GENETIC TESTING: AORTOPATHIES AND CONNECTIVE TISSUE DISORDERS

OVERVIEW

Hereditary connective tissue disorders are a group of disorders that affect the connective tissues that support the skin, bones, joints, heart, blood vessels, eyes, and other organs. While specific features vary by type, an unusually large range of joint movement (hypermobility) and cardiovascular disease (such as thoracic aortic aneurysms and dissections) are features that are present in many hereditary connective tissue disorders. Medical management may differ based on the underlying genetic etiology. A diagnosis may be made based on clinical examination; however, it can be difficult to reliably diagnose a hereditary connective tissue disorder based on clinical and family history alone.

Accurate diagnosis of a hereditary connective tissue disorder can lead to changes in clinical management, including surveillance of the aorta, surgical repair of the aorta, when necessary, pharmacologic management, as well as surveillance for multisystem involvement in syndromic conditions with risk for thoracic aortic aneurysms and dissection.

POLICY REFERENCE TABLE

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Known Familial Variant Analysis for Aortopathies and Connective Tissue Disorders				
Known Familial Variant Analysis	Targeted Mutation Analysis for a Known Familial Variant	81403		
Marfan Syndrome				

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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	1
	Marfan Syndrome via *FBN1* Gene (Prevention Genetics)			
Loeys-Dietz Syndrome				
Loeys-Dietz Syndrome Multigene Panel	Loeys-Dietz Syndrome Panel (Prevention Genetics)	81405, 81479	I71.00-I71.9	1, 2
	Loeys-Dietz Syndrome Panel (Invitae)	81405, 81408, 81479		
Familial Thoracic Aortic Aneurysm and Dissection (TAAD)				
Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel	Marfan syndrome, Loeys-Dietz syndrome, Familial thoracic aortic aneurysms & dissections, and Related disorders NGS Panel - Comprehensive (CTGT)	81405, 81406, 81408, 81479	I71.00-I71.9, Q87.5	1, 2, 9
	TAAD Panel Next Generation Sequencing (DDC Clinic Laboratory)			
	TAADNext (Ambry Genetics)	81410, 81411		
	Thoracic Aortic Aneurysm Panel (Cincinnati Children's Hospital Medical Center- Molecular Genetics and Cytogenetics Laboratories)			
	Marfan Syndrome and Thoracic Aortic Aneurysm and Dissection NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics)			
	Marfan/TAAD Panel (GeneDx)			
	Aortopathy Comprehensive Panel - Primary Genes (Invitae)			
Ehlers-Danlos Syndrome				
Classic Ehlers-Danlos Syndrome (cEDS)				

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COL5A1, COL5A2, and *COL1A1* Sequencing and/or Deletion/Duplication Analysis or Targeted Multigene Panel	*COL5A1* Full Gene Sequencing and Deletion/Duplication (Invitae)	81479, 81408	M35.7, Q79.61-Q79.62	3
	Ehlers-Danlos Syndrome, Classic Type via the *COL5A2* Gene (Prevention Genetics)			
	Ehlers-Danlos syndrome, arthochalasia type NGS panel (CTGT)	81408, 81479		
Vascular Ehlers-Danlos Syndrome (vEDS)				
COL3A1 Sequencing and/or Deletion/Duplication Analysis	*COL3A1* Full Gene Sequencing and Deletion/Duplication-Diagnostic (Invitae)	81479	Q79.63	3
Comprehensive Ehlers-Danlos Syndrome Multigene Panels				
Comprehensive Ehlers-Danlos Syndrome Multigene Panels	Ehlers-Danlos Syndrome Panel (Invitae)	81408, 81479	M35.7, Q79.60-Q79.69	5
	Ehlers-Danlos Syndromes (EDS) Panel (PreventionGenetics)	81405, 81406, 81408, 81479		
Connective Tissue Disorders Multi-Syndrome Panel				
Connective Tissue Disorders Multi-Syndrome Panels	Marfan/TAAD Panel (GeneDx)	81410, 81411	I71.00-I71.9, M35.7, Q12.1, Q79.60-Q79.69, Q87.40-Q87.43, Q87.5	4, 6, 7, 8
	Invitae Aortopathy Comprehensive Panel (Invitae)			
Other Covered Connective Tissue Disorders				
Other Covered Connective Tissue Disorders	See list below	81400-81408		10, 11, 12

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OTHER RELATED POLICIES

This policy document provides coverage criteria for genetic testing for cardiovascular disorders. Please refer to:

- ***Genetic Testing: Cardiac Disorders*** for coverage criteria related to arrhythmias and cardiomyopathies.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to genetic disorders that affect multiple organ systems.
- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing.
- ***Genetic Testing: Preimplantation Genetic Testing*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to aortopathies and connective tissue disorders not specifically discussed in this or another non-general policy.

COVERAGE CRITERIA

KNOWN FAMILIAL VARIANT ANALYSIS FOR AORTOPATHIES AND CONNECTIVE TISSUE DISORDERS

I. Targeted mutation analysis for a known familial variant (81403) for an aortopathies and connective tissue disorder is considered **medically necessary** when:

   A. The member has a close relative with a known pathogenic or likely pathogenic variant causing the condition.

II. Targeted mutation analysis for a known familial variant (81403) for an aortopathies and connective tissue disorder is considered **investigational** for all other indications.

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MARFAN SYNDROME

FBN1 Sequencing and/or Deletion/Duplication Analysis

I. *FBN1* sequencing and/or deletion/duplication analysis (81408, 81479) to confirm a diagnosis of Marfan syndrome is considered **medically necessary** when:

A. The member has some of the below symptoms of Marfan syndrome but does not meet the clinical criteria for a diagnosis.

1. The clinical criteria for diagnosis are as follows:

a) Aortic root enlargement (Z-score 2.0 or greater) or dissection, **AND**

b) Ectopia lentis, **OR**

c) A systemic score of 7 or greater, as demonstrated by the following clinical features and associated scores*:

(1) Wrist AND thumb sign (3)
(2) Wrist OR thumb sign (1)
(3) Pectus carinatum deformity (2)
(4) Pectus excavatum or chest asymmetry (1)
(5) Hindfoot deformity (2)
(6) Plain flat foot (pes planus) (1)
(7) Pneumothorax (2)
(8) Dural ectasia (2)
(9) Protrusio acetabulae (2)
(10) Reduced upper segment / lower segment AND increased arm span/height ratios (1)
(11) Scoliosis or thoracolumbar kyphosis (1)
(12) Reduced elbow extension (1)
(13) 3 of 5 facial features (dolichocephaly, downward slanting palpebral fissures, enophthalmos, retrognathia, malar hypoplasia) (1)
(14) Skin striae (1)
(15) Myopia (1)

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(16) Mitral valve prolapse (1) **OR**

B. The member has a close relative with a documented clinical diagnosis of Marfan syndrome, and the member has symptoms of Marfan syndrome, but the member does not meet clinical criteria for diagnosis of an individual with a family history of Marfan syndrome, which are:

1. Clinical diagnostic criteria for an individual with a family history of Marfan syndrome is as follows:

a) Ectopia lentis, **OR**

b) Multiple systemic features (see above), **OR**

c) A dilated aortic root (if over 20 years, greater than two standard deviations; if younger than 20, greater than three standard deviations)

II. *FBN1* sequencing and/or deletion/duplication analysis (81408, 81479) 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

I. Loeys-Dietz syndrome (LDS) multigene panel analysis (81405, 81408, 81479) to establish or confirm a diagnosis of Loeys-Dietz syndrome is considered **medically necessary** when:

A. The member meets all of the following:

1. Characteristic facial features, including widely spaced eyes and craniosynostosis, **AND**

2. Bifid uvula or cleft palate, **AND**

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3. Tortuosity of the aorta and its branches, **OR**

B. The member meets the following:

1. The member has a first degree relative with a clinical diagnosis of LDS, **AND**

C. The panel includes, at a minimum, the following genes*: *TGFBR1* and *TGFBR2*.

II. Loeys-Dietz syndrome (LDS) analysis (81405, 81408, 81479) 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* for Marfan syndrome 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

I. Familial thoracic aortic aneurysm and dissection (TAAD) multigene panel analysis (81405, 81406, 81408, 81410, 81411, 81479) to establish a genetic diagnosis for TAAD is considered **medically necessary** when:

A. The member has all of the following:

1. The member has aortic root enlargement or has had a type A or type B aortic dissection, **AND**

2. The member does not have any major criteria for diagnosis of another connective tissue disorder, **OR**

B. The member has a family history of dilation or dissection of the aortic root, consistent with autosomal dominant inheritance, **AND**

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C. The panel includes, at a minimum, the following genes*: *ACTA2*, *FBN1*, *MYH11*, *SMAD3*, *TGFBR1*, *TGFBR2*.

II. Thoracic aortic aneurysm and dissection (TAAD) multigene panel analysis (81405, 81406, 81408, 81410, 81411, 81479) 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)

Classic Ehlers-Danlos Syndrome Multigene Panel

I. Classic Ehlers-Danlos syndrome multigene panel analysis (81408, 81479) 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:

1. Generalized joint hypermobility, **OR**

2. 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

C. The panel is limited to the following genes*: *COL5A1*, *COL5A2*, and *COL1A1*.

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II. Classic Ehlers-Danlos syndrome multigene panel analysis (81408, 81479) to establish or confirm a diagnosis of cEDS is considered **investigational** for all other indications.

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

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Vascular Ehlers-Danlos Syndrome (vEDS)

COL3A1 Sequencing and/or Deletion/Duplication Analysis

I. *COL3A1* sequencing and/or deletion/duplication analysis (81479) to establish or confirm a diagnosis of vEDS is considered **medically necessary** when:

A. The member meets any of the following:

1. Arterial rupture or dissection under the age of 40, **OR**
2. Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology, **OR**
3. Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears, **OR**
4. Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma, **OR**
5. The member has a close relative that has a diagnosis of vEDS, **OR**
6. 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

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k) Gingival recession and gingival fragility
l) Early onset varicose veins (under the age of 30 and nulliparous if females)

II. *COL3A1* sequencing and/or deletion/duplication analysis (81479) to establish or confirm a diagnosis of vEDS is considered **investigational** for all other indications.

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Comprehensive Ehlers-Danlos Syndrome Multigene Panels

I. Comprehensive Ehlers-Danlos syndrome (EDS) multigene panel analysis (81405, 81406, 81408, 81479) is considered **investigational** for all indications, including hypermobile EDS.

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CONNECTIVE TISSUE DISORDERS MULTI-SYNDROME PANEL

I. Genetic testing using a comprehensive connective tissue disorders panel (81410, 81411)* is considered **medically necessary** when:

A. The member meets criteria for at least one of the following (see specific coverage criteria sections above):

1. Marfan Syndrome
2. Loeys-Dietz Syndrome
3. Classic Ehlers-Danlos Syndrome
4. Vascular Ehlers-Danlos Syndrome (vEDS)

II. Genetic testing using a comprehensive connective tissue disorders panel (81410, 81411) is considered **investigational** for all other indications.

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

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OTHER COVERED CONNECTIVE TISSUE DISORDERS

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

I. 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 (the list is not meant to be comprehensive, see II below):

   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. Epidermolysis Bullosa
   G. Kyphoscoliotic EDS (*PLOD1*, *FKBP14*)
   H. Musculocontractural EDS (*CHST14*, *DSE*)
   I. Myopathic EDS (*COL12A1*)
   J. Osteogenesis Imperfecta
   K. Periodontal EDS (*C1R*, *C1S*)
   L. Spondylodysplastic EDS (*B4GALT7*, *B3GALT6*, *SLC9A13*)

II. 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 Testing* (see policy for coverage criteria).

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

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NOTES AND 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

BACKGROUND AND RATIONALE

FBN1 Sequencing and/or Deletion/Duplication Analysis

American College of Medical Genetics and Genomics (ACMG)

American College of Medical Genetics and Genomics (Pyeritz, 2012) issued guidelines on the evaluation of adolescents or adults with some features of Marfan syndrome (MFS), which recommendations included the following:

- 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.

- If there is no family history of MFS, then the subject has the condition under any of the following four situations:
    - A dilated aortic root (defined as greater than or equal to two standard deviations above the mean for age, sex, and body surface area) and ectopia lentis
    - A dilated aortic root and a mutation [pathogenic variant] in *FBN1* that is clearly pathologic
    - A dilated aortic root and multiple systemic features or

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    - Ectopia lentis and a mutation [pathogenic variant] in *FBN1* that has previously been associated with aortic disease.

- If there is a positive family history of MFS (independently ascertained with these criteria), then the subject has the condition under any of the following three situations:

    - Ectopia lentis
    - Multiple systemic features or
    - A dilated aortic root (if over 20 years, greater than two standard deviations; if younger than 20, greater than three standard deviations)

Loeys-Dietz Syndrome

American College of Medical Genetics and Genomics (ACMG)

American College of Medical Genetics and Genomics (Pyeritz et al, 2012) issued guidelines on the evaluation of adolescents or adults with some features of Marfan syndrome (MFS) (including Loeys-Dietz syndrome (LDS)), and included the following recommendations:

Genetic testing for LDS can aid in the diagnosis of LDS in addition to physical exam, echocardiography, dilated eye exam and MRI of the head, neck, thorax, abdomen and pelvis. Features of LDS include characteristic facial features, craniosynostosis, bifid uvula or cleft palate, tortuosity of the aorta and its branches, aortic dilatation and dissection, and joint hypermobility (p. 175).

> Patients have had mutations in one or another of the receptors for TGFβ. In a patient found to have consistent facial features, bifid uvula, and arterial tortuosity, the diagnosis can be confirmed with molecular testing. Tortuosity can sometimes be isolated (e.g., found only in the head and neck) (p.175).

American College of Cardiology Foundation

The American College of Cardiology Foundation and 9 other medical associations published joint evidence-based guidelines (2010) for the diagnosis and management of thoracic aortic disease, including Marfan syndrome, which included the following guidelines regarding genetic testing:

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- If the mutant gene associated with aortic aneurysm and/or dissection is identified in a patient, first-degree relatives should undergo counseling and testing. Then, only the relatives with the genetic mutation [pathogenic variant] should undergo aortic imaging. [class 1, level of evidence C.] (p.1520)

Familial Thoracic Aortic Aneurysm and Dissection (TAAD)

American College of Cardiology Foundation

The American College of Cardiology Foundation and 9 other medical associations published joint evidence-based guidelines (Hiratzka et al, 2010) for the diagnosis and management of thoracic aortic disease, including Marfan syndrome, which included the following guidelines regarding genetic testing:

- If the mutant gene associated with aortic aneurysm and/or dissection is identified in a patient, first-degree relatives should undergo counseling and testing. Then, only the relatives with the genetic mutation [pathogenic variant] should undergo aortic imaging. [class 1, level of evidence C.] (p.1520)

American College of Medical Genetics and Genomics (ACMG)

American College of Medical Genetics and Genomics (Pyeritz et al, 2012) issued guidelines on the evaluation of adolescents or adults with some features of Marfan syndrome (MFS) (including TAAD), and included the following diagnostic criteria for TAAD:

> Autosomal dominant family history of dilation or dissection of the aortic root, ascending aorta, or descending aorta in the absence of major criteria for the diagnosis of MFS or another connective tissue disorder (p.175).

GeneReviews

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

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In the GeneReviews for Heritable Thoracic Aortic Disease Overview (Milewicz, updated 2017), the Clinical Characteristics: Heritable Thoracic Aortic Disease section defines the following:

- "Heritable thoracic aortic aneurysms and dissections" has been shortened to heritable thoracic aortic disease (HTAS).
- Nomograms for normal aortic diameter based on age, sex, and body size have been developed for the aortic root and the ascending aorta. Aortic diameters that exceed the upper limit in these nomograms are considered enlarged or dilated.
- Aortic dissections can be classified by the Stanford criteria based on the involvement of the ascending aorta:
    - Type A dissections involve the ascending aorta regardless of the site of origin and may or may not extend into the descending thoracic aorta.
    - Type B dissections originate at the descending thoracic aorta, typically distal to the left subclavian artery, and propagate variable distances down the descending thoracic aorta and abdominal aorta. Type B dissections do not involve the ascending aorta.

Table 1 describes the known genes associated with HTAS, and the list of genes included in this policy represent those that occur in 2% or more of families with HTAS who have had a mutation identified.

Ehlers-Danlos Syndrome

Malfait F, Francomano C, Byers P, et al.

The 2017 International Classification of the Ehlers-Danlos Syndromes included the following clinical features for the associated conditions:

Classical EDS (cEDS):

Major criteria
1. Skin hyperextensibility and atrophic scarring
2. Generalized joint hypermobility (GJH)

Minor criteria
1. Easy bruising
2. Soft, doughy skin
3. Skin fragility (or traumatic splitting)
4. Molluscoid pseudotumors
5. Subcutaneous spheroids
6. Hernia (or history thereof)

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7. Epicanthal folds
8. Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot)
9. Family history of a first degree relative who meets clinical criteria

Minimal Criteria suggestive for cEDS:

- Major criterion (1): skin hyperextensibility and atrophic scarring, Plus
- Either major criterion (2): GJH
- And/or: at least three minor criteria

Confirmatory molecular testing is obligatory to reach a final diagnosis.

Vascular EDS (vEDS)

Major criteria

1. Family history of vEDS with documented causative variant in *COL3A1*
2. Arterial rupture at a young age
3. Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology
4. Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears
5. Carotid-cavernous sinus fistula (CCSF) Formation in the absence of trauma

Minor criteria

1. Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back
2. Thin, translucent skin with increased venous visibility
3. Characteristic facial appearance
4. Spontaneous pneumothorax
5. Acrogeria
6. Talipes equinovarus
7. Congenital hip dislocation
8. Hypermobility of small joints
9. Tendon and muscle rupture
10. Keratoconus
11. Gingival recession and gingival fragility
12. Early onset varicose veins (under age 30 and nulliparous if female)

Minimal criteria suggestive for vEDS:

- A family history of the disorder, arterial rupture or dissection in individuals less than 40 years of age, unexplained sigmoid colon rupture, or spontaneous pneumothorax in the presence of other features consistent

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with vEDS should all lead to diagnostic studies to determine if the individual has vEDS.
- Testing for vEDS should also be considered in the presence of a combination of the other "minor" clinical features listed above. Even for experienced clinicians the clinical diagnosis of vEDS may be difficult.
- Because of implications for treatment, natural history, and recurrence risk, the diagnosis of vEDS rests on the identification of a causative variant in one allele of *COL3A1*.

Comprehensive Ehlers-Danlos Syndrome Multigene Panels

GeneReviews

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

In the GeneReviews for Hypermobile Ehlers-Danlos Syndrome (Levy, updated 2021), the Testing section advises the following:

> The etiology of hEDS is unknown. Genetic heterogeneity is likely. There are currently no biochemical or genetic tests clinically available to confirm or rule out a diagnosis of hEDS.

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Comprehensive Connective Tissue Disorders Panel

GeneReviews

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

In the GeneReviews for Marfan Syndrome (Dietz, updated 2017), the Diagnosis section advises the following:

> Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Although individuals with the distinctive findings of Marfan syndrome described in Suggestive Findings are likely to be diagnosed using gene-targeted testing, those who do not have sufficiently discriminating features to consider the diagnosis of Marfan syndrome are more likely to be diagnosed using genomic testing.

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In the GeneReviews for Loeys-Dietz Syndrome (Loeys and Dietz, updated 2018), the Diagnosis section advises the following:

> Molecular genetic testing approaches can include a combination of gene-targeted testing (serial single-gene testing or a multigene panel) and genomic testing (comprehensive genomic sequencing) depending on the phenotype.
> Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because of clinical overlap, it is difficult to predict which of the known LDS-related genes will be causative in any given affected individual. Although individuals with the distinctive findings of LDS described in Suggestive Findings are likely to be diagnosed using gene-targeted testing, those who do not have sufficiently discriminating features to consider the diagnosis of LDS are more likely to be diagnosed using genomic testing.

In the GeneReviews for Classic Ehlers-Danlos Syndrome (Malfait, updated 2018), the Establishing the Diagnosis section advises the following:

> The diagnosis of classic EDS is established in a proband with the minimal clinical diagnostic criteria and identification of a heterozygous pathogenic variant in one of the genes listed in Table 2. Molecular genetic testing approaches can include concurrent (or serial) single-gene testing, use of a multigene panel, and more comprehensive genomic testing.
>
> A multigene panel that includes *COL5A1, COL5A2, COL1A1*, and other genes of interest may also be considered.

In the GeneReviews for Vascular Ehlers Danlos (Byers, updated 2019), the Diagnosis section advises the following:

> Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of vEDS is broad, individuals with the distinctive major criteria findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing whereas those with a phenotype indistinguishable from many other inherited connective tissue disorders are more likely to be diagnosed using genomic testing

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REFERENCES

1. Pyeritz RE; American College of Medical Genetics and Genomics. Evaluation of the adolescent or adult with some features of Marfan syndrome. Genet Med. 2012;14(1):171-177. doi:10.1038/gim.2011.48
2. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons,and Society for Vascular Medicine [published correction appears in J Am Coll Cardiol. 2013 Sep 10;62(11):1039-40]. J Am Coll Cardiol. 2010;55(14):e27-e129. doi:10.1016/j.jacc.2010.02.015
3. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):8-26. doi:10.1002/ajmg.c.31552
4. Malfait F, Wenstrup R, De Paepe A. Classic Ehlers-Danlos Syndrome. 2007 May 29 [Updated 2018 Jul 26]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1244/
5. Levy HP. Hypermobile Ehlers-Danlos Syndrome. 2004 Oct 22 [Updated 2018 Jun 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1279/
6. Byers PH. Vascular Ehlers-Danlos Syndrome. 1999 Sep 2 [Updated 2019 Feb 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1494/
7. Dietz H. Marfan Syndrome. 2001 Apr 18 [Updated 2017 Oct 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1335/
8. Loeys BL, Dietz HC. Loeys-Dietz Syndrome. 2008 Feb 28 [Updated 2018 Mar 1]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1133/

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9. Milewicz DM, Regalado E. Heritable Thoracic Aortic Disease Overview. 2003 Feb 13 [Updated 2017 Dec 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1120/
10. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
11. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
12. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.

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