Policy Statement

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 and MYH11 (CPT code 81408) and ACTA2, TGFB1, and TGFB2 (CPT code 81405)—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 as defined by CPT codes 81405 and 81408 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 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 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 (HGVS) 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 (HUGO), and by the Human Genome Variation Society itself.
The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) 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

<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 PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</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

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.

### Coding Individual Gene Testing

For individual gene testing, the following codes may be used (see Table PG3).

### Table PG3. Coding for Individual Gene Testing

<table>
<thead>
<tr>
<th>Disease Associated Gene</th>
<th>Probands With a Pathogenic Variant Detected</th>
<th>CPT Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Method</td>
<td>Detection Rate</td>
</tr>
<tr>
<td>Diseases associated with TAAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>FBN1</td>
<td>• Sequence analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Deletion/duplication analysis</td>
</tr>
<tr>
<td>EDS type IV (vascular type)</td>
<td>COL3A1</td>
<td>• Sequence analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Deletion/duplication analysis</td>
</tr>
<tr>
<td>Loeys-Dietz syndrome</td>
<td>TG FBR1, TG FBR2, SMAD3, TG FB2</td>
<td>• Sequence analysis:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o TG FBR1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o TG FBR2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o SMAD3</td>
</tr>
<tr>
<td>Disease</td>
<td>Associated Genes</td>
<td>Probands With a Pathogenic Variant Detected</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------</td>
<td>---------------------------------------------</td>
</tr>
</tbody>
</table>
| **Familial TAAD**               | TGFBR1, TGFBR2, MYH11, ACTA2, FBN1, MYLK, SMAD3 | • Sequence and deletion/duplication analysis:  
  - TGFBR1  
  - TGFBR2  
  - MYH11  
  - ACTA2  
  - FBN1  
  - MYLK  
  - SMAD3 | 81411 |
|                                 |                  | • Generally not associated with AAs         | 81401, 81405, 81408, 81405, 81408, 81405, 81408, 81410, 81411 |
| **Arterial tortuosity syndrome**| SLC2A10          | • Sequence analysis and deletion/duplication analysis | 81410, 81411 |
| **Diseases not associated with TAAD** | MED12            | Pathogenic variant detection frequency unknown | MED12, 81401 |
| MED12-related disorders (FG syndrome type 1 and Lujan syndrome) | SK1              | Sequence analysis and deletion/duplication analysis | Unlisted 81479 |
| **EDS classic type** (EDS types I and II) | COL5A1, COL5A2 | Sequence analysis:  
  - COL5A1  
  - COL5A2 | 81401 |
| **EDS kyphoscoliotic form** (EDS type VI) | PLOD1           | • Sequence analysis  
  - Deletions/duplications analysis  
  - 100% with family history; 26% in simplex females  
  - Unknown | 81405 |
| **Periventricular heterotopia, EDS variant** | FLNA            | • Sequence analysis  
  - Deletion/duplication analysis  
  - 27%-75%  
  - Unknown | 81405 |
| **Congenital contractural arachnodactyly** | FBN2            | • Sequence analysis  
  - Deletion/duplication analysis  
  - 27%-75%  
  - Unknown | 81405 |


Code 81401 (Molecular pathology procedure level 2) includes:
- MED12 (mediator complex subunit 12) (e.g., FG syndrome type 1, Lujan syndrome), common variants (e.g., R961W, N1007S)

Code 81405 (Molecular pathology procedure level 6) includes:
- ACTA2 (actin, alpha 2, smooth muscle, aorta) (e.g., thoracic aortic aneurysms and aortic dissections), full gene sequence
- TGFBR1 (transforming growth factor, beta receptor 1) (e.g., Marfan syndrome), full gene sequence

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• TGFBR2 (transforming growth factor, beta receptor 2) (e.g., Marfan syndrome), full gene sequence

**Code 81408** (Molecular pathology procedure level 9) includes:
• FBN1 (fibrillin 1) (e.g., Marfan syndrome), full gene sequence
• MYH11 (myosin, heavy chain 11, smooth muscle) (e.g., thoracic aortic aneurysms and aortic dissections), full gene sequence

For genetic testing of genes not codified by CPT, the unlisted molecular pathology code 81479 would be used.

**Panel Testing**
There are specific CPT codes for the panel testing:
• **81410**: Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler 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
• **81411**: Aortic dysfunction or dilation (e.g., 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

**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.

**Related Policies**
• N/A

**Benefit Application**
Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
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, TGFB1, TGFB2, and TGFB3. 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, TGFB1, and TGFB2.

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, TGFB1, and TGFB2.

Rationale

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.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. 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**

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 (ectopia lentis) is a feature seen in 60% of affected individuals. Cardiovascular manifestations are the major source of morbidity and mortality and include dilation of the aorta at the level of the sinuses of Valsalva, predisposition for aortic tear and rupture, mitral valve prolapse, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery. With proper management, the life expectancy of a person with MFS can approximate that of the general population.

**Diagnosis**

The diagnosis of MFS is mainly clinical and based on the characteristic findings in multiple organ systems and family history. The Ghent criteria, revised in 2010, are used for the clinical diagnosis of MFS. The previous Ghent criteria had been criticized for taking insufficient account of the age-dependent nature of some of the clinical manifestations, making the diagnosis in children more difficult, and for including some nonspecific physical manifestations or poorly validated diagnostic thresholds. The revised criteria are based on clinical characteristics in large published patient cohorts and expert opinions. The revised criteria include several major changes, as follows. More weight is given to the 2 cardinal features of MFS—aortic root aneurysm and dissection and ectopia lentis. In the absence of findings that are not expected in MFS, the combination of these 2 features is sufficient to make the diagnosis. When aortic disease is present, but ectopia lentis is not, all other cardiovascular and ocular manifestations of MFS and findings in other organ systems contribute to a “systemic score” that guides diagnosis. Second, a more prominent role has been given to molecular testing of FBN1 and other relevant genes, allowing for the appropriate use when necessary. Third, some less specific manifestations of MFS were removed or given less weight in the diagnostic criteria. Fourth, the revised criteria formalized the concept that additional diagnostic considerations and testing may be required if a patient has findings that satisfy the criteria for MFS but shows unexpected findings, particularly if they are suggestive of a specific alternative diagnosis. Particular emphasis is placed on LDS, Shprintzen-Goldberg syndrome (SGS), and EDS vascular type. LDS and SGS have substantial overlap with MFS, including the potential for similar involvement of the aortic root, skeleton, skin, and dura. EDS vascular type occasionally overlaps with MFS. Each of these conditions has a unique risk profile and management protocol. Given the autosomal-dominant nature of inheritance, the number of physical findings needed to establish a diagnosis for a person with an established family history is reduced.

**Genetic Testing**

It is estimated that molecular techniques permit the detection of FBN1 pathogenic variants in up to 97% of Marfan patients who fulfill Ghent criteria, suggesting that the current Ghent criteria have excellent specificity. FBN1 is the only gene for which pathogenic variants are known to cause classic MFS.
Approximately 75% of individuals with MFS have an affected parent, while 25% have a de novo pathogenic variant. Over 1000 FBN1 pathogenic variants that cause MFS have been identified. The following findings in FBN1 molecular genetic testing should infer causality in making the diagnosis of MFS: a pathogenic variant previously shown to segregate in families with MFS and de novo pathogenic variants of a certain type (e.g., nonsense, certain missense variants, certain splice site variants, certain deletions and insertions).2

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.2 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 1 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 fistula or dissection, or may occur spontaneously. Such complications are often unexpected and may present as sudden death, stroke, internal bleeding, and/or shock. The vascular type is also associated with an increased risk of gastrointestinal perforation, organ rupture, and rupture of the uterus during pregnancy.

Diagnosis
The clinical diagnosis of EDS type IV can be made from major and minor clinical criteria. The combination of 2 major criteria (arterial rupture, intestinal rupture, uterine rupture during pregnancy, family history of EDS type IV) is highly specific.4 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 4 major groups of clinical findings, including vascular, skeletal, craniofacial, and cutaneous manifestations. Vascular findings include cerebral, thoracic, and abdominal arterial aneurysms and/or dissections. Skeletal findings include pectus excavatum or carinatum, scoliosis, joint laxity, arachnodactyly, and talipes equinovarus. The natural history of LDS is characterized by arterial aneurysms, with a mean age of death of 26 years and a high incidence of pregnancy-related complications, including uterine rupture and death. Treatment considerations take into account that aortic dissection tends to occur at smaller aortic diameters than MFS, and the aorta and its major branches can dissect in the absence of much if any, dilation. Patients with LDS require echocardiography at frequent intervals, to monitor the status of the ascending aorta, and angiography evaluation to image the entire arterial tree.

Genetic Testing
LDS is caused by pathogenic variants in the TGFBR1, TGFBR2, TGFB2, 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. 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 is an autosomal-dominant condition characterized by a Marfan-like appearance and long, slender toes and fingers. Other features may include "crumpled" ears, contractures of the knees and ankles at birth with improvement over time, camptodactyly, hip contractures, and progressive kyphoscoliosis. Mild dilatation of the aorta is rarely present. Congenital contractural arachnodactyly is caused by pathogenic variants in the FBN2 gene.

MED12-Related Disorders

The phenotypic spectrum of MED12-related disorders is still being defined but includes Lujan syndrome and FG syndrome type 1. 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. MED12-related disorders are inherited in an X-linked manner, with males being affected and carrier females not usually being affected.

Shprintzen-Goldberg Syndrome

Shprintzen-Goldberg syndrome is an autosomal-dominant condition characterized by a combination of major characteristics that include craniosynostosis, craniofacial findings, skeletal findings, cardiovascular findings, neurologic and brain anomalies, certain radiographic findings, and other findings. SK1 is the only gene for which pathogenic variants are known to cause 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 3 to 4 years. Heterozygous carriers (1/70 of the general population) have hyperhomocysteinemia without homocystinuria; however, their risk for premature cardiovascular disease is still increased.

Overlap with MFS can be extensive and includes a Marfanoid habitus with normal to tall stature, pectus deformity, scoliosis, and ectopia lentis. Central nervous system manifestations include mental retardation, seizures, cerebrovascular events, and psychiatric disorders. Patients have a tendency for intravascular thrombosis and thromboembolic events, which can be life-threatening. Early diagnosis and prophylactic medical and dietary care can decrease and even reverse some of the complications. The diagnosis depends on the measurement of cystathionine beta-synthase activity in tissue (e.g., liver biopsy, skin biopsy).

Literature Review

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.
Testing 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 connective tissue disease (CTD) linked to thoracic aortic aneurysms (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
The relevant intervention of interest is genetic testing for genes associated with CTDs.

Comparators
The following practice is being used to diagnose CTDs associated with TAAs: standard clinical management without genetic testing.

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 detect and treat aortic aneurysms and dissections before rupture or dissection.

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 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 an aortic aneurysm 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
Patients may be referred from primary care to a cardiologist or medical geneticist for investigation and management of CTDs related to TAAD. Referral for genetic counseling is important for the 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 Marfan syndrome (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.

Sequencing analysis for variant detection in Ehlers-Danlos syndrome (EDS) type IV is greater than 95%, and deletion and duplication analysis is approximately 2%.

**Panel Testing**
Next-generation sequencing (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 (e.g., 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 familial TAAD (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.

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 sequenc ing 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, TGFB2, 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 TGFB2, 3 TGFB2, 9 SMAD3, 4 ACTA2, and 3 COL3A1. Six variant of uncertain significance (VUS) in FBN1 were identified. Pathogenic variants in FBN1 (n=3), TGFB2 (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 TGFB2 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, TGFB1 and TGFB2, 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).

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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 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 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 (e.g., 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 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.

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.

Supplemental Information
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:

• 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
• A dilated aortic root and a mutation [pathogenic variant] in FBN1 that is clearly pathologic
• A dilated aortic root and multiple systemic features ... or
• Ectopia lentis and a mutation [pathogenic variant] in FBN1 that has previously been associated with aortic disease.”

“If there is a positive family history of MFS (independently ascertained with these criteria), then the subject has the condition under any of the following three situations:

• Ectopia lentis
• Multiple systemic features ... or
• 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.

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.”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.
Ongoing and Unpublished Clinical Trials

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

References


Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Previous diagnostic testing(s) and response(s) including duration
Family history
- How test result will impact clinical decision making
- Reason for performing test
- Signs/symptoms/test results related to reason for genetic testing

Post Service
- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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HCPCS
None

ICD-10 Procedure
None

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.