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

Policy # 00464
Original Effective Date: 10/21/2015
Current Effective Date: 11/13/2023

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, 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 (i.e., FBN1, MYH11, ACTA2, TGFBR1, TGFBR2, and COL3A1) when genetic testing was not done before and 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.****

Note:
Germline multi-gene small panel testing run on one testing platform that includes genes noted as eligible for coverage can be considered when patient selection criteria are met. In this situation procedure code representing focused panel (i.e., CPT code 81410, with 81411 only if initial sequencing represented by code 81410 did not identify pathogenic or likely pathogenic variant) should be reported rather than multiple codes representing individual or sequential gene testing.

Based on review of available data, the Company may consider 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, when there is a known pathogenic variant in the first-degree biological relative to be **eligible for coverage.****

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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, Ehlers-Danlos syndrome type IV, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders in all other situations and when not limited to focused genetic testing to be **investigational.***

When Services Are Considered Not Covered

Based on review of available data, the Company considers repeat germline testing to be **not covered****.

Note: *Repeat germline testing that investigates the same genetic information is not reasonable and necessary as it is duplicative and not required for medical treatment decisions. Examples of germline tests include, but are not limited to, single gene testing, gene panel tests, and whole exome or whole genome sequencing for inherited disorders.*

Policy Guidelines

Syndromes associated with thoracic aortic aneurysms may have established clinical criteria with major and minor criteria (eg, 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 (presymptomatic 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.

Background/Overview

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 (eg, 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 (eg, atherosclerosis). Thoracic aortic aneurysms may be associated with a genetic predisposition, which can either be familial or related to defined genetic disorders or syndromes.

Genetic predisposition to TAA is due to a genetic defect that leads to abnormalities in connective tissue metabolism. Genetically-related TAA accounts for approximately 5% of TAA. Some genetic syndromes associated with TAA have more aggressive rates of aortic expansion and are more likely to require intervention compared with sporadic TAA. MFS is the most common inherited form of syndromic TAA and 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. 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. 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 are based on clinical characteristics in large published patient cohorts and expert opinions. 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. 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.

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. Over 1000 *FBN1* pathogenic variants 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 pathogenic variants of a certain type (eg, nonsense, certain missense variants, certain splice site variants, certain deletions, and insertions).

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. 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 (eg, 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.tre

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. 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. 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.

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. 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.

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.

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.

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. 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.

***MED12*-Related Disorders**
The phenotypic spectrum of *MED12*-related disorders is still being defined but includes Lujan syndrome, FG syndrome type 1, and others. 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. *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 (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 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*.

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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*.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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.

Summary of Evidence

For individuals who have signs and/or symptoms of a connective tissue disease (CTD) linked to thoracic aortic aneurysms who received testing for genes associated with CTDs, the evidence includes mainly clinical validity data. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, and morbid events. Sequencing analysis for Marfan syndrome (MFS) has been reported to detect 90% to 93% of pathogenic variants in probands with MFS, and over 95% in Ehlers-Danlos syndrome type IV (vascular Ehlers-Danlos). Direct evidence of clinical usefulness is lacking; however, confirming a diagnosis leads to changes in clinical management, which improves health outcomes. These changes in management include treatment of

manifestations of a specific syndrome, prevention of primary manifestations and secondary complications, modifications to surveillance, and counseling on agents and circumstances to avoid. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a known familial pathogenic variant associated with thoracic aortic aneurysms and dissection who receive targeted familial variant testing, the evidence is generally lacking. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, and morbid events. Direct evidence of clinical usefulness is lacking; however, confirming a diagnosis leads to changes in clinical management, which improves health outcomes. Also, 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 an improvement in the net health outcome.

Supplemental Information

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). 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 (ie, serve as major criteria) or warrant changes in clinical management (ie, 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.

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. 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. 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 (eg, 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. 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. 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."

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

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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.

References

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Policy History

Original Effective Date: 10/21/2015
Current Effective Date: 11/13/2023

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
10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. No change to coverage.
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. No change to coverage. Added policy guidelines.
10/03/2019	Medical Policy Committee review
10/09/2019	Medical Policy Implementation Committee approval. No change to coverage.
10/01/2020	Medical Policy Committee review
10/07/2020	Medical Policy Implementation Committee approval. No change to coverage.

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 2022 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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Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders

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CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	81401, 81405, 81408, 81410, 81411, 81479
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*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. Food and Drug Administration (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 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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.