Marfan Syndrome Genetic Testing

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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What is Marfan syndrome

Definition

Marfan syndrome is an autosomal dominant disorder that affects connective tissue in many parts of the body. It affects about 1 in 5000 to 1 in 10000 individuals.¹

- Symptoms can present in males or females at any age and typically worsen over time. Infants who present with symptoms typically have the most severe disease course.¹
- Signs and symptoms of Marfan syndrome usually include (some combination of the following):¹
  - Cardiovascular system — dilatation of the aorta, predisposition for aortic tear or rupture, mitral valve prolapse (with or without congestive heart failure), tricuspid valve prolapse, and enlargement of the proximal pulmonary artery.¹
  - Skeletal system — long bone overgrowth and joint laxity, long arms and legs, scoliosis, sternum deformity (pectus excavatum or carinatum), pes planus, long thin fingers and toes, micrognathia, retrognathia, high-arched palate, deep set eyes, malar hypoplasia, down- slanting palpebral fissures, and long thin face.¹
- Ocular system — severe myopia, dislocated lens of eye (ectopia lentis), detached retina, glaucoma, early cataracts.\(^1\)
- Other symptoms – dural ectasia (stretching of the dural sac), hernias, stretch marks on the skin, and lung bullae.\(^1\)

**Clinical diagnosis-Ghent Criteria\(^{1\text{-}3}\)**

- With no known family history, a Marfan syndrome diagnosis is confirmed if any ONE of the following is met:\(^{1\text{-}3}\)
  - Significant aortic dilation (Z-score ≥2)/dissection + ectopia lentis\(^*\)
  - Significant aortic dilation (Z-score ≥2)/dissection + FBN1 mutation
  - Aortic dilation/dissection + sufficient points from other system findings\(^*\)
  - Ectopia lentis + FBN1 mutation known to be associated with aortic disease

- With a known family history, the presence of any ONE of the following is diagnostic:\(^{1\text{-}3}\)
  - Ectopia lentis
  - Significant aortic root enlargement (Z-score ≥2 in those >20 years of age or ≥3 in those <20 years of age)\(^*\)
  - Sufficient points (>7) from other system findings\(^*\)

** Marfan syndrome can be clinically diagnosed in these cases, provided there are not other findings that more strongly suggest Sphrintzen-Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome, which have clinical overlap. Or, these conditions are unlikely based on genetic or collagen testing.

- Systemic scoring system\(^{1\text{-}3}\)
  - Wrist and Thumb Sign - 3 points
  - Wrist or Thumb Sign - 1 point
  - Pectus Carinatum deformity - 2 points
  - Pectus Excavatum or chest asymmetry -1 point
  - Hindfoot deformity - 2 points
  - Plan pes planus -1 point
  - Pneumothorax - 2 points
  - Dural Ectasia - 2 points
  - Protrusio Acetabulae - 2 points
  - Reduced upper seg/lower seg and inc. arm span and height ratio - 1 point
- Scoliosis or thoracolumbar kyphosis - 1 point
- Reduced elbow extension - 1 point
- 3 of 5 facial features: Dolichocephaly, enophthalmos, downsloping palpebral fissures, malar hypoplasia, retrognathia - 1 point
- Skin striae - 1 point
- Myopia - 1 point
- Mitral Valve Prolapse - 1 point

According to the Ghent criteria, many of the manifestations of Marfan syndrome can emerge with age. Therefore, it is not advisable to establish definitive alternative diagnosis in individuals younger than age 20 years who have some physical manifestations of Marfan syndrome but not enough for a clinical diagnosis. In this circumstance, the following is suggested:\(^1,^2\)

- “If the systemic score is <7 and/or borderline aortic root measurements (Z-score <3) are present (without an FBN1 pathogenic variant), use of the term ‘nonspecific connective tissue disorder’ is suggested until follow-up echocardiographic evaluation shows aortic root dilation (Z-score ≥3).”  \(^1,^2\)
- “If an FBN1 pathogenic variant is identified in simplex or familial cases but aortic root Z-score is below 3.0, the term ‘potential Marfan syndrome’ should be used until the aorta reaches this threshold.”  \(^1,^2\)

• Diagnostic evaluations recommended:
  - Ophthalmologist evaluation with someone familiar with Marfan\(^1\)
  - Evaluation for skeletal manifestations by an orthopedist\(^1\)
  - Cardiovascular evaluations\(^1\)
  - Medical genetics evaluation\(^1\)

Genetics

- Marfan syndrome is caused by mutations in the FBN1 gene, located on chromosome 15.\(^1,^4\)
- Marfan syndrome is inherited in an autosomal dominant fashion. Everyone has 2 copies of the FBN1 gene. If one of these genes has a mutation, it is enough to cause Marfan syndrome. It affects males and females equally.\(^1\)
- A person who is found to have a FBN1 mutation has a 50% chance to pass the mutation to his/her children. Prenatal testing is available when the FBN1 mutation in the family is known.
- Genetic testing for Marfan syndrome typically starts with sequencing of the FBN1 gene. If negative, deletion/duplication of FBN1 should be considered.\(^1\)
• Mutations in the TGFBR1 or TGFBR2 gene have been found in some individuals with a clinical suspicion of MFS and no identifiable FBN1 mutation.\textsuperscript{1,3} Mutations in TGFBR1/2 are associated with Loeys-Dietz syndrome (LDS). Some features of MFS and LDS overlap. However, people with LDS typically have a greater risk of frequent aortic dissection and rupture at smaller dimensions and in early childhood.\textsuperscript{1}

• The presence of a mutation in the FBN1 gene alone does not diagnose Marfan syndrome. FBN1 mutations may cause conditions other than Marfan syndrome. Conversely, some people who meet the clinical diagnostic criteria for Marfan syndrome do not have an identifiable FBN1 mutation.\textsuperscript{1}

• Approximately 25\% of cases of Marfan syndrome are the result of a new genetic change (de novo mutation) in the affected person and are not inherited from a carrier parent.\textsuperscript{1}

**Test Information**

• **FBN1 Sequencing** identifies an FBN1 gene mutation in approximately 70-93\% of people with a clinical diagnosis of Marfan syndrome.\textsuperscript{1}

• **FBN1 Deletion/Duplication Analysis** can be performed to look for other types of gene mutations when sequencing is negative. The percentage of people with a clinical diagnosis of Marfan syndrome and a deletion/duplication mutation is unknown.\textsuperscript{1}

• **FBN1 Known Familial Mutation.** If a FBN1 mutation is found in an affected person, other family members may be offered testing.\textsuperscript{1,5}

• **Additional Testing Information**
  
  o **TGFBR1/2 Testing.** If a mutation is not found in FBN1 and there is a strong clinical suspicion of Marfan syndrome, TGFBR1/2 genetic testing may be indicated. Given the increased risk of aortic dissection and rupture at smaller dimensions and in early childhood in LDS,\textsuperscript{1} it is important to confirm whether there is a mutation in one of these two genes.

  o **Panel Testing.** There are other conditions which can cause familial aortic aneurysm and dissections and/or have overlapping features with Marfan syndrome. Many laboratories offer panel testing for FBN1 as well as other genes that cause these conditions.\textsuperscript{1} Detection rates of expanded panels vary by laboratory and depend on the genes included and the methods used for testing.\textsuperscript{1} A thorough clinical evaluation along with appropriate imaging studies will point to a specific diagnosis in many cases.\textsuperscript{1} Testing for conditions that are clinically indicated is most appropriate.\textsuperscript{1} Testing multiple genes, without supporting clinical features, has the potential to yield results that are difficult to interpret.\textsuperscript{1} The chance that a variant of uncertain significance will be found increases as more genes are tested. According to the American College of Medical Genetics and Genomics, “There is no case of classic, bona fide MFS due to mutations in a gene other than FBN1.” \textsuperscript{6} Therefore, when there is a strong clinical suspicion for
Marfan syndrome, genetic testing for genes other than FBN1 is typically not needed, with the exception of TGFBR1/2 testing.

Guidelines and evidence

• The European Society of Cardiology (ESC, 2014) stated the following:7
  o “Once a familial form of TAAD is highly suspected, it is recommended to refer the patient to a geneticist for family investigation and molecular testing.” (Class I, Level C)

• The Canadian Cardiovascular Society (2014) stated the following:8
  o “We recommend clinical and genetic screening for suspected Marfan syndrome to clarify the nature of the disease and provide a basis for individual counseling” (Strong recommendation, High quality evidence)
  o “We recommend that genetic counseling and testing be offered to first degree relatives of patients in whom the causal mutation of a TAD-associated gene is identified. We recommend that aortic imaging be offered only to mutation carriers.” (Strong recommendation, low quality evidence)

• Joint evidence-based guidelines from ACCF/AHA/AATS/ACR/ASA/SCA/SACI/SIR/STS/SVM (2010) for the diagnosis and management of thoracic aortic disease include Marfan syndrome. Genetic testing for Marfan syndrome is addressed in the following guidelines statements:
  o “If the mutant gene (FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) associated with aortic aneurysm and/or dissection is identified in a patient, first-degree relatives should undergo counseling and testing. Then, only the relatives with the genetic mutation should undergo aortic imaging.” 5 [Class 1, Level of Evidence C. Recommendation that procedure or treatment is useful/effective. It is based on very limited populations evaluated and only expert opinion, case studies or standard of care.]
  o “The criteria for Marfan syndrome is based primarily on clinical findings in the various organ systems affected in the Marfan syndrome, along with family history and FBN1 mutations status.” 5
  o Recommend echo at baseline, repeat at 6 months to look for progression then yearly if stable (Class 1).
  o Determining genetic etiology guides prophylactic aortic surgery.

• An international group of Marfan syndrome experts initially proposed clinical diagnostic criteria for Marfan syndrome in 1996, called the Ghent nosology that gained wide acceptance.9

• The Ghent criteria were updated in 2010 and now address the role of FBN1 genetic testing in the diagnosis of Marfan syndrome.2 They do not include guidelines about
when to test for a familial mutation, but do indicate that finding a familial mutation is not sufficient evidence alone to make a definitive diagnosis, stating: "If an FBN1 mutation is identified in sporadic or familial cases but aortic root measurements are still below Z=3, we propose to use the term 'potential MFS' [Marfan syndrome] until the aorta reaches threshold."

- According to the American College of Medical Genetics and Genomics, "There is no case of classic, bona fide MFS due to mutations in a gene other than FBN1. However, current clinical molecular testing of FBN1 successfully detects mutations in such unequivocal patients in only about 90-95% of cases. For all of these reasons, searching for mutations in FBN1 continues to have a circumscribed role in the diagnosis of equivocal cases. Said differently, MFS remains, by and large, a clinical diagnosis."

- Cardiac Society of Australia and New Zealand (CSANZ) Cardiovascular Genetic Diseases Council (2017):

  o "A definitive molecular genetic diagnosis can clarify an equivocal clinical picture or result in a diagnosis in an apparently phenotypically normal individual. It is unknown at this stage what proportion of patients with these different genetic mutations will develop aortic dilatation or dissection. Identification of a causal mutation allows for the provision of accurate genetic counselling, the screening of at-risk family members and offers the possibility of accurate prenatal or preimplantation genetic diagnosis."

  o "Molecular confirmation of a suspected clinical diagnosis is increasingly important for guiding patient management. As an example, an individual who looks marfanoid will have more extensive arterial imaging screening if identified to have a SMAD3 mutation as opposed to an FBN1 mutation."

Criteria

FBN1 Known Familial Mutation Analysis

- Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  o No previous genetic testing of FBN1, and
  o FBN1 mutation identified in 1st degree biological relative, OR

- Prenatal Testing for At-Risk Pregnancies:
  o FBN1 mutation identified in a previous child or either parent, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.
FBN1 Sequencing

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Testing:
  o No previous FBN1 sequencing, and
  o No known FBN1 mutation in the family, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Genetic testing is necessary because there is uncertainty in the clinical diagnosis, and
    ▪ Aortic root enlargement (Z-score >2.0) and a systemic score <7, without ectopia lentis, or
    ▪ Ectopia lentis, or
  o An individual has a clinical diagnosis of Marfan syndrome based on the revised Ghent Criteria, and
    ▪ Genetic testing is needed in order to offer testing to family members, or
    ▪ Genetic testing is needed for prenatal diagnosis purposes, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

FBN1 Deletion/Duplication Analysis

• Criteria for FBN1 Sequencing are met, AND
• No previous deletion/duplication analysis of FBN1, AND
• No mutations detected in full sequencing of FBN1, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

TGFBR1/2 Known Familial Mutation Analysis

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous genetic testing of TGFBR1/2, and
- TGFBR1/2 mutation identified in 1st degree biological relative, AND

 Rendering laboratory is a qualified provider of service per the Health Plan policy.

**TGFBR2 Sequencing**

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - No previous TGFBR2 testing performed, and
  - No mutations detected in full sequencing of FBN1, and
  - No mutations detected in deletion/duplication analysis of FBN1, AND

- Diagnostic Testing for Symptomatic Individuals:
  - There is a strong clinical suspicion of MFS based on the Ghent criteria (Member met testing guidelines for FBN1 sequencing), AND

 Rendering laboratory is a qualified provider of service per the Health Plan policy.

**TGFBR1 Sequencing**

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - No previous TGFBR1 testing performed, and
  - No mutations detected in full sequencing or deletion/duplication analysis of FBN1, and
  - No mutations detected in full sequencing of TGFBR2, AND

- Diagnostic Testing for Symptomatic Individuals:
  - There is a strong clinical suspicion of MFS based on the Ghent criteria (Member met testing guidelines for FBN1 sequencing), AND

 Rendering laboratory is a qualified provider of service per the Health Plan policy.
References


