Regence

Medical Policy Manual Genetic Testing, Policy No. 77

Genetic Testing for Heritable Disorders of Connective Tissue

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Next Review: June 2025
Last Review: July 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Heritable disorders of connective tissue have a high degree of clinical variability and phenotypes, often involving the cardiovascular, musculoskeletal, ocular, pulmonary, and gastrointestinal systems. Due to clinical overlap with other syndromes and disorders, diagnosis may be challenging.

MEDICAL POLICY CRITERIA

Note: Please see Cross References for individual gene and panel testing for genes not associated with connective tissue disorders.

I. Individual gene variant and targeted panel testing for connective tissue disorders (see Policy Guidelines) may be considered **medically necessary** when either of the following are met:
   A. To diagnose an individual with specific signs and symptoms of a connective tissue disorder; *or*
   B. Testing for an asymptomatic individual, when there is a known pathogenic variant in the family.

II. Individual gene variant testing and genetic panel testing for a connective tissue disorder is considered **not medically necessary** when the above criteria are not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

HERITIBLE DISORDRS OF CONNECTIVE TISSUE

There are over thirty disorders of connective tissues with overlapping features. The most common are listed below with examples of frequently occurring symptoms (list is not exhaustive):

Disorder	Symptoms
Ehlers-Danlos syndrome (EDS), type IV, also referred to as vascular EDS (vEDS)	Arterial aneurysms, dissection, or rupture; intestinal rupture; uterine rupture during pregnancy; and family history of vEDS. Additionally, thin, translucent skin; facial characteristics including thin lips, micrognathia, narrow nose, and prominent eyes; acrogeria; carotid-cavernous sinus arteriovenous fistula; and hypermobility of small joints.
Loeys-Dietz syndrome (LDS)	Vascular, skeletal, cardiofacial, cutaneous, allergic/inflammatory disease, and ocular manifestations. Aortic root dilatation is seen in more than 95% of probands.
Marfan syndrome (MFS)	Mild to severe manifestations of the ocular, skeletal, and cardiovascular systems. Myopia; bone overgrowth and joint laxity; disproportionately long extremities for the size of the trunk; pectus excavatum or pectus carinatum; and varying degrees of scoliosis.
Heritable thoracic aortic disease	Manifestations of the ocular, neurological, cardiovascular, and pulmonary systems.

GENES COMMONLY TESTED FOR CONNECTIVE TISSUE DISORDERS

- *ACTA2*
- *COL3A1*
- *COL5A1*
- *COL5A2*
- *FBN1*
- *FBN2*
- *FLNA*
- *MYH11*
- *MYLK*
- *PLOD1*
- *SLC2A10*
- *SMAD3*
- *TGFB2*
- *TGFBR1*
- *TGFBR2*

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

- Name of the genetic test(s) or panel test
- Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
- The exact gene(s) and/or variant(s) being tested
- Relevant billing codes
- Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
- Medical records related to this genetic test:
    - History and physical/chart notes, including *specific* signs and symptoms observed, related to a *specific* connective tissue disorder
    - Known family history related to a specific connective tissue disorder, if applicable
    - Conventional testing and outcomes
    - Conservative treatments, if any

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64

BACKGROUND

CONNECTIVE TISSUE DISEASES

Individuals suspected of having a systemic connective tissue disease (CTD) like Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and Ehlers-Danlos syndrome (EDS), type IV usually have multiple features that affect many different organ systems; most of these conditions can be diagnosed using clinical criteria. However, these syndromes may share 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 features found in these syndromes occur in the general population (e.g., pectus excavatum, tall stature, joint hypermobility, mitral valve prolapse, nearsightedness). The identification of the proper syndrome is important to address its manifestations and complications, including 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 (e.g., atherosclerosis). TAAs may be associated with a genetic predisposition, which can either be familial or related to defined genetic disorders or syndromes.[1]

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.[1] Some 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 CTDs associated with a risk of TAAD include Ehlers-Danlos syndrome (EDS) type IV, Loeys-Dietz syndrome (LDS), and arterial tortuosity syndrome.

Familial TAAD refers to patients with a family history of aneurysmal disease who do not meet criteria for a CTD.

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.[2] 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 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. With proper management, the life expectancy of a person with MFS can approximate that of the general population.

Diagnosis

The diagnosis of MFS is mainly clinical and based on the characteristic findings in multiple organ systems and family history.[3] The Ghent criteria, revised in 2010, are used for the clinical diagnosis of MFS.[3] The previous Ghent criteria had been criticized for taking insufficient account of the age-dependent nature of some of the 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 patient cohort studies and expert opinions.[3] The revised criteria include several major changes, as follows. More weight is given to the two 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 two 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.[3] 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.

Genetic Testing

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.[3]

FBN1 is the only gene for which pathogenic variants are known to cause classic MFS. Approximately 75% of individuals with MFS have an affected parent, while 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 (e.g., nonsense, certain missense variants, certain splice site variants, certain deletions and insertions).[2]

Most variants in the *FBN1* gene that cause MFS can be identified with sequence analysis (≈70% to 93%) and, although the yield of deletion and 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 and duplication analysis if a pathogenic variant is not identified.[2] However, the use of genetic testing for a diagnosis of MFS has limitations. More than 90% of pathogenic variants 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 when interpreting the identification of an *FBN1* variant, because other conditions with phenotypes that overlap with MFS can have an *FBN1* variant (e.g., MASS syndrome, familial mitral valve prolapse syndrome, SGS, isolated ectopia lentis).

Treatment

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.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a group of disorders that affect connective tissues and share common features characterized by skin hyperextensibility, abnormal wound healing, and joint hypermobility. The defects in connective tissues can vary from mildly loose joints to life-threatening complications. All types of EDS affect the joints and many affect the skin, but features vary by type. In 2017, the Ehlers-Danlos Society published updated classification and diagnostic parameters based on expert consensus by the International EDS Consortium.[4] The new classification recognizes 13 subtypes, wherein all but one type has a known associated gene.

The different types of EDS include, among others, types I and II (classical and classical-like types), type III (cardiac-valvular), type IV (vascular type), and type VI (arthrochalasia form), all of which are inherited in an autosomal-dominant pattern except types II and III, which are autosomal-recessive. It is estimated that affected individuals with types I, II, or IV may inherit

the pathogenic variant from an affected parent 50% of the time, and about 50% have a de novo pathogenic variant.

Most types of EDS are not associated with aortic dilation, except the vascular type (also known as type IV), which can involve serious and potentially life-threatening complications. The prevalence of the vascular type IV may affect 1 in 250,000 people. Vascular complications include rupture, aneurysm, and/or dissection of major or minor arteries. Arterial rupture may be preceded by an aneurysm, arteriovenous fistulae or dissection, or may occur spontaneously. Such complications are often unexpected and may present as sudden death, stroke, internal bleeding, and/or shock. The vascular type is also associated with an increased risk of gastrointestinal perforation, organ rupture, and rupture of the uterus during pregnancy.

Diagnosis

The clinical diagnosis of EDS type IV can be made from major and minor clinical criteria. The combination of two major criteria (arterial rupture, intestinal rupture, uterine rupture during pregnancy, family history of EDS type IV) is highly specific.[5] The presence of one or more minor clinical criteria supports the diagnosis but is insufficient to make the diagnosis by itself.

Genetic Testing

Pathogenic variants in the *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, *PLOD1*, and *TNXB* genes cause EDS. The vascular type (type IV) is caused by pathogenic variants in the *COL3A1* gene.

Loeys-Dietz Syndrome

LDS is an autosomal-dominant condition characterized by 4 major groups of clinical findings, including vascular, skeletal, craniofacial, and cutaneous manifestations. Vascular findings include cerebral, thoracic, and abdominal arterial aneurysms and/or dissections. Skeletal findings include pectus excavatum or carinatum, scoliosis, joint laxity, arachnodactyly, and talipes equinovarus. The natural history of LDS is characterized by arterial aneurysms, with a mean age of death of 26 years and a high incidence of pregnancy-related complications, including uterine rupture and death. Treatment considerations take into account that aortic dissection tends to occur at smaller aortic diameters than MFS, and the aorta and its major branches can dissect in the absence of much if any, dilation. Patients with LDS require echocardiography at frequent intervals, to monitor the status of the ascending aorta, and angiography evaluation to image the entire arterial tree.

Genetic Testing

LDS is caused by pathogenic variants in the *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD2,* and *SMAD3* genes.

Arterial Tortuosity Syndrome

Arterial tortuosity syndrome is inherited in an autosomal recessive pattern and characterized by tortuosity of the aorta and/or large- and middle-sized arteries throughout the body. Aortic root dilation, stenosis, and aneurysms of large arteries are common. Other features of the syndrome include joint laxity and skin hyperextensibility.

Genetic Testing

The syndrome is caused by pathogenic variants in the *SLC2A10* gene.

Familial TAAD

Approximately 80% of familial TAA and TAAD is inherited in an autosomal-dominant manner and may be associated with variable expression and decreased penetrance of the disease-associated variant.

The major cardiovascular manifestations of familial TAAD (fTAAD) include dilatation of the ascending thoracic aorta at the level of the sinuses of Valsalva or ascending aorta, or both, and dissections of the thoracic aorta involving ascending or descending aorta.[6] In the absence of surgical repair of the ascending aorta, affected individuals have progressive enlargement of the ascending aorta, leading to acute aortic dissection. Presentation of the aortic disease and the age of onset are highly variable.

Diagnosis

Familial TAAD is diagnosed based on the presence of thoracic aorta pathology; absence of clinical features of MFS, LDS, or vascular EDS; and a positive family history of TAAD.

Genetic Testing

Familial TAAD is associated with 16 genes, including pathogenic variants in *TGFBR1*, *TGFBR2*, *MYH11*, *ACTA2*, *MYLK*, *SMAD3*, and two loci on other chromosomes, *AAT1* and *AAT2*. Rarely, fTAAD can also be caused by *FBN1* pathogenic variants. To date, only about 20% of fTAAD is accounted for by variants in known genes. Early prophylactic repair should be considered in individuals with confirmed pathogenic variants in the *TGFBR2* and *TGFBR1* genes and/or a family history of aortic dissection with minimal aortic enlargement.

Other Syndromes and Disorders

The following syndromes and conditions may share some of the features of the above CTDs, however, the list is not exhaustive.

Congenital Contractural Arachnodactyly (Beal Syndrome)

Congenital contractural arachnodactyly is an autosomal-dominant condition characterized by a Marfan-like appearance and long, slender toes and fingers.[2] Other features may include “crumpled” ears, contractures of the knees and ankles at birth with improvement over time, camptodactyly, hip contractures, and progressive kyphoscoliosis. Mild dilatation of the aorta is rarely present. Congenital contractural arachnodactyly is caused by pathogenic variants in the *FBN2* gene.

MED12-Related Disorders

The phenotypic spectrum of *MED12*-related disorders is still being defined but includes Lujan syndrome and FG syndrome type 1.[7] Lujan syndrome and FG syndrome type 1 share the clinical findings of hypotonia, cognitive impairment, and abnormalities of the corpus callosum. Individuals with Lujan syndrome share some physical features with MFS, in that they have Marfanoid features including tall and thin habitus, long hands and fingers, pectus excavatum, narrow palate, and joint hypermobility.[7] *MED12*-related disorders are inherited in an X-linked manner, with males being affected and carrier females not usually being affected.

Shprintzen-Goldberg Syndrome

Shprintzen-Goldberg syndrome is an autosomal-dominant condition characterized by a combination of major characteristics that include craniosynostosis, craniofacial findings, skeletal findings, cardiovascular findings, neurologic and brain anomalies, certain radiographic findings, and other findings.[8] *SK1* is the only gene for which pathogenic variants are known to cause Shprintzen-Goldberg syndrome.

Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency

Homocystinuria is a rare metabolic disorder inherited in an autosomal recessive manner, characterized by an increased concentration of homocysteine, a sulfur-containing amino acid, in the blood and urine. The classical type is due to a deficiency of cystathionine beta-synthase. Affected individuals appear normal at birth but develop serious complications in early childhood, usually by age 3 to 4 years. Heterozygous carriers (1/70 of the general population) have hyperhomocysteinemia without homocystinuria; however, their risk for premature cardiovascular disease is still increased.

Overlap with MFS can be extensive and includes a Marfanoid habitus with normal to tall stature, pectus deformity, scoliosis, and ectopia lentis. Central nervous system manifestations include mental retardation, seizures, cerebrovascular events, and psychiatric disorders. Patients have a tendency for intravascular thrombosis and thromboembolic events, which can be life-threatening. Early diagnosis and prophylactic medical and dietary care can decrease and even reverse some of the complications. The diagnosis depends on the measurement of cystathionine beta-synthase activity in tissue (e.g., liver biopsy, skin biopsy).

REGULATORY STATUS

Commercially available, laboratory-developed tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

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 22 genes associated with TAADs, MFS, and related disorders. The panel detects variants 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*, *TGFBR2,* and *TGFBR3.* Deletion and duplication analyses are performed for all genes on the panel except *CBS, COL5A1*, *FLNA, SMAD4*, and *TGFB3.*

Prevention Genetics offers targeted familial variants testing, as well as “Marfan syndrome and related aortopathies next generation sequencing panel” testing, which includes 38 genes.

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*.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[9] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;

2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and

3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

TESTING PATIENTS WITH SIGNS AND/OR SYMPTOMS OF A CONNECTIVE TISSUE DISEASE

The purpose of genetic testing of patients who have signs and/or symptoms of a connective tissue disease (CTD) linked to thoracic aortic aneurysms (TAAs) when a diagnosis cannot be made clinically is to confirm a diagnosis and inform management decisions such as increased surveillance of the aorta, surgical repair of the aorta, when necessary, and surveillance for multisystem involvement in syndromic forms of thoracic aortic aneurysm and dissection (TAAD).

The potentially beneficial outcomes of primary interest would be improvements in overall survival and disease-specific survival and reductions in morbid events. For example, increased surveillance of the aorta, surgical repair of the aorta, when necessary, and surveillance for multisystem involvement in syndromic forms of TAAD are initiated to detect and treat aortic aneurysms and dissections before rupture or dissection.

The potentially harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to unnecessary surveillance of the aorta and surgical repair of the aorta. False-negative test results can lead to lack of surveillance of the aorta that allows for development and subsequent rupture of an aortic aneurysm or dissection.

Analytic Validity

Evidence from multiple studies has indicated that the clinical sensitivity of genetic testing for CTDs is highly variable. This may reflect the phenotypic heterogeneity of the associated

syndromes and the silent, indolent nature of TAAD development. The true clinical specificity is uncertain because different CTDs are defined by specific disease-associated variants.

Clinical Validity

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No literature on the direct impact of genetic testing for CTDs addressed in the evidence review was identified. However, given the nature of these disorders, randomized controlled trials are not expected to occur in the near future.

Clinical Utility

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, inferences are difficult to make about clinical utility. However, there is clear clinical benefit to early detection.

Establishing a definitive diagnosis can lead to:

- treatment of manifestations of a specific syndrome,
- prevention of primary manifestations,
- prevention of secondary complications,
- impact on surveillance,
- counseling on agents and circumstances to avoid,
- evaluation of relatives at risk, including whether to follow a relative who does or does not have the familial variant,
- pregnancy management, and
- future reproductive decision making.

Often, one of the CTDs that predisposes to severe progressing features has overlapping signs and symptoms of disorders that may not predispose to more severe diease. The overlapping phenotypic features of one of the syndromes associated with TAAD, for example, might made based on clinical criteria and evidence of an autosomal-dominant inheritance pattern by family history. However, there are cases in which the diagnosis cannot be made clinically because the patient does not fulfill necessary clinical criteria, the patient has an atypical presentation, and other CTDs cannot be excluded, or the patient is a child with a family history in whom certain age-dependent manifestations of the disease have not yet developed. In these circumstances, the clinical differential diagnosis is narrow, and single-gene testing or focused panel testing may be warranted, establishing the clinical usefulness of these types of tests. However, it is important to note that the incremental benefit of expanded NGS panel testing in these situations is unknown, and the VUS rate with these NGS panels is also unknown. Also, the more disorders that are tested in a panel, the higher the VUS rate is expected to be.

TARGETED FAMILIAL VARIANT TESTING OF ASYMPTOMATIC INDIVIDUALS WITH A KNOWN FAMILIAL PATHOGENIC VARIANT ASSOCIATED CONNECTIVE TISSUE DISORDERS

Clinical Context and Test Purpose

The purpose of familial variant testing of asymptomatic individuals with a first-degree relative with a CTD is to screen for the family-specific pathogenic variant to inform management decisions (e.g., increased cancer surveillance) or to exclude asymptomatic individuals from increased surveillance of potential progressing symptoms. The following practice is being used for targeted testing of asymptomatic individuals with a first-degree relative with a CTD: standard clinical management without targeted genetic testing for a familial variant related to the known familial disorder.

The potentially beneficial outcomes of primary interest would be improvements in overall survival and disease-specific survival and reductions in morbid events. An example would be increased surveillance of the aorta, surgical repair of the aorta, when necessary, as well as surveillance for multisystem involvement in syndromic forms of TAAD. These steps are initiated to monitor the development of aortic aneurysms and dissection and potentially repair them before rupture or dissection. If targeted genetic testing for a familial variant is negative, the asymptomatic individual can be excluded from increased cancer surveillance.

The potentially harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to unnecessary surveillance and surgical repair of the aorta. False-negative test results can lead to lack of surveillance of the aorta that allows for development and subsequent rupture of aortic aneurysms or dissection.

Analytic Validity

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinical Validity

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). Same as the discussion in the previous Clinical Validity section for patients with sign and/or symptoms of a CTD.

Clinically Useful

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials. No such trials were identified. No literature on the direct impact of genetic testing for CTDs addressed in the evidence review was identified.

Evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. When a disease-associated variant of a CTD has been identified in a proband, testing of first-degree relatives can identify those who also have the familial variant and may develop the disorder. Depending on the severity of the CTD, these individuals may need initial evaluation and ongoing surveillance.

Alternatively, first-degree relatives who test negative for the familial variant could be excluded from ongoing surveillance.

Direct evidence of the clinical usefulness of familial variant testing in asymptomatic individuals is lacking. However, for first-degree relatives of individuals affected individuals with a CTD associated, in particular those that predispose to TAAD, a positive test for a familial variant confirms the diagnosis of the TAAD-associated disorder and results in ongoing surveillance of the aorta while a negative test for a familial variant potentially reduces the need for ongoing surveillance of the aorta.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF PEDIATRICS

In 2023, the American Academy of Pediatrics updated its clinical report focused on health supervision for children with Marfan syndrome.[10] 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 MEDICAL GENETICS AND GENOMICS

The American College of Medical Genetics and Genomics issued guidelines (2012) on the evaluation of adolescents or adults with some features of Marfan syndrome (MFS).[11] The guidelines recommended the following:

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

- A dilated aortic root (defined as greater than or equal to two 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 three situations:

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

The systemic features are weighted by a scoring system.

AMERICAN COLLEGE OF CARDIOLOGY AND AMERICAN HEART ASSOCIATION

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 Genetic testing for thoracic aortic disease (TAD) was addressed in the following guideline statement:[12]

"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 include the following:

- 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.

- 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 (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.

- 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.

- 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.

In 2020, the American Heart Association issued a scientific statement focused on genetic testing and its implications for the management of inherited cardiovascular diseases.[13] 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

SUMMARY

For individuals who have signs and/or symptoms of a heritable connective tissue disorder who receive testing for genes associated with these disorders, there is enough evidence to show that overall health outcomes may be improved. Confirming a diagnosis may lead to changes in clinical management. In those who do not have signs and/or symptoms of a heritable connective tissue disorder, but who have relatives with a known pathogenic variant associated with these disorders, overall health outcomes may also be improved. There is less evidence regarding this situation, yet early detection may lead to clinical management for manifestations known to develop in those with these disorders. Therefore, genetic testing for heritable connective tissue disorders may be considered medically necessary when criteria are met.

Due to a lack of research and clinical practice guidelines, individual gene and panel testing for connective tissue disorders in the absence of signs and/or symptoms of a heritable connective tissue disorder or a known pathogenic variant in the family is considered not medically necessary.

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CODES

Codes	Number	Description
CPT	81405	Molecular pathology procedure, Level 6
	81408	Molecular pathology procedure, Level 9
	81410	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
	81411	Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
HCPCS	None	

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