BSC_CON_2.19	Genetic Testing: Aortopathies and Connective Tissue Disorders		
Original Policy Date:	January 1, 2024	**Effective Date:**	January 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 22

Example Test Table

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 criteria; 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.

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Connective Tissue Disorders		
Comprehensive Connective Tissue Disorders Multigene Panel	Heritable Disorders of Connective Tissue Panel (GeneDx)	81410, 81411
	Invitae Connective Tissue Disorders Panel (Invitae)	
Marfan Syndrome		
FBN1 Sequencing and/or Deletion/Duplication Analysis	FBN1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81408, 81479
	Marfan Syndrome via FBN1 Gene (PreventionGenetics, part of Exact Sciences)	
Loeys-Dietz Syndrome		
Loeys-Dietz Syndrome Multigene Panel	Loeys-Dietz Syndrome Panel (PreventionGenetics, part of Exact Sciences)	81405, 81408, 81479
	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
	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)	

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
	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
	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
Other Covered Connective Tissue Disorders		
Other Covered Connective Tissue Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408

Policy Statement

CONNECTIVE TISSUE DISORDERS
Comprehensive Connective Tissue Disorders Multigene Panel

I. Comprehensive connective tissue disorders multigene panel analysis (81410, 81411) may be 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).

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

MARFAN SYNDROME
FBN1 Sequencing and/or Deletion/Duplication Analysis

III. *FBN1* sequencing and/or deletion/duplication analysis (81408, 81479) to confirm a diagnosis of Marfan syndrome may be considered **medically necessary** when **EITHER** of the following criteria are met:
   A. The member has **one** of the following:
      1. Aortic root enlargement (Z-score of 2 or greater) or dissection

2. Ectopia lentis

B. The member has a systemic score of 7 or higher using the list of symptoms below (point values in parentheses):
   1. Wrist AND thumb sign (3)
   2. Wrist OR thumb sign (1)
   3. Pectus carinatum deformity (2)
   4. Pectus excavatum or chest asymmetry (1)
   5. Hindfoot deformity (2)
   6. Plain flat foot (pes planus) (1)
   7. Pneumothorax (2)
   8. Dural ectasia (2)
   9. Protrusio acetabulae (2)
   10. Reduced upper segment / lower segment AND increased arm span/height ratios (1)
   11. Scoliosis or thoracolumbar kyphosis (1)
   12. Reduced elbow extension (1)
   13. 3 of 5 facial features (dolichocephaly, downward slanting palpebral fissures, enophthalmos, retrognathia, malar hypoplasia) (1)
   14. Skin striae (1)
   15. Myopia (1)
   16. Mitral valve prolapse (1)

IV. *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

LOEYS-DIETZ SYNDROME
Loeys-Dietz Syndrome Multigene Panel

V. Loeys-Dietz syndrome (LDS) multigene panel analysis (81405, 81408, 81479)* to establish or confirm a diagnosis of Loeys-Dietz syndrome may be considered **medically necessary** when:
   A. The member meets **at least two** of the following:
      1. Characteristic facial features, including widely spaced eyes and craniosynostosis
      2. Bifid uvula or cleft palate
      3. Tortuosity of the aorta and its branches
      4. Aortic dilatation and dissection
      5. Joint hypermobility
      6. The member has a first-degree relative with a clinical diagnosis of LDS.

VI. 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 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.

FAMILIAL THORACIC AORTIC ANEURYSM AND DISSECTION (TAAD)
Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel

VII. Familial thoracic aortic aneurysm and dissection (TAAD) multigene panel analysis (81405, 81406, 81408, 81410, 81411, 81479) to establish a genetic diagnosis for TAAD may be considered **medically necessary** when **ALL** of the following criteria are met:

A. The member has a history of **any** of the following:
   1. Aortic root enlargement
   2. Thoracic aneurysm
   3. Type A or type B aortic dissection
B. The member does not otherwise meet diagnostic criteria for another connective tissue disorder
C. The member has a family history of dilation or dissection of the aortic root, consistent with autosomal dominant inheritance.

VIII. 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

EHLERS-DANLOS SYNDROME
Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel

IX. Classic Ehlers-Danlos syndrome multigene panel analysis (81408, 81479) to establish or confirm a diagnosis of cEDS may be considered **medically necessary** when **ALL** of the following criteria are met:
   A. The member has skin hyperextensibility and atrophic scarring
   B. The member meets **at least one** of the following:
      1. Generalized joint hypermobility
      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 includes, at a minimum, the following genes: *COL5A1* and *COL5A2*.

X. 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.

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

XI. *COL3A1* sequencing and/or deletion/duplication analysis (81479) to establish or confirm a diagnosis of vEDS may be considered **medically necessary** when:
   A. The member meets **any** of the following:
      1. Arterial rupture or dissection under the age of 40

2. Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology
3. Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears
4. Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma
5. The member has a close relative with a clinical diagnosis of vEDS
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 female).

XII. *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.

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.

XIII. 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 may be considered **medically necessary** when the member demonstrates clinical features consistent with the disorder (the list is not meant to be comprehensive, see XIV 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*)

XIV. 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).

> ***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.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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.

Coding
See the Codes table for details.

Description

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.

Related Policies

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

- ***Genetic Testing: Cardiac Disorders*** for coverage criteria related to arrhythmias and cardiomyopathies.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to genetic disorders that affect multiple organ systems.

- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing.
- ***Genetic Testing: Preimplantation Genetic Testing*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to aortopathies and connective tissue disorders not specifically discussed in this or another non-general policy, including known familial variant testing

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Rationale

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.

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Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier.
  The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81402	Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion

Type	Code	Description
		variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
	81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
	81410	Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
	81411	Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/01/2024	New policy.
01/01/2025	Annual review. Policy statement, guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Genetic Testing: Aortopathies and Connective Tissue Disorders **BSC_CON_2.19** **Policy Statement:** **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 may be 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 aortopathies and connective tissue disorder is considered **investigational** for all other indications. **CONNECTIVE TISSUE DISORDERS** **Comprehensive Connective Tissue Disorders Multigene Panel** III. Comprehensive connective tissue disorders multigene panel analysis (81410, 81411)* may be 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) IV. 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	**Genetic Testing: Aortopathies and Connective Tissue Disorders** **BSC_CON_2.19** **Policy Statement:** **CONNECTIVE TISSUE DISORDERS** **Comprehensive Connective Tissue Disorders Multigene Panel** I. Comprehensive connective tissue disorders multigene panel analysis (81410, 81411) may be 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). ***NOTE:*** If a panel is performed, the appropriate panel code should be used

POLICY STATEMENT	
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MARFAN SYNDROME ***FBN1* Sequencing and/or Deletion/Duplication Analysis** V. *FBN1* sequencing and/or deletion/duplication analysis (81408, 81479) to confirm a diagnosis of Marfan syndrome may be considered **medically necessary** when **EITHER** of the following criteria are met: 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 b. **At least two** of the following systemic symptoms reaching a score of 7 or higher (points are in parentheses): i. Wrist AND thumb sign (3) ii. Wrist OR thumb sign (1) iii. Pectus carinatum deformity (2) iv. Pectus excavatum or chest asymmetry (1) v. Hindfoot deformity (2) vi. Plain flat foot (pes planus) (1) vii. Pneumothorax (2) viii. Dural ectasia (2) ix. Protrusio acetabulae (2) x. Reduced upper segment / lower segment AND increased arm span/height ratios (1) xi. Scoliosis or thoracolumbar kyphosis (1) xii. Reduced elbow extension (1) xiii. 3 of 5 facial features (dolichocephaly, downward slanting palpebral fissures, enophthalmos, retrognathia, malar hypoplasia) (1) xiv. Skin striae (1) xv. Myopia (1) xvi. Mitral valve prolapse (1) B. The member has a close relative with a documented clinical diagnosis of Marfan syndrome, **AND**	MARFAN SYNDROME ***FBN1* Sequencing and/or Deletion/Duplication Analysis** III. *FBN1* sequencing and/or deletion/duplication analysis (81408, 81479) to confirm a diagnosis of Marfan syndrome may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has **one** of the following: 1. Aortic root enlargement (Z-score of 2 or greater) or dissection 2. Ectopia lentis B. The member has a systemic score of 7 or higher using the list of symptoms below (point values in parentheses): 1. Wrist AND thumb sign (3) 2. Wrist OR thumb sign (1) 3. Pectus carinatum deformity (2) 4. Pectus excavatum or chest asymmetry (1) 5. Hindfoot deformity (2) 6. Plain flat foot (pes planus) (1) 7. Pneumothorax (2) 8. Dural ectasia (2) 9. Protrusio acetabulae (2) 10. Reduced upper segment / lower segment AND increased arm span/height ratios (1) 11. Scoliosis or thoracolumbar kyphosis (1) 12. Reduced elbow extension (1) 13. 3 of 5 facial features (dolichocephaly, downward slanting palpebral fissures, enophthalmos, retrognathia, malar hypoplasia) (1) 14. Skin striae (1) 15. Myopia (1) 16. Mitral valve prolapse (1).

POLICY STATEMENT	
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1. The member does **not** have **any** of the following: a. Ectopia lentis b. Multiple systemic features (see above) c. A dilated aortic root (if over 20 years, greater than two standard deviations; if younger than 20, greater than three standard deviations).	
VI. *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.	IV. *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	***NOTE***: Full explanation of each feature and calculation can be found at https://www.marfan.org/dx/score
LOEYS-DIETZ SYNDROME **Loeys-Dietz Syndrome Multigene Panel**	**LOEYS-DIETZ SYNDROME** **Loeys-Dietz Syndrome Multigene Panel**
VII. Loeys-Dietz syndrome (LDS) multigene panel analysis (81405, 81408, 81479) to establish or confirm a diagnosis of Loeys-Dietz syndrome may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member meets **at least two** of the following: 1. Characteristic facial features, including widely spaced eyes and craniosynostosis 2. Bifid uvula or cleft palate 3. Tortuosity of the aorta and its branches 4. Aortic dilatation and dissection 5. Joint hypermobility 6. The member has a first-degree relative with a clinical diagnosis of LDS B. The panel includes, at a minimum, the following genes*: *SMAD2*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2*.	V. Loeys-Dietz syndrome (LDS) multigene panel analysis (81405, 81408, 81479)* to establish or confirm a diagnosis of Loeys-Dietz syndrome may be considered **medically necessary** when: A. The member meets **at least two** of the following: 1. Characteristic facial features, including widely spaced eyes and craniosynostosis 2. Bifid uvula or cleft palate 3. Tortuosity of the aorta and its branches 4. Aortic dilatation and dissection 5. Joint hypermobility 6. The member has a first-degree relative with a clinical diagnosis of LDS.
VIII. 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.	VI. 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.

POLICY STATEMENT	
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* 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	*NOTE:* If a panel is performed, the appropriate panel code should be used *NOTE*: If the member has both aortic root enlargement and ectopia lentis, *FBN1* should either be included in the panel or should have been previously performed and the results were negative.
FAMILIAL THORACIC AORTIC ANEURYSM AND DISSECTION (TAAD) **Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel**	**FAMILIAL THORACIC AORTIC ANEURYSM AND DISSECTION (TAAD)** **Familial Thoracic Aortic Aneurysm and Dissection (TAAD) Multigene Panel**
IX. Familial thoracic aortic aneurysm and dissection (TAAD) multigene panel analysis (81405, 81406, 81408, 81410, 81411, 81479) to establish a genetic diagnosis for TAAD may be considered **medically necessary** when **ALL** of the following criteria are met: A. The member has aortic root enlargement or has had thoracic aneurysm or a type A or type B aortic dissection B. The member does not otherwise meet diagnostic criteria for another connective tissue disorder 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.*	VII. Familial thoracic aortic aneurysm and dissection (TAAD) multigene panel analysis (81405, 81406, 81408, 81410, 81411, 81479) to establish a genetic diagnosis for TAAD may be considered **medically necessary** when **ALL** of the following criteria are met: A. The member has a history of **any** of the following: 1. Aortic root enlargement 2. Thoracic aneurysm 3. Type A or type B aortic dissection B. The member does not otherwise meet diagnostic criteria for another connective tissue disorder C. The member has a family history of dilation or dissection of the aortic root, consistent with autosomal dominant inheritance.
X. 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.	VIII. 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	*NOTE:* If a panel is performed, the appropriate panel code should be used
EHLERS-DANLOS SYNDROME **Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel**	**EHLERS-DANLOS SYNDROME** **Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel**

POLICY STATEMENT	
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XI. Classic Ehlers-Danlos syndrome multigene panel analysis (81408, 81479) to establish or confirm a diagnosis of cEDS may be considered **medically necessary** when **ALL** of the following criteria are met: A. The member has skin hyperextensibility and atrophic scarring B. The member meets at least one of the following: 1. Generalized joint hypermobility 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*.	IX. Classic Ehlers-Danlos syndrome multigene panel analysis (81408, 81479) to establish or confirm a diagnosis of cEDS may be considered **medically necessary** when **ALL** of the following criteria are met: A. The member has skin hyperextensibility and atrophic scarring B. The member meets **at least one** of the following: 1. Generalized joint hypermobility 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 includes, at a minimum, the following genes: *COL5A1* and *COL5A2*.
XII. 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)	X. 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.
Vascular Ehlers-Danlos Syndrome (vEDS) *COL3A1* Sequencing and/or Deletion/Duplication Analysis	**Vascular Ehlers-Danlos Syndrome (vEDS)** ***COL3A1* Sequencing and/or Deletion/Duplication Analysis**

POLICY STATEMENT	
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XIII. *COL3A1* sequencing and/or deletion/duplication analysis (81479) to establish or confirm a diagnosis of vEDS may be considered **medically necessary** when: A. The member meets **any** of the following: 1. Arterial rupture or dissection under the age of 40 2. Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology 3. Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears 4. Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma 5. The member has a close relative with a clinical diagnosis of vEDS 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 female).	XI. *COL3A1* sequencing and/or deletion/duplication analysis (81479) to establish or confirm a diagnosis of vEDS may be considered **medically necessary** when: A. The member meets **any** of the following: 1. Arterial rupture or dissection under the age of 40 2. Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology 3. Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears 4. Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma 5. The member has a close relative with a clinical diagnosis of vEDS 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 female).
XIV. *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).	XII. *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).

POLICY STATEMENT	
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	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.
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.	**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.
XV. 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 may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see XVI 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*)	XIII. 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 may be considered **medically necessary** when the member demonstrates clinical features consistent with the disorder (the list is not meant to be comprehensive, see XIV 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*)
XVI. 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).	XIV. 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).

POLICY STATEMENT	
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*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.	***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.