
Medical Policy



Nonprofit corporations and independent licensees
of the Blue Cross and Blue Shield Association

Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Marfan Syndrome, Ehlers-Danlos, Thoracic Aortic Aneurysms and Dissections, and Connective Tissue Related Disorders

Description/Background

Marfan syndrome (MFS) is a systemic connective tissue disease (CTD) with a high degree of clinical variability and phenotypes overlapping with other syndromes and disorders. The diagnosis of most suspected CTDs can be based on clinical findings and family history. Some of these disorders are associated with a predisposition to the development of progressive thoracic aortic aneurysms and dissection. Accurate diagnosis of one of these syndromes can lead to changes in clinical management, including surveillance of the aorta, and surgical repair of the aorta, when necessary, as well as surveillance for multisystem involvement in syndromic forms of thoracic aortic aneurysms and dissection. Known pathogenic variants are associated with MFS and the other connective tissue disorders that share clinical features with MFS.

Connective Tissue Diseases

Individuals suspected of having a systemic CTD like MFS usually have multiple features that affect many different organ systems; most of these conditions can be diagnosed using clinical criteria. However, these different syndromes may share features, overlapping phenotypes, and similar inheritance patterns, which can cause a diagnostic challenge. Additional difficulties in the diagnosis of one 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 of the 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.

Thoracic Aortic Aneurysms and Dissection

Most thoracic aortic aneurysms (TAAs) are degenerative and are often associated with the same risk factors as abdominal aortic aneurysms (e.g., atherosclerosis). TAAs may be associated with a genetic predisposition, which can either be familial or related to defined genetic disorders or syndromes.(1)

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.(1) Some of the 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 thoracic aortic aneurysms and dissection (TAAD). Other genetic systemic connective tissue disorders associated with a risk of TAAD include Ehlers-Danlos syndrome (EDS) type IV, Loeys-Dietz syndrome (LDS), and arterial tortuosity syndrome.

Familial TAAD refers to patients with a family history of aneurysmal disease, but who do not meet criteria for a connective tissue syndrome.

Marfan Syndrome

Marfan Syndrome (MFS) 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.(2) 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 hallmark 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.

Diagnosis

The diagnosis of MFS is mainly clinical and based on the characteristic findings in multiple organ systems, and family history.(3) The Ghent criteria, revised in 2010, are used for the clinical diagnosis of MFS.(3) The previous Ghent criteria had been criticized for taking insufficient account of the age-dependent nature of some of the clinical manifestations, making the diagnosis in children more difficult, and for including some nonspecific physical manifestations or poorly validated diagnostic thresholds. The revised criteria were based on clinical characteristics in large, published patient cohorts, and expert opinions.(3) The revised criteria have several major changes, as follows. More weight is given to the 2 cardinal features of MFS, aortic root aneurysm/dissection and ectopia lentis. In the absence of findings that are not expected in MFS, the combination of these 2 features is sufficient to make the diagnosis. When aortic disease is present, but ectopia lentis is not, all other cardiovascular and ocular manifestations of MFS and findings in other organ systems contribute to a “systemic score” that guides diagnosis. Second, a more prominent role has been given to molecular testing of

FBN1 and other relevant genes, allowing for the appropriate use when necessary. Third, some of the less specific manifestations of MFS were removed or given less weight in the diagnostic criteria. Fourth, the revised criteria formalize the concept that additional diagnostic considerations and testing may be required if a patient has findings that satisfy the criteria for MFS but show unexpected findings, particularly if they are suggestive of a specific alternative diagnosis. Particular emphasis is placed on LDS, Shprintzen-Goldberg syndrome (SGS), and EDS vascular type. LDS and SGS may have substantial overlap with MFS, including the potential for similar involvement of the aortic root, skeleton, skin, and dura. EDS vascular type occasionally overlaps with MFS. Each of these conditions has a unique risk profile and management protocol.(3) Given the autosomal-dominant nature of inheritance, the number of physical findings needed to establish a diagnosis for a person with an established family history is reduced.

Genetic Testing

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.(3)

FBN1 is the only gene in which mutations are known to cause classic MFS. Approximately 75% of individuals with MFS have an affected parent, and 25% have a de novo mutation pathogenic variant.(2) Over 1000 *FBN1* mutations that cause MFS have been identified. The following findings in *FBN1* molecular genetic testing should infer causality in making the diagnosis of MFS: a pathogenic variant previously shown to segregate in families with MFS and de novo mutations of a certain type (e.g., nonsense, certain missense mutations, certain splice site mutations, certain deletions and insertions).(2)

Most variants in the *FBN1* gene that cause MFS can be identified with sequence analysis (≈90% to 93%) and, although the yield of deletion/duplication analysis in patients without a defined coding sequence or splice site by sequence analysis is unknown, it is estimated to be about 30%. The most common testing strategy of a proband suspected of having MFS is sequence analysis followed by deletion/duplication analysis if a pathogenic variant is not identified.(2) However, the use of genetic testing for a diagnosis of MFS has limitations. More than 90% of pathogenic variants that have been described are unique, and most pathogenic variants are not repeated among nongenetically related patients. Therefore, the absence of a known pathogenic variant in a patient in whom MFS is suspected does not exclude the possibility that the patient has MFS. No clear genotype-phenotype correlation exists for MFS and, therefore, the severity of the disease cannot be predicted from the type of variant.

Caution should be used when interpreting the identification of an *FBN1* variant, because other conditions with phenotypes that overlap with MFS can have an *FBN1* variant (e.g., MASS syndrome, familial mitral valve prolapse syndrome, SGS, isolated ectopia lentis).

Treatment

Management of MFS includes both treatment of manifestations and prevention of complications, including surgical repair of the aorta depending on the maximal measurement, the rate of increase of the aortic root diameter, and the presence of progressive and severe aortic regurgitation.

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 with the exception of 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 disease-causing 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 the vascular type may affect about 1 in 50,000 to 250,000 people.(4) Vascular complications include rupture, aneurysm, and/or dissection of major or minor arteries. Arterial rupture may be preceded by 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 or organ rupture, and rupture of the uterus during pregnancy.

Diagnosis

The clinical diagnosis of EDS type IV can be made from major and minor clinical criteria. The combination of two major criteria (arterial rupture, intestinal rupture, uterine rupture during pregnancy, family history of EDS type IV) is highly specific.(5) The presence of one or more minor clinical criteria supports the diagnosis but is insufficient to make the diagnosis by itself.

Genetic Testing

Pathogenic variants in the *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, *PLOD1*, and *TNXB* genes cause EDS. The vascular type (type IV) is caused by mutations in the *COL3A1* gene.(6)

Loeys-Dietz Syndrome

Loeys-Dietz Syndrome (LDS) is an autosomal-dominant condition that is characterized by 4 major groups of clinical findings, including vascular, skeletal, craniofacial, and cutaneous manifestations.(7) 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 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.

Genetic Testing

LDS is caused by pathogenic variants in *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD2*, and *SMAD3* genes.(7)

Arterial Tortuosity Syndrome

Arterial tortuosity syndrome is inherited in an autosomal recessive pattern and characterized by tortuosity of the aorta and/or large- and middle-sized arteries throughout the body. Aortic root dilation, stenosis and aneurysms of large arteries are common. Other features of the syndrome include joint laxity and skin hyperextensible.

Genetic Testing

The syndrome is caused by pathogenic variants in the *SLC2A10* gene.(8)

Familial Thoracic Aortic Aneurysm Dissection

Approximately 80% of familial thoracic aortic aneurysm (TAA) and thoracic aortic aneurysm dissection (TAAD) is inherited in an autosomal-dominant manner and may be associated with variable expression and decreased penetrance of the disease-associated variant.(1)

The major cardiovascular manifestations of familial TAAD (fTAAD) 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 either the ascending or descending aorta.(9) In the absence of surgical repair of the ascending aorta, affected individuals have progressive enlargement of the ascending aorta, leading to acute aortic dissection. Presentation of the aortic disease and the age of onset are highly variable.

Diagnosis

Familial TAAD 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.

Genetic Testing

Familial TAAD is associated with pathogenic variants in 16 genes including: *TGFBR1*, *TGFBR2*, *MYH11*, *ACTA2*, *MYLK*, *SMAD3*, and two loci on other chromosomes, *AAT1* and *AAT2*. Rarely, fTAAD can also be caused by *FBN1* mutations. To date, only about 20% of fTAAD is accounted for by mutations in known genes. Early prophylactic repair should be considered in individuals with confirmed mutations in *TGFBR2* and *TGFBR1* genes and/or a family history of aortic dissection with minimal aortic enlargement.

Other Syndromes and Disorders

The following syndromes and conditions may share some of the features of these connective tissue syndromes, but do not share the risk of TAAD.

Congenital Contractural Arachnodactyly (Beal Syndrome)

Congenital contractural arachnodactyly (CCA) is an autosomal-dominant condition characterized by a Marfan-like appearance and long, slender toes and fingers. Other features may include “crumpled” ears, contractures of the knees and ankles at birth with improvement over time, camptodactyly, hip contractures, and progressive kyphoscoliosis. Mild dilatation of the aorta is rarely present. CCA is caused by pathogenic variants in the *FBN2* gene.(10)

MED12-Related Disorders

The phenotypic spectrum of *MED12*-related disorders is still being defined but includes Lujan syndrome (LS), FG syndrome type 1 (FGS1), and others.(11) LS and FGS1 share the clinical findings of hypotonia, cognitive impairment and abnormalities of the corpus callosum. *MED12*-related disorders are inherited in an X-linked manner, with males being affected and carrier females not usually being affected.

Shprintzen-Goldberg Syndrome

Shprintzen-Goldberg syndrome (SGS) is an autosomal-dominant condition characterized by a combination of major characteristics that include craniosynostosis, craniofacial findings, skeletal findings, cardiovascular findings, neurologic and brain anomalies, certain radiographic findings, and other findings.(12) *SK1* is the only gene for which pathogenic variants are known to cause SGS.

Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency

Homocystinuria is a rare metabolic disorder, inherited in an autosomal recessive manner, characterized by an increased concentration of homocysteine, a sulfur-containing amino acid, in the blood and urine. The classical type is due to a deficiency of cystathionine beta synthase (CBS). Affected individuals appear normal at birth but develop serious complications in early childhood, usually by age 3 to 4 years. Heterozygous carriers (1/70 of the general population) have hyperhomocysteinemia without homocystinuria, however, their risk for premature cardiovascular disease is still increased.

Overlap with MFS can be extensive and includes a Marfanoid habitus with normal to tall stature, pectus deformity, scoliosis, and ectopia lentis. Central nervous system manifestations include mental retardation, seizures, cerebrovascular events, and psychiatric disorders. Patients have a tendency for intravascular thrombosis and thromboembolic events, which can be life-threatening. Early diagnosis and prophylactic medical and dietary care can decrease and even reverse some of the complications. The diagnosis depends on measurement of CBS activity in tissue (e.g., liver biopsy, skin biopsy).

Regulatory Status:

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Several commercial laboratories currently offer individual mutation testing, as well as next-generation sequencing (NGS) panels that simultaneously analyze multiple genes associated with Marfan syndrome, thoracic aortic aneurysms and dissections (TAADs), and related disorders. NGS technology cannot detect large deletions or insertions, and therefore samples that are variant-negative after sequencing should be evaluated by other testing methodologies.

Ambry Genetics offers “TAADNext,” a next-generation sequencing (NGS) panel that simultaneously analyzes 35 genes associated with TAADs, MFS and related disorders. The panel detects mutations in all coding domains and splice junctions of *ACTA2*, *BGN*, *CBS*,

CHST14, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, EFEMP2, FBN1, FBN2, FKBP14, FLNA, FOXE3, LOX, MAT2A, MED12, MFAP5, MYH11, MYLK, NOTCH1, PLOD1, PRDM5, PRKG1, SKI, SLC2A10, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1, TGFBR2, TNXB and *ZNF469*. Deletion/duplication analysis are performed for all genes on the panel except *CBS*, and *TNXB* exons 32 to 44.

Prevention Genetics offers targeted familial variants testing, as well as “Marfan syndrome and related aortopathies panel,” which includes 38 genes: *ABL1, ACTA2, AEBP1, BGN, CBS, COL3A1, COL5A1, COL5A2, EFEMP2, ELN, FBLN5, FBN1, FBN2, FLNA, FOXE3, IPO8, LOX, LTBP3, MAT2A, MED12, MFAP5, MYH11, MYLK, NKAP, NOTHC1, PLOD1, PRKG1, SKI, SLC2A10, SMAD3, SMAD4, SMAD6, SMS, TGFB2, TGFB3, TGFBR1, and TGFBR2*.

GeneDx offers the "Custom Marfan/TAAD & Related Disorders Panel, “Marfan/TAAD panel,” and “Marfan/TAAD Sequencing & and deletion/duplication panel,” which include variant testing for *ACTA2, BGN, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, LOX, MAT2A, MED12, MFAP5, MYH11, MYLK, NOTCH1, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, TGFB2, TGFB3, TGFBR1, and TGFBR2*.

Medical Policy Statement

The safety and effectiveness of genetic testing for Marfan syndrome, Ehlers-Danlos syndrome type IV (vascular type), other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders have been established. It may be considered a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

Individual genetic testing for the diagnosis of Marfan syndrome, Ehlers-Danlos syndrome type IV (vascular type), other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders when:

- Focused genetic testing of the following genes: *FBN1, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, MYLK, TGFBR1, and TGFBR2* **OR**
- A panel of at least 9 genes which must include *FBN1, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, MYLK, TGFBR1, and TGFBR2* when:
 - Signs and symptoms of a connective tissue disorder are present, but a definitive diagnosis cannot be made using established clinical diagnostic criteria (i.e., Ghent criteria). **OR**
 - Assessing future risk of disease in an asymptomatic individual when there is a known pathogenic variant in the family.

Exclusions:

- Genetic testing panels for Marfan syndrome, Ehlers-Danlos syndrome type IV vascular type), other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders that do not include genes listed under inclusions.

CPT/HCPCS Level II Codes (Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)

Established codes:

81401 81405 81408 81410 81411 81479*

Other codes (investigational, not medically necessary, etc.):

N/A

* For individual mutation testing of genes that have not been codified by CPT, the unlisted molecular pathology code 81479 would be used.

Note: The above codes may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

TESTING OF PATIENTS WITH SIGNS AND/OR SYMPTOMS OF A CONNECTIVE TISSUE DISEASE

Clinical Context and Test Purpose

The purpose of genetic testing of individuals who have signs and/or symptoms of a connective tissue disease (CTD) linked to thoracic aortic aneurysms (TAAs) when diagnosis cannot be made clinically is to confirm a diagnosis and inform management decisions such increased surveillance of the aorta, surgical repair of the aorta, when necessary, as well as surveillance for multisystem involvement in syndromic forms of thoracic aortic aneurysm and dissection (TAAD).

The following PICOs were used to select literature to inform this review.

Populations

The relevant population of interest is individuals with clinical signs and/or symptoms of a CTD linked to TAAs when diagnosis cannot be made clinically.

Interventions

The relevant intervention of interest is genetic testing for genes associated with CTDs. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators

The following practice is being used to diagnose CTDs associated with TAAs: standard clinical management without genetic testing.

Outcomes

The potential beneficial outcomes of primary interest would be improvements in OS and disease-specific survival and reduction in morbid events. Increased surveillance of the aorta,

surgical repair of the aorta, when necessary, as well as surveillance for multisystem involvement in syndromic forms of TAAD are initiated to detect and treat aortic aneurysms and dissections prior to rupture or dissection.

The potential harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to unnecessary surveillance of the aorta and surgical repair of the aorta. False-negative test results can lead to a lack of surveillance of the aorta that allows for the development and subsequent rupture of aortic aneurysm or dissection.

The primary outcomes of interest would be related to the frequency of surveillance and the short-term and long-term survival after surgical repair of the aorta.

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for genes associated with CTDs, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Single-Gene Testing

Sequencing analysis for Marfan syndrome (MFS) has been reported to detect 90% to 93% of pathogenic variants in probands with MFS. This is influenced by the accuracy of the clinical diagnosis and variant type.(13) The yield of deletion/duplication analysis in individuals with MFS is unknown.

Sequencing analysis for variant detection in Ehlers-Danlos syndrome (EDS) type IV is greater than 95%, and deletion/duplication analysis is approximately 1%.(14)

Panel Testing

Next-generation sequencing (NGS) technology cannot detect large deletions or insertions, therefore, samples from patients with a high clinical suspicion of a thoracic aortic aneurysm disorder without identified that pathogenic variants after sequencing should be evaluated by other testing methodologies (e.g., multiplex ligation-dependent probe amplification).

Marfan Syndrome

Sequence analysis of all exons in the *FBN1* gene is expected to identify a mutation in 90% to 93% of individuals with a clinical suspicion of MFS, with the mutation detection rate approaching 93% in those fulfilling a clinical diagnosis of MFS based on the Ghent nosology. The test sensitivity significantly decreases for individuals who do not meet Ghent criteria for MFS. Large deletions have been detected in approximately 2% of individuals who did not have a variant identified by sequencing.

Loeys-Dietz Syndrome

The pathogenic variant detection rate for sequence analysis of all exons in the *TGFBR1* and *TGFBR2* genes in patients with Loeys-Dietz syndrome (LDS) has not been well established but may be as high as 87% in patients with a strong clinical suspicion of LDS. Of LDS patients with an identifiable pathogenic variant, 70% have a pathogenic variant in the *TGFBR2* gene, 20% in the *TGFBR1* gene, 5% in the *SMAD3* gene and approximately 1% in the *TGFB2* gene.

Familial Thoracic Aortic Aneurysm and Dissection

Sequence analysis of all exons in the *ACTA2* gene is expected to identify a pathogenic variant in up to 15% of cases of familial TAAD (fTAAD). The *TGFBR1* and *TGFBR2* genes are expected to identify pathogenic variant in 1% and 4%, respectively, of individuals with TAAD. Pathogenic variants reported in *SMAD3* account for about 2% of individuals with TAAD. Rarely, has TAAD has been associated with pathogenic variants in the 9 other genes on the panel.

In a 2017 study conducted in China, 70 TAAD patients were screened by NGS coupled with DNA target capture for 11 known causative genes of TAAD that included *ACTA2*, *COL3A1*, *COL5A2*, *FBN1*, *MSTN*, *MYH11*, *MYLK*, *SLC2A10*, *SMAD3*, *TGFBR1*, and *TGFBR2*.⁽¹⁵⁾ The study identified 40 variants in 36 (51%) patients. Among all variants, 12 pathogenic/likely pathogenic variants were in the *FBN1* gene, one likely pathogenic variant was in the *ACTA2* gene, and the other 27 variants of uncertain significance presented in 8 genes.

Ambry Genetics has indicated that TAADNext identifies greater than 99% of described pathogenic variants in the genes included in its NGS panel and that up to 93% of patients with MFS will have a pathogenic variant in the *FBN1* gene.⁽¹⁶⁾ In addition, testing of *COL3A1* will detect a pathogenic variant in more than 95% of patients with EDS type IV, and that 30% to 40% of patients with fTAAD will have a pathogenic variant detected by TAADNext.

Baetens et al (2011) described the validation of a variant discovery strategy using multiplex polymerase chain reaction (PCR) followed by NGS.⁽¹⁷⁾ The pilot stage involved analysis of DNA from 5 patients with MFS or LDS and pathogenic variants and/or benign variants in the *FBN1*, *TGFBR1*, and *TGFBR2* genes previously identified by Sanger sequencing; all expected variants were identified. NGS was then validated on 87 samples from patients with MFS fulfilling the Ghent criteria. Seventy-five *FBN1* pathogenic variants were identified, 67 of which were unique. Because sequencing methods cannot detect larger deletions or insertions, multiplex ligation-dependent probe amplification analysis was performed on the negative samples and identified 4 large deletions/duplications. The authors concluded that their technique of multiplex PCR, followed by NGS analysis coupled with multiplex-ligation dependent probe amplification, is a robust strategy for time- and cost-effective identification of pathogenic variants in MFS and LDS.

Campens et al (2015) performed NGS-based screening on 264 consecutive samples from unrelated probands referred for heritable thoracic aortic disorders.⁽¹⁸⁾ Patients presenting with Marfanoid features, LDS features and/or vascular EDS features were considered as syndromic patients. Panel testing was performed whenever overlapping and/or insufficient clinical features were present, or when patients fulfilled the criteria for MFS but targeted *FBN1* sequencing and duplication/deletion testing were negative. The panels were focused and included the 7 genes associated with the most commonly occurring and phenotypically

overlapping syndromic and nonsyndromic hereditary thoracic aortic disorders: *FBN1* (MFS); *TGFBR1* and *TGFBR2*, *TGFB2*, *SMAD3* (LDS); *ACTA2* (familial TAAAD) and *COL3A1* (EDS type IV). A causal variant was identified in 34 (13%) patients, 12 of which were *FBN1*, 1 *TGFBR1*, 2 *TGFRBR2*, 3 *TGFB2*, 9 *SMAD3*, 4 *ACTA2*, and 3 *COL3A1*. Six variants of uncertain significance in *FBN1* were identified. Pathogenic variants in *FBN1* (n=3), *TGFBR2* (n=1), and *COL3A1* (n=2) were identified in patients without characteristic clinical features of a syndromal hereditary thoracic aortic disorder. Six patients with a *SMAD3* and one patient with a *TGFB2* pathogenic variant fulfilled diagnostic clinical criteria for MFS.

Wooderchak-Donahue et al (2015) reported the clinical and molecular findings in 175 individuals submitted for aortopathy panel testing at ARUP Laboratories using NGS and comparative genomic hybridization array to detect variants in 10 genes that cause thoracic aortic aneurysms.(19) Most patients referred had aortic findings (dilation, dissection, rupture) and a positive family history. Pathogenic variants on the panel were *FBN1*, *FBN2*, *TGFBR1/2*, *SMAD3*, *ACTA2*, *COL3A1*, *MYH11*, *MYLK*, and *SLC2A10*, comprising fTAAAD, EDS type IV, MFS, congenital contractural arachnodactyly, TAAAD-patent ductus arteriosus, arterial tortuosity, and LDS. Of the 175 individuals, 18 had a pathogenic variant and 32 had a variant of uncertain significance. Most of the pathogenic mutations (72%) were identified in *FBN1*. The most frequently identified disorders were fTAAAD (11 variants, 2 pathogenic, 9 variant of uncertain significance), LDS (12 variants, 3 pathogenic, 9 VUS) and MFS (21 variants, 13 pathogenic, 8 variant of uncertain significance).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No literature on the direct impact of genetic testing for CTDs addressed in the evidence review was identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Establishing a definitive diagnosis can lead to:

- treatment of manifestations of a specific syndrome,
- prevention of primary manifestations,
- prevention of secondary complications,
- impact on surveillance,
- counseling on agents/circumstances to avoid,
- evaluation of relatives at risk, including whether or not to follow a relative who does or does not have the familial variant,
- pregnancy management,
- future reproductive decision making

Most of the time, a diagnosis of 1 of the connective tissue syndromes that predisposes to TAAD, or of 1 of the syndromes that may not predispose to TAAD but has overlapping phenotypic features of 1 of the syndromes associated with TAAD, can be made based on clinical criteria and evidence of an autosomal-dominant inheritance pattern by family history. However, there are cases in which the diagnosis cannot be made clinically because the patient does not fulfill necessary clinical criteria, the patient has an atypical presentation and other connective tissue diseases cannot be excluded, or the patient is a child with a family history in whom certain age-dependent manifestations of the disease have not yet developed. In these circumstances, the clinical differential diagnosis is narrow, and single-gene testing or focused panel testing may be warranted, establishing the clinical utility of these types of tests. However, the incremental benefit of expanded NGS panel testing in these situations is unknown, and the variant of uncertain significance rate with these NGS panels is also unknown. In addition, the more disorders that are tested in a panel, the higher the variant of uncertain significance rate is expected to be.

Section Summary: Testing Patients with Signs and/or Symptoms of a Connective Tissue Disease

Evidence from multiple studies has indicated that the clinical sensitivity of genetic testing for CTDs related to TAAD is highly variable. This may reflect the phenotypic heterogeneity of the associated syndromes and the silent, indolent nature of TAAD development. The true clinical specificity is uncertain because different CTDs are defined by specific disease-associated variants. Direct evidence of the clinical utility of genetic testing for CTDs related to TAAD is lacking. However, genetic testing can confirm the diagnosis in patients with clinical signs and symptoms of a CTD associated with TAAD who do not meet clinical diagnostic criteria. Management changes include increased surveillance of the aorta and surgical repair of the aorta.

TARGETED FAMILIAL VARIANT TESTING OF ASYMPTOMATIC INDIVIDUALS WITH A KNOWN FAMILIAL PATHOGENIC VARIANT ASSOCIATED WITH TAAD

Clinical Context and Test Purpose

The purpose of familial variant testing of asymptomatic individuals with a first-degree relative with a CTD related to TAAD is to screen for the family-specific pathogenic variant to inform management decisions (e.g., increased surveillance) or to exclude asymptomatic individuals from increased surveillance of the aorta.

The following PICOs were used to select literature to inform this review.

Populations

The relevant population of interest is asymptomatic individuals with a first-degree relative with a CTD related to TAAD.

Interventions

The relative intervention of interest is targeted genetic testing for a familial variant related to TAAD. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparators

The following practice is being used for targeted testing of asymptomatic individuals with a first-degree relative with a CTD related to TAAD: standard clinical management without targeted genetic testing for a familial variant related to TAAD.

Outcomes

The potential beneficial outcomes of primary interest would be improvement in overall survival and disease-specific survival and reduction in morbid events. Increased surveillance of the aorta, and surgical repair of the aorta, when necessary, as well as surveillance for multisystem involvement in syndromic forms of TAAD are initiated to monitor the development of aortic aneurysms and dissection and potentially repair them prior to rupture or dissection. If targeted genetic testing for a familial variant is negative, the asymptomatic individual can be excluded from increased surveillance.

The potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary surveillance and surgical repair of the aorta. False-negative test results can lead to lack of surveillance of the aorta that allows for development and subsequent rupture of aortic aneurysms or dissection.

The primary outcomes of interest would be related to the frequency of surveillance and the short-term and long-term survival after surgical repair of the aorta.

Study Selection Criteria

For the evaluation of clinical validity of targeted genetic testing for a familial variant related to TAAD, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinical Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Refer to the discussion in the previous Clinically Valid section for patients with sign and/or symptoms of a CTD associated with TAAD.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from RCTs.

Chain of Evidence

A chain of evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

When a disease-associated variant for a CTD associated with TAAD has been identified in a proband, testing of first-degree relatives can identify those who also have the familial variant and may develop TAAD. These individuals need initial evaluation and ongoing surveillance of the aorta. Alternatively, first-degree relatives who test negative for the familial variant could be excluded from ongoing surveillance of the aorta.

Section Summary: Targeted Familial Variant Testing of Asymptomatic Individuals with a Known Familial Pathogenic Variant Associated with Thoracic Aortic Aneurysm Dissection

Direct evidence of the clinical usefulness of familial variant testing in asymptomatic individuals is lacking. However, for first-degree relatives of individuals affected with a CTD associated with TAAD, a positive test for a familial variant confirms the diagnosis of the TAAD-associated disorder and results in ongoing surveillance of the aorta while a negative test for a familial variant potentially reduces the need for ongoing surveillance of the aorta.

SUMMARY OF EVIDENCE

For individuals who have signs and/or symptoms of a connective tissue disorders linked to thoracic aortic aneurysms who received testing for genes associated with CTDs, the evidence consists mainly of clinical validity data. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, and morbid events. Sequencing analysis for MFS has been reported to detect 90% to 93% of pathogenic mutations in probands with MFS, and greater than 95% in Ehlers-Danlos syndrome (EDS) type IV (vascular Ehlers-Danlos). Direct evidence of clinical utility is lacking; however, confirming a diagnosis leads to changes in clinical management, which improve health outcomes. These changes in management include treatment of manifestations of a specific syndrome, prevention of primary manifestations and secondary complications, modifications to surveillance, and counseling on agents and circumstances to avoid. The evidence is sufficient to determine that the technology results in improvement in the net health outcome.

For individuals who are asymptomatic with a known familial pathogenic variant associated with thoracic aortic aneurysms and dissection who receive targeted familial variant testing, the evidence is generally lacking. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, and morbid events. Direct evidence of clinical utility is lacking; however, confirming a diagnosis leads to changes in clinical management, which improve health outcomes. In addition, test results will determine whether to follow a relative who does or does not have the familial variant. The evidence is sufficient to determine that the technology results in improvement in the net health outcome.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Academy of Pediatrics

In 2023, the American Academy of Pediatrics updated its clinical report focused on health supervision for children with MFS.(20) This clinical report notes the following with regard to genetic testing:

- "Younger patients at risk for MFS 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."

American College of Cardiology

Joint evidence-based guidelines (2022) from the American College of Cardiology ACC) and American Heart Association (AHA) for the diagnosis and management of aortic disease include MFS, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome.(21) Genetic testing for thoracic aortic disease (TAD) was addressed in the following guideline statement:

- "Genetic testing is recommended for individuals with syndromic features, family history of TAD, and/or early age of disease onset. Thoracic aortic imaging is recommended for first-degree relatives of all individuals with TAD, regardless of age of onset, to detect asymptomatic aneurysms. Positive genetic testing should trigger gene-based management and cascade testing of at-risk relatives. When testing is negative or reveals variants of unknown significance, first-degree relatives should undergo screening aortic imaging."

Specific recommendations for genetic testing and screening of family members for TAD are provided in the table below.

Table 1. Genetic Testing and Screening of Family Members for Thoracic Aortic Disease*

COR	LOE	Recommendations
1	B-NR	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.
1	B-NR	In patients with an established pathogenic or likely pathogenic variant in a gene predisposing to HTAD, it is recommended that genetic counseling be provided and the patient's clinical management be informed by the specific gene and variant in the gene.
1	B-NR	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 family members who are found by genetic screening to have inherited the pathogenic/likely pathogenic variant, aortic imaging with TTE (if aortic root and ascending aorta are adequately visualized, otherwise with CT or MRI) is recommended.
1	B-NR	In a family with aortic root/ascending aortic aneurysms or aortic dissection, if the disease-causing variant is not identified with genetic testing, screening aortic imaging (as per recommendation 4) of at-risk biological relatives (i.e., cascade testing) is recommended.
1	B-NR	In patients with aortic root/ascending aortic aneurysms or aortic dissection, in the absence of either a known family history of TAD or pathogenic/likely pathogenic variant, screening aortic imaging (as per recommendation 4) of first-degree relatives is recommended.

B-NR: level B, non-randomized evidence; COR: class of recommendation; CT: computerized tomography; HTAD: heritable thoracic aortic disease; LOE: level of evidence; MRI: magnetic resonance imaging; TAD: thoracic aortic disease; TTE: transthoracic echocardiogram.

*adapted from Isselbacher et al (2022).(22)

American College of Cardiology Foundation

Joint evidence-based guidelines (2010) from the American College of Cardiology Foundation and 9 other medical associations for the diagnosis and management of thoracic aortic disease include MFS.(22) Genetic testing for MFS was addressed in the following guidelines statements:

- "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. Recommendation that procedure or treatment is useful/effective. It is based on very limited populations evaluated and only expert opinion, case studies, or standard of care.]
- "The criteria for MFS is based primarily on clinical findings in the various organ systems affected in the MFS, along with family history and *FBN1* mutations [pathogenic variants] status."

American College of Medical Genetics and Genomics

In 2012, the American College of Medical Genetics and Genomics issued guidelines on the evaluation of adolescents or adults with some features of MFS.(23) The guidelines recommended the following:

"If there is *no family history of MFS*, then the subject has the condition under any of the following 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) and ectopia lentis
- A dilated aortic root and a mutation [pathogenic variant] in *FBN1* that is clearly pathologic
- A dilated aortic root and multiple systemic features ... or
- Ectopia lentis and a mutation [pathogenic variant] 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 3 situations:

- Ectopia lentis
- Multiple systemic features ... or
- A dilated aortic root (if over 20 years, greater than 2 standard deviations; if younger than 20, greater than 3 standard deviations)"

The systemic features are weighted by a scoring system.

American Heart Association

In 2020, the AHA issued a scientific statement focused on genetic testing and its implications for the management of inherited cardiovascular diseases (Table 2).(24) 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. Briefly, the statement notes that:

- "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"
- "Pathogenic and likely pathogenic variants might confirm diagnoses of suspected diseases (i.e., 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 (see Table SI1)"

Table 2. Genetics-Guided Diagnosis and Management of Cardiovascular Condition*

Condition	Role in Diagnosis	Role in management
Familial thoracic aortic aneurysm and dissection	Confirm clinical diagnosis and subtype classification	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
Loeys-Dietz syndrome	Major criterion for diagnosis and subtype classification	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
Marfan syndrome	Major criterion for diagnosis	Confirmed diagnosis can affect timing of recommended surgical intervention

*adapted from Musunuru et al 2020.(25)

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*, *TGFBR1*, *TGFBR2*, *SMAD3*, *ACTA2*, *MYH11*.

In 2021, the AHA issued a scientific statement focused specifically on genetic testing in the pediatric population.(25) Key points and recommendations on pediatric cardiovascular genetic testing from the AHA statement 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."

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

Government Regulations

National:

Medicare does not have a national policy regarding genetic testing for Marfan syndrome specifically. There is an NCD for Cytogenetic Studies (190.3), effective date 7/16/98:

Item/Service Description

The term 'cytogenetic studies' is used to describe the microscopic examination of the physical appearance of human chromosomes.

Indications and Limitations of Coverage

Medicare covers these tests when they are reasonable and necessary for the diagnosis or treatment of the following conditions:

- Genetic disorders (e.g., mongolism) in a fetus; (See the Medicare Benefit Policy Chapter 15, "Covered Medical and Other Health Services," §20.1)
- Failure of sexual development;
- Chronic myelogenous leukemia;
- Acute leukemias lymphoid (FAB L1-L3), myeloid (FAB M0-M7), and unclassified; or
- Myelodysplasia

Local:

No Local Determination available

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling

References

1. Black JH. Epidemiology, risk factors, pathogenesis and natural history of thoracic aortic aneurysm. In: Lockwood C, ed. UpToDate. Waltham, MA: UpToDate Inc.; 2018.
2. Dietz HC. Marfan Syndrome. GeneReviews. 2001 (updated 2017). PMID 20301510.
3. Loeys BL, Dietz HC, Braverman AC, et al., The revised Ghent nosology for the Marfan syndrome. J Med Genet. Jul 2010;47(7):476-485. PMID 20591885
4. Eagleton MJ. Arterial complications of vascular Ehlers-Danlos syndrome. J Vasc Surg. Dec 2016; 64(6):1869-1880. PMID 27687326

5. Beridze N, Frishman WH. Vascular Ehlers-Danlos syndrome: pathophysiology, diagnosis, and prevention and treatment of its complications. *Cardiol Rev.* Jan-Feb 2012;20(1):4-7. PMID 22143279
6. Byers PH. Vascular Ehlers-Danlos Syndrome. In: Adam MP, ed. *Gene Reviews*. Seattle, WA: University of Washington; 2019. PMID: 20301667
7. Loeys BL, Dietz HC. Loeys-Dietz Syndrome. In: Adam MP, ed. *Gene Reviews*. Seattle, WA: University of Washington; 2018. PMID: 20301312
8. Callewaert B, De Paepe A, Coucke P. Arterial Tortuosity Syndrome. In: Adam MP, ed. *Gene Reviews*. Seattle, WA: University of Washington; 2022. PMID: 25392904
9. Milewicz DM, Regalado E. Heritable thoracic aortic disease. In: Adam MP, ed. *Gene Reviews*. Seattle, WA: University of Washington; 2017.
10. Callewaert B. Congenital Contractural Arachnodactyly. 2001 Jan 23 [Updated 2022 Jul 14]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. *Gene Reviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. PMID: 20301560
11. Lyons MJ. MED12-Related Disorders. 2008 Jun 23 [Updated 2021 Aug 12]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. *Gene Reviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. PMID: 20301719
12. Greally MT. Shprintzen-Goldberg Syndrome. *GeneReviews*. 2006 (updated 2013). PMID 20301454
13. Dietz HC. Marfan Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *Gene Reviews*. Seattle, WA: University of Washington; 2017.
14. Pepin MG, Byers PH. Ehlers-Danlos Syndrome Type IV. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *Gene Reviews*. Seattle, WA: University of Washington; 2015.
15. Fang M, Yu C, Chen S, et al. Identification of novel clinically relevant variants in 70 Southern Chinese patients with thoracic aortic aneurysm and dissection by next-generation sequencing. *Sci Rep.* Aug 30 2017;7(1):10035. PMID 28855619
16. TAADNext®. Ambry Genetics. Accessed December 31, 2023. <https://www.ambrygen.com/providers/genetic-testing/12/cardiology/taadnext>.
17. Baetens M, Van Laer L, De Leeneer K, et al., Applying massive parallel sequencing to molecular diagnosis of Marfan and Loeys-Dietz syndromes. *Hum Mutat.* Sep 2011;32(9):1053-1062. PMID 21542060
18. Campens L, Callewaert B, Muino Mosquera L, et al., Gene panel sequencing in heritable thoracic aortic disorders and related entities - results of comprehensive testing in a cohort of 264 patients. *Orphanet J Rare Dis.* 2015;10:9. PMID 25644172
19. Wooderchak-Donahue W, VanSant-Webb C, Tvrdik T, et al., Clinical utility of a next generation sequencing panel assay for Marfan and Marfan-like syndromes featuring aortopathy. *Am J Med Genet A.* Aug 2015;167A(8):1747-1757. PMID 25944730
20. Tinkle BT, Lacro RV, Burke LW. Health Supervision for Children and Adolescents With Marfan Syndrome. *Pediatrics.* Apr 01 2023; 151(4). PMID 36938616
21. Isselbacher EM, Preventza O, Hamilton Black J, et al. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation.* Dec 13 2022; 146(24): e334-e482. PMID 36322642
22. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. 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. J Am Coll Cardiol. Apr 6 2010;55(14):e27-e129. PMID 20359588
23. Pyeritz RE. Evaluation of the adolescent or adult with some features of Marfan syndrome. Genet Med. Jan 2012;14(1):171-177. PMID 22237449
 24. Musunuru K, Hershberger RE, Day SM, et al. Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association. Circ Genom Precis Med. Aug 2020; 13(4): e000067. PMID 32698598
 25. Landstrom AP, Kim JJ, Gelb BD, et al. Genetic Testing for Heritable Cardiovascular Diseases in Pediatric Patients: A Scientific Statement From the American Heart Association. Circ Genom Precis Med. Oct 2021; 14(5): e000086. PMID 34412507
 26. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD): Cytogenetic Studies. 1998. Pub 100-3. Sec 190.3. Ver 1. <https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=198&ncdver=1&keyword=cytogenetic%20studies&keywordType=starts&areald=s27&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1>. Accessed May 22, 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 5/22/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/2010	10/29/09	10/13/09	Joint policy established
3/1/12	12/13/11	12/21/11	Added Ghent criteria to policy; policy changed from investigational to established with inclusion/exclusion criteria changes; Medical policy statement revised; Rationale section updated
7/1/13	4/16/13	4/22/13	Routine maintenance; revisions to code descriptions effective 1/1/13; no changes in policy position.
1/1/15	10/24/14	11/3/14	Routine maintenance
5/1/16	2/16/16	2/24/16	<ul style="list-style-type: none"> • Routine maintenance • Policy updated to new BCBSA policy, “Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders.” • Title changed for clarity • Diverged from BCBSA inclusions • Inclusions to cover all genes per CPT code (81410)
5/1/17	2/21/17	2/21/17	Routine maintenance
5/1/18	2/20/18	2/20/18	<ul style="list-style-type: none"> • Routine maintenance • LCD updated
5/1/19	2/19/19		Routine maintenance
5/1/20	2/18/20		Routine maintenance
11/1/20	8/18/20		Routine maintenance
11/1/21	8/17/21		<ul style="list-style-type: none"> • Updated wording in MPS and criteria to include Ehlers-Danlos syndrome – no change to policy stance • Title updated from “Genetic Testing For Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders”

11/1/22	8/16/22		<ul style="list-style-type: none"> • Routine maintenance
11/1/23	8/15/23		<ul style="list-style-type: none"> • Routine maintenance (slp) • Vendor managed: N/A
11/1/24	8/20/24		<ul style="list-style-type: none"> • Routine maintenance (slp) • Vendor managed: N/A • Exclusion removed r/t prenatal and pre-implantation r/t Marfan syndrome

Next Review Date: 3rd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR MARFAN SYNDROME, EHLERS-DANLOS, THORACIC
AORTIC ANEURYSMS AND DISSECTIONS, AND CONNECTIVE TISSUE RELATED
DISORDERS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.