Comprehensive Connective Tissue Disorders Multigene Panel

I. Comprehensive connective tissue disorders multigene panel analysis is considered **medically necessary** when:

   A. The member meets criteria for at least one of the following (see specific coverage criteria sections below):

      1. Marfan Syndrome
      2. Loeys-Dietz Syndrome
      3. Classic Ehlers-Danlos Syndrome
      4. Vascular Ehlers-Danlos Syndrome (vEDS).

II. Comprehensive connective tissue disorders multigene panel analysis 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

FBN1 Sequencing and/or Deletion/Duplication Analysis

I. *FBN1* sequencing and/or deletion/duplication analysis to confirm a diagnosis of Marfan syndrome is considered **medically necessary** when:

   A. The member has one of the following:

      1. Aortic root enlargement (Z-score of 2 or greater) or dissection, **OR**
      2. Ectopia lentis, **OR**

   B. The member has a systemic score of 7 or higher using the list of symptoms below (point values in parentheses):

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

II. *FBN1* sequencing and/or deletion/duplication analysis 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 Multigene Panel

I. Loeys-Dietz syndrome (LDS) multigene panel analysis to establish or confirm a diagnosis of Loeys-Dietz syndrome is considered **medically necessary** when:

   A. The member meets at least two of the following:

      1. Characteristic facial features, including widely spaced eyes and craniosynostosis, **OR**
      2. Bifid uvula or cleft palate, **OR**
      3. Tortuosity of the aorta and its branches, **OR**
      4. Aortic dilatation and dissection, **OR**
      5. Joint hypermobility, **OR**
      6. The member has a first-degree relative with a clinical diagnosis of LDS.

II. Loeys-Dietz syndrome (LDS) multigene panel analysis 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.

Classic Ehlers-Danlos Syndrome (cEDS) Multigene Panel

I. Classic Ehlers-Danlos syndrome multigene panel analysis 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 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 investigational.

COL3A1 Sequencing and/or Deletion/Duplication Analysis

I. *COL3A1* sequencing and/or deletion/duplication analysis 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 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, 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 investigational.

RATIONALE AND REFERENCES

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…”

Malfait F, Symoens S, Syx D. Classic Ehlers-Danlos Syndrome. 2007 May 29 [Updated 2024 Feb 1]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1244/

GeneReviews: Hypermobile Ehlers-Danlos Syndrome

Per the Hypermobile Ehlers-Danlos Syndrome (EDS) GeneReviews, there are currently no genetic etiologies that have been identified for hypermobile EDS.

Levy HP. Hypermobile Ehlers-Danlos Syndrome. 2004 Oct 22 [Updated 2024 Feb 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews[Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1279/

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”.

Dietz H. FBN1-Related Marfan Syndrome. 2001 Apr 18 [Updated 2022 Feb 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1335/

GeneReviews: Loeys-Dietz Syndrome

Per the Loeys-Dietz Syndrome (LDS) GeneReviews, it may be appropriate to order a multigene panel for Marfan syndrome/LDS/familial thoracic aortic aneurysms and dissections for genes associated with disorders that can include aortic aneurysms and dissections.

Loeys BL, Dietz HC. Loeys-Dietz Syndrome. 2008 Feb 28 [Updated 2024 Sep 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1133/

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. **Dissection** refers to a tear in the inner layer of a main artery (aorta).
    a. **Type A aortic dissections** occur at the ascending part of the aorta, just as it branches off of the heart.
    b. **Type B aortic dissections** occur at the descending part of the aorta, and may extend into the abdomen.