Genetic testing: aortopathies and connective tissue disorders

These services may or may not be covered by your HealthPartners plan. Please see your plan documents for your specific coverage information. If there is a difference between this general information and your plan documents, your plan documents will be used to determine your coverage.

Administrative Process

Prior authorization is required for the following services:

- Genetic testing for Marfan Syndrome
- Genetic testing for Loeys-Dietz Syndrome
- Genetic testing for Familial Thoracic Aortic Aneurysm and Dissection (TAAD)
- Genetic testing for Ehlers Danlos Syndrome
- Connective Tissue Disorders Multi-Syndrome Panel
- Genetic testing for covered connective tissue disorders
- Testing that is associated with a procedure code listed in “Box A”, below.

Tests that require prior authorization will be reviewed for medical necessity of the testing as a whole. That is, a single coverage decision will apply to all of the tests, services, and/or procedure codes associated with the genetic test, whether they are requested/billed together or separately.

Box A: Genetic testing procedure codes that require prior authorization
Molecular pathology procedures, Tier 2 or unlisted (CPT 81400-81408, 81479)
Unlisted multianalyte assays (CPT 81599)
Any other listed or unlisted laboratory/pathology CPT code when it is used in association with a genetic test.

Policy Reference Table

If available, codes are listed below for informational purposes only, and do not guarantee member coverage or provider reimbursement. The list may not be all-inclusive.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes
Connective Tissue Disorders			
Comprehensive Connective Tissue Disorders Multigene Panel	Heritable Disorders of Connective Tissue Panel (GeneDx)	81410, 81411	I71.00-I71.9, M35.7, Q79.60, Q79.61, Q79.63, Q79.69, Q12.1, Q87.4, Q87.5
	Invitae Connective Tissue Disorders Panel (Invitae)		
Marfan Syndrome			
FBN1 Sequencing and/or Deletion/Duplication Analysis	*FBN1* Full Gene Sequencing and Deletion/Duplication (Invitae)	81408, 81479	I71.00-I71.9, Q12.1, Q87.40-Q87.43
	Marfan Syndrome via *FBN1* Gene (Prevention Genetics, part of Exact Sciences)		
Loeys-Dietz Syndrome			
Loeys-Dietz Syndrome Multigene Panel	Loeys-Dietz Syndrome Panel (Prevention Genetics, part of Exact Sciences)	81405, 81408, 81479	I71.00-I71.9
	Loeys-Dietz Syndrome Panel (Invitae)		
Familial Thoracic Aortic Aneurysm and Dissection (TAAD)			
Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel	Thoracic Aortic Aneurysm Panel (Cincinnati Children’s Hospital Medical Center- Molecular Genetics and Cytogenetics Laboratories)	81405, 81406, 81408, 81479	I71.00-I71.9, Q87.5

	TAAD Panel Next Generation Sequencing (DDC Clinic Laboratory)	81410, 81411	
	TAADNext (Ambry Genetics)		
	Marfan syndrome, Loeys-Dietz syndrome, Familial thoracic aortic aneurysms & dissections, and Related disorders NGS Panel - Comprehensive (CTGT)		
	Marfan Syndrome and Thoracic Aortic Aneurysm and Dissection NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics)		
	Marfan/TAAD Panel (GeneDx)		
	Aortopathy Comprehensive Panel (Invitae)		
Ehlers Danlos Syndrome			
Classic Ehlers-Danlos Syndrome (cEDS)			
Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel	Ehlers Danlos Panel (GeneDx)	81408, 81479	M35.7, Q79.61, Q79.63, Q79.69
	Ehlers-Danlos Syndrome Panel (Revvity)		
	Ehlers-Danlos syndrome, classic type NGS panel (CTGT)		
Vascular Ehlers-Danlos Syndrome (vEDS)			
COL3A1 Sequencing and/or Deletion/Duplication Analysis	*COL3A1* Full Gene Sequencing and Deletion/Duplication-Diagnostic (Invitae)	81479	Q79.63
Other Covered Connective Tissue Disorders			
Other Covered Connective Tissue Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408	

Coverage

Connective Tissue Disorders

Comprehensive Connective Tissue Disorders Multigene Panel*

1. Comprehensive connective tissue disorders multigene panel analysis is considered **medically necessary** when:
   - A. The member meets criteria for at least one of the following (see specific coverage criteria sections below):
     - i. Marfan Syndrome
     - ii. Loeys-Dietz Syndrome
     - iii. Classic Ehlers-Danlos Syndrome (cEDS)
     - iv. Vascular Ehlers-Danlos Syndrome (vEDS)
2. Comprehensive connective tissue disorders multigene panel analysis is considered investigational for all other indications, including isolated hypermobility and hypermobile Ehlers-Danlos syndrome (hEDS).

*If a panel is performed, the appropriate panel code should be used

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Marfan Syndrome

***FBN1* Sequencing and/or Deletion/Duplication Analysis**

1. *FBN1* sequencing and/or deletion/duplication analysis to confirm a diagnosis of Marfan syndrome is considered **medically necessary** when:
   - A. The member has one of the following:
     - i. Aortic root enlargement (Z-score 2.0 or greater) or dissection, **or**
     - ii. Ectopia lentis, **or**

iii. The member has a systemic score of 7 or higher (points values are in parentheses):
a) Wrist and thumb sign (3)
b) Wrist or thumb sign (1)
c) Pectus carinatum deformity (2)
d) Pectus excavatum or chest asymmetry (1)
e) Hindfoot deformity (2)
f) Plain flat foot (pes planus) (1)
g) Pneumothorax (2)
h) Dural ectasia (2)
i) Protrusio acetabulae (2)
j) Reduced upper segment / lower segment and increased arm span/height ratios (1)
k) Scoliosis or thoracolumbar kyphosis (1)
l) Reduced elbow extension (1)
m) 3 of 5 facial features (dolichocephaly, downward slanting palpebral fissures, enophthalmos, retrognathia, malar hypoplasia) (1)
n) Skin striae (1)
o) Myopia (1)
p) Mitral valve prolapse (1)

2. *FBN1* sequencing and/or deletion/duplication analysis to establish or confirm a molecular diagnosis of Marfan syndrome is considered **investigational** for all other indications.

*Full explanation of each feature and calculation can be found at https://www.marfan.org/dx/score

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Loeys-Dietz Syndrome

Loeys-Dietz Syndrome Multigene Panel

1. Loeys-Dietz syndrome (LDS) multigene panel analysis** to establish or confirm a diagnosis of Loeys-Dietz syndrome is considered **medically necessary** when:
   A. The member meets at least two of the following:
      i. Characteristic facial features, including widely spaced eyes and craniosynostosis **or**
      ii. Bifid uvula or cleft palate **or**
      iii. Tortuosity of the aorta and its branches **or**,
      iv. Aortic dilation and dissection **or**
      v. Joint hypermobility **or**
   B. The member has a first degree relative with a clinical diagnosis of LDS
2. Loeys-Dietz syndrome (LDS) multigene panel analysis to establish or confirm a diagnosis of Loeys-Dietz syndrome is considered **investigational** for all other indications.

*If the member has both aortic root enlargement and ectopia lentis, FBN1 should either be included in the panel or should have been previously performed and the results were negative.
** If a panel is performed, the appropriate panel code should be used

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Familial Thoracic Aortic Aneurysm and Dissection (TAAD)

Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel

1. Familial thoracic aortic aneurysm and dissection (TAAD) multigene panel to establish a genetic diagnosis for TAAD is considered **medically necessary** when:
   A. The member has a history of any of the following:
      i. Aortic root enlargement, **or**
      ii. Thoracic aneurysm, **or**
      iii. Type A or type B aortic dissection, **and**
   B. The member does not otherwise meet diagnostic criteria for another connective tissue disorder **and**
   C. The member has a family history of dilation or dissection of the aortic root, consistent with autosomal dominant inheritance.
2. Thoracic aortic aneurysm and dissection (TAAD) multigene panel analysis to establish a genetic diagnosis for TAAD is considered **investigational** for all other indications.

*If a panel is performed, the appropriate panel code should be used

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Ehlers-Danlos Syndrome

Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel

1. Classic Ehlers-Danlos syndrome multigene panel analysis to establish or confirm a diagnosis of cEDS is considered **medically necessary** when:
   A. The member has skin hyperextensibility and atrophic scarring, **and**

B. The member meets at least one of the following:
  i. Generalized joint hypermobility, **or**
  ii. At least three of the following:
    a) Easy bruising
    b) Soft, doughy skin
    c) Skin fragility (or traumatic splitting)
    d) Molluscoid pseudotumors
    e) Subcutaneous spheroids
    f) Hernia
    g) Epicanthal folds
    h) Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot)
    i) Family history of a first-degree relative that has a clinical diagnosis of cEDS **and**

C. The panel includes, at a minimum, the following genes: COL5A1 and COL5A2

2. Classic Ehlers-Danlos syndrome multigene panel analysis to establish or confirm a diagnosis of cEDS is considered **investigational** for all other indications, including isolated hypermobility and hypermobile Ehlers-Danlos syndrome (hEDS).

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Vascular Ehlers-Danlos Syndrome (vEDS)

COL3A1 Sequencing and/or Deletion/Duplication Analysis

1. *COL3A1* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of vEDS is considered **medically necessary** when:
  A. The member meets any of the following:
    i. Arterial rupture or dissection under the age of 40, **or**
    ii. Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology, **or**
    iii. Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears, **or**
    iv. Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma, **or**
    v. The member has a close relative with a clinical diagnosis of vEDS **or**
    vi. The member has at least two of the following minor criteria:
      a) Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back
      b) Thin, translucent skin with increased venous visibility
      c) Characteristic facial appearance
      d) Spontaneous pneumothorax
      e) Acrogeria
      f) Talipes equinovarus
      g) Congenital hip dislocation
      h) Hypermobility of small joints
      i) Tendon and muscle rupture
      j) Keratoconus
      k) Gingival recession and gingival fragility
      l) Early onset varicose veins (under the age of 30 and nulliparous if female)

2. *COL3A1* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of vEDS is considered **investigational** for all other indications, , including isolated hypermobility and hypermobile Ehlers-Danlos syndrome (hEDS)

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Covered Connective Tissue Disorders

1. Genetic testing to establish or confirm one of the following connective tissue disorders to guide management is considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder:
  A. Arthrochalasia EDS (*COL1A1*, *COL1A2*)
  B. Brittle cornea syndrome (*ZNF469*, *PRDM5*)
  C. Cardiac-valvular EDS (*COL1A2*)
  D. Classical-like EDS (*TNXB*)
  E. Dermatosparaxis EDS (*ADAMTS2*)
  F. Kyphoscoliotic EDS (*PLOD1*, *FKBP14*)
  G. Musculocontractural EDS (*CHST14*, *DSE*)
  H. Myopathic EDS (*COL12A1*)

I. Periodontal EDS (*C1R*, *C1S*)
J. Spondylodysplastic EDS (*B4GALT7*, *B3GALT6*, *SLC9A13*)

2. Genetic testing to establish or confirm the diagnosis of all other connective tissue disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in **General Approach to Genetic and Molecular Testing** (see policy for coverage criteria).

*Clinical features for a specific immune disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly source.

Of note, per GeneReviews, hypermobile Ehlers-Danlos syndrome (hEDS) is based entirely on clinical evaluation and family history and not genetic testing, as the gene(s) associated with hEDS are currently unknown. Therefore, clinical genetic testing for the sole purpose of evaluating for hEDS is not appropriate at this time.

Definitions

1. Close relatives include first, second, and third degree **blood** relatives:
   A. **First-degree relatives** are parents, siblings, and children
   B. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
   C. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins
2. **Type A aortic dissections** occur at the ascending part of the aorta, just as it branches off of the heart.
3. **Type B aortic dissections** occur at the descending part of the aorta and may extend into the abdomen.

Products

This information is for most, but not all, HealthPartners plans. Please read your plan documents to see if your plan has limits or will not cover some items. If there is a difference between this general information and your plan documents, your plan documents will be used to determine your coverage. These coverage criteria do not apply to Medicare Products. For more information regarding Medicare coverage criteria or for a copy of a Medicare coverage policy, contact Member Services at 952-883-7272 or 1-877-778-8384.

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