Genetic Testing for Ehlers-Danlos Syndrome

Humana®

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Medical Coverage Policy

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Related Medical/Pharmacy Coverage Policies

Genetic Testing

Description

Ehlers-Danlos syndrome (EDS) is a group of inherited disorders affecting the connective tissues. Common characteristics of EDS include easy bruising, skin hyperelasticity or laxity, joint hypermobility and tissue weakness. EDS is categorized by type:

- Classic (EDS types I and II)
- Hypermobility (EDS type III)
- Vascular (vEDS) (EDS type IV)
- Kyphoscoliosis (EDS type VI)
- Arthrochalasia (EDS types VIIA & B)
- Dermatosparaxis (EDS type VIIC)
- Periodontal (EDS type VIII)

Classic, hypermobility and vascular type occur more frequently than the other types. Other rarer forms include spondylocheirodysplasia EDS and musculocontractural EDS; additional rare variants of EDS have also been described.[11]

Genetic testing may be used to aid in the diagnosis of vEDS in an individual exhibiting signs and symptoms of the condition as well as for determining susceptibility in an unaffected individual with a family history of EDS. Genetic testing has been proposed for assisting in the diagnosis and prediction of risk in other types of EDS. **(Refer to Coverage Limitations section)**

Multigene panels have been proposed to evaluate genes associated with diseases or syndromes. Panels often include medically actionable genes but may also include those with unclear medical management. Targeted multigene panels are also commercially available. These panels limit the number of genes and are targeted to a specific condition. In general, multigene panels are not appropriate; however, in rare instances, targeted panel analysis may be applicable. **(Refer to Coverage Limitations section)**

Coverage Determination

Any state mandates for genetic testing for EDS take precedence over this medical coverage policy.

Genetic testing may be excluded by certificate. Please consult the member's individual certificate regarding Plan coverage.

Apply General Criteria for Genetic and Pharmacogenomics Tests when disease- or gene-specific criteria are not available on a medical coverage policy. For information regarding **General Criteria for Genetic and Pharmacogenomics Tests**, please refer to Genetic Testing Medical Coverage Policy.

vEDS – Known Familial Pathogenic or Likely Pathogenic Variant (KFV)
Humana members may be eligible under the Plan for **targeted analysis of *COL3A1* gene KFV** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**

- Individual to be tested has an affected first-degree relative with a pathogenic or likely pathogenic variant in the *COL3A1* gene. Genetic testing should be limited to the KFV.

vEDS – Affected Individual
Humana members may be eligible under the Plan for **sequence analysis of *COL3A1* gene for vEDS** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**

    - Individual to be tested has a clinical diagnosis of vEDS and at least one of the following indications:

        - Arterial rupture; **OR**

- First-degree relative diagnosed with vEDS; **OR**
- Intestinal rupture; **OR**
- Uterine rupture during pregnancy; **OR**

- Individual to be tested has at least **two** of the following signs and symptoms:
  - Acrogeria (aged appearance to extremities, particularly hands); **OR**
  - Arteriovenous carotid cavernous sinus fistula; **OR**
  - Characteristic facial appearance (eg, thin lips and philtrum, small chin, thin nose, large eyes); **OR**
  - Chronic joint subluxations/dislocations; **OR**
  - Clubfoot; **OR**
  - Congenital dislocation of the hips; **OR**
  - Early-onset varicose veins; **OR**
  - Easy bruising (spontaneous or with minimal trauma); **OR**
  - Gingival recession; **OR**
  - Hypermobility of small joints; **OR**
  - Pneumothorax/pneumohemothorax; **OR**
  - Tendon/muscle rupture; **OR**
  - Thin, translucent skin (especially noticeable on chest/abdomen)

vEDS – Unaffected Individual
Humana members may be eligible under the Plan for **sequence analysis of *COL3A1* gene for vEDS** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested is unaffected and has a first-degree relative who has been diagnosed with vEDS

Please refer to **Coverage Limitations section** for deletion/duplication analysis of COL3A1 gene.

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for **genetic testing for vEDS** for any indications other than those listed above including:

- Genetic testing for EDS, classic type (*COL5A1* and *COL5A2* genes)
- KFV detection analysis if the individual to be tested previously received KFV testing, single gene analysis or multigene panel testing that would have detected the KFV

This is considered **not medically necessary** as defined in the member's individual certificate. Please refer to the member's individual certificate for the specific definition.

Humana members may **NOT** be eligible under the Plan for **genetic testing for EDS** for any indications other than those listed above including, but not limited to, the following:

- Deletion/duplication analysis of *COL3A1* gene
- EDS, arthrochalasia (*COL1A1, COL1A2* genes)
- EDS, dermatosparaxis (*ADAMTS2* gene)
- EDS, hypermobility type (*TNXB* gene)
- EDS, kyphoscoliotic type (*PLOD1* gene)
- EDS, periodontal type (*C1R, C1S* genes)
- Multigene panels unless **ALL** genes in the panel meet disease- or gene-specific criteria (81410 and 81411) (Refer to Coverage Determination section)

These are considered experimental/investigational as they are not identified as widely used and generally accepted for any other proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments

81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)	**Not Covered if used to report any test outlined in Coverage Limitations section**
81408	MOLECULAR PATHOLOGY PROCEDURE LEVEL 9	**Not Covered if used to report any test outlined in Coverage Limitations section**
81410	Aortic dysfunction or dilation (eg, 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	**Not Covered**
81411	Aortic dysfunction or dilation (eg, 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	**Not Covered**
81479	Unlisted molecular pathology procedure	**Not Covered if used to report any test outlined in Coverage Limitations section**
84166	Protein; electrophoretic fractionation and quantitation, other fluids with concentration (eg, urine, CSF)	
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
S0265	Genetic counseling, under physician supervision, each 15 minutes	

References

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15. UpToDate, Inc. Overview of the management of Ehlers-Danlos syndromes. https://www.uptodate.com. Updated January 2024.

Appendix

Appendix A

Pre- and Post-Test Genetic Counseling Criteria

Pre- and post-test genetic counseling performed by any of the following qualified medical professionals
Genetic counselor who is board-certified or board-eligible by the American Board of Medical Genetics and Genomics (ABMGG) or American Board of Genetic Counseling, Inc (ABGC) and is not employed by a commercial genetic testing laboratory; **OR**
Genetic clinical nurse (GCN) or advanced practice nurse in genetics (APNG) who is credentialed by the Genetic Nursing Credentialing Commission (GNCC) or the American of Nurses Credentialing Center (ANCC) and is not employed by a commercial genetic testing laboratory; **OR**
Medical geneticist who is board-certified or board-eligible by ABMGG; **OR**
Treating physician who has evaluated the individual to be tested and has completed a family history of three generations

Appendix B
Family Relationships

Degree of Relationship	Relative of the Individual to be Tested
First-degree	Child, full-sibling, parent
Second-degree	Aunt, grandchild, grandparent, nephew, niece, half-sibling, uncle
Third-degree	Great aunt, great-grandchildren, great-grandparent, great-uncle, half-aunt, half-uncle, first cousin

Change Summary

- 02/29/2024 Annual Review, No Coverage Change.