Test Specific Guidelines

Ehlers-Danlos Syndrome Genetic Testing

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Introduction

Ehlers-Danlos syndrome genetic testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
EDS Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
EDS Known Familial Mutation Analysis	81403

What Is Ehlers-Danlos Syndrome?

Definition

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of connective tissue disorders. Although all types of EDS affect the joints and skin, additional features vary by type.[1]

Prevalence

The combined prevalence of all types of EDS appears to be at least 1 in 5,000 individuals worldwide, with the most common being the hypermobile type.[1]

Symptoms

An unusually large range of joint movement (hypermobility) occurs with most forms of EDS, and is especially prominent in the hypermobile type.[1]

Generalized joint hypermobility is typically assessed using a 9-point scale called the Beighton criteria. Adults 50 or younger with a Beighton score of ≥5, adults older than 50 with a Beighton score ≥4, and pre-pubertal children and adolescents with a Beighton score ≥6, are considered to have generalized joint hypermobility.[2-4] In people with a Beighton score 1 point below the age-specific cut-off, a positive 5-point questionnaire result (2 or more positive answers) can be taken as evidence of generalized joint hypermobility.[4]

Generalized joint hypermobility is relatively common, occurring in 2-57% of different populations.[2]

Joint hypermobility can be a feature of other connective tissue disorders (e.g. Marfan syndrome, skeletal dysplasias, and other disorders), myopathic disorders, and other chromosomal and molecular disorders. Joint hypermobility may also occur as an isolated, nonsyndromic finding.[3]

Joint hypermobility may be asymptomatic, or associated with musculoskeletal complications such as chronic pain and disturbed proprioception. Individuals with symptomatic joint hypermobility who do not have hypermobile EDS or another identifiable cause are considered to have “hypermobility spectrum disorders (HSDs).” [3]

Six types of EDS were originally delineated in 1997.[5] In 2017, clinical criteria were updated and revised to include thirteen EDS types:[4]

Classical EDS

Classical-like EDS

Cardiac-valvular EDS

Vascular EDS

Hypermobile EDS

Arthrochalasia EDS

Dermatosparaxis EDS

Kyphoscoliotic EDS

Brittle cornea syndrome

Spondylodysplastic EDS

Musculocontractural EDS

Myopathic EDS

Periodontal EDS

Cause and Inheritance

Ehlers-Danlos syndrome may be an autosomal recessive or autosomal dominant disorder, depending on the type.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Autosomal dominant inheritance

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

The genetic basis and inheritance of the various types of EDS are summarized in the table below:[4]

EDS Type	Inheritance	Genetic basis	Protein
Classical EDS	Autosomal dominant	Major: COL5A1, COL5A2 Rare: COL1A1 c.934C>T	Type V collagen Type I collagen
Classical-like EDS	Autosomal recessive	TNXB	Tenascin XB
Cardiac valvular EDS	Autosomal recessive	COL1A2 (biallelic mutations that lead to COL1A2 NMD & absence of pro α2(I) collagen chains)	Type I collagen
Vascular EDS	Autosomal dominant	COL3A1	Type III collagen

EDS Type	Inheritance	Genetic basis	Protein
Hypermobile EDS	Autosomal dominant	Unknown	Unknown
Arthrochalasia EDS	Autosomal dominant	COL1A1 COL1A2	Type I collagen
Dermatosparaxis EDS	Autosomal recessive	ADAMTS2	ADAMTS-2
Kyphoscoliotic EDS	Autosomal recessive	PLOD1 FKBP14	LH1 FKBP22
Brittle cornea syndrome	Autosomal recessive	ZNF469 PRDM5	ZNF469 PRDM5
Spondylodysplastic EDS	Autosomal recessive	B4GALT7 B3GALT6 SLC39A13	β4GalT7 β3GalT6 ZIP13
Musculocontractural EDS	Autosomal recessive	CHST14 DSE	D4ST1 DSE
Myopathic EDS	Autosomal recessive or dominant	COL12A1	Type XII collagen
Periodontal type	Autosomal dominant	C1R C1S	C1r C1s

Diagnosis

A diagnosis of EDS can be established with the identification of a pathogenic mutation or mutations in a causative gene. Furthermore, as outlined in the guidelines and evidence section, international clinical criteria have been published.[4]

Clinical genetic testing is available for most types of EDS (see table above), and is used to confirm the final diagnosis when it is clinically suspected.[4]

>90% of individuals with classical EDS have a mutation in COL5A1 or COL5A2.[4,6]

>95% of individuals with vascular EDS have a mutation in COL3A1.[7]

Mutation detection rates for the rarer EDS types are mostly unknown.

Hypermobile EDS (hEDS) continues to require a clinical diagnosis, since the genetic etiology of this type is not yet known.[4,8]

Management

There is no cure for EDS. Management may consist of medication for pain, physical therapy, protection of joints, monitoring for and treating hypertension, and psychosocial support. Other management and screening may be indicated for commonly associated symptoms for specific types of EDS.[9]

Survival

The prognosis will depend on the type of EDS and associated symptoms. Most types of EDS do not affect life expectancy. Given the rarity of some types (such as dermatosparaxis and musculocontractural), the natural history and prognosis may not be firmly established. The severe forms of EDS (vascular and cardiac-valvular) usually affect lifespan. The kyphoscoliotic form may also affect lifespan if there are vascular symptoms and/or restrictive lung disease.[9]

Test Information

Introduction

Testing for EDS may include known familial mutation analysis, single gene analysis, and/or multigene panel testing. Known familial mutation analysis and single gene analysis are addressed by this guideline.

Known Familial Mutation (KFM) Testing

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

Next Generation Sequencing Assay

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

Multigene Panel Testing

With the availability of NGS technology, EDS genetic testing is increasingly performed as a panel test that includes multiple EDS genes. In addition, these

panels often include other hereditary connective tissue disorders with overlapping phenotypes. For information on multigene panel testing, please refer to the guideline *Hereditary Connective Tissue Disorder Testing*, as this testing is not addressed here.

Guidelines and Evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to EDS testing.

International Consortium on the Ehlers-Danlos Syndromes

According to the International Consortium on the Ehlers-Danlos Syndromes (2017):[4]

"In view of the vast genetic heterogeneity and phenotypic variability of the EDS subtypes, and the clinical overlap between many of these subtypes, but also with other hereditary connective tissue disorders, the definite diagnosis relies for all subtypes, except hEDS, on molecular confirmation with identification of (a) causative variant(s) in the respective gene."

"Molecular diagnostic strategies should rely on NGS technologies, which offer the potential for parallel sequencing of multiple genes. Targeted resequencing of a panel of genes…is a time- and cost-effective approach for the molecular diagnosis of the genetically heterogeneous EDS. When no mutation (or in case of an autosomal recessive condition only one mutation) is identified, this approach should be complemented with a copy number variant (CNV) detection strategy to identify large deletions or duplications, for example Multiplex Ligation-dependent Probe Amplification (MLPA), qPCR, or targeted array analysis."

"The diagnosis of hEDS remains clinical as there is yet no reliable or appreciable genetic etiology to test for in the vast majority of patients."

As defined in the sections below, the International Consortium developed clinical criteria for the Ehlers-Danlos syndromes.[4]

2017 International Criteria for Classical EDS

Minimal criteria suggestive for Classical EDS (cEDS):

Major criterion 1, PLUS either:

Major criterion 2, and/or

At least three minor criteria.

Major criteria for cEDS	Minor criteria for cEDS
Skin hyperextensibility and atrophic scarring Generalized joint hypermobility	Easy bruising Soft, doughy skin Skin fragility (or traumatic splitting) Molluscoid pseudotumors Subcutaneous spheroids Hernia (or history thereof) Epicanthal folds Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot) Family history of a first-degree relative who meets clinical criteria

2017 International Criteria for Classical-like EDS

Minimal criteria suggestive for Classical-like EDS (clEDS):

All three major criteria, AND

A family history compatible with autosomal recessive transmission.

Major criteria for clEDS	Minor criteria for clEDS
Skin hyperextensibility, with velvety skin texture and absence of atrophic scarring Generalized joint hypermobility with or without recurrent dislocations (most commonly shoulder and ankle) Easy bruisable skin/spontaneous ecchymoses	Foot deformities: broad/plump forefoot, brachydactyly with excessive skin; pes planus; hallux valgus; piezogenic papules Edema in the legs in absence of cardiac failure Mild proximal and distal muscle weakness Axonal polyneuropathy Atrophy of muscles in hands and feet Acrogeric hands, mallet finger(s), clinodactyly, brachydactyly Vaginal/uterus/rectal prolapse

2017 International Criteria for Cardiac-Valvular EDS

Minimal criteria suggestive for Cardiac-Valvular EDS (cvEDS)

Major criterion 1, AND

A family history compatible with autosomal recessive inheritance, PLUS either:

One other major criterion, and/or

At least two minor criteria.

Major criteria for cvEDS	Minor criteria for cvEDS
Severe progressive cardiac-valvular problems (aortic valve, mitral valve) Skin involvement: skin hyperextensibility, atrophic scars, thin skin, easy bruising Joint hypermobility (generalized or restricted to small joints)	Inguinal hernia Pectus deformity (especially pectus excavatum) Joint dislocations Foot deformities: pes planus, pes planovalgus, hallux valgus

2017 International Criteria for Vascular EDS

Minimal criteria suggestive for Vascular EDS (vEDS):

A family history of the disorder, and/or

Arterial rupture or dissection in individuals less than 40 years of age, and/or

Unexplained sigmoid colon rupture, and/or

Spontaneous pneumothorax in the presence of other features consistent with vEDS, and/or

A combination of the other minor clinical features listed below.

Major criteria for vEDS	Minor criteria for vEDS
Family history of vEDS with documented causative variant in COL3A1 Arterial rupture at a young age Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma	Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back Thin, translucent skin with increased venous visibility Characteristic facial appearance Spontaneous pneumothorax Acrogeria Talipes equinovarus Congenital hip dislocation Hypermobility of small joints Tendon and muscle rupture Keratoconus Gingival recession and gingival fragility Early onset varicose veins (under 30 and nulliparous if female)

2017 International Criteria for Hypermobile EDS

Diagnosis of Hypermobile EDS (hEDS) requires the simultaneous presence of criteria 1 AND 2 AND 3:

Criteria 1: Generalized joint hypermobility

Criterion 2: Two or more among the features (A-C) listed in the table below must be present (for example: A and B; A and C; B and C; A and B and C).

Criterion 3: All of the following prerequisites must be met:

Absence of unusual skin fragility, and

Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions, and

Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity.

Feature A	Feature B	Feature C
A total of 5 must be present: Unusually soft or velvety skin Mild skin hyperextensibility Unexplained striae Bilateral piezogenic papules of the heel Recurrent or multiple abdominal hernia(s) Atrophic scarring involving at least two sites Pelvic floor, rectal, and/or uterine prolapes in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition Dental crowding and high or narrow palate Arachnodactyly Arm span-to-height ≥ 1.05 Mitral valve prolapse (MVP) Aortic root dilatation with Z-score > +2	Positive family history, with one or more first degree relatives independently meeting the current diagnostic criteria for hEDS.	Must have at least one Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months. Chronic, widespread pain for ≥ 3 months Recurrent joint dislocations or frank joint instability, in the absence of trauma: Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times, or Medical confirmation of joint instability at two or more sites not related to trauma

2017 International Criteria for Arthrochalasia EDS

Minimal criteria suggestive for Arthrochalasia EDS (aEDS):

Major criterion 1, PLUS either:

Major criterion 3, and/or

Major criterion 2 and at least two other minor criteria.

Major criteria for aEDS	Minor criteria for aEDS
Congenital bilateral hip dislocation Severe generalized joint hypermobility, with multiple dislocations/subluxations Skin hyperextensibility	Muscle hypotonia Kyphoscoliosis Radiologically mild osteopenia Tissue fragility, including atrophic scars Easy bruisable skin

2017 International Criteria for Dermatosparaxis EDS

Minimal criteria suggestive for Dermatosparaxis EDS (dEDS):

Major criterion 1, AND

Major criterion 2, PLUS either:

One other major criterion, and/or

Three minor criteria.

Major criteria for dEDS	Minor criteria for dEDS
Extreme skin fragility with congenital or postnatal skin tears Characteristic craniofacial features, which are evident at birth or early infancy, or evolve later in childhood Redundant, almost lax skin, with excessive skin folds at the wrist and ankles Increased palmar wrinkling Severe bruisability with a risk of subcutaneous hematomas and hemorrhage Umbilical hernia Postnatal growth retardation Short limbs, hands and feet Perinatal complications due to connective tissue fragility	Soft and doughy skin texture Skin hyperextensibility Atrophic scars Generalized joint hypermobility Complications of visceral fragility (e.g., bladder rupture, diaphragmatic rupture, rectal prolapse) Delayed motor development Osteopenia Hirsutism Tooth abnormalities Refractive errors (myopia, astigmatism) Strabismus

2017 International Criteria for Kyphoscoliotic EDS

Minimal criteria suggestive for Kyphoscoliotic EDS (kEDS):

Major criterion 1, AND

Major criterion 2, PLUS either:

Major criterion 3, and/or

Three minor criteria (either general or gene-specific criteria).

Major criteria for kEDS	Minor criteria for kEDS	Gene-specific minor criteria for kEDS
Congenital muscle hypotonia Congenital or early onset kyphoscoliosis (progressive or non-progressive) Generalized joint hypermobility with dislocations/subluxations (shoulders, hips, and knees in particular)	Skin hyperextensibility Easy bruisable skin Rupture/aneurysm of a medium-sized artery Osteopenia/osteoporosis Blue sclerae Hernia (umbilical or inguinal) Pectus deformity Marfanoid habitus Talipes equinovarus Refractive errors (myopia, hypermetropia)	PLOD1 Skin fragility (easy bruising, friable skin, poor wound healing), widened atrophic scarring Scleral and ocular fragility/rupture Microcornea Facial dysmorphology FKBP14 Congenital hearing impairment (any type) Follicular hyperkeratosis Muscle atrophy Bladder diverticula

2017 International Criteria for Brittle Cornea Syndrome

Minimal criteria suggestive for Brittle Cornea Syndrome (BCS):

Major criterion 1, PLUS either:

At least one other major criterion, and/or

Three minor criteria.

Major criteria for BCS	Minor criteria for BCS
Thin cornea, with or without rupture (central corneal thickness often <400 µm) Early onset progressive keratoconus Early onset progressive keratoglobus Blue sclerae	Enucleation or corneal scarring as a result of previous rupture Progressive loss of corneal stromal depth, especially in central cornea High myopia, with normal or moderately increased axial length Retinal detachment Deafness (often mixed, progressive, higher frequencies often more severely affected) Hypercompliant tympanic membranes Developmental dysplasia of the hip Hypotonia in infancy, usually mild if present Scoliosis Arachnodactyly Hypermobility of distal joints Pes planus, hallux valgus Mild contractures of fingers (especially fifth) Soft, velvety skin, translucent skin

2017 International Criteria for Spondylodysplastic EDS

Minimal criteria suggestive for Spondylodysplastic EDS (spEDS):

Major criterion 1, AND

Major criterion 2, PLUS

Characteristic radiographic findings and at least 3 other minor criteria (general or type-specific).

Major criteria for spEDS	Minor criteria for spEDS	Gene-specific minor criteria for spEDS
Short stature (progressive in childhood) Muscle hypotonia (ranging from severe congenital, to mild later-onset) Bowing of limbs	Skin hyperextensibility, soft, doughy skin, thin translucent skin Pes planus Delayed motor development Osteopenia Delayed cognitive development	B4GALT7 Radioulnar synostosis Bilateral elbow contractures or limited elbow movement Generalized joint hypermobility Single transverse palmar curve Characteristic craniofacial features Characteristic radiographic findings Severe hypermetropia Clouded cornea
		SLC39A13 Protuberant eyes with bluish sclerae Hands with finely wrinkled palms Atrophy of the thenar muscles, tapering fingers Hypermobility of distal joints Characteristic radiologic findings

Major criteria for spEDS	Minor criteria for spEDS	Gene-specific minor criteria for spEDS
		B3GALT6 Kyphoscoliosis (congenital or early onset, progressive) Joint hypermobility, generalized or restricted to distal joints, with joint dislocations Joint contractures (congenital or progressive) (especially hands) Peculiar fingers (slender, tapered, arachnodactyly, spatulate, with broad distal phalanges) Talipes equinovarus Characteristic craniofacial features Tooth discoloration, dysplastic teeth Characteristic radiographic findings Osteoporosis with multiple spontaneous fractures Ascending aortic aneurysm Lung hypoplasia, restrictive lung disease

2017 International Criteria for Musculocontractural EDS

Minimal criteria suggestive for Musculocontractural EDS (mcEDS):

At birth or in early childhood:

Major criterion 1, AND

Major criterion 2

In adolescence and in adulthood:

Major criterion 1, AND

Major criterion 3.

Major criteria for mcEDS	Minor criteria for mcEDS
Congenital multiple contractures, characteristically adduction-flexion contractures, and/or talipes equinovarus (clubfoot) Characteristic craniofacial features, which are evident at birth or in early infancy Characteristic cutaneous features including skin hyperextensibility, easy bruisability, skin fragility with atrophic scars, increased palmar wrinkling	Recurrent/chronic dislocations Pectus deformities (flat, excavated) Spinal deformities (scoliosis, kyphoscoliosis) Peculiar fingers (tapering, slender, cylindrical) Progressive talipes deformities (valgus, planus, cavum) Large subcutaneous hematomas Chronic constipation Colonic diverticula Pneumothorax/pneumohemothorax Nephrolithiasis/cystolithiasis Hydronephrosis Cryptorchidism in males Strabismus Refractive errors (myopia, astigmatism) Glaucoma/elevated intraocular pressure

2017 International Criteria for Myopathic EDS

Minimal criteria suggestive for Myopathic EDS (mEDS):

Major criterion 1, PLUS either:

One other major criterion and/or

Three minor criteria

Major criteria for mEDS	Minor criteria for mEDS
Congenital muscle hypotonia, and/or muscle atrophy, that improves with age Proximal joint contractures (knee, hip, and elbow) Hypermobility of distal joints	Soft, doughy skin Atrophic scarring Motor developmental delay Myopathy on muscle biopsy

2017 International Criteria for Periodontal EDS

Minimal criteria suggestive for Periodontal EDS (pEDS):

Major criterion 1, OR major criterion 2, PLUS

At least two other major criteria and one minor criterion.

Major criteria for pEDS	Minor criteria for pEDS
Severe and intractable periodontitis of early onset (childhood or adolescence) Lack of attached gingiva Pretibial plaques Family history of a first-degree relative who meets clinical criteria	Easy bruising Joint hypermobility, mostly distal joints Skin hyperextensibility and fragility, abnormal scarring (wide or atrophic) Increased rate of infections Hernias Marfanoid facial features Acrogeria Prominent vasculature

Selected Relevant Publication

An expert-authored review in 2018 stated the following regarding hEDS:

"If a patient's personal or family history is suggestive of one of the other types of EDS or another hereditary disorder of connective tissue or arterial fragility syndrome, analysis of an associated gene or multi-gene connective tissue disease panel may be appropriate. Failure to identify a pathogenic variant with such multiple gene testing reduces the likelihood of an arterial fragility syndrome, but does not completely rule it out, especially in the setting of a positive personal or family history of arterial fragility. Negative testing for an arterial fragility syndrome also does not confirm a diagnosis of EDS, hypermobility type. Therefore, such testing is not recommended in the absence of specific suggestive signs, symptoms, or family history."[8]

Criteria

Introduction

Requests for EDS testing are reviewed using the following criteria.

EDS Known Familial Mutation Analysis

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy) , AND

Previous Genetic Testing:

No previous testing that would detect the familial mutation, AND

Diagnostic Testing for an Autosomal Dominant EDS:

Known mutation identified in 1st degree biological relative. (Note: 2nd or 3rd degree relatives may be considered when 1st degree relatives are unavailable or unwilling to be tested), OR

Diagnostic Testing and Carrier Screening for an Autosomal Recessive EDS:

Known mutation(s) identified in 1st, 2nd, or 3rd degree biologic relative(s), OR

Prenatal Testing for At-Risk Pregnancies:

Family history of an autosomal dominant type of EDS with a known mutation identified in a previous child or either parent, or

Both parents carry a known mutation for an autosomal recessive type of EDS, AND

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

EDS Single Gene Analysis

Genetic Counseling:

Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

Previous Genetic Testing:

No previous sequencing of the requested gene, AND

The member does not have a known underlying cause for their symptoms (e.g. known genetic condition), AND

The member does not have a family history of a known EDS gene mutation that would explain their clinical symptoms, AND

The member meets the above 2017 minimal criteria suggestive for an EDS type associated with the requested gene test:

For COL5A1 and/or COL5A2 analysis: criteria for classical EDS met, or

For TNXB analysis: criteria for classical-like EDS met, or

For COL1A1* analysis: criteria met for one of the following EDS types:

Classical EDS, or

Vascular EDS, or

Arthrochalasia EDS, or

Member displays one or more of the following:

Arterial rupture at a young age, or

Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology, or

Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears, or

Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma, or

Member has one minor criterion for vEDS and a family history of arterial rupture, colonic rupture, uterine rupture, or carotid-cavernous sinus fistula (CCSF), OR

For COL1A2* analysis: criteria met for one of the following EDS types:

Cardiac valvular EDS, or

Arthrochalasia EDS, or

For COL3A1* analysis: criteria for vascular EDS met, or

Member displays one or more of the following:

Arterial rupture at a young age, or

Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology, or

Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears, or

Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma, or

Member has one minor criterion for vEDS and a family history of arterial rupture, colonic rupture, uterine rupture, or carotid-cavernous sinus fistula (CCSF), OR

For ADAMTS2 analysis: criteria for dermatosparaxis EDS met, or

For PLOD1 and/or FKBP14 analysis: criteria for kyphoscoliotic EDS met, or

For ZNF469 and/or PRDM5 analysis: criteria for brittle cornea syndrome met, or

For B3GALT6, B4GALT7, and/or SLC39A13 analysis: criteria for spondylodysplastic EDS met, or

For CHST14 and/or DSE analysis: criteria for musculocontractural EDS met, or

For COL12A1 analysis: criteria for myopathic EDS met, or

For C1R and/or C1S analysis: criteria for periodontal EDS met, AND

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

*** For non-EDS indications, refer to any available disorder-specific guidelines or general guidelines, *Hereditary Connective Tissue Disorder Testing*, or *Genetic Testing for Non-Cancer Conditions*, as appropriate. COL1A1 and COL1A2 are also associated with osteogenesis imperfecta, Caffey disease, and skeletal dysplasias. COL3A1 is also associated with familial thoracic aortic aneurysm and dissection (TAAD).**

For information on multigene panel testing, please refer to the guideline *Hereditary Connective Tissue Disorder Testing*, as this testing is not addressed here.

Exceptions and Other Considerations

The following are specifically non-reimbursable indications for EDS gene sequencing and deletion/duplication analysis:

Member's personal and/or family history are suggestive of hypermobile EDS or the related clinical entity, "joint hypermobility syndrome"

Isolated nonsyndromic joint hypermobility, including both asymptomatic and symptomatic forms (e.g., "hypermobility spectrum disorders")

References

Introduction

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