GENETIC TESTING: AORTOPATHIES AND CONNECTIVE TISSUE DISORDERS MP9588

Covered Service: Yes

Prior Authorization Required: No

Additional Information: Use the current applicable CPT/HCPCS code(s). An appropriate diagnosis code must appear on the claim. Claims will deny in the absence of applicable diagnosis and procedure code(s) and/or if the criteria for coverage outlined below are not met. The following codes are included below for informational purposes only, and may be subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

Medica Medical Policy:

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.

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 for Aortopathies and Connective Tissue Disorders	Targeted Mutation Analysis for a Known Familial Variant	81403		13
Connective Tissue Disorders Multi-Syndrome Panels				
Comprehensive Connective Tissue Disorders Multigene Panel	Heritable Disorders of Connective Tissue Panel (GeneDx) Invitae Connective Tissue Disorders Panel (Invitae)	81410, 81411	I71.00-I71.9, M35.7, Q79.60, Q79.61, Q79.63, Q79.69, Q12.1, Q87.4 Q87.5	4, 5, 6, 7, 8, 9
Marfan Syndrome				
FBN1 Sequencing and/or Deletion/Duplication Analysis	FBN1 Full Gene Sequencing and Deletion/Duplication (Invitae) Marfan Syndrome via FBN1 Gene (PreventionGenetics, part of Exact Sciences)	81408, 81479	I71.00-I71.9, Q12.1, Q87.40-Q87.43	1, 7
Loeys-Dietz Syndrome				
Loeys-Dietz Syndrome Multigene Panel	Loeys-Dietz Syndrome Panel (PreventionGenetics, part of Exact Sciences) Loeys-Dietz Syndrome Panel (Invitae)	81405, 81408, 81479	I71.00-I71.9	1, 8, 14
Familial Thoracic Aortic Aneurysm and Dissection (TAAD)				

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
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	1, 2, 9
	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 Multigene Panel	COL5A1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479, 81408	M35.7, Q79.61, Q79.63, Q79.69	3
	Ehlers-Danlos Syndrome, Classic Type via the COL5A2 Gene (PreventionGenetics, part of Exact Sciences)			
	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	3, 6

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Other Covered Connective Tissue Disorders				
Other Covered Connective Tissue Disorders	See list below	81400-81408		10, 11, 12

OTHER RELATED POLICIES

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

- ***Genetic Testing: Cardiac Disorders MP9589*** for coverage criteria related to arrhythmias and cardiomyopathies.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay MP9587*** for coverage criteria related to genetic disorders that affect multiple organ systems.
- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss MP9576*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing.
- ***Genetic Testing: Preimplantation Genetic Testing MP9574*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing MP9610*** 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 aortopathies and connective tissue disorders 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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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 some of the below symptoms of Marfan syndrome, but does **not** meet the following clinical criteria for a definitive diagnosis:

1. Aortic root enlargement (Z-score of 2 or greater) or dissection, **AND** one of the following:

a) Ectopia lentis, **OR**

b) At least two of the following systemic symptoms reaching a score of 7 or higher (points are in parentheses):

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

B. The member has a close relative with a documented clinical diagnosis of Marfan syndrome, **AND**

1. The member does not have any of the following:

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 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, **AND**

   B. The panel includes, at a minimum, the following genes*: *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *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* 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 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, **AND**

D. The panel includes, at a minimum, the following genes*: *ACTA2*, *FBN1*, *MYH11*, *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) 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 is limited to the following genes: *COL5A1*, *COL5A2*, and *COL1A1*.

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)

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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).

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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. Epidermolysis Bullosa
G. Kyphoscoliotic EDS (PLOD1, FKBP14)
H. Musculocontractural EDS (*CHST14*, *DSE*)
I. Myopathic EDS (*COL12A1*)
J. Periodontal EDS (*C1R*, *C1S*)
K. 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.

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.

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

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BACKGROUND AND RATIONALE

Known Familial Variant Analysis for Aortopathies and Connective Tissue Disorders

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on inheritance patterns says the following about testing for familial pathogenic variants:

> Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.

Comprehensive Connective Tissue Disorders Multigene Panel

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*, *COL1A1*, and other genes of interest may…be considered."

GeneReviews: Hypermobile 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.

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."

GeneRevierws: 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.

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

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 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.”

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*

GeneReviews: Arterial Tortuosity 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.

Per the Arterial Tortuosity Syndrome GeneReviews: "Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, exome array, genome sequencing) depending on the phenotype. A multigene panel that includes *SLC2A10* and other genes of interest is 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.

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), which 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)

  Molecular testing of *FBN1* has a role in the equivocal cases where patients have some of these features but not enough to meet a clinical diagnosis. (p. 173)

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 ≥2.0). Note: Aortic size must be standardized to age and body size for accurate interpretation. A Z-score ≥2.0 indicates a value at or above the 95th percentile, while a Z-score ≥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 ≥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 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)

MacCarrik 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: (page 4)

- Aortic root enlargement (defined as an aortic root z-score ≥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 (Pyeritz, 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. They include diagnostic criteria of 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 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 (p. 1520):

- If the mutant gene (*FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11*) 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.

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*). Rarely, specific variants in the genes encoding type I collagen (*COL1A1*) can be associated with a cEDS-phenotype. (p. 13)

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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