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

Policy # 00464
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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 mutation 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 mutation 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 mutation 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 mutation 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 mutation testing as defined by CPT codes 81405 and 81408 to be investigational.*

Background/Overview
Individuals suspected of having a systemic connective tissue disorder 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 (e.g., 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) are degenerative and are often associated with the same risk factors as abdominal aortic aneurysms (e.g., atherosclerosis). TAA 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 connective tissue syndrome.

**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. 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 fulfill 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 splice site mutations, certain deletions and insertions).

Most mutations 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 mutations that have been described are unique, and most mutations are not repeated among nongenetically related patients. Therefore, the absence of a known mutation 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 mutation.

Caution should be used in interpreting the identification of a \( FBN1 \) mutation, as other conditions with overlapping phenotypes with MFS can have an \( FBN1 \) mutation (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 disease-causing mutation.

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.

Mutations in the ADAMTS2, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, PLOD1, and TNXB genes cause EDS.

The vascular type (type IV) is caused by mutations 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 mutations 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 mutations 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 genetic mutation.

The major cardiovascular manifestations of familial TAAD (fTAAD) include dilatation of the ascending thoracic aorta at the level of the sinuses of Valsalva or ascending aorta or both and dissections of the thoracic aorta involving either the ascending or descending aorta. 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. fTAAD is diagnosed based on the presence of thoracic aorta pathology, absence of clinical features of MFS, LDS, or vascular EDS, and a positive family history of TAAD. Familial TAAD is associated with mutations in \( TGFBR2, TGFBR1, MYH11, ACTA2, MYLK, SMAD3 \), and 2 loci on other chromosomes, AAT1 and AAT2. Rarely, fTAAD can also be caused by \( FBN1 \) mutations. To date, only about 20% of fTAAD is accounted for by mutations in known genes. Early prophylactic repair should be considered in individuals with confirmed mutations in \( TGFBR2 \) and \( TGFBR1 \) 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 connective tissue syndromes, but do not share the risk of TAAD.

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

**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 that is characterized by a combination of major characteristics which include craniosynostosis, craniofacial findings, skeletal findings, cardiovascular findings, neurologic and brain anomalies, certain radiographic findings, and other findings. SK1 is the only gene in which mutations are known to cause SGS.

Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency
Homocystinuria is a rare metabolic disorder, inherited in an autosomal recessive manner, which is characterized by an increased concentration in the blood and urine, of homocysteine, a sulfur-containing amino acid. 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 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, TGFBR2, TGFB1, and TGFB2. Gross deletion/duplication analysis is performed for all genes on the panel except CBS, COL5A1, and FLNA.

Prevention Genetics offers targeted familial mutation testing, as well as panel testing “MFS and related aortopathies NGS panel,” which includes 14 genes: ACTA2, COL3A1, COL5A1, COL5A2, FBN1, FBN2, MYH11, MYLK, SKI, SLC2A10, SMAD3, TGFBR2, TGFB1, and TGFB2.
GeneDx offers panel testing “Marfan/TAAD sequencing panel” and “Marfan/TAAD deletion/duplication panel,” which include mutation testing for ACTA2, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, MED12, MYH11, SLC2A10, MED12, MYH11, SMAD3, TGFB2, 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 the test in detecting a mutation that is present or in excluding a mutation that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the 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).

Analytic Validity
Individual Mutation Testing
The analytic validity of direct sequencing analysis of single-gene mutations is expected to be high. This may be influenced by the accuracy of the clinical diagnosis and the type of mutation.

Panel Testing
Clinical laboratories offer multigene panels for several connective tissue disorders that may include aortic aneurysms (TAAs) or dissections (TAADs). Different laboratories may use different methods, and panels vary in the genes that are included in the panel; therefore, the ability of a panel to detect a pathogenic variant in any given individual also varies. No published data are identified that report the analytic validity of these panels.

Variants of Unknown Significance
A variant of unknown significance (VOUS) is an alteration in the normal sequence of a gene, the significance of which is unclear until further study of the genotype and corresponding 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 VOUS. The VOUS rate of NGS panels for TAAD is unknown.

Clinical Validity
Individual Mutation Testing
Sequencing analysis for MFS has been reported to detect 70% to 93% of pathogenic mutations in probands with MFS. This is influenced by the accuracy of the clinical diagnosis and the mutation type. The yield of deletion/duplication analysis in individuals with MFS is unknown.
Sequencing analysis for mutation detection in EDS type IV is greater than 95%, and deletion/duplication analysis is approximately 2%.

Panel Testing
Baetens et al describe the validation of a mutation discovery strategy using multiplex polymerase chain reaction followed by NGS. The pilot stage involved the analysis of the DNA from 5 patients with MFS or LDS and mutations and/or polymorphisms in 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 mutations were identified, 67 of which were unique. Because sequencing methods cannot detect larger deletions or insertions, multiplex ligation-dependent probe amplification (MLPA) analysis was performed on the negative samples and identified 4 large deletions/duplications. The authors concluded that their technique of NGS analysis, compared with conventional Sanger sequencing, coupled with MLPA is an effective method for identifying mutations in MFS and LDS.

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 5 or more base pairs.

Test sensitivity for the following conditions on the GeneDx panel area as follows.

**Marfan Syndrome**
Sequence analysis of all exons in the FBN1 gene is expected to identify a mutation in 72% to 93% of individuals with a clinical suspicion of MFS, with the mutation detection rate approaching 93% in individuals 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 mutation identified by sequencing.

**Loeys-Dietz Syndrome**
The mutation 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 patients with LDS with an identifiable mutation, 75% have a mutation in the TGFBR2 gene, 25% have a mutation in the TGFBR1 gene, and approximately 1% have a mutation in the TGFBR2 gene.

**Familial TAAD**
Sequence analysis of all exons in the ACTA2 gene is expected to identify a mutation in up to 15% of cases of TAAD, the TGFBR1 and TGFBR2 genes are expected to identify mutations in 1% and 4%, respectively, of individuals with TAAD, and mutations reported in SMAD3 account for about 2% of individuals with TAAD. Rarely, TAAD has been associated with mutations in the 9 other genes on the panel.

Ambry Genetics states that TAADNext identifies greater than 96% of described mutations in the genes included in their NGS panel and that up to 93% of patients with MFS will have a mutation in the FBN1 gene,
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Genetic testing of COL3A1 will detect a mutation in over 95% of patients with EDS type IV, and that 30% to 40% of patients with fTAAD will have a mutation detected by TAADNext.

Baetens et al describe the validation of a mutation discovery strategy using multiplex polymerase chain reaction (PCR) followed by NGS. The pilot stage involved the analysis of the DNA from 5 patients with MFS or LDS and mutations and/or polymorphisms in 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 mutations were identified, 67 of which were unique. Because sequencing methods cannot detect larger deletions or insertions, multiplex ligation-dependent probe amplification (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 mutations in MFS and LDS.

Campens et al 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 limited/focused and included the 7 genes associated with the most commonly occurring and phenotypically overlapping syndromic and nonsyndromic hereditary thoracic aortic disorders: FBN1 (MFS); TGFBR1/2, TGFB2, SMAD3 (LDS); ACTA2 (familial TAAD) and COL3A1 (EDS type IV). A causal mutation 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 VOUS in FBN1 were identified. Mutations 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 mutation fulfilled diagnostic clinical criteria for MFS.

Wooderchak-Donahue et al reported the clinical and molecular findings in 175 individuals submitted for aortopathy panel testing at ARUP Laboratories using NGS and comparative genomic hybridization array to detect mutations in 10 genes that cause thoracic aortic aneurysms. Most patients referred had aortic findings (dilation, dissection, rupture) and a positive family history. Mutations on the panel were FBN1, FBN2, TGFBR1/2, 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 mutation and 32 had a VOUS. Most of the pathogenic mutations (72%) were identified in FBN1. The most frequently identified disorders were fTAAD (11 mutations, 2 of which were pathogenic and 9 VOUS), LDS (12 mutations, 3 of which were pathogenic and 9 VOUS) and MFS (21 mutations, 13 of which were pathogenic and 8 VOUS).

Clinical Utility
No literature on the direct impact of genetic testing for the conditions addressed in the policy was identified. However, establishing a definitive diagnosis can lead to:

- Treatment of manifestations of a specific syndrome,
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- Prevention of primary manifestations,
- Prevention of secondary complications,
- Impact on surveillance,
- Counselling on agents/circumstances to avoid,
- Evaluation of relatives at risk, including whether or not to follow a relative who does or does not have the family-specific mutation
- Pregnancy management,
- Future reproductive decision making

Most of the time, a diagnosis of one of the connective tissue syndromes that predispose to TAAD, or of one of the syndromes that may not predispose to TAAD but has overlapping phenotypic features of one of the syndromes associated with TAAD, can be made based on clinical criteria and evidence of an autosomal-dominant inheritance pattern by family history. However, there are cases in which the diagnosis cannot be made clinically because the patient does not fulfill necessary clinical criteria, the patient has an atypical presentation and other connective tissue diseases cannot be excluded, or in 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 individual mutation testing may be warranted, establishing the clinical utility of individual mutation testing. However, the incremental benefit of NGS panel testing in these situations is unknown, and the VUS rate with the use of these NGS panels is also unknown.

Summary of Evidence
The evidence for genetic testing in individuals who have signs or symptoms of MFS, other connective tissue disorders associated with thoracic aortic aneurysms and dissections, and related disorders, when a definitive diagnosis cannot be made using established clinical diagnostic criteria, includes mainly of clinical validity data. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, change in disease status, 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 mutations in probands with MFS, and greater than 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/circumstances to avoid. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing in individuals who are asymptomatic, to assess future risk of MFS and other connective tissue disorders associated with thoracic aortic aneurysms and dissections, when there is a known pathogenic mutation in the family, is generally lacking. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, change in disease status, and morbid events. Published data on analytic validity of targeted mutation 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, the test results
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will determine whether or not to follow a relative who does or does not have the family-specific mutation. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

References

Policy History
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10/08/2015 Medical Policy Committee review
10/21/2015 Medical Policy Implementation Committee approval. New policy.
10/06/2016 Medical Policy Committee review
10/19/2016 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
Next Scheduled Review Date: 10/2017

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT)®, copyright 2015 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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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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*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 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.

**Medically Necessary (or “Medical Necessity”) – Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:
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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