Hereditary Connective Tissue Disorder Genetic Testing

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Introduction

Hereditary connective tissue disorder 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 disorder gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Hereditary connective tissue disorder known familial mutation analysis	81403

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Criteria

Introduction

Requests for hereditary connective tissue disorder genetic testing are reviewed using the following criteria.

Hereditary connective tissue disorder testing includes single genes as well as multi-gene panels, which are defined as assays that simultaneously test for more than one hereditary connective tissue disorder gene. Medical necessity determination generally relies on criteria established for testing individual genes.

Medical necessity criteria differ based on the type of testing being performed (i.e., individual hereditary connective tissue disorder genes separately chosen versus pre-defined panels of genes).

Hereditary Connective Tissue Disorder single gene tests are considered medically necessary when the following criteria are met:

- The member has or is suspected to have a condition that will benefit from information provided by the requested hereditary connective tissue disorder gene testing based on at least one of the following:
    - The member displays clinical features of the condition for which testing is being requested and a genetic diagnosis would result in changes to the member's medical management, OR
    - The member meets all criteria in a test-specific guideline, if available (see *table: Common hereditary connective tissue disorder 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.

Hereditary Connective Tissue Disorder multi-gene panels are considered medically necessary when the following criteria are met:

- Clinical documentation is provided stating that the member has, or is suspected to have, at least TWO conditions included in the panel, and medical necessity is established for these conditions based on the following:
    - The member displays clinical features of the condition for which testing is being requested, and a genetic diagnosis would result in changes to the member's medical management, OR
    - The member meets all criteria in a test-specific guideline, if available, (see table: *Common hereditary connective tissue disorder 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
- Clinical features are not sufficiently specific to suggest a single causative gene, 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.

Broad connective tissue disorder panels may not be medically necessary when a narrower panel is available and more appropriate based on the clinical findings.

Genetic testing is only medically necessary once per lifetime. Therefore, a single gene included in a panel or a multi-gene 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.

The following are not medically necessary indications for Hereditary Connective Tissue Disorder testing:

- Member's personal and/or family history are consistent with hypermobile EDS or the related clinical entity, "joint hypermobility syndrome"
- Isolated joint hypermobility, including both asymptomatic and symptomatic forms (e.g., “hypermobility spectrum disorders”)

Table: Common hereditary connective tissue disorder genes, associated conditions, and applicable guidelines

Condition, Gene, CPT, Applicable guideline

Condition	Gene	CPT	Applicable guideline
Arterial tortuosity syndrome	SLC2A10	81479	MOL.TS.268
Congenital contractural arachnodactyly	FBN2	81479	MOL.TS.268
Cutis laxa	ALDH18A1	81479	MOL.TS.268
	ATP6V0A2	81479	MOL.TS.268

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Condition	Gene	CPT	Applicable guideline
	EFEMP2	81479	MOL.TS.268
	ELN	81479	MOL.TS.268
	FBLN5	81479	MOL.TS.268
	LTBP4	81479	MOL.TS.268
	PYCR1	81479	MOL.TS.268
Ehlers-Danlos syndrome (EDS)	ADAMTS2	81479	MOL.TS.267
	B3GALT6	81479	MOL.TS.267
	B4GALT7	81479	MOL.TS.267
	C1R	81479	MOL.TS.267
	C1S	81479	MOL.TS.267
	CHST14	81479	MOL.TS.267
	COL1A1	81408	MOL.TS.267
	COL1A2	81408	MOL.TS.267
	COL12A1	81479	MOL.TS.267
	COL3A1	81479	MOL.TS.267
	COL5A1	81479	MOL.TS.267
	COL5A2	81479	MOL.TS.267
	DSE	81479	MOL.TS.267
	FKBP14	81479	MOL.TS.267
	PLOD1	81479	MOL.TS.267

Condition	Gene	CPT	Applicable guideline
	PRDM5	81479	MOL.TS.267
	SLC39A13	81479	MOL.TS.267
	TNXB	81479	MOL.TS.267
	AEBP1	81479	MOL.TS.267
	ZNF469	81479	MOL.TS.267
FLNA deficiency (periventricular nodular heterotopia)	FLNA	81479	MOL.TS.268
Homocystinuria (cystathionine beta-synthase deficiency)	CBS	81401 81406	MOL.TS.268
Juvenile polyposis/hereditary hemorrhagic telangiectasia	SMAD4	81406	MOL.TS.268
	SMAD4	81405	MOL.TS.268
Loeys-Dietz syndrome	SMAD3	81479	MOL.TS.268
	SMAD2	81479	MOL.TS.268
	TGFB2	81479	MOL.TS.268
	TGFB3	81479	MOL.TS.268
	TGFBR1	81405	MOL.TS.268
	TGFBR2	81405	MOL.TS.268
MED12-related disorders	MED12	81401 81479	MOL.TS.268
Marfan syndrome	FBN1	81408	MOL.TS.202
	TGFBR1	81405	MOL.TS.202

Condition	Gene	CPT	Applicable guideline
	TGFBR2	81405	MOL.TS.202
NOTCH1-related aortic valve disease/ Adams-Oliver syndrome	NOTCH1	81407	MOL.TS.268
Occipital horn syndrome/Menkes	ATP7A	81479	MOL.TS.268
Osteogenesis imperfecta	COL1A1	81408	MOL.TS.268
	COL1A2	81408	MOL.TS.268
Pseudoxanthoma elasticum	ABCC6	81479	MOL.TS.268
Shprintzen-Goldberg syndrome	SKI	81479	MOL.TS.268
Stickler syndrome	COL11A1	81479	MOL.TS.268
	COL11A2	81479	MOL.TS.268
	COL2A1	81479	MOL.TS.268
	COL9A1	81479	MOL.TS.268
	COL9A2	81479	MOL.TS.268
	COL9A3	81479	MOL.TS.268
Thoracic aortic aneurysm and dissection (TAAD)	ACTA2	81405	MOL.TS.227
	BGN	81479	MOL.TS.227
	COL3A1	81479	MOL.TS.227
	FBN1	81408	MOL.TS.227
	LOX	81479	MOL.TS.227

Condition	Gene	CPT	Applicable guideline
	MAT2A	81479	MOL.TS.227
	MFAP5	81479	MOL.TS.227
	MYH11	81408	MOL.TS.227
	MYLK	81479	MOL.TS.227
	PRKG1	81479	MOL.TS.227
	SMAD3	81479	MOL.TS.227
	TGFB2	81479	MOL.TS.227
	TGFB3	81479	MOL.TS.227
	TGFBR1	81405	MOL.TS.227
	TGFBR2	81405	MOL.TS.227

Note Several genes in this table are associated with multiple genetic disorders, including some not listed above. The test should be reviewed for the appropriate condition/indication.

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.
- Broad connective tissue disorder panels are not reimbursable when a narrower panel is available and more appropriate based on the clinical findings.

- 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 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.
    - Procedure codes representing multiple methods for deletion/duplication testing will not be reimbursable for the same panel. When deletion/duplication testing is not part of a single panel CPT code being billed, deletion/duplication testing is reimbursable in only one of the following ways:
        - A single CPT code specific to the performed deletion/duplication analysis panel (e.g. 81411, 81479), or
        - A single microarray procedure (e.g. 81228 or 81229)

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 connective tissue disorders?

Definition

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]

- While specific features vary by type, an unusually large range of joint movement (hypermobility) and cardiovascular disease (such as thoracic aortic aneurysms and dissections, or TAAD) are features that are present in many HCTDs. Medical management may differ based on the underlying genetic etiology.
- In many cases, a careful clinical examination by a specialist familiar with clinical features of these conditions can help to point toward one condition or group of conditions. In these cases, testing for gene(s) associated with a single condition or group of conditions would be most appropriate. However, in some cases, it can be difficult to reliably diagnose an HCTD based on clinical and family history alone.

- Although connective tissue disorders as a whole are common, individual hereditary connective tissue disorders are relatively uncommon.[1]
- There are more than 200 connective tissue disorders.[2] Some of the most common types are summarized below:

    - **Arterial tortuosity syndrome (ATS)** — An autosomal recessive disorder associated with severe and widespread tortuosity of the aorta and middle-sized arteries, with an increased risk of aneurysms and dissections. Other features include stenosis of the aorta and/or pulmonary arteries, characteristic facies with high palate and dental crowding, and soft/doughy skin. Additional connective tissue disorder features that may be present include skeletal findings (scoliosis, pectus anomalies, joint laxity), hernias, hypotonia, and ocular involvement (myopia, keratoconus). SLC2A10 is the only gene known to be associated with ATS. Sequence variants are the most common; exon deletions have been reported in a couple cases.[3]
    - **Congenital contractural arachnodactyly (CCA) (Beals syndrome)** — An autosomal dominant disorder characterized by a Marfan-like appearance (tall, slender habitus in which arm span exceeds height) and long, slender fingers and toes (arachnodactyly). Most affected individuals have a “crumpled” appearance to their ears and most have contractures of major joints (knees and ankles) at birth. Hip contractures, adducted thumbs, and club foot may occur. The majority of affected individuals have muscular hypoplasia. Kyphosis/scoliosis is present in about half of all affected individuals. Dilatation of the aorta is occasionally present. FBN2 is the only gene in which pathogenic variants are known to cause congenital contractural arachnodactyly, "however, locus heterogeneity is likely given that only 25%-75% of individuals with clinically diagnosed CCA have an identifiable FBN2 pathogenic variant."[4]
    - **Cutis laxa** — A group of disorders characterized by lax, sagging skin that often hangs in loose folds, causing the face and other parts of the body to have a droopy appearance. Extremely wrinkled skin may be particularly noticeable on the neck and in the armpits and groin. Other features may include arterial aneurysm and dissection, emphysema, and inguinal or umbilical hernia. There are autosomal dominant, autosomal recessive, and X-linked forms. Causative autosomal genes include ELN, FBLN5, ATP6V0A2, EFEMP2, ALDH18A1, PYCR1, and LTBP4.[5,6] The X-linked form is due to mutations in ATP7A (see also Occipital Horn Syndrome).[5]
    - **Ehlers Danlos syndromes (EDS)** — A heterogeneous group of disorders, the majority of which share the features of joint hypermobility and skin involvement. There are 13 types: classical, classical-like, cardiac-valvular, vascular, hypermobile (includes “joint hypermobility syndrome”), arthrochalasia, dermatosparaxis, kyphoscoliotic, spondylodysplastic, musculocontractural, myopathic, periodontal, and brittle cornea syndrome. Some types have autosomal dominant inheritance, while others are autosomal recessive. Hypermobile type is the most common, but its genetic etiology is currently unknown. Genetic testing is available for the other EDS types (see Table:

Common hereditary connective tissue disorder genes, associated conditions, and applicable guidelines for a list of genes).[7,8]

- **Homocystinuria due to cystathionine beta-synthase deficiency** — An autosomal recessive metabolic disorder in which affected individuals have markedly elevated plasma total homocysteine and methionine. Clinical features include involvement of the eye (ectopia lentis and/or severe myopia), skeletal system (excessive height, long limbs, scoliosis, and pectus excavatum), and vascular system (thromboembolism). Many have developmental delay/intellectual disability. Treatment involves maintenance of normal or near-normal plasma homocysteine concentrations using a specialized diet and vitamin supplementation. The diagnosis can be substantiated by detection of biallelic pathogenic mutations in the CBS gene. Sequence analysis detects 95-98% of mutations, while deletion/duplication analysis detects <5%.[9]
- **Loeys-Dietz syndrome (LDS)** — LDS is an autosomal dominant disorder that affects many parts of the body.[10] LDS is caused by mutations in six genes: TGFBR2 (55-60%), TGFBR1 (20-25%), SMAD3 (5-10%), TGFB2 (5-10%), TGFB3 (1-5%), or SMAD2 (1-5%). Major manifestations of this condition include "vascular findings (cerebral, thoracic, and abdominal arterial aneurysms and/or dissections), skeletal manifestations (pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus, cervical spine malformation and/or instability), craniofacial features (widely spaced eyes, strabismus, bifid uvula / cleft palate, and craniosynostosis that can involve any sutures), and cutaneous findings (velvety and translucent skin, easy bruising, and dystrophic scars)."[10] Given that there is no clinical diagnostic criteria established for LDS, genetic testing, either through serial single-gene testing or use of a multigene panel, can establish the diagnosis.[10]
- **Marfan syndrome (MFS)** — MFS is an autosomal dominant disorder that affects connective tissue in many parts of the body.[11] MFS is caused by mutations in the FBN1 gene. Up to 93% of people meeting diagnostic criteria for MFS will have a mutation in this gene. Diagnostic criteria, called the Ghent criteria, exist for MFS. Major manifestations of the disease include aortic enlargement and ectopia lentis. Other features include, but are not limited to, bone overgrowth and joint laxity, long arms and legs, scoliosis, sternum deformity (pectus excavatum or carinatum), long thin fingers and toes, dural ectasia (stretching of the dural sac), hernias, stretch marks on the skin, and lung bullae. Symptoms can present in males or females at any age. Symptoms typically worsen over time. Infants who present with symptoms typically have the most severe disease course.[11]
- **NOTCH1-related aortic valve disease** — NOTCH1 variants can be associated with autosomal dominant congenital heart defects affecting the left ventricular outflow tract (LVOT), most commonly bicuspid aortic valve (BAV). Adult-onset aortic valve calcification is a frequent feature. NOTCH1 variants have also been identified in 4-10% of individuals with sporadic BAV and much less frequently with other LVOT malformations. Mutations in this gene are also associated with

Adams-Oliver syndrome, which is characterized by aplasia cutis congenita of the scalp and malformations of the limbs, brain, and cardiovascular system.[12]

- **Osteogenesis imperfecta (OI)** — A group of disorders associated with a propensity to fractures with little or no trauma. Additional features may include skeletal anomalies, short stature, hearing loss, and blue/gray sclera. The severity is highly variable, ranging from a mild form with few fractures and normal life expectancy, to severe forms with neonatal lethality. OI types I-IV account for the majority of cases, and are caused by heterozygous mutations in the COL1A1 and COL1A2 genes. Inheritance is autosomal dominant. Autosomal recessive forms of OI are rare, and can be associated with mutations in a number of different genes.[13]
- **FLNA Deficiency** — FLNA deficiency is associated with a phenotypic spectrum that includes FLNA-related periventricular nodular heterotopia (PVNH). FLNA deficiency is an X-linked condition that is prenatally or neonatally lethal in most males. Therefore, most affected individuals are female. In addition to PVNH, some individuals have connective tissue anomalies such as joint hypermobility, aortic dilation, and other vascular anomalies. 90% of individuals with FLNA-related PVNH have a sequence variant; about 10% of probands have a variant detected by deletion/duplication analysis.[14]
- **Stickler syndrome** — A disorder characterized by ocular findings (myopia, cataract and retinal detachment), hearing loss, craniofacial findings (midfacial underdevelopment and cleft palate), mild spondyloepiphyseal dysplasia and/or early-onset arthritis. Clinical diagnostic criteria are available. Greater than 90% of cases are due to mutations in COL2A1 or COL11A1. Mutations in these genes are inherited in an autosomal dominant pattern. Mutations in COL9A1, COL9A2, and COL9A3 are rare, and inherited in an autosomal recessive pattern.[15]
- **Thoracic Aortic Aneurysm and Dissection (TAAD)** — Familial TAAD is defined as dilatation and/or dissection of the thoracic aorta, absence of clinical features of MFS, LDS or vascular EDS, and a positive family history of TAAD. Approximately 30% of families with heritable thoracic aortic disease (HTAD) who do not have a clinical diagnosis of MFS or another syndrome have a causative mutation in one of 15 known HTAD-related genes (see the Table: Common hereditary connective tissue disorder genes, associated conditions, and applicable guidelines).[16]

Test information

Introduction

Testing for hereditary connective tissue disorders may include 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 of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Clinical genetic testing is available for many HCTDs. However, hypermobile EDS (hEDS), joint hypermobility syndrome, and isolated joint hypermobility, including "hypermobility spectrum disorders", continue to require a clinical diagnosis, since the genetic etiology of these disorders is not yet known.[8]

Guidelines and evidence

- No current U.S guidelines address the use of multi-gene panels in HCTDs.
- An expert-authored review (updated in 2024)[17] stated the following regarding hEDS: "No underlying genetic etiology has been identified for hEDS, and thus molecular genetic testing cannot be used to establish the diagnosis."
- According to the International Consortium on the Ehlers-Danlos Syndromes (2017):[8]
    - "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."

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 disorder 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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