

(204129)

<b>Medical Benefit</b>		<b>Effective Date:</b> 07/01/18	<b>Next Review Date:</b> 05/21
<b>Preauthorization</b>	Yes	<b>Review Dates:</b> 05/15, 05/16, 05/17, 05/18, 05/19, 05/20	

**Preauthorization is required.**

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With signs and/or symptoms of a connective tissue disease linked to thoracic aortic aneurysms</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Testing for genes associated with connective tissue diseases</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Standard clinical management without genetic testing</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Disease-specific survival</li> <li>• Test accuracy</li> <li>• Test validity</li> <li>• Symptoms</li> <li>• Morbid events</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• Who are asymptomatic with a known familial pathogenic variant associated with thoracic aortic aneurysms and dissection</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Targeted familial variant testing</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Standard clinical management without targeted familial variant testing</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Disease-specific survival</li> <li>• Test accuracy</li> <li>• Test validity</li> <li>• Symptoms</li> <li>• Morbid events</li> </ul>

### 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 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 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 Ehlers-Danlos syndrome 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.

## POLICY

Individual genetic testing for the diagnosis of Marfan syndrome, 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, MYH11, ACTA2, TGFBR1, and TGFBR2 - may be considered **medically necessary**, when signs and symptoms of a connective tissue disorder are present, but a definitive diagnosis cannot be made using established clinical diagnostic criteria.

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.

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 in the following genes - FBN1, MYH11, ACTA2, TGFBR1, and TGFBR2 - are considered **investigational**.

## POLICY GUIDELINES

Syndromes associated with thoracic aortic aneurysms may have established clinical criteria with major and minor criteria (e.g., Marfan syndrome [Ghent criteria] and EDS 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 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 (TAAD) 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 protocol updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Genome 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

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.

Table PG3. Individual Gene Testing

Disease	Associated Gene	Probands With a Pathogenic Variant Detected	
		Method	Detection Rate
<b>Diseases associated with TAAD</b>			
Marfan syndrome	FBN1	<ul style="list-style-type: none"> <li>Sequence analysis</li> <li>Deletion/duplication analysis</li> </ul>	<ul style="list-style-type: none"> <li>70%-93%</li> <li>Unknown</li> </ul>
EDS type IV (vascular)	COL3A1	<ul style="list-style-type: none"> <li>Sequence analysis</li> </ul>	<ul style="list-style-type: none"> <li>&gt;95%</li> </ul>

Disease type)	Associated Gene	Probands With a Pathogenic Variant Detected	
Loeys-Dietz syndrome	TGFBR1, TGFBR2, SMAD3, TGFB2	<ul style="list-style-type: none"> <li>Deletion/duplication analysis</li> <li>Sequence analysis<sup>a</sup>:               <ul style="list-style-type: none"> <li>TGFBR1</li> <li>TGFBR2</li> <li>SMAD3</li> <li>TGFB2</li> </ul> </li> <li>Deletion/duplication analysis</li> </ul>	<ul style="list-style-type: none"> <li>≈2%</li> <li>20%</li> <li>70%</li> <li>5%</li> <li>1%</li> <li>Generally not associated with AAs</li> </ul>
Familial TAAD	TGFBR1, TGFBR2, MYH11, ACTA2, FBN1, MYLK, SMAD3	<ul style="list-style-type: none"> <li>Sequence and deletion/duplication analysis<sup>b</sup>:               <ul style="list-style-type: none"> <li>TGFBR1</li> <li>TGFBR2</li> <li>MYH11</li> <li>ACTA2</li> <li>FBN1</li> </ul> </li> <li>Sequence analysis:               <ul style="list-style-type: none"> <li>MYLK</li> <li>SMAD3</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>1%</li> <li>4%</li> <li>1%</li> <li>10%-14%</li> <li>Unknown</li> <li>1%</li> <li>2%</li> </ul>
Arterial tortuosity syndrome	SLC2A10	<ul style="list-style-type: none"> <li>Sequence analysis</li> <li>Deletion/duplication analysis</li> </ul>	<ul style="list-style-type: none"> <li>≈86%</li> <li>≈7%</li> </ul>
<b>Diseases not associated with TAAD</b>			
MED12-related disorders (FG syndrome type 1 and Lujan syndrome)	MED12	<ul style="list-style-type: none"> <li>Pathogenic variant detection frequency unknown</li> </ul>	<ul style="list-style-type: none"> <li>Unknown</li> </ul>
Shprintzen-Goldberg syndrome	SK1	<ul style="list-style-type: none"> <li>Sequence analysis and deletion/duplication analysis</li> </ul>	<ul style="list-style-type: none"> <li>Not reported</li> </ul>
EDS classic type (EDS types I and II)	COL5A1, COL5A2	<ul style="list-style-type: none"> <li>Sequence analysis<sup>c</sup>:               <ul style="list-style-type: none"> <li>COL5A1</li> <li>COL5A2</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>46%</li> <li>4%</li> </ul>
EDS kyphoscoliotic form (EDS type VI)	PLOD1	<ul style="list-style-type: none"> <li>Sequence analysis</li> <li>Deletions/duplications analysis</li> </ul>	<ul style="list-style-type: none"> <li>Unknown</li> <li>18%</li> </ul>
Periventricular heterotopia, EDS variant	FLNA	<ul style="list-style-type: none"> <li>Sequence analysis</li> <li>Deletion/duplication analysis</li> </ul>	<ul style="list-style-type: none"> <li>100% with family history; 26% in simplex females</li> <li>Unknown</li> </ul>
Congenital contractual arachnodactyly	FBN2	<ul style="list-style-type: none"> <li>Sequence analysis</li> <li>Deletion/duplication analysis</li> </ul>	<ul style="list-style-type: none"> <li>27%-75%</li> <li>Unknown</li> </ul>

AA: aortic aneurysms; EDS: Ehlers-Danlos syndrome; TAAD: Thoracic aortic aneurysms and dissection.

<sup>a</sup> EDS classic type.

<sup>b</sup> Loeys-Dietz syndrome.

<sup>c</sup> TAAD

### MEDICARE ADVANTAGE

For Medicare Advantage aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome type IV, arterial tortuosity syndrome) genomic sequence analysis panel and duplication/deletion analysis panel (including analyses for TGFBR1, TGFBR2, MYH11, and COL3A1) is considered **not medically necessary**.

## 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 (e.g., 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 (e.g., atherosclerosis). TAAs may be associated with a genetic predisposition, which can either be familial or related to defined genetic disorders or syndromes.<sup>1</sup>

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.<sup>1</sup> 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, Loews-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

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.<sup>2</sup> 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.<sup>3</sup> The Ghent criteria, revised in 2010, are used for the clinical diagnosis of MFS.<sup>3</sup> 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.<sup>3</sup> The revised criteria include several major changes, as follows. More weight is given to the two 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 two 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.<sup>3</sup> 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.<sup>3</sup>

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 1,000 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 (e.g., nonsense, certain missense variants, certain splice site variants, certain deletions and insertions).<sup>2</sup>

Most variants in the FBN1 gene that cause MFS can be identified with sequence analysis (≈70% 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.<sup>2</sup> 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 (e.g., MASS syndrome, familial mitral valve prolapse syndrome, SGS, isolated ectopia 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 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, 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 the vascular type IV may affect one in 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 two major criteria (arterial rupture, intestinal rupture, uterine rupture during pregnancy, family history of EDS type IV) is highly specific.<sup>4</sup> 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*

LDS is an autosomal-dominant condition characterized by four 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, 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 ascending or descending aorta.<sup>5</sup> 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 two 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.<sup>2</sup> 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 and FG syndrome type 1.<sup>6</sup> Lujan syndrome and FG syndrome type 1 share the clinical findings of hypotonia, cognitive impairment, and abnormalities of the corpus callosum. Individuals with Lujan syndrome 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.<sup>6</sup> 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.<sup>7</sup> SK1 is the only gene for which pathogenic variants are known to cause Shprintzen-Goldberg syndrome.

#### *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 three to four 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 (e.g., liver biopsy, skin biopsy).

### REGULATORY STATUS

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. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 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.

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Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

**REFERENCES**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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