



FEP Medical Policy Manual

FEP 2.04.129 Genetic Testing for Marfan Syndrome, Thoracic Aortic Aneurysms and Dissections, and Related Disorders

Annual Effective Policy Date: July 1, 2024

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Related Policies:

None

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

Description

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Marfan syndrome (MFS) is a systemic connective tissue disease (CTD) with a high degree of clinical variability and phenotypes overlapping with other syndromes and disorders. The diagnosis of most suspected CTDs can be based on clinical findings and family history. Some of these disorders are associated with a predisposition to the development of progressive thoracic aortic aneurysms and dissection. Accurate diagnosis of 1 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 syndromic forms of thoracic aortic aneurysms and dissection. Known pathogenic variants are associated with MFS and the other connective tissue disorders that share clinical features with MFS.

OBJECTIVE

The objective of this evidence review is to determine whether testing for genes associated with connective tissue diseases linked to thoracic aortic aneurysms improves the net health outcome in individuals symptomatic or asymptomatic with a familial pathogenic variant associated with thoracic aortic aneurysm dissection.

POLICY STATEMENT

Individual genetic testing for the diagnosis of Marfan syndrome, Ehlers-Danlos syndrome type IV, 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*; *ACTA2*, *TGFBR1*, and *TGFBR2*; and *COL3A1* 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, Ehlers-Danlos syndrome type IV, 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.

Genetic testing panels for Marfan syndrome, Ehlers-Danlos syndrome type IV, other syndromes associated with thoracic aortic aneurysms and dissections, and related disorders that are not limited to focused genetic testing are considered **investigational**.

POLICY GUIDELINES

Syndromes associated with thoracic aortic aneurysms may have established clinical criteria with major and minor criteria (eg, Marfan syndrome [Ghent criteria] and Ehlers-Danlos syndrome type IV) or may be associated with characteristic clinical findings. While most of these syndromes can be diagnosed based on clinical findings, these syndromes may be associated with variability in clinical presentation and may show overlapping features with each other, and with other disorders. The use of genetic testing to establish a diagnosis in an individual with a suspected connective tissue disorder is most useful in individuals who do not meet sufficient clinical diagnostic criteria at the time of initial examination, in individuals who have an atypical phenotype and other connective tissue disorders cannot be ruled out, and in individuals who belong to a family in which a pathogenic variant is known (presymptomatic diagnosis).

Genetic testing has conventionally been used when a definitive diagnosis of 1 of these syndromes cannot be made. More recently, panels using next-generation sequencing (NGS), which test for multiple genes simultaneously, have been developed for the syndromes associated with thoracic aortic aneurysms and dissections, and other conditions that may have overlapping phenotypes. Although the laboratory-reported sensitivity is high for some of the conditions on the panel, the analytic validity of these panels is unknown, and detection rates of variants of uncertain significance are unknown.

However, there may be certain clinical scenarios in which focused panel testing may be appropriate to include a narrow list of differential diagnoses of thoracic aortic aneurysms and dissection based on clinical findings.

The gene variants associated with thoracic aortic aneurysms are not infrequently *de novo* variants. Targeted testing of the parents of a proband with a confirmed variant to identify mode of transmission (germline vs. *de novo*) may be considered appropriate to guide clinical management.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology <97> "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" <97> to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the 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 next-generation sequencing panels that simultaneously analyze multiple genes associated with MFS, TAADs, and related disorders. Next-generation sequencing 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, a next-generation sequencing panel that simultaneously analyzes 35 genes associated with TAADs, MFS, and related disorders. The panel detects variants in all coding domains and splice junctions of genes: *ACTA2*, *BGN*, *CBS*, *CHST14*, *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, *EFEMP2*, *FBN1*, *FBN2*, *FKBP14*, *FLNA*, *FOXE3*, *LOX*, *MAT2A*, *MED12*, *MFAP5*, *MYH11*, *MYLK*, *NOTCH1*, *PLOD1*, *PRDM5*, *PRKG1*, *SKI*, *SLC2A10*, *SMAD3*, *SMAD4*, *TGFB2*, *TGFB3*, *TGFBR1*, *TGFBR2*, *TNXB*, and *ZNF469*. Deletion and duplication analyses are performed for all genes on the panel except *CBS* and *TNXB* exons 32 to 44.

Prevention Genetics offers targeted familial variants testing, as well as a "Marfan syndrome and related aortopathies panel" , which includes 38 genes: *ABL1*, *ACTA2*, *AEBP1*, *BGN*, *CBS*, *COL3A1*, *COL5A1*, *COL5A2*, *EFEMP2*, *ELN*, *FBLN5*, *FBN1*, *FBN2*, *FLNA*, *FOXE3*, *IPO8*, *LOX*, *LTBP3*, *MAT2A*, *MED12*, *MFAP5*, *MYH11*, *MYLK*, *NKAP*, *NOTCH1*, *PLOD1*, *PRKG1*, *SKI*, *SLC2A10*, *SMAD3*, *SMAD4*, *SMAD6*, *SMS*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2*.

GeneDx offers the "Custom Marfan/TAAD & Related Disorders Panel," "Marfan/TAAD panel," and "Rest of Marfan/TAAD Sequencing & Del/Dup panel," which include variant testing for *ACTA2*, *BGN*, *CBS*, *COL3A1*, *COL5A1*, *COL5A2*, *FBN1*, *FBN2*, *FLNA*, *LOX*, *MAT2A*, *MED12*, *MFAP5*, *MYH11*, *MYLK*, *NOTCH1*, *PRKG1*, *SKI*, *SLC2A10*, *SMAD2*, *SMAD3*, *SMAD4*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2*.

RATIONALE

Summary of Evidence

For individuals who have signs and/or symptoms of a connective tissue disease (CTD) linked to thoracic aortic aneurysms who received testing for genes associated with CTDs, the evidence includes mainly clinical validity data. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, and morbid events. Sequencing analysis for Marfan syndrome (MFS) has been reported to detect 90% to 93% of pathogenic variants in probands with MFS, and over 95% in Ehlers-Danlos syndrome type IV (vascular Ehlers-Danlos). Direct evidence of clinical usefulness is lacking; however, confirming a diagnosis leads to changes in clinical management, which improves health outcomes. These changes in management include treatment of manifestations of a specific syndrome, prevention of primary manifestations and secondary complications, modifications to surveillance, and counseling on agents and circumstances to avoid. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a known familial pathogenic variant associated with thoracic aortic aneurysms and dissection who receive targeted familial variant testing, the evidence is generally lacking. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, and morbid events. Direct evidence of clinical usefulness is lacking; however, confirming a diagnosis leads to changes in clinical management, which improves health outcomes. Also, test results will determine whether to follow a relative who does or does not have the familial variant. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of the management of conflict of interest.

American Academy of Pediatrics

In 2023, the American Academy of Pediatrics updated its clinical report focused on health supervision for children with marfan syndrome (MFS).²¹ This clinical report notes the following with regard to genetic testing:

- "Younger patients at risk for Marfan syndrome based on clinical features or a positive family history should be evaluated periodically until their growth is complete or preferably undergo appropriate genetic testing."
- "...genetic testing in Marfan syndrome has become an important part of the diagnosis and management of the condition."
- "For those suspected to have Marfan syndrome on clinical grounds after physical, cardiac, and ophthalmic evaluation but who may not meet full clinical criteria, one should consider FBN1 testing"
- "Patients who fit clinical criteria for Marfan syndrome in whom no pathogenic variant is found in the FBN1 gene should continue to be followed according to the health supervision for Marfan syndrome. In addition, broader genomic testing should be considered in these individuals."
- "When a new diagnosis of Marfan syndrome is made in a child or adolescent, both parents and at-risk first-degree relatives should have physical, ophthalmologic, and cardiac evaluations as well as consideration of genetic testing. Similarly, when a new diagnosis of Marfan syndrome is made in a parent, all children should be screened for manifestations of Marfan syndrome."
- "Prenatal genetic testing for FBN1 mutations may be helpful to confirm Marfan syndrome as well as reveal specific mutations in FBN1 that may be more typically associated with this severe form and, therefore, reduced survivability."

American College of Cardiology

Joint evidence-based guidelines (2022) from the American College of Cardiology (ACC) and American Heart Association (AHA) for the diagnosis and management of aortic disease include MFS, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome.²² Genetic testing for thoracic aortic disease (TAD) was addressed in the following guideline statement:

- "Genetic testing is recommended for individuals with syndromic features, family history of TAD, and/or early age of disease onset. Thoracic aortic imaging is recommended for first-degree relatives of all individuals with TAD, regardless of age of onset, to detect asymptomatic aneurysms. Positive genetic testing should trigger gene-based management and cascade testing of at-risk relatives. When testing is negative or reveals variants of unknown significance, first-degree relatives should undergo screening aortic imaging."

Specific recommendations for genetic testing and screening of family members for TAD are provided in the table below.

Table 1. Genetic Testing and Screening of Family Members for Thoracic Aortic Disease*

COR	LOE	Recommendations
1	B-NR	In patients with aortic root/ascending aortic aneurysms or aortic dissection and risk factors for HTAD, genetic testing to identify pathogenic/likely pathogenic variants (i.e., mutations) is recommended.
1	B-NR	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.
1	B-NR	In patients with TAD who have a pathogenic/likely pathogenic variant, genetic testing of at-risk biological relatives (i.e., 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.
1	B-NR	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 (as per recommendation 4) of at-risk biological relatives (i.e., cascade testing) is recommended.
1	B-NR	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 (as per recommendation 4) of first-degree relatives is recommended.

B-NR: level B, non-randomized evidence; COR: class of recommendation; CT: computerized tomography; HTAD: heritable thoracic aortic disease; LOE: level of evidence; MRI: magnetic resonance imaging; TAD: thoracic aortic disease; TTE: transthoracic echocardiogram.

*adapted from Isselbacher et al (2022).²²

American College of Cardiology Foundation

Joint evidence-based guidelines (2010) from the American College of Cardiology Foundation and 9 other medical associations for the diagnosis and management of thoracic aortic disease include MFS.²³ Genetic testing for MFS was 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 [pathogenic variant] 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 MFS is based primarily on clinical findings in the various organ systems affected in the MFS, along with family history and *FBN1* mutations [pathogenic variants] status."

American College of Medical Genetics and Genomics

In 2012, the American College of Medical Genetics and Genomics issued guidelines on the evaluation of adolescents or adults with some features of MFS.²⁴ The guidelines recommended the following:

"If there is *no family history of MFS*, then the subject has the condition under any of the following 4 situations:

- A dilated aortic root (defined as greater than or equal to 2 standard deviations above the mean for age, sex, and body surface area) and ectopia lentis
- A dilated aortic root and a mutation [pathogenic variant] in *FBN1* that is clearly pathologic
- A dilated aortic root and multiple systemic features ... or
- Ectopia lentis and a mutation [pathogenic variant] in *FBN1* that has previously been associated with aortic disease."

"If there is *a positive family history of MFS* (independently ascertained with these criteria), then the subject has the condition under any of the following 3 situations:

- Ectopia lentis
- Multiple systemic features ... or
- A dilated aortic root (if over 20 years, greater than 2 standard deviations; if younger than 20, greater than 3 standard deviations)"

The systemic features are weighted by a scoring system.

American Heart Association

In 2020, the AHA issued a scientific statement focused on genetic testing and its implications for the management of inherited cardiovascular diseases (Table 2).²⁵ Approaches for the evaluation of patients with a confirmed or suspected diagnosis of inherited cardiovascular disease, as well as individuals with secondary or incidental genetic findings are summarized in the statement. Briefly, the statement notes that:

- "Genetic testing typically should be reserved for patients with a confirmed or suspected diagnosis of an inherited cardiovascular disease or for individuals at high *a priori* risk resulting from a previously identified pathogenic variant in their family"
- "Pathogenic and likely pathogenic variants might confirm diagnoses of suspected diseases (ie, serve as major criteria) or warrant changes in clinical management (ie, are actionable) if they occur in certain genes in patients with certain diseases (see Table S11)"

Table 2. Genetics-Guided Diagnosis and Management of Cardiovascular Condition*

Condition	Role in Diagnosis	Role in management
Familial thoracic aortic aneurysm and dissection	Confirm clinical diagnosis and subtype classification	Causative gene can affect (1) timing of recommended surgical intervention and (2) extent and type of screening for other abnormalities; aids with identification of family members at risk for the condition
Loeys-Dietz syndrome	Major criterion for diagnosis and subtype classification	Confirmed diagnosis can affect (1) timing of recommended surgical intervention and (2) extent and type of screening for other abnormalities; aids with identification of family members at risk for the condition
Marfan syndrome	Major criterion for diagnosis	Confirmed diagnosis can affect timing of recommended surgical intervention

*adapted from Musunuru et al 2020.²⁵

This statement also recommends further evaluation of secondary/incidental findings of pathogenic or likely pathogenic variants in any of the following genes associated with Marfan syndrome (MFS), Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections: *FBN1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *ACTA2*, *MYH11*.

In 2021, the AHA issued a scientific statement focused specifically on genetic testing in the pediatric population.²⁶ Key points and recommendations on pediatric cardiovascular genetic testing from the AHA statement are noted below:

- "Diagnostic genetic testing should be considered only in children with a high likelihood of disease."
- "Risk-predictive genetic testing should be performed in children after identification of a P/LP [pathogenic/likely pathogenic] variant in a family member with disease."
- "The timing of genetic testing in children should take into account disease-specific considerations of disease penetrance, the likelihood of pediatric disease presentation, the availability of effective therapies or lifestyle modifications, and the possibility of psychological distress in the family attributable to uncertainty."
- "Continued follow-up of genetic test results is important to re-evaluate or confirm variant pathogenicity over time."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2015	New policy	Individual mutation 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 mutation testing limited to the following genes: FBN1 and MYH11 and ACTA2, TGFBR1, and TGFBR2, 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 mutation 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 mutation in the family. 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.
June 2018	Replace policy	Policy updated with a literature review through December 11, 2017; references 9 and 14 added. The policy is revised with updated format. Policy statements unchanged except "Individual, targeted mutation 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 mutation in the family" omitted due to benefit application of "diagnose and/or manage a patient's existing medical condition"
June 2019	Replace policy	Policy updated with literature review through December 14, 2018; no references added. The policy is revised with updated format. Policy statements unchanged.
June 2020	Replace policy	Policy updated with literature review through December 9, 2019; no references added. Policy statements unchanged.
June 2021	Replace policy	Policy updated with literature review through December 21, 2020; no references added. Ehlers-Danlos syndrome type IV syndrome added to policy statements; intent of statements unchanged. Due to benefits, "policy does not address testing in asymptomatic individuals" added to Policy Objective for clarity.
June 2022	Replace policy	Policy updated with literature review through December 15, 2021; reference added. Policy statements unchanged.
June 2023	Replace policy	Policy updated with literature review through December 8, 2022; reference added. Minor editorial refinements to policy statements; intent unchanged.
June 2024	Replace policy	Policy updated with literature review through December 20, 2023; references added. Policy statements unchanged.

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