MAYO CLINIC LABORATORIES

Test Definition: PMMFR

Postmortem Marfan and Related Panel, Varies

Overview

Useful For

Providing a comprehensive postmortem genetic evaluation in the setting of a sudden death attributed to thoracic aortic dissection or with a personal or family history suggestive of Marfan syndrome, Loeys-Dietz syndrome, thoracic aortic aneurysm and dissections, or a related disorder

Identification of a pathogenic variant in the decedent, which may assist with risk assessment and 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, TGFB2, TGFBR1*, and *TGFBR2* genes.

Special Instructions

- Informed Consent for Genetic Testing
- Marfan and Related Disorders Patient Information
- Informed Consent for Genetic Testing for Deceased Individuals
- Informed Consent for Genetic Testing (Spanish)

Highlights

This test is intended for use on postmortem samples (eg, formalin-fixed, paraffin-embedded [FFPE] tissue block) when whole blood is not available.

This test uses next-generation sequencing to test for variants in the *ACTA2, CBS, COL3A1, FBN1, FBN2, MYH11, MYLK, SKI, SLC2A10, SMAD3, TGFB2, TGFBR1,* and *TGFBR2* genes.

This test may aid in the postmortem diagnosis of Marfan syndrome, Loeys-Dietz syndrome, familial thoracic aortic aneurysm and dissection (TAAD), or a related disorder.

Identification of a pathogenic variant may assist with familial risk assessment, screening, and genetic counseling.

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

This test is intended for use when EDTA whole blood is not available and formalin-fixed, paraffin-embedded (FFPE) tissue or blood spots are the only available samples. If EDTA whole blood is available, order MFRGP / Marfan Syndrome and Related Disorders Multi-Gene Panel, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Mutation, Targeted Testing, Varies.

Necessary Information

1. **Marfan and Related Disorders Patient Information (T636) is required,** see Special Instructions. Testing may proceed without the patient information however it aids in providing a more thorough interpretation. Ordering providers are strongly encouraged to complete the form and send it with the specimen.
2. Pathology report **must** accompany specimen in order for testing to be performed. Include physician name and phone number with the specimen.

Specimen Required

Preferred:
Specimen Type: Tissue
Container/Tube: Tissue block
Collection Instructions: Submit a formalin-fixed, paraffin-embedded tissue block.
Additional Information: Testing will be attempted on blocks of any age but may be canceled if adequate DNA concentration cannot be obtained.
Specimen Stability Information: Ambient

Acceptable:
Specimen Type: Blood spot
Container/Tube: Whatman FTA Classic Card or Whatman Protein Saver 903 Card
Specimen Volume: 3-5 blood spots
Collection Instructions:
1. Completely fill at least 3 circles on the filter paper card.
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for 3 hours.
3. Do not expose specimen to heat or direct sunlight.
4. Do not stack wet specimens.
5. Keep specimen dry.
Specimen Stability Information: Ambient (preferred)/Refrigerated

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
-Informed Consent for Genetic Testing for Deceased Individuals (T782)
2. Marfan and Related Disorders Patient Information (T636) in Special Instructions.
3. If not ordering electronically, complete, print, and send a Cardiovascular Test Request Form (T724) with the specimen.

Specimen Minimum Volume

Tissue: See Specimen Required

Blood Spots: 3

Reject Due To

No specimen should be rejected.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical & Interpretive

Clinical Information

Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (ages 15-35), the incidence of SCD is between 1 to 2 per 100,000 young individuals. Sudden cardiac death, particularly in young individuals, may suggest an inherited form of heart disease. In some cases of sudden death, autopsy may identify a structural abnormality such as aortic aneurysm or dissection. Postmortem diagnosis of a hereditary form of aortic aneurysm/dissection may assist in confirmation of the cause of death, as well as risk assessment in living family members.

Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue and 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 variants 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 aortic root dilatation/dissection and mitral valve prolapse 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), familial 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 variants 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. Variants in the *SMAD3* gene have been reported in families with a LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis.

Thoracic aortic aneurysm and dissections (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*. Variants in the *MYLK* gene have been reported in a small subset of families with familial TAAD. *TGFB2* variants 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 variants of the *FBN2* gene are known to cause congenital contractural arachnodactyly (CCA), which has several overlapping features with Marfan syndrome, including dolichostenomelia, scoliosis, pectus deformity, arachnodactyly, and a risk for thoracic aortic aneurysm.

Variants 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.

Variants 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 variants 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.

Many of these described disorders have distinct genetic causes but may present phenotypically similarly, leading to difficulty in accurate diagnosis. However, gene-based management strategies have been described for some of these disorders. Therefore, comprehensive genetic analysis may be useful for accurate diagnosis and gene-based management.

Genes included in Postmortem Marfan and Related Panel:

Gene	Protein	Inheritance	Known Association
ACTA2	Actin, alpha-2, smooth muscle, aorta	AD	TAAD
CBS	Cystathionine beta-synthase	AR	Homocystinuria
COL3A1	Collagen, type III, alpha-1	AD	Ehlers-Danlos syndrome type IV (vascular type)
FBN1	Fibrillin 1	AD	Marfan syndrome/TAAD/ectopia lentis/ MASS phenotype/Shprintzen-Goldberg syndrome/Weill-Marchesani syndrome
FBN2	Fibrillin 2	AD	Congenital contractural arachnodactyly

MYH11	Myosin, heavy chain 11, smooth muscle	AD	TAAD
MYLK	Myosin light chain kinase	AD	TAAD
SKI	V-SKI avian sarcoma viral oncogene homolog	AD	Shprintzen-Goldberg syndrome
SLC2A10	Solute carrier family 2 (facilitated glucose transporter), member 10	AR	Arterial Tortuosity syndrome/TAAD (autosomal recessive)
SMAD3	Mothers against decapentaplegic, drosophila, homolog of, 3	AD	Loeys-Dietz syndrome/TAAD
TGFB2	Transforming growth factor, beta-2	AD	TAAD
TGFBR1	Transforming growth factor-beta receptor, type I	AD	Loeys-Dietz syndrome/TAAD
TGFBR2	Transforming growth factor-beta receptor, type II	AD	Loeys-Dietz syndrome/TAAD

Abbreviations: Autosomal dominant (AD), autosomal recessive (AR)

Reference Values

An interpretive report will be provided.

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.

Cautions

Sample Quality:

This test is intended for use when EDTA whole blood is not available and formalin-fixed, paraffin-embedded (FFPE) tissue or blood spots are the only available samples. DNA extracted from FFPE tissue can be degraded, which results in a higher failure rate (approximately 5%) for next-generation sequencing when compared to DNA extracted from whole blood. Due to the quality of DNA extracted from FFPE, the acceptable coverage threshold is lower than that of the equivalent blood assays. Coverage of at least 40X is expected for all regions assessed but may be adjusted on a case-by-case basis at the discretion of the laboratory director. Sanger sequencing may be used in regions that do not achieve this rate of coverage at the discretion of laboratory director. Genomic regions that are not sufficiently covered for analysis and interpretation will be indicated on the laboratory report. Sanger sequencing on DNA extracted from FFPE may also result in quality limitations when compared to testing on DNA extracted from blood.

Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a variant that is not identified

by the methods used (eg, promoter mutations, deep intronic mutations). The absence of a variant, therefore, does not eliminate the possibility of Marfan syndrome or a related disorder.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a family history of Marfan syndrome or a related disorder, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual would allow for more informative testing of at risk individuals.

Technical Limitations:
Next-generation sequencing may not detect all types of genetic variants. Additionally, rare variants may be present that could lead to false-negative or false-positive results. If results do not match clinical findings, consider alternative methods for analyzing these genes.

For blood spot sample type: If the patient has had an allogeneic blood or marrow transplant or a recent (ie, <6 weeks from time of sample collection) heterologous blood transfusion these results may be inaccurate due to the presence of donor DNA.

Reclassification of Variants Policy:
At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.
Contact the laboratory if additional information is required regarding the transcript and/or human genome assembly used for the analysis of this patient's results.

Clinical Reference

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13. Doyle AJ, Doyle JJ, Bessling SL, et al: Mutations in the TGF-beta repressor SKI cause Shprintzen-Goldberg syndrome with aortic aneurysm. Nat Genet. 2012;44(11):1249-1254
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16. Boileau C, Guo DC, Hanna N, et al: *TGFB2* mutations cause familial thoracic aortic aneurysms and dissections associated with mild systemic features of Marfan syndrome. Nat Genet. 2012;44(8):916-921

Performance

Method Description

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data are analyzed with a bioinformatics software pipeline. Supplemental and/or confirmatory Sanger sequencing is performed when necessary.(Unpublished Mayo method)

The following genes are evaluated in this multigene panel: *ACTA2, CBS, COL3A1, FBN1, FBN2, MYH11, MYLK, SKI, SLC2A10, SMAD3, TGFB2, TGFBR1,* and *TGFBR2*.

PDF Report

No

Day(s) Performed

Monday

Report Available

6 to 8 weeks

Specimen Retention Time

Extracted DNA: 2 months; Client provided paraffin blocks (FFPE) will be returned to client after testing is complete.

Performing Laboratory Location

Rochester

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81410

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
PMMFR	Postmortem Marfan and Related Panel	In Process

Result ID	Test Result Name	Result LOINC® Value
BA1415	Gene(s) Evaluated	48018-6
BA1416	Result Summary	50397-9
BA1417	Result Details	82939-0
BA1418	Interpretation	69047-9
BA1419	Additional Information	48767-8
BA1420	Method	85069-3
BA1421	Disclaimer	62364-5
BA1422	Reviewed by	18771-6