Investigational and Experimental Molecular and Genomic Testing

Introduction

Investigational and experimental (I&E) 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.

<table>
<thead>
<tr>
<th>Procedures address by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil (5-FU) Toxicity and Chemotherapeutic Response</td>
<td>81232 81346</td>
</tr>
<tr>
<td>Accelerate PhenoTest BC kit</td>
<td>0086U</td>
</tr>
<tr>
<td>AmHPR Helicobacter pylori Antibiotic Resistance Next Generation Sequencing Panel</td>
<td>0008U</td>
</tr>
<tr>
<td>Bacterial Typing by Whole Genome Sequencing</td>
<td>0010U</td>
</tr>
<tr>
<td>BBDRisk Dx</td>
<td>0067U</td>
</tr>
<tr>
<td>ChemoFX</td>
<td>81535 81536</td>
</tr>
<tr>
<td>DEPArray</td>
<td>0009U</td>
</tr>
<tr>
<td>ExosomeDx®Prostate(IntelliScore)</td>
<td>0005U</td>
</tr>
<tr>
<td>INFINITI Neural Response Panel</td>
<td>0078U</td>
</tr>
<tr>
<td>MatePair Acute Myeloid Leukemia</td>
<td>0056U</td>
</tr>
<tr>
<td>MatePair Targeted Rearrangements, Hematologic</td>
<td>0014U</td>
</tr>
<tr>
<td>MatePair Targeted Rearrangements, Oncology</td>
<td>0013U</td>
</tr>
<tr>
<td>miR-31now</td>
<td>0069U</td>
</tr>
<tr>
<td>Molecular Microscope MMDx—Heart</td>
<td>0087U</td>
</tr>
<tr>
<td>Molecular Microscope MMDx—Kidney</td>
<td>0088U</td>
</tr>
</tbody>
</table>
### What is I&E molecular and genomic testing

**Definition**

An investigational and experimental (I&E) 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. I&E molecular and genomic tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact.

**Investigational and experimental 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 I&E by the Health Plan are addressed by this guideline or a test-specific guideline and are not eligible for reimbursement.

**FDA clearance**

In the case of molecular and genomic testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. FDA clearance often does not assess clinical utility.

**Criteria**

**Introduction**

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

**Novel oncology molecular and genomic tests**

The following tests used in the screening, diagnosis, prognostication, and/or treatment decision-making for various neoplasms do not meet the above criteria and are not eligible for reimbursement.

**Gene Expression Assays**

- BluePrint Molecular Subtyping Profile [Proprietary 80-gene expression signature to classify Basal-type, Luminal-type and ERBB2-type breast cancers from Agendia]
• ColonSentry [Proprietary 7-gene signature to detect colorectal cancer from Innovative Diagnostic Laboratory]
• ColoPrint [Proprietary 18-gene signature to assess colon cancer recurrence risk from Agenda]
• DecisionDx - Cutaneous Melanoma assay [Proprietary 31-gene signature to assess melanoma metastatic risk from Castle Biosciences]
• Envisia Genomic Classifier [Proprietary gene expression assay designed to aid in the diagnosis of idiopathic pulmonary fibrosis from Veracyte]
• ExosomeDx® 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.]
• 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]
• 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 Myriad Genetics]
• OncoDefender - CRC [Proprietary gene expression assay to predict recurrence risk in early stage colorectal cancer within 3 years after surgery from Everist Genomics]
• 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]
• Percepta Bronchial Genomic Classifier [Proprietary gene expression assay designed to assess the risk of malignancy of lung nodules from Veracyte]
• Pervenio Lung NGS Test [Proprietary 25-gene expression assay for risk stratification of early stage NSCLC from Life Technologies]
• RNA-Sequencing by NGS [Oncology (solid organ neoplasia), mRNA, gene expression profiling by massively parallel sequencing for analysis of 51 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a normalized percentile rank from Life Technologies]

**Other Novel Assays**

• 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]
• ChemoFX [Proprietary test from Helomics to assess chemosensitivity] CPT 81535 and 81536
• 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]
• HERmark Breast Cancer Assay [Proprietary test designed to evaluate Her-2 total proteins in formalin-fixed, paraffin-embedded (FFPE) tissue specimens from LabCorp]
• Know error [Proprietary test for DNA based specimen provenance confirmation from Strand Diagnostics]
• MatePair Acute Myeloid Leukemia Panel [Hematology (acute myelogenous leukemia), DNA, whole genome next-generation sequencing to detect gene rearrangement(s), blood or bone marrow, report of specific gene rearrangement(s) by Mayo Clinic]
• MatePair Targeted Rearrangements, Oncology, [Oncology (solid organ neoplasia), gene rearrangement detection by whole genome next-generation sequencing, DNA, fresh or frozen tissue or cells, report of specific gene rearrangement(s) from Mayo Clinic]
• MatePair Targeted Rearrangements, Hematologic, [Hematology (hematolymphoid neoplasia), gene rearrangement detection by whole genome next generation sequencing, DNA, whole blood or bone marrow, report of specific gene rearrangement(s) from Mayo Clinic]
• mi-KIDNEY Cancer Test [Proprietary microRNA-based assay that differentiates 4 main histological types of primary kidney tumors from Rosetta Genomics]
• mi-LUNG Cancer Test [Proprietary microRNA-based assay that identifies four main subtypes of lung cancer from Rosetta Genomics]
• miRInform Pancreas Test [Proprietary score based on expression levels of seven microRNAs to differentiate pancreatic ductal adenocarcinoma from chronic pancreatitis from Asuragen]
• NADiA ProsVue [Proprietary nucleic acid detection immunoassay designed to determine the rate of change of serum total prostate specific antigen over time to predict prostate cancer recurrence risk from Iris Personalized Medicine]
• 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]
• PAULA [Proprietary panel of four proteins designed to detect lung cancer in asymptomatic individuals at high risk from Genesys Biolabs]
• Prostate Cancer Risk Panel [FISH analysis of 4 genes (ASAP1, HDAC9, CHD1 and PTEN), needle biopsy specimen, algorithm reported as probability of higher tumor grade from Mayo Clinic]

• Prostate Core Mitomic Test [Proprietary test using mitochondrial DNA to detect prostate cancer not identified by standard biopsy pathology from MDNA Life Sciences]

• ProstaVysion [Proprietary panel of two biomarkers designed to predict prostate cancer prognosis from Bostwick Laboratories]

• 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]

• ToxLok [Comparative DNA analysis using multiple selected single-nucleotide polymorphisms (SNPs), urine and buccal DNA, for specimen identity verification from InSource Diagnostics]

Cardiovascular molecular and genomic tests

The following tests used to predict cardiovascular disease and/or direct therapy do not meet the above criteria and are not eligible for reimbursement.

• 4q25-AF Risk Genotype Test (rs2200733 allele)

• 9p21 Genotype Test (rs10757278 and rs1333049 alleles)

• Apolipoprotein E Genotype (APOE)

• C-GAAP (Clopidogrel Genetic Absorption Activation Panel) [Proprietary test from Transgenomic Lab, includes ABCB1 and CYP2C19 gene variants]

• KIF6 Genotype Test

• LPA-Aspirin Genotype Test (4399Met allele)

• LPA-Intron 25 Genotype Test

• myTAIHEART

• PAI-1 Testing for Cardiovascular Disease Risk Assessment

• Statin Induced Myopathy Genotype (SLCO1B1)

Gene variant or marker risk assessment tests

The following tests that make use of inherited genomic information to assess disease risk, prognosis, or subtyping do not meet the above criteria and are not eligible for reimbursement.

• ARISk Autism Risk Assessment Test [Proprietary test from IntegraGen]
- BREVAGen [Proprietary sporadic breast cancer risk based on genetic markers from Phenogen Sciences]
- Cardiac DNA Insight [Proprietary test from Pathway Genomics that assesses genetic markers for cardiac-related conditions]
- Crohn's prognostic test [NOD2/CARD15 gene variant testing]
- IBD sgi Diagnostic [Proprietary test from Prometheus with genomic components including ATG16L1, STAT3, NKX2-3, and ECM1 gene variants.]
- LactoTYPE [Proprietary test from Prometheus that assesses the hypolactasia C/T genetic variant]
- Pathway Fit [Proprietary test from Pathway Genomics that focuses on metabolism, diet, and exercise traits]
- RetnaGene AMD [Proprietary test from Sequenom CMM to predict risk of wet AMD progression]
- Twin zygosity [genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood from Natera]

**Pharmacogenomic panels**

- 5-Fluorouracil (5-FU) Toxicity and Chemotherapeutic Response [Proprietary panel of DPYD and TYMS gene variants to assess risk of 5-fluorouracil toxicity from ARUP Laboratory]
- Genecept Assay [Proprietary panel of biomarker tests to predict response to different psychiatric treatments from Genomind]
- GeneSightRx ADHD [Proprietary test from AssureRx assessing three genes]
- GeneSightRx Analgesic [Proprietary test from AssureRx assessing two genes]
- GeneSightRx Psychotropic [Proprietary test from AssureRx assessing six genes]
- Mental Health DNA Insight [Proprietary test from Pathway Genomics]
- INFINITI® Neural Response Panel [Pain management (opioid-use disorder) genotyping panel, 16 common variants (ie, ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder from PersonalizeDx Labs, AutoGenomics Inc]
- OneOme RightMed, [Drug metabolism (adverse drug reactions), DNA, 22 drug metabolism and transporter genes, real-time PCR, blood or buccal swab, genotype and metabolizer status for therapeutic decision support from OneOme, LLC]
- Pain Medication DNA Insight [Proprietary test from Pathway Genomics]
Non-cancer gene expression assays

- Renal Transplant Monitoring (FOXP3, Granzyme B, Perforin, IP10) [Gene expression panel that is an indirect indicator of immune response designed to detect or monitor renal transplant rejection from Quest Diagnostics]
- VectraDA [Proprietary panel of 12 biomarkers that yields a rheumatoid arthritis disease activity score from Crescendo Bioscience]

Infectious disease assays

- AmHPR Helicobacter pylori Antibiotic Resistance Next Generation Sequencing Panel, [Helicobacter pylori detection and antibiotic resistance, DNA, 16S and 23S rRNA, gyrA, pbp1, rdxA and rpoB, next generation sequencing, formalin-fixed paraffin embedded or fresh tissue, predictive, reported as positive or negative for resistance to clarithromycin, fluoroquinolones, metronidazole, amoxicillin, tetracycline and rifabutin from American Molecular Laboratories, Inc.]
- Bacterial Typing by Whole Genome Sequencing, [Infectious disease (bacterial), strain typing by whole genome sequencing, phylogenetic-based report of strain relatedness, per submitted isolate from Mayo Clinic]
- PCR Fungal Screen for Onychomycosis [Proprietary PCR test to identify genus and species of fungus causing onychomycosis from Bako]
- SmartGut [Proprietary test designed to sequence the 16S rRNA gene to identify 33 species and 32 genera of the gastrointestinal (GI) microbiome related microorganisms, including 5 pathogenic organisms from uBiome]