Medical Policy

Title: Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders

Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With signs and/or symptoms of a connective tissue disease linked to thoracic aortic aneurysms	Interventions of interest are: • Testing for genes associated with connective tissue disease	Comparators of interest are: • Standard clinical management without genetic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Symptoms • Morbid events
Individuals: • Who are asymptomatic with a known familial pathogenic variant associated with thoracic aortic	Interventions of interest are: • Targeted familial variant testing	Comparators of interest are: • Standard clinical management without targeted familial variant testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity

Populations	Interventions	Comparators	Outcomes
aneurysms and dissection			• Symptoms • Morbid events

DESCRIPTION
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 1 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.

OBJECTIVE
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 1 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.

BACKGROUND

Connective Tissue Diseases
Individuals suspected of having a systemic connective tissue disease (CTD) like Marfan syndrome (MFS) usually have multiple features that affect many different organ systems; most of these conditions can be diagnosed using clinical criteria. However, these syndromes may share features, overlapping phenotypes, and similar inheritance patterns, which can cause a diagnostic challenge. 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.

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). Thoracic aortic aneurysms

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.[Black JH and Burke CR. Epidemiology, risk factors,.... ham, MA: UpToDate Inc.; 2021.] 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 thoracic aortic aneurysm and dissection (TAAD).
Other genetic, systemic CTDs 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 who do not meet criteria for a CTD.

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.[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 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 are based on clinical characteristics in large published patient cohorts and expert opinions.[3,] The revised criteria include several major changes, as follows. More weight is given to the 2 cardinal features of MFS: aortic root aneurysm and 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 less specific manifestations of MFS were removed or given less weight in the diagnostic criteria. Fourth, the revised criteria formalized the concept that additional diagnostic considerations and testing may be required if a patient has findings that satisfy the criteria for MFS but shows 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 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 for which pathogenic variants are known to cause classic MFS. Approximately 75% of individuals with MFS have an affected parent, while 25% have a de novo pathogenic variant.[2,] Over 1000 *FBN1* pathogenic variants that cause MFS have been identified.[1,]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 pathogenic variants of a certain type (e.g., nonsense, certain missense variants, certain splice site variants, 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 and 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 and 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 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 treatments 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 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.[4,]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.

Diagnosis

The clinical diagnosis of EDS type IV can be made from major and minor clinical criteria. The combination of 2 major criteria (arterial rupture, intestinal rupture, uterine rupture during pregnancy, family history of EDS type IV) is highly specific.[5,] The presence of 1 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 pathogenic variants in the *COL3A1* gene.[6,]

Loeys-Dietz Syndrome

Loeys-Dietz Syndrome is an autosomal-dominant condition 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 the *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 hyperextensibility.

Genetic Testing

The syndrome is caused by pathogenic variants in the *SLC2A10* gene.[8]

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.[1]

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.[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 (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.

Genetic Testing

Familial TAAD is associated with pathogenic variants in 16 genes including: *TGFBR1*, *TGFBR2*, *MYH11*, *ACTA2*, *MYLK*, *SMAD3*, and 2 loci on other chromosomes, *AAT1* and *AAT2*. Rarely, fTAAD can also be caused by *FBN1* pathogenic variants. To date, only about 20% of fTAAD is accounted for by variants in known genes. Early prophylactic repair should be considered in individuals with confirmed pathogenic variants in the *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 CTDs, but do not share the risk of TAAD.

Congenital Contractural Arachnodactyly (Beal Syndrome)

Congenital contractural arachnodactyly 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. Congenital contractural arachnodactyly 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, FG syndrome type 1, and others.[11] Lujan syndrome and FG syndrome type 1 share the clinical findings of hypotonia, cognitive impairment, and abnormalities of the corpus callosum.

lity*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 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. 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 the measurement of cystathionine beta-synthase 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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the 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 targeted genetic testing, as well as next-generation sequencing panels that simultaneously analyze multiple genes associated with MFS, TAADs, and related disorders. Next-generation sequencing 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 panel that simultaneously analyzes 35 genes associated with TAADs, MFS, and related disorders. The panel detects variants in all coding domains and splice junctions of genes: *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 and duplication analyses 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 a “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, NOTCH1, 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 “Rest of Marfan/TAAD Sequencing & Del/Dup 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*.

POLICY

A. Individual genetic testing for the diagnosis of Marfan syndrome, Ehlers-Danlos syndrome type IV, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders, and panels comprised entirely of focused genetic testing limited to the following genes: *FBN1* and *MYH11*; *ACTA2*, *TGFBR1*, and *TGFBR2;* and COL3A1 may be considered **medically necessary**, when signs and symptoms of a connective tissue disorder are present, but a definitive diagnosis cannot be made using established clinical diagnostic criteria.

B. Individual, targeted familial variant testing for Marfan syndrome, Ehlers-Danlos syndrome type IV, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders, for assessing future risk of disease in an asymptomatic individual, may be considered **medically necessary** when there is a known pathogenic variant in the family.

C. Genetic testing panels for Marfan syndrome, Ehlers-Danlos syndrome type IV, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders that are not limited to focused genetic testing are considered **experimental / investigational**.

POLICY GUIDELINES

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 type IV), 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 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 (pre-symptomatic diagnosis).

Genetic testing has conventionally been used when a definitive diagnosis of 1 of these syndromes cannot be made. More recently, 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.

However, 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.

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 vs. *de novo*) may be considered appropriate to guide clinical management.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology — "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through December 8, 2022.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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

Clinical Context and Test Purpose

The purpose of genetic testing of patients who have signs and/or symptoms of a connective tissue disease (CTD) linked to thoracic aortic aneurysms (TAAs) when a diagnosis cannot be made clinically, is to confirm a diagnosis and inform management decisions such as 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 PICO was 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 a 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 the 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 potentially beneficial outcomes of primary interest would be improvements in overall survival and disease-specific survival and reductions 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 before rupture or dissection.

The potentially 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 an 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 and 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 and 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 TAA disorder without identified 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 pathogenic variant in 90% to 93% of individuals with a clinical suspicion of MFS, with the variant 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 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, 1 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 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 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 and duplications. The authors concluded that their technique of multiplex polymerase chain reaction, 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, and deletion testing was 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* (fTAAD); and *COL3A1* (EDS type IV). A causal variant was identified in 34 (13%) patients, 12 of which were *FBN1*, 1 *TGFBR1*, 2 TGFBR2, , 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* pathogenic variant and 1 patient with a *TGFB2* pathogenic variant fulfilled diagnostic clinical criteria for MFS.

Wooderchak-Donahue et al (2015) reported on 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 TAAs.[19,] Most patients referred had aortic findings (dilation, dissection, rupture) and positive family history. Pathogenic variants on the panel were identified in *FBN1*, *FBN2*, *TGFBR1* and *TGFBR2*, *SMAD3*, *ACTA2*, *COL3A1*, *MYH11*, *MYLK*, and *SLC2A10*, comprising fTAAD, EDS type IV, MFS, congenital contractual arachnodactyly, TAAD-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 pathogenic variants (72%) were identified in *FBN1*. The most frequently identified disorders were fTAAD (11 variants: 2 pathogenic, 9 variants of uncertain significance), LDS (12 variants: 3 pathogenic, 9 variants of uncertain significance), and MFS (21 variants: 13 pathogenic, 8 variants 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, 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 (RCTs).

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 and circumstances to avoid,
- evaluation of relatives at risk, including whether to follow a relative who does or does not have the familial variant,
- pregnancy management, and
- future reproductive decision making.

Most of the time, a diagnosis of 1 of the CTDs 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 CTDs 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 usefulness of these types of tests. However, the incremental benefit of expanded NGS panel testing in these situations is unknown, and the variants of uncertain significance rate with these NGS panels is also unknown. Also, the more disorders that are tested in a panel, the higher the variants 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 usefulness 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 THORACIC AORTIC ANEURYSM DISSECTION

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 PICO was used to select literature to inform this review.

Populations

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

Interventions

The relevant intervention of interest is targeted genetic testing for a familial variant related to TAAD. Referral for genetic counseling is important for the 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 potentially beneficial outcomes of primary interest would be improvements in overall survival and disease-specific survival and reductions 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 monitor the development of aortic aneurysms and dissection and potentially repair them before rupture or dissection. If targeted genetic testing for a familial variant is negative, the asymptomatic individual can be excluded from increased surveillance.

The potentially harmful outcomes are those resulting from 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 the 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.

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

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, 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.

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

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 of 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.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given

to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of the management of conflict of interest.

American Heart Association
In 2020, the American Heart Association (AHA) issued a scientific statement focused on genetic testing and its implications for the management of inherited cardiovascular diseases (Table 1).[20,] 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 1. 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.[20,]

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.[21,] 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."

American Academy of Pediatrics
In 2019, the American Academy of Pediatrics reaffirmed its 2013 clinical report focused on health supervision for children with MFS.[22] This clinical report notes the following with regard to genetic testing:

"Genetic testing of *FBN1* is best reserved for those patients in whom there is a strong clinical suspicion of MFS, including those with the "emerging" phenotype, using established guidelines of the interpretation of such results."

"Younger patients at risk for MFS on the basis of clinical features or a positive family history should be evaluated periodically (e.g., at 5, 10, 15, and 18 years of age) in lieu of genetic testing."

"For those suspected to have MFS based on clinical grounds after physical, cardiac, and ophthalmic evaluation but who may not meet full clinical criteria, one can consider *FBN1* testing."

"Genetic testing for *FBN1* mutations by using amniocentesis may be helpful to confirm the diagnosis of MFS and to reveal specific mutations in *FBN1* that may be more typically associated with neonatal MFS and, therefore, reduced survivability."

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 College of Cardiology
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.[24,] 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."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in December 2022 did not identify any ongoing or unpublished trials that would likely influence this review.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
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)
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)
81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
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, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
81411	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 TGFBR1, TGFBR2, MYH11, and COL3A1
81479	Unlisted molecular pathology procedure

REVISIONS	
05-21-2015	Policy added to the bcbsks.com web site on 04-21-2015.
04-25-2016	Description section updated
	In Policy Section: ▪ Updated Policy Guidelines
	Rationale section updated
	References updated
	Added Appendix Table 1. Categories of Genetic Testing addressed in Policy
03-28-2018	Description section updated
	In Policy Section: ▪ In Items A, B, and C removed "mutation" and replaced with "genetic" or "variant" ▪ In Item B added "familial" to read "Individual targeted familial variant testing for Marfan syndrome…" ▪ Updated Policy Guidelines (moved the Coding for Individual Gene Testing chart to the Coding section from the Policy Guidelines section)
	Rationale section updated

REVISIONS	
	In Coding section: ▪ Added Coding for Individual Gene Testing chart (moved from the Policy Guidelines section) ▪ Updated Coding notations
	References updated
04-24-2019	Description section updated
	In Policy section: ▪ In Item A revised "mutation" to "genetic" to read Individual genetic testing for the diagnosis of Marfan syndrome…" ▪ Policy Guidelines updated.
	Rationale section updated
	References updated
05-14-2021	Description section updated
	In Policy section: ▪ In Item A added "Ehlers-Danlos syndrome type IV, and COL3A1" ▪ In Items B and C added "Ehlers-Danlos syndrome type IV" ▪ In Policy Guidelines added "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 vs. *de novo*) may be considered appropriate to guide clinical management."
	Rationale section updated
	In Coding section: ▪ Removed: Table PG3. Coding for Individual Gene Testing
	References updated
04-08-2022	Updated Description Section
	Updated Policy Guidelines Section
	Updated Rationale Section
	Update References Section
03-28-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 codes
	Updated References Section

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