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				

FBN1 Sequencing and/or Deletion/Duplication Analysis	FBN1 Sequencing Analysis	81408	I71.00-I71.9, Q12.1, Q87.40-Q87.43	1, 2, 7, 10
	FBN1 Deletion/Duplication Analysis	81479		
Loeys-Dietz Syndrome				
Loeys-Dietz Syndrome Multigene Panel	Loeys-Dietz Syndrome Panel (Prevention Genetics)	81405, 81408 81410, 81411, 81479	I71.00-I71.9	1, 2, 8, 10
	Loeys-Dietz Syndrome NGS Panel (CTGT)			
	Loeys-Dietz Syndrome NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics)			
Familial Thoracic Aortic Aneurysm and Dissection (TAAD)				
Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel	Thoracic Aortic Aneurysm Panel (Cincinnati Children's Hospital Medical Center- Molecular Genetics and Cytogenetics Laboratories)	81405, 81408, 81479	I71.00-I71.9, Q87.5	1, 2, 9, 10, 11, 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)			
	Invitae Aortopathy Comprehensive Panel - Primary Genes Only (Invitae)			
Ehlers Danlos Syndrome				

Classic Ehlers-Danlos Syndrome (cEDS)				
COL5A1, *COL5A2*, and *COL1A1* Sequencing and/or Deletion/Duplication Analysis or Targeted Multigene Panel	Ehlers-Danlos syndrome, classic type NGS Panel (CTGT) Ehlers-Danlos syndrome type 1 and 2 (sequence analysis of COL5A1 and COL5A2 genes) (CGC Genetics USA)	81479, 81408	M35.7, Q79.61-Q79.62	3, 4
Vascular Ehlers-Danlos Syndrome (vEDS)				
COL3A1 Sequencing and/or Deletion/Duplication Analysis	COL3A1 Sequencing Analysis COL3A1 Deletion/Duplication Analysis	81479	Q79.63	1, 2, 3, 6, 10
Comprehensive Ehlers-Danlos Syndrome Multigene Panels				
Comprehensive Ehlers-Danlos Syndrome Multigene Panels	Ehlers-Danlos Syndrome Panel (BluePrint) Ehlers-Danlos syndrome NGS Panel - Dominant & Recessive - Comprehensive (CTGT) Ehlers-Danlos Syndrome NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics) Invitae Ehlers-Danlos Syndrome Panel (Invitae)	81479	M35.7, Q79.60-Q79.69	3, 5
Other Covered Connective Tissue Disorders				
Other Covered Connective Tissue Disorders	See list below	81400-81408		13, 14, 15

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 symptoms of Marfan syndrome but does not meet the clinical criteria for a diagnosis.

1. The clinical diagnostic criteria are as follows:

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

b) Ectopia lentis, **OR**

c) A systemic score of ≥7, 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)
(16) Mitral valve prolapse (1) **OR**

B. The member has a close relative with a documented clinical diagnosis of Marfan syndrome and symptoms of Marfan syndrome, but the member

does not meet clinical criteria for diagnosis of an individual with a family history of Marfan syndrome

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 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, 81410, 81411) to establish or confirm a diagnosis of Loeys-Dietz syndrome is considered **medically necessary** when:

    A. The member meets the following:

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

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

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

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

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

II. Loeys-Dietz syndrome (LDS) analysis (81405, 81408, 81479, 81410, 81411) 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, 81408, 81410, 81411, 81479) to establish a genetic diagnosis for TAAD is considered **medically necessary** when:

A. The member has aortic root enlargement (Z-score ≥2.0) or has had a type A or type B aortic dissection, **AND**

B. The member does not have the major criteria for diagnosis of 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.

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, 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*.

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.

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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
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 (81479) is considered **investigational** for all indications, including hypermobile EDS.

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CONNECTIVE TISSUE DISORDERS MULTI-SYNDROME PANEL*

I. Multigene panels that address multiple connective tissue disorders (Marfan syndrome, Loeys-Dietz syndrome, Familial Thoracic Aortic Aneurysm and Dissection, vascular Ehlers-Danlos syndrome) are covered if the member meets criteria for at least one of the connective disorders described above.
II. Multigene panels to establish or confirm a diagnosis of a connective tissue disorder are considered **investigational** for all other indications.

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

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

Practice Guidelines and Position Statements

American College of Medical Genetics and Genomics

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 or
    - 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)

American College of Cardiology Foundation, et. al.

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:

- 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. [class 1, level of evidence C.]

- The criteria for Marfan syndrome is based primarily on clinical findings in the various organ systems affected in the Marfan syndrome, along with family history and FBN1 mutations [pathogenic variants] status.

2017 International Classification of the Ehlers-Danlos Syndromes

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)
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 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.

<u>CSANZ Cardiovascular Genetic Diseases Council</u>

CSANZ Cardiovascular Genetic Diseases Council (2017) published a position statement with updates on the diagnosis and management of inherited aortopathies, including Marfan syndrome, that stated the following key points:

1. A number of inherited conditions can predispose the aorta, and less commonly other blood vessels, to dilatation and/ or rupture.
2. Broadly speaking, these conditions are recognised as syndromic when accompanied by a number of systemic features or non-syndromic when the aortic dilatation appears to exist in isolation.
3. The commonest syndromic aortopathy is Marfan syndrome and the commonest non-syndromic aortopathy is that which accompanies congenital bicuspid aortic valve.
4. Mutations in a number of genes have been identified, particularly in syndromic aortopathy.
5. Although genotype-phenotype relationships exist, the phenotypes of the syndromic aortopathies may have significant overlap.
6. When a syndromic aortopathy is suspected, review by a clinical geneticist is instrumental in characterising the clinical signs and the family history.
7. Confirmation of a diagnosis (either clinically or by gene testing) allows identification of individuals at increased risk of aortic sequelae who will benefit from active medical management.
8. Medical management is usually undertaken by a cardiologist with referral to other specialists (e.g. cardiothoracic surgeons) as appropriate.
9. At risk family members should be offered predictive testing if a mutation is identified, and should otherwise be screened in keeping with the presumptive clinical diagnosis and assessment of risk.
10. Pregnancy and the post-partum period confer a higher risk for aortic complications:
    a. Women with a personal or family history of aortopathy need appropriate pre-conception screening and counselling.
    b. Intervention may be required pre-conception and they should be managed closely throughout pregnancy, ideally in a high-risk obstetric clinic, with joint management by an obstetrician and a cardiologist.
    c. Management may include appropriate cessation and commencement/continuation of medication ((ACE inhibitors and ARB are teratogenic and contraindicated in pregnancy, beta blockers can be used in pregnancy) and should include involvement of a cardiologist in the management during pregnancy and decision making for delivery.
11. A clinical diagnosis of an inherited aortopathy can be made in the absence of a positive genetic test if the systemic features are consistent with a specific syndromic aortopathy. A familial history of aortic dissection in the absence of both a positive gene test and systemic examination findings may be more difficult to manage without a working clinical diagnosis. However, an inherited risk of

dissection should nonetheless be considered in this setting, particularly if the process has affected young individuals and/or in the absence of traditional risk factors.

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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/
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. Zentner D, West M, Adès LC; CSANZ Cardiovascular Genetic Diseases Council. Update on the Diagnosis and Management of Inherited Aortopathies, Including Marfan Syndrome. Heart Lung Circ. 2017;26(6):536-544. doi:10.1016/j.hlc.2016.10.023
11. Callewaert B, De Paepe A, Coucke P. Arterial Tortuosity Syndrome. 2014 Nov 13 [Updated 2020 Nov 19]. 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/NBK253404/
12. National Library of Medicine (US). Familial thoracic aortic aneurysm and dissection (updated 18 August 2020). MedlinePlus website. Available at: https://medlineplus.gov/genetics/condition/familial-thoracic-aortic-aneurysm-and-dissection/.
13. 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/
14. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
15. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.

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