

---

## Overview

### Useful For

Aiding in the diagnosis of:

-*FBN1*-associated Marfan syndrome

-Autosomal dominant ectopia lentis

-Isolated ascending aortic aneurysm and dissection

-Isolated skeletal features of Marfan syndrome

-MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS)-Shprintzen-Goldberg syndrome

-Autosomal dominant Weill-Marchesani syndrome

### Genetics Test Information

[Pathogenic \*FBN1\* variants are most commonly associated with Marfan syndrome \(MFS\) but have also been reported in other rare phenotypes with variable overlap with classic MFS.](#)

Approximately 25% to 33% of individuals with a pathogenic *FBN1* variant have no family history of disease due to the variant being de novo.

Genetic testing for pathogenic *FBN1* variants aids in the diagnosis of *FBN1*-associated MFS and other *FBN1*-associated conditions. Confirmation of 1 of these conditions allows for proper treatment, management, and genetic counseling.

[Prior Authorization](#) is available for this assay.

### Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Marfan and Related Disorders Patient Information](#)
- [FBN1, Full Gene Sequence Prior Authorization Ordering Instructions](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

### Highlights

This test uses next-generation sequencing (NGS) to evaluate for the presence of *FBN1* variants associated with Marfan syndrome (MFS) or other *FBN1*-associated conditions. Additionally, NGS is used to test for the presence of large

---

deletions and duplications.

**Method Name**

Sequence Capture and Targeted Next-Generation Sequencing

**NY State Available**

Yes

**Specimen****Specimen Type**

Varies

**Ordering Guidance**

In cases where there are hallmark features of Marfan syndrome, in particular the combination of ectopia lentis and aortic aneurysm or dissection in a patient or their family, *FBN1* analysis (this assay) may be an appropriate first step in testing. In cases with more nonspecific features, such as isolated ascending aortic aneurysm or isolated skeletal features of Marfan syndrome, MFRGP / Marfan Syndrome and Related Disorders Multi-Gene Panel, Varies may be the more appropriate test to choose. Professional clinical judgment should be used by the ordering clinician. A genetic consultation may be helpful in determining the appropriate testing strategy for your patient.

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

**Shipping Instructions**

Specimen preferred to arrive within 96 hours of collection.

**Necessary Information**

1. [Marfan and Related Disorders Patient Information](#) (T636) is strongly recommended, but not required, to be filled out and sent with the specimen. This information aids in providing a more thorough interpretation of test results. Ordering providers are strongly encouraged to complete the form and send it with the specimen.

2. Include physician name and phone number with specimen.

3. [Prior Authorization](#) is available for this test. **Submit the required form with the specimen.**

**Specimen Required**

**Patient Preparation:** A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

**Submit only 1 of the following specimens:**

**Specimen Type:** Whole blood

**Container/Tube:** Lavender top (EDTA)

**Specimen Volume:** 3 mL

**Collection Instructions:**

1. Invert several times to mix blood.
2. Send specimen in original tube. [Do not aliquot.](#)

**Specimen Stability Information:** Ambient (preferred) 4 days/Refrigerated 14 days

**Specimen Type:** Extracted DNA

**Container/Tube:** 2 mL screw top tube

**Specimen Volume:** 100 µL (microliters)

**Collection Instructions:**

1. The preferred volume is 100 µL at a concentration of 250 ng/µL.
2. Include concentration and volume on tube.

**Specimen Stability Information:** Frozen (preferred)/Ambient/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:

-[Informed Consent for Genetic Testing](#) (T576)

-[Informed Consent for Genetic Testing-Spanish](#) (T826)

2. [FBN1, Full Gene Sequence Prior Authorization Ordering Instructions](#)

3. [Marfan and Related Disorders Patient Information](#) (T636) is recommended.

4. If not ordering electronically, complete, print, and send a [Cardiovascular Test Request Form](#) (T724) with the specimen.

## Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

## Specimen Minimum Volume

Whole blood: 1 mL

## Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies (preferred)		

## Clinical & Interpretive

### Clinical Information

Fibrillin-1 is a 320-kDa, cysteine-rich glycoprotein found in the extracellular matrix. Monomers of fibrillin-1 associate to form microfibrils that provide mechanical stability and elastic properties to connective tissues. Fibrillin-1 is encoded by the *FBN1* gene, which contains 65 exons and is located at chromosome 15q21.

Pathogenic *FBN1* variants are most commonly associated with Marfan syndrome (MFS), an autosomal dominant connective tissue disorder involving the ocular, skeletal, and cardiovascular systems. Ocular MFS manifestations most commonly include myopia and lens displacement. Skeletal manifestations can include arachnodactyly (abnormally long and slender fingers and toes), dolichostenomelia (long limbs), pectus (chest wall) deformity, and scoliosis. Cardiovascular manifestations, which are the major cause of early morbidity and mortality in MFS, include aortic aneurysm and dissection, as well as mitral valve and tricuspid valve prolapse. There is significant inter- and intrafamilial variability in the MFS phenotype.

Pathogenic *FBN1* variants have also been reported in several other rare phenotypes with variable overlap with classic MFS. In some cases, MFS may present in the neonatal period with severe, rapidly progressive disease (previously termed "neonatal Marfan syndrome"). Other *FBN1*-associated conditions include autosomal dominant ectopia lentis (displacement of the lens of the eye), familial thoracic aortic aneurysm and dissection, 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).

---

Hundreds of pathogenic variants have been identified in *FBN1*, many of them unique to individual families. There is a wide range of variability, including intrafamilial variability, in expressivity among pathogenic *FBN1* variants. Approximately two-thirds of pathogenic *FBN1* variants are missense changes, with the majority of these being cysteine substitutions. Approximately 25% to 33% of pathogenic *FBN1* variants are de novo, in which an individual has no family history of disease. Pathogenic *FBN1* variants have been shown to occur across the gene. Some genotype-phenotype correlations have been observed, including the association with truncating and splicing variants with risk for aortic dissection, cysteine-based variants, and ectopia lentis, and severe, early onset MFS and variants in exons 24 through 32.

Marfan syndrome has significant clinical overlap with a condition called Loeys-Dietz syndrome (LDS); however, the vascular phenotype of LDS can be more severe, and LDS is caused by pathogenic variants in different genes (*TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2*). When the diagnosis of MFS, LDS, or a related disorder is suspected, the use of genetic testing is important to verify the diagnosis and provide appropriate clinical management. Confirmation of the genetic diagnosis also allows for preconception, prenatal, and family counseling.

### Reference Values

An interpretive report will be provided.

### Interpretation

Evaluation and categorization of variants is performed using American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline.<sup>(1)</sup> 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.

Unless reported or predicted to impact splicing, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported.

### Cautions

Absence of a pathogenic variant does not preclude the diagnosis of Marfan syndrome or other *FBN1*-associated condition unless a specific pathogenic variant has already been identified in an affected family member.

### Clinical Correlations:

Test results should be interpreted in the 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 alterations (ie, polymorphisms) 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, such as Sanger sequencing or large deletion/duplication analysis. Contact a genetic counselor at 800-533-1710 to discuss alternative testing methods.

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 or human genome assembly used for the analysis of the patient's results.

**Clinical Reference**

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015 May;17(5):405-424
2. Baudhuin LM, Kotzer KE, Lagerstedt SA: Increased frequency of FBN1 truncating and splicing variants in Marfan syndrome patients with aortic events. *Genet Med.* 2015 Mar;17(3):177-187. doi: 10.1038/gim.2014.91
3. Baudhuin LM, Kotzer KE, Lagerstedt SA: Decreased frequency of FBN1 missense variants in Ghent criteria-positive Marfan syndrome and characterization of novel FBN1 variants. *J Hum Genet.* 2015 May;60(5):241-252. doi: 10.1038/jhg.2015.10
4. Faivre L, Collod-Beroud G, Loeys BL, et al: Effect of mutation type and location on clinical outcome of 1,013 probands with Marfan syndrome or related phenotypes and FBN1 mutations: an international study. *Am J Hum Genet.*

---

2007;81(3):454-466. doi: 10.1086/520125

5. Loeys BL, Dietz HC, Braverman AC, et al: The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010;47:476-485. doi: 10.1136/jmg.2009.072785

6. Boileau C, Jondeau G, Mizuguchi T, Matsumoto N: Molecular genetics of Marfan syndrome. Curr Opin Cardiol. 2005 May;20(3):194-200. doi: 10.1097/01.hco.0000162398.21972.cd

7. Faivre L, Gorlin RJ, Wirtz MK, et al: In frame fibrillin-1 gene deletion in autosomal dominant Weill-Marchesani syndrome. J Med Genet. 2003 Jan;40(1):34-36. doi: 10.1136/jmg.40.1.34

## 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 is analyzed with a bioinformatics software pipeline for sequence variants and the presence of large intragenic deletions and duplications. Supplemental Sanger sequencing or quantitative polymerase chain reaction (qPCR) may be performed occasionally in regions where NGS is insufficient for data capture or not specific enough to correctly identify a variant. Sanger sequencing or qPCR may also be used for confirmatory testing. (Unpublished Mayo method)

### PDF Report

No

### Specimen Retention Time

Extracted DNA: 2 months

### Performing Laboratory Location

Rochester

## Fees & Codes

### 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

81408

**Prior Authorization**

Insurance preauthorization is available for this testing; forms are available.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.

**LOINC® Information**

Test ID	Test Order Name	Order LOINC Value
FBN1B	FBN1 Full Gene Sequence	77114-7

Result ID	Reporting Name	LOINC®
37289	Result Summary	50397-9
37290	Result Details	82939-0
37291	Interpretation	69047-9
37292	Additional Information	48767-8
37293	Method	85069-3
37294	Disclaimer	62364-5
37295	Reviewed By	18771-6