Marfan Syndrome Genetic Testing

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Introduction

Marfan syndrome genetic testing is addressed by this guideline.

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.

Procedures addressed by this guideline	Procedure codes
FBN1 Deletion/Duplication Analysis	81479
FBN1 Known Familial Mutation Analysis	81403
FBN1 Sequencing	81408
TGFBR1 Known Familial Mutation Analysis	81403
TGFBR1 Sequencing	81405
TGFBR2 Known Familial Mutation Analysis	81403
TGFBR2 Sequencing	81405

Criteria

Introduction

Requests for Marfan syndrome testing are reviewed using the following criteria.

FBN1 Known Familial Mutation Analysis

- 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 genetic testing of FBN1 that would detect the familial mutation, and
  - FBN1 mutation identified in 1st degree biological relative, AND

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

FBN1 Sequencing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous FBN1 sequencing, and
  - No known FBN1 mutation in the family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Genetic testing is necessary because there is uncertainty in the clinical diagnosis, and
    - Aortic root enlargement (Z-score greater than or equal to 2.0) and a systemic score less than 7, without ectopia lentis, or
    - Ectopia lentis, or
  - 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:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:

  - No previous genetic testing of TGFBR1/2 that would detect the familial mutation, 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.

What is Marfan syndrome?

Definition

Marfan syndrome is an autosomal dominant disorder that affects connective tissue in many parts of the body.

Incidence

Marfan syndrome affects 1 in 5,000 to 1 in 10,000 individuals.[1]

Symptoms

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, downslanting palpebral fissures, and long thin face.[1]
- Ocular system — severe myopia, dislocated lens of eye (ectopia lentis), elongation of the globe with or without flattened cornea, 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]

Cause

Marfan syndrome is caused by mutations in the FBN1 gene, located on chromosome 15.[1]

- Genetic testing for Marfan syndrome typically starts with sequencing of the FBN1 gene. If negative, deletion/duplication of FBN1 should be considered.[1]
    - Sequencing of the FBN1 gene will find a causative mutation in approximately 90-93% of people with a clinical diagnosis of Marfan syndrome.[1]
    - Deletions and duplications have been described in approximately 5% of individuals with a clinical diagnosis of Marfan syndrome.[1]
- Mutations in the TGFBR1 or TGFBR2 gene have been found in some individuals with a clinical suspicion of Marfan syndrome and no identifiable FBN1 mutation.[1]

Mutations in TGFBR1/2, and 4 other genes, are associated with Loeys-Dietz syndrome (LDS). Some features of Marfan syndrome 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.[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.[1]

Inheritance

Marfan syndrome is inherited in an autosomal dominant fashion.[1]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

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.[1]

Diagnosis

A clinical diagnosis of Marfan syndrome is made according to Ghent Criteria.[1-3]

- With no known family history, a Marfan syndrome diagnosis is confirmed if any ONE of the following is met:[1-3]
  - 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:[1-3]
  - 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[1-3]

- 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/height ratios - 1 point
- Scoliosis or thoracolumbar kyphosis - 1 point
- Reduced elbow extension - 1 point
- 3 of 5 facial features: Dolichocephaly, enophthalmos, downslanting 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:[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).” [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."[2]

Diagnostic evaluations recommended:

- Ophthalmologist evaluation with someone familiar with Marfan syndrome[1]
- Evaluation for skeletal manifestations by an orthopedist[1]

- Cardiovascular evaluations[1]
- Evaluation by a clinical geneticist and/or genetic counselor[1]

Management

The healthcare needs of individuals with Marfan syndrome are best managed by a multidisciplinary team including a clinical geneticist, cardiologist, ophthalmologist, orthopedist, and cardiothoracic surgeon. Management includes:

- Ophthalmology: annual examination with correction of refractive errors. Surgical removal of dislocated lens with artificial lens implantation.[1]
- Orthopedist: stabilization, and if needed surgical correction, of scoliosis. Repair of pectus deformity, although this is often cosmetic. Orthotics and arch supports as indicated.[1]
- Cardiology: annual echocardiography to monitor the dimensions of the ascending aorta. Medications (such as beta blockers or angiotensin receptor blockers) that reduce the stress on the aorta are usually started at diagnosis or with the notation of aortic dilatation that is significant and/or progressive.
    - Cardiothoracic surgery: "Surgical repair of the aorta is indicated either when the maximal measurement of the aortic root approaches 5.0 cm in adults or older children, when the rate of increase of the aortic root diameter approaches 0.5-1.0 cm per year, or if there is progressive and severe aortic regurgitation. For younger children, aortic root surgery should be considered once: (1) the rate of increase of the aortic root diameter approaches 0.5-1.0 cm per year, or (2) there is progressive and severe aortic regurgitation."[1] Children with Marfan syndrome may have severe and progressive mitral valve regurgitation with ventricular dysfunction requiring surgery.[1]

Avoidance of certain activities and agents are also recommended. Examples include:[1]

- Isometric exercises, contact sports, and competitive sports and activities that can exacerbate joint pain or cause injury
- Decongestants and excessive caffeine as these stimulate the cardiovascular system
- Medications that cause vasoconstriction
- Correction of refractive errors with LASIK

Survival

The greatest impact to the survival of individuals with Marfan syndrome are the manifestations in the cardiovascular system. With proper surveillance and management, the life expectancy of individuals with Marfan syndrome approximates that of individuals without Marfan syndrome.[1]

Test information

Introduction

Testing for Marfan syndrome may include known familial mutation testing, next generation sequencing, or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Additional Testing Information

Additional testing information includes the following:

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,[1] it is important to confirm whether there is a mutation in one of these two genes.

Multigene 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.[1] Detection rates of expanded panels vary by laboratory and depend on the genes included and the methods used for testing.[1] A thorough clinical evaluation along with appropriate imaging studies will point to a specific diagnosis in many cases.[1] Testing for conditions that are clinically indicated is most appropriate.[1] Testing multiple genes, without supporting clinical features, has the potential to yield results that are difficult to interpret.[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." [5] 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. For information on multigene panel testing that includes Marfan Syndrome, please refer to the guideline *Hereditary Connective Tissue Disorder Genetic Testing,* as this testing is not addressed here.

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Marfan syndrome.

American College of Medical Genetics and Genomics

According to the American College of Medical Genetics and Genomics (ACMG, 2012), "There is no case of classic, bona fide MFS [Marfan syndrome] 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." [5]

American Heart Association and American College of Cardiology

The American Heart Association and American College of Cardiology published clinical practice guidelines for the diagnosis and management of aortic disease. They stated the following regarding genetic evaluation and family screening:[6]

- Risk factors for familial thoracic aortic disease (TAD), also known as heritable thoracic aortic disease (HTAD), were outlined as:
    - "TAD and syndromic features of Marfan syndrome, Loeys-Dietz syndrome, or vascular EDS syndrome
    - TAD presenting at <60 years
    - A family history of either TAD or peripheral/intracranial aneurysms in a first- or second-degree relative

  - A history of unexplained sudden death at a relatively young age in a first- or second-degree relative"

- "In patients with aortic root/ascending aortic aneurysms or aortic dissection, obtaining a multigenerational family history of TAD, unexplained sudden deaths, and peripheral and intracranial aneurysms is recommended."
- "In patients with aortic root/ascending aortic aneurysms or aortic dissection and risk factors for HTAD, genetic testing to identify pathogenic/likely pathogenic variants (ie, mutations) is recommended."
- "In patients with an established pathogenic or likely pathogenic variant in a gene predisposing to HTAD, it is recommended that genetic counseling be provided and the patient's clinical management be informed by the specific gene and variant in the gene."
- " In patients with TAD who have a pathogenic/likely pathogenic variant, genetic testing of at-risk biological relatives (ie, cascade testing) is recommended. In family members who are found by genetic screening to have inherited the pathogenic/likely pathogenic variant, aortic imaging with TTE (if aortic root and ascending aorta are adequately visualized, otherwise with CT or MRI) is recommended."
- " In a family with aortic root/ascending aortic aneurysms or aortic dissection, if the disease-causing variant is not identified with genetic testing, screening aortic imaging of at-risk biological relatives (ie, cascade testing) is recommended."
- "In patients with aortic root/ascending aortic aneurysms or aortic dissection, in the absence of either a known family history of TAD or pathogenic/likely pathogenic variant, screening aortic imaging of first-degree relatives is recommended."
- "In patients with acute type A aortic dissection, the diameter of the aortic root and ascending aorta should be recorded in the operative note and medical record to inform the management of affected relatives."

Canadian Cardiovascular Society

The Canadian Cardiovascular Society (CCS, 2014) stated the following:[7]

- “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)
- “We recommend that genetic counselling and testing be offered to first degree relatives of patients in whom a 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)

Cardiac Society of Australia and New Zealand Cardiovascular Genetic Diseases Council

The Cardiac Society of Australia and New Zealand (CSANZ, 2017) Cardiovascular Genetic Diseases Council stated the following:[8]

- "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 counseling, the screening of at-risk family members and offers the possibility of accurate prenatal or preimplantation genetic diagnosis."
- "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."

European Reference Network on Rare Multisystemic Cardiovascular Disease

The HTAD Rare Disease Working Group of the European Reference Network on Rare Multisystemic Cardiovascular Diseases (VASCERN, 2023) recommended a strategy for evaluation and diagnosis of individuals and families with hereditary thoracic aortic disease.[9] They recommended consideration of genetic testing, under supervision of a provider with experience in HTAD, when "there is a high suspicion of an underlying genetic aortopathy and includes:

- patients with a familial form with or without hypertension (2 first or second-degree affected relatives) of thoracic aortic dissection or aneurysm (TAA/TAD)
- sporadic TAA/TAD as defined above, at
    - any age, in the absence of arterial hypertension, or
    - <70 years of age in presence of hypertension
- patients with non-traumatic ectopia lentis compatible with MFS
- patients with a combination of TAAD and syndromic features of Marfan or LDS."

European Society of Cardiology

The European Society of Cardiology (ESC, 2014) stated the following: [10]

- “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)

Joint Committee Guidelines

Joint evidence-based guidelines from the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine.
(ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM, 2010) for the diagnosis and management of thoracic aortic disease include Marfan syndrome.[4] Genetic testing for Marfan syndrome is addressed in the following guidelines statements:

- "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." [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.]
- "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."
- Recommend echo at baseline, repeat at 6 months to look for progression then yearly if stable (Class 1, Level of Evidence C).
- Determining genetic etiology guides prophylactic aortic surgery.

Selected Relevant Publications

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.[11]

- 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" [2]

References

Introduction

This guideline cites the following references:

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