Introduction

Connective tissue is one kind of tissue that is found in the body. It connects and provides support to other tissues such as muscles, nerves, and the skin. For example, fat, bone and cartilage are types of connective tissues. Some problems with connective tissue can be inherited. This policy describes when it may be medically necessary to do genetic testing to look for inherited connective tissue disorders.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Testing</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual genetic testing for the diagnosis of Marfan syndrome, other syndromes associated with thoracic aortic</td>
<td></td>
</tr>
<tr>
<td>Testing</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Testing way syndrome</td>
<td>aneurysms and dissections, and related disorders, and panels comprised entirely of focused genetic testing limited to the following genes—FBN1 and MYH11 and ACTA2, TGFBR1, and TGFBR2 may be considered medically necessary when:</td>
</tr>
<tr>
<td></td>
<td>• Signs and symptoms of a connective tissue disorder are present, but a definitive diagnosis cannot be made using established clinical diagnostic criteria.</td>
</tr>
<tr>
<td>Individual, targeted familial variant testing for Marfan syndrome</td>
<td>Individual, targeted familial variant testing for Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders, for assessing future risk of disease in an asymptomatic individual, may be considered medically necessary when there is a known pathogenic variant in the family. (See Additional Information section below)</td>
</tr>
<tr>
<td>Genetic testing panels for Marfan syndrome</td>
<td>Genetic testing panels for Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders that are not limited to focused genetic testing that do not meet the criteria for limited focused gene variant testing described above are considered investigational. (See Additional Information section below)</td>
</tr>
</tbody>
</table>

**Additional Information**

- Tissues that surround organs, blood vessels, and bones are called connective tissue. Changes to certain genes may cause problems with connective tissue. Specific genes can be tested to diagnose connective tissue problems.
- 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 a patient with a suspected connective tissue disorder is most useful in those patients who do not meet sufficient clinical diagnostic criteria at the time of initial examination, in patients who have an
**Additional Information**

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.

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81401</td>
<td>MED12 (mediator complex subunit 12)(eg, FG syndrome type 1, Lujan syndrome), common variants (eg, R961W, N1007S)</td>
</tr>
<tr>
<td>81405</td>
<td>ACTA2 (actin, alpha 2, smooth muscle, aorta) (eg, thoracic aortic aneurysms and aortic dissections), full gene sequence TGFBR1 (transforming growth factor, beta receptor 1) (eg, Marfan syndrome), full gene sequence</td>
</tr>
<tr>
<td>81408</td>
<td>FBN1 (fibrillin 1) (eg, Marfan syndrome), full gene sequence MYH11 (myosin, heavy chain 11, smooth muscle) (eg, thoracic aortic aneurysms and aortic dissections), full gene sequence</td>
</tr>
<tr>
<td>81410</td>
<td>Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehlers-Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK</td>
</tr>
<tr>
<td>81411</td>
<td>Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1</td>
</tr>
</tbody>
</table>
## Individual Gene Testing

For individual gene testing, the CPT codes in Table 1 may be used.

### Table 1: Coding for Individual Gene Testing

<table>
<thead>
<tr>
<th>Disease</th>
<th>Associated Gene</th>
<th>Percentage of Probands With a Pathogenic Variant Detected by Method</th>
<th>CPT Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diseases associated with TAAD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>FBN1</td>
<td>Sequence analysis detects 70%-93%</td>
<td>Included in 81408</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/duplication analysis detection rate unknown</td>
<td></td>
</tr>
<tr>
<td>EDS type IV (vascular type)</td>
<td>COL3A1</td>
<td>Sequence analysis detects &gt;95%</td>
<td>Unlisted 81479</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/duplication analysis detects ≈2%</td>
<td></td>
</tr>
<tr>
<td>LDS</td>
<td>TGFBR1</td>
<td>Percentage of LDS attributed to variants in following genes by sequence analysis:</td>
<td>TGFBR1: in 81405</td>
</tr>
<tr>
<td></td>
<td>TGFBR2</td>
<td>TGFBR1: 20%</td>
<td>TGFBR2: in 81405</td>
</tr>
<tr>
<td></td>
<td>SMAD3</td>
<td>TGFBR2: 70%</td>
<td>SMAD3 and TGFBR2: unlisted 81479</td>
</tr>
<tr>
<td></td>
<td>TGFBR2</td>
<td>SMAD3: 5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TGFBR2: 1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>In general, variants detected in LDS by deletion/duplication analysis are not associated with aortic aneurysms</td>
<td></td>
</tr>
<tr>
<td>Familial TAAD</td>
<td>TGFBR1</td>
<td>Percentage of familial TAAD attributed to variants in following genes by sequence and deletion/duplication analysis:</td>
<td>TGFBR1: in 81405</td>
</tr>
<tr>
<td></td>
<td>TGFBR2</td>
<td>TGFBR1: 1%</td>
<td>TGFBR2: in 81405</td>
</tr>
<tr>
<td></td>
<td>MYH11</td>
<td>TGFBR2: 4%</td>
<td>MYH11: in 81408</td>
</tr>
<tr>
<td></td>
<td>ACTA2</td>
<td>MYH11: 1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FBN1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MYLK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Associated Gene</td>
<td>Percentage of Probands With a Pathogenic Variant Detected by Method</td>
<td>CPT Codes</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Disease Associated Gene Percentage of Probands With a Pathogenic Variant Detected by Method CPT Codes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMAD3</td>
<td>ACTA2: 10%-14%</td>
<td>FBN1: unknown Sequence analysis: MYLK: 1% SMAD3: 2%</td>
<td>unlisted 81479</td>
</tr>
<tr>
<td>Arterial tortuosity syndrome SLC2A10</td>
<td>Sequence analysis detects ≈86% Deletion/duplication analysis detects ≈7%</td>
<td>Unlisted 81479</td>
<td></td>
</tr>
<tr>
<td>Diseases not associated with TAAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MED12-related disorders (FGS syndrome type 1 and Lujan syndrome) MED12</td>
<td>Variant detection frequency unknown</td>
<td>Included in 81401</td>
<td></td>
</tr>
<tr>
<td>Shprintzen-Goldberg syndrome SK1</td>
<td>Sequence analysis and deletion/duplication analysis rates of detection have not been reported</td>
<td>Unlisted 81479</td>
<td></td>
</tr>
<tr>
<td>EDS classic type (EDS I and II) COL5A1 COL5A2</td>
<td>Percentage of EDS classic type attributed to variants in following genes by sequence analysis: COL5A1: 46% COL5A2: 4%</td>
<td>Unlisted 81479</td>
<td></td>
</tr>
<tr>
<td>EDS kyphoscoliotic form (EDS type VI) PLOD1</td>
<td>Variant detection frequency by sequence analysis is unknown Deletions/duplications have been detected with a frequency of 18%</td>
<td>Unlisted 81479</td>
<td></td>
</tr>
<tr>
<td>Periventricular heterotopia, EDS variant FLNA</td>
<td>Sequence analysis 100% in those with family history and 26% in simplex females Detection by deletion/duplication analysis is unknown</td>
<td>Unlisted 81479</td>
<td></td>
</tr>
<tr>
<td>Congenital contractural arachnodactyly FBN2</td>
<td>Sequence analysis has been reported to detect 27%-75% of variants Variant detection by deletion/duplication analysis is unknown</td>
<td>Unlisted 81479</td>
<td></td>
</tr>
</tbody>
</table>


a EDS classic type.
b Loeys-Dietz syndrome.
c TAAD
Panel Testing

Specific CPT codes for genetic panel tests associated with aortic dysfunction or dilation syndromes (81410 and 81411) are described in the coding table above with the genes included in each test.

Related Information

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 (see Table 2). 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 3 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 2. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Previous</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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.

Evidence Review

Description

Marfan syndrome (MFS) is a systemic connective tissue disease (CTD) with a high degree of clinical variability and phenotypes overlapping with other syndromes and disorders. The diagnosis of most suspected CTDs can be based on clinical findings and family history. Some of these disorders are associated with a predisposition to the development of progressive thoracic aortic aneurysms and dissection. Accurate diagnosis of one 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
Background

Connective Tissue Diseases

Individuals suspected of having a systemic connective tissue disease (CTD) like Marfan syndrome (MFS) usually have multiple features that affect many different organ systems; most of these conditions can be diagnosed using clinical criteria. However, these syndromes may share features, overlapping phenotypes, and similar inheritance patterns, which can cause a diagnostic challenge. Additional difficulties in the diagnosis of 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 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). TAAs may be associated with a genetic predisposition, which can either be familial or related to defined genetic disorders or syndromes.¹

Genetic predisposition to TAA is due to a genetic defect that leads to abnormalities in connective tissue metabolism. Genetically related TAA accounts for approximately 5% of TAA.¹ 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 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 (MFS) is an autosomal dominant condition. 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 is 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.

**Diagnosis**

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. They were also criticized for including some non-specific physical manifestations or poorly validated diagnostic thresholds. The revised criteria were based on clinical characteristics in large published patient cohorts, as well as 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, Sphrintzen-Goldberg syndrome (SGS), and EDS-vascular type. LDS and SGS may have substantial overlap with MFS, including the potential for similar involvement of the aortic root, skeleton, skin and dura. EDS-vascular type occasionally shows overlap with MFS. Each of these conditions has a unique risk profile and management protocol. Given the autosomal dominant inheritance, the number of physical findings needed to establish a diagnosis for someone with an established family history is reduced.

**Genetic Testing**

It is estimated that molecular techniques allow for the detection of FBN1 variants 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 variants are known to cause classic MFS. Approximately 75% of individuals with MFS have an affected parent, and 25% have a de novo variant. Over 1000 FBN1 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 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 (≈70%-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 variants that have been described are unique, and most variants are not repeated among non-genetically related patients. Therefore, the absence of a known 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 variant, 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**

Ehlers-Danlos Syndrome (EDS) is a group of disorders that affect connective tissues and share common features characterized by skin hyperelasticity or laxity, abnormal wound healing, and joint hypermobility. The defects in connective tissues can vary from mildly loose joints to life-threatening complications. All types of EDS affect the joints and many affect the skin, but features vary by type.

The different types of EDS include types I and II (classic type), type III (hypermobility type), type IV (vascular type), type VI (kyphoscoliotic form), all of which are inherited in an autosomal dominant pattern with the exception of type VI, which is autosomal recessive. It is estimated that affected individuals with types I, II or IV may inherit the disease-causing variant from an affected parent 50% of the time, and about 50% have a de novo disease-causing 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 one 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 (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 to image the entire arterial tree.

**Genetic Testing**

LDS is caused by pathogenic variants in TGFBR1, TGFBR2, TGFB2, 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 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 either the ascending or descending aorta. In the absence of surgical repair of the ascending aorta, affected individuals have progressive enlargement of the ascending aorta, leading to acute aortic dissection. Presentation of the aortic disease and the age of onset are highly variable.

**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 variants in TGFBR2, TGFBR1, MYH11, ACTA2, MYLK, SMAD3, and 2 loci on other chromosomes, AAT1 and AAT2. Rarely, fTAAD can also be caused by FBN1 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 variants in TGFBR2 and TGFBR1 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 connective tissue syndromes, but do not share the risk of TAAD.
**Congenital Contractural Arachnodactyly (Beal Syndrome)**

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

Shprintzen-Goldberg Syndrome (SGS) is an autosomal dominant condition that is characterized by a combination of major characteristics which include craniosynostosis, craniofacial findings, skeletal findings, cardiovascular findings, neurologic and brain anomalies, certain radiographic findings and other findings. SK1 is the only gene in which 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, which is 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 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).

**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.
Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in December 2017 did not identify any ongoing or unpublished trials that would likely influence this policy.

Practice Guidelines and Position Statements

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics issued guidelines (2012) on the evaluation of adolescents or adults with some features of Marfan syndrome (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 four situations:

1. A dilated aortic root (defined as greater than or equal to two standard deviations above the mean for age, sex, and body surface area) and ectopia lentis
2. A dilated aortic root and a pathogenic variant in FBN1 that is clearly pathologic
3. A dilated aortic root and multiple systemic features or
4. Ectopia lentis and a 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 three situations:

1. Ectopia lentis
2. Multiple systemic features or
3. A dilated aortic root (if over 20 years, greater than two standard deviations; if younger than 20, greater than three standard deviations)

The systemic features are weighted by a scoring system for systemic features.
American College of Cardiology Foundation et al

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 Marfan syndrome is based primarily on clinical findings in the various organ systems affected in the Marfan syndrome, along with family history and FBN1 mutations [pathogenic variants] status."

Medicare National Coverage

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

Regulatory Status

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 Amendments (CLIA). Laboratories that offer LDTs must be licensed by 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 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 variant-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.

References


**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/12/15</td>
<td>New Policy. Policy created with a literature review through November 6, 2014. The use of panels for the detection of mutations in syndromes that may be associated with thoracic aortic aneurysms and dissection is investigational. In certain circumstances, individual mutation testing may be considered medically necessary.</td>
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<tr>
<td>05/01/16</td>
<td>Annual Review, approved April 12, 2016. Policy updated with a literature review through December 9, 2015; references 10-11 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>09/01/16</td>
<td>Interim Update, approved August 9, 2016. Removed codes 81405 and 81408 from panel testing policy statement.</td>
</tr>
<tr>
<td>10/01/17</td>
<td>Policy moved to new format. No changes to policy statement.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with a literature review through December 2017; references 9 and 14 added. The policy is revised with updated format. Policy statements unchanged.</td>
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**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

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