Individual Gene Variant Testing

Individual genetic testing for the diagnosis of Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders may be considered medically necessary when:

- Using established diagnostic criteria the signs and symptoms of a connective tissue disorder are present, but a definitive diagnosis cannot be made without genetic testing.

  AND

- The focused variant testing panel is limited to the following genes: ACTA2, TGFBR1, TGFBR2 (CPT 81405) and/or FBN1 and MYH11 (CPT 81408). (See Policy Guidelines)

Individual, targeted familial variant testing may be considered medically necessary for assessing future risk of disease in an asymptomatic individual, when there is a known pathogenic variant in the family for Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders. (See Policy Guidelines)

Panel testing

Genetic testing panels that do not meet criteria for limited focused gene variant testing described above are considered investigational. (See Policy Guidelines)

Related Policies

None

Policy Guidelines

Tissues that surround organs, blood vessels, and bones are called connective tissue. Changes to certain genes may cause problems with connective tissue. Specific genes can be tested to diagnose connective tissue...
problems.

Syndromes associated with thoracic aortic aneurysms may have established clinical criteria with major and minor criteria, eg, Marfan syndrome (Ghent criteria) and Ehlers-Danlos syndrome type IV, or may be associated with characteristic clinical findings. While most of these syndromes can be diagnosed based on clinical findings, these syndromes may be associated with variability in clinical presentation and may show overlapping features with each other, and with other disorders. The use of genetic testing to establish a diagnosis in a patient with a suspected connective tissue disorder is most useful in those patients who do not meet sufficient clinical diagnostic criteria at the time of initial examination, in patients who have an 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.

Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Individual Gene Testing
For individual gene testing, the CPT codes in Table PG1 may be used.

Table PG1: Coding for Individual Gene Testing

<table>
<thead>
<tr>
<th>Disease</th>
<th>Associated Gene</th>
<th>Percentage of Probands With a Pathogenic Variant Detected by Method</th>
<th>CPT Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases associated with TAAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>FBN1</td>
<td>• Sequence analysis detects 70%-93%</td>
<td>Included in 81408</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Deletion/duplication analysis detection rate unknown</td>
<td></td>
</tr>
<tr>
<td>EDS type IV (vascular type)</td>
<td>COL3A1</td>
<td>• Sequence analysis detects &gt;95%</td>
<td>Unlisted 81479</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Deletion/duplication analysis detects ≈2%</td>
<td></td>
</tr>
<tr>
<td>LDS</td>
<td>TGFBR1, TGFBR2, SMAD3, TGFB2</td>
<td>• Percentage of LDS attributed to variants in following genes by sequence analysis: TGFBR1: 20% TGFBR2: 70% SMAD3: 5% TGFB2: 1%</td>
<td>TGFBR1: in 81405 TGFBR2: in 81405 SMAD3 and TGFB2: unlisted 81479</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• In general, variants detected in LDS by deletion/duplication analysis are not associated with aortic aneurysms</td>
<td></td>
</tr>
<tr>
<td>Familial TAAD</td>
<td>TGFBR1, TGFBR2, MYH11, ACTA2, FBN1, MYLK, SMAD3</td>
<td>• Percentage of familial TAAD attributed to variants in following genes by sequence and deletion/duplication analysis: TGFBR1: 1% TGFBR2: 4% MYH11: 1% ACTA2: 10%-14%</td>
<td>TGFBR1: in 81405 TGFBR2: in 81405 MYH11: in 81408 ACTA2: in 81405 FBN1: in 81408 MYLK and SMAD3: unlisted 81479</td>
</tr>
<tr>
<td>Arterial tortuosity syndrome</td>
<td>SLC2A10</td>
<td>• Sequence analysis detects ~86%</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------</td>
<td>-------------------------------</td>
<td></td>
</tr>
</tbody>
</table>

**Diseases not associated with TAAD**

<table>
<thead>
<tr>
<th>MED12-related disorders (FGS syndrome type 1 and Lujan syndrome)</th>
<th>MED12</th>
<th>Variant detection frequency unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shprintzen-Goldberg syndrome</td>
<td>SK1</td>
<td>Sequence analysis and deletion/duplication analysis rates of detection have not been reported</td>
</tr>
<tr>
<td>EDS classic type (EDS I and II)</td>
<td>COL5A1, COL5A2</td>
<td>Percentage of EDS classic type attributed to variants in following genes by sequence analysis: COL5A1: 46%, COL5A2: 4%</td>
</tr>
<tr>
<td>EDS kyphoscoliotic form (EDS type VI)</td>
<td>PLOD1</td>
<td>• Variant detection frequency by sequence analysis is unknown</td>
</tr>
<tr>
<td>Periventricular heterotopia, EDS variant</td>
<td>FLNA</td>
<td>• Sequence analysis 100% in those with family history and 26% in simplex females</td>
</tr>
<tr>
<td>Congenital contractual arachnodactyly</td>
<td>FBN2</td>
<td>• Sequence analysis has been reported to detect 27%-75% of variants</td>
</tr>
</tbody>
</table>

**Coding**

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81401</td>
<td>MED12 (mediator complex subunit 12)(e.g., FG syndrome type 1, Lujan syndrome), common variants (e.g., R961W, N1007S)</td>
</tr>
<tr>
<td>81405</td>
<td>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</td>
</tr>
<tr>
<td>81408</td>
<td>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</td>
</tr>
<tr>
<td>81410</td>
<td>Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK</td>
</tr>
<tr>
<td>81411</td>
<td>Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology code</td>
</tr>
</tbody>
</table>

**Panel Testing**

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

**Description**

Marfan syndrome (MFS) is a systemic connective tissue disorder that may have a high degree of clinical
variability and overlapping phenotypes with other syndromes and disorders. The diagnosis of most suspected connective tissue disorders can be made 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 (TAAD). 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 TAAD. Known genetic variants are associated with MFS and the other connective tissue disorders that may share clinical features with MFS.

**Background**

**Connective Tissue Diseases**

Individuals suspected of having a systemic connective tissue disorder like MFS usually have multiple features that affect many different organ systems; most of these conditions can be diagnosed using clinical criteria. However, these different syndromes may show shared features, overlapping phenotypes, and similar inheritance patterns, which can cause a diagnostic challenge. Additional difficulties in the diagnosis of one of these syndromes may occur due to the age-dependent development of many of the physical manifestations of the syndrome (making the diagnosis more difficult in children); many show variable expression, and many of the features found in many of these syndromes occur in the general population (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**

Thoracic Aortic Aneurysms and Dissection Most 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. Genetic predisposition to TAA is due to a genetic defect that leads to abnormalities in connective tissue metabolism. Genetically-related TAA accounts for approximately 5% of TAA. Some of the genetic syndromes associated with TAA have more aggressive rates of aortic expansion and are more likely to require intervention compared with sporadic TAA. MFS is the most common inherited form of syndromic TAA and TAAD. Other genetic systemic connective tissue disorders associated with a risk of TAAD include Ehlers-Danlos syndrome (EDS) type IV, Loeys-Dietz syndrome (LDS), and arterial tortuosity syndrome.

Familial TAAD refers to patients with a family history of aneurysmal disease, but who do not meet criteria for a connective tissue syndrome.

**Marfan Syndrome**

Marfan Syndrome (MFS) is an autosomal dominant condition, in which there is a high degree of clinical variability of systemic manifestations, ranging from isolated features of MFS to neonatal presentation of severe and rapidly progressive disease in multiple organ systems. Despite the clinical variability, the principal manifestations involve the skeletal, ocular and cardiovascular systems. Involvement of the skeletal system is characterized by bone overgrowth and joint laxity, disproportionately long extremities for the size of the trunk (dolichostenomelia), overgrowth of the ribs which can push the sternum in or out (pectus excavatum or carinatum, respectively), and scoliosis which can be mild or severe and progressive. Ocular features include myopia, and displacement of the lens from the center of the pupil (ectopic lentis) is a hallmark feature and seen in 60% of affected individuals. Cardiovascular manifestations are the major source of morbidity and mortality and include dilation of the aorta at the level of the sinuses of Valsalva, predisposition for aortic tear and rupture, mitral valve prolapse, tricuspid valve prolapse and enlargement of the proximal pulmonary artery. However, with proper management, the life expectancy of someone with MFS can approximate that of the general population.

The diagnosis of MFS is mainly a clinical one and based on the characteristic findings in multiple organ systems, as well as the family history. The Ghent criteria, revised in 2010, are used for the clinical diagnosis of MFS. The previous Ghent criteria had been criticized for taking insufficient account of the age-dependent nature of some of the clinical manifestations, making the diagnosis in children more difficult, and for including some non-specific physical manifestations or poorly validated diagnostic thresholds. The revised criteria were based on clinical characteristics in large published patient cohorts, and expert opinions of panel members with extensive experience in application of the criteria, the differential diagnosis of MFS, and the strengths and limitations of
molecular genetic testing. The revised criteria have 5 major changes to the previous diagnostic guidelines. First, more weight is given to the 2 cardinal features of MFS, aortic root aneurysm/dissection and ectopic lentis. In the absence of findings that are not expected in MFS, the combination of these 2 features is sufficient to make the diagnosis. When aortic disease is present, but ectopia lentis is not, all other cardiovascular and ocular manifestations of MFS and findings in other organ systems contribute to a "systemic score" that guides diagnosis. Second, a more prominent role has been given to molecular testing of FBN1 and other relevant genes, allowing for the appropriate use when necessary. Third, some of the less specific manifestations of MFS were removed or made less influential in the diagnostic criteria. Fourth, the revised criteria formalize the concept that additional diagnostic considerations and testing may be required if a patient has findings that satisfy the criteria for MFS but show unexpected findings, particularly if they are suggestive of a specific alternative diagnosis. Particular emphasis is placed on LDS, Sphrintzen-Goldberg syndrome (SGS), and EDS-vascular type. LDS and SGS may have substantial overlap with MFS, including the potential for similar involvement of the aortic root, skeleton, skin and dura. EDS-vascular type occasionally shows overlap with MFS. Each of these conditions has a unique risk profile and management protocol. Fifth, Given the autosomal dominant inheritance, the number of physical findings needed to establish a diagnosis for someone with an established family history is reduced.

It is estimated that molecular techniques allow the detection of FBN1 mutations in up to 97% of Marfan patients who fulfil Ghent criteria, suggesting that the current Ghent criteria have excellent specificity.

FBN1 is the only gene in which mutations are known to cause classic MFS. Approximately 75% of individuals with MFS have an affected parent, and 25% have a de novo mutation. Over 1000 FBN1 mutations that cause MFS have been identified. The following findings in FBN1 molecular genetic testing should infer causality in making the diagnosis of MFS: a pathogenic variant previously shown to segregate in families with MFS and de novo mutations of a certain type (eg, nonsense, certain missense mutations, certain splice site mutations, certain deletions and insertions).

Most mutations in the FBN1 gene that cause MFS can be identified with sequence analysis (≈70%-93%) and, although the yield of deletion/duplication analysis in patients without a defined coding sequence or splice site by sequence analysis is unknown, it is estimated to be about 30%. The most common testing strategy of a proband suspected of having MFS is sequence analysis followed by deletion/duplication analysis if a pathogenic variant is not identified. However, the use of genetic testing for a diagnosis of MFS has limitations. More than 90% of mutations that have been described are unique, and most mutations are not repeated among non-genetically related patients. Therefore, the absence of a known mutation 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 mutation.

Caution should be used in interpreting the identification of a FBN1 mutation, as other conditions with overlapping phenotypes with MFS can have an FBN1 mutation (eg, MASS syndrome, familial mitral valve prolapse syndrome, SGS, isolated ectopic lentis).

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

**Ehlers-Danlos Syndrome**

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

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

Most types of EDS are not associated with aortic dilation, with the exception of the vascular type (also known as type IV), which can involve serious and potentially life-threatening complications. The prevalence of the vascular type may affect about 1 in 250,000 people. Vascular complications include rupture, aneurysm, and/or dissection.
of major or minor arteries. Arterial rupture may be preceded by aneurysm, arteriovenous fistulae or dissection, or may occur spontaneously. Such complications are often unexpected and may present as sudden death, stroke, internal bleeding and/or shock. The vascular type is also associated with an increased risk of gastrointestinal perforation or organ rupture, and rupture of the uterus during pregnancy.

The clinical diagnosis of EDS type IV can be made from major and minor clinical criteria. The combination of 2 major criteria (arterial rupture, intestinal rupture, uterine rupture during pregnancy and a family history of EDS type IV) is highly specific.(4) The presence of one or more minor clinical criteria supports the diagnosis, but is insufficient to make the diagnosis by itself.

Pathogenic variants in the COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, PLOD1, and TNXB genes cause EDS. The vascular type (type IV) is caused by pathogenic variants in the COL3A1 gene.

**Loeys-Dietz Syndrome**

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

LDS is caused by pathogenic variants in TGFBR1, TGFBR2, TGFB2, and SMAD3 genes.

**Arterial Tortuosity Syndrome**

Arterial tortuosity syndrome is inherited in an autosomal recessive pattern and is characterized by tortuosity of the aorta and/or large- and middle-sized arteries throughout the body. Aortic root dilation, stenosis and aneurysms of large arteries are common. Other features of the syndrome include joint laxity and hyperextensible skin. The syndrome is caused by pathogenic variants in the SLC2A10 gene.

**Familial TAAD**

Approximately 80% of familial TAA and TAAD is inherited in an autosomal-dominant manner and may be associated with variable expression and decreased penetrance of the disease-associated variant.

The major cardiovascular manifestations of familial TAAD (fTAAD) include dilatation of the ascending thoracic aorta at the level of the sinuses of Valsalva or ascending aorta or both and dissections of the thoracic aorta involving either the ascending or descending aorta.(5) 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. fTAAD is diagnosed based on the presence of thoracic aorta pathology, absence of clinical features of MFS, LDS, or vascular EDS, and a positive family history of TAAD. fTAAD is associated with variants in TGFBR2, TGFBR1, MYH11, ACTA2, MYLK, SMAD3, and 2 loci on other chromosomes, AAT1 and AAT2. Rarely, fTAAD can also be caused by FBN1 variants. To date, only about 20% of fTAAD is accounted for by variants in known genes. Early prophylactic repair should be considered in individuals with confirmed variants in TGFBR2 and TGFBR1 and/or a family history of aortic dissection with minimal aortic enlargement.

The following syndromes and conditions may share some of the features of these connective tissue syndromes, but do not share the risk of TAAD.

**Congenital Contractural Arachnodactyly (Beal Syndrome)**

Congenital contractural arachnodactyly (CCA) is an autosomal dominant condition characterized by a Marfan-like appearance and long, slender toes and fingers.(2) Other features may include "crumpled" ears, contractures of the knees and ankles at birth with improvement over time, camptodactyly, hip contractures, and progressive kyphoscoliosis. Mild dilatation of the aorta is rarely present. CCA is caused by the pathogenic variants in the
MED12-Related Disorders
The phenotypic spectrum of MED12-related disorders is still being defined, but includes Lujan syndrome (LS) and FG syndrome type 1 (FGS1). LS and FGS1 share the clinical findings of hypotonia, cognitive impairment and abnormalities of the corpus callosum. Individuals with LS share some physical features with MFS, in that they have Marfanoid features including tall and thin habitus, long hands and fingers, pectus excavatum, narrow palate and joint hypermobility. MED12-related disorders are inherited in an X-linked manner, with males being affected and carrier females not usually being affected.

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

Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency
Homocystinuria is a rare metabolic disorder, inherited in an autosomal recessive manner, which is characterized by an increased concentration in the blood and urine, of homocysteine, a sulfur-containing amino acid. The classical type is due to a deficiency of cystathionine beta synthase (CBS). Affected individuals appear normal at birth but develop serious complications in early childhood, usually by age 3 to 4 years. Heterozygous carriers (1/70 of the general population) have hyperhomocysteinemia without homocystinuria, however, their risk for premature cardiovascular disease is increased.

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

Regulatory Status
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Several commercial laboratories currently offer targeted genetic testing, as well as NGS panels that simultaneously analyze multiple genes associated with MFS, TAADs, and related disorders. NGS technology cannot detect large deletions or insertions, and therefore samples that are mutation-negative after sequencing should be evaluated by other testing methodologies.

Ambry Genetics offers “TAADNEXT,” an NGS panel that simultaneously analyzes 20 genes that are 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, TGFBR1, and TGFBR2. Gross deletion/duplication analysis is performed for all genes on the panel except CBS, COL5A1, and FLNA.

GeneDx offers panel testing “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, TGFBR2, TGFB1, and TGFBR2.

Prevention Genetics offers targeted familial variant testing, as well as panel testing “Marfan syndrome and related aortopathies next generation sequencing [NGS] panel,” which includes 14 genes: ACTA2, COL3A1, COL5A1, COL5A2, FBN1, FBN2, MYH11, MYLK, SKI, SLC2A10, SMAD3, TGFBR2, TGFB1, and TGFBR2.
Scope

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

Benefit Application

N/A

Rationale

This policy was created in November 2014 with a literature search of the Medline database. The most recent literature review is through December 20, 2016.

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

Genetic Testing of Patients with Signs and/or Symptoms of a connective tissue disease

Clinical Context and Test Purpose

The purpose of genetic testing of patients who have signs and/or symptoms of a 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 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 policy is: Does genetic testing improve health outcomes in individuals with signs and/or symptoms of a CTD linked to TAAs?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients with clinical signs and/or symptoms of a CTD linked to TAAs and diagnosis cannot be made clinically.

Interventions

Genetic testing for genes associated with CTDs.

Comparators

Standard clinical management without genetic testing.
Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival, and morbid events. The potential beneficial outcomes of primary interest would be improvements in OS and disease-specific survival and reduction in morbid events. Increased surveillance of the aorta, surgical repair of the aorta, when necessary, as well as surveillance for multisystem involvement in syndromic forms of TAAD is initiated to detect and treat aortic aneurysms and dissections prior to rupture or dissection.

The potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary surveillance of the aorta and surgical repair of the aorta. False-negative test results can lead to lack of surveillance of the aorta that allows for development and subsequent rupture of aortic aneurysm or dissection.

Time
The primary outcomes of interest would be related to the frequency of surveillance and the short-term and long-term survival after surgical repair of the aorta.

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

Analytic Validity

Single-Gene Testing
The analytic validity of direct sequencing analysis of single gene variants is expected to be high. This may be influenced by the accuracy of the clinical diagnosis and the type of variant.

Panel Testing
Clinical laboratories offer multigene panels for several connective tissue disorders that may include aortic aneurysms (TAAs) or dissections (TAADs). Different laboratories may use different methods, and panels vary in the genes that are included in the panel; therefore, the ability of a panel to detect a pathogenic variant in any given individual also varies.(2) No published data are identified that report the analytic validity of these panels.

Variants of Unknown Significance
A variant of unknown significance (VOUS) is an alteration in the normal sequence of a gene, the significance of which is unclear until further study of the genotype and corresponding phenotype is conducted in a sufficiently large population. Complete gene sequencing often identifies numerous (sometimes hundreds) allelic variants for a given gene.

Multigene panel testing poses an increased risk of erroneous interpretation of VOUS.(2)

The VOUS rate of next generation sequencing (NGS) panels for TAAD is unknown.

Clinical Validity

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 the variant type.(2) The yield of deletion/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/duplication analysis is approximately 2%.(8)
Panel Testing

NGS technology cannot detect large deletions or insertions, and therefore, samples from patients with a high clinical suspicion of a thoracic aortic aneurysm disorder that are variant-negative after sequencing should be evaluated by other testing methodologies (eg, multiplex ligation-dependent probe amplification).

According to GeneDx, the technical sensitivity of their panel test is estimated to be 98%; however, the test will not detect large chromosomal aberrations and deletions, insertions, or rearrangements of 5 or more base pairs. Test sensitivity for the following conditions on the GeneDx panel are as follows.

MFS

Sequence analysis of all exons in the FBN1 gene is expected to identify a variant in 72% to 93% of individuals with a clinical suspicion of MFS, with the variant detection rate approaching 93% in individuals 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.

LDS

The pathogenic variant detection rate for sequence analysis of all exons in the TGFBR1 and TGFBR2 genes in patients with LDS has not been well established but may be as high as 87% in patients with a strong clinical suspicion of LDS. Of patients with LDS 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 variant in up to 15% of cases of familial TAAD (fTAAD), the TGFBR1 and TGFBR2 genes are expected to identify variants in 1% and 4%, respectively, of individuals with TAAD, and variants reported in SMAD3 account for about 2% of individuals with TAAD. Rarely, TAAD has been associated with variants in the 9 other genes on the panel.

Ambry Genetics states that TAADNext identifies greater than 96% of described pathogenic variants in the genes included in their NGS panel and that up to 93% of patients with MFS will have a pathogenic variant in the FBN1 gene, testing of COL3A1 will detect a pathogenic variant in over 95% of patients with EDS type IV, and that 30% to 40% of patients with fTAAD will have a pathogenic variant detected by TAADNext.

Baetens et al describe the validation of a variant discovery strategy using multiplex polymerase chain reaction (PCR) followed by NGS. (9) The pilot stage involved the analysis of the DNA from 5 patients with MFS or LDS and variants and/or polymorphisms in 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 variants were identified, 67 of which were unique. Because sequencing methods cannot detect larger deletions or insertions, multiplex ligation-dependent probe amplification (MLPA) analysis was performed on the negative samples and identified 4 large deletions/duplications. The authors concluded that their technique of multiplex PCR followed by NGS analysis coupled with MLPA, is a robust strategy for time- and cost-effective identification of variants in MFS and LDS.

Campens et al performed NGS based screening on 264 consecutive samples from unrelated probands referred for heritable thoracic aortic disorders. (10) Patients presenting with Marfanoid features, LDS features, and/or vascular EDS features were considered as syndromic patients. Panel testing was performed whenever overlapping and/or insufficient clinical features were present, or when patients fulfilled the criteria for MFS but targeted FBN1 sequencing and duplication/deletion testing were negative. The panels were limited/focused and included the 7 genes associated with the most commonly occurring and phenotypically overlapping syndromic and non-syndromic hereditary thoracic aortic disorders: FBN1 (MFS); TGFBR1/2, TGFBR2, SMAD3 (LDS); ACTA2 (familial TAAD) and COL3A1 (EDS type IV). A causal variant was identified in 34 (13%) patients, 12 of which were FBN1, 1 TGFBR1, 2 TGFBR2, 3 TGFBR2, 9 SMAD3, 4 ACTA2, and 3 COL3A1. Six VOUS in FBN1 were identified. Variants in FBN1 (n=3), TGFBR2 (n=1), and COL3A1 (n=2) were identified in patients without characteristic clinical features of a syndromal hereditary thoracic aortic disorder. Six patients with a SMAD3 and 1 patient with a TGFBR2 variant fulfilled diagnostic clinical criteria for MFS.
Wooderchak-Donahue et al reported 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 thoracic aortic aneurysms. Most patients referred had aortic findings (dilation, dissection, rupture) and a positive family history. Variants on the panel were FBN1, FBN2, TGFBR1/2, SMAD3, ACTA2, COL3A1, MYH11, MYLK, and SLCA10, 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 VOUS. Most of the pathogenic variants (72%) were identified in FBN1. The most frequently identified disorders were fTAAD (11 variants, 2 of which were pathogenic and 9 VOUS), LDS (12 variants, 3 of which were pathogenic and 9 VOUS) and MFS (21 variants, 13 of which were pathogenic and 8 VOUS).

**Section Summary**
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.

**Clinical Utility**
Clinical utility is how the results of a diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

**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 (RCTs). No such trials were 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.

No literature on the direct impact of genetic testing for CTDs addressed in the policy was identified. However, 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 connective tissue syndromes 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 connective tissue diseases cannot be excluded, or in 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 individual variant testing may be warranted, establishing the clinical utility of individual variant testing. However, the incremental benefit of NGS panel testing in these situations is unknown, and the VUS rate with the use of these NGS panels is also unknown, and the VOUS rate with the use of these NGS panels is also unknown. In addition, the more disorders that are tested in a panel, the higher the VOUS rate is expected to be.
Section Summary
Direct evidence of the clinical utility 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 such increased cancer surveillance or to exclude asymptomatic individuals from increased surveillance of the aorta.

The question addressed in this policy is: Does genetic testing improve health outcomes in asymptomatic individuals with a first-degree relative with 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 with a CTD related to TAAD.

Interventions
Targeted genetic testing for a familial variant related to TAAD.

Comparators
Standard clinical management without targeted genetic testing for a familial variant related to TAAD.

Outcomes
The general outcomes of interest are OS, disease-specific survival, and morbid events. The potential beneficial outcomes of primary interest would be improvement in OS and disease-specific survival and reduction in morbid events. Increased surveillance of the aorta, and 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 prior to rupture or dissection. If targeted genetic testing for a familial variant is negative, the asymptomatic individual can be excluded from increased cancer surveillance.

The potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary surveillance 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.

Time
Same as above for patients with sign and/or symptoms of a CTD related to TAAD.

Setting
Asymptomatic individuals may be referred from primary care to an cardiologist or medical geneticist if a familial variant related to TAAD is identified. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.
**Analytic Validity**
Same as the previous section for patients with sign and/or symptoms of a CTD associated with TAAD.

**Clinical Validity**
Same as the previous section for patients with sign and/or symptoms of a CTD associated with TAAD.

**Clinical Utility**
Clinical utility is how the results of a diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

**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 RCTs. No such trials were 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.

**Family Members**
When a disease-associated variant for 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 potentially be excluded from ongoing surveillance of the aorta.

**Section Summary**
Direct evidence of the clinical utility 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 connective tissue disease (CTD) linked to thoracic aortic aneurysms who received testing for genes associated with CTDs, the evidence includes mainly clinical validity data. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, and morbid events. Published data on analytic validity of individual and panel testing of genes is lacking. Sequencing analysis for Marfan syndrome (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 utility 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 counselling 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. Published data on analytic validity of targeted familial variant testing is lacking, but is expected to be high. Direct evidence of clinical utility is lacking; however, confirming a diagnosis leads to changes in clinical management, which improve health outcomes, similar to those in the proband. In addition, test results will determine whether to follow a relative who does or does not have the familial variant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in December 2016 did not identify any ongoing or unpublished trials that would likely influence this policy.

Practice Guidelines and Position Statements

The American College of Medical Genetics
The American College of Medical Genetics issued guidelines on the evaluation of the adolescent or adult with some features of MFS.(12)
If there is no family history of MFS, then the subject has the condition under any of the following four situations:
1. A dilated aortic root (defined as greater than or equal to two standard deviations above the mean for age, sex, and body surface area) and ectopia lentis
2. A dilated aortic root and a mutation in FBN1 that is clearly pathologic
3. A dilated aortic root and multiple systemic features or
4. Ectopia lentis and a mutation in FBN1 that has previously been associated with aortic disease

If there is a positive family history of MFS (independently ascertained with these criteria), then the subject has the condition under any of the following three situations:
1. Ectopia lentis
2. Multiple systemic features or
3. A dilated aortic root (if over 20 years, greater than two standard deviations; if younger than 20, greater than three standard deviations)

The systemic features are weighted by a scoring system for systemic features.

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

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

References


Appendix

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N/A

History

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<tr>
<th>Date</th>
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<td>New Policy. Policy created with a literature review through November 6, 2014. The use of panels for the detection of mutations in syndromes that may be associated with thoracic aortic aneurysms and dissection is investigational. In certain circumstances, individual mutation testing may be considered medically necessary.</td>
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<tr>
<td>05/01/16</td>
<td>Annual Review, approved April 12, 2016. Policy updated with a literature review through December 9, 2015; references 10-11 added. Policy statements unchanged.</td>
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<tr>
<td>09/01/16</td>
<td>Interim Update, approved August 9, 2016. Removed codes 81405 and 81408 from panel testing policy statement.</td>
<td></td>
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<tr>
<td>05/01/17</td>
<td>Annual review, approved April 11, 2017. Policy statements reformatted for readability. Policy updated with a literature review through December 20, 2016; no references added. Policy updated with genetics nomenclature – “mutation” changed to “variant” when applicable. Policy statements unchanged.</td>
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Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.
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- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance:

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PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at: https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)


Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):

الوعي: هذا الإشعار معلومات هامة. قد يحتوي هذا الإشعار معلومات مهمة وتتضمن:
- قد تكون هناك ترجمات ورقية ومزهلة للعنوان.
- لمزيد من المعلومات، يرجى الاتصال بالمكتب المحلي للمساعدة. للحصول على معلومات بديلة عن ترجمات الإشعار، يرجى الاتصال بـ 800-722-1471 (TTY: 800-842-5357) توصيل.

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本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或提供的重要資訊。本通知可能有重要的日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Italiano (Italian):


Français (French):


Kreyòl ayisyen (Creole):


Deutsche (German):


Hmoob (Hmong):


Ilokano (Ilocano):

Daytoy a Pakdaak ket naglaon iti Napatge nga Impormasion. Daytoy a pakdaak mabalin nga adda ket naglaon iti napatge nga impormasion maipanggep iti aplikasyonyo wenn coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelsa iti daytoy a pakdaak. Mabalin nga adda rumbeng nga aramidenyo nga addang sakay dagiti partikular a naituding nga aidaw tapo napaglaitayeday nga coverage ti salun-atyo Wenn yuag dagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodo a pagasazo nga awan iti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Oromoo (Cushite):


Oromo (Cushitic):
Este aviso puede contener información importante privada, cuya utilización puede requerir el consentimiento de los interesados. Por favor, lea atentamente este aviso antes de tomar cualquier decisión.

Este aviso tiene como objetivo informar sobre los derechos y obligaciones del titular de la póliza de Premera Blue Cross. Se detallan determinados plazos para mantener la cobertura de salud o ayuda de terceros. Se recomienda consultar el aviso en su idioma para obtener una mejor comprensión de los contenidos.

Si tiene alguna duda o pregunta, no dude en ponerse en contacto con Premera Blue Cross a través del número de teléfono 800-722-1471 (TTY: 800-842-5357).

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Si desea obtener más información o realizar alguna consulta, no dude en ponerse en contacto con Premera Blue Cross a través del número de teléfono 800-722-1471 (TTY: 800-842-5357).

El aviso se actualiza regularmente para asegurar que los consumidores estén informados de los cambios en la política de cobertura de salud. Es importante que consulte regularmente el aviso para mantenerse al día con los cambios en su cobertura de salud.

El aviso se puede descargar en el sitio web de Premera Blue Cross o puede solicitar una copia por correo electrónico o por teléfono. En caso de que no tenga acceso al aviso en su idioma, Premera Blue Cross dispone de servicios de traducción gratuitos para ayudarle a entender mejor el contenido del aviso.

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El aviso está diseñador...