considered for germline testing of APC and/or MUTYH."
- "Germline testing of MUTYH can be initiated by screening for the most common mutations ([p.]G396D, [p.]Y179C) in the white population followed by analysis of the entire gene in heterozygotes. Founder mutations among ethnic groups should be taken into account. For nonwhite individuals, full sequencing of MUTYH should be considered."

American Society of Gastrointestinal Endoscopy

Consensus guidelines from the American Society of Gastrointestinal Endoscopy (ASGE, 2020) recommended:[11]

- "...genetic counseling and testing in patients with clinical polyposis defined as 10 or more adenomas found on single endoscopy and 20 or more adenomas during their lifetime." [low quality]
- "...genetic counseling and testing in all first-degree relatives of confirmed polyposis syndrome patients. ... suspected AFAP and MAP should be tested at age 18-20 years." [low quality]

National Comprehensive Cancer Network

Guidelines from the National Comprehensive Cancer Network (NCCN, 2025) stated:[2]

- MUTYH testing criteria:
  - At least 10 adenomas
  - Meets criteria for SPS [Serrated Polyposis Syndrome] and some adenomas. (see below)
  - Known deleterious MUTYH mutation(s) in the family
- SPS clinical diagnostic criteria:
  - "≥5 serrated lesions/polyps proximal to the rectum, all being ≥5 mm in size, with ≥2 being ≥10 mm in size."
  - ">20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum."
  - Note: "any histological subtype of serrated lesion/polyp (hyperplastic polyp, sessile serrated lesion without or with dysplasia, traditional serrated adenoma, and unclassified serrated adenoma) is included in the final polyp count. The polyp count is cumulative over multiple colonoscopies."
- "Siblings of a patient with MAP are recommended to have site-specific testing for the familial PVs [pathogenic variants]. Full sequencing of MUTYH may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not have a MUTYH PV [pathogenic variant], genetic testing in the children is not necessary to determine MAP status. If the unaffected parent is not tested, comprehensive testing of MUTYH should be considered in the adult children. If the unaffected parent is found to have one MUTYH PV, testing the adult children for the familial MUTYH PVs is indicated."
- "When colonic polyposis is present only in the proband and/or in siblings, consider recessive inheritance or de novo APC gene mutations … Overall, the decision to order APC, MUTYH, or germline multi-gene testing including these genes should be at the discretion of the clinician."
- All recommendations are category 2A.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for MUTYH testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Mitochondrial Disorders Genetic Testing

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Introduction

Mitochondrial disorders genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Genomic Unity Comprehensive Mitochondrial Disorders Analysis	0417U
Mitochondrial disorder known familial mutation analysis	81403
MT-ATP6 targeted mutation analysis	81401
MT-ND1 targeted mutation analysis	81479
MT-ND4, MT-ND6 targeted mutation analysis	81401
MT-ND5 targeted mutation analysis	81401
MT-TK targeted mutation analysis	81401
MT-TL1 targeted mutation analysis	81401
Nuclear encoded mitochondrial gene sequencing panel	81440
TYMP sequencing	81405
Whole mitochondrial genome sequencing	81460
Whole mitochondrial genome deletion/ duplication analysis	81465

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Criteria

Introduction

Requests for mitochondrial disorders genetic testing are reviewed using the following criteria.

Known Familial Mutation Testing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, and
  - Disease causing mutation(s) identified in 1st degree biological relative, and
  - Member is at risk to have the familial mutation based on inheritance pattern of the disorder in question, AND
- Predictive Testing for Asymptomatic Individuals:
  - 18 years of age or older, or
  - Under the age of 18 years, and
    - Test results are needed for treatment or medical screening, OR
- Diagnostic Testing for Symptomatic Individuals:
  - Clinical examination and/or biochemical results are suggestive, but not confirmatory, of the familial diagnosis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Targeted Mutation Analysis or Single Gene Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing for the mitochondrial disorder to be targeted, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Clinical examination and/or biochemical results are suggestive, but not confirmatory, of the targeted disorder (see table titled *Select Mitochondrial Disorders)*, and
  - Inheritance pattern is consistent with the targeted mitochondrial disorder, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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Whole Mitochondrial DNA (mtDNA) Sequencing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - Member has not had previous whole mtDNA sequencing performed, and
  - Targeted mitochondrial testing, if performed, was negative, and
  - Biochemical testing appropriate for the suspected disorder has been performed and is not confirmatory of a diagnosis of a specific mitochondrial condition, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Member has multiple organ system involvement defined as altered function in two or more organ systems, suggestive of a mitochondrial disorder, and
  - Member has one or more of the following clinical features: newborn hypotonia, metabolic acidosis, failure to thrive, myopathy with exercise intolerance, cardiomyopathy, encephalopathy, seizures, dementia, stroke-like episodes, ataxia, spasticity, ptosis, ophthalmoparesis, ophthalmoplegia, optic neuropathy or atrophy, pigmentary retinopathy, optic nerve hypoplasia, sensorineural hearing loss, cyclic vomiting, diabetes mellitus, unexplained liver failure, episodes of acute rhabdomyolysis, brain magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS) results consistent with a mitochondrial process, and/or pathology results consistent with a mitochondrial process, and
  - Targeted mutation analysis is not feasible because of one of the following:
    - Member's clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available (see table titled *Select Mitochondrial Disorders*), or
    - Member's clinical presentation fits a well-described syndrome and applicable single-gene or targeted mutation analysis was negative, and
  - Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), and
  - Family history strongly suggests mitochondrial inheritance (e.g., no evidence of paternal transmission), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Whole Mitochondrial DNA (mtDNA) Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - Member has not had previous whole mtDNA deletion/duplication analysis performed, and

  - Targeted mitochondrial deletion testing, if performed, was negative, and
  - Biochemical testing appropriate for the suspected disorder has been performed and is not confirmatory of a diagnosis of a specific mitochondrial condition, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Member has multiple organ system involvement defined as altered function in two or more organ systems, suggestive of a mitochondrial disorder, and
  - Member has one or more of the following clinical features: newborn hypotonia, metabolic acidosis, failure to thrive, myopathy with exercise intolerance, cardiomyopathy, encephalopathy, seizures, dementia, stroke-like episodes, ataxia, spasticity, ptosis, ophthalmoparesis, ophthalmoplegia, optic neuropathy or atrophy, pigmentary retinopathy, optic nerve hypoplasia, sensorineural hearing loss, cyclic vomiting, diabetes mellitus, unexplained liver failure, episodes of acute rhabdomyolysis, brain magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS) results consistent with a mitochondrial process, and/or pathology results consistent with a mitochondrial process, and
  - Targeted mutation analysis is not feasible because of one of the following:
    - Member's clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available (see table titled *Select Mitochondrial Disorders*), or
    - Member's clinical presentation fits a well-described syndrome and applicable single-gene or targeted mutation analysis was negative, and
  - Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), and
  - Family history strongly suggests mitochondrial inheritance (e.g., no evidence of paternal transmission), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Nuclear Encoded Mitochondrial Gene Sequencing Panel

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - Member has not had a previous nuclear encoded mitochondrial gene sequencing panel testing performed, and
  - Targeted nuclear-encoded mitochondrial gene testing (e.g., TYMP or POLG analysis), if performed, was negative, and
  - Biochemical testing appropriate for the suspected disorder has been performed and is not confirmatory of a diagnosis of a specific mitochondrial condition, AND
- Diagnostic Testing for Symptomatic Individuals:

- Member has multiple organ system involvement defined as altered function in two or more organ systems, suggestive of a mitochondrial disorder, and
- Member has one or more of the following clinical features: newborn hypotonia, metabolic acidosis, failure to thrive, myopathy with exercise intolerance, cardiomyopathy, encephalopathy, seizures, dementia, stroke-like episodes, ataxia, spasticity, ptosis, ophthalmoparesis, ophthalmoplegia, optic neuropathy or atrophy, pigmentary retinopathy, optic nerve hypoplasia, sensorineural hearing loss, cyclic vomiting, diabetes mellitus, unexplained liver failure, episodes of acute rhabdomyolysis, brain magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS) results consistent with a mitochondrial process, and/or pathology results consistent with a mitochondrial process, and
- Targeted mutation analysis is not feasible because of one of the following:
  - Member's clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available (see table titled *Select Mitochondrial Disorders*), or
  - Member's clinical presentation fits a well-described syndrome and applicable single-gene or targeted mutation analysis was negative, and
- Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), and
- Family history does not strongly suggest mitochondrial inheritance (e.g., paternal transmission is observed, autosomal inheritance is likely), AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

- For information on POLG-related disorders, please refer to the guideline *Polymerase Gamma (POLG) Related Disorders Genetic Testing*, as this testing is not addressed here.
- Testing addressed in this guideline applies to individuals in whom a mitochondrial disorder is suspected based on a constellation of findings commonly seen in these conditions. Mitochondrial genetic testing is considered not medically necessary in the following cases:
  - The individual's findings could be explained nonspecifically by a neurological, metabolic, or myopathic condition not related to mitochondria for which a different genetic test may be considered; or
  - Individuals who have no increased risk above the general population risk to have inherited a mitochondrial disease and have just one of the following findings in isolation: fatigue; muscle weakness; developmental delay; autism; migraines; abnormal biochemical test results (e.g., elevated lactate); psychiatric symptoms.

Table: Select Mitochondrial Disorders

Disorder, genes, CPT code, symptoms

Mitochondrial Disorder	Associated Genes / Mitochondrial DNA Mutations	CPT Code(s)	Symptoms
Leber Hereditary Optic Neuropathy (LHON)	MT-ND1, MT-ND4, MT-ND6	81401, 81479	Unilateral or bilateral painless subacute vision loss, central or cecocentral scotomas, and/or impaired color vision
Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS)	MT-TL1, MT-ND5	81401	Stroke-like episodes, encephalopathy with seizures, and/or dementia, muscle weakness and exercise intolerance, recurrent headaches, recurrent vomiting, hearing impairment, peripheral neuropathy, learning disability, and/or short stature, with abnormal neuroimaging during SLEs
Mitochondrial Epilepsy with Ragged Red Fibers (MERRF)	MT-TK	81401	Myoclonus, generalized epilepsy, ataxia, muscle weakness, dementia, and/or ragged red fibers on muscle biopsy
Mitochondrial Neurogastrointestinal Encephalopathy (MNGIE)	TYMP	81405	Progressive gastrointestinal dysmotility, cachexia, ptosis, ophthalmoplegia, leukoencephalopathy, and/or peripheral neuropathy
Neurogenic Muscle Weakness, Ataxia, and Retinitis Pigmentosa (NARP)	MT-ATP6	81401	Proximal neurogenic muscle weakness with sensory neuropathy, ataxia, learning difficulties, and/or pigmentary retinopathy

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Mitochondrial Disorder	Associated Genes / Mitochondrial DNA Mutations	CPT Code(s)	Symptoms
POLG-Related Disorders (Alpers-Huttenlocher syndrome (AHS), Childhood Myocerebrohepatopathy Spectrum (MCHS), Myoclonic Epilepsy Myopathy Sensory Ataxia (MEMSA), Ataxia Neuropathy Spectrum (ANS), Autosomal Dominant or Autosomal Recessive Progressive External Ophthalmoplegia (adPEO/arPEO))	POLG	81406	Please refer to the guideline *Polymerase Gamma (POLG) Related Disorders Genetic Testing*
Mitochondrial Nonsyndromic Hearing Loss and Deafness	MT-RNR1, MT-TS1	81401, 81403	Please refer to the guideline *Nonsyndromic Hearing Loss and Deafness Genetic Testing*

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Mitochondrial Disorder	Associated Genes / Mitochondrial DNA Mutations	CPT Code(s)	Symptoms
mtDNA Deletion Syndromes (Kearns-Sayre Syndrome (KSS), Pearson syndrome, Progressive External Ophthalmoplegia (PEO), rarely Leigh syndrome)	Full mtDNA Deletion Analysis	81465	KSS: childhood onset of pigmentary retinopathy, progressive external ophthalmoplegia, and cardiac conduction abnormalities Pearson syndrome: pancytopenia, exocrine pancreas dysfunction, lactic acidosis, and poor weight gain PEO: ptosis, ophthalmoplegia, proximal limb weakness and/or exercise intolerance, oropharyngeal weakness Leigh syndrome: developmental delays and/or neurodevelopmental regression, abnormal neuroimaging, and lactic acidosis

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g., ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- When otherwise reimbursable, the following limitations apply:

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When a whole mtDNA analysis or a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81460 for Whole mtDNA Sequencing, 81465 for Whole mtDNA Deletion/ Duplication, and 81440 for Nuclear Encoded Mitochondrial Gene Sequencing Panels)*.
- When use of a panel code is not possible, each billed component procedure will be assessed independently.
- In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
- If more than one test or procedure code is requested at one time, the member meets criteria for all tests requested, and mtDNA and nuclear DNA mutations (or causes) are equally likely based on personal history, clinical findings, and family history, the testing will be tiered in the following order: 81460, 81465, 81440.
- If a single panel code is requested that includes testing of both mtDNA and nuclear DNA (e.g., 0417U), the member meets criteria for all tests described by the requested code, and mtDNA and nuclear DNA mutations (or causes) are equally likely based on personal history, clinical findings, and family history, the code will be reimbursable.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code and general coding requirements, please refer to the guideline *Laboratory Billing and Reimbursement*.

What are mitochondrial disorders?

Mitochondrial disorders are conditions resulting from mutations in the nuclear (nDNA) or mitochondrial (mtDNA) genes that are involved in the production, function, maintenance, or transmission of mitochondria.

Incidence

Mitochondrial disorders have an estimated minimum incidence of 1 in 5,000.[1]

Symptoms

Mitochondrial disorders are a clinically diverse group of diseases that may present at any age and affect a single organ or present as a multi-system condition in which

neurologic and myopathic features predominate. Extensive clinical variability and phenotypic overlap exists among the many discrete mitochondrial disorders.[2,3]

Mitochondrial disease is suspected in individuals with a combination of clinical features which can include any of the following:[1,2]

- Neurologic: cerebral stroke-like lesions, basal ganglia disease, encephalopathy, neurodegeneration, epilepsy, myoclonus, ataxia, MRI findings consistent with Leigh disease, characteristic MRS peaks, neuropathy
- Cardiovascular: hypertrophic cardiomyopathy with rhythm disturbance, unexplained heart block particularly in a child, cardiomyopathy with lactic acidosis, dilated cardiomyopathy with muscular weakness, Wolff-parkinson-White arrhythmia
- Ophthalmologic: retinal degeneration with signs of night blindness, color-vision deficits, decreased visual acuity, or pigmentary retinopathy, ophthalmoplegia/paresis, fluctuating, disconjugate eye movements, ptosis, sudden- or insidious-onset optic neuropathy/atrophy
- Gastroenterologic: unexplained or valproate-induced liver failure, severe dysmotility, pseudo-obstructive episodes
- Other: a newborn, infant, or young child with unexplained hypotonia, weakness, failure to thrive, and a metabolic acidosis (particularly lactic acidosis), exercise intolerance that is not in proportion to weakness, hypersensitivity to general anesthesia, episodes of acute rhabdomyolysis; mid-pregnancy or late-pregnancy fetal loss

Several mitochondrial disorders, due to mutations in the mtDNA, are characterized by a cluster of clinical features or syndromic presentation. These disorders are described in the table titled *Select Mitochondrial Disorders.*

Cause

Mitochondrial disorders result from dysfunction of the mitochondrial respiratory chain due to abnormality of the production, function, maintenance, or transmission of mitochondria.[2] They can be caused by mutations in either mitochondrial or nuclear DNA.

Underlying nDNA and mtDNA causes are frequently indistinguishable based on this symptomology. Diagnosis of the majority of mitochondrial conditions is based on a combination of clinical findings and genetic testing.[4,5]

For all mtDNA mutations, clinical expressivity depends on the three following factors:[2]

- The percentage of mtDNA that contains the mutation (mutational load or heteroplasmy)
- The organs and tissues in which the mtDNA mutation is found (tissue distribution), and
- The point at which each organ or tissue begins to dysfunction due to reaching a critical point of impaired oxidative metabolism (threshold effect).

Inheritance

Mitochondrial conditions due to mutations in the mtDNA are maternally inherited or may be de novo. Mitochondrial conditions caused by mutations in the nuclear DNA can be maternally or paternally inherited and may follow autosomal dominant, autosomal recessive, or X-linked inheritance.

Mitochondrial Inheritance

MtDNA mutations may be de novo (not inherited) or follow maternal inheritance. This means that a female who carries the mtDNA mutation at a high mutation load will typically pass it on to all of her children. However, due to the meiotic bottleneck, the heteroplasmy level may vary significantly between generations. A male who carries the mtDNA mutation cannot pass it on to his children. Clinical expressivity of mtDNA mutations depends on the degree of heteroplasmy and the organs and tissues most affected by the mutation.

A female who carries a mtDNA mutation will have a recurrence risk ranging from 0-100% for passing it down to her offspring; however, mtDNA deletions are rarely transmitted (less than 1% empiric risk).[2]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

X-Linked Inheritance

In X-linked inheritance, the mutation is carried on the X chromosome. Females have two X chromosomes, and males have one. Males typically have more severe symptoms than females. A female with a mutation has a 50% chance to pass that mutation to her children. A male with a mutation cannot pass the mutation to any sons, but will pass it to all daughters. A process called X-inactivation in females results in random inactivation of expression of one X-chromosome in each cell of the body. For females with one mutation, the percentage and distribution of cells with

expression of the X chromosome carrying the mutation can influence the degree of severity.

Identification of a mutation in a proband may allow for informative testing of at-risk relatives.

Diagnosis

Clinical findings may point to a specific, well-described mitochondrial disorder, and the clinical diagnosis is often confirmed with molecular testing.[6] However, underlying nuclear and mitochondrial DNA causes are frequently indistinguishable based on this symptomology.

The investigation and diagnosis of individuals with mitochondrial disease often necessitate a combination of techniques including clinical assessment, biochemical assessment, neuroimaging, molecular genetic studies, and sometimes biopsy of the muscle, liver, or skin.

Biochemical assessment includes measurement of plasma or CSF lactate and pyruvate, glucose, creatine kinase (CK), transaminases (AST, ALT), ketone bodies, plasma acylcarnitines, quantitative amino acids, and urinary organic acids. Normal levels for any of the biochemical studies do not exclude the presence of a mitochondrial disorder. Biochemical studies that are abnormal but not confirmatory, may aid in the diagnosis of a mitochondrial disorder if other clinical features are present.[2,7]

Brain magnetic resonance imaging (MRI) is recommended if CNS symptoms are present. Brain magnetic resonance spectroscopy (MRS) for elevated lactate is also useful. Neuroimaging results are not confirmatory, but may aid in the diagnosis of a mitochondrial disorder if other clinical features are present, though for Leigh syndrome and MELAS they may be highly indicative.[6,8]

Molecular genetic testing should ideally be directed by the clinical phenotype and results of these other investigations.[2]

If a specific disorder is not evident, analysis of an individual's family history may provide information regarding most likely inheritance patterns for a suspected mitochondrial condition. This may guide decisions to perform mtDNA sequencing, mtDNA deletion/duplication testing, nuclear encoded DNA sequencing, and/or nuclear encoded DNA deletion/duplication testing.

Management

Mitochondrial disease is not curable. However, in some cases, specific treatment recommendations can be made based on a person's definitive diagnosis. Consensus based recommendations have been published by the Mitochondrial Medicine Society for the routine care and management of individuals with mitochondrial disease.[1] Individuals

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at-risk for mitochondrial conditions may also benefit from clinical assessment to initiate baseline evaluations (neurology, cardiology, ophthalmology, and audiology) and potential intervention prior to exhibiting clinical manifestations.[1,4,8]

Survival

Mitochondrial disorders are clinically heterogeneous with a wide range of severity and age of onset, depending upon the specific disorder.[1] While genetic test results alone cannot predict the exact course or phenotype of the disease, severity does correlate with mutation load for most mtDNA mutations.[7,9]

Test information

Introduction

Testing for mitochondrial diseases may include known familial mutation analysis, targeted mutation analysis, mitochondrial genome sequencing, mitochondrial genome deletion/duplication analysis, and next-generation sequencing (NGS) panels.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

If an individual’s clinical findings clearly correlate with a specific mitochondrial condition, then testing can be focused on the most appropriate approach for that condition. "False negative rates vary by genomic region; therefore, genomic testing may not be as accurate as targeted single-gene testing or multigene molecular genetic testing panels."[2]

Whole Mitochondrial Genome Sequencing

Full sequencing of the entire mitochondrial genome by NGS is capable of simultaneously detecting point mutations, deletions, and point mutation heteroplasmies in the assessment of a number of overlapping mitochondrial syndromes. When clinical suspicion for a mitochondrial disorder is high following biochemical screening and without clear correlation with a specific mitochondrial condition, mtDNA genome testing is often the preferred test. DNA testing can be performed on a blood or saliva specimen, and while generally not necessary, some labs accept muscle biopsy samples as well.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

A number of large panels are available that sequence numerous nuclear-encoded mitochondrial genes for a broad approach to testing. Multi-gene panel tests, even for similar clinical scenarios, vary considerably laboratory by laboratory in the genes that are included and in technical specifications (e.g., depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis).

NGS testing is capable of simultaneously detecting point mutations, deletions, and when mtDNA is analyzed, point mutation heteroplasmy. Typically, Sanger sequence analysis will miss heteroplasmy below 20%. With suitable depth of coverage, NGS can detect heteroplasmy down to ~1%.[10,11]

Test Strategy

Due to overlap of clinical findings of mitochondrial conditions and non-mitochondrial conditions, affected individuals are more likely to have multiple tests performed before a molecular genetic cause is identified.

When mtDNA genome or nDNA panel testing does not yield a diagnosis, further investigations may involve a range of other clinical tests, including more comprehensive

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genetic testing. Testing of alternative tissues by biochemical and/or molecular analysis may be required, especially if blood testing is negative and the phenotype is highly suggestive of the presence of a mutation associated with a specific gene or set of genes, or when there is a need to assess reproductive risk.[2,12]

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2013) states the following regarding testing individuals with isolated autism for mitochondrial disorders:[13]

- "As with metabolic disorders, testing for mitochondrial disorders in persons with ASDs is recommended only if supporting symptoms or laboratory abnormalities are present."

European Federation of Neurological Sciences

The European Federation of Neurological Sciences (EFNS, 2009)[5] provided molecular diagnostic consensus-based guidelines based on literature reviews: "If the phenotype suggests syndromic MID [mitochondrial disease] due to mtDNA point mutations (MELAS, MERRF, NARP, LHON) DNA-microarrays using allele-specific oligonucleotide hybridisation, real-time-PCR or single-gene sequencing are indicated."

International Consensus Statement on Leber Hereditary Optic Neuropathy

An international consensus conference (2017) with a panel of experts from Europe and North America made the following statements regarding the clinical and therapeutic management of LHON.[14]

- "LHON primarily is a clinical diagnosis…. A definitive diagnosis of LHON is rapidly obtained by the molecular identification of one of the 3 common mtDNA mutations (m.11778G>A/MT-ND4, m.3460G>A/MT-ND1, m.14484T>C/MTND6), accounting for about 90% of cases. If this primary screen is negative and there is a high index of clinical suspicion supported by a maternal mode of inheritance in a patient with a family history, sequencing the entire mtDNA is advisable to identify other, but rare, mtDNA mutations."
- "The diagnosis of LHON should be based on a careful history, evaluation of key structural and functional visual parameters, and on a molecular confirmation of a pathogenic mtDNA mutation. The management of LHON includes genetic counseling, informing the patient about potentially preventable lifestyle risk factors and, for subacute and dynamic cases, the use of idebenone at the currently approved dose. Idebenone should be discontinued in nonresponder patients and is currently not recommended in patients in the chronic stages of the disease. These guidelines

and recommendations are based on a consensus developed on the current state of the literature. Further investigations and clinical trials are needed to lead to better disease-modifying treatments and to improve the management of patients with LHON."

Mitochondrial Medicine Society

The Mitochondrial Medicine Society (MMS, 2015) developed consensus recommendations using the Delphi method.[12]

- Recommendations for DNA Testing
  - "Massively parallel sequencing/NGS of the mtDNA genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic point mutations."
  - "Patients with a strong likelihood of mitochondrial disease because of a mtDNA mutation and negative testing in blood, should have mtDNA assessed in another tissue to avoid the possibility of missing tissue-specific mutations or low levels of heteroplasmy in blood; tissue-based testing also helps assess the risk of other organ involvement and heterogeneity in family members and to guide genetic counseling."
  - "When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no mutation is identified via known NGS panels, then whole exome sequencing should be considered."
- Recommendations for pathology testing
  - Biopsy should only be considered when the diagnosis cannot be confirmed with DNA testing of other more accessible tissues. Muscle (and/or liver) biopsies are often not necessary and should be avoided when possible due to their invasive nature, unless other types of analyses such as pathology, enzymology, or mtDNA copy number analyses are required for diagnosis.

MNGIE International Network

The MNGIE International Network (2021) position paper on the diagnosis and treatment of mitochondrial neurogastrointestinal encephalomyopathy stated:[15]

- Homozygous or compound heterozygous pathogenic variants in TYMP are diagnostic and no further genetic testing is needed.
- When a single pathogenic TYMP variant is identified, biochemical assessment of TP activity should be performed.

United Kingdom Best Practices Guideline

A working group of Clinical Scientists from the NHS Highly Specialised Service, in collaboration with national laboratory consultation, published (2023) best practice guidelines for genetic testing for mitochondrial disease.[16] The guidelines summarize current recommended technologies and methodologies for analysis of mtDNA and nuclear-encoded genes in patients with suspected mitochondrial disease, as well as genetic testing strategies for diagnosis. The guidelines outline two main alternative strategies:[16]

- "Targeted testing of 'common' mtDNA variants and/or targeted nuclear testing, followed by more comprehensive testing if required and if resources allow."
- "NGS of the mitochondrial genome and/or nuclear genes, e.g., by whole exome sequencing (WES) or whole genome sequencing (WGS)."

Targeted testing can be appropriate for routine referrals where there is not an urgent clinical need to obtain a diagnosis, for clinical presentations which are highly suggestive of a particular variant or gene, and/or where resources are limited.

Comprehensive NGS-based testing can be used for all referral indications but is particularly appropriate for more complex phenotypes and/or for urgent referrals. Simultaneous testing of both mtDNA and nDNA is recommended, as both account for a significant proportion of childhood-onset and adult-onset mitochondrial disorders.

Selected Relevant Publications

An expert-authored consensus statement (2019) regarding the diagnosis and management of mitochondrial stroke-like episodes stated:[17]

- "If a stroke-like episode is suspected in an individual without a pre-existing diagnosis of mitochondrial disease, urgent genetic testing should be considered as this will have implications for the clinical management."
- "We recommend that at least two tissue samples (e.g. blood and urine samples or blood and buccal samples) should be sent for the genetic studies because mtDNA pathogenic variants such as the m.3243A>G mutation (or other) may not be detectable in blood. If the m.3243A>G or other mtDNA variant is detected, their heteroplasmy level in different tissues should be quantified."
- "Muscle biopsy should be considered after excluding m.3243A>G and POLG variants. Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered if muscle biopsy not possible in patients present with classical stroke-like episodes."

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for mitochondrial disorders genetic testing will ensure

that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Neurofibromatosis Type 1 Genetic Testing

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Neurofibromatosis Type 1 (NF1) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
NF1 deletion/duplication analysis	81479
NF1 known familial mutation analysis	81403
NF1 sequencing	81408

Criteria

Requests for neurofibromatosis type 1 (NF1) genetic testing are reviewed using the following criteria.

NF1 Known Familial Mutation Analysis

Genetic Counseling:

- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:

- No previous genetic testing of NF1 that would detect the familial mutation, AND
- NF1 mutation identified in 1st degree biological relative, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

NF1 Sequencing

Genetic Counseling:

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- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:
- No previous genetic testing of NF1, and
- No known pathogenic NF1 mutation in biological relatives, AND

Diagnostic Testing for Symptomatic Individuals:
- The member is suspected to have neurofibromatosis type 1 but the diagnosis is in question because member meets only one of the following:
  - Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals, or
  - Six or more café-au-lait macules over 15 mm in greatest diameter in postpubertal individuals, or
  - Freckling in the axillary or inguinal regions, or
  - Two or more neurofibromas of any type or one plexiform neurofibroma, or
  - Optic glioma, or
  - Two or more Lisch nodules (iris hamartomas) or two or more choroidal abnormalities, or
  - A distinctive osseous lesion (e.g., sphenoid dysplasia or long bone pseudoarthrosis), or
  - The member displays at least two of the following findings:
    - Less than 6 café-au-lait macules of any size
    - One neurofibroma
    - One Lisch nodule or choroidal abnormality, AND
- The results of the test will directly impact the diagnostic and treatment options that are recommended for the individual, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

NF1 Deletion/Duplication Analysis

- Criteria for NF1 Sequencing are met, AND
- No previous deletion/duplication analysis of NF1, AND
- No mutation detected in full sequencing of NF1, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

NF1 Testing on Tissue Samples

Requests for NF1 testing on café-au-lait macules or neurofibromas after negative NF1 testing on a blood sample in individuals with a clinical suspicion of segmental NF will be reviewed on a case-by-case basis.

What is Neurofibromatosis Type 1?

Neurofibromatosis Type 1 (NF1) is a neurocutaneous condition characterized by the growth of tumors along nerves in the skin, brain, eyes, and other parts of the body and changes in skin pigmentation (café-au-lait macules and freckling).[1]

Incidence

NF1 is one of the most common dominantly inherited genetic disorders. This condition has an incidence at birth of approximately 1 in 2500 to 1 in 3000 individuals.[2,3]

Symptoms

The signs and symptoms of NF1 develop gradually over time. Initial clinical features of NF1 are café-au-lait macules. These macules increase in size and number with age. Freckling in the axilla and inguinal area (groin) develop later in childhood. Lisch nodules are present in fewer than 50% of affected children under the age of 5 years. However, these benign iris tumors (hamartomas) are present in almost all affected adults.[4]

The spectrum and severity of symptoms vary greatly between individuals with NF1, even in the same family.[5] Skin findings and Lisch nodules may be the only clinical features in some individuals with NF1. Multi-systemic manifestations of NF1 include short stature, macrocephaly, scoliosis, distinctive osseous lesions, learning differences, seizures, and attention deficit hyperactivity disorder (ADHD). Cardiovascular complications include high blood pressure, cerebral and peripheral arterial stenosis, and stroke.[4,6] "Juvenile xanthogranuloma and nevus anemicus are more common than expected in people with NF1 and may be useful in supporting the diagnosis in young children who do not meet the standard diagnostic criteria."[4]

NF1 is associated with an increased risk of benign tumors, including cutaneous and plexiform neurofibromas, optic glioma, and pheochromocytoma. There is also an increased risk of certain cancers, including malignant peripheral nerve sheath tumors, brain tumors, leukemia, and breast cancer.[7] Malignant peripheral nerve sheath tumors may develop by malignant transformation of neurofibromas during adolescence or adulthood.

Diagnosis

Revised diagnostic criteria for NF1 were formulated by the International Consensus Group on Neurofibromatosis Diagnostic Criteria (2021).[8] A full description can be found in the Guidelines and Evidence section.

"Negative NF1 molecular testing does not rule out a diagnosis of NF1. Some individuals diagnosed with NF1 based on clinical criteria do not have a pathogenic variant detectable by current technology. Many clinical features of NF1 increase in frequency

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with age, and some individuals who have unequivocal NF1 as adults cannot be diagnosed in early childhood, before these features become apparent."[4]

NF1 has overlapping clinical features with Legius syndrome, other forms of neurofibromatosis, conditions with café-au-lait and pigmented macules, and overgrowth syndromes.[2,4,9]

Genotype-Phenotype Correlations

Only a few clear correlations between specific NF1 mutations and distinct clinical phenotypes have been described.

Individuals with a single amino acid deletion p.Met922del in the NF1 gene have a very mild phenotype with typical pigmentary features of NF1 without cutaneous neurofibromas or other tumors.[10,11] Missense mutations affecting p.Arg1809 are associated with a distinct presentation including pulmonic stenosis, learning disabilities, short stature, and Noonan-like features, in addition to mild NF1 phenotype.[12]

NF1 microdeletions are associated with early appearance of numerous cutaneous neurofibromas, severe cognitive abnormalities, somatic overgrowth, large hands and feet, and dysmorphic facial features.[13]

Individuals with missense mutations in codons 844-848 have a high risk of plexiform and spinal neurofibromas, optic gliomas, skeletal abnormalities, and other malignant tumors.[14]

Segmental NF

Segmental NF1 (also called mosaic NF1) is a rare subtype that results from a post-zygotic mutation in the NF1 gene leading to somatic mosaicism. Neurofibromas, café-au-lait macules, and axillary freckling are typically unilateral and localized to one area of the body, usually following the lines of Blashko.[15] There is an increased risk of malignancies.[14,15]

Cause

Neurofibromatosis Type 1 is caused by mutations in the NF1 gene which produces the protein product, neurofibromin. Neurofibromin functions as a tumor suppressor. NF1 gene mutations lead to defective or missing neurofibromin resulting in uncontrolled cell proliferation and growth of tumors common in NF1.[5]

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Inheritance

Neurofibromatosis type 1 is inherited in an autosomal dominant fashion.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Almost half of all NF1 cases are the result of a new or de novo gene mutation. The mutation rate for NF1 is among the highest known for any gene in humans.[16] The remainder of NF1 cases are inherited from an affected parent. Individuals with NF1 have a 50% chance of passing the mutation to their children. Additionally, parents and siblings of known affected individuals have a 50% chance of having the same mutation. Penetrance is virtually complete after childhood; however, there is significant clinical variability.[4,9]

Management

There is no cure for Neurofibromatosis type 1. Long-term management includes multi-system surveillance for potential complications, treatment of bulky tumors and cancers, and therapies and medications for other systemic manifestations.[6] Clinical trials are underway to study new medications for the treatment of tumors common in NF1.

Selumetinib (Koselugo) is an FDA-approved treatment for children 2 years of age and older with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas.[17]

Survival

The lifespan of individuals with Neurofibromatosis Type 1 is reported to be approximately 8 years less than the general population. The most important causes of early death are malignancy, especially malignant peripheral nerve sheath tumors, and vasculopathy.[4]

Test Information

Testing for Neurofibromatosis Type 1 may include known familial mutation analysis, NF1 gene sequencing, or NF1 deletion/duplication analysis.

Sequence Analysis

NF1 sequence analysis may involve a multistep protocol to increase the detection of splicing mutations. This protocol combines sequence analysis in genomic DNA and

cDNA (mRNA). NF1 sequencing variants, such as missense, nonsense, and splice site variants, account for up to 95% of mutations seen in NF1.[4]

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Segmental NF

Testing of various sample types is available to help identify individuals with segmental or mosaic NF1. “RNA-based NF1/SPRED1 testing on cultured cells from affected tissues is offered starting from biopsies of café-au-lait macules (CALM) and/or neurofibromas.”[18]

"Detection of the causal NF1 PVs [pathogenic variants] in individuals with a mosaic/segmental phenotype requires special attention to (1) the sensitivity of the technology used to detect variants, as well as (2) the type of cells to be analyzed in affected tissue if the variant is not detectable in blood, i.e., melanocytes (but not keratinocytes or fibroblasts) from CALMs or Schwann cells from the cutaneous or plexiform neurofibromas."[8]

Guidelines and Evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2019) stated the following in regard to genetic testing for NF1 in children:[9]

- "The following can be summarized about genetic testing:
  - can confirm a suspected diagnosis before a clinical diagnosis is possible
  - can differentiate NF1 from Legius syndrome
  - may be helpful in children who present with atypical features
  - usually does not predict future complications; and
  - may not detect all cases of NF1; a negative genetic test rules out a diagnosis of NF1 with 95% (but not 100%) sensitivity."
- "There are also other, less common, conditions associated with CALMs [café-au-lait macules]. The condition that could appear most similar to NF1 is Legius syndrome, which is caused by pathogenic variants in SPRED1, which encodes a protein that also functions within the Ras signaling pathway. People with Legius syndrome have multiple CALMs, intertriginous freckling, learning disabilities, and relative macrocephaly that is indistinguishable from findings in mild cases

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of NF1. Other manifestations of NF1, such as neurofibromas or other tumors, ophthalmologic findings, and skeletal manifestations, are not present in families with Legius syndrome. The absence of neurofibromas in adults with multiple CALMs in an extended pedigree is helpful to establish a diagnosis of Legius syndrome versus NF1, and molecular testing for SPRED1 versus NF1 should be considered in these cases."

The American College of Medical Genetics and Genomics (ACMG, 2018) stated the following in regard to genetic testing for NF1 in adults:[19]

- "In childhood, NF1 genetic testing can quickly establish a diagnosis and relieve anxiety, but that is less likely an issue for adults."
- "Most adults with NF1 are clinically diagnosed in childhood, according to NIH consensus criteria. The criteria are both highly specific and sensitive in adults with NF1."

International Consensus Panel

An international consensus panel (2021) updated the diagnostic criteria set forth by the National Institute of Health in 1988. The panel stated:[8]

In an individual who does not have a parent with NF, two or more of the following must be present:

- Six or more café-au-lait macules >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary and/or inguinal (groin) regions
- Optic glioma
- Two or more Lisch nodules (iris hamartomas) or two or more choroidal abnormalities
- A distinctive osseous lesion such as sphenoid dysplasia, tibial anterolateral bowing, or long bone pseudoarthrosis
- Heterozygous pathogenic NF1 variant present in 50% of apparently normal tissue (e.g: white blood cells)

If an individual has a parent diagnosed with NF based on the criteria above, at least one of the criteria above must be present to merit a diagnosis of NF1.

"As panel testing by next-generation sequencing and exome/genome sequencing analysis is ordered with increasing frequency in individuals with a variable set of clinical features, some individuals have been found to carry an NF1 variant (P, LP, VUS) in unaffected tissue such as blood, although NF1 was not clinically suspected. NF1 experts agreed that identification of an NF1 variant alone does not suffice to make a diagnosis of NF1 but does require further clinical and genetic evaluation..."

National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC, 2020) stated the following regarding genetic testing for NF1:[20]

- "The two primary reasons for targeted genetic testing for NF1, NF2, or SWN are to confirm a diagnosis for management purposes, and to provide information for reproductive decision-making. In familial cases with a known pathogenic variant it is appropriate to offer testing to children as all of these conditions may present in childhood."

Selected Relevant Publications

An expert authored review (2022) stated:[4]

- "If the phenotypic findings suggest the diagnosis of NF1, single-gene testing may be considered. Sequence analysis of NF1 genomic DNA (gDNA) and/or cDNA (complementary DNA, copied from mRNA) is performed in association with gene-targeted deletion analysis. Because of the frequency of pathogenic variants that affect splicing (22%-30%, more than 1/3 of which are not detected by gDNA sequencing of protein-coding regions), methods that include cDNA sequencing have higher detection rates than methods based solely on analysis of gDNA."
  - "If an NF1 variant is not detected, sequence analysis and deletion/duplication analysis of SPRED1 may be considered in individuals with only pigmentary features of NF1...Clinically distinguishing Legius syndrome from NF1 may be impossible in a young child because neurofibromas and Lisch nodules do not usually arise until later in childhood or adolescence in those with NF1. Examination of the parents for signs of Legius syndrome or NF1 may distinguish the two conditions, but in simplex cases, reevaluation of the individual after adolescence or molecular testing may be necessary to establish the diagnosis." For information on SPRED1 genetic testing, please refer to the guideline *Legius Syndrome Genetic Testing*, as this testing is not addressed here.
  - "Chromosomal microarray analysis (CMA) may be performed instead of sequence analysis to detect NF1 whole-gene deletions if the NF1 microdeletion phenotype is suspected clinically." For information on CMA testing, please refer to the guideline *Chromosomal Microarray Testing For Developmental Disorders (Prenatal and Postnatal)*, as this testing is not addressed here.
  - "A karyotype [chromosome analysis] may be considered to look for a translocation or complex cytogenetic abnormality if a clinical diagnosis of NF1 is certain, but no pathogenic variant is found on sequence analysis of NF1 gDNA or cDNA and gene-targeted deletion analysis." For information on chromosome analysis, please refer to the guideline *Chromosome Analysis for Reproductive Disorders, Prenatal Testing, and Developmental Disorders*, as this testing is not addressed here
- "If neither parent of an individual with NF1 has features that meet the clinical diagnostic criteria for NF1 after detailed medical history, physical examination, and

ophthalmologic examination, the proband most likely has NF1 as the result of a de novo pathogenic variant. Alternatively, the proband may have NF1 as the result of a disease-causing variant inherited from a parent who is mosaic or, rarely, from a heterozygous parent with incomplete penetrance. If the disease-causing variant has been identified in a child with NF1, targeted molecular testing of the parents can be performed to look for mosaicism and determine if a parent is heterozygous (but apparently unaffected due to incomplete penetrance)."

- "An individual in whom NF1 appears to have arisen as the result of [a] de novo mutation may have somatic mosaicism associated with segmental or unusually mild manifestations of NF1. The risk of a parent with mosaicism for an NF1 pathogenic variant transmitting the disorder to his or her child is less than 50%, but if the pathogenic variant is transmitted, it will be present in every cell in the child's body and the child may be much more severely affected...If neither parent of an individual with NF1 meets the clinical diagnostic criteria for NF1... the risk to the sibs of the affected individual of having NF1 is low but greater than that of the general population because of the possibility of parental germline mosaicism."

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Neurofibromatosis Type 1 testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Non-Invasive Prenatal Screening

MOL.TS.209.A
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Introduction

Non-invasive prenatal screening (NIPS) is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Non-Invasive Prenatal Screening for Fetal Aneuploidy	81420
Non-Invasive Prenatal Screening for Fetal Aneuploidy with Risk Score	81507
Non-Invasive Prenatal Screening for Fetal Chromosomal Microdeletions	81422
Non-Invasive Prenatal Screening for Single-Gene Mutations	81105-81479
UNITY Fetal Risk Screen	0489U
Vasistera	0327U

Criteria

Introduction

Requests for non-invasive prenatal screening (NIPS) are reviewed using the following criteria.

Cell-free DNA-based prenatal screening for fetal aneuploidy

- Genetic Counseling:

NIPT

  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Prenatal Screening:
  - Prenatal cell-free DNA screening for fetal aneuploidy (e.g. trisomy 13, 18, and 21) is medically necessary when all of the following criteria are met:
    - Singleton or twin pregnancy, AND
    - Gestational age within the window validated by the selected testing laboratory, AND
    - Rendering laboratory is a qualified provider of service per the Health Plan policy.
- Prenatal cell-free DNA screening is not medically necessary in the following circumstances:
  - A pregnancy in which a fetal demise has occurred
  - Triplet and higher-order multi-fetal gestation pregnancies
  - More than one prenatal cell-free DNA screen performed per pregnancy (exceptions for repeat screening will be considered on a case-by-case basis when requested due to initial results being unobtainable as a result of low fetal fraction)
  - When karyotyping, aneuploidy FISH, and/or cytogenomic microarray analysis (CMA) have already been performed on the pregnancy
- It is not medically necessary to perform maternal serum screening for aneuploidy and non-invasive prenatal screening (prenatal cell-free DNA screening) concurrently.
- Prenatal diagnosis by amniocentesis or CVS following NIPS is medically necessary when NIPS results are screen positive, inconclusive, or uninterpretable, or when additional information becomes available throughout the pregnancy that suggests additional risk factors.
- If non-invasive prenatal screening (prenatal cell-free DNA screening) has been successfully performed in the current pregnancy, other aneuploidy screening (by first or second trimester screening or integrated, step-wise sequential, or contingent sequential screening) is not medically necessary. Maternal serum screening for neural tube defects (AFP-only) is medically necessary.

Prenatal cell-free DNA screening for chromosome microdeletions

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.

- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

Prenatal cell-free DNA screening for single-gene mutations

For information regarding fetal Rh(D) genotyping using NIPS, please see the guideline *Human Platelet and Red Blood Cell Antigen Genotyping*, as that testing is not addressed here.

For all other indications, this test is Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

Other Considerations

For information regarding prenatal maternal serum screening for aneuploidy and open neural tube defects, please refer to the guideline, *Prenatal Maternal Serum Screening*, as that testing is not addressed here.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Prenatal cell-free DNA screening is not reimbursable for pregnancies in which a fetal demise has occurred, or for triplet and other higher-order multiple gestations. These

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are defined by the presence of one of the diagnosis codes from Table: *ICD Codes Indicating Fetal Demise and Triplet or Higher-Order Multiple Gestations*.

- Screening for aneuploidy of the X and Y chromosomes and/or detection of less common trisomies, are not separately reimbursable under these coverage guidelines. Additional procedure codes billed with cell-free DNA screening for this purpose are not eligible for reimbursement.
- Prenatal cell-free DNA screening for chromosome microdeletions (CPT: 81422) is not reimbursable.
- When prenatal cell-free DNA screening is otherwise reimbursable, the following limitations apply:
  - No more than one prenatal cell-free DNA screening is reimbursable per pregnancy, defined as no more than one paid prenatal cell-free DNA screen procedure code (e.g., 81420 or 81507) within 10 weeks.
  - Non-specific procedure codes (e.g. 81479, 81599) or any procedure codes that do not accurately describe the test methodology performed (e.g. 88271) are not eligible for reimbursement.

ICD Codes

ICD codes used for automated claims processing for this guideline.

Table: ICD Codes Indicating Fetal Demise and Triplet or Higher-Order Multiple Gestations

Codes and descriptions

Code or Range	Description
O30.1X	Triplet pregnancy
O30.2X	Quadruplet pregnancy
O31.00X0-O31.00X9	Papyraceous fetus, unspecified trimester
O31.01X0-O31.01X9	Papyraceous fetus, first trimester
O31.02X0-O31.02X9	Papyraceous fetus, second trimester
O31.03X0-O31.03X9	Papyraceous fetus, third trimester
O31.10X0-O31.10X9	Continuing pregnancy after spontaneous abortion of one fetus or more, unspecified trimester
O31.11X0-O31.11X9	Continuing pregnancy after spontaneous abortion of one fetus or more, first trimester

Code or Range	Description
O31.12X0-O31.12X9	Continuing pregnancy after spontaneous abortion of one fetus or more, second trimester
O31.13X0-O31.13X9	Continuing pregnancy after spontaneous abortion of one fetus or more, third trimester
O31.20X0-O31.20X9	Continuing pregnancy after intrauterine death of one fetus or more, unspecified trimester
O31.21X0-O31.21X9	Continuing pregnancy after intrauterine death of one fetus or more, first trimester
O31.22X0-O31.22X9	Continuing pregnancy after intrauterine death of one fetus or more, second trimester
O31.23X0-O31.23X9	Continuing pregnancy after intrauterine death of one fetus or more, third trimester
O31.30X0-O31.30X9	Continuing pregnancy after elective fetal reduction of one fetus or more, unspecified trimester
O31.31X0-O31.31X9	Continuing pregnancy after elective fetal reduction of one fetus or more, first trimester
O31.32X0-O31.32X9	Continuing pregnancy after elective fetal reduction of one fetus or more, second trimester
O31.33X0-O31.33X9	Continuing pregnancy after elective fetal reduction of one fetus or more, third trimester
O31.8X13	Other complications specific to multiple gestation, first trimester, fetus 3
O31.8X14	Other complications specific to multiple gestation, first trimester, fetus 4
O31.8X15	Other complications specific to multiple gestation, first trimester, fetus 5

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Code or Range	Description
O31.8X23	Other complications specific to multiple gestation, second trimester, fetus 3
O31.8X24	Other complications specific to multiple gestation, second trimester, fetus 4
O31.8X25	Other complications specific to multiple gestation, second trimester, fetus 5
O31.8X33	Other complications specific to multiple gestation, third trimester, fetus 3
O31.8X34	Other complications specific to multiple gestation, third trimester, fetus 4
O31.8X35	Other complications specific to multiple gestation, third trimester, fetus 5
O31.8X93	Other complications specific to multiple gestation, unspecified trimester, fetus 3
O31.8X94	Other complications specific to multiple gestation, unspecified trimester, fetus 4
O31.8X95	Other complications specific to multiple gestation, unspecified trimester, fetus 5

What is a chromosome abnormality?

A chromosome abnormality is any difference in the structure, arrangement, or amount of genetic material packaged into the chromosomes.[1]

Humans typically have 23 pairs of chromosomes. Each chromosome has a characteristic appearance that should be the same in each person. Chromosome abnormalities can lead to a variety of developmental and reproductive disorders. Common chromosome abnormalities include Down syndrome (trisomy 21), trisomy 18, trisomy 13, Turner syndrome, and Klinefelter syndrome. Chromosome abnormalities occur in approximately 1 in 150 live births. A higher percentage of pregnancies are affected but lost during pregnancy.

About 6%-11% of stillbirths or neonatal deaths are associated with a chromosome abnormality.[2,3]

The risk of having a child with an extra chromosome, notably Down syndrome, increases as a woman gets older.[3] However, many babies with Down syndrome are

born to women under 35 and the risk of having a child with other types of chromosome abnormalities, such as Turner syndrome or 22q11 deletion syndrome, is not related to maternal age. Therefore, prenatal screening for Down syndrome and certain other chromosome abnormalities is now routinely offered to all pregnant women. As a result, prenatal diagnosis via amniocentesis or chorionic villus sampling (CVS) is now also an option for most pregnant women.

Test information

Introduction

Non-invasive prenatal screening (NIPS, also called prenatal cell-free DNA screening or cfDNA screening) is performed on a maternal plasma sample generally collected after 9 weeks' gestation.[4]

Methodology and Performance

Testing methodology relies on the presence of cell-free placental DNA in maternal circulation.[4] Approximately 10% of cell-free DNA in maternal circulation is of placental origin.[5]

Analysis of cell-free placental DNA is performed to identify pregnancies at increased risk for chromosomal aneuploidy. Detection rates for trisomies 21, 18, and 13 are greater than 98%, with false positive rates of less than 0.5%.[4]

Some laboratories also test for sex chromosome aneuploidies (such as Turner syndrome or Klinefelter syndrome) and rare chromosome microdeletion syndromes (such as 22q11 deletion syndrome or 1p36 microdeletion syndrome), with variable performance.

Each commercial or academic laboratory offering NIPS has a proprietary platform and bioinformatics pipeline.

Chromosome analysis via CVS and amniocentesis is also routinely available for diagnosis of fetal chromosome abnormalities in pregnancy.

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2023) published a practice guideline regarding Non Invasive Prenatal Screening (NIPS) and recommended the following:[5]

- "ACMG recommends NIPS over traditional screening methods for all pregnant patients with singleton gestation for fetal trisomies 21, 18, and 13 (Strong recommendation based on high certainty of evidence)"
- "ACMG recommends NIPS over traditional methods for trisomy screening in twin gestations (Strong recommendation, based on high certainty of evidence)"
- Regarding sex chromosome aneuploidies (SCAs): "ACMG recommends that NIPS be offered to patients with a singleton gestation to screen for fetal SCA (Strong recommendation, based on high certainty of evidence)"
- "ACMG suggests that NIPS for 22q11.2 deletion syndrome be offered to all patients (Conditional recommendation, based on moderate certainty of evidence)"
- Regarding other copy number variants (CNVs): "At this time, there is insufficient evidence to recommend routine screening for CNVs other than 22q11.2 deletions (No recommendation, owing to lack of clinically relevant evidence and validation)"
- Regarding rare autosomal trisomies (RATs): "At this time, there is insufficient evidence to recommend or not recommend NIPS for the identification of RATs (No recommendation, owing to lack of clinically relevant evidence)"
- Regarding pregnancies with a vanishing twin: "There was no evidence ... to support altering the option of NIPS in a pregnancy with a known vanishing twin, although the patient should be counseled that accuracy may be impacted. The American College of Obstetricians and Gynecologists states that NIPS should not be performed in such circumstances."

The American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2019; reaffirmed September 2023) issued a practice advisory on the use of cell-free DNA to screen for single-gene disorders and stated the following:[6]

- "The continued innovation in cell-free technology combined with the desire for a maternal blood test to predict the risk for fetal genetic disorders during a pregnancy has broadened the application of cell-free DNA screening beyond aneuploidy to single-gene disorders. Examples of single-gene disorders include various skeletal dysplasias, sickle cell disease and cystic fibrosis. Although this technology is available clinically and marketed as a single-gene disorder prenatal screening option for obstetric care providers to consider in their practice, often in presence of advanced paternal age, there has not been sufficient data to provide information regarding accuracy and positive and negative predictive value in the general population. For this reason, single-gene cell-free DNA screening is not currently recommended in pregnancy."

The American College of Obstetricians and Gynecologists and Society for Maternal Fetal Medicine

In 2020, The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM) published a joint practice bulletin and stated:[7]

- "Prenatal genetic screening (serum screening with or without nuchal translucency [NT] ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling [CVS] or amniocentesis) options should be discussed and offered to all pregnant women regardless of maternal age or risk of chromosome abnormality." [Level A Recommendation: based on good and consistent scientific evidence]
- "If screening is accepted, patients should have one prenatal screening approach, and should not have multiple screening tests performed simultaneously." [Level A Recommendation: based on good and consistent scientific evidence]
- "Cell-free DNA is the most sensitive and specific screening test for the common fetal aneuploidies. Nevertheless, it has the potential for false-positive and false-negative results. Furthermore, cell-free DNA testing is not equivalent to diagnostic testing." [Level A Recommendation: based on good and consistent scientific evidence]
- "Cell-free DNA screening can be performed in twin pregnancies. Overall, performance of screening for trisomy 21 by cell-free DNA in twin pregnancies is encouraging, but the total number of reported affected cases is small. Given the small number of affected cases it is difficult to determine an accurate detection rate for trisomy 18 and 13." [Level B Recommendation: based on limited or inconsistent scientific evidence]
- "In multifetal gestations, if a fetal demise, vanishing twin, or anomaly is identified in one fetus, there is a significant risk of an inaccurate test result if serum-based aneuploidy screening or cell-free DNA is used. This information should be reviewed with the patient and diagnostic testing should be offered." [Level C Recommendation: based primarily on consensus and expert opinion]

American Society of Human Genetics and European Society of Human Genetics

A 2015 joint statement by the American Society of Human Genetics (ASHG) and European Society of Human Genetics (ESHG) included the following recommendations:[8]

- "NIPT offers improved accuracy when testing for common autosomal aneuploidies compared with existing tests such as cFTS. However, a positive NIPT result should not be regarded as a final diagnosis… Thus women should be advised to have a positive result confirmed through diagnostic testing, preferably by amniocentesis, if they are considering a possible termination of pregnancy."

- "Expanding NIPT-based prenatal screening to also report on sex chromosomal abnormalities and microdeletions not only raises ethical concerns related to information and counseling challenges but also risks reversing the important reduction in invasive testing achieved with implementation of NIPT for aneuploidy, and is therefore currently not recommended."

The International Society for Prenatal Diagnosis

The International Society for Prenatal Diagnosis (ISPD, 2023) issued a position statement on the use of NIPT for the detection of chromosomal conditions in singleton pregnancies that stated:[9]

- "NIPT is the most accurate screening test for the common autosomal aneuploidies (trisomies 21, 13 and 18) in unselected singleton populations, and those at known increased probability."
- "NIPT for the common autosomal aneuploidies performs sufficiently well to be offered in primary or contingent screening models."
- "FPR [false positive results] occur with NIPT. Therefore, ISPD strongly recommends that all patients with a high chance NIPT result have genetic counseling and diagnostic testing if they are considering termination of pregnancy."
- "NIPT for SCA [sex chromosome aneuploidy] is sufficiently accurate to be offered alongside autosomal aneuploidy screening with specific pretest counseling and consent."
- There is insufficient data to assess the performance and clinical utility of routine NIPT for rare autosomal trisomies, sub-chromosomal imbalances and microdeletion/duplication syndromes.

The ISPD issued a position statement (2020) on cfDNA screening for Down syndrome in twin and triplet pregnancies. The statement compared cfDNA screening to other screening methods available for multiple gestation pregnancies, focusing on test characteristics. This approach is in contrast to other professional guidelines that compare the performance of cfDNA in twin pregnancies to that reported for cfDNA screening in singleton pregnancies. ISPD summarized recommendations for evidence-based practices:[10]

- "The use of first trimester cfDNA screening for the common autosomal trisomies is appropriate for twin pregnancies due to sufficient evidence showing high detection and low false positive rates with high predictive values. Moderate."
- "The finding of an increased risk on a cfDNA screening test in multiple pregnancies should be followed by counseling and an offer of diagnostic testing to confirm results. Strong."

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The National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC, 2021) issued a position statement regarding the use of prenatal cell-free DNA screening:[11]

- "The National Society of Genetic Counselors believes that all pregnant patients, regardless of aneuploidy risk, should have access to prenatal aneuploidy screening using cell-free DNA (cfDNA)."
- "Patients who receive increased risk or inconclusive/atypical results should receive post-test genetic counseling with a knowledgeable healthcare provider, such as a genetic counselor. In such cases, confirmatory diagnostic testing may be indicated, and patients should be counseled that no irreversible actions should be taken based on the cfDNA screening alone."

Society of Obstetricians and Gynaecologists of Canada

The Society of Obstetricians and Gynaecologists of Canada (SOGC, 2017) stated: “Routine cfDNA screening for fetal microdeletions is not currently recommended (II-2B).”[12,13]

Selected Relevant Publications

Selected relevant publications pertaining to twin pregnancies, microdeletion testing, and single gene testing.

Multiple Gestation Pregnancies

The evidence base for NIPS in twin pregnancies suggested that NIPS may be useful as a screening test for common aneuploidies. However, well-designed clinical validity and clinical utility studies evaluating the performance of NIPS in triplet and higher order multifetal pregnancies in the general obstetric population are needed. A systematic evidence-based review published by the American College of Medical Genetics and Genomics (ACMG, 2022) included 7 studies in a meta-analysis evaluating the performance of cfDNA screening for aneuploidy in multi-fetal gestations.[14] The authors stated: "The results from our meta-analyses show NIPS performance in this population [twin gestations] are generally comparable to performance in singleton pregnancies for T21, T18, and T13. Results for other aneuploidies or microdeletions were less frequently reported and no firm conclusions can be drawn about the performance of NIPS for these outcomes. Very limited data is available on triplets or higher order multiple gestations."

Microdeletion Syndromes

The evidence base for the use of NIPS for microdeletion detection was of low quality.[14-37] Several systematic reviews have concluded that the evidence is insufficient to draw firm conclusions related to the use of NIPS for microdeletion testing. Diagnostic performance estimates were highly variable, there was insufficient

utilization of reference testing in the available studies, and significant heterogeneity existed between studies due to differing NIPS methodologies, the number and type of deletions screened, and patient populations. Well-designed clinical validity studies with comprehensive reference test use in low-risk patient populations are needed along with clinical utility studies that evaluate pregnancy and postnatal outcomes. These studies should also allow for comparison of methodologies and the number and type of microdeletion/microduplication syndromes.

Single Gene Disorders

The strength of the available evidence for NIPS use in detecting single-gene disorders was low.[30,38--61] There are few clinical studies evaluating the performance of NIPS in detecting these disorders. The majority of available clinical studies have focused on targeted testing for common or familial variants; however, the number of studies screening for multiple monogenic disorders with NIPS is increasing. Sample failures and interpretation issues are common and related to a number of factors, including: low fetal fraction, difficulty distinguishing fetal from maternal variants, insufficient SNP numbers in the target region, and DNA recombination events. The evidence base is insufficient to permit definitive conclusions regarding the performance of NIPS to identify single-gene disorders. Large well-designed clinical validity and clinical utility studies evaluating NIPS for this indication in general obstetric and/or high-risk populations are needed.

Sex Chromosome Aneuploidies

The evidence base for NIPS use in SCA detection was of low quality.[34,62-64] Clinical performance data suggests that NIPS has high sensitivity and specificity for SCAs, but reported positive predictive values (PPVs) vary significantly based on subtype, test platform, and patient population. Accurate screening for Turner syndrome is difficult due to confined placental mosaicism and maternal somatic mosaicism, often leading to a low PPV and increased false positive results. Clinical utility data is limited and does not allow for assessment of the overall impact of SCA screening. Ethical concerns related to use of this screening include the challenges involved in provision of pre- and post-test parental counseling, the mild and highly variable phenotypic presentations of SCAs, increased rates of unnecessary invasive diagnostic testing, and a lack of consensus on therapeutic benefits for prenatally diagnosed patients.[65]

Vanishing Twin Pregnancies

The performance of non-invasive prenatal screening in vanishing twin pregnancies is relatively unknown. A systematic review of available literature notes pooled data for 1592 cases showed no report of discordant negative result. It also notes successful detection of common autosomal trisomies but with a higher false positive rate (attributed to the detection of cfDNA from the demised twin that was aneuploid).[66]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for non-invasive prenatal screening will ensure that testing will be available to those members most likely to benefit from the information provided by the assay. For those not meeting criteria, it ensures alternate management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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Nonsyndromic Hearing Loss and Deafness Genetic Testing

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Introduction

Nonsyndromic hearing loss and deafness genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
GJB2 gene analysis	S3844
GJB2 known familial mutation analysis	81253
GJB2 sequencing	81252
GJB6 common variant analysis	81254
Hearing loss (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1	81430
Hearing loss (e.g, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes	81431

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Procedures addressed by this guideline	Procedure codes
Hearing loss and deafness gene tests	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
MT-RNR1 sequencing	81403
MT-RNR1 targeted mutation analysis	81401
MT-TS1 sequencing	81403
MT-TS1, MT-RNR1 targeted mutation analysis	81401

Criteria

Introduction

Requests for nonsyndromic hearing loss and deafness testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Previous testing:
  - Member has not previously had testing that would detect the known familial mutation(s), AND
- Member has a 1st, 2nd, or 3rd degree biological relative with a pathogenic mutation(s) in a gene associated with nonsyndromic hereditary hearing loss or deafness, AND

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- Member is at risk of inheriting the pathogenic mutation based on the family history and the inheritance pattern associated with the mutation, AND
- Diagnostic testing:
  - Member has nonsyndromic hearing loss or deafness that is consistent with the mutation in the family, OR
- Carrier testing:
  - Member is of reproductive age, and
  - Member has ability and intention to reproduce, or
  - Member is currently pregnant.

GJB2 Sequencing

- Previous testing:
  - Member has not previously had GJB2 sequencing, and
  - No known pathogenic hearing loss/deafness gene variants in a biological relative, AND
- Diagnostic Testing:
  - Member has a diagnosis of bilateral sensorineural hearing loss, and
  - Prelingual onset of hearing loss (prior to speech development), and
  - No known cause for the member's hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and
  - Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss, and
  - Member's family history is consistent with autosomal recessive inheritance (including simplex cases), OR
- Carrier screening
  - Member is of reproductive age, and
  - Has potential and intention to reproduce, and
  - Has a reproductive partner who is a carrier of a GJB2/GJB6 mutation, or
  - Has a reproductive partner with GJB2/GJB6-related deafness.

GJB6 Common Variant Analysis for 309kb and 232kb Deletions

- Previous testing:
  - Member has not previously had GJB6 common variant analysis or deletion/duplication analysis, AND
- Diagnostic Testing:
  - Member meets criteria for GJB2 sequencing, and

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- No mutation or only one mutation identified on GJB2 sequencing, OR
- Carrier screening
  - Member is of reproductive age, and
  - Has potential and intention to reproduce, and
  - Has a 1st, 2nd, or 3rd-degree biological relative with a GJB6 variant, or
  - Member meets criteria for GJB2 sequencing, and
  - No mutation identified on GJB2 sequencing.

MT-RNR1 Targeted Mutation Analysis for m.1555A>G Mutation

- Previous testing:
  - Member has not previously had MT-RNR1 targeted mutation analysis, and
  - No known pathogenic hearing loss/deafness gene variants in a biological relative, AND
- Diagnostic Testing:
  - Member has a diagnosis of bilateral sensorineural hearing loss, and
  - No known cause for the member's hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and
  - Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss, and
  - Member has at least one of the following risk factors for MT-RNR1 related deafness:
    - History of aminoglycoside antibiotic exposure (gentamycin, tobramycin, amikacin, kanamycin, or streptomycin), or
    - Member's family history is strongly suggestive of mitochondrial inheritance (no transmission through a male).

MT-RNR1 Sequencing

- Previous testing:
  - Member has not previously had MT-RNR1 sequencing, and
  - No mutations detected in any previous MT-RNR1 testing (targeted m.1555A>G mutation analysis), and
  - No known pathogenic hearing loss/deafness gene variants in a biological relative, AND
- Diagnostic Testing:
  - Member has a diagnosis of bilateral sensorineural hearing loss, and
  - No known cause for the member's hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and

- Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss, and
- Member has at least one of the following risk factors for MT-RNR1 related deafness:
  - Aminoglycoside antibiotic exposure (gentamycin, tobramycin, amikacin, kanamycin, or streptomycin) prior to hearing loss onset, or
  - Member's family history is strongly suggestive of mitochondrial inheritance (no transmission through a male).

MT-TS1 Sequencing

- Previous testing:
  - Member has not previously had MT-TS1 analysis, and
  - No mutations detected in any previous MT-TS1 testing (targeted variant analysis), and
  - No known pathogenic hearing loss/deafness gene variants in a biological relative, AND
- Diagnostic Testing:
  - Member has a formal diagnosis of bilateral sensorineural hearing loss, and
  - No known cause for the member's hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and
  - Absence of significant dysmorphism, congenital anomalies, or other signs of syndromic hearing loss, and
  - Member's family history is strongly suggestive of mitochondrial inheritance (no transmission through a male).

Nonsyndromic Hearing Loss and Deafness Multigene Panel Testing

Multigene panels will be considered medically necessary when the following criteria are met:

- Previous testing:
  - Member has not previously had a hearing loss panel, and
  - No known pathogenic hearing loss/deafness gene variants in a biological relative, AND
- Diagnostic Testing:
  - Member has a diagnosis of bilateral sensorineural hearing loss, and
  - No known cause for the member's hearing loss (e.g., prenatal exposure to ototoxic medication or TORCH infection, known genetic disorder), and

- Absence of significant dysmorphism, congenital anomalies or other signs of syndromic hearing loss.

Other considerations

Broad hearing loss and deafness panels may not be medically necessary when a narrower panel is available and more appropriate based on the clinical findings.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multigene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81430 to represent a sequencing panel and 81431 to represent a deletion/duplication panel)*.
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
    - If appropriate first-tier tests cannot be determined on the basis of clinical and family histories, only the following genes may be considered for reimbursement: GJB2, STRC, SLC26A4, TECTA, MYO15A, MYO7A.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is nonsyndromic hearing loss and deafness?

Nonsyndromic hearing loss (NSHL) is defined as partial or total hearing loss that does not occur with other medical conditions or symptoms.[1]

Prevalence

It is estimated that up to 3/1000 children are born with hearing loss in one or both ears.[1] About 15% of adults in America have some level of hearing loss.[2]

Symptoms

Approximately 70-80% of genetic hearing loss is nonsyndromic, with no related systemic findings.[3,4] Some syndromic forms of hearing loss and deafness may masquerade as nonsyndromic in infancy and early childhood, before additional symptoms emerge. For example, goiter does not develop until puberty or adulthood in Pendred syndrome; retinitis pigmentosa emerges in adolescence in Usher syndrome; and males with Deafness-Dystonia-Optic Neuronopathy (Mohr-Tranebjaerg) Syndrome begin having progressive neurological symptoms in their teens.[3,5]

Cause

Approximately 35% of cases of prelingual hearing loss are attributed to environmental causes, including viral (cytomegalovirus) or bacterial (meningitis) infection, trauma, prenatal exposure to certain drugs, and other environmental factors.[3] The remaining 65% of cases are thought to be genetic, either as part of a recognized genetic syndrome, or as isolated, nonsyndromic hearing loss (NSHL).[3]

GJB2-related autosomal recessive hearing loss is the most common cause of congenital severe-to-profound non-progressive sensorineural hearing loss.[6] Carrier frequency for GJB2-related hearing loss is dependent on population. Based on current available data, the highest carrier rate (~8%) is reported in the East Asian population.[6]

According to a large study of individuals with nonsyndromic hearing loss tested with multigene panels, the following genes were most often implicated: GJB2, STRC, SLC26A4, TECTA, MYO15A, and MYO7A.[5]

Inheritance

NSHL can exhibit autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance patterns.[3,6,7] Autosomal recessive inheritance accounts for 80% of NSHL, while 15-19% is autosomal dominant, and ~1% is mitochondrial or X-linked.

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Diagnosis

In the United States, >98% of newborns have hearing screening which can identify congenital hearing loss.[3] Diagnosis of hearing loss may involve physiologic testing (including auditory brainstem response or ABR/BAER) and/or audiometry.[3]

Management

Management of congenital hearing loss or deafness may include hearing aids, cochlear implants, and appropriate educational interventions[1]. Uncovering the genetic etiology of the hearing loss may also identify (or allay concerns about) comorbidities that may require referral for specialty care.[3,4]

Survival

NSHL is not associated with decreased survival.

Test information

Introduction

Testing for NSHL may include known familial mutation analysis, targeted mutation analysis, multigene panel testing, or single gene analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap

between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Single Gene Analysis

Under certain circumstances, technologies used in multigene testing may fail to identify mutations that might be identifiable through single-gene testing. If high clinical suspicion remains for a particular syndrome after negative multigene test results, consultation with the testing lab and/or additional targeted genetic testing may be warranted.

NSHL and deafness multigene panels include a wide variety of genes associated with nonsyndromic hearing loss and deafness. Multigene nonsyndromic hearing loss and deafness panels may also include genes for syndromes that mimic nonsyndromic hearing loss (e.g. Usher syndrome, Pendred syndrome, Jervell and Lange-Nielsen syndrome, etc.).

A study of 440 individuals with genetic hearing loss found mutations in ~40% of cases tested with a multigene panel. The only feature with an adverse effect on test yield was unilateral hearing loss, for which the panel only identified mutations in 1% of cases.[5] In another study, the mutation detection rate was ~60% via multigene panel; multigene panel testing was noted to be more cost-effective than single gene testing.[8]

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2022) stated:[4]

- A comprehensive genetic evaluation is recommended for all cases of congenital deafness or hearing loss with onset in childhood or early adulthood. Cytomegalovirus (CMV) testing is important for cases of congenital hearing loss (HL). The testing should be completed within the first three weeks of life if possible. Ancillary testing (e.g. electrocardiogram, renal ultrasound, temporal bone imaging and ophthalmology examination) remains important, as results may support genetic testing selection or interpretation of variants. The clinical utility of these tests should be evaluated on a case-by-case basis since genetic testing via NGS panels may soon become more cost-effective.
- Genetic testing to confirm a diagnosis of suspected syndromic hearing loss is recommended based on clinical findings. For apparently nonsyndromic hearing loss, a tiered approach was recommended: "Unless clinical and/or family history suggests a specific etiology, comprehensive HL [hearing loss] gene panel testing should be initiated. If panel testing is negative, genome-wide testing, such as ES

[exome sequencing] or GS [genome sequencing], may be considered. However, issues related to genomic testing, such as the likelihood of incidental or secondary findings, will have to be addressed."

- Hearing loss panels should include those genes recommended by the ClinGen Hearing Loss Gene Curation Expert Panel.[9]
- "If genetic testing reveals variant(s) in an HL-related gene, gene-specific genetic counseling should be provided, followed by appropriate medical evaluations and referrals."
- "If genetic testing fails to identify an etiology for a patient's HL, the possibility of a genetic etiology remains. This point must be emphasized because it can be misunderstood by clinicians and by patients and their families. For interested patients and families, further genetic testing may be pursued on a research basis."

International Pediatric Otolaryngology Group

The International Pediatric Otolaryngology Group (IPOG, 2016) stated:[10]

- "In the setting of unilateral hearing loss, genetic testing has a limited role unless syndromic hearing loss is suspected."
- "After and [sic] audiogram and physical exam, comprehensive genetic testing (CGT) that relies on next generation sequencing (NGS) methodologies should guide subsequent workup in children with bilateral sensorineural hearing loss."
- "Diagnostic rates for single gene testing for GJB2/GJB6 vary significantly based on the patient's ethnicity, and do not outperform the diagnostic rates for comprehensive genetic testing. In cases where CGT is unavailable, single gene testing can be directed by the audiometric phenotype and ethnicity."
- The general consensus of the authors was that temporal bone imaging "should not be a routine part of the diagnostic algorithm for bilateral symmetric sensorineural hearing loss."

Selected Relevant Publications

Expert-authored reviews of nonsyndromic hearing loss stated:

- "A hearing loss multigene panel that includes all genes implicated in nonsyndromic hearing loss and disorders that mimic nonsyndromic hearing loss including GJB2and other genes of interest … is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype."[6]
- "Analytic methods used for this panel must include the detection of deletions of GJB2, either intragenic or whole gene, and deletions that include sequences upstream of GJB2 (comprising either GJB6 and portions of CRYL1or just portions of CRYL1) that delete cis-regulatory regions of GJB2, thereby abolishing GJB2 expression."[6]

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- Regarding mitochondrial NSHL, the diagnosis should be suspected in individuals with moderate-to-profound hearing loss and a family history suggestive of maternal inheritance (e.g. no transmission through a male), or onset of hearing loss after exposure to an aminoglycoside antibiotic.[7]
  - "In individuals with hearing loss following aminoglycoside exposure, molecular testing for the pathogenic variants m.1555A>G and m.1494C>T in MT-RNR1 and m.7445A>C/T/G in MT-TS1 can be done first."
  - An alternative strategy is to perform multigene panel testing that includes both MT-RNR1 and MT-TS1, plus other genes of interest.
  - If targeted mtDNA testing and/or multigene panel testing including these mtDNA genes fail to confirm a diagnosis, mitochondrial genome sequencing can be considered. Mitochondrial genome sequencing should be performed prior to multigene panel testing if there is a clear mitochondrial inheritance pattern.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for nonsyndromic hearing loss and deafness genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Noonan Spectrum Disorder Genetic Testing

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Noonan spectrum disorder (NSD) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Known familial mutation analysis	81403
Noonan spectrum disorder gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1	81442

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Criteria

Introduction

Requests for Noonan spectrum disorder (NSD) genetic testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Known familial mutation in a causative gene in a 1st-degree biologic relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Single Gene Sequence Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous testing of the requested gene, and
  - No known NSD mutation in a biologic relative, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Two or more of the following major features:
    - Hypertrophic cardiomyopathy
    - Congenital pulmonary valve stenosis
    - Electrocardiogram characteristic of NSD associated with the requested gene
    - Facial dysmorphism suggestive of NSD associated with the requested gene
    - Stature less than 3rd percentile for age and gender
    - Pectus carinatum and/or excavatum
    - First-degree relative with known or suspected NSD associated with the requested gene, or
  - One major feature as listed above, in combination with one or more of the following:
    - Other cardiac abnormality suggestive of the Noonan Spectrum disorder associated with the requested gene (e.g., atrial septal defect, ventricular septal defect, branch pulmonary artery stenosis, tetralogy of Fallot, etc.)

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        - Stature 3rd to 10th percentile for age and gender
        - Broad thorax/widely-spaced nipples
        - Developmental delay, intellectual disability, or diagnosed learning disability
        - Cryptorchidism
        - Broad or webbed neck
        - Lymphatic dysplasia
        - Coagulopathy confirmed with hematologic studies
        - Skin abnormality characteristic of the NSD associated with the requested gene (e.g. multiple lentigines, follicular keratosis, etc.)
        - Pubertal delay and/or infertility, OR
- Prenatal Testing:
    - Prenatal chromosome study is not diagnostic, and
    - Fetal ultrasound exhibits features of the NSD associated with the requested gene based on the presence of one or more of the following:
        - Nuchal edema (e.g., increased nuchal translucency, increased nuchal fold, or cystic hygroma) and/or hydrops fetalis
        - Pulmonary valve stenosis
        - Hypertrophic cardiomyopathy
        - A combination of TWO or more of the following: Polyhydramnios, distended jugular lymphatic sacs (JLS), pleural effusion, cardiac anomaly, renal anomaly, ascites, facial abnormalities suggestive of a NSD and/or first-degree relative known or suspected to have the associated NSD, and
    - No known cause for the above features (e.g., known genetic disorder, etc), and
    - The requested single gene sequencing test is appropriate due to one or more of following:
        - The requested gene is the only gene known to be associated with the suspected type of NSD (e.g., HRAS for Costello syndrome, etc.)
        - Mutations in the requested gene are the most common cause of the suspected type of NSD (e.g., PTPN11 for classic NS or NSML, etc.)
        - Sequencing of genes more frequently associated with the suspected Noonan Spectrum Disorder have been completed and was not diagnostic, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Multigene Panel Testing

When a multi-gene panel is requested and billed with the appropriate CPT panel code, 81442, the panel will be considered medically necessary when the following criteria are met:

- Genetic Counseling:

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- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - No previous NSD panel testing, and
  - No known NSD mutation in a biologic relative, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Two or more of the following major features:
    - Hypertrophic cardiomyopathy
    - Congenital pulmonary valve stenosis
    - Electrocardiogram characteristic of an NSD
    - Facial dysmorphism suggestive of an NSD
    - Stature less than 3rd percentile for age and gender
    - Pectus carinatum and/or excavatum
    - First-degree relative with known or suspected NSD, or
  - One major feature as listed above, in combination with one or more of the following:
    - Other cardiac abnormality suggestive of the NSD (e.g., atrial septal defect, ventricular septal defect, branch pulmonary artery stenosis, tetralogy of Fallot, etc.)
    - Stature 3rd to 10th percentile for age and gender
    - Broad thorax/widely-spaced nipples
    - Developmental delay, intellectual disability, or diagnosed learning disability
    - Cryptorchidism
    - Broad or webbed neck
    - Lymphatic dysplasia
    - Coagulopathy confirmed with hematologic studies
    - Skin abnormality characteristic of the NSD (e.g., multiple lentigines, follicular keratosis, etc.)
    - Pubertal delay and/or infertility, OR
- Prenatal Testing:
  - Prenatal chromosome study is not diagnostic, and
  - Fetal imaging exhibits features of an NSD based on the presence of one or more of the following:
    - Nuchal edema (e.g. increased nuchal translucency, increased nuchal fold, or cystic hygroma) and/or hydrops fetalis
    - Pulmonary valve stenosis
    - Hypertrophic cardiomyopathy
    - A combination of TWO or more of the following: polyhydramnios, distended jugular lymphatic sacs (JLS), pleural effusion, cardiac anomaly, renal anomaly,

ascites, facial abnormalities suggestive of an NSD and/or first-degree relative known or suspected to have the associated NSD, and
  - No known cause for the above features (e.g., known genetic disorder, etc), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Deletion/Duplication Analysis

Deletion/duplication analysis for NSD is not medically necessary due to the extremely low diagnostic yield.

Other Considerations

Broad NSD panels may not be medically necessary when a more targeted test is available and more appropriate based on clinical findings.

The criteria stated in this section applies only to germline diagnostic testing for NSDs. For information on somatic (tumor marker) testing, please refer to the appropriate test-specific guideline or to the guideline *Somatic Mutation Testing*, as this testing is not addressed here. For information on non-invasive screening, please refer to the guideline *Non-Invasive Prenatal Screening*, as this testing is not addressed here.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Deletion/Duplication analysis for NSD is not reimbursable.
- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81442*).
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.

- When the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement, based on which NSD is most likely:
  - Classic NS: PTPN11, followed by SOS1, RAF1, RIT1 and LZTR1 if PTPN11 sequencing is negative.
  - CFC syndrome: BRAF, followed by MAP2K1, MAP2K2, and KRAS if BRAF sequencing is negative.
  - NSML/LEOPARD syndrome: PTPN11, followed by RAF1, BRAF, and MAP2K1 if PTPN11 sequencing is negative.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is Noonan spectrum disorder?

Noonan spectrum disorders (NSDs) are a group of disorders that includes Noonan syndrome (NS), Cardiofaciocutaneous (CFC) syndrome, Noonan syndrome with multiple lentigines (NSML or LEOPARD syndrome), Costello syndrome, Noonan syndrome-like disorder with loose anagen hair, and Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia (JMML). These disorders are often referred to as “RASopathies” due the associated gene products being involved in the Ras/MAPK-pathway.[1-4]

Prevalence

The prevalence of NS is between 1:1,000 and 1:2,500 individuals. Though mild expression of the condition is likely to be overlooked. Other NSDs are relatively rare.[1-4]

Symptoms

NSDs are multisystem disorders characterized by facial features, short stature, cardiovascular abnormalities (particularly pulmonary valve stenosis and hypertrophic cardiomyopathy), and developmental delay of variable degree.[1-4]

Cause

NSDs are associated with mutations in a number of genes involved in the Ras/MAPK-pathway, with genetic overlap between many of the NSD types:[1-5]

- NS: Causative mutations are found in PTPN11 (50-60%), SOS1 (10-13%), LZTR1 (~8%), RAF1 (5-9%), RIT1 (5%), and KRAS (<5%). BRAF, MAP2K1, MRAS, NRAS, RASA2, RRAS2, and SOS2 mutations each account for 4% or fewer cases.

- CFC: Caused by mutations in BRAF (~75%), MAP2K2/MEK2 and MAP2K1 (~25%), KRAS (<2%), and rarely YWHAZ.
- NSML or LEOPARD syndrome: Caused by mutations in PTPN11 (>95%), RAF1 (<3%), BRAF, and MAP2K1.
- Costello syndrome: Caused by mutations in HRAS (~99%).
- Noonan syndrome-like disorder with loose anagen hair: Caused by mutations in SHOC2, particularly a recurrent 4A>G pathogenic variant. Pathogenic variants in SHOC2 are often associated with classic loose anagen hair. This is also caused by mutation in PPP1CB.
- JMML: Caused by mutations in the CBL gene.

Inheritance

Inheritance is autosomal dominant, with the exception of mutations in LZTR1, which can be inherited in either an autosomal dominant or autosomal recessive manner.[1-4]

Individuals with NS and NSML may have an affected parent. In contrast, CFC and Costello syndrome are almost always the result of a de novo mutation.[1-4]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Diagnosis

The diagnosis of an NSD is established with molecular testing, which can be accomplished with the use of a multigene panel or serial single-gene testing. Once the causative mutation in the family has been identified, prenatal diagnosis is possible via CVS or amniocentesis.

Additionally, NSDs are usually diagnosed on clinical grounds based on the presence of key features. Clinical diagnostic criteria are available for NSML. No formal diagnostic

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criteria exist for NS, CFC or Costello syndrome. The diagnosis should be suspected in individuals with the following:[1-4]

- **NS:**
  - Characteristic facies: "low-set, posteriorly rotated ears with fleshy helices; vivid blue or blue-green irises; widely spaced and downslanted palpebral fissues; epicanthal folds; fullness or droopiness of the upper eyelids (ptosis)."[1]
  - "Short stature for sex and family background
  - Congenital heart defects, most commonly pulmonary valve stenosis, atrial septal defect, and/or hypertrophic cardiomyopathy
  - Developmental delay of variable degree
  - Broad or webbed neck
  - Unusual chest shape with superior pectus carinatum and, inferior pectus excavatum
  - Widely spaced nipples
  - Cryptorchidism in males
  - Lymphatic dysplasia of the lungs, intestines, and/or lower extremities"[1]
  - "Coagulation defects"[1]
  - Per a recent expert summary, "No consensus clinical diagnostic criteria for Noonan syndrome have been published."[1] However, diagnostic scoring systems for NS were developed by van der Burgt and published in 2007.[6] These are also embedded in the Dyscerene 2010 guidelines for NS, and similar recommendations were provided by Romano et al 2010 and Roberts et al 2013.[7-9] Each feature has a major finding and minor finding as indicated below. Per the scoring systems, a clinical diagnosis of NS is definitive when an individual has: two major signs OR one major sign plus two minor signs OR three minor signs.
    - Facial
      - Major: typical face dysmorphology
      - Minor: suggestive face dysmorphology
    - Cardiac
      - Major: pulmonary valve stenosis, HOCM [hypertrophic obstructive cardiomyopathy] and/or ECG typical of NS
      - Minor: other defect
    - Height
      - Major: height less than third percentile for age
      - Minor: height less than tenth percentile for age
    - Chest wall
      - Major: pectus carinatum/excavatum
      - Minor: broad thorax
    - Family history

    - Major: first degree relative with definite NS
    - Minor: first degree relative with suggestive NS
  - Other
    - Major: intellectual disability, cryptorchidism, and lymphatic dysplasia
    - Minor: intellectual disability, cryptorchidism, and/or lymphatic dysplasia
- **CFC:**
  - Cardiac features: pulmonic stenosis, atrial septal defects, ventricular septal defects, hypertrophic cardiomyopathy, heart valve anomalies, and rhythm disturbances.
  - Craniofacial features: "relative macrocephaly, triangular facies, bitemporal narrowing, hypoplasia of the supraorbital ridges, widely spaced eyes, telecanthus, downslanting palpebral fissures, epicanthal folds, ptosis, short nose with depressed bridge and anteverted nares, ear lobe creases, low-set ears that may be posteriorly rotated, deep philtrum, cupid's bow configuration of the upper lip, high-arched palate, relative micrognathia."
  - Ectodermal features: characteristic skin, hair, and nail abnormalities.
  - Neurological features: developmental delay, intellectual disability, epilepsy, hypotonia, abnormal brain MRIs.
  - Gastrointestinal and growth features: feeding problems, failure to thrive, growth delays, gastrointestinal dysmotility.[4]
- **NSML (previously LEOPARD) syndrome:**
  - "Lentigines
  - Cardiac abnormalities, particularly hypertrophic cardiomyopathy
  - Poor linear growth/short stature
  - Pectus deformity"
  - Craniofacial features including widely spaced eyes and ptosis
  - Clinical diagnostic criteria are:
    - "Multiple lentigines plus two of the other cardinal features, OR
    - In the absence of lentigines, three of the other cardinal features plus a first-degree relative with NSML"[3]
- **Costello syndrome:**
  - Prenatal findings: "increased nuchal thickness, polyhydramnios (>90%), characteristic ulnar deviation of the wrists, short humeri and femurs, fetal tachycardia (various forms of atrial tachycardia), preterm delivery
  - Postnatal findings: severe postnatal feeding difficulties extending throughout early childhood, failure to thrive, short stature, macrocephaly (relative or absolute), coarse facial features, curly or sparse, fine hair
  - Skin: loose, soft skin, increased pigmentation, deep palmar and plantar creases, papillomata of face and/or perianal region (typically absent in infancy but may appear in childhood), hyperkeratosis and calluses, premature aging with hair loss

- Musculoskeletal system: diffuse hypotonia, joint laxity, and low muscle mass, ulnar deviation of wrists and fingers; splayed fingers resulting in characteristic hand posture, spatulate finger pads, abnormal fingernails, tight Achilles tendons (often evolving throughout childhood), positional foot deformity, vertical talus, kyphoscoliosis, pectus carinatum, pectus excavatum, asymmetric rib cage, developmental hip dysplasia
- Cardiovascular system: cardiac hypertrophy, usually hypertrophic cardiomyopathy (i.e., idiopathic subaortic stenosis, asymmetric septal hypertrophy), although other forms (e.g., biventricular hypertrophy) have been reported; congenital heart defects, usually valvar pulmonic stenosis; arrhythmia, usually supraventricular tachycardia (known as non-reentrant tachycardias); aortic dilation (typically mild, noted in fewer than 10% of individuals); hypertension
- Neurologic: Chiari I malformation (may develop over time), hydrocephalus, syringomyelia, tethered cord, seizures
- Tumors: increased occurrence of malignant solid tumors including rhabdomyosarcoma and neuroblastoma in young children and transitional cell carcinoma of the bladder in adolescents and young adults
- Psychomotor development: developmental delay or intellectual disability, findings suggestive of autism spectrum disorder in early infancy (that typically improve by age four years), sociable, outgoing personality, anxiety"[2]

Management

Surveillance is indicated for anomalies in any organ system, particularly the cardiovascular system. Heart defects are usually treated the same as in the general population. Developmental delay is addressed by early intervention programs and individualized education strategies. Growth hormone (GH) treatment may be used to increase growth velocity. Coagulation screening, including CBC with differential and PT/PTT, and treatment of serious bleeding problems as needed.[1-4,7,9] Some genotype-phenotype correlations are present, which may help to guide medical management. [10]

Survival

An individual with an NSD can have a normal lifespan. However, lifespan can vary depending on the medical complications, such as cardiovascular defects, present in the affected individual.[1-4]

Test information

Testing for NSDs may include known familial mutation analysis, next generation sequencing, and/or multigene panel testing.

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Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

- Research has demonstrated that postnatal NGS panel testing in symptomatic individuals has a diagnostic yield of 19-47%.[11-13]
- One study of multigene NSD panel testing in individuals with apparently isolated cardiomyopathy (per clinical information obtained from test requisition forms) demonstrated a detection rate of 0.6%.[14] NSDs are estimated to account for ~6% of pulmonary valve stenosis.[15]
- Approximately 3-15% of fetuses with normal chromosomes and increased nuchal translucency are estimated to have NS.[1]
- Nearly all pathogenic mutations associated with an NSD are detected with sequence analysis. Very rare cases of duplication and/or deletion have been reported in some genes; the yield of such testing is expected to be extremely low.[1-4] There is also some question as to whether these case reports with copy number variation did indeed have a clinical diagnosis of an NSD.[16]

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- Roughly 10% of individuals who fit the clinical diagnosis of an NSD do not have an identifiable pathogenic mutation in any of the known genes, suggesting that additional genes are involved.[17]

Guidelines and evidence

Selected Relevant Publications

A 2023 expert-authored review on CFC stated:[4]

- "The diagnosis of CFC syndrome is established in a proband with suggestive findings by the identification of a heterozygous pathogenic (or likely pathogenic) variant in BRAF, MAP2K1, MAP2K2, or KRAS by molecular genetic testing."
- "Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing) depending on the phenotype. Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not."
- "A RASopathy multigene panel… is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype."

A 2022 expert-authored review on NS stated:[1]

- "When the phenotypic findings suggest the diagnosis of Noonan syndrome, molecular genetic testing approaches usually include the use of a multigene panel."
- "Serial single-gene testing can be considered if panel testing is not feasible. Approximately 50% of individuals with NS have a pathogenic missense variant in PTPN11; therefore, single-gene testing starting with PTPN11 would be the next best first test. Appropriate serial single-gene testing if PTPN11 testing is not diagnostic can be determined by the individual's phenotype (e.g., RIT1 if there is hypertrophic cardiomyopathy, LZTR1 if autosomal recessive inheritance is suspected); however, continued sequential single-gene testing is not recommended as it is less efficient and more costly than panel testing."
- "Since Noonan syndrome occurs through a gain-of-function mechanism and large intragenic deletions or duplications have not been reported, testing for intragenic deletions or duplications is unlikely to result in a diagnosis; however, rare cases have been reported for some genes."
- "Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing or genome sequencing) depending on the phenotype."
- "When the diagnosis of Noonan syndrome has not been considered because an individual has atypical phenotypic features or if some but not all characteristic phenotypic features are present (e.g., a "Noonan-like" phenotype), comprehensive

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genomic testing, which does not require the clinical to determine which gene is likely involved, may be used. Exome sequencing is most commonly used; genome sequencing is also possible."

A 2022 expert-authored review on NSML stated:[3]

- "Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing) depending on the phenotype."
- "Although gene-targeted deletion/duplication analysis could be considered, the variant detection frequency is unknown and expected to be extremely low."

A 2023 expert-authored review on Costello syndrome stated:[2]

- "When the clinical findings suggest the diagnosis of Costello syndrome, molecular genetic testing approaches can include single-gene testing or use of a multigene panel."
- "When the diagnosis of Costello syndrome is not considered because an individual has atypical phenotypic features, comprehensive genomic testing does not require the clinician to determine which gene is likely involved. Exome sequencing is most commonly used; genome sequencing is also possible."

A 2014 expert-authored review on NS made the following recommendations:[18]

- Noonan syndrome should be considered in anyone with two or more of the following:
  - "Characteristic facial features
  - Developmental delay and/or learning disability
  - Heart defect
  - Pubertal delay and/or infertility
  - Short stature
  - Typical chest deformity
  - Undescended testes
  - First-degree relative who has Noonan syndrome or any of the above features"
- "The diagnosis of Noonan syndrome should be considered in all fetuses with a normal karyotype and increased nuchal translucency, especially when cardiac anomaly, polyhydramnios, and/or multiple effusions are observed [Evidence rating: C]."
- "Management of patients with Noonan syndrome is optimized by adherence to age-specific guidelines that emphasize screening and testing for common health issues [Evidence rating: C]. U.S. and United Kingdom age-specific guidelines are available."
- "Referral to a clinical geneticist for assistance in diagnosis and management of Noonan syndrome is helpful [Evidence rating: C]."
- "The appropriateness and sequence of genetic testing should be determined by a clinical geneticist [Evidence rating: C]. Mutation testing will prove a diagnosis in approximately 70% of cases. Mutation testing may benefit a family if reproductive decisions depend on this information."

Tangshewinsirikul, et al (2024) stated:[19]

- The most consistent prenatal findings were:
  - "(1) Lymphatic drainage disorders: The most consistent finding is thickened NT [nuchal translucency] in the first trimester, followed by various features of fluid collection in body spaces in the second/third trimesters (either cystic hygroma, pleural/pericardial effusion, ascites or skin edema), with a wide spectrum of severity ...
  - (2) Cardiac abnormalities: The most consistent finding and relatively specific findings were ventricular hypertrophy … as well as pulmonary stenosis. Other less specific abnormalities are also increased, especially VSD [ventricular septal defect] and small left-sided heart
  - (3) Polyhydramnios in late gestation ...
  - (4) Other associated anomalies with low frequency include pyelectasis, short femur, absent ductus venosus, single umbilical artery and distinctive craniofacial appearances
- "Of fetuses with lymphatic drainage disorders with normal karyotyping, Noonan syndrome must be listed in the differential diagnosis, and RASopathy genetic testing must be performed, especially in cases associated with abnormalities commonly seen in the syndrome mentioned above."

Gripp KW, et al (2019) stated the following regarding Costello syndrome: [20]

- "Genetic testing coordinated by a genetics professional is important to confirm the diagnosis.
  - HRAS sequencing, or common mutation panel followed by full analysis if common panel is negative.
  - Multi-gene RASopathies panel if diagnosis is unclear or negative HRAS testing.
  - Additional testing may be considered by medical genetics professionals including chromosome microarray and exome testing."

Tafazoli A, et al (2017) stated:[21]

- "All cases should be confirmed by molecular testing for appropriate specific treatments and follow-up procedures in addition to making correct genotype-phenotype correlations…Karyotype and copy number analysis are suggested only in cases with intense neurocognitive involvement and are not performed routinely for patients with typical phenotypes of NS."

Roberts AE, et al (2013) stated: [8]

- "Genetic testing can be useful in several scenarios. Because the presentation of cardiofaciocutaneous and Costello syndromes overlaps substantially in the first year of life, genotyping can aid diagnosis. If a patient has a mild or atypical presentation, genotyping could establish the diagnosis. For an adult with suspected Noonan syndrome, establishing the molecular genetic cause will enable preimplantation, prenatal, or postnatal testing if desired. The specific genotype of a child with Noonan syndrome is useful to know in order to provide specific guidance—for example,

to address the increased prevalence of hypertrophic cardiomyopathy in RAF1-associated Noonan syndrome or short stature and growth hormone abnormalities in PTPN11-associated Noonan syndrome."

Romano, AA et al (2010) stated: [9]

- "If sequential molecular testing is determined to be indicated (rather than simultaneous chip based analysis):
  - PTPN11 sequencing should be performed first, because this gene explains the highest number of cases
  - If normal, phenotype should be used to guide the choice of the next gene to sequence
  - If developmental delays are absent or mild, CFC syndrome–like skin and hair findings are present, and/or patient is of normal stature, consider SOS1 sequencing
  - If HCM is present, consider RAF1 sequencing
  - For significant developmental delays or cognitive issues, consider KRAS sequencing
  - For sparse, thin, slow-growing hair, consider SHOC2 sequencing
  - If a variant is found, consider testing the parents to provide accurate recurrence risks."
- "...routine karyotyping or copy-number analysis is not recommended at this time for typical NS cases. It may be considered for atypical cases or when there is particularly severe neurocognitive involvement."

Special Considerations

There is considerable debate about when genetic testing for an NSD should be pursued in a pregnancy with abnormal ultrasound findings and absence of a known family history. Some authors recommend that testing for NS be undertaken for any pregnancy with an increased nuchal translucency and normal chromosome studies, even if there are no additional associated abnormalities, while others recommend that testing only be performed if there is at least one additional ultrasound finding, such as polyhydramnios, hydrops fetalis, renal anomalies, distended JLS, hydrothorax, cardiac anomalies or ascites.[18,22-30]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Noonan spectrum disorder testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered.

However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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PALB2 Genetic Testing for Cancer Risk

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Introduction

PALB2 genetic testing is addressed by this guideline.

Procedure addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure(s) addressed by this guideline	Procedure code(s)
PALB2 deletion/duplication analysis	81479
PALB2 known familial mutation analysis	81308
PALB2 sequencing	81307

Criteria

Introduction

Requests for PALB2 testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous testing that would detect the familial mutation, and
  - Known family mutation in PALB2 identified in 1st, 2nd, or 3rd degree relative(s), AND
- Age 18 years or older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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Full Sequence Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - Member has had BRCA1/2 analysis and no mutations were found, and
  - Member has not had previous PALB2 sequencing, AND
- Diagnostic Testing in Symptomatic Individuals and Presymptomatic Testing in Asymptomatic individuals:
  - Member has met criteria for BRCA1/2 analysis,** AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**For information on BRCA1/2 testing, please refer to the guideline *BRCA Analysis,* as this testing is not addressed here.

Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - Member meets above criteria for PALB2 full sequence analysis, and
  - Member has had PALB2 full sequence analysis and no mutations were found, and
  - Member had not had previous PALB2 deletion/duplication analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

PALB2 testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

What is PALB2 genetic testing?

Breast cancer is the most frequently diagnosed malignancy and one of the leading causes of cancer mortality in women around the world. Hereditary breast cancer accounts for 5% to 10% of all breast cancer cases.[1] Two cancer susceptibility genes, BRCA1 and BRCA2, are implicated in 40-50% of all hereditary breast cancer cases.[1,2] Other genes have also been identified in the literature as being associated with inherited breast cancer risk, including ATM, BARD1, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, and TP53.[1-5] PALB2 is a gene that encodes a protein that

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may be involved in tumor suppression and is considered a partner and localizer of BRCA2.[2] Mutations in PALB2 increase the chance a person will develop certain cancers and, in particular, female breast cancer.[1-6]

Prevalence

In one study, pathogenic mutations in 12 genes associated with hereditary breast cancer were found in 5.06% of 32,347 women with breast cancer. Of those with a mutation, 9.13% had a mutation in PALB2.[1] Prevalence of PALB2 mutations in women with breast cancer has been reported in multiple studies, ranging from 0.46% to 0.84%.[7] Over 160 truncating mutations in PALB2 have been detected among families with breast cancer worldwide.[8]

Symptoms

One study of over 500 families with PALB2 pathogenic variants estimated a relative risk (RR) of 7.8 (95% CI, 5.82-8.85) for female breast cancer, 2.91 (95% CI, 1.40-6.04) for ovarian cancer, 2.37 (95% CI, 1.24-4.50) for pancreatic cancer and 7.34 (95% CI, 1.28-42.18) for male breast cancer.[8] A meta-analysis of three studies estimated a RR of 5.3 (90% CI, 3.0-9.4) for female breast cancer.[9] Another study documented a lifetime risk of breast cancer of 32% in women with a PALB2 mutation.[1] Per the National Comprehensive Cancer Network, the absolute risk for breast, ovarian, and pancreatic cancer are quoted as 32-53%, 3-5% and 2-5%, respectively.[10]

Cause

Pathogenic mutations in the PALB2 gene cause the aforementioned associated cancer risks.[1-10]

Diagnosis

The diagnosis is established with identification of a pathogenic mutation in the PALB2 gene.

Inheritance

PALB2 mutations are inherited in an autosomal dominant manner.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each

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offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

PALB2 mutations inherited in an autosomal recessive manner cause Fanconi Anemia.[10] Testing for Fanconi Anemia is not addressed in this guideline.

Management

Screening and prevention options are available to specifically address the increased risk of cancer in an individual with a PALB2 pathogenic mutation.[10]

Test information

Introduction

PALB2 testing may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

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Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2021) published a clinical practice resource for management of individuals with PALB2 pathogenic mutations. They stated the following:[11]

- "ACMG recommends:
  - the use of personalized risk estimates (e.g., CanRisk) in guiding clinical management.
  - that PALB2 should be included in breast, ovarian, and pancreas germline cancer gene panels.
  - that PALB2 VUS [variants of uncertain significance] are not used to guide clinical management.
  - prospective collection of clinical data from PALB2 heterozygotes to establish clear metrics on treatment outcome and survival.
  - surveillance for breast cancer should be equivalent to that for BRCA1/2 heterozygotes.
  - risk-reducing mastectomy can be considered as an option. The decision should be guided by personalized risk assessment.
  - ovarian cancer surveillance should not be offered, and risk-reducing salpingo-oophorectomy should include shared decision making and should rarely be considered before the age of 50.
  - pancreatic cancer surveillance should be considered, but ideally as part of a clinical trial.
  - PALB2 heterozygotes should be considered for the same therapeutic regimens and trials as those for BRCA1/2."
- "ACMG does not recommend testing partners of PALB2 heterozygotes in the reproductive setting, unless they are from a country with founder variants or it can be justified by the partner's family history of cancer."

American Society of Breast Surgeons

The American Society of Breast Surgeons (ASBrS, 2019) published a consensus guideline on genetic testing for hereditary breast cancer. They stated the following:[12]

- "Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing. When the patient’s history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful. Genetic testing is increasingly provided through multi-gene panels. There are a wide variety of panels

available, with different genes on different panels. There is a lack of consensus among experts regarding which genes should be tested in different clinical scenarios. There is also variation in the degree of consensus regarding the understanding of risk and appropriate clinical management of mutations in some genes."

- "Genetic testing should be made available to all patients with a personal history of breast cancer. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies."
- “Patients who had genetic testing previously may benefit from updated testing. Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. In particular, a patient who had negative germline BRCA1 and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing. Genetic testing performed prior to 2014 most likely would not have had PALB2 or other potentially relevant genes included and may not have included testing for large genomic rearrangements in BRCA1 or BRCA2."
- “Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines. Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves. When it is not feasible to test the affected relative first, then the unaffected family member should be considered for testing if they are interested, with careful pre-test counseling to explain the limited value of “uninformative negative” results. It is also reasonable to order a multi-gene panel if the family history is incomplete (i.e., a case of adoption, patient is uncertain of exact type of cancer affecting family members, among others) or other cancers are found in the family history, as described above."

American Society of Clinical Oncology and Society of Surgical Oncology

A 2024 American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) joint guideline for germline testing in individuals with breast cancer stated the following:[13]

- "Testing for high penetrance genes beyond BRCA1/2, including PALB2, TP53, PTEN, STK11, and CDH1, could inform medical therapy, influence surgical decision making, refine estimates of risks of second primary cancer, and inform family risk assessment, and thus should be offered to appropriate patients."

European School of Oncology and European Society of Medical Oncology

The European School of Oncology (ESO, 2022) and the European Society of Medical Oncology (ESMO, 2022) held the fifth International Consensus Conference for Breast Cancer in Young Women leading to the publication of consensus recommendations. The following was stated regarding PALB2 genetic testing:[14]

- "Although BRCA1/2 are the most frequently mutated genes, other additional moderate- to high-penetrance genes may be considered, if deemed appropriate by the geneticist/genetic counselor or if they will impact therapeutic interventions."
- "When a hereditary cancer syndrome is suspected and a mutation in BRCA1/2 has not been identified, multi-gene panel testing may be considered. Practice should be guided by high quality national/international guidelines."
- "As commercially available multi-gene panels include different panels of genes, the choice of the specific panel and quality-controlled laboratory is crucial."
- "For BRCA1/2 mutation carriers and others at high risk based on family history or predisposing mutations in other genes (e.g. p53, PALB2, CHEK2, ATM) and for those at increased risk because of a personal history of therapeutic radiation, annual surveillance with MRI and mammography with or without ultrasound is recommended."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) evidence and consensus-based guidelines addressed test indications for breast, ovarian, pancreatic and prostate cancer susceptibility genes, including PALB2.[10] These guidelines included recommendations related to unaffected individuals with a family history of cancer, those with a known mutation in the family, those with a personal history of breast cancer, exocrine pancreatic cancer, ovarian cancer, a confirmed diagnosis of prostate cancer and men with breast cancer. They take into consideration age of diagnosis, tumor pathology, degree of relationship, treatment implications, and Ashkenazi Jewish ancestry.

These recommendations are Category 2A, defined as "lower-level evidence" with "uniform NCCN consensus that the intervention is appropriate" and are frequently updated.[10]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for PALB2 testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible

that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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PCA3 Testing for Prostate Cancer

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Introduction

PCA3 testing for prostate cancer is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
PCA3 Score	81313

Criteria

Introduction

Requests for PCA3 testing are reviewed using these criteria.

Prostate cancer antigen testing (PCA3) is medically necessary in males with ALL of the following:

- Age >50 years, and
- One or more previous negative prostate biopsies, and
- Continued clinical suspicion of prostate cancer based on digital rectal exam (DRE) or elevation of prostate specific antigen (PSA) of >3 ng/mL, and for whom a repeat biopsy would be recommended by a urologist based on current standard of care, and
- Atypical small acinar proliferation (ASAP) was NOT identified on the most recent biopsy.

What is prostate cancer antigen 3 (PCA3)?

Prostate cancer antigen 3 (PCA3) is a non-protein-coding messenger RNA (mRNA) that is highly overexpressed in >95% prostate cancer tissue compared with normal prostate tissue or benign prostatic hyperplasia.[1]

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Test information

Introduction

The strong association between PCA3 mRNA levels and prostate cancer led to the development of a urinary assay to measure this analyte to aid in cancer detection.[1]

PCA3 Testing for Prostate Cancer Detection

- Following a digital rectal examination, first-void urine is collected, rapidly processed, and the mRNAs for the PCA3 gene and the PSA gene are quantified. A PCA3 score is calculated from the ratio of PCA3 RNA to PSA RNA.
- A high (>25) PCA3 Score indicates an increased likelihood of a positive biopsy. A low (<25) PCA3 Score is associated with a decreased likelihood of a positive biopsy.[2]
- A multi-center study which included a total of 466 men found that at a score cutoff of 25 for men with at least one previous negative biopsy, PCA3 demonstrated 77.5% sensitivity, 57.1% specificity, and negative and positive predictive values of 90% and 33.6%, respectively. Men with a PCA3 score of <25 were 4.56 times more likely to have a negative repeat biopsy than men with a score of >25.[3]

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to PCA3 testing.

American Urological Association

The American Urological Association (AUA, 2023) guideline on the early detection of prostate cancer stated:[4]

- "When screening for prostate cancer, clinicians should use PSA as the first screening test. (Strong Recommendation; Evidence Level: Grade A)"
- "For people with a newly elevated PSA, clinicians should repeat the PSA prior to a secondary biomarker, imaging, or biopsy. (Expert Opinion)"
- "Clinicians may use adjunctive urine or serum markers when further risk stratification would influence the decision regarding whether to proceed with biopsy. (Conditional Recommendation; Evidence Level: Grade C)"
- "After a negative biopsy, clinicians may use blood, urine, or tissue-based biomarkers selectively for further risk stratification if results are likely to influence the decision regarding repeat biopsy or otherwise substantively change the patient's management. (Conditional Recommendation; Evidence Level: Grade C) Blood, urine, or tissue-

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based biomarkers may provide additional information for risk stratification in patients with a prior negative biopsy and with ongoing suspicion for GG2+ prostate cancer."
- "While there are a plethora of serum, urine, tissue, and imaging biomarkers to assess the likelihood of high-grade prostate cancer, there is little knowledge on comparative effectiveness, how they may complement or supplement each other, and how various stepwise algorithms perform."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2024) guidelines for prostate cancer early detection recognized the FDA-approved use of PCA3 testing and stated:[5]
- "Results were reported from an NCI Early Detection Research Network (EDRN) validation study of the PCA3 urinary assay in 859 individuals scheduled for a diagnostic prostate biopsy in 11 centers. The primary outcomes were reported at a PPV of 80% (95% CI, 72%–86%) in the initial biopsy setting and an NPV of 88% (95% CI, 81%–93%) in the repeat biopsy setting. Based on the data, use of PCA3 in the repeat biopsy setting would reduce the number of biopsies by almost half, and 3% of men with a low PCA3 score would have high-grade prostate cancer that would be missed. In contrast, the risk of high-grade disease in men without prior biopsy with a low PCA3 is 13%. Thus, the panel believes that this test is not appropriate to use in the initial biopsy setting."
- "The FDA has approved the PCA3 assay to help decide, along with other factors, whether a repeat biopsy in individuals aged ≥50 years with one or more previous negative prostate biopsies is necessary. This assay is recommended for men with previous negative biopsy in order to avoid repeat biopsy by the Molecular Diagnostic Services Program (MolDX) and is therefore covered by CMS (Centers for Medicare & Medicaid Services) in this setting. The panel also includes PCA3 as an option in the post-biopsy setting."

U.S. Food and Drug Administration

The U.S Food and Drug Administration (FDA, 2012) approved the Progensa PCA3 assay with the following intended use:[6]
- “The PROGENSA PCA3 Assay is indicated for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had one or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on current standard of care, before consideration of PROGENSA PCA3 Assay results.”
- "The Clinical Study only included men who were recommended by urologists for repeat biopsy. Therefore, the performance of the PROGENSA PCA3 Assay has not been established in men for whom a repeat biopsy was not already recommended."
- "Black Box Warning: The PROGENSA PCA3 Assay should not be used for men with atypical small acinar proliferation (ASAP) on their most recent biopsy. Men with ASAP

on their most recent biopsy should be treated in accordance with current medical guidelines."

Selected Relevant Publications

Data from many peer-reviewed publications suggest that PCA3 gene testing, when used with other patient information, may help address some of the well-known challenges urologists face, such as identifying prostate cancers while reducing unnecessary repeat biopsies.[7-9]

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for PCA3 testing for prostate cancer will ensure that testing will be available to those members most likely to benefit from the information provided by the assay. For those not meeting criteria, it ensures alternate management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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PTEN Hamartoma Tumor Syndromes Genetic Testing

MOL.TS.223.A
v1.0.2026

Introduction

PTEN hamartoma tumor syndromes (PHTS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Genomic Unity PTEN analysis	0235U
PTEN deletion/duplication analysis	81323
PTEN known familial mutation analysis	81322
PTEN sequencing	81321

Criteria

Introduction

Requests for PTEN hamartoma tumor syndromes (PHTS) testing are reviewed using the following criteria.

PTEN Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing that would detect the familial mutation, AND

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- Diagnostic and Predisposition Testing:
  - Known deleterious family mutation in PTEN identified in 1st, 2nd, or 3rd degree biologic relative(s), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

PTEN Sequencing with Promoter Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous sequencing of PTEN, AND
- Diagnostic Testing for Symptomatic Individuals
  - Personal history of ANY of the following:
    - Bannayan Riley-Ruvalcaba syndrome (BRRS); or
    - Adult Lhermitte-Duclos disease (LDD); or
    - Autism spectrum disorder and macrocephaly; or
    - At least two biopsy-proven trichilemmomas; or
    - At least two major criteria** (one must be macrocephaly); or
    - Three major criteria** without macrocephaly; or
    - One major** and at least three minor criteria***; or
    - Four or more minor criteria***, OR
- Predisposition testing for Presymptomatic/Asymptomatic Individuals:
  - At-risk person with a family history of:
    - A relative (includes first-degree relative or more distant relatives if the first-degree relative is unavailable or unwilling to be tested) with a clinical diagnosis of Cowden syndrome or BRRS (no previous genetic testing); and
    - One major** OR two minor criteria*** in the at-risk person, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

PTEN Deletion/Duplication Analysis:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - Sequence analysis of PTEN has been performed and resulted negative, and
  - Criteria for PTEN full gene sequencing are met, and

  - No previous deletion/duplication testing, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Criteria for testing purposes are:

**Major:	***Minor:
• Breast cancer • Endometrial cancer • Follicular thyroid cancer • Multiple GI hamartomas or ganglioneuromas • Macrocephaly (at least 97th percentile: 58cm in adult females and 60cm in adult males) • Macular pigmentation of glans penis • Mucocutaneous lesions: one biopsy-proven trichilemmoma, multiple palmoplantar keratoses, multifocal or extensive oral mucosal papillomatosis, multiple cutaneous facial papules (often verrucous)	• Autism spectrum disorder • Colon cancer • ≥ 3 esophageal glycogenic acanthoses • Lipomas • Intellectual disability (IQ≤75) • Papillary or follicular variant of papillary thyroid cancer • Thyroid structural lesions (e.g., adenoma, nodule(s), goiter) • Renal cell carcinoma • Single GI hamartoma or ganglioneuroma • Testicular lipomatosis • Vascular anomalies (including multiple intracranial developmental venous anomalies)

Other Considerations

PHTS testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

For information on germline testing after somatic testing, please refer to the guideline *Hereditary (Germline) Testing After Tumor (Somatic) Testing*, as this testing is not addressed here.

What is PTEN hamartoma tumor syndrome?

PTEN hamartoma tumor syndrome (PHTS) is used to describe the group of conditions caused by PTEN mutations that include hamartomatous growths: Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome and PTEN-related Proteus-like syndrome, and autism spectrum disorder with macrocephaly.[1]

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Prevalence

The prevalence is unknown. The prevalence of CS was previously estimated to be 1 in 200,000 individuals, although this is likely low due to underdiagnosis.[1]

Symptoms

Historically, these conditions have been considered clinically distinct but share an underlying genetic etiology, and show some overlap in families.[1]

- **Cowden syndrome** (CS) is characterized by an increased risk for benign and malignant tumors of the breast, endometrium, and thyroid (non-medullary).[1,2]
  - Other common features include macrocephaly and growths on the skin or mucous membranes (mucocutaneous lesions). The lifetime risk for breast cancer is 25-50% with an average age at diagnosis of 38-46 years.[1] However, a 2012 publication by Tan et al. reports that this lifetime risk may be as high as 85%, particularly in individuals with PTEN promoter mutations.[3]
  - The lifetime risk for thyroid cancer can range from 10% to as high as 35%.[1,3] If it occurs, thyroid cancer is usually follicular. It is rarely papillary and is never medullary. Benign thyroid growths are also found in up to 75% of individuals with CS.[1] "However, the high frequency of thyroid disease in the general population means that when taken on their own, thyroid neoplasms have a low predictive value for identifying mutations carriers."[4]
  - Endometrial cancer has a reported lifetime risk of up to 28%.[3]
  - The gastrointestinal polyp risk (often colonic) in individuals with CS may be 80% or higher and the lifetime risk for colorectal cancer is estimated to be 9%.[3]
  - Early onset colorectal cancer has been reported in 13% of individuals with PTEN associated CS indicating earlier and more frequent colonoscopy is warranted in this population.[3,5,6]
  - Additionally, an increased lifetime risk for kidney cancer (approximately 34%) and melanoma (about 5-6%) has been reported.[1-3]
- **Lhermitte-Duclos disease** (LDD) is a rare, benign tumor of the cerebellum called dysplastic gangliocytoma that may present in childhood or adulthood.[1,2] Most adult-onset LDD is caused by a PTEN mutation even when no other signs of CS are present.[1]
- **Bannayan-Riley-Ruvalcaba syndrome** (BRRS) is a genetic disorder characterized by macrocephaly, multiple benign intestinal polyps (hamartomatous type), lipomas, colored spots on the tip of the penis (pigmented macules of the glans penis), and hemangiomas. Some people with BRRS have intellectual disability and/or birth defects. There may be an increased risk for several types of cancer, including breast, thyroid and endometrial.[2]
- **PTEN-related Proteus and PTEN-related Proteus-like syndromes** are highly variable conditions characterized by overgrowth of several different tissues usually in

a patchy asymmetric pattern (mosaic) that is often present from birth but gets worse over time.[1] Clinical signs and symptoms include connective tissue and epidermal nevi (hamartomatous growths), ovarian cystadenomas, parotid monomorphic adenomas, lipomas, capillary/venous/lymphatic malformations, and a characteristic facial dysmorphology.

- **Autism spectrum disorder with macrocephaly** (defined as >2.5 SDs above the age mean or ≥97th percentile) may be caused by a mutation in the PTEN gene.[1]
- **Juvenile polyposis of infancy** may be caused by mutations in PTEN. In this condition, juvenile polyposis is diagnosed before six years of age and the phenotype may be similar to BRRS. “GI manifestations (bleeding, diarrhea, & protein-losing enteropathy) are often severe."[1]

Cause

Pathogenic mutations in the PTEN gene cause PHTS.

- Up to 80% of people with a clinical diagnosis of CS have a PTEN mutation in the coding region.[1] Ten percent of individuals with CS have a PTEN mutation in the promotor region.[1]
- The majority of CS cases are simplex. Approximately 10-50% of individuals with CS have an affected parent.[1] De novo PTEN pathogenic variants occur in 10-44% of individuals with PHTS.
- Nearly all individuals with a PTEN mutation will develop symptoms (complete penetrance).[1,2]
- Up to 71% of individuals with a clinical diagnosis of BRRS have a PTEN mutation.[1] Up to 50% of individuals with Proteus-like syndrome and 20% of individuals with Proteus syndrome have a PTEN mutation.[1] An estimated 10-20% of all individuals with ASD/macrocephaly have a PTEN mutation.[1,7] The likelihood may be greater if other family members have signs and symptoms in the PHTS spectrum.

Inheritance

PHTS are autosomal dominant disorders.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

The diagnosis of PHTS can be established with the identification of a pathogenic mutation in the PTEN gene.

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- Sequence analysis of the PTEN gene will detect a mutation in about 80% of people with a clinical diagnosis of CS and 60% of people with a clinical diagnosis of BRRS.[1]
  - **Sequencing of the promoter region** will detect an additional 10% of PTEN mutations that cause CS.[1] As such, it is important to determine whether or not the selected laboratory includes PTEN promoter analysis in their testing.
- The likelihood of identifying a deletion or duplication in people with clinically diagnosed CS is unknown but expected to be relatively low.[1] About 11% of people with BRRS have large PTEN gene deletions.[1]

Clinical diagnostic criteria have been developed. A clinical diagnosis of PHTS is based on the major and minor criteria in the table below.[2]

An operational diagnosis of CS is established if an individual meets any of the following criteria:

- Three or more major criteria* (one must include macrocephaly, Lhermitte-Duclos disease, or GI hamartomas); or
- Two major* and three minor** criteria

If an individual meets the clinical criteria noted above or has a PTEN pathogenic mutation, the family members would meet criteria for an operational diagnosis of CS if they meet one of the following criteria:

- Two major criteria* with or without minor criteria; or
- One major* and two minor criteria**; or
- Three minor** criteria

The major and minor criteria for a clinical diagnosis of PHTS are:[2]

Major:*	Minor:**
• Breast cancer • Endometrial cancer • Follicular thyroid cancer • Three or more GI hamartomas (including ganglioneuromas but excluding hyperplastic polyps) • Adult Lhermitte-Duclos disease • Macrocephaly (at least 97th percentile: 58cm in adult females and 60cm in adult males) • Macular pigmentation of glans penis • Mucocutaneous lesions: ◦ Trichilemmomas: at least three and at least one biopsy proven ◦ Palmoplantar keratotic pits and/or acral hyperkeratotic papules: at least three ◦ Mucocutaneous neuromas: at least three ◦ Oral papillomas (particularly on tongue or gingiva): at least three or one biopsy proven or dermatolologist diagnosed	• Autism spectrum disorder • Colon cancer • At least three esophageal glycogenic acanthoses • At least three lipomas • Intellectual disability (IQ of 75 or less) • Renal cell carcinoma • Testicular lipomatosis • Papillary or follicular variant of papillary thyroid cancer • Thyroid structural lesions (e.g., adenoma, nodule(s), goiter) • Single GI hamartoma or ganglioneuroma • Vascular anomalies (including multiple intracranial developmental venous anomalies)

Management

People with CS need heightened cancer surveillance starting at age 18 years. This may begin earlier if warranted: “For individuals with a family history of a particular cancer type at an early age, screening should be considered five to ten years prior to the youngest diagnosis in the family”.[1] The exception is children should have a yearly thyroid ultrasound starting at age 7 years and skin check with physical examination.[1] Because of the overlap in clinical phenotypes, people with other PTEN-related conditions are advised to follow the same heightened cancer surveillance guidelines as for CS.[8,9]

Survival

Given the phenotypic spectrum of PHTS and underdiagnosis, especially of individuals with non-classic phenotypes, the prognosis for individuals with PHTS is unknown. The increased risk for malignant tumors is the largest factor impacting survival.

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Test information

Introduction

Testing for PHTS may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2013) issued consensus practice guidelines on the genetics evaluation of autism. They proposed an evaluation scheme with three tiers. The first tier included routine studies such as chromosome analysis and fragile X genetic testing. PTEN gene testing is recommended as a second-tier test when the head circumference is greater than 2.5 SDs above the mean (if no diagnosis is made via first tier testing).[10]

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National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) supported the use of PTEN genetic testing in those with clinical features or a family history. They recommended PTEN genetic testing in any of the following situations:[2]

- Family history of a known PTEN mutation [PTEN known familial mutation testing is appropriate]
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting clinical diagnostic criteria, as defined by NCCN, for CS/PHTS
- Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of any of the following:
  - Adult-onset Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma)
  - Autism spectrum disorder and macrocephaly (greater than or equal to 97th percentile)
  - Two or more biopsy proven trichilemmomas
  - Macrocephaly and at least one other major*** criteria
  - Three major*** criteria without macrocephaly
  - One major*** and three or more minor**** criteria
  - Four or more minor**** criteria
- At-risk relative of someone clinically diagnosed with Cowden syndrome or BRRS (who has not had genetic testing), when the at-risk relative has at least one major*** or two minor**** criteria. Ideally, the at-risk person is a first-degree relative (parent, sibling, child) of someone clinically diagnosed, but testing more distant relatives is acceptable if closer relatives are not available or willing to have testing.
- Affected individuals with pathogenic/likely pathogenic variant identified on tumor genomic testing that may have implications if also identified on germline testing. "This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic PTEN P/LP [pathogenic/likely pathogenic] variants are common in many tumor types in absence of a germline P/LP variant." For information on germline testing after somatic testing, please refer to the guideline *Hereditary (Germline) Testing After Tumor (Somatic) Testing*, as this testing is not addressed here.

The major and minor criteria to determine appropriateness of genetic testing are:

***Major:	****Minor:
• Breast cancer • Endometrial cancer • Follicular thyroid cancer • Multiple GI hamartomas or ganglioneuromas • Lhermitte-Duclos disease (adult) • Macrocephaly (at least 97th percentile: 58 cm in adult females and 60 cm in adult males) • Macular pigmentation of glans penis • Mucocutaneous lesions: one biopsy-proven trichilemmoma, multiple palmoplantar keratoses, multifocal or extensive oral mucosal papillomatosis, multiple cutaneous facial papules (often verrucous)	• Autism spectrum disorder • Colon cancer • 3 or more esophageal glycogenic acanthoses • Lipomas • Intellectual disability (IQ less than or equal to 75) • Papillary or follicular variant of papillary thyroid cancer • Thyroid structural lesions (e.g., adenoma, nodule(s), goiter) • Renal cell carcinoma • Single GI hamartoma or ganglioneuroma • Testicular lipomatosis • Vascular anomalies (including multiple intracranial developmental venous anomalies)

US Multi-Society Task Force on Colorectal Cancer

The US Multi-Society Task Force on Colorectal Cancer issued a consensus statement on the diagnosis and management of hamartomatous polyposis syndromes that stated:[11]

- "We recommend patients with any of the following undergo a genetic evaluation: 2 or more lifetime hamartomatous polyps, a family history of hamartomatous polyps, or a cancer associated with a hamartomatous polyposis syndrome in first or second-degree relatives. Genetic testing (if indicated) should be performed using a multigene panel test. (Strong recommendation, low quality of evidence)"

Selected Relevant Publication

An expert-authored review of the PHTS stated:[1]

- "Sequence analysis of PTEN is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found. If a pathogenic variant is not identified with deletion/duplication analysis, perform sequence analysis of the PTEN promoter region for variants that decrease PTEN gene expression."
- "The most serious consequences of PHTS relate to the increased risk of cancers including breast, thyroid, endometrial, renal, and to a lesser extent, colon. In this

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regard, the most important aspect of management of any individual with a PTEN pathogenic variant is increased cancer surveillance to detect any tumors at the earliest, most treatable stages."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for PTEN hamartoma tumor syndromes testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Polymerase Gamma (POLG) Related Disorders Genetic Testing

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Introduction

Polymerase gamma (POLG) related disorders genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
POLG deletion/duplication analysis	81479
POLG full gene sequencing	81406
POLG known familial mutation analysis	81403

Criteria

Introduction

Requests for genetic testing for polymerase gamma (POLG)-related disorders, including Alpers-Huttenlocher syndrome (AHS), childhood myocerebrohepatopathy spectrum (MCHS), myoclonic epilepsy myopathy sensory ataxia (MEMSA), ataxia neuropathy spectrum (ANS), autosomal dominant progressive external ophthalmoplegia (adPEO), or autosomal recessive progressive external ophthalmoplegia (arPEO), are reviewed using the following criteria.

Known POLG Family Mutation Testing

- Genetic Counseling:

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- Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Diagnostic Testing for Symptomatic Individuals
  - No previous genetic testing of POLG that would detect the familial mutation, and
  - If adPEO is suspected:
    - Clinical examination is consistent with a diagnosis of adPEO, and
    - POLG mutation identified in 1st degree biological relative, OR
  - If AHS, MCHS, MEMSA, ANS, or arPEO is suspected:
    - Clinical examination is consistent with a diagnosis of AHS, MCHS, MEMSA, ANS, or arPEO, and
    - Two POLG mutations identified in a sibling, or
    - One POLG mutation identified in both parents

POLG Full Gene Sequencing

- Genetic Counseling:
  - Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous POLG sequencing, and
  - No known POLG mutation in the family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - If adPEO is suspected:
    - Clinical examination is consistent with a diagnosis of adPEO, and
    - Genetic testing is needed to confirm the diagnosis, OR
  - If AHS, MCHS, MEMSA, ANS, or arPEO is suspected:
    - Clinical examination is consistent with a diagnosis of AHS, MCHS, MEMSA, ANS, or arPEO, and
    - Genetic testing is needed to confirm the diagnosis, OR
  - If evaluating the risk for valproate-induced hepatic toxicity:
    - The member has epilepsy, and
    - There is suspicion for a POLG-related disorder based on the presence of at least one of the following:
      - unexplained encephalopathy, or
      - refractory epilepsy, or

- status epilepticus at presentation, or
- developmental delays, or
- psychomotor regression, or
- axonal sensorimotor neuropathy, or
- myopathy and/or hypotonia, or
- progressive spastic paraparesis, or
- renal tubular acidosis, or
- sensorineural hearing loss, or
- cyclic vomiting, or
- pancreatitis, or
- movement disorder (incl extrapyramidal movement disorders such as parkinsonism & chorea, & cerebellar ataxia), or
- ophthalmoplegia and/or ptosis, or
- cortical blindness and/or cataracts, or
- complicated migraine with occipital aura, and

▪ The member is currently on Depakene (valproate) or Depakote ER (divalproex sodium) therapy, or the use of one of these medications is being proposed.

POLG Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Criteria for POLG Full Gene Sequencing is met, AND
- If adPEO is suspected:
  - No mutations found on POLG Full Gene Sequencing, OR
- If AHS, MCHS, MEMSA, ANS, or arPEO is suspected:
  - No mutations or only one mutation found on POLG Full Gene Sequencing, OR
- If evaluating the risk for valproate-induced hepatic toxicity:
  - No mutations or only one mutation found on POLG Full Gene Sequencing

What are POLG-related disorders?

"POLG-related disorders" is a term used to describe medical conditions caused by mutations in the POLG gene. This is a wide spectrum of conditions that may involve multiple organ systems and have variable severity and age at onset.[1,2]

Prevalence

Although Alpers-Huttenlocher syndrome (AHS) is clinically reported to occur in 1/51,000 individuals, disease frequency calculated based on prevalence of the most common POLG mutations may be as high as 1/10,000.[1]

Symptoms

There are 6 main phenotypes attributed to POLG mutations. Onset of the POLG-related disorders can range from infancy to late adulthood. Younger individuals typically present with seizures and lactic acidosis.[3] Later in life, the most common presenting symptoms are myopathy, chronic progressive external ophthalmoplegia (CPEO), and sensory ataxia.[3] Liver failure may also occur, particularly with exposure to the antiepileptic drug, valproic acid.[1,4,5] Most affected individuals have some features ascribed to each phenotype, but rarely have all.

- Alpers- Huttenlocher syndrome (AHS):[6,7]
  - Most common symptoms
    - seizures (commonly refractory)
    - severe and progressive encephalopathy
    - liver disease and/or liver failure
  - Other possible symptoms
    - migraine with visual auras
    - stroke or stroke-like episodes
    - cortical blindness
    - hypotonia
    - ataxia
    - episodic psychomotor regression
    - extrapyramidal movements and/or myoclonus
    - peripheral neuropathy and/or areflexia
    - progressive spastic paraparesis
    - renal tubular acidosis
    - hearing loss
    - cyclic vomiting
    - pancreatitis
  - Development is often normal until disease onset, which is typically before 4 years of age. However, congenital static encephalopathy and juvenile-onset have also been described.[2] Disease progression varies, however life expectancy is shortened with individuals typically passing away between 3 months to over a decade from symptom onset. When seizure etiology is unknown, valproic acid must be used with extreme caution, as it can precipitate liver dysfunction and/or failure in AHS.[4,5]

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- Childhood myocerebrohepatopathy spectrum (MCHS):[8]
  - Most common / presenting symptoms:
    - failure to thrive
    - lactic acidosis
    - developmental delay
    - encephalopathy
    - dementia
    - myopathy
    - hypotonia
  - Other possible symptoms:
    - liver failure
    - renal tubular acidosis
    - pancreatitis
    - cyclic vomiting
    - hearing loss
  - MCHS is a rapidly progressive disease with a fatal outcome that usually presents between the first few months of life and 3 years. MCHS has a similar presentation to AHS, however severe myopathy, specific liver pathology, and nonspecific brain MRI brain findings (diffuse atrophy) help differentiate MCHS from AHS. In addition, seizures are less prominent and more easily controlled in MCHS compared to AHS.
- Myoclonic epilepsy myopathy sensory ataxia (MEMSA):[9]
  - Common symptoms:
    - epilepsy
    - myopathy (proximal, distal, or including exercise intolerance)
    - ataxia
    - ophthalmoplegia
  - MEMSA has also been known as spinocerebellar ataxia with epilepsy (SCAE). Disease onset typically occurs in adolescence and presents with cerebellar and sensory ataxia. Epilepsy usually follows, with refractory seizures leading to a progressive encephalopathy.
- Ataxia neuropathy spectrum (ANS):[10]
  - Common symptoms:
    - migraine headaches
    - ataxia
    - neuropathy (sensory, motor, or mixed)
    - encephalopathy with seizures
  - Other possible symptoms:
    - myoclonus

        - blindness
        - hearing loss
        - liver dysfunction and/or failure
        - stroke-like episodes
        - psychiatric diagnoses (commonly depression)
    - Disease onset ranges between adolescence and adulthood. Migraine headaches may be the first presenting symptom and precede the other symptoms by many years. Clinical myopathy is very rare. The encephalopathy present in most, but not all, affected individuals is often milder than AHS and more slowly progressive. ANS was previously referred to as mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO).
- Autosomal recessive progressive external ophthalmoplegia (arPEO):[11]
    - Common symptoms:
        - ptosis
        - ophthalmoparesis
    - Onset is typically in adulthood and is isolated to progressive weakness of the extraocular muscles, without associated systemic involvement. Of note, apparently isolated arPEO can present with additional symptoms later in life causing the individual to be reclassified as having another POLG-related disorder.
- Autosomal dominant progressive external ophthalmoplegia (adPEO):[1,10]
    - Common symptoms:
        - ptosis
        - ophthalmoparesis
        - strabismus
        - generalized myopathy (early fatigue and exercise intolerance)
        - sensorineural hearing loss (of varying degree)
        - axonal neuropathy
        - ataxia
        - depression
        - Parkinsonism
        - hypogonadism
        - cataracts
    - Previously, adPEO was called Chronic Progressive External Ophthalmoplegia plus (CPEO+). Onset is typically in adulthood with all individuals presenting with progressive weakness of the extraocular muscles and at least one other symptom listed above. Less commonly, cardiomyopathy and gastrointestinal dysmotility are reported.

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Cause

POLG-related disorders are caused by mutations in the POLG gene. POLG codes for a subunit of DNA polymerase protein that replicates and repairs mitochondrial DNA (mtDNA). Disease-causing mutations can affect polymerase activity, processing, DNA binding, or subunit association.[1]

Inheritance

POLG-related disorders can be inherited in an autosomal recessive or autosomal dominant pattern.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

AHS, MCHS, MEMSA, ANS, and arPEO are inherited in an autosomal recessive inheritance pattern, while adPEO is inherited in an autosomal dominant pattern. There is not always a clear genotype-phenotype relationship for all POLG variants and associated disorder/inheritance, which can make correlation to clinical presentation difficult for individuals with single variants identified. A case of arPEO caused by digenic inheritance of POLG and TWNK mutations has been reported.[1]

Diagnosis

As no clinical diagnostic criteria exist, genetic testing of POLG is required to confirm clinical suspicion of a disorder in this spectrum.

Management

Management is supportive and based on presenting symptoms, and typically involves referral for speech therapy, physical therapy, and occupational therapy. Respiratory and nutritional support are provided as needed.

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Any medications metabolized by hepatic enzymes should be carefully dosed to avoid liver toxicity. Certain antiepileptic drugs should be avoided due to the risk for precipitating or accelerating liver disease.[1]

Occurrence of dehydration, fever, anorexia and infection can create physical stress and hasten medical deterioration. These events should be avoided as much as possible.

Survival

The range of survival is broad and is largely dependent on the presenting phenotype, age at onset, and the occurrence of secondary complications.

Test information

Introduction

Testing for POLG-related disorders may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Sequence analysis for this group of disorders is typically limited to full sequencing of the POLG gene only, although POLG may appear on multigene panels for mitochondrial-related disorders.

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Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Given that clinical diagnostic criteria do not exist, genetic testing of POLG is required in order to confirm the diagnosis of a POLG-related disorder.[1]

- For individuals with suspected adPEO, identification of one POLG mutation is required to confirm the diagnosis.
- For individuals presenting with clinical features consistent with one of the five other phenotypes, identification of two (biallelic) mutations is required to confirm the diagnosis.

While biochemical analyses of an affected tissue may be informative, they are not sensitive or specific enough to definitively diagnose a POLG-related disorder. Muscle biopsy can be completely normal in children and adults with a POLG-related disorder and in clinically unaffected tissue.[12]

Guidelines and evidence

European Federation of Neurological Sciences/European Neurological Society

The European Federation of Neurological Sciences/European Neurological Society (EFNS/ENS, 2014) consensus guidelines on the diagnosis and management of chronic ataxias in adulthood recommended POLG testing in the following evaluation of individuals with autosomal recessive cerebellar ataxia:[13]

- "Step 1: mutation analysis of the FRDA gene for Friedreich's ataxia (although one can refrain from this in the case of severe cerebellar atrophy), and biochemical testing that includes cholestanol, vitamin E, cholesterol, albumin, creatine kinase (CK) and a-fetoprotein. Also consider doing nerve conduction studies/EMG (presence versus absence of peripheral neuropathy, axonal versus demyelinating) and referral to an ophthalmologist (retinitis pigmentosa, cataract, cherry red spot etc.) (Table S2) (good practice point)."
- "Step 2: mutation analysis of the SACS, POLG, Aprataxin (APTX) and SPG7 genes (taking into account specific phenotypes, as given in Table S2), and biochemical testing for white cell enzymes, phytanic acid and long chain fatty acids (good practice point)."
- "Step 3: referral to a specialized centre, e.g. for skin or muscle biopsy targeted at diagnoses such as Niemann - Pick type C, recessive ataxia with coenzyme Q deficiency [aarF domain containing kinase 3 (ADCK3)/autosomal recessive

spinocerebellar ataxia 9 (SCAR9)] and mitochondrial disorders, or for extended genetic screening using gene panel diagnostics (good practice point)."

Mitochondrial Medicine Society

Although not specific to genetic testing for POLG, the Mitochondrial Medicine Society (MMS, 2015)[14] developed consensus recommendations for the diagnosis and management of mitochondrial disease. Testing strategies, including strategies for genetic testing, were discussed. Recommendations for testing included:

- "When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no mutation is identified via known NGS panels, then whole-exome sequencing should be considered."

US Food and Drug Administration

The Food and Drug Administration (FDA) stated that Depakene (valproic acid) capsules and oral solution (2020), Depakote ER (divalproex sodium) extended-release tablets (2023), Depakote (divalproex sodium) delayed-release tablets (2020), and Depakote Sprinkles Capsules (2023) are contraindicated for individuals known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder:[15-18]

- "Valproate-induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA polymerase γ (POLG) (e.g., Alpers-Huttenlocher Syndrome) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents."[15]
- "POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to: unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders. The A467T and W748S mutations are present in approximately 2/3 of patients with autosomal recessive POLG-related disorders."[16]
- "There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA Polymerase γ (POLG) gene (e.g. Alpers Huttenlocher Syndrome). Depakote Sprinkle Capsules is contraindicated in patients

known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder. … In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, Depakote Sprinkle Capsules should only be used after other anticonvulsants have failed. This older group of patients should be closely monitored during treatment with Depakote Sprinkle Capsules for the development of acute liver injury with regular clinical assessments and serum liver testing. POLG mutation screening should be performed in accordance with current clinical practice."[17]

Selected Relevant Publications

An expert-authored review (updated 2024) suggested the following testing strategy for those with a known or suspected diagnosis of a POLG-related disorder:[1]

- "POLG-related disorders comprise a continuum of overlapping phenotypes that were clinically defined before the molecular basis was known. POLG-related disorders can therefore be considered an overlapping spectrum of disease presenting from early childhood to late adulthood. The age of onset broadly correlates with the clinical phenotype."
- "Establishing the diagnosis of a POLG-related disorder relies on clinical findings and the identification of biallelic POLG pathogenic variants on molecular genetic testing for all phenotypes except autosomal dominant progressive external ophthalmoplegia (adPEO), for which identification of a heterozygous POLG pathogenic variant on molecular genetic testing is diagnostic."
- "Sequence analysis of POLG is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect intragenic and whole-gene deletions or duplications."
- "In individuals with a suspected autosomal recessive POLG-related disorder but in whom only one POLG pathogenic variant has been identified by single-gene testing, identification of a second in trans pathogenic variant in POLG, use of RNA sequencing of POLG, or identification of pathogenic variants in other genes known to be associated with the phenotype may be revealing."
- "Sequence analysis of TWNK (formerly C10orf2 or PEO1) may be considered in persons with a suspected autosomal recessive POLG-related disorder but in whom only one POLG pathogenic variant was identified by single-gene testing, to investigate the possibility of digenic inheritance."
- "A multigene panel that includes POLG, TWNK (formerly C10orf2 or PEO1), and other genes of interest ... may be considered to identify the genetic cause of the

condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype."

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for POLG testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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POLG Related Disorders

Prader-Willi Syndrome Genetic Testing

MOL.TS.217.A
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Introduction

Prader-Willi syndrome (PWS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Chromosomal microarray [BAC], constitutional	81228
Chromosomal microarray [CGH], constitutional	S3870
Chromosomal microarray [SNP], constitutional	81229
Chromosome 15 uniparental disomy	81402
Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis	81349
FISH probe for 15q11-q13 deletion	88271
Imprinting center defect analysis	81479
Imprinting center known familial mutation analysis	81403
SNRPN/UBE3A methylation analysis	81331

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Criteria

Introduction

Requests for Prader-Willi syndrome (PWS) genetic testing are reviewed using the following criteria.

Imprinting Center (IC) Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous IC defect analysis testing that would detect the familial mutation, AND
- Family History:
  - Familial IC defect mutation known in blood relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

SNRPN Methylation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous SNRPN methylation analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Neonatal hypotonia and feeding problems (i.e., poor suck), OR
  - Developmental delay/intellectual disability, with some combination of the following:
    - Neonatal hypotonia, or
    - Feeding problems (i.e., poor suck) or poor growth in infancy, or
    - Obesity and/or food-related behavior problems (i.e., hyperphagia; obsession with food), or
    - Characteristic facial features, or
    - Hypogonadism AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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Deletion Analysis (FISH Analysis for 15q11-q13 Deletion or Chromosomal Microarray)

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous 15q11-q13 deletion analysis, and
  - No previous chromosomal microarray, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Neonatal hypotonia and feeding problems (i.e., poor suck), OR
  - Developmental delay/intellectual disability, with some combination of the following:
    - Neonatal hypotonia, or
    - Feeding problems (i.e., poor suck) or poor growth in infancy, or
    - Obesity and/or food-related behavior problems (i.e., hyperphagia; obsession with food) or
    - Characteristic facial features, or
    - Hypogonadism, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Chromosome 15 Uniparental Disomy (UPD)

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - SNRPN methylation analysis results are abnormal, and
  - 15q11-q13 deletion analysis is negative, and
  - No previous chromosome 15 UPD studies, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Meets clinical criteria for SNRPN methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Imprinting Center (IC) Defect Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:

  - SNRPN methylation analysis results are abnormal, and
  - 15q11-q13 deletion analysis is negative, and
  - Previous chromosome 15 UPD studies negative, and
  - No previous IC analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Meets clinical criteria for SNRPN methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

What is Prader-Willi syndrome?

Prader-Willi syndrome (PWS) is a multi-system genetic disorder that is due to a loss of specific genes on chromosome 15. Infants present with low muscle tone (hypotonia) and feeding difficulties which can result in failure to thrive. In the childhood years, children with PWS develop an increased appetite with decreased satiety which, without proper management, results in obesity and an increased risk of type 2 diabetes. Cognitive impairment and behavioral problems are usually present in addition to an increased risk for specific medical diagnoses.[1]

Prevalence

The prevalence is estimated to be 1/10,000 to 1/30,000.[1]

Symptoms

PWS is characterized by:[1,2]

- Decreased muscle tone (hypotonia) and feeding difficulties in early infancy
- Strabismus
- Insatiable appetite in childhood that often results in obesity
- Developmental delay
- Short stature
- Behavior problems
- Small hands and feet
- Underdeveloped genitalia and infertility

Cause

PWS is caused when the Prader-Willi critical region (PWCR) on chromosome 15 is only inherited from the mother and there is no copy from the father.

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PWS can be caused by a chromosome deletion, uniparental disomy (two copies of the maternal chromosome), or imprinting center (IC) defect. There are several genetic tests available that can help diagnose PWS.[1-4]

Diagnosis

If an individual has all of the clinical findings denoted below at the indicated age, diagnostic testing is recommended.[1,5] PWS is established in individuals who have abnormal DNA methylation analysis consistent with absence of the paternal contribution of the PWCR.[1]

Neonatal period

- Hypotonia with poor suck

One month to two years

- Hypotonia with poor appetite and poor suck
- Developmental delay

Two to six years

- Hypotonia with history of poor suck
- Developmental delay

Six year to 12 years

- History of hypotonia with poor suck
- Developmental delay
- Excessive eating and, if uncontrolled, central obesity

13 years to adulthood

- Cognitive impairment which is most often mild intellectual disability
- Excessive eating and, if uncontrolled, central obesity
- Hypothalamic hypogonadism and/or typical behavior problems

Determination of recurrence risk following a diagnosis of PWS may require additional genetic testing of the individual and testing of one or both parents depending on the identified molecular cause.[4]

Management

Individuals with PWS have age-specific medical needs. Some of the more common treatments and management include: [1]

Infancy

- Ensuring adequate nutrition through feeding support
- Physical therapy for improved muscle strength
- Screening for strabismus
- Managing cryptorchidism through hormonal and surgical treatments
- Growth hormone treatment may be initiated in infancy

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Childhood through adulthood

- Monitoring of daily food intake
- Determining if calcium and vitamin D supplementation is indicated
- Encouraging physical activity
- Growth hormone replacement therapy
- Evaluating for sleep disturbance
- Educational planning
- Addressing behavioral concerns with applied behavioral analysis therapy, behavior management strategies, and/or medication
- Assessing for hypothyroidism
- Assessing for scoliosis

Teenage years

- Sex hormone replacement at puberty as indicated

Adulthood

- Housing in a group home familiar with the needs of individuals with PWS to regulate behavior and weight management
- Growth hormone may help with maintaining muscle bulk
- Evaluate for possible osteoporosis every two years

Survival

Obesity and the associated complications contribute to the higher mortality rate in individuals with PWS. The current death rate is 1.25% per year and is lower than previous reports. The decrease is attributed to improved management. [1]

Test information

Introduction

Testing for PWS may include known familial mutation analysis, SNRPN methylation analysis, chromosomal microarray, FISH analysis for 15q11-q13 deletion, chromosome 15 uniparental disomy (UPD), or imprinting center defect analysis.

Known Familial Mutation Analysis: Known familial mutation analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing. Analysis for known familial mutations typically includes only the specific mutation identified in the family, but if available, a targeted mutation panel that includes the familial mutation(s) may be performed.

SNRPN/UBE3A Methylation Analysis: This test is typically the first test in the evaluation of both Angelman syndrome (AS) and Prader-Willi syndrome (PWS). It will detect about 80% of individuals with AS and greater than 99% of individuals with PWS. However,

DNA methylation analysis does not identify the underlying cause, which is important for determining the risk to future siblings. This risk ranges from less than 1% to up to 50%, depending on the genetic mechanism. Follow-up testing for these causes may be appropriate.

Chromosomal Microarray or FISH Analysis for 15q11-q13 Deletion: If DNA methylation analysis for AS or PWS is abnormal, deletion analysis is typically the next step. Approximately 70% of cases of both AS and PWS have a deletion in one copy of chromosome 15 involving the 15q11.2-q13 region. FISH (fluorescence in situ hybridization) analysis and chromosomal microarray (CMA, array CGH) can detect such deletions. If CMA has already been done, FISH is not likely to be necessary.

Chromosome 15 Uniparental Disomy (UPD): If DNA methylation analysis is abnormal but deletion analysis is normal, UPD analysis may be an appropriate next step for evaluation of both AS and PWS. About 28% of PWS cases are due to maternal UPD (both chromosome 15s are inherited from the mother). About 7% of cases of AS are due to paternal UPD (both chromosome 15s are inherited from the father). Both parents must be tested to diagnose UPD.

Imprinting Center Defect Analysis: This test may be considered in the evaluation of AS and PWS when methylation is abnormal, but FISH (or array CGH) and UPD studies are normal. Individuals with such results are presumed to have an imprinting defect. An abnormality in the imprinting process has been described in a minority of cases. However, imprinting center deletions may be familial, and if familial, the recurrence risk can be up to 50%.

Guidelines and evidence

Prader-Willi Syndrome Association

The Prader-Willi Syndrome Association (PWSA, 2023) stated the following in regards to PWS genetic testing and diagnosis.[3]

- "The physical examination and history are very important parts of making the diagnosis and should be done before genetic testing. All hypotonic children in the Neonatal Intensive Care Unit (NICU) who do not have a diagnosis should be tested for PWS."
- "All persons suspected of having PWS should be tested with a DNA methylation analysis. This test detects nearly all (>99%) cases of PWS."

Selected Relevant Publications

An expert-authored review (2023) stated the following regarding testing for PWS:[1]

- Methylation-specific analysis … can establish the diagnosis of PWS by identification of maternal-only imprinting at 15q11.2-q13 but cannot identify the cause of the abnormal DNA methylation. ..."
- Additional testing is necessary to establish the mechanism of disease and recurrence risk.
- This review recommended the following test strategy:
  - Methylation analysis and deletion analysis (Oligo-SNP Array) as first-tier testing.
    - If methylation is normal and deletion analysis is abnormal but does not include the SNORD116 gene cluster, workup for a chromosomal abnormality may be considered.
  - Absence of heterozygosity (AOH) analysis of chromosome 15: If only the maternal methylated imprint is present but deletion testing is normal, AOH analysis is recommended.
  - DNA polymorphism analysis: If only the maternal methylated imprint is present but deletion and AOH analysis are normal, DNA polymorphism analysis is recommended.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Prader-Willi Syndrome testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Primary Ciliary Dyskinesia Genetic Testing

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Primary ciliary dyskinesia (PCD) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
Primary ciliary dyskinesia known familial mutation analysis	81403
Miscellaneous primary ciliary dyskinesia gene analysis	81479
Primary ciliary dyskinesia multi gene panel	81479, 81443

Criteria

Requests for PCD genetic testing are reviewed using the following criteria.

Known familial mutation analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation(s), AND
- Diagnostic Testing or Carrier Testing:
  - Known disease-causing mutation in a PCD-related gene identified in a 1st, 2nd, or 3rd degree biological relative, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

Single Gene Analysis

- Genetic Counseling:

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  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous analysis of the requested gene, AND
- Diagnostic Testing for Symptomatic Individuals:
  - A diagnosis of PCD is suspected, but has not been confirmed, and
  - Clinical findings suggest the requested gene is the likely cause for the member's symptoms, and
  - High suspicion for PCD based on having at least two of the following:
    - Unexplained neonatal respiratory distress as a term infant, with lobar collapse and/or need for respiratory support with CPAP (continuous positive airway pressure) and/or oxygen for >24 hours, and/or
    - Daily cough that is year-round and has been present since infancy or bronchiectasis on chest CT, and/or
    - Daily nasal congestion that is year-round and has been present since infancy or pansinusitis on sinus CT, and/or
    - Situs abnormality, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Multi-Gene Panel Testing

When a multi-gene panel is being requested and will be billed with a panel CPT code (e.g. 81479), the panel is medically necessary when the following criteria are met:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing of the genes included on the panel, AND
- Diagnostic Testing for Symptomatic Individuals:
  - A diagnosis of PCD is suspected, but has not been confirmed, and
  - Alternate etiologies have been considered and ruled out when possible (e.g., cystic fibrosis, immunodeficiency), and
  - Absence of features suggestive of a complex genetic syndrome (e.g., retinitis pigmentosa, digital anomalies, cystic kidneys) for which more targeted testing is available, and
  - High suspicion for PCD based on having two or more of the following
    - Unexplained neonatal respiratory distress as a term infant, with lobar collapse and/or need for respiratory support with CPAP and/or oxygen for >24 hr, and/or
    - Daily cough that is year-round and has been present since infancy or bronchiectasis on chest CT, and/or

    - Daily nasal congestion that is year-round and has been present since infancy or pansinusitis on sinus CT, and/or
    - Situs abnormality, AND
- Rendering laboratory is a qualified provider of service per Health Plan policy.

Other Considerations

Broad ciliopathy panels or immunodeficiency panels may not be medically necessary when a narrower panel is available and more appropriate based on the clinical findings.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
    - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g. 81479, 81443*).
    - When use of a panel code is not possible, each billed component procedure will be assessed independently.
    - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
    - When the test is billed with multiple stacked codes, only sequencing of the following genes may be considered for reimbursement:
        - DNAH5
        - DNAH11
        - CCDC39
        - DNAI1

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

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What is primary ciliary dyskinesia?

Primary ciliary dyskinesia (PCD) is a genetic disorder that causes chronic lung disease, situs abnormalities, and male infertility[1]

Prevalence

PCD is expected to affect approximately 1 in 7,500-20,000 births.[2,3] Limitations in diagnostic methods make it difficult to determine if the published incidence is accurate.[1]

Symptoms

- Pulmonary disease: Neonatal respiratory distress occurs in approximately 75% of full-term babies with PCD. Chronic airway infection with a cough, sputum, and wheezing are present in most children by early childhood. Bronchiestasis usually develops by adulthood.[1]
- Sinus infections and nasal congestion: Sinus symptoms are often noted in the first few months of life. Sinus infections are a frequent issue for adults with PCD.[1]
- Chronic/recurrent ear infection: Ear infections are most common in young children before they reach school age.[1] Chronic ear infections often lead to conductive hearing loss and can affect speech development.[1]
- Male infertility: Abnormal sperm motility causes the majority of males with PCD to be infertile. Women can also have a reduction in fertility due to impaired ciliary function in the oviduct.[1]
- Situs abnormalities: Situs inversus totalis (all internal organs are arranged in a mirror image of what occurs normally) occurs in 40-50% of individuals with PCD.[1] Heterotaxy (internal organs develop on the opposite side of the body as what occurs normally) occurs in approximately 12% of individuals with PCD.[1] Heterotaxy can involve a single organ or multiple organs. Complex cardiac defects are more common in individuals with heterotaxy than the general population.[4]

Cause

PCD is caused by genetic mutations that affect the function of motile cilia. Motile cilia are involved in directing the movement of fluids and other materials along cell surfaces. Motile cilia play roles in embryogenesis, reproduction, and airway clearance.[2]

A few disorders can include PCD along with other features. X-linked oral-facial-digital type I syndrome caused by a mutation in OFD1, and X-linked Retinitis Pigmentosa and PCD caused by a mutation in RPGR are two such disorders.[1,5]

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Inheritance

The majority of the genes associated with PCD show autosomal recessive inheritance.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

A few genes associated with PCD have been shown to display autosomal dominant or X-linked inheritance.[1]

Diagnosis

Diagnostic testing for PCD is only recommended for individuals with a high suspicion for PCD based on clinical history. No diagnostic testing is recommended for individuals without major clinical features of PCD.[6]

PCD symptoms can overlap with other health conditions including: cystic fibrosis (CF), immunodeficiency, pulmonary aspiration, asthma, and recurrent viral respiratory infections. CF may be differentiated from PCD, as individuals with CF "typically do not have neonatal respiratory distress or chronic otitis media, nor do they have daily cough until lung disease has significantly progressed. Nonetheless, children being evaluated for PCD should undergo sweat chloride testing at a laboratory certified to perform sweat chloride measurements. Similarly, various immunodeficiencies may also present with chronic upper and lower respiratory tract infections, though not typically with daily, year-round symptoms."[6]

"There no single gold standard diagnostic test for PCD."[4] A combination of clinical history and diagnostic tests is often required to make a diagnosis."[5]

Diagnosis of PCD can be limited by an individual's access to diagnostic procedures. The recommended tests, other than genetic testing, are typically found at testing centers that specialize in PCD. Transmission electron microscopy (TEM), high-speed video microscopy analysis (HVMA) and nasal nitric oxide (nNO) measurement are often recommended when available. Both TEM and HVMA require a high level of training and experience to perform and interpret. False positives and false negatives are common when these tests are performed without sufficient expertise.[5,6]

Nasal nitric oxide (nNO) measurement is a recommended part of a diagnostic work-up for individuals 5-6 years of age or older who are suspected to have PCD.[4,5] An nNO value of less than 77nl/min is suggestive of PCD, but some individuals with known PCD

have a normal or high nNO level.[4,5] nNO testing requires confirmatory testing since low values can be caused by infection or sinusitis.[6]

Transmission electron microscopy (TEM) of ciliary cross sections from nasal epithelium allows for a definitive diagnosis of PCD.[4] This analysis can confirm, but is unable to rule out, a diagnosis. At least 30% of individuals with PCD may not be identified by this method.[4] If the member's clinical history strongly suggests PCD, and TEM is non-diagnostic, other diagnostic testing is recommended.[4]

High-speed video microscopy analysis (HVMA) may be used in a PCD work-up with CBF/CBP (ciliary beat frequency/ciliary beat pattern) assessment. CBF of less than 11 beats per second has been suggested as a cutoff value.[4] This testing is not sufficiently standardized to rule in or rule out PCD in isolation.[4,6]

Multi-gene panels are commonly used to establish a diagnosis in individuals suspected to have PCD. More than 50 genes have been implicated in PCD.[7] Next-generation sequencing is expected to identify biallelic pathogenic mutations in 70-80% of individuals with PCD.[6]

Management

The main components of PCD management include airway clearance, infection control, and the elimination of inflammatory triggers.[2,4] Lung transplantation may be an option for individuals that develop end-stage lung disease.[4] Individuals with PCD are recommended to have routine monitoring of their pulmonary symptoms and for early diagnosis of infection.[8]

Survival

Lung disease varies considerably among individuals with PCD.[1] Some adults seem to have stable lung function over time, while others have a progressive disease course and develop end-stage lung disease.[4]

Test information

PCD genetic testing consists of known familial mutation analysis, next generation sequencing, or multi-gene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

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Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Given that the majority of cases cannot be easily categorized into subtypes and genetic testing is a first-tier diagnostic test for PCD, a comprehensive panel approach is acceptable for individuals whose clinical history is highly suspicious for PCD.

Genes commonly included on multi-gene panels include: DNAH5, DNAH11, CCDC39, DNAI1, CCDC40, CCDC103, SPAG1, ZMYND10, ARMC4, and CCDC151.[1]

Guidelines and evidence

American Thoracic Society Clinical Practice Guideline for the Diagnosis of Primary Ciliary Dyskinesia

The American Thoracic Society (ATS, 2018) evidence-based Clinical Practice Guideline for the Diagnosis of Primary Ciliary Dyskinesia stated:[6]

- An extended genetic panel is suggested over TEM ciliary testing in the diagnostic evaluation of PCD based on concern for accuracy and accessibility of TEM testing. Genetic testing is expected to yield a higher sensitivity, is more feasible, and provides the added benefit of family planning information. This recommendation was made with an acknowledgment that the overall evidence is limited in regards to the impact on long-term clinical outcomes.

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- A few studies have allowed for a comparison of sensitivities for different sizes of genetic panel tests for PCD. As a whole, the sensitivity of genetic panel testing for establishing a PCD diagnosis increased as the panel size increased. When 12 genes were tested, the sensitivity was 71.9%, while the sensitivity for a 32 gene panel that included deletion/duplication analysis and used the same population was 93.9%.
- When available, nNO testing should precede genetic testing or TEM testing for individuals 5 years of age or older with a clinical history suspicious for PCD. Low nNO values require verification (measured low on two separate occasions) when used as a PCD diagnostic test, as infections or sinusitis can decrease nNO values. A diagnosis of PCD made using nNO should be confirmed by other testing. Individuals with normal nNO levels should only have further diagnostic testing if strong clinical features of PCD are present.
- The use of CBP/F analysis by HSVM is not recommended as a diagnostic test for PCD. Standardization of this type of testing for PCD is insufficient and access is limited to select few testing centers

European Respiratory Society Task force Guideline

The European Respiratory Society (ERS, 2017) released evidence-based guidelines for the diagnosis and management of children with PCD that stated:[8]

- Nasal NO measurement is recommended as a screening test for individuals with a clinical history suspicious for PCD. Some individuals with PCD have normal nNO levels, so "patients presenting with a strong clinical history should undergo further testing, even if nNO is normal (weak recommendation)"
- "High speed video analysis, including ciliary beat frequency and beat pattern analysis, should be used as part of the diagnostic work-up of patients suspected of having PCD (weak recommendation)."
- "Ciliary ultrastructure analysis by transmission electron microscopy should be used as part of the diagnostic work-up of patients suspected of having PCD (strong recommendation)."
  - "Further diagnostic investigations should be performed in patients with normal ultrastructure if the clinical history is strong (strong recommendation)."
  - "In patients with hallmark ciliary ultrastructure defects for PCD further confirmatory diagnostic investigations are not required (strong recommendation)."
- Genetic testing can be used to confirm a diagnosis, or can be used when there is high clinical suspicion for PCD but other diagnostic testing was unavailable or unable to establish a diagnosis.
- A proposed diagnostic algorithm recommends nNO and HSVMA with CBF/P as a first tier test for screening individuals with clinical history suspicious for PCD. If these tests are normal, further testing is not needed. If the results are abnormal or equivocal, TEM and cell culture should be completed. If a diagnosis can be made based on a defect found by TEM, no further testing is needed. If TEM is suggestive of PCD or the

TEM results are normal or equivocal but the individual's history is strongly suggestive of PCD, genetic testing for PCD is recommended.

Primary Ciliary Dyskinesia Foundation

The Primary Ciliary Dyskinesia Foundation (PCDF, 2016) released guidelines for the diagnosis, monitoring and treatment of individuals with PCD.[5] These guidelines included age-dependent diagnostic criteria for PCD and major clinical criteria. The recommendations for diagnostic testing suggest using a combination of diagnostic tests.

PCD Diagnostic Criteria[5]

- "Newborns (0-1 month of age)
  - Situs inversus totalis and unexplained neonatal respiratory distress at term birth plus at least one of the following:
  - Diagnostic ciliary ultrastructure on electron micrographs
  - Biallelic c mutations in one PCD-associated gene
  - Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions
- Children (1 month to 5 years)
  - Two or more major PCD clinical criteria ... plus at least one of the following (nasal nitric oxide not included in this age group, since it is not yet sufficiently tested):
  - Diagnostic ciliary ultrastructure on electron micrographs
  - Biallelic mutations in one PCD-associated gen
  - Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions
- Children 5-18 years of age and adults
  - Two or more major PCD clinical criteria...plus at least one of the following:
  - Nasal nitric oxide during plateau <77 nl/min on 2 occasions, >2 months apart, with cystic fibrosis excluded
  - Diagnostic ciliary ultrastructure on electron micrographs
  - Bialelic mutations in one PCD-associated gene
  - Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions"

Four major PCD clinical criteria include:[5]

- "Unexplained neonatal respiratory distress (at term birth) with lobar collapse and/or need for respiratory support with CPAP and/or oxygen for >24 hr.
- Any organ laterality defect—situs inversus totalis, situs ambiguous, or heterotaxy.
- Daily, year-round wet cough starting in the first year of life or bronchiectasis on chest CT.
- Daily, year-round nasal congestion starting in first year of life or pansinusitis on sinus CT."

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Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for primary ciliary dyskinesia testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Prolaris

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Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Prolaris	81541

Criteria

Introduction

Requests for Prolaris testing are reviewed using the following criteria.

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

What are gene expression profiling tests for prostate cancer?

Prostate cancer (PC) is the most common cancer in men, and metastatic prostate cancer is a leading cause of cancer-related deaths worldwide. It is considered a heterogeneous disease with highly variable prognosis.[1]

- At the time of diagnosis of localized PC, patients typically undergo a prognostic risk assessment with routine clinical and pathological tests to assess the probability of subsequent progression or metastasis. These prognostic assessments help to identify

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lower risk patients with indolent disease who may opt for active surveillance (AS), or higher risk patients with more aggressive disease who may benefit from a treatment intervention.

- High-risk prostate cancer (PC) patients treated with radical prostatectomy (RP) also undergo risk assessment to assess future disease prognosis and determine optimal treatment strategies. Post-RP pathology findings, such as disease stage, baseline Gleason score, time of biochemical recurrence (BCR) after RP, and PSA doubling-time, are considered strong predictors of disease-associated metastasis and mortality. Following RP, up to 50% of patients have pathology or clinical features that are considered at high risk of recurrence and these patients usually undergo post-RP treatments, including adjuvant or salvage therapy or radiation therapy, which can have serious risks and complications. According to clinical practice guideline recommendations, high risk patients should undergo 6 to 8 weeks of radiation therapy (RT) following RP. However, approximately 90% of high-risk patients do not develop metastases or die of prostate cancer, and instead may be appropriate candidates for alternative treatment approaches, including AS. As such, many patients may be subjected to unnecessary follow-up procedures and their associated complications, highlighting the need for improved methods of prognostic risk assessment.[2,3]
- Several genomic biomarkers have been commercially developed to augment the prognostic ability of currently available routine clinical and pathological tests and identify those patients either at the time of diagnosis of localized PC or after radical prostatectomy (RP) most and least likely to benefit from a specific treatment strategy. Prognostic genomic tests, including gene expression profiling tests, may help to avoid overtreatment by reclassifying those men originally identified as high risk, but who are unlikely to develop metastatic disease. Genomic biomarkers may also play a role in assisting clinicians to tailor personalized and more appropriate treatments for subgroups of PC patients, and improve overall health outcomes.[2,3]

Test information

- Gene expression profiles (GEPs) evaluate the expression of several genes using one sample. Gene expression is determined through RNA analysis, using either reverse transcriptase (RT) polymerase chain reaction (PCR) or DNA microarrays.[4]
- Prolaris® (Myriad® Genetics)[5-9]
  - According to the manufacturer, Prolaris is a genomic test developed to predict 10 year prostate cancer-specific mortality risk in patients after needle biopsy. This test is designed to assist clinicians with predicting tumor aggressiveness combined with clinical and pathologic variables (Gleason score, PSA).
  - The test is performed on formalin-fixed, paraffin-embedded tissue obtained from either prostate biopsy or surgically removed tissue. The expression of 31 cell-cycle genes and 15 housekeeping genes is measured by quantitative reverse-

transcriptase-PCR and used to generate a Prolaris Score. A patient's Prolaris score is reported as a number between 1 and 10. Higher scores represent more aggressive disease, with each 1-unit increase representative of a doubling in risk
    - The Prolaris score is combined with the patient's Cancer of the Prostate Risk Assessment (CAPRA) score to generate the 10-year prostate cancer-specific mortality risk.

Guidelines and evidence

American Association of Clinical Urologists

The American Association of Clinical Urologists (AACU, 2018) has issued a position statement on genomic testing in prostate cancer that states the following:[10]

- “The AACU supports the use of tissue-based molecular testing as a component of risk stratification in prostate cancer treatment decision making. ... We also support ongoing research to further refine the prognostic power of these tests.”

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO, 2020) issued a guideline in molecular biomarkers in prostate cancer. This guideline states:[11]

- "Are there molecular biomarkers to diagnose clinically significant prostate cancer?"
    - "Recommendation 2.1. Commercially available molecular biomarkers (ie, Oncotype Dx Prostate [now Genomic Prostate Score], Prolaris, Decipher, and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended (Type: Evidence based; Evidence quality: Intermediate; Recommendation: Moderate)."
    - "Recommendation 2.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate)."
- "Are there molecular biomarkers to guide the decision of postprostatectomy adjuvant versus salvage radiation?"
    - "Recommendation 3.1. The Expert Panel recommends consideration of a commercially available molecular biomarker (eg, Decipher Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the postprostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate)."

Prolaris

- "Recommendation 3.2. Any additional molecular biomarkers evaluated do not have sufficient data to be clinically actionable or are not commercially available and thus should not be offered (Type: Evidence based; Evidence quality: Insufficient; Strength of recommendation: Moderate)."

American Urological Association and American Society of Radiation Oncology

The American Urological Association and American Society for Radiation Oncology (AUA/ASTRO, 2022) published an evidence-based guideline on localized prostate cancer endorsed by the Society of Urologic Oncology (SGO) that stated:[12]

- "Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)"
- "Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)"
- "Regarding tissue-based genomic biomarkers, several currently available commercial tests, including Prolaris, Oncotype Dx [now Genomic Prostate Score], and Decipher, variously offer prediction of adverse pathology as well as the risks of biochemical recurrence, metastasis, and prostate cancer death. However, most of the reported studies to date that evaluated the prognostic ability of these genomic tests did not meet inclusion criteria for the systematic review as the studies used surgical (ie, prostatectomy) rather than biopsy specimens."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) Clinical Practice Guidelines on Prostate Cancer state the following regarding molecular assays:[13]

- "Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN or CAPRA risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or EBRT [external beam radiation therapy], likelihood of adverse pathologic features after radical prostatectomy, and likelihood of developing metastasis after operation, definitive EBRT, or post-recurrence EBRT."
- "These molecular biomarker tests have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous U.S. Food and Drug Administration (FDA) regulatory pathways for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that men with low or favorable intermediate disease and life expectancy greater than or equal to 10 years may consider the use of Decipher, Oncotype DX Prostate [now Genomic Prostate Score], or Prolaris during initial risk stratification. Patients with unfavorable intermediate- and high-risk disease and life expectancy greater than or equal to 10 years may consider the use of Decipher or Prolaris."

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- NCCN does not include Prolaris in its table of advanced molecular tools with evidence to support clinical use.

Selected Relevant Publications

Overall, the evidence base for Prolaris consists primarily of retrospective clinical validity studies reporting on the strength of the association of Prolaris scores with biochemical recurrence or disease-specific mortality.[14-45] Several decision impact studies were identified that serve as surrogate studies for direct clinical utility evaluation. It remains unclear if the use of Prolaris in newly diagnosed patients leads to improvements in patient-important outcomes, such as morbidity, mortality, or quality of life. This conclusion is echoed by several systematic reviews.

Several ongoing clinical trials could provide meaningful insight upon their completion regarding these gaps in the evidence. Additional information can be found at **https://clinicaltrials.gov**.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Prolaris will ensure that members will not receive testing for which there is not a body of evidence demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[46] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

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Prolaris

Somatic Mutation Testing

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Introduction

Somatic mutation testing in solid tumors and hematological malignancies is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
ABL1 mutation analysis	81170
ABL1 targeted mutation analysis	81401
APC sequencing	81201
ASXL1 full gene sequencing	81175
ASXL1 mutation analysis	81176
Aventa FusionPlus	0444U
Aventa Lymphoma	0592U
BCR-ABL1 detection, major breakpoint	81206
BCR-ABL1 detection, minor breakpoint	81207
BCR-ABL1 detection, other breakpoint	81208
BCR-ABL1 major and minor breakpoint fusion transcripts	0016U
BRAF V600 targeted mutation analysis	81210
BRCA1/2 sequencing	81163
BRCA1 sequencing	81165

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Procedures addressed by this guideline	Procedure codes
BRCA2 sequencing	81216
BTK gene analysis	81233
CALR exon 9 mutation analysis	81219
CCND1/IGH (t(11;14)) translocation analysis, major breakpoint	81168
CEBPA full gene sequencing	81218
clonoSeq	0364U
CRCdx RAS Mutation Detection Kit	0471U
EGFR targeted mutation analysis	81235
EZH2 common variant(s) (e.g. codon 646)	81237
EZH2 full gene sequencing	81236
FISH analysis for t(9;22) BCR-ABL1	88271
FLT3 Internal Tandem Duplication MRD-Invivoscribe	0046U
FLT3 mutation analysis (internal tandem duplication variants)	81245
FLT3 mutation analysis (tyrosine kinase domain variants)	81246
FoundationOne CDx	0037U
Guardant360 Tissue	0334U
Hematolymphoid neoplasm molecular profiling	81450
IDH1 mutation analysis	81120
IDH2 mutation analysis	81121
IDH1, IDH2, and TERT Mutation Analysis, Next-Generation Sequencing, Tumor (IDTRT)	0481U

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Procedures addressed by this guideline	Procedure codes
IGH@/BCL2 (t(14;18)) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints	81278
JAK2 exons 12 to 15 sequencing	0027U
JAK2 mutation	0017U
JAK2 targeted mutation analysis (e.g exons 12 and 13)	81279
JAK2 V617F mutation analysis	81270
KIT D816 targeted mutation analysis	81273
KIT targeted sequence analysis	81272
KRAS exon 2 targeted mutation analysis	81275
KRAS targeted mutation analysis, additional variants	81276
LeukoStrat CDx FLT3 Mutation Assay	0023U
Lung HDPCR	0478U
MGMT promoter methylation analysis	81287
MI Cancer Seek - NGS Analysis	0211U
MLH1 sequencing	81292

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Procedures addressed by this guideline	Procedure codes
Molecular tumor marker test	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Molecular tumor marker test	88271
MPL common variants (e.g. W515A, W515K, W515L, W515R)	81338
MPL mutation analysis, exon 10	81339
MRDx® BCR-ABL Test	0040U
MSH2 sequencing	81295
MSH6 sequencing	81298
MSK-IMPACT	0048U
MyAML NGS- Invivoscribe	0050U
myChoice CDx	0172U
MYD88 mutation analysis	81305
MyMRD NGS Panel	0171U
NPM1 MRD- Invivoscribe	0049U
NPM1 mutation analysis	81310
NRAS exon 2 and exon 3 analysis	81311
NTRK1 translocation analysis	81191

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Procedures addressed by this guideline	Procedure codes
NTRK2 translocation analysis	81192
NTRK3 translocation analysis	81193
NTRK translocation analysis	81194
Oncomine Dx Target Test (NSCLC)	0022U
oncoReveal CDx	0523U
Oncotype MAP PanCancer Tissue Test	0244U
OptiSeq Dual Cancer Panel Kit	0499U
PALB2 sequencing	81307
PDGFRA targeted sequence analysis	81314
PGDx Elio Tissue Complete	0250U
PIK3CA targeted sequence analysis	81309
PLCG2 common variants (e.g. R665W, S707F, L845F)	81320
PMS2 sequencing	81317
Praxis Extended RAS Panel	0111U
PredicineATLAS Assay	0538U
PTEN sequencing	81321
RUNX1 mutation analysis	81334
SF3B1 common variants (e.g. A672T, E622D, L833F, R625C, R625L)	81347
Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis	81445

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Procedures addressed by this guideline	Procedure codes
Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability	81457
Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability	81458
Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements	81459
Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis	81455
Solid Tumor Expanded Panel	0379U
SRSF2 common variants (e.g. P95H, P95L)	81348
TERT targeted sequence analysis	81345
therascreen FGFR RGQ RT-PCR Kit	0154U
therascreen PIK3CA RGQ PCR Kit	0155U
TP53 sequencing	81351
TP53 targeted sequence analysis	81352
TruSight Oncology Comprehensive	0543U
U2AF1 common variants (e.g. S34F, S34Y, Q157R, Q157P)	81357

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Procedures addressed by this guideline	Procedure codes
xT CDx (Tempus)	0473U
ZRSR2 common variants (e.g. E65fs, E122fs, R448fs)	81360

Criteria

Introduction

Requests for molecular somatic mutation testing in solid tumors and hematological malignancies are reviewed using the following criteria.

Medical necessity criteria differ based on the type of testing being performed (i.e., tests for individual genes separately chosen based on the cancer type, versus pre-defined panels of genes) and how that testing will be billed (one or more individual gene-specific procedure codes, specific panel procedure codes, or unlisted procedure codes).

Note:

This guideline addresses molecular markers only. It is intended to address DNA and RNA markers that are present on tumor marker panels, including microsatellite instability (MSI) when requested as part of panel. It does not address immunohistochemistry (IHC) or other markers that may be detected through other methods such as FISH, chromosomal microarray, routine chromosome analysis, etc.

Individual Tumor Markers

When separate procedure codes will be billed for individual tumor markers (e.g., Tier 1 MoPath codes 81200-81355 or Tier 2 MoPath codes 81400-81408), each individually billed tumor marker test will be evaluated separately for medical necessity. The following criteria will be applied:

- The member has a tumor type that will benefit from information provided by the requested tumor marker test based on at least one of the following:
  - All criteria are met from an EviCore test-specific guideline, if one is available, or
  - An oncology therapy FDA label requires results from the tumor marker test to effectively or safely use the therapy for the member's cancer type, or
  - NCCN guidelines include the tumor marker test in the management algorithm for that particular cancer type and all other requirements are met (specific pathology findings, staging, etc.); however, the tumor marker must be explicitly included in the guidelines and not simply included in a footnote as an intervention that may be considered

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Note:

If five or more individually billed tumor marker tests are under review together (a "panel") and the member meets criteria for 5 or more individual tumor markers on an NGS panel, the panel will be approved. However, the laboratory will be redirected to use a panel CPT code for billing purposes.

Companion Diagnostic (CDx) Tumor Marker Panels

Somatic mutation companion diagnostic assay panels are considered medically necessary when the member meets ALL of the following criteria:

- Member has a diagnosis of cancer, AND
- Treatment with a medication for which there is an FDA-approved companion diagnostic assay is being considered, AND
- FDA approval for the CDx being requested must include the member's specific cancer type as an approved indication, AND
- FDA label for the drug and indication being considered states companion diagnostic testing is necessary for patient selection, AND
- Member has not had previous somatic and/or germline testing that would have identified the genetic change required to prescribe medication under consideration, AND
- Family History:
  - Member does not have a close (1st or 2nd degree) biological relative with a known germline mutation in a gene that is a target of the requested companion diagnostic test (e.g. known familial mutation in BRCA1/2 and requested test is myChoice CDx), or
  - Member has a close (1st or 2nd degree) biological relative with a known germline mutation in a gene that is a target of the requested companion diagnostic test (e.g. known familial mutation in BRCA1/2 and requested test is myChoice CDx), and the member's germline test was negative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Multigene Tumor Marker Panel Testing (Non-CDx)

When a multigene panel is being requested and will be billed with a single panel CPT code, the panel will be considered medically necessary when the following criteria are met:

- The member is a candidate for a targeted therapy associated with a specific tumor biomarker(s) or disease site and has a diagnosis of one of the following cancers:
  - Advanced, metastatic solid tumor
  - Recurrent cutaneous melanoma
  - Non-small cell lung cancer

  - Recurrent pancreatic cancer
  - Epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer
  - Recurrent or unresectable salivary gland tumors
  - Unresectable biliary tract cancer
  - Myeloproliferative disease
  - Multiple myeloma
  - Systemic mastocytosis
  - Acute lymphoblastic leukemia (ALL), OR
- The member has a confirmed or suspected diagnosis of acute myeloid leukemia (AML), OR
- The member has a confirmed or suspected diagnosis of myelodysplastic syndrome (MDS), OR
- The member has a diagnosis of cancer with at least 5 tumor markers included in the panel that individually meet criteria for the member's tumor type based on the medical necessity criteria for individual tumor markers listed above, OR
- Tumor mutational burden (TMB) testing is recommended in the NCCN management algorithm for the member's particular cancer type and all other requirements are met (specific pathology findings, staging, etc.); however, TMB testing must be explicitly included in the guidelines and not simply included in a footnote as an intervention that may be considered

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Note:

If the member meets criteria for less than 5 of the individual tumor markers in the panel, the panel will not be reimbursed. The laboratory will be redirected to billing for individual tests for which the member meets criteria.

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clonoSEQ

clonoSEQ testing is medically necessary for individuals with:

- A diagnosis of chronic lymphocytic leukemia (CLL), and one of the following:
  - For the initial assessment of dominant clonal sequences, or
  - For response assessment after induction therapy when there is no evidence of progression,* OR
- A diagnosis of acute lymphoblastic leukemia (ALL), and one of the following:
  - For the initial assessment of dominant clonal sequences, or
  - For response assessment after certain phases of treatment (e.g., induction therapy or consolidation therapy) when there is no evidence of progression,* OR
- A diagnosis of multiple myeloma (MM), and one of the following:
  - For the initial assessment of dominant clonal sequences, or

- For response assessment after certain phases of treatment (e.g., induction therapy, consolidation therapy, or hematopoietic stem cell transplant) when there is no evidence of progression,* or
- For surveillance in an individual with no evidence of progression and no clonoSEQ testing performed in the past year, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Note:

*Induction therapy refers to first-line therapy with the aim of achieving remission. Consolidation therapy refers to further treatment after induction therapy with the aim of eliminating any remaining cancer cells, often utilizing stem cell transplant and/or high-dose chemotherapy. Testing can be approved once for each approvable time point during treatment. Exceptions to the timing limits for acute lymphoblastic leukemia requests may be considered on a case-by-case basis.

Other Considerations

- For hematological malignancies, panels over 50 genes are considered not medically necessary as they are excessive.
- For information on tumor markers assayed by liquid biopsy, please refer to the guideline *Liquid Biopsy Testing*, as this testing is not addressed here.
- For information on MSI performed outside of a somatic mutation panel, please refer to the guideline *Microsatellite Instability and Immunohistochemistry Testing in Cancer*, as this testing is not addressed here.
- For information on testing for germline (inherited) mutations in genes related to hereditary cancer syndromes (e.g. Hereditary Breast and Ovarian Cancer, Lynch syndrome, etc), please refer to the appropriate EviCore test-specific guideline, as this testing is not addressed here. Although some of the same genes may be tested for inherited or acquired (somatic) mutations, this guideline addresses only testing for acquired mutations.
- For information on genetic testing for BCR-ABL negative myeloproliferative neoplasms, please refer to the guideline *BCR-ABL Negative Myeloproliferative Neoplasm Genetic Testing*, as this testing is not addressed here.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable

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test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

When otherwise reimbursable, the following limitations will apply:

- For hematological malignancies, panels over 50 genes, typically billed with CPT code 81455, are not reimbursable.
  - If the laboratory's testing platform consists of more than 50 genes, yet a panel of 5 to 50 genes is considered medically necessary based on the above criteria, the laboratory can choose to bill using a panel procedure code (e.g., 81450) that represents a smaller number of genes on the panel.
- TMB testing may be considered an eligible tumor marker only when testing is performed by NGS on a solid tumor with a panel size of >667 Kb (typically more than 50 genes and billed with an appropriate panel code).
- Multigene panels will only be considered for reimbursement when billed with an appropriate panel CPT code (e.g. 81445, 81450, 81455, a PLA code, etc.)*.
- CDx biomarker panels billed with an appropriate code should only be considered for reimbursement following CDx criteria. The Multigene Tumor Marker Panel Testing (Non-CDx) criteria should not be applied when a CDx panel is requested.
- Only one somatic mutation biomarker panel will be considered for reimbursement per occurrence of cancer.
  - If multiple CDx biomarker panels are ordered simultaneously based on FDA label requirements, only one panel will be considered for reimbursement. Additional unique biomarkers from the second panel may be considered for reimbursement if appropriate single marker or single gene procedure codes are billed.
  - If a biomarker panel was previously performed and an additional panel is being requested, only testing for the medically necessary, previously untested biomarkers will be reimbursable. Therefore, only the most appropriate procedure codes will be considered for reimbursement.

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What are somatic mutation tests?

Somatic mutation tests are broadly defined here as any test that measures changes in DNA, RNA, or chromosomes found in malignant tissue that is used to make cancer management decisions.

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- Somatic mutation tests are increasingly useful for therapy selection. Many cancer therapies are targeted at particular gene functions (therapeutic targets) and some require information about tumor genetics to use the therapies effectively (companion diagnostics). In these cases, NCCN as well as the FDA have outlined somatic testing that is recommended for specific cancers and the associated treatment implications.[1-5]

Test information

Somatic Mutation Testing

The specific methodology used to identify somatic mutations is dependent upon the type of mutation being investigated.

- DNA mutations are generally detected through direct analysis of individual mutations, portions of a gene, a whole gene, panels of genes, or the entire exome.
- Chromosome abnormalities, such as translocations or deletions, may be detected through direct visualization of the chromosomes (karyotyping), in situ hybridization of probes (e.g., FISH) to detect deletions or duplications that are too small to see directly, or by DNA-based methods (hybridization arrays or sequencing) that identify deletions or translocation breakpoints.
- Gene expression profiling simultaneously measures the amount of RNA being made by many genes. Expression patterns may be used to predict the type of cancer present, the aggressiveness of the malignancy, and therapies that are likely to be effective.

The efficiency of next generation sequencing (NGS) has led to an increasing number of large, multi-gene somatic mutation panels. Given that malignancies can have multiple and unexpected genetic changes, these panels may provide physicians with information about therapeutic targets that would not otherwise be considered.

Tumor Mutation Burden (TMB) Testing

Tumor mutational burden (TMB) is a quantitative measure of the number of mutations in the genome of a solid tumor "sometimes defined as the total number of non-synonymous point mutations per coding area of a tumor genome".[5] High TMB, typically defined as ≥10 mut/Mb for formalin-fixed paraffin-embedded (FFPE) tumor tissue, is thought to be a useful marker in predicting tumor response to immune checkpoint inhibitor therapies and is often used as a type of biomarker.[5-8] "Panel sizes >667 Kb are necessary to maintain adequate PPA [positive percent agreement] and NPA [negative percent agreement] for calling TMB high versus TMB low across the range of cut-offs used in practice."[8]

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While TMB testing can be completed by whole exome sequencing (WES), this method tends to be high cost and requires an extensive analysis and data management.[6] As a result, NGS testing through targeted panels has become a preferred method for measuring TMB; however, this allows for variation among panels, including "sample input, tumor content, panel size, gene content, quality control (QC), NGS platform, and bioinformatics pipeline, which may influence TMB estimates and lead to inconsistent TMB calculation and reporting."[8] This has resulted in the need to align variability between TMB assays, which led to the formation of the Friends of Cancer Research (Friends) TMB Harmonization Consortium, which is made up of "diagnostic manufacturers, academics, pharmaceutical companies, the National Cancer Institute (NCI), Frederick National Laboratory for Cancer Research, and the FDA.[8]

Guidelines and evidence

American Society of Clinical Oncology

The American Society of Clinical Oncology guidelines for germline and somatic genomic testing for metastatic prostate cancer (ASCO, 2025)[9] and neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer (ASCO, 2025)[10] stated the following:

- "Those patients with metastatic prostate cancer (both CSPC and CRPC) who are being considered for biomarker-directed systemic treatment should undergo somatic testing with next-generation sequencing technologies."[9]
- "All patients with EOC [epithelial ovarian cancer] should be offered germline and somatic testing for BRCA1 and BRCA2. Germline testing for other ovarian cancer susceptibility genes is recommended. Somatic tumor testing should include measure(s) of homologous recombination. Testing should occur at the time of diagnosis or as soon as feasibly possible."[10]

College of American Pathologists

The College of American Pathologists, in collaboration with the Association for Molecular Pathology, American Society of Clinical Oncology, and patient advocacy group Fight Colorectal Cancer (CAP/AMP/ASCO/FCC, 2022) examined the best methodology for testing for MSI and published the following recommendations:[11]

- "For patients with CRC being considered for immune checkpoint inhibitor therapy, pathologists should use MMR [mismatch repair]-IHC and/or MSI by PCR for the detection of DNA mismatch repair defects. Although MMR-IHC or MSI by PCR are preferred, pathologists may use a validated MSI by NGS assay for the detection of DNA mismatch repair defects. Note: MSI by NGS assay must be validated against MMR-IHC or MSI by PCR and must show equivalency." (Strong Recommendation)

- "For patients with gastroesophageal and small bowel cancer being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC and/or MSI by PCR over MSI by NGS for the detection of DNA mismatch repair defects. Note: This recommendation does not include esophageal squamous cell carcinoma." (Strong Recommendation)
- "For patients with endometrial cancer being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC over MSI by PCR or NGS for the detection of DNA mismatch repair defects." (Strong Recommendation)
- "For patients with cancer types other than CRC, GEA [gastroesophageal adenocarcinoma], small bowel, and endometrial being considered for immune checkpoint inhibitor therapy, pathologists should test for DNA mismatch repair, although the optimal approach for the detection of mismatch repair defects has not been established. Note: Assays must be adequately validated for the specific cancer type being tested with careful consideration of performance characteristics of MMR-IHC and MSI by NGS or PCR for the detection of DNA mismatch repair defects." (Conditional Recommendation)
- "For all cancer patients being considered for immune checkpoint inhibitor therapy based on defective mismatch repair, pathologists should not use TMB as a surrogate for the detection of DNA mismatch repair defects. If a tumor is identified as TMB-High, pathologists may perform IHC and/or MSI by PCR to determine if high TMB is secondary to mismatch repair deficiency." (Strong Recommendation)

The Friends TMB Harmonization Consortium

The Friends TMB Harmonization Consortium reported the following:[8]

- "At a TMB cutoff of 10[mut/Mb], the panels assayed have a theoretical NPA [negative percent agreement] of at least 95%, with a theoretical NPA falling <95% for panel sizes under 667 Kb," supporting the claim that "a sufficiently sized panel is required to maintain reasonable PPA [positive percent agreement] of panel TMB measurements"
- An observed "substantial acceleration of the decrease in PPA of panels at critical intersections of small panel sizes and low TMB cut-offs", supporting the claim that "small panels are insufficient to maintain adequate PPA and NPA for calling TMB high versus TMB low across the range of cut-offs for positivity likely to be used in practice"

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) provided the following guidance on somatic mutation testing.

Solid Tumors:

- NCCN Guidelines for Treatment of Cancer by Site provided detailed guidelines on the use of individual tumor markers for each cancer type addressed.[2,4,12-19]

- NCCN made the following recommendations specifically for using multi-gene panels in the evaluation of non-small cell lung cancer (NSCLC): "The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is defined as molecular testing that identifies all biomarkers identified in NSCL-20 [gene rearrangements in ALK, NTRK1/2/3, RET, and ROS1, BRAF V600E mutation, certain EGFR mutations, KRAS G12C mutation, ERBB2 mutations, and MET exon 14 skipping mutation], in either a single assay or a combination of a limited number of assays, and optimally identifies emerging biomarkers. Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC."[2]
- NCCN made the following recommendations specifically for using multi-gene panels in the evaluation of metastatic colorectal cancer: “All patients with metastatic colorectal cancer (CRC) should have tumor genotyped for RAS (KRAS and NRAS) and BRAF mutations individually or as part of a next-generation sequencing (NGS) panel.”[12]
- NCCN made the following recommendation for cutaneous melanoma: “For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in BRAF, and in the appropriate clinical setting, KIT from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (eg, larger NGS panels, BRAF non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. If BRAF single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (eg, KIT, BRAF non-V600).”[13]
- NCCN made the following recommendation for locally advanced/metastatic pancreatic adenocarcinoma: "Tumor/somatic molecular profiling, preferably using a NGS assay, is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify clinically actionable and/or emerging alterations. These alterations include, but are not limited to: fusions (ALK, NRG1, NTRK, ROS1, FGFR2, and RET), mutations (BRAF, BRCA1/2, KRAS, and PALB2), amplifications (HER2), MSI, dMMR, or TMB using comprehensive genomic profiling via an FDA-approved and/or validated NGS-based assay, and HER2 overexpression via IHC ± FISH. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible."[14]
- NCCN made the following recommendation for epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer, prior to selection of systemic therapy

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for refractory or recurrent disease: “Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), BRCA1/2, HRD status, microsatellite instability (MSI), mismatch repair (MMR), tumor mutational burden (TMB), BRAF, FRα (FOLR1), RET, and NTRK if prior testing did not include these markers.”[15]

- NCCN made the following recommendation for ampullary adenocarcinoma: "Tumor/somatic molecular profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to: fusions (ALK, NRG1, NTRK, ROS1, FGFR2, and RET), mutations (BRAF, BRCA1/2, KRAS, and PALB2), amplifications (HER2), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) via an FDA-approved and/or validated next-generation sequencing (NGS)-based assay. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS. Testing on tumor tissue is preferred; however, cell-free DNA can be considered if tumor tissue testing is not feasible."[16]
- NCCN made the following recommendation for distantly metastatic salivary gland tumors: "Targeted systemic therapy is increasingly becoming an option for patients with distantly metastatic salivary gland tumors. NGS and other biomarker tests should be used to evaluate AR, NTRK, HRAS, PIK3CA, TMB, and HER2 status."[17]
- NCCN recommended TMB testing and "multigene tumor testing for alterations in HRR [homologous recombination repair] genes" in patients with metastatic prostate cancer.[18]
- NCCN made the following recommendation for patients with unresectable or metastatic biliary tract cancer (BTC): "Comprehensive molecular profiling is recommended for patients with unresectable or metastatic BTC who are candidates for systemic therapy. ... If tissue is too scant or not available, consider repeat biopsy depending on tumor accessibility, safety, and clinical context. A cell-free DNA (cfDNA) test may also be considered for identifying gene mutations. This technique may not reliably identify gene fusions or rearrangements depending on the panel used and the specific partner gene."[19]

Hematological Malignancies:

- NCCN Guidelines for Treatment of Cancer by Site provided detailed guidelines on the use of individual markers for each cancer type addressed.[4,20-24]
- NCCN stated the following for individuals with acute lymphoblastic leukemia (ALL):[20]

  - molecular characterization by "comprehensive testing by next-generation sequencing (NGS) for gene fusions and pathogenic mutations is recommended" for determining risk and planning treatment.
  - MRD assessment is recommended after initial induction and after consolidation. Additional time points should be based on the regimen and risk features.
- NCCN stated that for individuals with cytopenia when myelodysplasia is suspected, "genetic testing for somatic mutations (ie, acquired mutations) in genes associated with myelodysplastic syndromes (MDS)" was recommended.[21]
- NCCN stated that for individuals being evaluated for and with acute myeloid leukemia (AML): "The field of genomics in myeloid malignancies and related implications in AML are evolving rapidly. Mutations should be tested in all patients. Multiplex gene panels and targeted next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML in various phases of treatment."[22] Multiplex gene panel testing is also recommended by NCCN during the evaluation and initial workup for blastic plasmacytoid dendritic cell neoplasm.[22]
- NCCN stated that for individuals with chronic lymphocytic leukemia (CLL): "Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of time-limited treatment is an important predictor of efficacy. … MRD evaluation should be performed using an assay with a sensitivity of 10-4 according to the standardized European Research Initiative on CLL (ERIC) method or standardized NGS method."[23]
- NCCN stated that a response evaluation for individuals with multiple myeloma should include MRD information "at the time of suspected complete response" after each stage of treatment, including induction, high-dose therapy/autologous stem cell transplants (ASCT), consolidation, and maintenance treatment.[24]

U.S. Food and Drug Administration

Some FDA labels require results from biomarker tests to effectively or safely use the therapy for a specific cancer type.[3] A list of all Pharmacogenomic Biomarkers included in FDA labeling and associated implications can be found **here**. While these tumor marker tests generally consist of a single biomarker, some larger panels of biomarkers are also included in the FDA labeling.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for somatic mutation testing will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit

from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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Spinal Muscular Atrophy Genetic Testing

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Introduction

Genetic testing for spinal muscular atrophy is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Genomic Unity SMN1/2 Analysis	0236U
SMN1 Gene Analysis; Dosage/Deletion Analysis (e.g., carrier testing), includes SMN2 Analysis, if performed	81329
SMN1 Full Gene Sequencing	81336
SMN1 Known Familial Mutation Analysis	81337
SMN2 Dosage/Deletion Analysis	81479
SMN2 Targeted Mutation Analysis (c.859G>C)	81479

Criteria

Introduction

Requests for genetic testing for spinal muscular atrophy (SMA) are reviewed using the following criteria.

SMN1 Known Familial Mutation Analysis

- Genetic Counseling:

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  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Known familial mutation(s) in biological relative, OR
- Carrier Screening
  - Known familial mutation(s) in biological relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

SMN1 Exon 7 Deletion

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing of the SMN1 gene, AND
- Diagnostic Testing:
  - Child with hypotonia and weakness (generally symmetrical, proximal more than distal), or
  - Young adult (through twenties) onset of weakness more severely affecting the legs than arms (may be associated with frequent falls, difficulty with stairs), and
  - No obvious signs of a different neurological disorder, OR
- Prenatal Testing:
  - Both parents are carriers of an SMA mutation (at least one of which is an exon 7 deletion mutation), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Note:

Carrier Screening: SMN1 exon 7 deletion testing is not suitable for carrier screening. SMN1/SMN2 dosage analysis is the required test. Please see that section for required medical necessity criteria.

SMN1/SMN2 Deletion/Dosage Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing of the SMN1 gene in the carrier testing setting, AND

- Diagnostic Testing:
  - Infants with an abnormal result on newborn screening and the diagnosis of SMA is still uncertain, or
  - Index of suspicion for SMA remains high based on:
    - Proximal greater than distal weakness, and
    - Normal creatine kinase (CK), OR
- Carrier Screening:
  - Be of reproductive age, and
  - Have potential and intention to reproduce, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Note:

Prenatal Testing: SMN1/SMN2 Dosage Analysis is not suitable for preimplantation/ prenatal diagnosis. Other forms of SMA testing may be indicated based on the mutation status of parents. Please see those sections for guidance.

SMN1 Sequencing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - SMN1 exon 7 deletion testing did not reveal a homozygous SMN1 deletion or SMN1/SMN2 gene dosage analysis identified a single copy of SMN1 exon 7 in the diagnostic setting, or
  - SMN1/SMN2 gene dosage analysis did not confirm carrier status of an exon 7 deletion in the carrier testing setting, AND
- Diagnostic Testing:
  - Individual is suspected to have compound heterozygous SMA based previous test results, and
  - Proximal greater than distal weakness, and
  - Normal creatine kinase (CK), OR
- Carrier Screening:
  - Have one of the following increased risk indications with a noninformative SMN1/ SMN2 gene dosage analysis result:
    - Have a reproductive partner who is a carrier of SMA, or
    - Have a reproductive partner with SMA, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Note:

Prenatal Testing: SMN1 full gene sequencing is not generally necessary for preimplantation/prenatal diagnosis as parental mutation status should have already been determined with SMN1 exon 7 deletion testing, SMN1 known familial variant analysis, and/or SMN1 sequencing.

SMN2 Deletion/Dosage Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Member meets the following criteria:
  - Member has a genetically confirmed diagnosis of SMA, and
  - Member has a diagnosis of either SMA Type 1 or SMA Type 2, and
  - Member has not had previous SMN2 copy number analysis performed, and
  - Documentation is provided that SMN2 copy number is needed to obtain insurance approval for medication being considered for treatment, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

SMN2 Targeted Mutation Analysis (c.859G>C)

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Member meets the following criteria:
  - Member has a genetically confirmed diagnosis of SMA, and
  - Member has a diagnosis of either SMA Type 1 or SMA Type 2, and
  - Member has not had previous c.859G>C analysis performed, and
  - Documentation is provided that c.859G>C analysis is needed to obtain insurance approval for medication being considered for treatment, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Exclusions and Other Considerations

SMN2 gene copy analysis for the purpose of predicting SMA prognosis is not medically necessary.

Targeted analysis of c.859G>C, c.835-44A>G, or any other modifier variants for the purpose of predicting SMA prognosis is not medically necessary.

For information regarding carrier screening for SMA performed as part of a large carrier screening panel, please see the guideline *Carrier Screening Panels, Including Targeted, Pan-Ethnic, Universal, and Expanded*, as this testing is not addressed here.

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What is Spinal Muscular Atrophy?

Spinal muscular atrophy (SMA) is a severe, inherited neuromuscular disease.[1-5] SMA is caused by loss of lower motor neurons (anterior horn cells) in the spinal cord, resulting in progressive symmetrical muscle weakness and atrophy.[1-5]

Incidence

The incidence and carrier frequencies are dependent on ethnicity. SMA affects 1/7,829 to 1/20,134 people.[5] The carrier frequency ranges from 1/45 to 1/100.[5] SMA is present in all ethnic groups.[1-5]

Symptoms

SMA is commonly divided into five clinical subtypes based on age of onset and clinical course. While genetic testing has shown these clinical subtypes are not completely distinct, they are still widely used, and include:[1-5]

- Prenatal onset form ("Type 0" proposed): characterized by polyhydramnios, decreased fetal movements, breech presentation, arthrogryposis multiplex congenita, and respiratory failure at birth.
- Type I (infantile or Werdnig-Hoffmann type): most common form (60-70% of cases). It presents before 6 months of age and the cause of death is often respiratory failure. Affected children have severe, generalized weakness and do not ever sit without support.
- Type II (intermediate type): causes muscle weakness with onset after 6 months, although children often are able to sit alone and can survive through childhood. Intelligence is normal.
- Type III (juvenile, Kugelberg-Welander type): milder. Onset ranges from infancy to youth, but affected people usually walk unassisted albeit with frequent falls or trouble with stairs. Intelligence is normal.
- Type IV (adult type): much later onset with muscle weakness generally presenting at 20-30 years of age. People may or may not become wheelchair dependent and have normal intelligence.

Cause

SMA is caused by mutations in the SMN1 gene.

- Large gene deletions (exon 7 +/- exon 8) cause SMA in the vast majority (95-98%) of affected individuals.[5]
- The remaining 2-5% of individuals with SMA have a deletion in one copy of the SMN1 gene and a different mutation in the other.[5]

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The clinical severity of SMA can be influenced by the number of copies an individual has of the SMN2 gene.[5] The SMN2 gene is almost identical to SMN1 and is located on the same chromosome. SMN2 gene mutations do not cause SMA. In fact, about 15% of unaffected people have no copies of the SMN2 gene. Individuals may have between 0-5 copies of SMN2 and SMN2 has been shown to modify the disease severity in people with SMA.

Although a higher copy number of SMN2 (usually 3 or more) is generally associated with a milder phenotype, SMA is still a highly variable disease. It is difficult to use SMN2 copy number to reliably predict the clinical manifestations of SMA in an affected individual because other modifying factors not yet fully delineated are likely contributing to the variability in clinical presentation.[5] Identifying SMN2 copy number greater than 3 is technically challenging, sometimes inaccurate, and may require repeat testing for confirmation.[6,7]

Other potential genetic modifiers have been identified; however, the significance of these potential modifiers is yet to be determined.[8]

Inheritance

SMA is an autosomal recessive disorder.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

About 2% of individuals with SMA have a de novo (new) mutation in one of their two SMN1 genes. In this case, only one parent is a carrier of SMA.[5]

About 4% of carriers have two copies of SMN1 on a single chromosome. These individuals with two copies of SMN1 on one chromosome (a [2+0] genotype) are misdiagnosed as non-carriers by the SMN1 dosage test (i.e., a false negative test result).[5]

Diagnosis

The diagnosis of SMA is established in a proband with a history of motor difficulties, evidence of motor unit disease on physical examination, and identification of biallelic pathogenic variants in SMN1 on molecular genetic testing.[5] Most states include SMA

testing with newborn screening, which enables earlier diagnosis and treatment for affected individuals.[9]

Carrier screening for SMA is recommended preconceptionally or prenatally.[10] Asymptomatic carriers typically have one intact copy of the SMN1 gene and one SMN1 gene with the common deletion. However, some unaffected carriers have two intact copies of the SMN1 gene. These may be on the same chromosome with no intact SMN1 gene on the other chromosome. Carriers of rare mutations and those carrying two SMN1 genes on the same chromosome will not be detected by gene dosage analysis. Therefore, a negative gene dosage analysis result reduces the carrier risk but cannot completely rule out that an individual is an SMA carrier.[5,11] The detection rate of carrier screening varies based on ethnicity, ranging from 71% in African Americans to 95% in Caucasians.[2-4]

Management

Since 2016, three medications for SMA have met FDA Approval. Spinraza/nusinersen, Zolgensma/onasemnogene abeparvovec-xioi, and Evrysdi/risdiplam are used to treat disease manifestations for specific types of SMA. These treatments have the best efficacy when treatment is started before symptoms appear. Onset of symptoms may be prevented or delayed; however, long-term effects of these treatments are unknown.[5] For symptomatic individuals, treatment and care are best coordinated through a multidisciplinary team. Care may include support for feeding, neuromuscular, pulmonary, gastrointestinal, and skeletal symptoms.[5]

Survival

Treatment with Spinraza/nusinersen, Zolgensma/onasemnogene abeparvovec-xioi, and/or Evrysdi/risdiplam impacts the natural history of SMA with longer survival. Historically, the survival of individuals with SMA with supportive care only has correlated with the subtype:[5]

- Prenatal onset form: survival less than 6 months
- Type I: median survival 8-10 months
- Type II: approximately 70% of affected individuals are alive at 25 years
- Types III and IV: normal life span

Test information

Introduction

Testing for SMA may include known familial mutation analysis, deletion analysis, gene dosage analysis, sequencing, or targeted mutation analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

SMN1 Exon 7 Deletion

Diagnostic testing in an affected individual begins with deletion or copy number analysis, which will identify a deletion of exon 7 in the SMN1 gene. For most affected individuals, both SMN1 genes will be missing exon 7. If one or both SMN1 genes do not have an exon 7 deletion, SMN1 gene sequencing can be considered.

SMN1/SMN2 Deletion/Dosage Analysis

SMN1/SMN2 deletion/dosage analysis is performed by multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next generation sequencing (NGS) to determine the number of full copies of the SMN1/SMN2 genes. Dosage analysis is commonly performed in the diagnostic testing of affected individuals and in carrier testing.[5,11]

SMN1 Sequencing

SMN1 sequencing is typically performed in reflex, when one or no deletions are identified by deletion/dosage analysis in a symptomatic individual. About 2-5% of affected individuals fall into this group. Sequencing detects the other mutation in virtually all cases.[2-5]

SMN2 Deletion/Dosage Analysis

SMN2 deletion/dosage analysis is performed in individuals following SMN1 genetic testing that established a diagnosis of SMA. SMN2 genetic testing serves to provide a better understanding of the expected severity and to determine eligibility for certain treatments.[5]

SMN2 Targeted Mutation Analysis

The c.859G>C mutation in SMN2 is a positive modifier variant.[5,8] This testing may be indicated when treatment is being considered. Other positive modifier variants have been identified in SMN2, including the c.835-44A>G mutation.[8]

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Guidelines and evidence

Diagnostic Testing

The following organizations have published guidelines regarding diagnostic testing for SMA.

European Neuromuscular Centre

The 218th European Neuromuscular Centre (ENMC, 2017) workshop revisited the consensus statement that was published in 2007 from the International Standard of Care Committee for Spinal Muscular Atrophy.[11] They stated the following regarding testing for SMA:[12]

- "There was consensus that genetic testing is the first line investigation when this condition is suspected in a typical case and that muscle biopsy or electromyography should not be performed in a typical presentation."
- "There was also consensus that, at variance with previous recommendations, the current gold standard is SMN1 deletion/mutation and SMN copy number testing, with a minimal standard of SMN1 deletion testing. Other areas concerning the value of SMN2 copy number were more controversial and a further Delphi round was planned to complete the task."

The 270th European Neuromuscular Center (ENMC, 2024) international workshop developed a consensus statement regarding SMN2 genetic analysis that included the following recommendations:[13]

- "It has been verified that errors in SMN2 quantification are too frequent, particularly in less-experienced laboratories. Certification and quality controls of the labs are, therefore, strongly recommended"
- "SMN2 modifier variants (c.859G>C and c.835-44A>G) should be routinely tested and reported (also in NBS [newborn screening]). Sanger sequencing is recommended for the analysis of these variants"
- "In symptomatic patients, access to therapy should be independent of SMN2 copies. Given the principle of autonomy, treatment initiation is the final decision and responsibility of the family"
- "The implications of SMN2 modifier variants and hybrid genes for treatment are not currently known and, therefore there is no indication that the therapeutic approach should be altered. Collaborative studies are recommended to obtain longitudinal data in carriers of these variants"

International Conference on the Standard of Care for Spinal Muscular Atrophy

An international consensus statement (2018) provided recommendations regarding the diagnosis and management of SMA and stated:[14]

- Clinical suspicion for SMA is often based on hypotonia with progressive symmetric proximal weakness affecting legs more than arms and sparing of facial muscles along with normal creatinine kinase (CK) levels. Electromyography is typically not needed in individuals with SMA type 1 and 2, nor is muscle biopsy.
- Genetic testing is considered a first line investigation when SMA is suspected. Multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next generation sequencing (NGS) that allow for quantitative analysis of SMN1 and SMN2 is recommended. SMN2 copy number inversely correlates with disease severity and may be required for inclusion in therapy.
- If neither full SMN1 copy is present, a diagnosis of SMA may be made. If the phenotype is suggestive of SMA, but one or both full copies of the SMN1 gene are present, SMN1 gene sequencing is recommended. If SMN1 genetic testing is unable to make a diagnosis, "other motor neuron diseases should be considered."

U.S. Secretary of Health and Human Services (HHS)

The U.S. Secretary of HHS released a national guideline (HHS, 2023) that made recommendations related to which disorders should be included in the state universal newborn screening programs, which includes screening for SMA.[15] The recommended follow-up for an abnormal newborn screening result is SMN1 and SMN2 gene dosage testing.[16]

Carrier Testing

The following organizations have published guidelines regarding carrier testing for SMA.

American College of Medical Genetics and Genomics

The American College of Medical Genetics (ACMG, 2021) released an educational practice resource on carrier screening. This consensus statement asserted that general population carrier screening should be ethnicity and family history agnostic.[17] To accomplish this, screening all individuals in the prenatal/preconception period for autosomal recessive and X-linked conditions with a carrier frequency of >1/200 was suggested, including SMA.

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2017; Reaffirmed 2023) stated the following in regard to carrier testing for SMA in an updated Committee Opinion:[10]

- "Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant."

Treatments

The FDA has approved use of Spinraza (nusinersen), Zolgensma (onasemnogene abeparvovec-xioi), and Evrysdi (risdiplam) in individuals with SMA.

Spinraza (nusinersen)

Spinraza (nusinersen) is FDA approved for use in individuals with SMA. While the FDA label does not require SMN2 copy number analysis, the study of 121 affected individuals on which FDA approval was based used the following inclusion criteria:[18]

- 5q SMN1 homozygous gene deletion or mutation or compound heterozygous mutation
- 2 copies of the SMN2 gene (98% of enrolled individuals had 2 copies of SMN2)
- Onset of SMA symptoms at or before 6 months of age
- No hypoxemia at baseline screening at age 7 months or younger

Zolgensma (onasemnogene abeparvovec-xioi)

Zolgensma (onasemnogene abeparvovec-xioi) is FDA approved for use in individuals with SMA who are full-term to 2 years old. While the FDA label does not require SMN2 copy number analysis, the study of the 21 affected individuals on which FDA approval was based used the following inclusion criteria:[19]

- Confirmed bi-allelic SMN1 gene deletions
- 2 copies of the SMN2 gene
- Onset of SMA symptoms before 6 months of age
- Absence of the c.859G>C positive modifier variant in exon 7 of the SMN2 gene

Evrysdi (risdiplam)

Evrysdi/risdiplam is FDA approved for use in individuals with SMA at any age.

- Clinical studies included infantile onset SMA and later onset SMA. The overall findings of these studies support the effectiveness of Evrysdi in SMA patients of any age and appear to support the early initiation of treatment with Evrysdi.[20]
- Infantile onset SMA study enrolled patients with genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene, and two SMN2 gene copies.
- Later onset SMA study enrolled 180 non-ambulatory patients with Type 2 (71%) or Type 3 (29%) SMA. The median age of patients at the start of treatment was 9.0 years (range 2 to 25), and the median time between onset of initial SMA symptoms and first treatment was 102.6 months (range 1 to 275).

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for spinal muscular atrophy testing will ensure

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that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Tissue of Origin Testing for Cancer of Unknown Primary

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Introduction

Tissue of origin testing for cancer of unknown primary is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Oncology (tissue of origin), microarray gene expression profiling of greater than 2000 genes (e.g. tissue of origin testing)	81504
Oncology (tumor of unknown origin), mRNA, gene expression profiling of real-time RT-PCR of 92 genes to classify tumor into main cancer type and subtype (e.g. CancerTYPE ID)	81540
Unlisted molecular testing for tumor of unknown origin	81479
Unlisted multianalyte assay for tumor of unknown origin	81599

Criteria

Introduction

Requests for tissue of origin testing for cancer of unknown primary are reviewed using the following criteria.

This test is considered Experimental, Investigational, or Unproven.

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- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

What is cancer of unknown primary testing?

In order to determine the most effective treatment regimen for an individual with cancer it is important to identify the cancer cell type.[1]

- When a cancer is found in one or more metastatic sites but the primary site is not known, it is called a cancer of unknown primary (CUP) or an occult primary cancer.[2] This happens in a small portion of cancers.
- The most commonly used techniques to identify tissue of origin (TOO) for CUP include light microscopy, immunohistochemistry (IHC) staining and computed tomography (CT) or positron emission tomography (PET) imaging.[1,3] However, conventional methods have had poor success.[4,5]
- With advances in technology, some laboratory tests utilize gene expression profiling (GEP) or other molecular techniques in cancer cells. Ramaswamy et al. found that a cancer-intrinsic gene expression pattern distinguished primary from metastatic adenocarcinomas.[6] By comparing the pattern of gene expression in the CUP sample to the patterns seen with other known types of cancer, a CUP may be identified as belonging to a particular cancer type. Survival, quality of life (QOL), and/or disease symptoms may improve in some cases if the site and type of primary origin can be accurately detected and appropriate therapy administered early in the disease course.[7,8]

Test information

Introduction

A number of different companies and approaches are being utilized to diagnose metastatic neoplasms for individuals with CUP, typically using gene expression analysis.

A representative example of a tissue-of-origin test, CancerTYPE ID (Hologic, Inc), is a gene expression test designed to identify the most likely tissue of origin from 50 tumor

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types in individuals with cancer of unknown primary.[9] "CancerTYPE ID uses real-time RT-PCR to measure the expression of 92-genes in the patient's tumor and classifies the tumor by matching the gene expression pattern to a database of over 2,000 known tumor types and subtypes...The test reports a molecular diagnosis of the cancer type with the highest probability match, as well as a list of tumor types that may be ruled out with 95% confidence."[9]

Guidelines and evidence

European Society for Medical Oncology

The European Society for Medical Oncology (ESMO, 2023) Clinical Practice Guideline for the diagnosis, treatment and follow-up of cancer of unknown primary stated the following:[10]

- "Despite a promising pilot study, two randomised trials failed to demonstrate superiority of gene expression profiling-based 'site-specific' therapy over standard empiric [(neo)adjuvant chemotherapy] with either carboplatine–paclitaxel or cisplatine–gemcitabine, respectively. Consequentially, no recommendation for the use of gene expression profiling-based 'site-directed' therapy can currently be provided."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network Guidelines in Oncology: Occult Primary (NCCN, 2024) stated the following regarding tissue of origin testing:[11]

- "...the Panel does not currently recommend use of gene sequencing to predict tissue of origin."
- "...the clinical benefit of using molecular profiling to guide treatment decisions in CUP remains to be determined."
- "Currently there is no evidence of improved outcomes with the use of site-specific therapy guided by molecular testing in patients with CUP."
- "While there may be a diagnostic benefit to GEP, a clinical benefit has not been demonstrated. Consequently, the panel does not currently recommend use of gene sequencing to predict tissue of origin. Until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of IHC and GEP on a case-by-case basis, with the best possible individualized patient outcome in mind."

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE, 2023) clinical guideline for metastatic malignant disease of unknown primary origin stated that further research

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is required to determine whether gene-expression-based profiling "could be beneficial addition to standard management in CUP."[12]

Select Relevant Publications

In systematic reviews of cancer of unknown primary site, gene-profiling diagnosis was noted to have high sensitivity, but additional prospective studies were deemed necessary to establish whether outcomes for individual's with cancer are improved by its clinical use.[1,13-22]

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for tissue of origin testing for cancer of unknown primary will ensure that members will not receive testing for which there is not a body of evidence demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[23] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

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Li-Fraumeni Syndrome Genetic Testing

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Li-Fraumeni syndrome (LFS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
TP53 deletion/duplication analysis	81479
TP53 known familial mutation analysis	81353
TP53 sequencing	81351
TP53 targeted sequence analysis	81352

Criteria

Requests for Li-Fraumeni syndrome (LFS) genetic testing are reviewed using the following criteria.

TP53 Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing that would detect the familial mutation, AND
- Diagnostic and Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Known family mutation in TP53, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

TP53 Sequence Analysis

- Genetic Counseling:

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- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy). AND

- Previous Testing:
  - No previous sequencing of TP53, and
  - No known familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Classic LFS when **ALL** of the following are present:
    - Combination of an individual diagnosed less than age 45 years of age with a sarcoma, and
    - First-degree relative diagnosed less than 45 years of age with cancer, and
    - An additional first- or second-degree relative in the same lineage with cancer diagnosed less than 45 years of age, or a sarcoma at any age, OR
  - Chompret Criteria (2015) are met when **ANY** of the following are present:
    - Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma) before age 46 years, and
      - at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) under the age of 56 years, or
      - at least one first- or second-degree relative with multiple primary cancers at any age, or
    - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma) with the initial cancer occurring before the age of 46 years, regardless of the family history, or
    - Individual with adrenocortical carcinoma or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of the family history, OR
  - Early onset breast cancer
    - Individual with breast cancer diagnosed before 31 years of age, OR
  - Individual with a tumor from LFS tumor spectrum and one or more biologic relatives (1st, 2nd, or 3rd degree) with a clinical diagnosis of LFS (relative meets classic LFS criteria or Chompret criteria, as listed above) and no known family mutation or no testing to date, OR
  - Individual who was diagnosed with hypodiploid acute lymphoblastic leukemia (ALL) before age 21 years, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - One or more biologic relatives (1st, 2nd, or 3rd degree) with a clinical diagnosis of LFS (relative meets classic LFS criteria or Chompret criteria as listed above) and no known family mutation or no testing to date, AND

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- Rendering laboratory is a qualified provider of service per the Health Plan policy.

TP53 Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous deletion/duplication analysis of TP53, and
  - No mutation detected on full sequencing of TP53, AND
- Diagnostic or Presymptomatic Testing:
  - Meets clinical criteria for TP53 sequence analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

LFS testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels,* as this testing is not addressed here.

For information on germline testing after somatic testing, please refer to the guideline *Hereditary (Germline) Testing After Tumor (Somatic) Testing*, as this testing is not addressed here.

What is Li-Fraumeni syndrome?

Li-Fraumeni syndrome (LFS) is a hereditary cancer-predisposition syndrome typically associated with soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumors, and adrenocortical carcinomas. People with LFS also have an increased risk of a variety of other childhood and adult-onset cancers.[1-3]

Prevalence

In Brazil, a high prevalence of LFS is present due to a founder mutation. A specific germline TP53 mutation (c.1010G>A; p.R337H) is present in 0.3% of individuals from the South/Southeastern regions, and it is estimated that more than 300,000 Brazilian individuals have LFS.[4]

The prevalence of inherited TP53 mutations is not well established but is estimated to be 1/3,000 to 1/10,000.[1]

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Symptoms

Men with LFS have a 70% or higher lifetime risk of cancer while women have a 90% or higher lifetime risk of cancer. However, penetrance may be overestimated as more individuals with non-classic personal and/or family histories of cancer are identified to have TP53 mutations.[1]

Cause

LFS is caused by mutations in the TP53 gene.

Inheritance

LFS is an autosomal dominant disorder.[1]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

The identification of a pathogenic mutation in the TP53 gene establishes the diagnosis.[1]

Complete TP53 gene sequencing will detect approximately 89% of known mutations.[1]

Deletion/duplication testing may be considered as a reflex test if a mutation is not found by sequencing. This method will identify gene rearrangements in an additional 1% of cases.

Management

The recommended surveillance for individuals with LFS includes whole-body MRI, ultrasound of the abdomen and pelvis, mammogram and breast MRI, clinical breast exam, brain MRI, upper endoscopy and colonoscopy, dermatologic exam, and complete physical examination.[1,4] The age for initiation of screening and the frequency at which the screenings are repeated are well-defined.[1,2]

Survival

A study followed 89 individuals who pursued or declined recommended surveillance. The five year survival rate was 88.8% and 59.6% for those in the surveillance group versus those who declined, respectively.[5]

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Test information

Testing for LFS may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and evidence

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) guidelines for Genetic/ Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate outlined the following LFS testing criteria. These are considered a category 2A recommendation "lower level evidence with uniform NCCN consensus":[2]

- "Individual from a family with a known TP53 P/LP [pathogenic/likely pathogenic] variant," OR
- Classic LFS when ALL of the following are present:

- "Combination of an individual diagnosed at age less than 45 years with a sarcoma AND
- A first-degree relative diagnosed at age less than 45 years with cancer AND
- An additional first- or second-degree relative in the same lineage with cancer diagnosed at age less than 45 years, or a sarcoma at any age," OR

- Chompret Criteria (2015 version)[6], when ANY of the following are present:
  - "Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, central nervous system (CNS) tumor, breast cancer, adrenocortical carcinoma [ACC]), before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancer (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age OR
  - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years OR
  - Individual with ACC or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of the family history OR
  - Breast cancer before 31 years of age".
- The presence of a P/LP TP53 variant on tumor only genomic testing "should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic TP53 P/LP variants are common in many tumor types in absence of a germline P/LP variant."
- "In individuals with cancer with a P/LP TP53 variant identified on tumor-only genomic testing, germline testing should be considered for:
  - (1) Those meeting one or more of the other LFS testing criterion above after reevaluation of personal and family history
  - (2) Those diagnosed age <30 with any cancer
  - (3) Those with clinical scenario not meeting these criteria but warranting germline evaluation per clinician discretion."
- Hypodiploid Pediatric Acute Lymphoblastic Leukemia (ALL)
  - The National Comprehensive Cancer Network Guidelines (NCCN, 2025) for the treatment of Pediatric Acute Lymphoblastic Leukemia stated that germline TP53 variants are common in low hypodiploid ALL and testing should be considered.[7]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Li-Fraumeni syndrome testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered.

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However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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Administrative Guidelines

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Date of Service and Authorization Period Effective Date

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This guideline addresses the date of service (DOS) and effective date of the authorization period for laboratory testing.

Description

The DOS for a laboratory test or service is generally deemed to be either the date of specimen collection or the date of retrieval for archived specimens. This guideline outlines the rules for establishing the laboratory test DOS and the resultant effective date of the authorization for testing.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's Date of Service and Authorization Period Effective Date guideline will ensure adherence to EviCore's timeline requirements for test requests. However, it is possible that there will be a delay in care until the outlined procedures in the guideline are followed.

Criteria

INSERTED FOR VALIDITY

The following rules and definitions outline a laboratory test or service billing DOS:

- Date of Service (DOS)
  - The DOS for clinical diagnostic laboratory tests or services is generally the date the specimen is collected (collection date).[1]
  - An archived specimen is defined as a previously collected specimen that has been stored for more than 30 calendar days prior to testing (e.g. a tumor sample obtained from previous biopsy, isolated DNA that has been in frozen storage, etc.). The DOS for archived specimens is the date the specimen was removed from storage (retrieval date).[2]
  - Specimens stored for 30 days or less are required to use the date the specimen was collected (collection date) for the DOS.
- Authorization Effective Date

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  - The effective date of the authorization for testing is established by the DOS, as determined by the collection or retrieval date (see above criteria).
  - Tests or services submitted for medical necessity determination prior to the DOS will use the case determination date as the authorization effective date.
    - Case determination date is defined as the decision date of the medical necessity determination.
- Authorization Time Period
  - The time period of the authorization (i.e., the number of days between the authorization effective date and the expiration date) is established per health plan policy or regulatory authority.
- Medical Necessity Determinations
  - Medical necessity determinations are conducted using coverage criteria for tests or services outlined within the appropriate clinical guideline.
  - The DOS of the requested tests or services determine whether EviCore's clinical guidelines will be used (DOS on or after the health plan's effective date for utilization management services by EviCore) or the health plan's policies will be used (DOS prior to the health plan's effective date for utilization management services by EviCore).
  - The DOS will also be used to establish which version of a guideline is used for the medical necessity determination, based upon the specific guideline version's effective date.
- Billable Event
  - Standard laboratory billing practices define the billable event at the time when valid test results are generated AND the test report is provided to the ordering physician.
  - Depending on the test, the assay may take multiple days for results to generate.
  - Consequently, pre-service requests for medical necessity determination are permitted at any time prior to claim submission to the health plan (the billable event).

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Laboratory Billing and Reimbursement

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Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Molecular Pathology	81105 - 81479
Molecular Multianalyte Assays with Algorithmic Analyses (MAAA)	81490 - 81599; Molecular* administrative MAAA codes (ending in M)
Molecular Proprietary Laboratory Analyses (PLA)	Molecular* PLA codes (ending in U)
Molecular Infectious Testing	Molecular tests* within range 87149 – 87912 G0476
Molecular HCPCS Codes	S3800 - S3870 G0452, G0327, G9143 U0001-U0002
Molecular Cytopathology Procedures (Flow Cytometry, In Situ Hybridization)	88120 - 88121 88182 - 88199
Cytogenetics	88230 - 88299

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Procedures addressed by this guideline	Procedure codes
Molecular Surgical Pathology Procedures (Immunohistochemistry, In Situ Hybridization)	88341 - 88344 88360 - 88361 88364 –88377 88380 - 88387
Other Molecular Codes	86152 86153

Note:

*Generally defined as codes that include "DNA", "RNA", "nucleic acid", "genotype", "phenotype" or related language in the code description.

Description

The administrative handling of procedure codes by the EviCore Laboratory Management Program is addressed by this guideline. This guideline provides general guidance on what forms of review may be employed. It is intended to augment other clinical and administrative guidelines and should not be considered all-inclusive. The assessment of medical necessity of tests requested with these codes is addressed separately.

What Are Laboratory Procedure Codes

Common Procedural Terminology (CPT) codes are five-digit codes developed by the American Medical Association (AMA), and intended to report a wide range of tests and procedures.

The AMA issues guidance regarding the appropriate use of CPT codes in annual publications of the AMA CPT Professional manual. CPT codes that represent lab testing are generally published in the Pathology and Laboratory section and/or Appendix O of the CPT manual.[1]

The Healthcare Common Procedure Coding System (HCPCS) is the system used by the Centers for Medicare & Medicaid Services (CMS) to ensure consistent coding of claims for Medicare and other health insurance programs. Level I of the HCPCS simply utilizes the CPT coding system. In contrast, level II of the HCPCS includes alpha-numeric codes that describe drugs, supplies, and services that are not addressed by the CPT codes. These level II codes are developed and maintained by CMS. Various HCPCS codes

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beginning with "G", "P", "Q", "S", and "U" may apply to laboratory procedures. These codes are allowed to be used by non-Medicare insurers.[2]

Guidelines and Evidence

The National Correct Coding Initiative (NCCI)

CMS provides Pathology/Laboratory Services coding guidance in chapter 10 of the NCCI Policy Manual, which is often broadly adopted by other non-CMS payers.[3]

The NCCI Policy Manual's general guidance for laboratory procedure codes included, but was not limited to, the following statements:[3]

- "Providers/suppliers shall report the HCPCS/CPT code that describes the procedure performed to the greatest specificity possible. A Healthcare Common Procedure Coding System/Current Procedural Terminology (HCPCS/CPT) code shall be reported only if all services described by the code are performed. A provider/supplier shall not report multiple HCPCS/CPT codes if a single HCPCS/CPT code exists that describes the services. This type of unbundling is incorrect coding."
- "HCPCS/CPT codes include all services usually performed as part of the procedure as a standard of medical/surgical practice. A provider/supplier shall not separately report these services simply because HCPCS/CPT codes exist for them."
- "The "CPT Professional" also includes coding instructions which may be found in the "Introduction", individual chapters, and appendices. In individual chapters, the instructions may appear at the beginning of a chapter, at the beginning of a subsection of the chapter, or after specific CPT codes. Providers/suppliers should follow "CPT Professional" instructions unless CMS has provided different coding or reporting instructions."
- "Medicare does not pay for duplicate testing. Multiple tests to identify the same analyte, marker, or infectious agent shall not be reported separately. For example, it would not be appropriate to report both direct probe and amplified probe technique tests for the same infectious agent."
- "If a laboratory procedure produces multiple reportable test results, only a single HCPCS/CPT code shall be reported for the procedure. If there is no HCPCS/CPT code that describes the procedure, the laboratory shall report a miscellaneous or unlisted procedure code with a single unit of service."

NCCI also maintains lists of procedure code standards (i.e. "edits") that are used to promote national correct coding of Medicare Part B claims.[4-6] These edits have been adopted by some non-CMS payers as well.

Procedure Coding Guidelines by Category

The AMA organizes their laboratory CPT codes into the categories listed below.[1]

- CPT Codes 80047-80081: Organ or Disease Oriented Panels
- CPT Codes 80143-80299: Drug Assay
- CPT Codes 80305-83992: Therapeutic Drug Assays
- CPT Codes 80400-80439: Evocative/Suppression Testing Procedures
- CPT Codes 80503-80506: Pathology Clinical Consultations
- CPT Codes 81000-81099: Urinalysis Procedures
- CPT Codes 81105-81408; 81479: Molecular Pathology
- CPT Codes 81410-81471: Genomic Sequencing Procedures (GSP) and Other Molecular Multianalyte Assays
- CPT Codes 0002M-81599: Multianalyte Assays with Algorithmic Analyses (MAAA)
- CPT Codes 82009-84999: Chemistry Procedures
- CPT Codes 85002-85999: Hematology and Coagulation Procedures
- CPT Codes 86000-86849: Immunology Procedures
- CPT Codes 86850-86999: Transfusion Medicine Procedures
- CPT Codes 87003-87999: Microbiology Procedures
- CPT Codes 88000-88099: Anatomic Pathology Procedures
- CPT Codes 88104-88199: Cytopathology Procedures
- CPT Codes 88230-88299: Cytogenetic Studies
- CPT Codes 88300-88399: Surgical Pathology Procedures
- CPT Codes 88720-88749: In Vivo [eg, Transcutaneous] Laboratory Procedures
- CPT Codes 89049-89240: Other Pathology and Laboratory Procedures
- CPT Codes 89250-89398: Reproductive Medicine Procedures
- CPT Codes ending in "U": Proprietary Laboratory Analyses (PLA) Codes

A comprehensive review of all laboratory and pathology procedure coding guidelines is beyond the scope of this guideline. A discussion of coding guidelines that have particular relevance for EviCore's management of these procedure code categories can be found below.

Molecular Pathology Procedures (81105-81408; 81479)

Tier 1 Molecular Pathology Codes (81105-81383) represent gene-specific and genomic procedures.[1] Only one specific molecular pathology procedure is associated with each code.

Tier 2 Molecular Pathology CPT Codes (81400-81408) are a set of CPT codes designed to represent the level of technical and interpretive effort required for a large number of molecular and genomic tests that have not been assigned a unique CPT code (i.e., are not addressed by Tier 1, GSP, MAAA, or PLA codes). Specific tests, or analytes, are assigned to these Tier 2 codes by the AMA and cannot be self-assigned by the laboratory.

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The AMA codebook stated that 81403 may be used to represent known familial mutation analysis when a Tier 1 code is not available; see the guideline *Genetic Testing for Known Familial Mutations* for more details on this type of test.

Unlisted Molecular Pathology Code 81479 is assigned to molecular and genomic test procedures that are not addressed by a Tier 1, Tier 2, or Genomic Sequencing Procedure (GSP) code.

The AMA codebook stated the following regarding the use of these codes:[1]

- "The molecular pathology codes include all analytical services performed in the test (eg, cell lysis, nucleic acid stabilization, extraction, digestion, amplification, and detection). Any procedures required prior to cell lysis (eg, microdissection, codes 88380 and 88381) should be reported separately."
- For Tier 2 codes in particular: "Use the appropriate molecular pathology procedure level code that includes the specific analyte listed after the code descriptor. If the analyte tested is not listed under one of the Tier 2 codes or is not represented by a Tier 1 code, use the unlisted molecular pathology procedure code, 81479."

The NCCI Manual stated the following regarding the use of these codes:[3]

- "Molecular pathology procedures (e.g., CPT codes 81161-81408) include all aspects of sample preparation, cell lysis, internal measures to assure adequate quantity of DNA or RNA, and performance of the assay. These procedures include DNA analysis and/or RNA analysis."
- "A Tier 1 or Tier 2 molecular pathology procedure CPT code should not, in general, be reported with a genomic sequencing procedure, molecular multianalyte assay, multianalyte assay with algorithmic analysis, or proprietary laboratory analysis CPT code where the CPT code descriptor includes testing for the analyte described by the Tier 1 or Tier 2 molecular pathology code."

When multiple Tier 1, Tier 2, and/or unlisted codes are billed together, this is considered a panel (see "Multigene Panel Coding").

Genomic Sequencing Procedures (GSP) (81410-81471)

GSP codes represent DNA or RNA sequence analysis methods that simultaneously assay multiple genes or genetic regions relevant to a specific clinical situation (e.g., multi-gene panels), typically via next generation sequencing (NGS) or massively parallel sequencing (MPS).[1]

The AMA codebook stated the following regarding the use of GSP codes:[1]

- "The analyses listed below are often performed using NGS/MPS technology; however, the analyses may also be performed by other molecular techniques (polymerase chain reaction [PCR] methods and microarrays). These codes should be used when the components of the descriptor(s) are fulfilled regardless of the

technique used to provide the analysis, unless specifically noted in the code descriptor."
- "When all of the components of the descriptor are not performed, use individual Tier 1 codes, Tier 2 codes, or 81479 (Unlisted molecular pathology procedure)."

Multianalyte Assays with Algorithmic Analyses (MAAA) (0002M-81599)

MAAA codes represent procedures that incorporate different types of assays, in combination with an algorithmic analysis and other patient information (if applicable), to generate a numeric score or probability. The AMA maintains a list of all MAAA codes, along with the associated proprietary name (if applicable) in Appendix O of the CPT Professional manual. These tests are typically unique to a single laboratory.[1]

The AMA codebook stated the following regarding the use of MAAA codes:[1]
- "The results of individual component procedure(s) that are inputs to the MAAAs may be provided on the associated laboratory report, however these assays are not reported separately using additional codes."
- "In order to report a MAAA code, the analysis performed must fulfill the code descriptor and, if proprietary, must be the test represented by the proprietary name listed in Appendix O. When a specific MAAA procedure is not listed below or in Appendix O, the procedure must be reported using the Category I MAAA unlisted code (81599)."
- "These codes encompass all analytical services required (eg, cell lysis, nucleic acid stabilization, extraction, digestion, amplification, hybridization and detection) in addition to the algorithmic analysis itself. Procedures that are required prior to cell lysis (eg, microdissection, codes 88380 and 88381) should be reported separately."

Microbiology Procedures (87003-87999)

These codes are used to identify microorganisms such as viruses, bacteria, and other infectious agents. Some of these procedures involve the use of molecular diagnostic testing with nucleic acid probes.[1]

The NCCI manual stated the following regarding the use of these codes:[3]
- "With one exception, CMS policy prohibits separate payment for testing for a single microorganism from an anatomic site by more than one methodology. For example, if a physician performs tests for cytomegalovirus antigen at an anatomic site by immunoassay (CPT code 87332) and by nucleic acid direct probe (CPT code 87495), only one of these codes may be reported for the testing. If a culture independent diagnostic testing method is positive for a microorganism, it may be medically reasonable and necessary to additionally culture the microorganism for drug sensitivity testing or (rarely) for community surveillance identification."

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Proprietary Laboratory Analyses (PLA) (CPT Codes ending in "U")

PLA codes are used to describe proprietary clinical laboratory analyses that can only be provided by a single laboratory or set of providing laboratories. A list of these codes is included in Appendix O of the CPT Professional manual, along with the test's proprietary name. Unlike other categories of CPT codes, new PLA codes are typically released on a quarterly basis.[1]

The AMA CPT Professional codebook stated the following regarding PLA codes:[1]

- "When a PLA code is available to report a given proprietary laboratory service, that PLA code takes precedence. The service should not be reported with any other CPT code(s) and other CPT code(s) should not be used to report services that may be reported with that specific PLA code."
- "These codes encompass all analytical services required for the analysis (eg, cell lysis, nucleic acid stabilization, extraction, digestion, amplification, hybridization and detection). For molecular analyses, additional procedures that are required prior to cell lysis (eg, microdissection [codes 88380 and 88381]) may be reported separately."
- "In order to report a PLA code, the analysis performed must fulfill the code descriptor and must be the test represented by the listed proprietary name in Appendix O."

Multigene Panel Coding

For laboratory procedures that include multiple molecular/genomic components, the NCCI Manual provided the following coding guidance:[3]

- "If one laboratory procedure evaluates multiple genes using a next generation sequencing procedure, the laboratory shall report only one unit of service of one genomic sequencing procedure, molecular multianalyte assay, multianalyte assay with algorithmic analysis, or proprietary laboratory analysis CPT code. If no CPT code accurately describes the procedure performed, the laboratory may report CPT code 81479 (Unlisted molecular pathology procedure) with one unit of service or may report multiple individual CPT codes describing the component test results when medically reasonable and necessary. Procedures reported together must be both medically reasonable and necessary (e.g., sequencing of procedures) and ordered by the physician who is treating the beneficiary and using the results in the management of the beneficiary's specific medical problem."
- "All genomic sequencing procedures and molecular multianalyte assays (e.g., CPT codes 81410-81471), many multianalyte assays with algorithmic analyses (e.g., CPT codes 81490-81599, 0004M-XXXXM), and many Proprietary Laboratory Analyses (PLA) (e.g., CPT codes 0001U-XXXXU) are DNA or RNA analytic methods that simultaneously assay genes or genetic regions. A provider/supplier shall not additionally separately report testing for the same gene or genetic region by a different methodology (e.g., CPT codes 81105-81408, 81479, 88364-88377). CMS

payment policy does not allow separate payment for multiple methods to test for the same analyte."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's Laboratory Billing and Reimbursement guideline will ensure adherence to appropriate billing, coding, and reimbursement processes. However, it is possible that there will be a delay in care until the outlined procedures in the guideline are followed.

Criteria: Manual Procedure Code Review

All procedure codes included in the Laboratory Management Program may be subject to specific coding requirements. The following define many, but not all, of the most commonly applied coding requirements under this program. Any procedure codes that do not meet these criteria will not be reimbursable, even if medical necessity criteria for the associated test(s) are met. Exceptions to these requirements will be handled on a case-by-case basis.

Correct Coding Requirements

Any procedure codes managed by the program will be subject to the requirements outlined below.

- Any test-specific coding requirements, which are generally addressed in the Billing and Reimbursement Considerations section of applicable clinical guidelines, must be met.
- NCCI coding guidance is generally adopted by EviCore in the absence of coding requirements addressed in test-specific guidelines.
- All procedure code(s) must be an accurate representation of the associated test(s). This includes:
  - The procedure code(s) must be in effect on the date of service associated with the case review or claim (please refer to the *Date of Service and Authorization Period Effective Date* guideline for details about how this date is determined for prior authorizations).
  - The test must fulfill all of the minimum requirements of the AMA/CMS code description. This includes, but is not limited to, specimen type, test content, and test methodology (e.g. sequencing, deletion/duplication analysis, targeted mutation analysis, etc.).
  - Proprietary codes (e.g., PLA codes and proprietary MAAA codes) will only be accepted when used by the single laboratory or set of providing laboratories to

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which the AMA has assigned the code. The code will not be accepted for use by a different laboratory, even if their test is similar in nature.
    - Tier 2 Codes (81400-81408) will only be accepted when the AMA has specifically assigned the test to the Tier 2 code. Laboratories may not self-assign tests to Tier 2 codes that are not specifically listed as analytes by the AMA.
    - GSP codes (81410-81471) will only be accepted for panels that include the minimum gene content required per the AMA descriptor. When this gene list is directly preceded by the word "including", all of the specified genes must be included on the associated panel. When the gene list is directly preceded by the abbreviation "e.g.", these genes are considered examples, and do not need to be included on the panel.
    - When a specific code that accurately describes the test is not available, the appropriate unlisted/miscellaneous procedure code should be used (e.g., 81479, 81599, etc.).
- Add-on codes (e.g. 81266, 88185, etc.) will be addressed as follows:
    - The add-on code(s) will only be reimbursed when billed with the appropriate primary code(s) on the same date of service by the same provider.
    - If none of the primary code(s) meet medical necessity criteria, any accompanying add-on code(s) will not be separately reimbursable.
- Panel coding and billing should reflect the efficiency gains for the laboratory in testing multiple candidate genes simultaneously. Currently, laboratories are billing for panels in a variety of ways. When a panel approach to testing is determined to be medically necessary, the following billing guidelines will apply:
    - If a panel is billed with multiple procedure codes representing individual genes analyzed, the panel will be redirected to an appropriate panel code. If the laboratory will not accept redirection to a single code, the medical necessity of each billed component procedure will be assessed independently. Only the individual panel components that meet medical necessity criteria as a first tier of testing will be reimbursed. The remaining individual components will not be reimbursable.
    - Examples of appropriate panel codes include:
        - An appropriate proprietary laboratory analyses (PLA) code, or
        - An appropriate genomic sequencing procedure (GSP) code (if there are two different GSP codes to describe the sequencing and deletion/duplication analysis components of the test, both codes will be reimbursable as long as medical necessity is established for both methodologies), or
        - If no more specific code exists, the panel will be redirected to a single unit of the unlisted molecular pathology code 81479, which can be used to represent a panel in total.
    - If the member meets medical necessity, billing of the deletion/duplication portion of the panel with a microarray code (typically billed with 81228 or 81229) is allowed

when at least 3 genes are included on the panel. Panels with less than 3 genes are more appropriately billed with individual CPT codes.
    - If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.
- When multiple codes are submitted that address the same test content for the same date of service, only the most appropriate code(s) will be eligible for reimbursement, and the redundant/overlapping code(s) will not be reimbursable. Codes meeting medical necessity requirements will be prioritized for approval in the following manner:
    - Any guidance provided in the applicable clinical guideline will be followed, when available.
    - A proprietary code (e.g. PLA code or proprietary MAAA code) will be prioritized over non-proprietary codes when available for the providing laboratory.
    - An appropriate test-specific code will be prioritized over a non-specific code for a single gene/analyte test (e.g., a tier 1 code is prioritized over an unlisted code).
    - For procedures with multiple components, a single code will be prioritized over a combination of codes.
- When a prior authorization request is submitted for a group of procedure codes and at least one procedure code requires prior authorization, all submitted procedure codes that are under management by the Program (in any form) will be reviewed regardless of the authorization requirements for each code.

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Medical Necessity Review Information Requirements

MOL.AD.304.A
v1.0.2026

This guideline addresses the minimum information needed to perform a medical necessity review of laboratory testing.

Description

In order to accurately and effectively conduct medical necessity reviews, certain information is necessary when the case is submitted. This guideline outlines the information that is required to conduct a medical necessity review.

This information must be provided before applicable medical necessity criteria can be applied. If the below information is not received, the testing will be denied, as medical necessity cannot be determined.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's Medical Necessity Review Information Requirements guideline will ensure EviCore receives complete and timely information required to process test requests. However, it is possible that there will be a delay in care until the outlined procedures in the guideline are followed.

Criteria

The following information must be submitted to perform a medical necessity review for any test:

- Details about the test being performed (test name, description, and/or unique identifier), and
- Laboratory that will be performing the test, and
- All CPT codes and units that will be billed related to the entire test, and
- Clinical information, which may include:
  - All information required by applicable guideline, or
  - Test indication, including any applicable signs and symptoms or other reasons for testing, and
  - Any applicable test results (laboratory, imaging, pathology, etc.), and
  - Any applicable family history, and

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- How test results will impact patient care

When procedure codes are not provided with the request, code(s) will be assigned by the EviCore Laboratory Management Program based on one of the following methods:

- Any documentation provided with the request and/or publicly available on the laboratory's website will be used to assign the code(s), or
- If documentation is neither provided with the request, nor readily available on the laboratory's website, the most appropriate code(s) will be assigned according to relevant clinical guidelines or the guideline *Laboratory Billing and Reimbursement*, or
- If appropriate code(s) are unable to be identified with the above methods, an unlisted molecular pathology code (81479) will be assigned as a placeholder

Medical Necessity Review Requirements

Special Circumstances Influencing Coverage Determinations

MOL.AD.364.A
v1.0.2026

Introduction

EviCore performs independent Healthcare Technology Assessments (HTA) to assess analytical validity, clinical validity, and clinical utility of laboratory testing. These HTAs are used as the foundation for EviCore's coverage determinations and medical necessity criteria. However, there may be special circumstances, including state and federal legislation, which may override or supplement EviCore criteria. This guideline outlines special circumstances that may impact coverage determinations for certain laboratory testing.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's Special Circumstances Influencing Coverage Determinations guideline will ensure adherence to state and federal regulations. However, it is possible that there will be a delay in care until the outlined procedures in the guideline are followed.

Special Circumstances

Federal Legislation

Preventive Services Addressed by the Affordable Care Act

EviCore's position is that the Affordable Care Act does not preclude EviCore's laboratory management program from determining the medical necessity of preventive services.

While private health plans must provide coverage for such preventive services without cost sharing, these tests may be subject to medical necessity requirements. A list of preventive services covered under the regulation can be found at **https://www.healthcare.gov/preventive-care-benefits**.

Section 2713 of the Public Health Service Act (PHS Act), added by the Patient Protection and Affordable Care Act, as amended, states that:[1]

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- "Section 2713 of the PHS Act requires coverage without cost sharing of certain preventive health services by non-grandfathered group health plans and health insurance coverage."
- "[T]o the extent not specified in a recommendation or guideline, a plan or issuer may rely on the relevant evidence base and established reasonable medical management techniques to determine the frequency, method, treatment, or setting for the provision of a recommended preventive service."

Therefore, EviCore's managed procedure codes for a Health Plan are subject to medical necessity requirements, even if the requested test is considered a preventive service.

State Mandates

Please note: The information included in this guideline is current as of the publication date. Any additional laws and/or regulations impacting laboratory services not referenced in this guideline would be considered using the criteria outlined below.

Autism Screening

EviCore's position is that because autism is a diagnosis that is made clinically based on an individual's symptoms, genetic testing is not required by state mandate unless explicitly stated.

According to the National Conference of State Legislatures (NCSL), "[m]ost states require insurers to provide coverage for the treatment of autism."[2]

Such state mandates typically apply to the diagnosis, screening, and/or treatment of autism, for which genetic testing is not relevant, as autism is diagnosed through evaluation of an individual's development and behaviors by an appropriate specialist (such as neurodevelopmental pediatrician or developmental-behavioral pediatrician).[3] While genetic testing may identify an underlying genetic cause for the individual's autism, it does not diagnose autism. In addition, there is not a specific genetic test to diagnose autism, as there are numerous genetic syndromes which may include autism as a component of the condition. For example, a child who has a clinical diagnosis of autism may have genetic testing to determine if there is an underlying genetic condition, such as Fragile X Syndrome, that may explain the child's autism. However, the genetic test is not required to make a diagnosis of autism or to treat the child's autism. For information on the medical necessity criteria that must be

met for coverage of genetic testing for autism, please refer to the guideline *Autism, Intellectual Disability, and Developmental Delay Genetic Testing*.

Delaware State Mandate: House Bill 319

House Substitute No. 1 for HB 319 "An Act to Amend Title 18 of the Delaware Code Relating to Experimental Treatment Health Insurance Coverage" states that no individual or group policy or health insurance contract:[4]

- "...shall deny coverage, payment, or reimbursement for a National Coverage Determination Service on the basis that the treatment is experimental or investigational. ... "National Coverage Determination Service" as used in this section shall mean a service, item, or test which receives reimbursement from the Centers for Medicare and Medicaid Services pursuant to the Social Security Act 1869 (f)."

A synopsis of the Delaware General Assembly House Bill 319 (HB319) states:[4]

- "This legislation creates a benchmark for determining when a treatment or service is no longer experimental or investigational. Essentially, when Medicare determines that a treatment is safe for its population, commercial insurers in Delaware may no longer deny coverage on that basis. This will remove inconsistencies for properly-evidenced treatments between payers."

Therefore the state of Delaware prohibits denial of a service as investigational/ experimental if the service is coverable under CMS National Policy outlined in an National Coverage Determination (NCD) or National Coverage Analysis (NCA). If EviCore has an experimental, investigational, or unproven (E/I/U) coverage determination for the billed procedure code(s) and CMS has a current NCD or NCA with specific coverage of that procedure code, EviCore will apply the CMS national coverage policy for non-Medicare members identified as Delaware residents. This policy application may occur during pre-service review, through automated claim edits (such as enforcing ICD requirements), or through post-service medical necessity review.

Applicable Laws

States are increasingly addressing the coverage and management of certain laboratory tests. EviCore monitors evolving legislation to ensure compliance.

These bills can generally be grouped into 3 categories:

- Broad Biomarker Bills: these bills generally govern biomarker testing across medical diagnoses
- Cancer-Specific Biomarker Bills: these bills govern biomarker testing for individuals with a medical diagnosis of cancer
- Other State Bills: these bills are specific to a type of clinical test (e.g. BRCA testing), or address the requirement for prior authorization in specific circumstances

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The EviCore process for assessing these types of bills differs, and is detailed below.

Broad Biomarker Bills

The following is a list of broad biomarker bills that are applicable to laboratory testing at the time of this guideline. These bills generally address tests performed specifically for diagnosis, treatment, management, or monitoring of a disease or condition. Note that this excludes screening tests or any test that is not focused on a specific diagnosis, management, or treatment decision.

State	Bill	Effective Date	Line(s) of Business*	Jurisdiction**
Arizona	HB 2144[5]	January 1, 2023	Commercial	Situsd
California	SB 496[6]	July 1, 2024	Commercial; Medicaid	Situsd; Residents
Colorado	SB 124[7]	January 1, 2025	Commercial	Situsd
Connecticut	SB 307[8]	July 1, 2024	Medicaid	Situsd
Florida	HB 885[9]	July 1, 2024	State Employee Plans; Medicaid	Situsd
Georgia	HB 85[10]	July 1, 2023	Commercial	Situsd
Illinois	HB 1779[11]	January 1, 2022	Commercial	Situsd
Indiana	S 273[12]	July 1, 2024	Commercial	Situsd
Iowa	HF 2668[13]	January 1, 2025	Commercial; Medicaid	Situsd
Kentucky	HB 180[14]	January 1, 2024	Commercial; Medicaid	Situsd; Residents
Louisiana	SB 104[15]	January 1, 2024	Commercial	Situsd; Residents
Maryland	HB 1217[16]	January 1, 2024	Commercial	Situsd
Minnesota	SF 2995[17]	January 1, 2025	Commercial; Medicaid	Situsd; Residents
New Jersey	A4163[18]	July 22, 2025	Commercial	Situsd

State	Bill	Effective Date	Line(s) of Business*	Jurisdiction**
New Mexico	HB 73[19]	January 1, 2024	Commercial	Situsued; Residents
New York***	A 8502[20]	January 1, 2025	Commercial; Medicaid	Situsued
Oklahoma	SB 513[21]	January 1, 2024	Commercial	Situsued
Rhode Island	HB 7587[22]	January 1, 2024	Commercial	Situsued
Texas	SB 989[23]	January 1, 2024	Commercial; Medicaid	Situsued; Residents

Note:

*There are some insurance products within these broad categories subject to the biomarker bills, but certain products may be excluded (e.g. Federal Employee Health Plans or those serving military members).

**Situsued indicates the jurisdiction in which the health insurance is issued. Residents indicates the state in which the member lives.

Decision hierarchy criteria

When making medical necessity determinations subject to broad biomarker bill requirements, EviCore will employ the following strategy for both utilization management case reviews and automated claim edit application:

- Apply EviCore criteria and approve if possible.
- If not approvable under EviCore criteria, approve if consistent with coverable indications based on Medicare National Coverage Determinations (NCDs), Medicare Local Coverage Determinations (LCDs), U.S. Food and Drug Administration (FDA) approved tests, FDA cleared tests, indicated tests for a drug that is approved by the FDA, nationally recognized clinical practice guidelines, and/or consensus statements as defined by applicable legislation.

*** New York A 8502 adds a provision to consider peer-reviewed literature that "recognizes the efficacy and appropriateness" of biomarker testing. EviCore already considers all published clinical utility literature in its coverage guideline development. However, given the development rate and quantity of such literature, EviCore will consider clinical utility studies outside of this usual process when submitted by the laboratory for the purposes of biomarker coverage decisions only.

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Cancer-Specific Biomarker Bills

The following is a list of biomarker bills specific to cancer tests that are applicable to laboratory testing at the time of this guideline. Note that this excludes screening tests or any test that is not focused on a specific diagnosis, management, or treatment decision.

State	Bill	Effective Date	Line(s) of Business*	Jurisdiction**
Arkansas	HB 1121[24]	July 31, 2023	Commercial	Situsd; Residents
Louisiana	SB 84[25]	January 1, 2022	Commercial	Situsd; Residents
Nevada	AB 155[26]	October 1, 2023	Commercial	Situsd; Residents

Note:

*There are some insurance products within these broad categories subject to the biomarker bills, but certain products may be excluded (e.g. Federal Employee Health Plans or those serving military members).

**Situsd indicates the jurisdiction in which the health insurance is issued. Residents indicates the state in which the member lives.

Decision hierarchy criteria

When making medical necessity determinations subject to cancer specific biomarker bill requirements, EviCore will employ the following strategy for both utilization management case reviews and automated claim edit application:

- Purpose of the requested test is for one or more of the following:
  - early detection of cancer
  - diagnosis of cancer
  - treatment of cancer
  - appropriate management of cancer
  - ongoing monitoring of cancer
- Apply EviCore criteria and approve if possible.
- If not approvable under EviCore criteria, approve if consistent with coverable indications based on Medicare NCDs, Medicare LCDs, FDA approved tests, FDA cleared tests, indicated tests for a drug that is approved by the FDA, national guidelines, and/or consensus statements

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Other Applicable Bills

The following is a list of bills applicable to laboratory testing at the time of this guideline.

- Arkansas (AR)
  - AR HB 1042 requires that commercial health insurance issued in AR and health insurance covering AR residents on or after January 1, 2023 provide prostate cancer screening coverage for "at least one (1) screening per year for any man forty (40) years of age or older according to the National Comprehensive Cancer Network guidelines."[27]
    - In order to comply with this legislation, EviCore will use the screening requirements published in HB 1042 when evaluating the medical necessity of prostate cancer screening tests for members who live in AR or have health insurance under AR jurisdiction.
- California (CA)
  - CA SB 535 prohibits commercial insurers that contract in CA on or after July 1, 2022 from requiring prior authorization for biomarker testing for enrollees with advanced or metastatic stage 3 or 4 cancer. Biomarker testing is defined as "a diagnostic test, such as single or multigene, of the cancer patient's biospecimen, such as tissue, blood, or other bodily fluids, for DNA or RNA alterations, including phenotypic characteristics of a malignancy, to identify an individual with a subtype of cancer, in order to guide patient treatment." The prior authorization exemption only applies to biomarker testing necessary for an FDA-approved therapy.[28]
    - In order to comply with this legislation, a minimum amount of information must be registered with EviCore to document that the member is exempt from the prior authorization process.
- Connecticut (CT)
  - CT SB 358 requires that commercial and Medicaid health insurance issued in CT on or after January 1, 2023 provide coverage for "Genetic testing of the breast cancer gene one, breast cancer gene two, any other gene variant that materially increases the insured's risk for breast and ovarian cancer or any other gynecological cancer to detect an increased risk for breast and ovarian cancer when recommended by a health care provider in accordance with the United States Preventive Services Task Force recommendations for testing." USPSTF recommendations state "[t]esting for BRCA1/2 mutations should be done when an individual has personal or family history that suggests an inherited cancer susceptibility, when an individual is willing to see a health professional who is suitably trained to provide genetic counseling and interpret test results, and when test results will aid in decision -making."[29,30]
    - EviCore's guidelines are consistent with the USPSTF requirements and can be used as published to determine coverage.
- Illinois (IL)

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- IL HB 2109 requires that commercial health insurance issued in IL on or after January 1, 2022 provide "coverage for medically necessary comprehensive cancer testing and testing of blood or constitutional tissue for cancer predisposition testing." According to the bill, "Comprehensive cancer testing" includes, but is not limited to, the following forms of testing: (1) Targeted cancer gene panels. (2) Whole-exome genome testing. (3) Whole-genome sequencing. (4) RNA sequencing. (5) Tumor mutation burden." Also, "Testing of blood or constitutional tissue for cancer predisposition testing includes, but is not limited to, the following forms of testing: (1) Targeted cancer gene panels. (2) Whole-exome genome testing. (3) Whole-genome sequencing."[31]
  - As EviCore's guidelines are evidence-based, they are consistent with these requirements, and can be used as published to determine coverage.
- IL HB 5334 requires that commercial health insurance issued in IL on or after January 1, 2024 provide coverage for the cost of BRCA1 and BRCA2 genetic testing when recommended by a health care provider in accordance with the United States Preventive Services Task Force's (USPSTF) recommendations for testing. USPSTF recommendations state "[t]esting for BRCA1/2 mutations should be done when an individual has personal or family history that suggests an inherited cancer susceptibility, when an individual is willing to see a health professional who is suitably trained to provide genetic counseling and interpret test results, and when test results will aid in decision -making."[30,32]
  - EviCore's guidelines are consistent with the USPSTF requirements and can be used as published to determine coverage.
- IL HB 3817 requires that beginning January 1, 2024, the State Employee Group Insurance Program "shall provide coverage for diagnosis and treatment of infertility, including, but not limited to, in vitro fertilization, uterine embryo lavage, embryo transfer, artificial insemination, gamete intrafallopian tube transfer, zygote intrafallopian tube transfer, and low tubal ovum transfer. The coverage required shall include procedures necessary to screen or diagnose a fertilized egg before implantation, including, but not limited to, preimplantation genetic diagnosis, preimplantation genetic screening, and prenatal genetic diagnosis."[33]
  - EviCore will determine the medical necessity of laboratory infertility services for this membership group in the following manner:
    - Preimplantation Genetic Diagnosis: The EviCore Preimplantation Genetic Screening and Diagnosis guideline addresses the medically necessary indications for preimplantation genetic diagnosis. It is compliant with the legislation and will used to determine coverage for these services.
    - Preimplantation Genetic Screening: Coverable for those seeking diagnosis and treatment of infertility as defined in the legislation.

- Prenatal Diagnosis: Coverable when related to preimplantation genetic screening or diagnosis (i.e., to confirm such results) for those seeking diagnosis and treatment of infertility as defined in the legislation.

- IL HB 3202 requires that commercial health insurance issued in IL beginning January 1, 2025 provides coverage for "medically necessary home saliva cancer screening every 24 months if the patient is asymptomatic and at high risk for the disease being tested for or demonstrates symptoms of the disease being tested for at a physical exam." For members subject to this law, home saliva cancer screening testing will be considered medically necessary when one of the following criteria are met:[34]
  - Member is asymptomatic and at high risk for oral cancer by one of the following:
    - tobacco and/or alcohol use
    - male
    - older age
    - use of betel quid
    - ultraviolet light exposure
    - infection with Candida or bacterial flora
    - compromised immune system, OR
  - Member demonstrates symptoms of oral cancer as described by their provider.
- IL HB 2350 requires that commercial health insurance issued in IL beginning January 1, 2025 provide coverage for "an annual prostate cancer screening for insureds upon the recommendation of a physician licensed to practice medicine in all its branches for: (A) asymptomatic individuals age 50 and over; (B) African-American individuals age 40 and over; and (C) individuals age 40 and over with a family history of or genetic predisposition to prostate cancer." Further, "prostate cancer screening" includes medically necessary subsequent follow-up testing as directed by a health care provider, including, but not limited to: (1) urinary analysis; (2) serum biomarkers; and (3) medical imaging, including, but not limited to magnetic resonance imaging."[35]
  - In order to comply with this legislation, EviCore will use its own medical necessity criteria in conjunction with the criteria published in HB 2350 when making medical necessity determinations for individuals seeking prostate cancer screening (as defined in the regulations) who have health insurance under IL jurisdiction.
- IL SB 2697 requires that commercial health insurance issued in IL beginning January 1, 2026 provide coverage for "clinical genetic testing for an inherited gene mutation for individuals with a personal or family history of cancer, as recommended by a health care professional in accordance with current evidence-based clinical practice guidelines, including, but not limited to, the current version of the National Comprehensive Cancer Network clinical practice guidelines."[36]

        - In order to comply with this legislation, EviCore will use its own medical necessity criteria in conjunction with the current version of the National Comprehensive Cancer Network clinical practice guidelines when making medical necessity determinations for individuals seeking germline multi-gene testing for an inherited mutation (as defined by the regulations).
- Louisiana (LA)
    - LA SB 154 requires that commercial and Medicaid health insurance issued in LA on or after January 1, 2023 provide coverage for "traditional whole genome sequencing, rapid whole genome sequencing, and other genetic and genomic screening that includes individual sequencing, trio sequencing for a parent or parents of the infant, and ultra-rapid sequencing for an infant who is one year of age or younger, is receiving inpatient hospital services in an intensive care unit or in a pediatric care unit, and has a complex illness of unknown etiology."[37]
        - In order to comply with this legislation, EviCore will use the medical necessity criteria published in SB 154 when making medical necessity determinations for critically ill infants (as defined in the regulations) who have health insurance under LA jurisdiction.
- Minnesota
    - MN HF 5247 requires that commercial health insurance issued in MN and health insurance covering MN residents on or after January 1, 2025 provide coverage for rapid whole genome sequencing "if the enrollee: (1) is 21 years of age or younger; (2) has a complex or acute illness of unknown etiology that is not confirmed to have been caused by an environmental exposure, toxic ingestion, an infection with a normal response to therapy, or trauma; and (3) is receiving inpatient hospital services in an intensive care unit or a neonatal or high acuity pediatric care unit."[38]
        - In order to comply with this legislation, EviCore will use the clinical criteria published in HF 5247 when evaluating the medical necessity of rapid whole genome sequencing requests for members who live in MN or have health insurance under MN jurisdiction.
- New Jersey
    - NJ A5235 requires that commercial health insurance issued in NJ on or after August 1, 2024 provide coverage "for any services related to infertility in accordance with American Society for Reproductive Medicine guidelines and as determined by a physician, which includes, but is not limited to: diagnosis and diagnostic tests; … genetic testing."[39]
        - As EviCore's guidelines are evidence-based, they are consistent with these requirements, and can be used as published to determine coverage.
- Pennsylvania (PA)
    - PA SB 8 requires that commercial health insurance issued in PA on or after January 1, 2024 provide "coverage for BRCA-related genetic counseling and genetic testing…The minimum coverage required shall include all costs associated

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with…a genetic laboratory test of the BRCA1 and BRCA2 genes for individuals assessed to be at an increased risk, based on a clinical risk assessment tool, of potentially harmful mutations in the BRCA1 or BRCA2 genes due to a personal or family history of breast or ovarian cancer."[40]

- In order to comply with this legislation, when reviewing cases related to BRCA1/2 testing for members with PA jurisdiction, EviCore will consider the results of clinical risk assessment tools and approve if these results indicate a lifetime risk of breast cancer greater than 20%.

- Washington (WA)
  - WSR 21-16-076, effective July 1, 2022, applies to commercial and Medicaid health insurers that contract in WA as well as residents living in the state of Washington. "The purpose of WSR 21-16-076 "is to update the state board of health's (board) existing rules outlining prenatal screenings and diagnostic tests required to be covered by certain payers to align with current clinical standards and best practices."[41]
    - In order to comply with this regulation, EviCore will use the medical necessity criteria published in WSR 21-16-076 when making medical necessity determinations for the specific prenatal screening and diagnostic testing described within the regulation.
  - WA HB 1689 prohibits commercial insurers that contract in WA on or after January 1, 2023 from requiring prior authorization for biomarker testing for enrollees with stage 3 or 4 cancer; or recurrent, relapsed, refractory, or metastatic cancer.163 Biomarker testing must "be recommended in the latest version of nationally recognized guidelines or biomarker compendia." The biomarker test must also be a covered service and prescribed by an in-network provider.[42]
    - In order to comply with this legislation, a minimum amount of information must be registered with EviCore to document that the member is exempt from the prior authorization process.

Health Plan Exclusions

Benefit Exclusions

EviCore performs medical necessity determination for any laboratory test that is within the delegated scope of management for the Health Plan (see each Plan's managed procedure code list). However, health plans set varying limitations and exclusions; EviCore's medical necessity review does not take such member-specific benefits into account. Therefore, a medical necessity approval is not a guarantee of payment. Please see the Certificate of Coverage for detail regarding benefit limitations or exclusions (e.g. screening, fertility benefits).

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Introduction

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Unique Test Identifiers for Non-Specific Procedure Codes

MOL.AD.107.A
v1.0.2026

Introduction

Unique test identifiers for non-specific procedures codes are addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
MOPATH PROCEDURE LEVEL 1	81400
MOPATH PROCEDURE LEVEL 2	81401
MOPATH PROCEDURE LEVEL 3	81402
MOPATH PROCEDURE LEVEL 4	81403
MOPATH PROCEDURE LEVEL 5	81404
MOPATH PROCEDURE LEVEL 6	81405
MOPATH PROCEDURE LEVEL 7	81406
MOPATH PROCEDURE LEVEL 8	81407
MOPATH PROCEDURE LEVEL 9	81408
UNLISTED MOLECULAR PATHOLOGY	81479
UNLISTED MAAA	81599

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Description

This policy provides instruction on how to submit a unique test identifier when a procedure code is billed that does not adequately describe the performed molecular or genomic test referred to here as "non-specific procedure codes."

Given the large and rapidly increasing number of molecular and genomic tests, many tests do not have unique procedure codes and are instead billed with non-specific procedure codes. These non-specific procedure codes generally fall into one of the following categories.

Tier 2 codes

Tier 2 Molecular Pathology codes (81400-81408) are a set of CPT codes designed to represent the level of technical and interpretive effort required for a large number of molecular and genomic tests that have not been assigned a unique CPT code (i.e., are not addressed by Tier 1, GSP, MAAA, PLA, etc. codes). Specific tests, or analytes, are assigned to these Tier 2 codes by the AMA a few times yearly and cannot be self-assigned by the laboratory.

The AMA publishes a set of gene abbreviations or analyte identifiers, called claim designation codes, for each test assigned to a Tier 2 code. These codes are intended to provide billing transparency such that the combination of a Tier 2 code and the applicable claim designation code on a claim form are reasonably specific to the test performed. Where the test is specific to a gene, the claim designation code is generally the standard gene name. The claim designation codes are published in the annual AMA CPT Professional codebook.[1]

Unlisted codes

If a molecular or genomic test has not been assigned to any test-specific or Tier 2 CPT code, those tests are generally billed under one of the following unlisted codes:

- 81479: Unlisted molecular pathology procedure
- 81599: Unlisted multianalyte assay with algorithmic analysis

The proper unlisted code depends on the nature of the test, but most molecular tests are best described by 81479 or 81599.

There is no publicly-available, widely-adopted source of unique codes for tests billed under unlisted codes.

The Palmetto MolDX program requires that most molecular tests be registered with the program and obtain a unique identifier (McKesson Z-Code or Palmetto Test Indicator) for the purposes of claim processing.[2] However, this identifier is both lab and test-specific and is currently primarily utilized by only certain Medicare jurisdictions.

Note:

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This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's Unique Test Identifiers for Non-Specific Procedure Codes guideline will ensure assignment of consistent IDs to test requests. However, it is possible that there will be a delay in care until the outlined procedures in the guideline are followed.

Criteria

Unique test identifier assignment

Tier 2 AMA claim designation codes

For tests billed under a Tier 2 CPT code, the unique test identifier is the same as the original claim designation code published by the AMA when available, provided the claim designation code described only a single test assigned to that Tier 2 code. In the event that the same claim designation code described more than one test assigned to the same Tier 2 code, EviCore assigned a unique code (not the original AMA claim designation code) to at least one of these tests. When the AMA has not published a claim designation code, a unique code is developed by EviCore. No separate registration or notification process is required on the part of the laboratory.

Tier 2 special cases

Tier 2 code 81403 allows for known familial variant testing to be billed without specific gene assignment. The unique test identifier for known familial variants not otherwise specified is generally either: "KFMNOS" or the AMA assigned claim designation code for the gene if one exists with the addition of "KFM" (e.g., ATM and ATMKFM).

Unlisted codes

For tests billed under unlisted procedure codes, a unique code will be developed by EviCore. No separate registration or notification process is required on the part of the laboratory.

Obtaining a unique test identifier

When a medical necessity review is performed for a test that will be billed under a non-specific procedure code, billing instructions will include the appropriate unique test identifier if required in the determination communication.

If a medical necessity review is not performed for a test that will be billed under a non-specific procedure code, a unique test identifier can be obtained by contacting EviCore through the phone number provided by the health plan. However, most non-specific procedure codes require medical necessity determination. If pre-service

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medical necessity determination is required and not obtained, that requirement will take precedence over any other billing requirements.

Billing tests using non-specific procedure codes

When a unique test identifier is provided in the medical necessity determination communication, it must be included on the claim regardless of medical necessity review requirements or determination outcome. Enter the unique test identifier in one of the following narrative fields based on the type of claim being submitted:

Claim type	Electronic claim	Paper claim
Professional	837P: Enter in the 2400 SV101-7 field (Line Item Description) associated with the non-specific CPT code. Each non-specific CPT code should have a unique identifier in the associated field.	CMS-1500: Enter in box 24 in the shaded line above the service line that contains the non-specific CPT code. Each non-specific CPT code should have a unique identifier entered above it. Each test identifier should have the qualifier "ZZ" appended at the beginning (e.g., ZZBRAF) to assist in recognition of the code.
Institutional	837I: Enter in the 2400 SV202-7 field (Line Item Description) associated with the non-specific CPT code. Each non-specific CPT code should have a unique identifier in the associated field.	UB-04: Enter in box 80 (Remarks). Only a single non-specific CPT code should be billed per claim form due to the limitations of a single descriptive field. The test identifier should have the qualifier "ZZ" appended at the beginning (e.g., ZZBRAF) to assist in recognition of the code.

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Glossary

Term	Definition
adenoma	An ordinarily benign neoplasm of epithelial tissue. If an adenoma becomes cancerous, it is known as an adenocarcinoma.
adenomatous polyposis coli	Adenomatous polyposis coli (APC) is a gene located on chromosome 5q. Inherited APC gene mutations are associated with Familial Adenomatous Polyposis (FAP) and Attenuated FAP. Most colorectal cancer polyps have mutations in both copies of the APC gene, even in people that don't have FAP.
adjuvant therapy	When discussing cancer treatment, adjuvant therapy is given after a primary treatment (like surgery) to increase the chances of a cure. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, or biological therapy.
adverse drug reaction	A harmful or unpleasant reaction to a drug that generally means the drug should be prescribed differently or avoided.
aerobic exercise	Any physical activity that causes the heart to pump faster and harder and breathing to quicken. Strengthens the heart muscle and may also help lower high blood pressure and increase good cholesterol.
AFAP	Attenuated FAP (AFAP) is a form of FAP characterized by a less dramatic proliferation of polyps (between 20-99 cumulative polyps) and age of onset for colorectal cancer of approximately 50 years. Polyps generally localize to the proximal (right-sided) colon. The American Gastroenterological Association (AGA) recommends genetic testing once a person has developed 20 or more cumulative polyps.
AFP	Short for "alpha-fetoprotein", a substance found in pregnant women's blood. High levels of AFP are associated with risk for spina bifida and abdominal wall defects.
amniotic fluid	The protective fluid that surrounds the developing baby. This fluid fills the amniotic sac, or "bag of water" inside the mother's uterus.

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Term	Definition
ancestry	Can be represented by a family tree showing how biological family members are related to each other. It is sometimes used interchangeably with "lineage."
anemia	A condition caused by too little oxygen in the blood, usually caused by too little hemoglobin or too few red blood cells
angina	Pain, pressure, or a feeling of indigestion in the chest caused by too little oxygen-rich blood reaching the heart. Usually caused by coronary artery disease.
anticipation	A way certain genetic diseases are inherited that causes them to get worse over the generations.
anticoagulant	Medications that prevent the blood from clotting -- often call "blood thinners."
anticonvulsant drug	Medications used to prevent or treat seizures. Common anticonvulsant drugs include Dilantin, Zarontin, Klonopin, Valium, Tegretol, Depakote and others.
antidepressant	A medication used to prevent or treat depression. Current antidepressants categories include SSRIs, MAOIs, tricyclics, tetracyclics, and others.
antipsychotic	Medications used to treat schizophrenia, schizoaffective disorder, bipolar disorder and other conditions that distort a person's grasp of reality
antiretroviral	A medication used to treat a retrovirus infection, such as HIV
APOB	A gene for the protein that normally helps deliver LDL cholesterol to the liver to be broken down. An APOB gene mutation causes a person not to clear LDL from the body as well as usual and it builds up. APOB mutations are one cause of familial hypercholesterolemia, although LDLR mutations are the most common.
Apolipoprotein B100	ApoB100 is short for apolipoprotein B100. It is a normal protein that is a major part of "bad" cholesterol. High ApoB100 is a strong risk factor for heart disease.

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Term	Definition
aromatase inhibitor	A class of drugs used to treat postmenopausal women who have hormone-dependent breast cancer. AIs work by blocking the enzyme aromatase responsible for converting androgen to estrogen. This limits the amount of estrogen available to promote breast cancer growth.
arrhythmia	Any variation from the normal heart rate or rhythm. The heart might beat faster than usual (tachycardia), slower than usual (bradycardia), or with an unusual pattern.
artery	Blood vessels that carry oxygen-rich blood throughout the body. The coronary arteries carry blood to the heart muscle.
Ashkenazi Jewish	Jewish people whose ancestors are from Eastern Europe -- mostly Germany, Poland, Russia, and some parts of France. Whereas Sephardic Jewish people have ancestry from Spain, Portugal, parts of France, Italy, North Africa, and the Middle East. Most American Jews are Ashkenazi.
atherosclerosis	A disease caused by plaque buildup inside the arteries that limits blood flow. Also called hardening of the arteries.
autosomal dominant	A pattern of inheritance where only one gene from a pair isn't working properly and causes the condition. Anyone with an autosomal dominant condition has a 50% chance of passing on the nonworking gene -- and, therefore, the condition -- to each child.
autosomal recessive	Describes a pattern of inheritance where both genes from a pair must be working abnormally to cause the condition. People with one abnormal and one normally working gene don't have the condition and are called carriers. When both parents are unaffected carriers of a condition, there is a 25% chance to have an affected child with each pregnancy.
average woman	The "average woman" is someone picked at random from the general public.
Beta-thalassemia	An inherited blood disorder that causes anemia, which is a shortage of red blood cells. This disorder causes lower than usual amounts of oxygen in the blood.
b-hCG	Short for "beta-human chorionic gonadotropin", this substance is known as the pregnancy hormone. It is produced by the placenta.

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Term	Definition
biopsy	The process of removing tissue from living patients for diagnostic evaluation.
black box warning	A warning required by the U.S. Food and Drug Administration (FDA) on the package inserts of some prescription drugs. These are the strongest warnings from the FDA about a significant risk for serious or life-threatening complications of a drug. Black box refers to the heavy black line surrounding the warning.
blood clot	Proteins change liquid blood into a solid blood clot usually in response to an injury to prevent further blood loss. Imbalance in the clotting proteins can lead to too little or too much clotting (thrombosis). When an abnormal clot forms, it can block blood flow and cause tissue damage or death.
blood clotting factor	Proteins and enzymes in the blood that control changing liquid blood into a solid blood clot. Imbalance of these factors can cause too little or too much clotting.
blood transfusion	Transferring blood or components of blood, such as blood plasma, into a patient.
blood vessel	The channels that carry blood throughout the body: arteries, veins and capillaries
bone marrow transplant	A procedure that replaces diseased or damaged bone marrow with healthy bone marrow. The damaged bone marrow may be destroyed by chemotherapy or radiation. The healthy bone marrow can come from the patient or a donor.
bowel preparation	Purging and cleansing of the bowel of fecal and other matter to assure clear evaluation of the bowel.
BRCA1	A gene located on chromosome 17 that normally produces a protein to help restrain cell growth. A harmful change in BRCA1 may predispose a person toward developing breast and/or ovarian cancer.
BRCA2	A gene located on chromosome 13 that normally produces a protein to help to restrain cell growth. A harmful change in BRCA2 may predispose a person toward developing breast and/or ovarian cancer.

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Term	Definition
breast MRI	MRI uses powerful magnets and radio waves to create detailed pictures of the breast and surrounding tissues. It provides clear pictures of parts of the breast that are difficult to see clearly on ultrasound or mammogram, but it's not a replacement for mammography.
cancer	A disease where abnormal cells grow and divide without control. Cancer cells can invade nearby tissues and spread through the bloodstream and lymphatic system to other parts of the body (called metastasis).
carbohydrate	Carbohydrates are the most abundant nutrients we eat and are broken down by the liver into glucose (sugar) to provide energy.
carcinoma	A cancer that begins in the skin or tissues that line or cover internal organs.
cardiomyopathy	A heart muscle disease that usually leads to a weakened heart muscle and a reduced ability to pump blood effectively. Any damage to the heart muscle can cause cardiomyopathy. Recognized causes include genetic factors, heart attack, alcoholism, and certain viral infections.
carrier	A person who has one copy of a changed gene and one normal copy of that gene.
CBC	An abbreviation for "complete blood count". A standard test that provides information including the white blood cell count, red blood cell count, amount of hemoglobin, platelet count and more.
CCR5-tropic	A form of HIV virus that uses a protein on the outside of a cell, called the CCR5 receptor, to enter and infect the cell.
CD4 cells	A kind of white blood cell, also called "helper T cells", which help protect the body against infection. These are the cells that the HIV virus infects.
cell	The basic building block of the tissues and organs in the body. Most cells have a complete copy of our genetic code and all cells are made by copying existing cells.
chelation therapy	Treatment to remove iron from the body using a chemical that attaches to heavy metals inside the body to remove them.

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Term	Definition
chemoprevention	The administration of any chemical or drug to treat a disease or condition and limit its further progress, or to prevent the condition from ever occurring.
cholesterol	A waxy, fat-like substance used by the body to make hormones, vitamin D, and other important substances. Eating too much cholesterol increases the risk of heart disease.
chromosome	A threadlike strand of DNA that carries genes and transmits hereditary information. Each chromosome can contain hundreds or thousands of individual genes. The number of chromosomes in the normal human cell is 46 (23 pairs).
chromosome translocation	A genetic condition where material from one chromosome breaks off and sticks to another chromosome, or switches places with a part of another chromosome. There are different types of translocations, and they can have different effects on health and development.
CHRPE	Congenital Hypertrophy of Retinal Pigmented Epithelium - a benign eye abnormality common in those with FAP.
close relative	A close relative is defined as a mother, father, sister, brother or child.
colectomy	The surgical removal of the colon. A total colectomy is the surgical removal of the colon and rectum. A subtotal colectomy is the surgical removal of the colon or portions of the colon only (not rectum).
colon	Another name for the large intestine; the section of the large intestine extending from the cecum to the rectum. An adult colon is approximately five to six feet in length and is responsible for absorbing water and forming, storing, and expelling waste.
colonoscopy	A procedure that examines the entire rectum and colon. A colonoscope is a long, flexible, lighted tube with a tiny lens on the end used to directly examine the whole colon and look for the presence of growths. Colonoscopy is the most effective way to evaluate the inside of your entire colon for the presence of colorectal cancer or polyps. This procedure is considered "invasive," because it requires sedation and the insertion of the colonoscope through the rectum.

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Term	Definition
colorectal cancer	Cancer that occurs in the rectum or the colon.
Comprehensive Analysis	Comprehensive Analysis is the most complete BRCA test. It looks at all the coding DNA of the BRCA1 and BRCA2 genes, to see if there are any changes or mutations. It can find: changes that are known to cause cancer, changes that are harmless, and changes whose link to cancer is unknown.
congenital heart defect	A problem with the structure of the heart, or the vessels connected to it, which is present from birth. Many types of heart defects exist. They can affect how the blood flows through the heart, or its rhythm.
corneal arcus	Also called "arcus cornealis". An accumulation of cholesterol around the cornea (the clear front surface of the eye) that causes a grey ring around the colored part of the eye. May be a normal feature of aging, but may also be a sign of unusually high cholesterol levels.
CXCR4-tropic	A form of HIV virus that uses a protein on the outside of a cell, called the CXCR4 receptor, to enter and infect the cell.
CYP1A2	An enzyme involved in the metabolism of many drugs, including caffeine. Some people have a form of CYP1A2 that is particularly susceptible to tobacco smoke and may have adverse reactions when taking drugs metabolized by CYP1A2 while smoking.
CYP2C19	An enzyme involved in the metabolism of many drugs, including several ulcer and reflux drugs. Variants in the gene can cause adverse reactions to drugs metabolized by CYP2C19.
CYP2C9	An enzyme involved in the metabolism of many drugs, including warfarin and celecoxib. and several anti-inflammatories. Variants in the gene can cause adverse reactions to drugs metabolized by CYP2C9.
CYP2D6	An enzyme involved in the metabolism of many drugs, including codeine, tamoxifen, and several antidepressants. Variants in the gene can cause adverse reactions to drugs metabolized by CYP2D6.

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Term	Definition
cytochrome P450	Cytochrome P450, abbreviated CYP450, is a large family of drug metabolizing enzymes, including CYP1A2, CYP2C9, CYP2C19, and CYP2D6.
de novo mutation	A mutation that is not running in the family yet, but occurs when a gene is damaged at conception. A de novo mutation can also then be passed on to one's children.
Desmoid tumor	Fibrous growth identified generally in the abdominal area associated with FAP and AFAP.
detection rate	Also called "sensitivity". Refers to the likelihood that a test will actually find the condition that it is looking for. If a test has a 90% detection rate, it will find 90% (9 out of 10) of people with the condition. Most tests don't have a 100% detection rate, so you should pay attention to detection rates to understand the limitations of any test you consider.
diabetes	A disease that causes you to have too much glucose (sugar) in your blood because of a problem with the hormone insulin. People with diabetes either can't make insulin (type I) or they can't use it well enough (type II).
DNA	Stands for "deoxyribonucleic acid". The chemical inside the nucleus of the cell that encodes the genetic instructions passed from generation to generation. Genes are made of DNA.
DNA replication	The duplication process of genetic material.
drug interaction	When a drug reacts with another drug (prescribed, over-the-counter, herbs, supplements, etc.), food, or other environmental exposure to cause an altered response. The effect may be an increased or decreased response or an adverse drug reaction.
environment	When talking about what causes disease, environment refers to basically everything that isn't controlled by genetics. Environment can include what we eat, physical activity, medications we take, chemicals we are exposed to, our physical surroundings, and countless other factors.

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Term	Definition
enzyme	A protein made by the body that encourages a biochemical reaction. Humans make hundreds of different enzymes from the instructions in our genes. If any one enzyme isn't working normally, it can cause a disease.
epithelium	Membranous tissue constructed of one or more layers of cells that cover the internal and external surfaces of the body and its organs.
ethnic background	The geographical and racial identity of a person's ancestors
ethnic group	A group of people whose ancestors lived in the same region of the world, and thus, who share a common genetic background
ethnicity	A group of people who frequently share some common ancestry and are, therefore, more likely to share certain genetic traits or mutations. May be based on descending from the same geographical location, a shared religion, a tribal connection, or other cultural practices. People often belong to more than one ethnic group.
extensive metabolizer	Extensive metabolizers have two "normal" drug metabolism genes. They make the average amount of enzyme and usually have normal drug response. Most people are extensive metabolizers. People have many drug metabolism genes and can be different kinds of metabolizers for each.
false negative	A test result that is read as negative when the disease is present.
false positive	A test result that is read as positive when the disease is not present.
familial adenomatous polyposis	Familial Adenomatous Polyposis (FAP) is an inherited condition that causes the formation of hundreds to thousands of precancerous polyps within the colon, often before age 20. FAP is usually caused by an inherited mutation in one copy of the APC gene.
familial hypercholesterolemia	An inherited condition that causes people to have very high levels of LDL, or "bad", cholesterol and a high risk for heart disease if not aggressively treated with cholesterol-lowering drugs.

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Term	Definition
family history	Family history may refer to whether or not you have any biological relative with a specific condition. It may also refer to the collective medical histories of all of your biological relatives. An accurate family history is one of the most important tools available to predict and prevent conditions that you may be at risk for.
FDA	U.S. Food and Drug Administration, a department of the federal government, that regulates drugs, foods, some tests, medical devices, and other things that may impact public health and safety.
fecal immunochemical test	Fecal immunochemical test (FIT) is a test, similar to FOBT, to check for hidden blood in the stool. Blood may signal cancer or one of many non-cancer related causes of bleeding.
fecal occult blood test	Fecal occult blood test (FOBT) is a test to check for hidden blood in the stool. The presence of blood in stool may be a sign of cancer or one of the many non-cancer related causes of bleeding (e.g. hemorrhoids).
fibrate	A group of drugs that work to lower your "bad" (LDL) cholesterol by reducing your triglycerides (another type of fat) and raising your "good" (HDL) cholesterol. Commonly prescribed fibrates include fenofibrate (brand name examples include: Antara, Fenoglide, Lipofen, Lofibra, TriCor, Triglide, and Lipidil) and gemfibrozil (brand name: Lopid).
flexible sigmoidoscopy	Procedure used to examine the rectum and lower third of the colon. A sigmoidoscope is a long, flexible, slender tube with a lens on the end used to visualize a portion of the colon to look for the presence of growths.
functional	Functional refers to genes or proteins that are not affected by genetic changes that disrupt their normal structure or behavior.
gastrointestinal tract	The digestive system, consisting of the esophagus, stomach, small intestine and large intestine.
gene	A piece of DNA that acts as an instruction to the body for how to make a specific protein (enzyme, hormone, etc.). Genes are inherited, passed from parent to child.
gene sequencing	A genetic test that is considered the gold standard for finding genetic changes known as mutations.

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Term	Definition
genetic	Refers to any trait that is inherited, or passed from generation to generation through genes. These traits may range from having specific diseases to our response to certain drugs to simply our physical characteristics, like eye and hair color.
genetic condition	A genetic condition is any disease, disorder, syndrome, or trait that is caused, at least in part, from alterations in genes or chromosomes.
genetic counseling	Genetic counseling is a process to help people learn about, cope with, and manage their risk of genetic disorders. This risk may be uncovered because the person is diagnosed with a condition, has a family history, has an affected child, and/or has an abnormal genetic test result.
genetic counselor	A healthcare professional with specialized training in how the science of genetics relates to medical care. A genetic counselor can evaluate your personal and family history, identify any risk factors for birth defects or genetic conditions, and help you understand and make decisions about testing or other options you may have.
genetic discrimination	Treatment or consideration based on genetic status or category rather than individual merit or actual conditions.
genetic modifier	A gene that changes how another gene is expressed.
genetic predisposition	Any condition in which genetic make-up leaves the individual more susceptible to disease.
genetic test	A specific type of laboratory test that is designed to find out if a person has a genetic disorder, is a carrier of a genetic disease, or has a predisposition to develop a genetic problem. Genetic testing can look at chromosomes, genes, or proteins -- depending on the specific condition being tested.
genomics	The study of the genome and its significance to pathology and disease.
genotype	The version of genes a person, organism, or cancer has.
genotyping	Tests that look specifically at the genetic information of a person, organism, or cancer. These tests may predict a certain characteristic ("phenotype") but don't actually test for that characteristic.

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Term	Definition
glucose	A form of sugar made from carbohydrates we eat that the body uses for energy. Too much glucose in their blood may be a sign of diabetes.
HBB	A gene involved in making a piece of a protein called hemoglobin. Genetic changes, or mutations, in the HBB gene can cause sickle cell disease and beta-thalassemia.
HDL	High density lipoprotein cholesterol. Also called the "good" cholesterol. High HDL lowers the risk for heart disease.
HDL2	A subtype of HDL (the "good" cholesterol). HDL2 is the "best" cholesterol because high levels give you the most protection against heart disease -- even more than just high total HDL.
HDL3	A subtype of HDL (the "good" cholesterol). HDL3 is not as good for you as other types of HDL. Some studies show that high levels of HDL3 may actually increase your risk for heart disease.
heart	A muscular organ whose primary job is to pump blood to all parts of the body.
heart attack	When the blood supply to part of the heart muscle is suddenly blocked. The heart muscle may be damaged or start to die if blood doesn't return quickly.
heart disease	A general term for any condition that threatens the heart's ability to function normally. Because coronary artery disease (plaque buildup that may cause a heart attack) is by far the most common type, it is often just called heart disease.
hemochromatosis	A condition in which too much iron builds up in the body, which can lead to organ damage.
hemoglobin	A protein found in red blood cells that carries oxygen throughout the body
hemoglobin analysis	A test that measures the different types of hemoglobin in the blood. It is used to diagnose diseases caused by abnormal hemoglobin, such as sickle cell anemia.
hereditary	Genetically transmitted -- or capable of being transmitted -- from parent to child.

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Term	Definition
hereditary nonpolyposis colorectal cancer	Hereditary non-polyposis colorectal cancer (HNPCC) is an inherited disorder in which there is a tendency to develop colorectal cancer without a significant number of polyp precursors. HNPCC is specifically associated with inherited mutations in five mismatch repair genes.
HFE gene	The HFE gene makes a protein that regulates how much iron your body absorbs from your diet.
high performance liquid chromatography	A laboratory procedure that can separate a liquid mixture into its individual compounds. As an example, this procedure is used is to separate different kinds of hemoglobins in a person's blood.
HNPCC-related cancer	Other primary cancers included in an inherited cancer syndrome because of the increased prevalence in syndrome carriers. In addition to colon cancer, HNPCC-related cancers include cancer of the endometrium, ovary, stomach, kidney/ urinary tract, brain, biliary tract, central nervous system and small bowel.
hormone	Chemical messengers made mostly in our glands that influence our growth and development, sexual function, reproduction, mood, and metabolism. Hormone medications include oral contraceptive pills, patches or rings; hormonal treatments for infertility; hormone replacement therapy; or serum estrogen modifiers (sometimes taken to treat or prevent certain forms of cancer).
human immunodeficiency virus	A retrovirus that attacks the human immune system, thus affecting the body's ability to fight off the organisms that cause disease. HIV is the cause of acquired immune deficiency syndrome or AIDS.
hypertension	Blood pressure that stays at 140/90 mmHg or higher over a period of time. Average blood pressure is about 120/80 mmHg.
IDL	Intermediate density lipoprotein -- a type of "bad" cholesterol. High IDL increases the risk for heart disease even more than just high total LDL levels. IDL is under strong genetic control so close relatives of someone with high IDL should also consider testing.

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Term	Definition
in vitro fertilization	A laboratory procedure in which sperm fertilize eggs outside the body in a laboratory setting to facilitate pregnancy. The fertilized egg is then placed in the woman's uterus for implantation.
inherited	Any trait that is passed from generation to generation through our genes. These traits may range from having a specific disease to how we respond to certain drugs to simply our physical characteristics, like eye and hair color.
inhibin A	A substance made by the placenta during pregnancy and found in the mother's blood. Also abbreviated "DIA."
insulin	A hormone that helps glucose, the sugar used by the body for energy, get into the cells that need it. When you don't make enough insulin or you can't use insulin effectively, you are likely to develop diabetes.
intermediate metabolizer	Intermediate metabolizers have a drug metabolism gene that doesn't work properly. They make less of the enzyme coded for by those genes, but usually make enough to process most drugs. People have many drug metabolism genes and can have be different kinds of metabolizers for each.
iron overload	A condition in which higher-than-usual amounts of iron collect in the tissues of the body. Over time, iron overload can damage organs like the liver and cause problems like diabetes.
K-RAS	A gene that when mutated contributes to converting a normal cell into a cancerous cell.
LDL	Low-density lipoprotein cholesterol. Also called the "bad" cholesterol. High LDL increases the risk of heart disease.
LDLR	Stands for low density lipoprotein receptor. The LDLR gene normally makes a protein that helps to remove LDL ((bad≈ cholesterol) from the blood. An LDLR gene mutation causes a person not to get rid of LDL as quickly and it builds up. LDLR mutations are the most common cause of familial hypercholesterolemia.
leukemia	A cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream.

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Term	Definition
lifestyle	In talking about health conditions, lifestyle generally refers to factors within your control like diet, physical activity, smoking, alcohol use, and use of other preventive health measures.
lipid	A fat that acts as a source of energy and helps the body use certain vitamins. Cholesterol and triglycerides are examples of lipids. High lipid levels increase the risk for heart disease and diabetes and may be caused by eating too much fat, alcohol use, inactivity, inherited conditions, and certain medications and disease.
lipoprotein a	Lp(a) stands for lipoprotein a -- a type of "bad" cholesterol. High Lp(a) increases the risk of heart disease 2 to 10 times more than just high total LDL levels and may cause heart disease earlier than usual. Drug therapy is usually needed. Lp(a) is under strong genetic control so close relatives of someone with high Lp(a) should also consider testing.
liver	An organ involved in a wide range of functions, including helping with digestion and the detoxification of chemicals.
liver biopsy	A surgical procedure that removes a small piece of liver so it can be examined in a lab.
lymphoma	Cancer that begins in the cells of the immune system.
maintenance dose	The amount of drug that is needed over the long-term to reach a stable, therapeutic response.
malignant	Cancerous. Malignant tumors, or cancer, have the ability to invade adjacent tissues and spread throughout the body. Thus, malignant tumors can become life threatening.
mammogram	An X-ray picture of the breast. The x-ray images make it possible to detect tumors that cannot be felt. They can also find microcalcifications that may signal the presence of cancer.
maraviroc	The generic name of Selzentry, a drug used to treat HIV infection that only works in people whose HIV uses a specific receptor (CCR5) to infect the cell.
maternal serum screening test	A blood test that looks at the levels of certain substances in a pregnant woman's blood. These tests are used to find the risk for having certain birth defects. They can't tell for sure whether a pregnancy has a birth defect.

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Term	Definition
MCH	An abbreviation for "mean corpuscular hemoglobin". The average amount of hemoglobin in the average red blood cell. The normal range for the MCH is 27 - 32 picograms. MCH is a standard part of a CBC (complete blood count) test.
MCV	An abbreviation for "mean corpuscular volume". The average size of a red blood cell. The normal range for the MVC is 80 - 100 femtoliters. MVC is a standard part of the CBC (complete blood count) test.
Mediterranean	Someone whose ancestors come from one of the countries bordering the Mediterranean Sea. These countries include but are not limited to: Spain, southern France, Italy, and Greece.
metabolic syndrome	Also called "insulin resistance". A combination of factors (like abnormal cholesterol, abdominal obesity, high blood sugar, and high blood pressure) that increases the risk of getting both heart disease and diabetes.
metabolism or metabolize	The way drugs and other substances are broken down for use in the body and elimination.
metastasis	The spread of cancer from one part of the body to another.
methylation	A process by which a methyl group is added to the DNA base cytosine. This process often decreases the amount of gene product that is made. For example, tumor suppressor genes are often methylated which decrease their function and lead to cancer.
mlh1	A mismatch repair (MMR) gene located on chromosome 3. Mutations in MLH1 are associated with Lynch syndrome (also called HNPCC) and greatly increase the chance of cancer -- especially colon.
MMR gene	Mismatch repair gene, a gene that functions as a part of the "spell check" system of a cell. Mutations in MMR genes are involved in causing some hereditary cancer syndromes.
morbidity	A diseased state.
MSH2	A mismatch repair (MMR) gene located on chromosome 2. Mutations in MLH1 are associated with Lynch syndrome (also called HNPCC) and greatly increase the chance of cancer -- especially colon.

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Term	Definition
multifactorial inheritance	Conditions that are caused by an interaction between more than one gene and environmental (non-genetic) factors. Most common human diseases seem to be multifactorial, including diabetes, heart disease, mental illness, and most birth defects. A family history of a multifactorial condition usually increases the risk for other relatives.
multiple myeloma	Cancer that begins in the cells of the immune system.
multisite	Multisite Testing looks for the three BRCA gene mutations that cause 80% to 90% of all hereditary breast and ovarian cancers in Ashkenazi Jewish people. This test gives you a clear result: either you have one of these three mutations, or you don't. If you don't, it is possible to have a different BRCA mutation that was not tested for.
mutation	A change in the DNA code that may cause a gene not to function in the normal way.
newborn screening	Testing that is done routinely after birth, to look for serious developmental, genetic and metabolic disorders. This testing is done so that important medical treatments or other actions can start before symptoms develop.
niacin	Also called "nicotinic acid". Part of vitamin B3 found in foods like meat, fish, milk, eggs, green vegetables, and grains. Niacin supplements increase HDL, lower Lp(a), and to a lesser degree, lower LDL cholesterol. Common brand names include: Niacor, Niaspan, Nicolar, Nicotinex Elixir, and Slo-Niacin.
non-invasive procedure	Procedures that do not require insertion of an instrument or device through the skin or a bodily orifice for diagnosis or treatment.
Noonan syndrome	A genetic disorder that causes abnormal development of many parts of the body. It can be caused by a defect in one of four different genes (KRAS, PTPN11, RAF1, SOS1). Noonan syndrome may be inherited from a parent who has the condition, or may happen by chance in a pregnancy.
obesity	Having a high amount of body fat. Usually defined by a body mass index (BMI) of 30 or higher.

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Term	Definition
omega 3-fatty acid	Also called "fish oil". Omega-3 fatty acids from eating oily fish or taking fish oil supplements may lower triglycerides, slow the buildup of plaque in the arteries, and raise HDL ("good") cholesterol. Too much omega-3 fatty acid is dangerous, so you should always talk to your doctor before starting supplements.
organs	A grouping of tissue that works together to perform a common function. Examples of organs include: stomach, lungs, and liver.
osteoma	Benign, bony tumors often on the skull or mandible (sometimes a clinical finding with FAP patients).
over-the-counter	OTC or over-the-counter drugs can be bought without a prescription. OTC drugs still carry certain risks and may interact with other drugs.
P-53	A gene which normally regulates the cell cycle and protects the cell from damage to its genome. Mutations in this gene cause cells to develop cancer.
PAPP-A	Short for "pregnancy-associated plasma protein A", a substance found in pregnant women's blood. Low levels of PAPP-A at 8-14 weeks of pregnancy have been associated with risk for Down syndrome and pregnancy complications.
pedigree	A diagram of biological relationships that usually includes information on each relative's medical history.
premenopausal	The time when a women is entering menopause until it is complete -- often defined as from the time periods become irregular until 12 months after the last period.
phenotype	Characteristics that can be seen or measured and are often the result of genes and environment working together. Examples include things like eye color, weight, IQ, cholesterol levels, or drug response.
phenotyping	Tests that measure specific traits or characteristics that can be caused by genes and/or environmental factors. This is in contrast to genotype testing that only looks at genetic information.

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Term	Definition
placebo	A phony treatment or "sugar pill". Researchers often compare people taking a drug with those taking a placebo to better measure the real effects of the drug.
placenta	Also called the afterbirth, the placenta is the tissue that connects the developing baby to the mother's uterus. It develops as part of the pregnancy and has the same DNA as the developing baby. The placenta allows for the exchange of nutrients, waste and gases between the developing baby and the mother.
plaque	Related to heart disease, plaque is the buildup of cholesterol, calcium, and other substances on the inside walls of the arteries causing the arteries to be more narrow and less flexible.
plasma	The liquid part of the blood that carries blood cells and other components
polymorphism	Natural differences in a DNA sequence that are usually common and do not cause disease
polyp	A usually non-cancerous growth or tumor protruding from the lining of an organ, such as the colon. Left untreated, polyps have an increased risk of becoming cancerous.
poor metabolizer	Produce inactive drug metabolism enzyme or no enzyme at all. Poor metabolizers may have a reduced response or no response and may have increased side effects
poor metabolizer	Poor metabolizers have a pair of drug metabolism genes that don't work properly. They make very little or none of the enzyme coded for by that pair of genes. This causes slower metabolism or the inability to process certain drugs. People have many drug metabolism genes and can be different kinds of metabolizers for each.
postmenopausal	The time in a woman's life after menopause is complete -- often defined as starting 12 months after the last period.
pre-cancerous	Condition of the tissue, such as a polyp, that can turn into a cancer if not treated or removed.

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Term	Definition
preconception	Generally considered the period of time when a person is planning pregnancy but has not yet conceived (become pregnant).
pre-diabetes	Diagnosed when glucose (sugar) levels are higher than normal, but not high enough to make the diagnosis of diabetes -- usually a fasting glucose of 100 to 125 mg/dL or a glucose of 140 to 199 mg/dL after glucose tolerance test.
predisposition	Any condition, genetic or other, that renders an individual more susceptible to disease.
preimplantation genetic diagnosis	A technique used with in vitro fertilization to test early-stage embryos for disease-causing genes, so that embryos without the disease-causing genes can be implanted in the mother's uterus.
prenatal diagnosis	Testing for diseases in the fetus or embryo before it is born.
presymptomatic	The stage prior to an individual presenting with symptoms that are clinically relevant to the disease in question.
prophylactic bilateral mastectomy	A risk-reducing treatment where both breasts, as well as some of the surrounding tissue, are surgically removed in order to keep cancerous cells from forming.
prophylactic bilateral oophorectomy	A risk-reducing treatment where ovaries are surgically removed in order to keep cancerous cells from forming; recommended after childbearing is complete.
protein	Large, complex molecules made of amino acids that form body structures, enzymes, hormones, and antibodies. Proteins are all made based on the instructions in our genes. The amino acids we need to make new proteins are consumed in the protein we eat or made by the body.
protein(s)	The molecules that form the body, allow it to grow, and regulate how it works. Our bodies make the proteins we need using the instructions from our genes.
receptor	A protein on the surface of a cell that only binds with certain other molecules. When this happens, a cellular process can occur.
rectum	The last portion of the digestive tract, at the end of the colon.

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Term	Definition
red blood cells	A cell in the blood that carries oxygen to all parts of the body. Also called an erythrocyte.
risk factor	Anything that increases the chance of developing a certain disease or having a child with a specific condition. Risk factors might include your family history, lifestyle, other health conditions, blood test results, age, gender, and countless other factors.
sarcoma	A cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissues.
screening	In medicine, screening generally refers to a test or exam that is reasonably simple, inexpensive, and harmless that can be given to a large group of people in order to find a smaller group with a higher-than-average chance for a certain condition. These people will sometimes have more specific testing or be treated early before symptoms appear.
selective estrogen receptor modulator	Selective Estrogen Receptor Modulator (SERM) is a hormone-like drug that affects multiple tissues by interacting with receptors for the hormone estrogen. A particular SERM may have estrogen-like effects in some tissues and anti-estrogen effects in others.
Selzentry	The brand name of maraviroc, a drug used to treat HIV infection that only works in people whose HIV uses a specific receptor (CCR5) to enter the cell.
sequencing	A lab method that looks at each DNA nucleotide (A,T,G, and C) in a piece of DNA for differences (mutations) from the usual DNA sequence. A more labor intensive and expensive test that is often used when the specific mutations that cause a disease aren't known.
serum CA-125	A blood test used in an effort to detect ovarian cancer.
serum ferritin	A protein your body makes when it stores iron.
siblings	Brothers and/or sisters.
sickle cell disease	An inherited disorder in which the red blood cells have an abnormal crescent shape that affects blood flow. This disorder causes anemia because the abnormal blood cells don't survive long.

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Term	Definition
sickle/beta-thalassemia	A disease that occurs when someone inherits a sickle-cell anemia gene mutation from one parent and a beta-thalassemia gene mutation from the other parent. Symptoms are usually very similar to sickle cell disease.
side effect	An unintended and usually undesired reaction to a drug or treatment.
Single Site	Single Site Testing looks for just one BRCA mutation. This test can only be done for people who know the DNA sequence of a BRCA mutation that is running in their family. This test gives you a clear result: Either you have the mutation that was tested for or you don't.
southeast Asian	Someone whose ancestors come from one of the countries south of China and east of India. These countries include but are not limited to: Vietnam, Cambodia, Laos, Burma, or Indonesia.
spleen	An organ in the abdomen that supports the immune system, destroys and filters out old blood cells, and holds a reserve of blood cells. People can live without a spleen.
sporadic	In reference to cancer, this means a cancer not caused by hereditary genetic mutations. Most cancers are sporadic.
statin	A group of drugs that lower the amount of cholesterol made naturally by the liver. When diet and exercise changes aren't enough, statins are often the first choice for drug therapy. Commonly prescribed statins include: Lovastatin (Mevacor, Altoprev), Pravastatin (Pravachol), Simvastatin (Zocor), Fluvastatin (Lescol), Atorvastatin (Lipitor), and Rosuvastatin (Crestor).
Stevens-Johnson syndrome	An allergic reaction to a drug or infection that causes flu-like symptoms, skin wounds, and may affect other organs like the eyes and mouth.
stroke	Caused by a sudden lack of blood supply and oxygen to the brain. Usually happens because either a blood clot blocks a blood vessel in the brain (ischemic stroke) or a blood vessel breaks and bleeds into the brain (hemorrhagic stroke).

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Term	Definition
symptom	Any sign that a person has a condition or disease. Symptoms, like headache, fever, fatigue, nausea, vomiting, and pain, may not be specific but together point to an underlying cause.
symptoms	Changes or signs that are caused by or accompany a disease or condition. Symptoms are the evidence of that underlying disease or condition. Symptoms can be used to help diagnose a problem.
tamoxifen	A drug commonly used to treat patients with breast cancer, certain other cancers, and those at high risk for breast cancer. It works by interfering with the activity of the hormone estrogen, which feeds the growth of many, but not all breast cancers.
toxic epidermal necrolysis	A life-threatening allergic reaction started by certain drugs, infections, illnesses, and unknown factors. TEN can cause large areas of the skin to peel away, flu-like symptoms, and other complications. The condition gets worse quickly and usually requires hospitalization.
transferrin saturation	The percentage of transferrin (a protein that carries iron in the blood) that is currently carrying iron.
translocation	A genetic condition where material from one chromosome breaks off and sticks to another chromosome, or switches places with a part of another chromosome. There are different types of translocations, and they can have different effects on health and development.
transvaginal ultrasound	A type of ultrasound done by inserting an ultrasound probe into the vagina. This allows a view of a woman's reproductive organs, including the uterus, ovaries, cervix, and vagina.
triglycerides	A type of energy-rich fat. High triglycerides (over 200mg/dL) increase the risk for heart disease and stroke.
tropism	The specific cell types that a virus can recognize and infect.
tumor	An abnormal mass of tissue that results from excessive cell division. Tumors may be benign (not cancerous) or malignant (cancerous).

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Term	Definition
Turner syndrome	A genetic condition in which a girl or woman does not have the usual pair of two X chromosomes. Instead, some or all of her cells are missing an X chromosome, or part of an X chromosome. Symptoms are variable but usually include short stature and infertility.
ultra metabolizer	Have more than two functional copies of a drug metabolism gene, and produce a larger-than-normal amount of enzyme. Ultra metabolizers may have a reduced or no response and may have increased side effects
ultrarapid metabolizer	Ultrarapid metabolizers have extra copies of a gene involved in drug metabolism, so they make more enzyme than the average person. This results in faster metabolism of drugs processed by that enzyme.
umbilical cord	The cord that connects the developing baby to the placenta, which is attached to the mother's uterus. The umbilical cord carries oxygen- and nutrient-rich blood to the developing baby.
unconjugated estriol	One of the three main estrogens produced by the body. Low levels of this substance are associated with risk for certain birth defects, including Down syndrome and trisomy 18. Also abbreviated "uE3."
variant	Gene variations contribute to diversity and make people unique. When a certain form of a gene is seen in at least 1% of people, but not most people, it is called a variant. Variants may also increase or decrease a person's risk for certain genetic diseases but usually don't cause the disease themselves.
vein	Blood vessels that carry blood low in oxygen back to the heart.
virtual colonoscopy	A method of examining the colon by taking a series of X-rays (called a CT scan) and using a high-powered computer to reconstruct 2-D and 3-D pictures of the interior surfaces of the colon from these X-rays.
VKORC1	A gene that tells the body how to make vitamin K epoxide reductase (VKOR), an enzyme important in forming blood-clotting factors. A common VKORC1 gene variant (-1639G>A) puts people at increased risk for complications when taking warfarin at standard doses.

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Term	Definition
VLDL	Very low density lipoprotein -- a type of "bad" cholesterol. High VLDL increases the risk for plaque buildup in the arteries and heart disease.
VLDL3	A subtype of VLDL (a "bad" cholesterol). High VLDL3 increases heart disease risk the most and is a risk factor even when total cholesterol levels are normal. Diet and exercise changes are very effective for lowering VLDL3.
warfarin	The most commonly prescribed drug for preventing harmful blood clots from forming or from growing larger. Belongs to a class of drugs called anticoagulants or "blood thinners."
white blood cells	A cell found in the blood whose primary job is to defend the body against infection.
xanthoma	Fat buildup that looks like a yellow lump under the skin, most commonly on the heels, hands, elbows, other joints, feet, and buttocks. Especially common in people with inherited high cholesterol like familial hypercholesterolemia.'

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