Revision log
Coding_Implications

CONCERT GENETIC TESTING: AORTOPATHIES AND CONNECTIVE TISSUE DISORDERS

See Important Reminder at the end of this policy for important regulatory and legal information.

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, and 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

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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

Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Connective Tissue Disorders				
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	3, 4, 5, 6
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	5
Loeys-Dietz Syndrome				

Loeys-Dietz Syndrome Multigene Panel	Loeys-Dietz Syndrome Panel (PreventionGenetics, part of Exact Sciences)	81405, 81408, 81479	I71.00-I71.9	1
	Loeys-Dietz Syndrome Panel (Invitae)			
Familial Thoracic Aortic Aneurysm and Dissection (TAAD)				
Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel	Thoracic Aortic Aneurysm Panel (Cincinnati Children's Hospital Medical Center- Molecular Genetics and Cytogenetics Laboratories)	81405, 81406, 81408, 81479	I71.00-I71.9, Q87.5	1, 7, 11
	TAAD Panel Next Generation Sequencing (DDC Clinic Laboratory)	81410, 81411		
	TAADNext (Ambry Genetics)			
	Marfan syndrome, Loeys-Dietz syndrome, Familial thoracic aortic aneurysms & dissections, and Related disorders NGS Panel - Comprehensive (CTGT)			
	Marfan Syndrome and Thoracic Aortic Aneurysm and Dissection NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics)			
	Marfan/TAAD Panel (GeneDx)			
	Aortopathy Comprehensive Panel (Invitae)			
Ehlers-Danlos Syndrome				
Classic Ehlers-Danlos Syndrome (cEDS)				
Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel	Ehlers Danlos Panel (GeneDx)	81408, 81479	M35.7, Q79.61, Q79.63, Q79.69	2, 3
	Ehlers-Danlos Syndrome Panel (Revvity)			
	Ehlers-Danlos syndrome, classic type NGS panel (CTGT)			
Vascular Ehlers-Danlos Syndrome (vEDS)				

COL3A1 Sequencing and/or Deletion/Duplication Analysis	COL3A1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479	Q79.63	2
Other Covered Connective Tissue Disorders				
Other Covered Connective Tissue Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408		8, 9, 10

OTHER RELATED POLICIES

This policy document provides coverage 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 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 related to aortopathies and connective tissue disorders not specifically discussed in this or another non-general policy, including known familial variant testing

back to top

CRITERIA

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related 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/enrollee meets criteria for at least one of the following (see specific coverage 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).

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

back to top

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/enrollee 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/enrollee 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

back to top

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/enrollee 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/enrollee 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.

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

NOTE**:** If the member/enrollee 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.

back to top

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/enrollee has a history of any of the following:

      1. Aortic root enlargement, **OR**
      2. Thoracic aneurysm, **OR**
      3. Type A or type B aortic dissection, **AND**

   B. The member/enrollee 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.

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

back to top

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.

back to top

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.

back to top

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).

NOTE: 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.

back to top

DEFINITIONS

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

back to top

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 “Sequence analysis of *COL5A1* and *COL5A2* (multigene targeted panels may also include *COL1A1* and other EDS-related genes…) is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions…”

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."

FBN1 Sequencing and/or Deletion/Duplication Analysis

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)

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 (p. 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 AHA and ACC 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 years of age
- 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 [heritable thoracic aortic disease] 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.

"Sequencing analysis of *COL5A1* and *COL5A2*…is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions."

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

International EDS Consortium

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.

back to top

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding reference table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria For Policy Reference Table: Removed "Comprehensive Ehlers-Danlos Syndrome Multigene Panels…" For Other Related Policies: added "and Molecular". For Comprehensive Connective Tissue Disorders Multigene Panel and Classic Ehlers-Danlos Syndrome Multigene Panel:, added "including isolated hypermobility…"; For vascular Ehlers-Danlos Syndrome (vEDS): under II. removed "Comprehensive Ehlers-Danlos Syndrome…" and added "including isolated hypermobility…"; For Other Covered Connective Tissue Disorders: removed "81411, 81410"; and added statement "Of note, per GeneReviews…"; For Background and Rationale: removed "some of all of the 16 genes…" and added "genes associated with HTAD…"; added "GeneReviews: FBN1-Related Marfan Syndrome…"; for Familial Thoracic Aortic Aneurysm and Dissection (TAAD)	10/23	10/23

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Multigene Panel: removed "The recommended diagnostic testing for TAAD…"; and added "Per the Heritable Thoracic Aortic Disease…". Removed "Hypermobile Ehlers-Danlos syndrome…"		
Semi-annual review. Updated title to reflect V2.2024 version. In Known Familial Variant Analysis for Aortopathies and Connective Tissue Disorders criteria, moved criteria to policy "Genetic Testing: General Approach to Genetic and Molecular Testing" to consolidate criteria for known familial variant tests. In FBN1 Sequencing and/or Deletion/Duplication Analysis criteria, made a minor expansion to criteria to better align with guidelines and allow for coverage of genetic testing for individuals with a clinical diagnosis of Marfan syndrome. In criteria for Loeys-Dietz Syndrome Multigene Panel, removed minimum gene list. In Classic Ehlers-Danlos syndrome (cEDS) Multigene panel criteria, made a minor expansion in gene list to align with current test offerings on the market and removed COL1A1 from the minimum gene list. In Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel criteria, removed minimum gene list. In Other Covered Connective Tissue Disorders criteria, genes added to disease name in list for consistency and to provide further clarity. Minor rewording for clarity throughout. Coding, reference-table, background and references updated.	04/24	04/24
Semi-annual review. Updated title to reflect V1.2025 version. Marfan Syndrome - FBN1 Sequencing and/or Deletion/Duplication Analysis: Removed ACMG reference from the Background and Rationale and from the references section because this reference is over 10 years old. Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel: Updated formatting in the criteria, including changing "The member has" to "The member has a history of any of the following". Loeys-Dietz Syndrome Multigene Panel: Removed MacCarrick et al. (2014 (doi: 10.1038/gim.2014.11)) and related information, as this source was used to support a minimum gene list that is no longer used in this criteria. Other Covered Connective Tissue Disorders: Updated the CPT codes in the policy reference table to list individual codes rather than a range of codes. COL3A1 Sequencing and/or Deletion/Duplication Analysis: Updated grammar in Background and Rationale. Comprehensive Connective Tissue Disorders Multigene Panel: Updated Background and Rationale: Removed "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."; Added: "The GeneReviews for Ehlers-Danlos Syndrome (EDS) states that "Sequence analysis of COL5A1 and COL5A2 (multigene targeted panels may also include COL1A1 and other EDS-related genes…) is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions…".	11/24	11/24

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back to top

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.