Genetic Testing for Marfan Syndrome and Related Conditions

Humana®

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Medical Coverage Policy

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Description

Marfan syndrome is a genetic disorder in which the body's connective tissue is abnormal. The disorder affects many parts of the body; primarily, blood vessels, bones, connective tissue of the heart, covering of the spinal cord, eyes and lungs.

Marfan syndrome diagnosis relies on a set of strict major and minor criteria known as the Ghent nosology, a scoring system developed to aid in the clinical diagnosis of Marfan syndrome.[33] Two fundamental features of the Ghent nosology are aortic root dilatation and ectopia lentis. In the absence of a family history of Marfan syndrome, the presence of aortic root dilatation and ectopia lentis are sufficient to diagnose Marfan syndrome. Without these two conditions or a combination of systemic features described in the Ghent nosology, genetic testing may be required to confirm a diagnosis. Even with the availability of genetic testing, establishing a diagnosis of Marfan syndrome depends heavily upon significant clinical findings.

A variety of conditions including, but not limited to, Loeys-Dietz syndrome (LDS) and familial thoracic aortic aneurysm and dissection (TAAD) have overlapping clinical manifestations of Marfan syndrome and should be distinguished from Marfan syndrome with documentation of discriminating features, biochemical and/or genetic testing, when indicated.

Familial TAAD is an inherited disorder that causes the aorta to weaken and stretch. Variants in any of several genes are associated with familial TAAD. **(Refer to Coverage Limitations section)**

LDS is an inherited connective tissue disorder characterized by aortic aneurysms and other blood vessel abnormalities.

Predictive genetic testing for LDS, Marfan syndrome and TAAD may be sought for unaffected or presymptomatic family members to detect variants in the genes known to cause these disorders to determine if the individual will develop the condition.

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. **(Refer to Coverage Limitations section)**

Coverage Determination

Any state mandates for genetic testing for familial TAAD, LDS or Marfan syndrome 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 Tests when disease- or gene-specific criteria are not available on a medical coverage policy. For information regarding **general criteria for genetic tests**, please refer to Genetic Testing Medical Coverage Policy.

Familial Thoracic Aortic Aneurysm and Dissection (TAAD) – *ACTA2, FBN1, LOX, MYH11, MYLK, PRKG1, SMAD3, TGFB2, TGFBR1* and *TGFBR2* Genes
Humana members may be eligible under the Plan for **genetic testing for familial TAAD** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
    - Individual to be tested is affected and is being considered for prophylactic surgery for aortic dissection; **OR**
    - Individual to be tested is unaffected and has an affected first-degree relative with a known pathogenic or likely pathogenic variant. **Testing strategy:** Test for known familial variant (KFV).

Loeys-Dietz Syndrome (LDS) – *TGFBR1* and *TGFBR2* Genes

Humana members may be eligible under the Plan for ***TGFBR1* and *TGFBR2* gene testing for LDS** 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 known pathogenic or likely pathogenic variant. **Testing strategy**: Test for KFV; **OR**
  - To confirm or establish a diagnosis of LDS when at least 2 of the following are present:
    - Aortic/arterial aneurysms/tortuosity
    - Arachnodactyly
    - Bicuspid aortic valve and patent ductus arteriosus
    - Blue sclerae
    - Camptodactyly
    - Cerebral, thoracic or abdominal arterial aneurysms and/or dissections
    - Cleft palate/bifid uvula
    - Club feet
    - Craniosynostosis
    - Eosinophilic esophagitis/gastritis
    - Ocular hypertelorism
    - Pectus carinatum or pectus excavatum
    - Scoliosis
    - Talipes equinovarus
    - Widely spaced eyes

  Testing strategy: Begin with *TGFBR2* gene sequencing. If negative, proceed with *TGFBR1* gene sequencing.

Marfan Syndrome – *FBN1* Gene

Humana members may be eligible under the Plan for ***FBN1* gene testing for Marfan syndrome** 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 known pathogenic or likely pathogenic variant. **Testing strategy**: Test for KFV; **OR**
  - Individual to be tested does not meet clinical diagnostic criteria for Marfan syndrome but diagnosis is highly suspected

Testing strategy: Begin with *FBN1* gene sequencing. If negative, proceed to *FBN1* gene deletion/duplication analysis.

Coverage Limitations

Humana members may **NOT** be eligible for **genetic testing for TAAD, LDS or Marfan syndrome** for any genes, indications or tests other than those listed above including, but may not be limited to:

- LDS for any gene other than *TGFBR1* and *TGFBR2* (81410, 81411)
- Marfan syndrome for any gene other than *FBN1* (81410, 81411)
- TAAD for any gene (alone or in a panel) other than *ACTA2, FBN1, LOX, MYH11, PRKG1, SMAD3, TGFB2, TGFBR1* and *TGFBR2* including, but may not be limited to:
    - *BGN*
    - *COL3A1**
    - *EFEMP2*
    - *FBN2*
    - *FLNA*
    - *FOXE3*
    - *HCN4*
    - *MAT2A*
    - *MFAP5*
    - *MYLK*
    - *NOTCH1*
    - *SLC2A10*
    - *SMAD2*
    - *TGFB3*

  * For information regarding ***COL3A1* gene testing for Ehler's Danlos syndrome**, please refer to Genetic Testing for Ehlers-Danlos Syndrome Medical Coverage Policy.

- To diagnose Marfan syndrome when a diagnosis can be established using clinical diagnostic criteria
- Multigene panels unless **ALL** genes in the panel meet disease- or gene-specific criteria (for single genes included in a panel, apply appropriate criteria in Coverage Determinations section). Examples include, but may not be limited to:
    - Aortic dysfunction or dilation duplication/deletion analysis panel
    - Aortic dysfunction or dilation genomic sequence analysis panel
    - GeneDx – Heritable Disorders of Connective Tissue Panel
    - GeneDx – Marfan/TADD panel(s)
    - Invitae Aortopathy Comprehensive Panel

- TAADNext

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

Humana members may **NOT** be eligible under the Plan for **genetic testing for familial TAAD, LDS or Marfan syndrome** when the individual to be tested is unaffected and an affected first-, second- or third-degree relative **IS** available for genetic testing (if the relative is unavailable [eg, deceased, declines genetic testing or inability to contact] for testing, apply disease or gene-specific criteria for the unaffected individual). 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.

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
81401	MOLECULAR PATHOLOGY PROCEDURE LEVEL 2	**Not Covered if used to report test outlined in Coverage Limitations section**
81405	MOLECULAR PATHOLOGY PROCEDURE LEVEL 6	**Not Covered if used to report test outlined in Coverage Limitations section**
81406	MOLECULAR PATHOLOGY PROCEDURE LEVEL 7	**Not Covered if used to report test outlined in Coverage Limitations section**
81408	MOLECULAR PATHOLOGY PROCEDURE LEVEL 9	**Not Covered if used to report 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 test outlined in Coverage Limitations section**
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	

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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, uncle, grandchild, grandparent, nephew, niece, half-sibling
Third-degree	First cousin, great aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half-uncle

Appendix C
Clinical Diagnostic Criteria for Marfan Syndrome

No family history of Marfan syndrome and **ANY** of the following are diagnostic for Marfan syndrome:

- Ectopia lentis or Marfan syndrome systemic score at least 7 (systemic score calculator); **AND**
    - Aortic diameter Z score at least 2 (Z score calculator); **OR**
    - Aortic root dissection

Family history of Marfan syndrome and **ANY** of the following are diagnostic for Marfan syndrome:

- Individual is 20 years of age or older and aortic diameter Z score at least 7 (Z score calculator); **OR**
- Individual is 19 years of age or younger and aortic diameter Z score at least 3 (Z score calculator); **OR**
- Aortic root dissection**; OR**
- Ectopia lentis; **OR**
- Marfan syndrome systemic score at least 7 (systemic score calculator)

Change Summary

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