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

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider individual genetic testing for the diagnosis of Marfan syndrome (MFS), 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 (CPT code 81408) and ACTA2, TGFBR1, and TGFBR2 (CPT code 81405), when signs and symptoms of a connective tissue disorder are present, but a definitive diagnosis cannot be made using established clinical diagnostic criteria to be eligible for coverage.

Based on review of available data, the Company may consider individual, targeted familial variant testing for Marfan syndrome (MFS), other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders, for assessing future risk of disease in an asymptomatic individual, when there is a known pathogenic variant in the family to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing panels for Marfan syndrome (MFS), other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders that are not limited to focused genetic testing as defined by CPT codes 81405 and 81408 to be investigational.*

Background/Overview

CONNECTIVE TISSUE DISEASES
Individuals suspected of having a systemic connective tissue disorder (CTD) like MFS usually have multiple features that affect many different organ systems and are required to establish a diagnosis, and most of these conditions can be diagnosed using clinical criteria. However, these different syndromes may show shared 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 many of these syndromes occur in the general population (eg, pectus excavatum, tall stature, joint hypermobility, mitral valve prolapse, nearsightedness). The identification of the proper syndrome is important to address the manifestations and complications of the specific syndrome, in particular, the risk of aortic aneurysms and dissection.

**Thoracic Aortic Aneurysms and Dissection**

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

Genetic predisposition to TAA is due to a genetic defect that leads to abnormalities in connective tissue metabolism. Genetically-related TAA accounts for approximately 5% of TAA. Some 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 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 CTD.

**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. 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 (ectopic lentis) is a hallmark feature and 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. However, with proper management, the life expectancy of someone with MFS can approximate that of the general population.

The diagnosis of MFS is mainly a clinical one and based on the characteristic findings in multiple organ systems, as well as the family history. The Ghent criteria, revised in 2010, are used for the clinical diagnosis
of MFS. 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 of panel members with extensive experience in application of the criteria, the differential diagnosis of MFS, and the strengths and limitations of molecular genetic testing. The revised criteria have 5 major changes to the previous diagnostic guidelines. First, more weight is given to the 2 cardinal features of MFS, aortic root aneurysm/dissection and ectopic 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 made less influential 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 shows overlap with MFS. Each of these conditions has a unique risk profile and management protocol. Given the autosomal-dominant inheritance, the number of physical findings needed to establish a diagnosis for someone with an established family history is reduced.

It is estimated that molecular techniques allow the detection of FBN1 mutations in up to 97% of Marfan patients who fulfil Ghent criteria, suggesting that the current Ghent criteria have excellent specificity.

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. 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 (eg, nonsense, certain missense mutations, certain splice site mutations, certain deletions and insertions).

Most variants in the FBN1 gene that cause MFS can be identified with sequence analysis (~70% 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. 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 in interpreting the identification of a FBN1 mutation, as other conditions with overlapping phenotypes with MFS can have an FBN1 variant (eg, MASS syndrome, familial mitral valve prolapse syndrome, SGS, isolated ectopic lentis).

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**

EDS are a group of disorders that affect connective tissue disorders and share common features characterized by skin hyperelasticity or laxity, 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 types I and II (classic type), type III (hypermobility type), type IV (vascular type), 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 disease-causing mutation 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, with the exception of 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 250,000 people. 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.

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 and a family history of EDS type IV) is highly specific. The presence of 1 or more minor clinical criteria supports the diagnosis, but is not considered sufficient to make the diagnosis.

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.

**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. 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.

LDS is caused by pathogenic variants in TGFBR1, TGFBR2, TGFB2, and SMAD3.

**Arterial Tortuosity Syndrome**

Arterial tortuosity syndrome is inherited in an autosomal recessive pattern and is 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 hyperextensible skin. The syndrome is caused by pathogenic variants in the SLC2A10 gene.

**Familial TAAD**

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.

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 ascending or descending aorta. 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. 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. Familial TAAD is associated with pathogenic variants in 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.
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 (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.

**MED12-Related Disorders**

The phenotypic spectrum of \(MED12\)-related disorders is still being defined, but includes Lujan syndrome (LS) and FG syndrome type 1 (FGS1). LS and FGS1 share the clinical findings of hypotonia, cognitive impairment, and abnormalities of the corpus callosum. Individuals with LS share some physical features with MFS, in that they have Marfanoid features including tall and thin habitus, long hands and fingers, pectus excavatum, narrow palate, and joint hypermobility. \(MED12\)-related disorders are inherited in an X-linked manner, with males being affected and carrier females not usually being affected.

**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. \(SK1\) 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 (eg, liver biopsy, skin biopsy).
FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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. FDA 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 MFS, TAADs, and related disorders. NGS technology cannot detect large deletions or insertions, and therefore samples that are mutation-negative after sequencing should be evaluated by other testing methodologies.

Ambry Genetics offers “TAADNEXT,” an NGS panel which simultaneously analyzes 20 genes that are associated with TAADs, MFS and related disorders. The panel detects mutations in all coding domains and splice junctions of ACTA2, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, MED12, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, SKI, SLC2A10, SMAD3, SMAD4, TGFBR1, and TGFBR2. Deletion/duplication analysis is performed for all genes on the panel except CBS, COL5A1, and FLNA, SMAD4, and TGFBR3.

Prevention Genetics offers targeted familial variants testing, as well as “MFS and related aortopathies NGS panel,” which includes 14 genes: ACTA2, COL3A1, COL5A1, COL5A2, FBN1, FBN2, MYH11, MYLK, SKI, SLC2A10, SMAD3, TGFBR1, and TGFBR2.

GeneDx offers panel testing “Marfan/TAAD sequencing panel” and “Marfan/TAAD deletion/duplication panel,” which include variant testing for ACTA2, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, MED12, MYH11, SKI, SLC2A10, SMAD3, TGFBR1, and TGFBR2.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source
The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of a test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of a test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (ie, how the results of a diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).
GENETIC TESTING OF 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 CTD linked to TAAs and 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 question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals with signs and/or symptoms of a CTD linked to TAAs?

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

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

Interventions
Genetic testing for genes associated with CTDs.

Comparators
Standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival, and morbid events. 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 a 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 lack of surveillance of the aorta that allows for development and subsequent rupture of aortic aneurysm or dissection.

Time
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.
Setting
Patients may be referred from primary care to a cardiologist or medical geneticist for investigation and management of CTDs related to TAAD. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity
Single-Gene Testing
The analytic validity of direct sequencing analysis of single genes is expected to be high. This may be influenced by the accuracy of the clinical diagnosis and the type of variant.

Panel Testing
Clinical laboratories offer multigene panels for several CTDs that may include TAAs or TAADs. Different laboratories may use different methods, and panels vary in the genes included; therefore, the ability of a panel to detect a pathogenic variant in any given individual also varies. No published data were identified that reported the analytic validity of these panels.

Variants of Uncertain Significance
A variant of uncertain significance (VUS) is an alteration in the normal sequence of a gene, the significance of which is unclear until further study of the genotype and phenotype is conducted in a sufficiently large population. Complete gene sequencing often identifies numerous (sometimes hundreds) allelic variants for a given gene.

Multigene panel testing poses an increased risk of erroneous interpretation of VUS. The VUS rate of NGS panels for TAAD is unknown.

Clinical Validity
Single-Gene Testing
Sequencing analysis for MFS has been reported to detect 70% to 93% of pathogenic variants in probands with MFS. This is influenced by the accuracy of the clinical diagnosis and variant type. The yield of deletion/duplication analysis in individuals with MFS is unknown.

Sequencing analysis for variant detection in EDS type IV is greater than 95%, and deletion/duplication analysis is approximately 2%.

Panel Testing
NGS technology cannot detect large deletions or insertions and, 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 (eg, multiplex ligation-dependent probe amplification [MLPA]).
According to GeneDx, the technical sensitivity of their panel test is estimated to be 98%; however, the test will not detect large chromosomal aberrations and deletions, insertions, or rearrangements of 5 or more base pairs. Test sensitivity for the following conditions on the GeneDx panel are as follows.

**Marfan Syndrome**
Sequence analysis of all exons in the *FBN1* gene is expected to identify a pathogenic variant in 70% 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 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 TAAD**
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.

Amby Genetics has indicated that TAADNext identifies greater than 96% 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. 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) has described the validation of a variant discovery strategy using multiplex polymerase chain reaction (PCR) followed by NGS. 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, MLPA 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 MLPA, 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. 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 (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 VUS 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 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. Most patients referred had aortic findings (dilation, dissection, rupture) and a 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 contractural arachnodactyly, TAAD-patent ductus arteriosus, arterial tortuosity, and LDS. Of the 175 individuals, 18 had a pathogenic variant and 32 had a VUS. Most pathogenic variants (72%) were identified in FBN1. The most frequently identified disorders were fTAAD (11 variants: 2 pathogenic, 9 VUS), LDS (12 variants: 3 pathogenic, 9 VUS) and MFS (21 variants: 13 pathogenic, 8 VUS).

Section Summary: Clinical Validity
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.

Clinical Utility
Clinical utility is how the results of a diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.
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 randomized controlled trials (RCTs). No such trials were 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.

No literature on the direct impact of genetic testing for CTDs addressed in the evidence review was identified. However, 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 utility of these types of tests. However, the incremental benefit of expanded NGS panel testing in these situations is unknown, and the VUS rate with these NGS panels is also unknown. In addition, the more disorders that are tested in a panel, the higher the VUS rate is expected to be.

Section Summary: Clinical Utility

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 such as increased cancer surveillance or to exclude asymptomatic individuals from increased surveillance of the aorta.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in asymptomatic individuals with a first-degree relative with a CTD related to TAAD?

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

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

Interventions
Targeted genetic testing for a familial variant related to TAAD.

Comparators
Standard clinical management without targeted genetic testing for a familial variant related to TAAD.

Outcomes
The general outcomes of interest are OS, disease-specific survival, and morbid events. The potential beneficial outcomes of primary interest would be improvement in OS 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 cancer 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.

Time
Same as above for patients with sign and/or symptoms of a CTD related to TAAD.
Setting
Asymptomatic individuals may be referred from primary care to a cardiologist or medical geneticist if a familial variant related to TAAD is identified. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity
Same as the previous section for patients with sign and/or symptoms of a CTD associated with TAAD.

Clinical Validity
Same as the previous section for patients with sign and/or symptoms of a CTD associated with TAAD.

Clinical Utility
Clinical utility is how the results of a diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

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 such trials were 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.

Family Members
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 potentially be excluded from ongoing surveillance of the aorta.

Section Summary: Clinical Utility
Direct evidence of the clinical utility of familial variant testing in asymptomatic individuals is lacking. However, for first-degree relatives of individuals affected individuals 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 CTD linked to thoracic aortic aneurysms who received testing for genes associated with CTDs, the evidence includes mainly of clinical validity data. Relevant
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outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, and morbid events. Published data on analytic validity of individual and panel testing of genes is lacking. Sequencing analysis for MFS has been reported to detect 70% to 93% of pathogenic variants in probands with MFS, and over 95% in Ehlers-Danlos syndrome type IV. 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, impact on surveillance, and counselling on agents and circumstances to avoid. The evidence is sufficient to determine that the technology results in a meaningful 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. Published data on analytic validity of targeted familial variant testing is lacking, but is expected to be high. Direct evidence of clinical utility is lacking; however, confirming a diagnosis leads to changes in clinical management, which improve health outcomes, similar to those in the proband. 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 a meaningful improvement in the net health outcome.

References

Policy History
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<tr>
<td>CPT</td>
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<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means
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of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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