



Louisiana

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

Policy # 00464

Original Effective Date: 10/21/2015

Current Effective Date: 10/17/2018

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**.*

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

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diagnosis in a patient with a suspected connective tissue disorder is most useful in patients who do not meet sufficient clinical diagnostic criteria at the time of initial examination, in patients 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 one 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.

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
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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

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

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, 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 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.

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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

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of physical findings needed to establish a diagnosis for someone with an established family history is reduced.

Genetic Testing

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 ($\approx 70\%$ 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).

Treatment

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

Ehlers-Danlos syndrome

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.

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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.

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 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.

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

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.

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Genetic Testing

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.

Genetic Testing

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.

Diagnosis

Familial TAAD is diagnosed based on the presence of thoracic aorta pathology; absence of clinical features of MFS, LDS, or vascular EDS; and a positive family history of TAAD.

Genetic Testing

Familial TAAD is associated with pathogenic variants in *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 (CCA) is an autosomal-dominant condition characterized by a Marfan-like appearance and long, slender toes and fingers. Other features may include “crumpled” ears,

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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.

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Several commercial laboratories currently offer individual mutation testing, as well as 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, a next-generation sequencing panel that simultaneously analyzes 22 genes associated with TAADs, MFS, and related disorders. The panel detects variants 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*, *TGFB2*, *TGFBR1*, *TGFBR2*, and *TGFBR3*. Deletion and duplication analyses are performed for all genes on the panel except *CBS*, *COL5A1*, *FLNA*, *SMAD4*, and *TGFB3*.

Prevention Genetics offers targeted familial variants testing, as well as “Marfan syndrome and related aortopathies next generation sequencing panel” testing, which includes 14 genes: *ACTA2*, *COL3A1*, *COL5A1*, *COL5A2*, *FBN1*, *FBN2*, *MYH11*, *MYLK*, *SKI*, *SLC2A10*, *SMAD3*, *TGFB2*, *TGFBR1*, and *TGFBR2*.

GeneDx offers the “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*, *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

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

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

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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 as increased surveillance of the aorta, surgical repair of the aorta, when necessary, as well as surveillance for multisystem involvement in syndromic forms of thoracic aortic aneurysm and dissection (TAAD).

The 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.

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Setting

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

Simplifying Test Terms

There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

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

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 and duplication analysis in individuals with MFS is unknown.

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

Policy # 00464

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Sequencing analysis for variant detection in EDS type IV is greater than 95%, and deletion and 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).

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

Familial TAAD

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

In a 2017 study conducted in China, 70 TAAD patients were screened by NGS coupled with DNA target capture for 11 known causative genes of TAAD that included *ACTA2*, *Col3A1*, *Col5A2*, *FBN1*, *MSTN*, *MYH11*, *MYLK*, *SLC2A10*, *SMAD3*, *TGFBR1*, and *TGFBR2*. The study identified 40 variants in 36 (51%) patients. Among all variants, 12 pathogenic/likely pathogenic variants were in the *FBN1* gene, one likely pathogenic variant was in the *ACTA2* gene, and the other 27 VUS presented in 8 genes.

Ambry 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.

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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 and duplications. The authors concluded that their technique of multiplex polymerase chain reaction, followed by NGS analysis coupled with multiplex ligation-dependent probe amplification, is a robust strategy for time- and cost-effective identification of pathogenic variants in MFS and LDS.

Campens et al (2015) performed NGS-based screening on 264 consecutive samples from unrelated probands referred for heritable thoracic aortic disorders. Patients presenting with Marfanoid features, LDS features, and/or vascular EDS features were considered as syndromic patients. Panel testing was performed whenever overlapping and/or insufficient clinical features were present, or when patients fulfilled the criteria for MFS but targeted *FBN1* sequencing and duplication, and deletion testing was negative. The panels were focused and included the 7 genes associated with the most commonly occurring and phenotypically overlapping syndromic and nonsyndromic hereditary thoracic aortic disorders: *FBN1* (MFS); *TGFBR1* and *TGFBR2*, *TGFBR2*, *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 *TGFBR2*, 9 *SMAD3*, 4 *ACTA2*, and 3 *COL3A1*. Six variant of uncertain significance (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* pathogenic variant and 1 patient with a *TGFBR2* 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 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 Valid

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

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the silent, indolent nature of TAAD development. The true clinical specificity is uncertain because different CTDs are defined by specific disease-associated variants.

Clinically Useful

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

Direct Evidence

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

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

Chain of Evidence

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

Establishing a definitive diagnosis can lead to:

- Treatment of manifestations of a specific syndrome,
- Prevention of primary manifestations,
- Prevention of secondary complications,
- Impact on surveillance,
- Counseling on agents 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 one of the CTDs that predisposes 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 CTDs cannot be excluded, or the patient is a child with a family history in whom certain age-dependent manifestations of the disease have not yet developed. In these circumstances, the clinical differential diagnosis is narrow, and single-gene testing or focused panel testing may be warranted, establishing the clinical usefulness of these types of tests. However, the incremental benefit of expanded

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NGS panel testing in these situations is unknown, and the VUS rate with these NGS panels is also unknown. Also, the more disorders that are tested in a panel, the higher the VUS rate is expected to be.

Section Summary: Clinically Useful

Direct evidence of the clinical usefulness of genetic testing for CTDs related to TAAD is lacking. However, genetic testing can confirm the diagnosis in patients with clinical signs and symptoms of a CTD associated with TAAD who do not meet clinical diagnostic criteria. Management changes include increased surveillance of the aorta and surgical repair of the aorta.

TARGETED FAMILIAL VARIANT TESTING OF ASYMPTOMATIC INDIVIDUALS WITH A KNOWN FAMILIAL PATHOGENIC VARIANT ASSOCIATED WITH 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 (eg, 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 who has 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 who has a CTD related to TAAD.

Interventions

The relevant intervention of interest is targeted genetic testing for a familial variant related to TAAD.

Comparators

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

Outcomes

The potentially beneficial outcomes of primary interest would be improvements in overall survival and disease-specific survival and reductions in morbid events. Increased surveillance of the aorta, surgical repair of the aorta, when necessary, as well as surveillance for multisystem involvement in syndromic forms of TAAD, are initiated to monitor the development of aortic aneurysms and dissection and potentially repair

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them before rupture or dissection. If targeted genetic testing for a familial variant is negative, the asymptomatic individual can be excluded from increased cancer surveillance.

The potentially 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.

Timing

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

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 the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

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

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

Clinically Useful

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

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials. No such trials were identified.

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

Chain of Evidence

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

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

Section Summary: Clinically Useful

Direct evidence of the clinical usefulness 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 clinical validity data. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, and morbid events. Sequencing analysis for MFS has been reported to detect 70% to 93% of pathogenic variants in probands with MFS, and over 95% in EDS type IV. Direct evidence of clinical usefulness 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 counseling 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. Direct evidence of clinical usefulness is lacking; however, confirming a diagnosis leads to changes in clinical management, which improve health outcomes, similar to those in the proband. 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 a meaningful improvement in the net health outcome.

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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 |
| 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. |

Next Scheduled Review Date: 10/2019

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