Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders

Marfan syndrome (MFS) is a systemic connective tissue disorder that may have a high degree of clinical variability and phenotypes overlapping with other syndromes and disorders. The diagnosis of most suspected connective tissue disorders can be made based on clinical findings and family history. Some of these disorders are associated with a predisposition to the development of progressive thoracic aortic aneurysms (TAAs) and dissection (TAAD). Accurate diagnosis of one of these syndromes can lead to changes in clinical management, including surveillance of the aorta, and surgical repair of the aorta, when necessary, as well as surveillance for multisystem involvement in syndrome forms of TAAD. Known pathogenic variants are associated with MFS and the other connective tissue disorders that may share clinical features with MFS.

Individuals suspected of having a systemic connective tissue disorder like Marfan syndrome (MFS) usually have multiple features that affect many different organ systems; most of these conditions can be diagnosed using clinical criteria. However, these different syndromes may show shared features, overlapping phenotypes, and similar inheritance patterns, which can cause a diagnostic challenge. Additional difficulties in the diagnosis of one of these syndromes may occur due to the age-dependent development of many of the physical manifestations of the syndrome (making the diagnosis more difficult in children); many show variable expression, and many of the features found in a number of these syndromes occur in the general population (eg, pectus excavatum, tall stature, joint hypermobility, mitral valve prolapse, nearsightedness). The identification of the proper syndrome is important to address its manifestations and complications, in particular, the risk of aortic aneurysms and dissection.

Thoracic Aortic Aneurysms and Dissection
Most thoracic aortic aneurysms (TAAs) are degenerative and are often associated with the same risk factors as abdominal aortic aneurysms (eg, atherosclerosis). TAAs may be associated with a genetic predisposition, which can either be familial or related to defined genetic disorders or syndromes. Genetic predisposition to TAA is due to a genetic defect that leads to abnormalities in connective tissue metabolism. Genetically related TAA accounts for approximately 5% of TAA. Some of the genetic syndromes associated with TAA have more aggressive rates of aortic expansion and are more likely to require intervention compared with sporadic TAA. MFS is the most common inherited form of syndromic TAA and thoracic aortic aneurysm dissection (TAAD). Other genetic systemic connective tissue disorders associated with a risk of TAAD include Ehlers-Danlos syndrome (EDS) type IV, Loeys-Dietz syndrome (LDS), and arterial tortuosity syndrome.
Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders

Familial TAAD refers to patients with a family history of aneurysmal disease, but who do not meet criteria for a connective tissue syndrome.

Marfan Syndrome
MFS is an autosomal-dominant condition, in which there is a high degree of clinical variability of systemic manifestations, ranging from isolated features of MFS to neonatal presentation of severe and rapidly progressive disease in multiple organ systems. Despite the clinical variability, the principal manifestations involve the skeletal, ocular, and cardiovascular systems. Involvement of the skeletal system is characterized by bone overgrowth and joint laxity, disproportionately long extremities for the size of the trunk (dolichostenomelia), overgrowth of the ribs which can push the sternum in or out (pectus excavatum or carinatum, respectively), and scoliosis which can be mild or severe and progressive. Ocular features include myopia, and displacement of the lens from the center of the pupil (ectopia lentis) is a hallmark feature seen in 60% of affected individuals. Cardiovascular manifestations are the major source of morbidity and mortality and include dilation of the aorta at the level of the sinuses of Valsalva, predisposition for aortic tear and rupture, mitral valve prolapse, tricuspid valve prolapse and enlargement of the proximal pulmonary artery. However, with proper management, the life expectancy of a person with MFS can approximate that of the general population.

The diagnosis of MFS is mainly a clinical one and based on the characteristic findings in multiple organ systems, as well as the family history. The Ghent criteria, revised in 2010, are used for the clinical diagnosis of MFS. The previous Ghent criteria had been criticized for taking insufficient account of the age-dependent nature of some clinical manifestations, making the diagnosis in children more difficult, and for including some nonspecific physical manifestations or poorly validated diagnostic thresholds. The revised criteria are based on clinical characteristics in large published patient cohorts and expert opinions. The revised criteria include several major changes, as follows. More weight is given to the 2 cardinal features of MFS—aortic root aneurysm and dissection and ectopia lentis. In the absence of findings that are not expected in MFS, the combination of these 2 features is sufficient to make the diagnosis. When aortic disease is present, but ectopia lentis is not, all other cardiovascular and ocular manifestations of MFS and findings in other organ systems contribute to a “systemic score” that guides diagnosis. Second, a more prominent role has been given to molecular testing of FBN1 and other relevant genes, allowing for the appropriate use when necessary. Third, some less specific manifestations of MFS were removed or given less weight in the diagnostic criteria. Fourth, the revised criteria formalized the concept that additional diagnostic considerations and testing may be required if a patient has findings that satisfy the criteria for MFS but shows unexpected findings, particularly if they are suggestive of a specific alternative diagnosis. Particular emphasis is placed on LDS, Shprintzen-Goldberg syndrome (SGS), and EDS vascular type. LDS and SGS have substantial overlap with MFS, including the potential for similar involvement of the aortic root, skeleton, skin, and dura. EDS vascular type occasionally overlaps with MFS. Each of these conditions has a unique risk profile and management protocol. Given the autosomal-dominant nature of inheritance, the number of physical findings needed to establish a diagnosis for a person with an established family history is reduced. It is estimated that molecular techniques permit the detection of FBN1 pathogenic variants in up to 97% of Marfan patients who fulfill Ghent criteria, suggesting that the current Ghent criteria have excellent specificity.

FBN1 is the only gene in which pathogenic variants are known to cause classic MFS. Approximately 75% of individuals with MFS have an affected parent, and 25% have a de novo pathogenic variant. Over 1000 FBN1 pathogenic variants that cause MFS have been identified. The following findings in FBN1 molecular genetic testing should infer causality in making the diagnosis of MFS: a pathogenic variant previously shown to segregate in families with MFS and de novo pathogenic variants of a certain type (eg, nonsense, certain missense variants, certain splice site variants, certain deletions and insertions).
Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders

Most variants in the FBN1 gene that cause MFS can be identified with sequence analysis (≈70% to 93%) and, although the yield of deletion/duplication analysis in patients without a defined coding sequence or splice site by sequence analysis is unknown, it is estimated to be about 30%. The most common testing strategy of a proband suspected of having MFS is sequence analysis followed by deletion/duplication analysis if a pathogenic variant is not identified. However, the use of genetic testing for a diagnosis of MFS has limitations. More than 90% of pathogenic variants that have been described are unique, and most pathogenic variants are not repeated among nongenetically related patients. Therefore, the absence of a known pathogenic variant in a patient in whom MFS is suspected does not exclude the possibility that the patient has MFS. No clear genotype-phenotype correlation exists for MFS and, therefore, the severity of the disease cannot be predicted from the type of variant.

Caution should be used in interpreting the identification of an FBN1 variant, because other conditions with phenotypes that overlap with MFS can have an FBN1 variant (eg, MASS syndrome, familial mitral valve prolapse syndrome, SGS, isolated ectopia lentis).

Management of MFS includes both treatment of manifestations and prevention of complications, including surgical repair of the aorta depending on the maximal measurement, the rate of increase of the aortic root diameter, and the presence of progressive and severe aortic regurgitation.

REGULATORY STATUS
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Several commercial laboratories currently offer targeted genetic testing, as well as NGS panels that simultaneously analyze multiple genes associated with MFS, TAADs, and related disorders. NGS technology cannot detect large deletions or insertions, and therefore samples that are variant-negative after sequencing should be evaluated by other testing methodologies.

Ambry Genetics offers TAADNext, an NGS panel which simultaneously analyzes 22 genes that are associated with TAADs, MFS and related disorders. The panel detects mutations in all coding domains and splice junctions of ACTA2, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, MED12, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, SKI, SLC2A10, SMAD3, SMAD4, TGFB2, TGFBR1, and TGFBR2. Deletion/duplication analysis is performed for all genes on the panel except CBS, COL5A1, FLNA, SMAD4 and TGFB3.

Prevention Genetics offers targeted familial variant testing, as well as “Marfan syndrome and related aortopathies next generation sequencing [NGS] panel” testing, which includes 14 genes: ACTA2, COL3A1, COL5A1, COL5A2, FBN1, FBN2, MYH11, MYLK, SKI, SLC2A10, SMAD3, TGFBR2, TGFBR1, and TGFBR2.

GeneDx offers the “Marfan/TAAD sequencing panel” and “Marfan/TAAD deletion/duplication panel,” which include variant testing for ACTA2, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, MED12, MYH11, SKI, SLC2A10, SMAD3, TGFB2, TGFBR1, and TGFBR2.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders

BCBSNC will provide coverage for individual genetic testing for the diagnosis of Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders, when it is determined to be medically necessary because the medical criteria and guidelines below are met.

Genetic testing panels for Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders that are not limited to focused genetic testing are considered investigational. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore, member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders is covered

Individual genetic testing for the diagnosis of Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders, and panels comprised entirely of focused genetic testing limited to the following genes: FBN1 and MYH11 (CPT code 81408) and ACTA2, TGFBR1, and TGFBR2 (CPT code 81405), may be considered medically necessary, when signs and symptoms of a connective tissue disorder are present, but a definitive diagnosis cannot be made using established clinical diagnostic criteria.

Individual, targeted familial variant testing for Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders, for assessing future risk of disease in an asymptomatic individual, may be considered medically necessary when there is a known pathogenic variant in the family.

When Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders is not covered

Genetic testing panels for Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders that are not limited to focused genetic testing as defined by CPT codes 81405 and 81408 are considered investigational.

Policy Guidelines

The evidence for genetic testing in individuals for the diagnosis of Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders, when a definitive diagnosis cannot be made using established clinical diagnostic criteria, consists mainly of clinical validity data. Relevant outcomes are overall survival, disease-specific survival, test accuracy, test validity, symptoms, and morbid events. Published data on analytic validity of individual and panel testing of genes is lacking. Sequencing analysis for MFS has been reported to detect 70% to 93% of pathogenic variants in probands with MFS, and greater than 95% in Ehlers-Danlos syndrome type IV. Direct evidence of clinical utility is lacking, however, confirming a diagnosis leads to changes in clinical management which improve health outcomes. These changes in management include treatment of manifestations of a specific syndrome, prevention of primary manifestations and secondary complications, impact on surveillance, and counselling on
Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders

agents/circumstances to avoid. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing in individuals who are asymptomatic, to assess future risk of Marfan syndrome and other connective tissue disorders associated with thoracic aortic aneurysms and dissections, when there is a known pathogenic variant in the family (familial variant) who receives targeted familial variant testing is generally lacking. Relevant outcomes are overall survival, disease-specific survival, test accuracy, test validity, symptoms, and morbid events. Published data on analytic validity of targeted familial variant testing is lacking, but is expected to be high. Direct evidence of clinical utility is lacking, however, confirming a diagnosis leads to changes in clinical management which improve health outcomes, similar to those in the proband. In addition, the test results will determine whether or not to follow a relative who does or does not have the familial variant. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina website at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81405, 81408, 81410, 81411

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Medical Director review 03/2015


Specialty Matched Physician Advisory Panel review 3/2016

Medical Director review 03/2016


Medical Director review 2/2017

Specialty Matched Physician Advisory Panel review 3/2017

Medical Director review 03/2017

Policy Implementation/Update Information

4/28/15 New policy developed. Policy Statement states, “coverage for individual mutation testing for the diagnosis of Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders, when determined to be medically
Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders

necessary because the medical criteria and guidelines are met. Genetic testing panels for Marfan syndrome, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders that are not limited to focused mutation testing are considered investigational.” Medical Director review 03 2015. (td)

5/26/15 When Covered and When Not Covered section titles updated. Policy Statement unchanged. (td)


3/31/17 Description section updated to include clarifying information related to Marfan Syndrome and TAAD. Added updated genetic terminology throughout policy, policy statement remains unchanged. Policy guidelines and reference updates. Medical Director review 2/2017.(jd)


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