

# GENETIC TESTING: AORTOPATHIES AND CONNECTIVE TISSUE DISORDERS

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## 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.

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. Genetic evaluation for other types of EDS are addressed within this policy.

## POLICY REFERENCE TABLE

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the [Concert Genetics Platform](#) for a comprehensive list of registered tests.

<a href="#">Coverage Criteria Sections</a>	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	<a href="#">Ref</a>
<b><a href="#">Connective Tissue Disorders Multi-Syndrome Panels</a></b>				
<a href="#">Comprehensive Connective Tissue Disorders Multigene Panel</a>	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	3, 4, 5, 6
	Invitae Connective Tissue Disorders Panel (Invitae)			
<b><a href="#">Marfan Syndrome</a></b>				
<a href="#">FBN1 Sequencing and/or Deletion/Duplication Analysis</a>	FBN1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81408, 81479	I71.00-I71.9, Q12.1, Q87.40-Q87.43	1, 5
	Marfan Syndrome via FBN1 Gene (PreventionGenetics, part of Exact Sciences)			
<b><a href="#">Loeys-Dietz Syndrome</a></b>				
<a href="#">Loeys-Dietz Syndrome Multigene Panel</a>	Loeys-Dietz Syndrome Panel (PreventionGenetics, part of Exact Sciences)	81405, 81408, 81479	I71.00-I71.9	1, 6, 11
	Loeys-Dietz Syndrome Panel (Invitae)			
<b><a href="#">Familial Thoracic Aortic Aneurysm and Dissection (TAAD)</a></b>				
<a href="#">Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel</a>	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	1, 7, 12
	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)			
<b><u>Ehlers-Danlos Syndrome</u></b>				
<b><u>Classic Ehlers-Danlos Syndrome (cEDS)</u></b>				
<b><u>Classic Ehlers-Danlos Syndrome Multigene Panel</u></b>	Ehlers Danlos Panel (GeneDx)	81479, 81408	M35.7, Q79.61, Q79.63, Q79.69	2, 3
	Ehlers-Danlos Syndrome Panel (PerkinElmer Genomics)			
	Ehlers-Danlos syndrome, classic type NGS panel (CTGT)			
<b><u>Vascular Ehlers-Danlos Syndrome (vEDS)</u></b>				
<b><u>COL3A1 Sequencing and/or Deletion/Duplication Analysis</u></b>	COL3A1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479	Q79.63	2
<b><u>Other Covered Connective Tissue Disorders</u></b>				
<b><u>Other Covered Connective Tissue Disorders</u></b>	See list below	81400-81408		8, 9, 10

## 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 and Molecular Testing** for coverage criteria related to aortopathies and connective tissue disorders not specifically discussed in this or another non-general policy.

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## COVERAGE CRITERIA

### CONNECTIVE TISSUE DISORDERS

#### Comprehensive Connective Tissue Disorders Multigene Panel

- I. Comprehensive connective tissue disorders multigene panel analysis (81410, 81411)\* is considered **medically necessary** when:
  - A. The member meets criteria for at least one of the following (see specific coverage criteria sections below):
    1. [Marfan Syndrome](#)
    2. [Loeys-Dietz Syndrome](#)

3. [Classic Ehlers-Danlos Syndrome](#)
  4. [Vascular Ehlers-Danlos Syndrome \(vEDS\)](#)
- II. Comprehensive connective tissue disorders multigene panel analysis (81410, 81411) 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**

- 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 one of the following:
    1. Aortic root enlargement (Z-score of 2 or greater) or dissection, **OR**
    2. Ectopia lentis, **OR**
  - B. The member has a systemic score of 7 or higher using the list of symptoms below (point values in parentheses):
    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)
16. Mitral valve prolapse (1).

- 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.

**NOTE:** 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 at least two of the following:
    1. Characteristic facial features, including widely spaced eyes and craniosynostosis, **OR**
    2. Bifid uvula or cleft palate, **OR**
    3. Tortuosity of the aorta and its branches, **OR**
    4. Aortic dilatation and dissection, **OR**
    5. Joint hypermobility, **OR**
    6. The member has a [first-degree relative](#) with a clinical diagnosis of LDS
- 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 a panel is performed, the appropriate panel code should be used

**NOTE:** 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.

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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 aortic root enlargement or has had thoracic aneurysm or a 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.
- 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) 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, **OR**
      - b) Soft, doughy skin, **OR**
      - c) Skin fragility (or traumatic splitting), **OR**
      - d) Molluscoid pseudotumors, **OR**
      - e) Subcutaneous spheroids, **OR**
      - f) Hernia, **OR**
      - g) Epicanthal folds, **OR**
      - h) Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot), **OR**
      - 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*.
- 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, including isolated hypermobility and hypermobile Ehlers-Danlos syndrome (hEDS).

**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.

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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](#) with a clinical 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, **OR**
      - b) Thin, translucent skin with increased venous visibility, **OR**
      - c) Characteristic facial appearance, **OR**
      - d) Spontaneous pneumothorax, **OR**
      - e) Acrogeria, **OR**
      - f) Talipes equinovarus, **OR**
      - g) Congenital hip dislocation, **OR**
      - h) Hypermobility of small joints, **OR**
      - i) Tendon and muscle rupture, **OR**
      - j) Keratoconus, **OR**
      - k) Gingival recession and gingival fragility, **OR**
      - l) Early onset varicose veins (under the age of 30 and nulliparous if female).

- II. *COL3A1* sequencing and/or deletion/duplication analysis (81479) to establish or confirm a diagnosis of vEDS is considered **investigational** for all other indications, including isolated hypermobility and hypermobile Ehlers-Danlos syndrome (hEDS).

**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.

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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 (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408) 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. [Kyphoscoliotic EDS](#) (*PLOD1*, *FKBP14*)
  - G. Musculocontractural EDS (*CHST14*, *DSE*)
  - H. Myopathic EDS (*COL12A1*)
  - I. Periodontal EDS (*C1R*, *C1S*)
  - J. Spondylodysplastic EDS (*B4GALT7*, *B3GALT6*, *SLC39A13*)
- II. Genetic testing to establish or confirm the diagnosis of all other connective tissue disorders (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408) 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 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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## 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

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## BACKGROUND AND RATIONALE

### Comprehensive Connective Tissue Disorders Multigene Panel

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.

#### *GeneReviews: Classic Ehlers-Danlos Syndrome*

The GeneReviews for Ehlers-Danlos Syndrome (EDS) states that “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...be considered.”

#### *GeneReviews: Hypermobile Ehlers-Danlos Syndrome*

Per the Hypermobile Ehlers-Danlos Syndrome (EDS) GeneReviews, “if an individual's personal or family history is suggestive of one of the other types of EDS or another

hereditary disorder of connective tissue or arterial fragility syndrome, analysis of an associated gene or multigene connective tissue disease panel may be appropriate."

#### *GeneReviews: FBN1-Related Marfan Syndrome*

Per the *FBN1*-Related Marfan Syndrome Gene Reviews, "molecular genetic testing approaches can include a combination of gene-targeted testing (single-gene testing, multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing) depending on the phenotype. A Marfan syndrome/Loeys-Dietz syndrome/familial thoracic aortic aneurysms and dissections multigene panel that includes *FBN1* and 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."

#### *GeneReviews: Loeys-Dietz Syndrome*

Per the Loeys-Dietz Syndrome (LDS) GeneReviews, "When the clinical findings suggest the diagnosis of LDS, molecular genetic testing approaches can include serial single-gene testing or use of a multigene panel. A multigene Marfan syndrome/Loeys-Dietz syndrome/familial thoracic aortic aneurysms and dissections panel that includes *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2* as well as a number of other genes associated with disorders that include aortic aneurysms and dissections may be offered by clinical laboratories."

### **Marfan Syndrome - *FBN1* Sequencing and/or Deletion/Duplication Analysis**

#### *American College of Medical Genetics and Genomics (ACMG)*

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

- 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
  - 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)

### *GeneReviews: FBN1-Related Marfan Syndrome*

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.

Marfan syndrome should be suspected in individuals with the following clinical findings and family history:

- Aortic root enlargement (Z-score  $\geq 2.0$ ). Note: Aortic size must be standardized to age and body size for accurate interpretation. A Z-score  $\geq 2.0$  indicates a value at or above the 95th percentile, while a Z-score  $\geq 3.0$  indicates a value at or above the 99th percentile. References and calculators for this determination are available at the Marfan Foundation website.
- Ectopia lentis; most reliably diagnosed by slit-lamp examination after maximal pupillary dilatation
- A systemic score  $\geq 7$

Additionally, GeneReviews states the diagnosis of Marfan syndrome is established in a proband (by definition a person without a known family history of Marfan syndrome) who has an *FBN1* pathogenic variant known to be associated with Marfan syndrome and EITHER of the following [Loeys et al 2010]:

- Aortic root enlargement (Z-score  $> 2.0$ )
- Ectopia lentis

### **Loeys-Dietz Syndrome Multigene Panel**

*American College of Medical Genetics and Genomics (ACMG)*

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

Genetic testing for Loeys-Dietz Syndrome (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.

Patients have had mutations in one or another of the receptors for TGF $\beta$ . 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)

*MacCarrick et al; 2014*

MacCarrick et al (2014) proposed a nosology in which a mutation in *TGFBR1*, *TGFBR2*, *SMAD3* or *TGFB2* in combination with documented aneurysm or dissection should be sufficient for the diagnosis of LDS. (p. 576)

*GeneReviews: Loeys-Dietz Syndrome*

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. The GeneReviews for Loeys-Dietz syndrome (Loeys and Dietz, 2018) indicates the diagnosis of Loeys-Dietz syndrome is established in a proband (by definition a person without a known family history of LDS) who has a heterozygous pathogenic (or likely pathogenic) variant in *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2* and EITHER of the following: (p. 4)

- Aortic root enlargement (defined as an aortic root z-score  $\geq 2.0$ ) or type A dissection
- Compatible systemic features including characteristic craniofacial, skeletal, cutaneous, and/or vascular manifestations found in combination. Special emphasis is given to arterial tortuosity, prominently including the head and neck vessels, and to aneurysms or dissections involving medium-to-large muscular arteries throughout the arterial tree.

## **Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel**

*American College of Medical Genetics and Genomics (ACMG)*

American College of Medical Genetics and Genomics (2012) issued guidelines on the evaluation of adolescents or adults with some features of Marfan syndrome (MFS) (including TAAD), which recommendations included the following (pages 174-175):

Genetic testing for TAAD can aid in the diagnosis in addition to physical exam, family history, dilated eye exam, echocardiography and vasculature imaging. Diagnostic criteria for TAAD include autosomal dominant history of dilatation or dissection of the aortic root, ascending aorta or descending aorta in the absence of major criteria for the diagnosis of Marfan syndrome or other connective tissue disease.

#### *American Heart Association/American College of Cardiology*

The ACC and AHA published a joint guideline (2022) in which genetic testing is recommended for patients with aortic root/ascending aortic aneurysms or aortic dissection and risk factors for hereditary thoracic aortic disease (strong recommendation, moderate quality of evidence). These risk factors include:

- Thoracic aortic disease (TAD) and syndromic features of Marfan, Loeys-Dietz or vascular Ehlers-Danlos syndrome
- TAD presentation under 60
- Family history of either TAD or peripheral/intracranial aneurysms in first or second degree relative
- History of unexplained sudden death at a relatively young age in first or second degree relative. (p. e361)
- A multigene panel comprising all genes suspected to cause HTAD is the most cost-effective and clinically useful approach to testing. (p. e362)

#### *GeneReviews: Heritable Thoracic Aortic Disease Overview*

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.

Per the Heritable Thoracic Aortic Disease GeneReviews article, “A multigene panel that includes genes associated with HTAD [heritable thoracic aortic disease] is recommended.” Per Table 1 of this article, these genes include: *ACTA2*, *COL3A*, *FBN1*, *MYH11*, *MYLK*, *SMAD3*, *TGFB2*, *TGFBR1*, *TGFBR2*, *LOX*, *PRKG1*, *EFEMP2*, *FOXE3*, *MFAP5*, *SMAD2*, *BGN*, *CBS*, *COL4A5*, *ELN*, *FBN2*, *FLNA*, *HCN4*, *NOTCH1*, *MAT2A*, *PKD1*, *PKD2*, *SKI*, *SLC2A10*, *SMAD4*, *TGFB3*.

## **EHLERS-DANLOS SYNDROME**

## Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel

### *International EDS Consortium*

The 2017 International Classification of the Ehlers-Danlos Syndromes (p. 11 and 13) included the following clinical features for the associated conditions. Confirmatory molecular testing is needed to reach a final diagnosis.

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)
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

More than 90% of cEDS patients harbor a heterozygous mutation in one of the genes encoding type V collagen (*COL5A1* and *COL5A2*). (p. 13)

### *GeneReviews: Classic Ehlers-Danlos Syndrome*

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.

The GeneReviews for Ehlers-Danlos Syndrome (EDS) states that “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*... and other genes of interest may...be considered.”

### **Vascular Ehlers-Danlos Syndrome (vEDS) - COL3A1 Sequencing and/or Deletion/Duplication Analysis**

The 2017 International Classification of the Ehlers-Danlos Syndromes (Malfait et al, 2017, p. 16) included the following clinical features for the associated conditions:

#### 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 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*.

Patients with vEDS typically harbor a heterozygous variant in the *COL3A1* gene, encoding type III collagen, with the rare exception of specific heterozygous variants in *COL1A1*. Verification of clinical diagnosis via Molecular screening by Sanger sequencing of *COL3A1*, or targeted resequencing of a gene panel that includes *COL3A1* and *COL1A1* is indicated. When no variant is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications.

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## REFERENCES

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