

MEDICAL POLICY

Medical Policy Title	Genetic Testing for Thoracic Aortic Aneurysms/ Dissections and Connective Tissue Related Disorders
Policy Number	2.02.61
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Our medical policies are guides to evaluate technologies or services for medical necessity. Criteria are established through the assessment of evidence based, peer-reviewed scientific literature, and national professional guidelines. Federal and state law(s), regulatory mandates and the member's subscriber contract language are considered first in the determination of a covered service.

(Link to [Product Disclaimer](#))

POLICY STATEMENT(S)

Ehlers Danlos, Vascular type

- I. COL3A1 gene testing may be considered **medically necessary** for the diagnosis of Ehlers Danlos, Vascular type (vEDS) when offered in a setting with adequately trained health care professionals to provide appropriate pre- and post-test counseling in **ANY** of the following situations:
 - A. Individual is symptomatic with **ONE** (1) of the following major criteria:
 1. Arterial rupture or dissection in individuals less than 40 years of age;
 2. Spontaneous sigmoid colon perforation;
 3. Uterine rupture during pregnancy; **or**
 4. First degree relative with history of vEDS.
 - B. Individual is symptomatic with **TWO** (2) of the following minor criteria:
 1. Acrogeria (aged appearance to extremities, particularly hands);
 2. Arteriovenous carotid cavernous sinus fistula;
 3. Characteristic facial appearance (e.g., thin lips and philtrum, small chin, thin nose, large eyes);
 4. Chronic joint subluxations/dislocations;
 5. Clubfoot;
 6. Congenital dislocation of the hips;
 7. Early-onset varicose veins;
 8. Easy bruising (spontaneous or with minimal trauma);
 9. Gingival recession;
 10. Hypermobility of small joints;

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11. Pneumothorax/pneumohemothorax;
 12. Tendon/muscle rupture; **or**
 13. Thin, translucent skin (especially noticeable on chest/abdomen).
- II. Genetic testing for other types of Ehlers Danlos (e.g., classic type, EDS arthrochalasia, or hypermobility type) is considered **not medically necessary**.

Marfan Syndrome

- III. FBN1 gene testing may be considered **medically necessary** for the diagnosis of Marfan Syndrome (MFS) when offered in a setting with adequately trained health care professionals to provide appropriate pre- and post-test counseling in **ANY** of the following situations:
- A. Individual with no family history of MFS and is symptomatic with **ONE** (1) of the following:
 1. Presence of ectopia lentis with any aortic dilation; **or**
 2. Significant aortic dissection/dilation (Z-score ≥ 2).
 - B. Individual with a family history of MFS and is symptomatic with **ONE** (1) of the following:
 1. Ectopia lentis; **or**
 2. Significant aortic root enlargement (Z-score ≥ 2 in those >20 years of age or ≥ 3 in those <20 years of age).
 - C. Individual is symptomatic with **TWO** (2) of the following minor criteria:
 1. Wrist AND thumb sign;
 2. Pectus carinatum deformity, pectus excavatum, or chest asymmetry;
 3. Hindfoot deformity, plain pes planus;
 4. Pneumothorax;
 5. Dural ectasia;
 6. Protrusio acetabuli;
 7. Reduced upper-to-lower segment ratio AND increased arm/ height AND no severe scoliosis;
 8. Scoliosis or thoracolumbar kyphosis;
 9. Reduced elbow extension;
 10. Facial features (three of five including dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, and retrognathia);
 11. Skin striae;
 12. Myopia >3 diopters; **or**
 13. Mitral Valve prolapse (all types).

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Loeys-Dietz Syndrome

IV. TGFBR1, TGFBR2, SMAD3, TGFB2, and TGFB3 gene testing may be considered **medically necessary** for the diagnosis of Loeys-Dietz syndrome (LDS) when offered in a setting with adequately trained health care professionals to provide appropriate pre- and post-test counseling in the following situation:

- A. Individual has at least **TWO** (2) of the following:
1. Aortic aneurysms/tortuosity or dissection;
 2. Arterial aneurysms/tortuosity or dissection other than aorta;
 3. Arachnodactyly;
 4. Blue sclerae;
 5. Cleft palate/bifid uvula;
 6. Club feet;
 7. Craniosynostosis;
 8. Dystrophic scars;
 9. Eosinophilic esophagitis/gastritis;
 10. Easy bruising;
 11. Inflammatory bowel disease;
 12. Joint hypermobility, laxity, or contracture (typically involving the fingers);
 13. Milia, predominantly on the face;
 14. Ocular hypertelorism;
 15. Pectus carinatum or pectus excavatum;
 16. Scoliosis;
 17. Soft and velvety skin or translucent skin with easily visible underlying veins; **or**
 18. Talipes equinovarus.

Thoracic Aortic Aneurysm Disorder

V. Genetic testing, by individual gene test or limited panel comprised entirely of FBN1, LOX, COL3A1, TGFBR1, TGFBR2, SMAD3, TGFB2, ACTA2, MYH11, MYLK, and PRKG1 genes may be considered **medically necessary** for the diagnosis of Thoracic Aortic Aneurysm Disorders (TAAD) when offered in a setting with adequately trained health care professionals to provide appropriate pre- and post-test counseling in **ANY** of the following situations:

- A. TAD and syndromic features of Marfan syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome but do not meet above criteria or single gene testing was negative;

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- B. TAD presenting before 60 years of age;
 - C. A family history of either TAD or peripheral/intracranial aneurysms in a first- or second-degree relative; **or**
 - D. A history of unexplained sudden death at a relatively young age in a first- or second-degree relative.
- VI. Known family variant testing for Ehlers-Danlos syndrome vascular type, Marfan syndrome, Loeys-Dietz syndrome, Thoracic Aortic Aneurysm Disorder, and other syndromes associated with thoracic aortic aneurysms and dissections, may be considered **medically necessary** for assessing future risk of disease in an asymptomatic individual.
- VII. Broad, multigene panels, which are not limited to focused genetic testing listed above for Ehlers-Danlos syndrome vascular type, Marfan syndrome, Loeys-Dietz syndrome, Thoracic Aortic Aneurysm Disorder are considered **not medically necessary**.

RELATED POLICIES

Corporate Medical Policy

2.02.03 Genetic Testing for Inherited Disorders

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

- I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.
- II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.
- III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.
- IV. Supporting documentation required:

The following factors will be considered when determining the medical appropriateness of a genetic test:
 - A. There must be reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists. Autosomal recessive disorders may be present without a family history.

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- B. The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.
 - C. The clinical utility of the test must be established (e.g., test results will influence decisions concerning disease treatment or prevention).
 - D. Genetic testing should be performed for management or treatment of the patient and not only for knowledge purposes. Documentation should demonstrate how test results will impact treatment or medical management.
 - E. When there is family history or phenotype suggestive of a specific syndrome, results of targeted testing for the mutation associated with the syndrome should be documented prior to any panel testing. If targeted testing has not been performed, rationale as to why panel testing is medically necessary should be documented. There may be certain clinical scenarios in which focused panel testing may be appropriate to include a narrow list of differential diagnoses of thoracic aortic aneurysms and dissection based on clinical findings.
- V. The gene variants associated with thoracic aortic aneurysms are not infrequently de novo variants. Targeted testing of the parents of a proband with a confirmed variant to identify mode of transmission (germline versus de novo) may be considered appropriate to guide clinical management.

DESCRIPTION

Most thoracic aortic aneurysms (TAAs) are degenerative and are often associated with the same risk factors as abdominal aortic aneurysms (eg, atherosclerosis). Thoracic aortic aneurysms may be associated with a genetic predisposition, which can either be familial or related to defined genetic disorders or syndromes (Black 2025).

Genetic predisposition to TAA is due to a genetic defect that leads to abnormalities in connective tissue metabolism. Genetically related TAA accounts for approximately 5% of TAA. Some genetic syndromes associated with TAA have more aggressive rates of aortic expansion and are more likely to require intervention compared with sporadic TAA. MFS is the most common inherited form of syndromic TAA and TAAD. Other genetic, systemic connective tissue disorders (CTDs) associated with a risk of TAAD include EDS vascular type, LDS, and arterial tortuosity syndrome.

Familial TAAD refers to patients with a family history of aneurysmal disease who do not meet criteria for a CTD.

Syndromes associated with thoracic aortic aneurysms may have established clinical criteria with major and minor criteria (e.g., Marfan syndrome [Ghent criteria] and Ehlers-Danlos syndrome vascular type) or may be associated with characteristic clinical findings. While most of these syndromes can be diagnosed based on clinical findings, these syndromes may be associated with variability in clinical presentation and may show overlapping features with each other, and with other disorders. The use of genetic testing to establish a diagnosis in an individual with a suspected connective tissue disorder is most useful in individuals who do not meet sufficient clinical diagnostic

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criteria at the time of initial examination, in individuals who have an atypical phenotype and other connective tissue disorders cannot be ruled out, and in individuals who belong to a family in which a pathogenic variant is known (presymptomatic diagnosis). Additional difficulties in the diagnosis of 1 of these syndromes may occur due to the age-dependent development of many of the physical manifestations of the syndrome (making the diagnosis more difficult in children); many show variable expression, and many features found in these syndromes occur in the general population (e.g., pectus excavatum, tall stature, joint hypermobility, mitral valve prolapse, nearsightedness). The identification of the proper syndrome is important to address its manifestations and complications, in particular, the risk of aortic aneurysms and dissection.

Genetic testing has conventionally been used when a definitive diagnosis of one of these syndromes cannot be made. Panels using next-generation sequencing (NGS), which test for multiple genes simultaneously, have been developed for the syndromes associated with thoracic aortic aneurysms and dissections, and other conditions that may have overlapping phenotypes. Although the laboratory-reported sensitivity is high for some of the conditions on the panel, the analytic validity of these panels is unknown, and detection rates of variants of uncertain significance are unknown.

Ehlers-Danlos Syndrome

Ehlers-Danlos Syndrome (EDS) is a group of disorders that affect connective tissues and share common features characterized by skin hyperextensibility, abnormal wound healing, and joint hypermobility. The defects in connective tissues can vary from mildly loose joints to life-threatening complications. All types of EDS affect the joints, and many affect the skin, but features vary by type.

The different types of EDS include, among others, types I and II (classical type), type III (hypermobility type), type IV (vascular type), and type VI (kyphoscoliotic form), all of which are inherited in an autosomal-dominant pattern except type VI, which is autosomal-recessive. It is estimated that affected individuals with types I, II, or IV may inherit the pathogenic variant from an affected parent 50% of the time, and about 50% have a de novo pathogenic variant.

Most types of EDS are not associated with aortic dilation, except the vascular type (also known as type IV), which can involve serious and potentially life-threatening complications. The prevalence of vascular type IV may affect 1 in 50,000 to 250,000 people (Eagleton 2016). Vascular complications include rupture, aneurysm, and/or dissection of major or minor arteries. Arterial rupture may be preceded by an aneurysm, arteriovenous fistulae, or dissection, or may occur spontaneously. Such complications are often unexpected and may present as sudden death, stroke, internal bleeding, and/or shock. The vascular type is also associated with an increased risk of gastrointestinal perforation, organ rupture, and rupture of the uterus during pregnancy.

The clinical diagnosis of EDS type IV can be made from major and minor clinical criteria. The combination of two (2) major criteria (arterial rupture, intestinal rupture, uterine rupture during pregnancy, family history of EDS type IV) is highly specific (Beridze 2012). The presence of one (1) or more minor clinical criteria supports the diagnosis but is insufficient to make the diagnosis by itself.

Pathogenic variants in the COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, PLOD1, and TNXB genes

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cause EDS. The vascular type (type IV) is caused by pathogenic variants in the COL3A1 gene (Byers 2025).

Marfan Syndrome

Marfan Syndrome is an autosomal-dominant condition, in which there is a high degree of clinical variability of systemic manifestations, ranging from isolated features of MFS to neonatal presentation of severe and rapidly progressive disease in multiple organ systems (Dietz 2022). Despite the clinical variability, the principal manifestations involve the skeletal, ocular, and cardiovascular systems. Involvement of the skeletal system is characterized by bone overgrowth and joint laxity, disproportionately long extremities for the size of the trunk (dolichostenomelia), overgrowth of the ribs which can push the sternum in or out (pectus excavatum or carinatum, respectively), and scoliosis, which can be mild or severe and progressive. Ocular features include myopia, and displacement of the lens from the center of the pupil (ectopia lentis) is a feature seen in 60% of affected individuals. Cardiovascular manifestations are the major source of morbidity and mortality and include dilation of the aorta at the level of the sinuses of Valsalva, predisposition for aortic tear and rupture, mitral valve prolapse, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery. With proper management, the life expectancy of a person with MFS can approximate that of the general population.

The diagnosis of MFS is mainly clinical and based on the characteristic findings in multiple organ systems and family history. The Ghent criteria, revised in 2010, are used for the clinical diagnosis of MFS (Loeys 2010).

With no known family history, a Marfan syndrome diagnosis is confirmed if any ONE of the following is met:

- Significant aortic dilation (Z-score ≥ 2)/dissection + ectopia lentis
- Significant aortic dilation (Z-score ≥ 2)/dissection + FBN1 mutation
- Aortic dilation/dissection + sufficient points from other system findings
- Ectopia lentis + FBN1 mutation known to be associated with aortic disease

With a known family history, the presence of any ONE of the following is diagnostic:

- Ectopia lentis
- Significant aortic root enlargement (Z-score ≥ 2 in those >20 years of age or ≥ 3 in those <20 years of age)
- Sufficient points (≥ 7) from other system findings

Systemic scoring system:

- Wrist and Thumb Sign - 3 points
- Wrist or Thumb Sign - 1 point
- Pectus Carinatum deformity - 2 points

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- Pectus Excavatum or chest asymmetry -1 point
- Hindfoot deformity - 2 points
- Plan pes planus -1 point
- Pneumothorax - 2 points
- Dural Ectasia - 2 points
- Protrusio Acetabulae - 2 points
- Reduced upper seg/lower seg and inc. arm span/height ratios - 1 point
- Scoliosis or thoracolumbar kyphosis - 1 point
- Reduced elbow extension - 1 point
- 3 of 5 facial features: Dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia - 1 point
- Skin striae - 1 point
- Myopia - 1 point
- Mitral Valve Prolapse - 1 point

It is estimated that molecular techniques permit the detection of FBN1 pathogenic variants in up to 97% of Marfan patients who fulfill Ghent criteria, suggesting that the current Ghent criteria have excellent specificity (Loeys 2010).

Loeys-Dietz Syndrome

Loeys-Dietz Syndrome is an autosomal-dominant condition characterized by four (4) major groups of clinical findings, including vascular, skeletal, craniofacial, and cutaneous manifestations (Loeys 2024). Vascular findings include cerebral, thoracic, and abdominal arterial aneurysms and/or dissections. Skeletal findings include pectus excavatum or carinatum, scoliosis, joint laxity, arachnodactyly, and talipes equinovarus. The natural history of LDS is characterized by arterial aneurysms, with a mean age of death of 26 years and a high incidence of pregnancy-related complications, including uterine rupture and death. Treatment considerations should take into account that aortic dissection tends to occur at smaller aortic diameters than MFS, and the aorta and its major branches can dissect in the absence of much if any, dilation. Patients with LDS require echocardiography at frequent intervals, to monitor the status of the ascending aorta, and angiography evaluation to image the entire arterial tree.

Loeys-Dietz syndrome should be suspected in individuals with the following vascular, skeletal, craniofacial, cutaneous, allergic/inflammatory, ocular, and family history findings (Loeys 2005, Bart 2024):

- Dilatation or dissection of the aorta and other arteries. Aortic root dilatation is seen in more than 95% of probands; the aortic root is the most common site for a dissection to occur. In rare

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circumstances, aneurysms or dissections can be seen in other arteries in the head, chest, abdomen, or extremities in the absence of aortic involvement.

- Other arterial aneurysms and tortuosity
- Pectus excavatum or pectus carinatum
- Scoliosis
- Joint laxity or contracture (typically involving the fingers)
- Arachnodactyly
- Talipes equinovarus
- Cervical spine malformation and/or instability
- Osteoarthritis
- Hypertelorism
- Bifid uvula/ cleft palate
- Craniosynostosis
- Soft and velvety skin or translucent skin with easily visible underlying veins
- Easy bruising
- Dystrophic scars
- Milia, predominantly on the face
- Allergies (food and seasonal), asthma, chronic sinusitis
- Eczema
- Eosinophilic esophagitis/gastritis
- Inflammatory bowel disease

LDS caused by a pathogenic variant in SMAD2, SMAD3, TGFB2, TGFB3, TGFBR1, or TGFBR2 is inherited in an autosomal dominant manner. IPO8-related LDS is inherited in an autosomal recessive manner (Loeys 2024).

Familial Thoracic Aortic Aneurysm Dissection

Approximately 80% of familial TAA and TAAD is inherited in an autosomal-dominant manner and may be associated with variable expression and decreased penetrance of the disease-associated variant (Black 2025).

The major cardiovascular manifestations of TAAD include dilatation of the ascending thoracic aorta at the level of the sinuses of Valsalva or ascending aorta, or both, and dissections of the thoracic aorta involving ascending or descending aorta (Milewicz 2023). In the absence of surgical repair of the ascending aorta, affected individuals have progressive enlargement of the ascending aorta, leading to

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acute aortic dissection. Presentation of the aortic disease and the age of onset are highly variable. Familial TAAD (fTAAD) is diagnosed based on the presence of thoracic aorta pathology; absence of clinical features of MFS, LDS, or vascular EDS; and a positive family history of TAAD. Familial TAAD is associated with pathogenic variants in multiple genes including: ACTA2, COL3A1, FBN1, MYH11, MYLK, SMAD3, TGFB2, TGFB1, and TGFB2. Clinical and family history findings that increase the likelihood of identifying a pathogenic variant in an HTAD-related gene include:

- Thoracic aortic aneurysm or dissection at age <60 years;
- Family history of thoracic aortic disease, unexplained sudden death, or aneurysms/dissections in other arteries;
- Syndromic features associated with Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, or smooth muscle dysfunction syndrome; and
- Aneurysms and dissections/ruptures of other arteries in an individual with thoracic aortic disease (Milewicz 2023).

SUPPORTIVE LITERATURE

Erez and colleagues (2024) analyzed the effectiveness of the current genetic testing guidelines for patients with thoracic aortic aneurysms. The authors evaluated genetic tests for thoracic aortic disease (TAD) from 2012 to 2023 in patients aged 18 and older with a thoracic aorta diameter greater than 4 cm. Mutation rates were compared by American College of Cardiology/American Heart Association testing criteria met by patients: age younger than 60 years, syndromic features of connective tissue diseases (CTDs), family history, or none. Results were classified as pathogenic, variants of uncertain significance (VUS), or negative. Genes tested were analyzed in 2 categories: primary (strongly associated with heritable diseases) or secondary (less strongly associated). In total, 1034 patients were included: 42.4% aged younger than 60 years, 19.1% with syndromic features of CTD, 41.8% with family history, and 30.7% meeting no criteria. Overall, 3.97% had pathogenic mutations, and 27.27% had VUS. Mutation rates were greatest in patients with syndromic features of CTD (13.2%), followed by patients aged younger than 60 years (5.48%), with a family history (4.63%), and with no criteria met (2.21%). Primary genes had pathogenic mutation rates of 3.29% and VUS rates of 12.19%. Secondary genes had lower pathogenic rates (0.68%) but greater VUS (17.5%). Mutation rates in primary genes peaked at 22% in patients meeting all criteria, whereas those younger than 60 years without family history or syndromic features of CTD had the lowest rate (0.54%). The authors concluded refining genetic testing guidelines to incorporate multiple patient criteria could enhance risk stratification and support informed decision-making in genetic testing for TAD. Limiting testing to genes strongly associated with TAD could lower VUS rates.

PROFESSIONAL GUIDELINE(S)

In 2024, the American Heart Association issued a scientific statement regarding the cardiovascular management of aortopathy in children (Morris 2024). They state the role of genetic testing for aortopathy has expanded with greater recognition of the importance of a specific genetic diagnosis in risk assessment as well as medical and surgical management.

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- Genetic testing should be targeted to those with the highest likelihood of confirming a diagnosis and those for whom a genetic diagnosis would affect clinical management. Multigene panels that include genes associated with HTAD are most commonly used; however, the genes included vary widely by laboratory.
- When there is a known familial pathogenic variant or when the clinical presentation strongly suggests a specific diagnosis, single gene testing can be used; for example, in the presence of ectopia lentis (lens dislocation), MFS associated with a variant in FBN1 is most likely.
- An HTAD panel may be considered for nonsyndromic presentations or in those with predominant systemic connective tissue findings.
- Overall, disease-causing variants are identified by genetic testing in 8% to 36% of individuals evaluated for thoracic aortic disease, with a higher yield in young children with syndromic manifestations.
- Once a pathogenic or likely pathogenic variant is identified in one affected family member, cascade genetic testing of at-risk family members should follow. Family members without the familial variant do not need ongoing cardiac evaluation, and their offspring are not at increased risk for aortopathy.

Joint evidence-based guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA) for the diagnosis and management of aortic disease include Marfan Syndrome, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome (Isselbacher 2022). Genetic testing for thoracic aortic disease (TAD) was addressed in the following guideline statement:

- In patients with TAD who have a pathogenic/likely pathogenic variant, genetic testing of at-risk biological relatives (i.e., cascade testing) is recommended.
- In patients with aortic root/ascending aortic aneurysms or aortic dissection and risk factors for HTAD, genetic testing to identify pathogenic/likely pathogenic variants (i.e., mutations) is recommended.
- The HTAD genetic testing panels include (at the time of this writing) 11 genes that are confirmed to confer a highly penetrant risk for TAD: FBN1, LOX, COL3A1, TGFB1, TGFB2, SMAD3, TGFB2, ACTA2, MYH11, MYLK, and PRKG1. These panels also include genes that increase the risk for TAD and/or lead to systemic features that overlap with Marfan syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome. Clinical genetic testing is integral to the diagnostic evaluation of patients with TAD who have clinical indicators suggestive of an underlying single gene disorder.
- Among patients undergoing genetic testing, many will not have a pathogenic variant identified, despite other clinical evidence that the disease is likely genetically triggered (e.g., extensive family history of TAD or early onset sporadic TAD with no risk factors). Despite the absence of a pathogenic variant among the currently known genes that were tested, TAD could still be inherited in the family attributable to a causative genetic variant that has yet to be identified.
- Risk factors for familial TAD include:

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- o TAD and syndromic features of Marfan syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome
- o TAD presenting at age <60 y
- o A family history of either TAD or peripheral/intracranial aneurysms in a first- or second-degree relative
- o A history of unexplained sudden death at a relatively young age in a first- or second-degree relative

A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine published joint guidelines for the diagnosis and management of patients with thoracic aortic disease (Hiratzka 2010). Genetic testing was addressed in the following guidelines statement and table:

- If the mutant gene (FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) associated with aortic aneurysm and/or dissection is identified in a patient, first-degree relatives should undergo counseling and testing. Then, only the relatives with the genetic mutation [pathogenic variant] should undergo aortic imaging (class 1, level of evidence C).

Genetic Syndrome	Common Clinical Features	Genetic Defect	Diagnostic Test	Comments on Aortic Disease
Marfan syndrome	Skeletal features Ectopia lentis Dural ectasia	FBN1 mutations	Ghent diagnostic criteria DNA for sequencing	Surgical repair when the aorta reaches <5.0 cm unless there is a family history of aortic dissection at 5.0 cm, a rapidly expanding aneurysm or presence or significant aortic valve regurgitation
Loeys-dietz syndrome	Bifid uvula or cleft palate	TGFBR2 or TGFBR1 mutations	DNA for sequencing	Surgical repair recommended at an aortic diameter

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	Arterial tortuosity Hypertelorism Skeletal features similar to MFS Craniosynostosis Aneurysms and dissections of other arteries			of >4.2 cm by TEE (internal diameter) or 4.4 to >4.6 cm by CT and/or MR (external diameter)
Ehlers-Danlos syndrome, vascular form	Thin, translucent skin Gastrointestinal rupture Rupture of the gravid uterus Rupture of medium-sized to large arteries	COL3A1 mutations	DNA for sequencing Dermal fibroblasts for analysis of type III collagen	Surgical repair is complicated by friable tissues Noninvasive imaging recommended

In 2020, the American Heart Association Council on Genomic and Precision Medicine issued a scientific statement focused on genetic testing and its implications for the management of inherited cardiovascular diseases (Musunuru 2020). Approaches for the evaluation of patients with a confirmed or suspected diagnosis of inherited cardiovascular disease, as well as individuals with secondary or incidental genetic findings are summarized in the statement:

- "Genetic testing typically should be reserved for patients with a confirmed or suspected diagnosis of an inherited cardiovascular disease or for individuals at high a priori risk resulting from a previously identified pathogenic variant in their family."
- "The choice of testing ranges from targeted sequencing of a single gene or a few genes most likely to be involved in the disease to large gene panels that include limited-evidence genes to unbiased exome or genome sequencing that queries all genes. The natural temptation might be to test more genes, perhaps all genes, with the thinking that more data are better, especially because next-generation sequencing has made even complete genome sequencing relatively affordable. The additional information might be useful in the research context, that is, improving our knowledge of gene-disease relationships, but panels that include genes with little support for the gene-phenotype association under investigation may not increase the likelihood of clinically actionable results in adult patients. In addition, expanded test panels may increase the number of variants of uncertain significance (VUSs) identified and, for exome or genome sequencing,

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may increase the chance of picking up secondary or incidental findings that are not relevant to the disease in question. This can lead to confusion and uncertainty."

- "Pathogenic and likely pathogenic variants might confirm diagnoses of suspected diseases (ie, serve as major criteria) or warrant changes in clinical management (i.e., are actionable) if they occur in certain genes in patients with certain diseases:"
 - o Familial thoracic aortic aneurysm and dissection -Causative gene can affect (1) timing of recommended surgical intervention and (2) extent and type of screening for other abnormalities; aids with identification of family members at risk for the condition.
 - o Loeys-Dietz syndrome- Confirmed diagnosis can affect (1) timing of recommended surgical intervention and (2) extent and type of screening for other abnormalities; aids with identification of family members at risk for the condition.
 - o Marfan syndrome- Confirmed diagnosis can affect timing of recommended surgical intervention.

This statement also recommends further evaluation of secondary/incidental findings of pathogenic or likely pathogenic variants in any of the following genes associated with Marfan syndrome (MFS), Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections: FBN1, TGFB1, TGFB2, SMAD3, ACTA2, MYH11, and the following genes associated with Ehlers-Danlos syndrome (vascular type): COL3A1.

In 2021, the American Heart Association issued a scientific statement focused specifically on genetic testing for heritable cardiovascular diseases in the pediatric population (Landstrom 2021). Key points and recommendations are noted below:

- Diagnostic genetic testing should be considered only in children with a high likelihood of disease.
- Risk-predictive genetic testing should be performed in children after identification of a P/LP [pathogenic/likely pathogenic] variant in a family member with disease.
- The timing of genetic testing in children should take into account disease-specific considerations of disease penetrance, the likelihood of pediatric disease presentation, the availability of effective therapies or lifestyle modifications, and the possibility of psychological distress in the family attributable to uncertainty.
- Continued follow-up of genetic test results is important to re-evaluate or confirm variant pathogenicity over time.
- Typically, genetic testing should be limited to genes associated with the clinical phenotype identified, whereas broader genetic testing such as exome/genome sequencing may be considered in cases that do not meet diagnostic criteria for a single, well-defined syndrome but a genetic origin is suspected.

Marfan Syndrome

In 2023, the American Academy of Pediatrics updated its clinical report focused on health supervision

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for children with Marfan syndrome (MFS) (Tinkle 2023). This clinical report notes the following with regard to genetic testing:

- Younger patients at risk for Marfan syndrome based on clinical features or a positive family history should be evaluated periodically until their growth is complete or preferably undergo appropriate genetic testing.
- Genetic testing in Marfan syndrome has become an important part of the diagnosis and management of the condition.
- For those suspected to have Marfan syndrome on clinical grounds after physical, cardiac, and ophthalmic evaluation but who may not meet full clinical criteria, one should consider FBN1 testing
- Patients who fit clinical criteria for Marfan syndrome in whom no pathogenic variant is found in the FBN1 gene should continue to be followed according to the health supervision for Marfan syndrome. In addition, broader genomic testing should be considered in these individuals.
- When a new diagnosis of Marfan syndrome is made in a child or adolescent, both parents and at-risk first-degree relatives should have physical, ophthalmologic, and cardiac evaluations as well as consideration of genetic testing. Similarly, when a new diagnosis of Marfan syndrome is made in a parent, all children should be screened for manifestations of Marfan syndrome.
- Prenatal genetic testing for FBN1 mutations may be helpful to confirm Marfan syndrome as well as reveal specific mutations in FBN1 that may be more typically associated with this severe form and, therefore, reduced survivability.

In 2012, the American College of Medical Genetics and Genomics issued guidelines on the evaluation of adolescents or adults with some features of Marfan syndrome (Pyeritz 2012). The guidelines recommended the following:

If there is no family history of MFS, then the subject has the condition under any of the following four (4) situations:

- A dilated aortic root (defined as greater than or equal to 2 standard deviations above the mean for age, sex, and body surface area, i.e., a Z-score of $> +2$) and ectopia lentis;
- A dilated aortic root and a mutation in FBN1 that is clearly pathologic;
- A dilated aortic root and multiple systemic features; or
- Ectopia lentis and a mutation in FBN1 that has previously been associated with aortic disease.

If there is a positive family history of MFS (independently ascertained with these criteria), then the subject has the condition under any of the following three (3) situations:

- Ectopia lentis;
- Multiple systemic features;

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- A dilated aortic root (if over 20 years, greater than 2 standard deviations; if younger than 20, greater than 3 standard deviations).

The scoring system for systemic features involves the following:

- Wrist AND thumb sign = 3 (wrist OR thumb sign = 1)
- Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)
- Hindfoot deformity = 2 (plain pes planus = 1)
- Pneumothorax = 2
- Dural ectasia = 2
- Protrusio acetabuli = 2
- Reduced upper-to-lower segment ratio AND increased arm/ height AND no severe scoliosis = 1
- Scoliosis or thoracolumbar kyphosis = 1
- Reduced elbow extension = 1
- Facial features (three of five including dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, and retrognathia) = 1
- Skin striae = 1
- Myopia >3 diopters = 1
- Mitral valve prolapse (all types) = 1
- Maximum total: 20 points; score of 7 or more indicates systemic involvement

Ehlers-Danlos Syndrome

The International Consortium on the Ehlers-Danlos Syndromes (Malfait 2017) published paper states “in view of the vast genetic heterogeneity and phenotypic variability of the EDS subtypes, and the clinical overlap between many of these subtypes, but also with other hereditary connective tissue disorders, the definite diagnosis relies for all subtypes, except hypermobile EDS, on molecular confirmation with identification of (a) causative variant(s) in the respective gene.” Vascular EDS is described as autosomal dominant inheritance with major COL3A1 gene involvement and sometimes rare COL1A1 gene variants.

The 2017 International Consortium developed clinical criteria for the Ehlers-Danlos syndromes. Minimal criteria suggestive for Vascular EDS (vEDS):

- A family history of the disorder, and/or
- Arterial rupture or dissection in individuals less than 40 years of age, and/or
- Unexplained sigmoid colon rupture, and/or
- Spontaneous pneumothorax in the presence of other features consistent with vEDS, and/or

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- A combination of the other minor clinical features listed below.

Major Criteria for vEDS	Minor Criteria for vEDS
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	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 30 and nulliparous if female)

The International Consortium states 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. Molecular screening by Sanger sequencing of COL3A1, or targeted resequencing of a gene panel that includes COL3A1 and COL1A1 is indicated. When no mutation is identified, this approach should be complemented with a CNV detection strategy to identify large deletions or duplications.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA).

Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. More information is available at: [Clinical Laboratory Improvement Amendments \(CLIA\) | FDA](#) [accessed 2026 Sep 17]

CODE(S)

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- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
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) [Known family variant]
81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion 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) [TGFB1, TGFB2, ACTA2]
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)

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Code	Description
81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis) [FBN1, MYH11]
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, TGFB1, TGFB2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
81411 (NMN)	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 TGFB1, TGFB2, MYH11, and COL3A1
81479	Unlisted molecular pathology procedure [COL3A1]

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HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
I71.0-I71.9	Aortic aneurysm and dissection [code range]
Q79.60	Ehlers-Danlos syndrome, unspecified
Q79.63	Vascular Ehlers-Danlos syndrome
Q87.4-Q87.43	Marfan syndrome with cardiovascular manifestations [code range]
Q87.89	Other specified congenital malformation syndromes, not elsewhere classified [Loeys Dietz syndrome]

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

[Billing and Coding: Molecular Pathology Procedures \(Article A56199\)](#) [accessed 2026 Sep 17]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.

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- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION	
Committee Approval Dates	
09/18/25, 09/17/26	
Date	Summary of Changes
09/17/26	• Annual review, policy intent unchanged.
01/15/26	• Original effective date