

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR MARFAN SYNDROME, THORACIC AORTIC ANEURYSMS AND DISSECTIONS, AND RELATED DISORDERS
POLICY NUMBER	MP 2.331

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	9/1/2024

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I. POLICY

Individual genetic testing and panels may be considered **medically necessary**, when all of the following criteria are met:

- The diagnosis in question is:
 - o Marfan syndrome, **or**
 - o Ehlers-Danlos syndrome type IV, **or**
 - o Another syndrome associated with thoracic aortic aneurysms and dissections, **or**
 - o Related disorders, **AND**
- A definitive diagnosis cannot be made using established clinical diagnostic criteria, **AND**
- Signs and/or symptoms of one of these connective tissue disorders are present, or the individual is asymptomatic, but there is a known pathogenic variant in the family causing a need to assess future disease risk, **AND**
- Genetic testing is limited to one or more of the following genes:
 - o FBN1
 - o MYH11
 - o ACTA2
 - o TGFBR1
 - o TGFBR2
 - o COL3A1
 - o LOX
 - o SMAD3
 - o TGFB2

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- o MYLK
- o PRKG1

Other genetic testing for Marfan syndrome, Ehlers-Danlos syndrome type IV, other syndromes associated with thoracic aortic aneurysms and dissections, or related conditions are considered **investigational** as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

Syndromes associated with thoracic aortic aneurysms may have established clinical criteria with major and minor criteria (e.g., 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 a individual with a suspected connective tissue disorder is most useful in those 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 mutation is known (presymptomatic diagnosis).

Genetic testing has conventionally been used when a definitive diagnosis of one 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.

Per their 2022 Guidelines for the Diagnosis and Management of Aortic Disease, The American College of Cardiology and American Heart Association, genetic testing panels should include the 11 genes that are confirmed to confer a highly penetrant risk for thoracic aortic disease: *FBN1*, *LOX*, *COL3A1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *ACTA2*, *MYH11*, *MYLK*, and *PRKG1*.

Once patients are diagnosed with heritable thoracic aortic disease (HTAD), it is essential to identify and refer those at risk for heritable HTAD for genetic testing. Diagnosing associated genetic variants and syndromes is critical because the underlying genetics have an implication in medical management, surveillance, surgical intervention threshold, surgical risk, pregnancy

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risk, and risk of inheritance by the offspring. A panel that includes all genes known to cause HTAD is essential. Genetic counseling should always accompany genetic testing.

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

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 Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and 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—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Diseased-Assoc. Variant	Disease-associated change in the DNA sequence.
	Variant	Change in 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 of Molecular Pathology.

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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.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

<https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>.

III. DESCRIPTION/BACKGROUND

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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.

CONNECTIVE TISSUE DISEASES

Individuals suspected of having a systemic CTD like 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 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 of the features found in these syndromes occur in the general population (e.g., pectus excavatum, tall stature, joint hypermobility, mitral

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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 (e.g., 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. From a pathological perspective, patients with hereditary thoracic aortic disease (HTAD) show destructive matrix remodeling with elastin fragmentation, proliferation of vascular smooth muscle cells, and a less prominent inflammatory component without atheroma. Eleven genes are confirmed to cause a highly penetrant risk for HTAD: *FBN1*, *LOX*, *COL3A1*, *TGFBR1M*, *TGFBR2*, *SMAD3*, *TGFB2*, *ACTA2*, *MYH11*, *MYLK*, and *PRKG1*. Genetically related TAA accounts for approximately 5% of TAA.

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. 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.

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Diagnosis

The diagnosis of MFS is mainly clinical and based on the characteristic findings in multiple organ systems and 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 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 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.

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.

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).

Most variants in the *FBN1* gene that cause MFS can be identified with sequence analysis (~90% 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

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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 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 hyperelasticity, 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.

The different types of EDS include, among others, types I and II (classical type), type III (hypermobility type), type IV (vascular type), and type VI (kyphoscoliotic form), all of which are inherited in an autosomal dominant pattern except type VI, which is 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 50,000 to 250,000 people. Vascular complications include rupture, aneurysm, and/or dissection of major or minor arteries. Arterial rupture may be preceded by 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 2 major criteria (arterial rupture, intestinal rupture, uterine rupture during

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pregnancy, family history of EDS type IV) is highly specific. The presence of 1 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

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*, *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 Thoracic Aortic Aneurysm Dissection

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 TAAD include dilatation of the ascending thoracic aorta at the level of the sinuses of Valsalva or ascending aorta, or both, and dissections of the

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thoracic aorta involving ascending or descending aorta. 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 (fTAAD) 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 pathogenic variants in 16 genes including: *TGFBR1*, *TGFBR2*, *MYH11*, *ACTA2*, *MYLK*, *SMAD3*, and 2 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 these CTDs, but do not share the risk of TAAD.

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. 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, FG syndrome type 1 and others. Lujan syndrome and FG syndrome type 1 share the clinical findings of hypotonia, cognitive impairment, and abnormalities of the corpus callosum. *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 (SGS) is an autosomal-dominant condition characterized by a combination of major characteristics that include craniosynostosis, craniofacial findings, skeletal

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findings, cardiovascular findings, neurologic and brain anomalies, certain radiographic findings, and other findings. *SK1* is the only gene for which pathogenic variants are known to cause SGS.

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 measurement of cystathionine beta-synthase activity in tissue (e.g., liver biopsy, skin biopsy).

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 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, TGFB1, TGFB2, TNXB, and ZNF469. Deletion and duplication analyses are performed for all genes on the panel except CBS and TNXB exons 32 to 44.

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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, TGFB1, and TGFB2.

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, TGFB1, and TGFB2.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For individuals who have signs and/or symptoms of a 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 MFS has been reported to detect 90% to 93% of pathogenic variants in probands with MFS, and over 95% in EDS type IV. Direct evidence of clinical usefulness 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, 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 improve 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.

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the

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applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes								
81401	81405	81408	81410	81411	81479			

ICD-10-CM Diagnosis Code	Description
Z13.79	Encounter for screening for genetic and chromosomal anomalies
Z82.79	Family history of other congenital malformations, deformations, and chromosomal abnormalities

IX. REFERENCES

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MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR MARFAN SYNDROME, THORACIC AORTIC ANEURYSMS AND DISSECTIONS, AND RELATED DISORDERS
POLICY NUMBER	MP 2.331

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X. POLICY HISTORY

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MP 2.331	01/27/2020 Consensus Review. No change to policy statements.
	01/08/2021 Consensus Review. No change to policy statements. References updated. Added dx code Z13.79.
	05/16/2022 Minor Review. Added Ehlers-Danlos syndrome Type IV to policy statements; updated coding so 81411 is now MN; updated FEP, references.
	03/23/2023 Minor Review. Added genes (LOX, SMAD3, TGFB2, MYLK, PRKG1) to policy per ACA/AHA guidelines. Updated policy guidelines,

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	background, and references. CPT code 81410 now MN, added CPT code 81479
	03/21/2024 Consensus Review. No change to policy statement. Policy Guidelines, Background and References updated. Added CPT code 81401.

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