USEFUL FOR

- Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Marfan syndrome, Loeys-Dietz syndrome, thoracic aortic aneurysm and dissections, or a related disorder
- Second-tier testing for patients in whom previous targeted gene mutation analyses for specific Marfan and related genes were negative
- Establishing a diagnosis of a Marfan or a related disorder in some cases, allowing for appropriate management and surveillance for aneurysms and other disease features based on the gene involved
- Identifying mutations within genes known to be associated with increased risk for aneurysms and other disease features allowing for predictive testing of at-risk family members

GENETICS TEST INFORMATION

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate for variants in the ACTA2, CBS, COL3A1, FBN1, FBN2, MYH11, MYLK, SKI, SLC2A10, SMAD3, TGB2, TGFBR1, and TGFBR2 genes.

Prior Authorization is available for this assay; see Special Instructions.

CLINICAL INFORMATION

Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue that occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by mutations in the FBN1 gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature, and mitral valve prolapse and aortic root dilatation/dissection are the main cardiovascular features. Diagnosis is based on the revised Ghent nosology and genetic testing of FBN1. Management aims to monitor and slow the rate of aortic root dilatation, and initiate appropriate medical and/or surgical intervention as needed. Other phenotypes associated with the FBN1 gene include autosomal dominant ectopia lentis (displacement of the lens of the eye), thoracic aortic aneurysm and dissections (TAAD), isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis).
Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome, but may include involvement of other organ systems and is primarily caused by mutations in \( TGFBR1 \) and \( TGFBR2 \). Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities, and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Mutations of the \( SMAD3 \) gene have been reported in families with a LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis.

TAAD is a genetic condition primarily involving dilatation and dissection of the thoracic aorta, but may also include aneurysm and dissection of other arteries. TAAD has a highly variable age of onset and presentation, and may involve additional features such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in familial TAAD is \( ACTA2 \), followed by \( TGFBR1 \) and \( TGFBR2 \), and \( MYH11 \). Mutations in the \( MYLK \) gene have been reported in a small subset of families with familial TAAD. TGFB2 mutations have also been reported in families with TAAD and systemic features that overlap with LDS and MFS.

The \( COL3A1 \) gene causes Ehlers Danlos syndrome type IV (vascular type), an autosomal dominant connective tissue disease with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection, or may occur spontaneously.

Autosomal dominant mutations of the \( FBN2 \) gene are known to cause congenital contractual arachnodactyly (CCA), which has several overlapping features with Marfan syndrome, including dolichostenomelia, scoliosis, pectus deformity, arachnodactyly, and a risk for thoracic aortic aneurysm.

Mutations of the \( CBS \) gene cause homocystinuria an autosomal recessive disorder of amino acid metabolism with clinical overlap with Marfan syndrome; including lens dislocation and skeletal abnormalities, as well as increased risk for abnormal blood clotting.

Mutations in the \( SKI \) gene cause Shprintzen-Goldberg syndrome (SGS), an autosomal dominant condition with overlap with LDS and MFS. Distinguishing features of SGS include hypotonia and intellectual disability. Aortic root dilatation is less frequent in SGS than in LDS or MFS, but, when present, it can be severe.

Homozygous and compound heterozygous loss of function mutations in the \( SLC2A10 \) gene have been described in arterial tortuosity syndrome, a condition characterized by generalized tortuosity and elongation of all major arteries in addition to other connective tissue disease features.

Indications for testing include but are not limited to:

- Patients who meet clinical diagnostic criteria (Revised Ghent nosology) for Marfan syndrome
- Patients in whom no specific Marfan or related disorder is evident but for whom there is a clear familial component
- Patients whose family history is consistent with TAAD
- Patients with a personal or family history of thoracic aortic aneurysm and/or dissection or a personal or family history of multiple arterial aneurysms

**INTERPRETATION**

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.