Ehlers-Danlos Syndrome Genetic Testing

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Introduction

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

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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

Criteria

Introduction

Requests for Ehlers-Danlos syndrome (EDS) genetic testing are reviewed using the following criteria.

EDS Known Familial Mutation Analysis

- Genetic Counseling:

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- 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
- 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 below 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 and/or AEBP1 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 Genetic Testing*, or *Genetic Testing to Diagnose 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).

Exceptions and Other Considerations

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

The following are not medically necessary indications for EDS gene sequencing and deletion/duplication analysis:

- Member's personal and/or family history are consistent with 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”)

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]

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- 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:[4,6]

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 AEBP1	Tenascin XB Aortic carboxypeptidase-like protein (ACLP)
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
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

EDS Type	Inheritance	Genetic basis	Protein
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.[4,7]
- >95% of individuals with vascular EDS have a mutation in COL3A1.[8]
- 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.[4,9,10]

Management

There is no cure for EDS. Management is focused on prevention and treatment of symptoms. This may consist of medication for pain, physical therapy, protection of joints, monitoring for and treating common complications, and psychosocial support.[11]

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.[8] The kyphoscoliotic form may also affect lifespan if there are vascular symptoms and/or restrictive lung disease.[12]

Test information

Introduction

Testing for EDS may include known familial mutation analysis and/or single gene analysis.

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.

Guidelines and evidence

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
1. Skin hyperextensibility and atrophic scarring 2. Generalized joint hypermobility	1. Easy bruising 2. Soft, doughy skin 3. Skin fragility (or traumatic splitting) 4. Molluscoid pseudotumors 5. Subcutaneous spheroids 6. Hernia (or history thereof) 7. Epicanthal folds 8. Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot) 9. 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
1. Skin hyperextensibility, with velvety skin texture and absence of atrophic scarring 2. Generalized joint hypermobility with or without recurrent dislocations (most commonly shoulder and ankle) 3. Easy bruisable skin/spontaneous ecchymoses	1. Foot deformities: broad/plump forefoot, brachydactyly with excessive skin; pes planus; hallux valgus; piezogenic papules 2. Edema in the legs in absence of cardiac failure 3. Mild proximal and distal muscle weakness 4. Axonal polyneuropathy 5. Atrophy of muscles in hands and feet 6. Acrogeric hands, mallet finger(s), clinodactyly, brachydactyly 7. 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
1. Severe progressive cardiac-valvular problems (aortic valve, mitral valve) 2. Skin involvement: skin hyperextensibility, atrophic scars, thin skin, easy bruising 3. Joint hypermobility (generalized or restricted to small joints)	1. Inguinal hernia 2. Pectus deformity (especially pectus excavatum) 3. Joint dislocations 4. 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
1. Family history of vEDS with documented causative variant in COL3A1 2. Arterial rupture at a young age 3. Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology 4. Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears 5. Carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma	1. Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back 2. Thin, translucent skin with increased venous visibility 3. Characteristic facial appearance 4. Spontaneous pneumothorax 5. Acrogeria 6. Talipes equinovarus 7. Congenital hip dislocation 8. Hypermobility of small joints 9. Tendon and muscle rupture 10. Keratoconus 11. Gingival recession and gingival fragility 12. 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: 1. Unusually soft or velvety skin 2. Mild skin hyperextensibility 3. Unexplained striae 4. Bilateral piezogenic papules of the heel 5. Recurrent or multiple abdominal hernia(s) 6. Atrophic scarring involving at least two sites 7. 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 8. Dental crowding and high or narrow palate 9. Arachnodactyly 10. Arm span-to-height ≥ 1.05 11. Mitral valve prolapse (MVP) 12. 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 1. Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months. 2. Chronic, widespread pain for ≥ 3 months 3. Recurrent joint dislocations or frank joint instability, in the absence of trauma: a. Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times, or b. 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
1. Congenital bilateral hip dislocation 2. Severe generalized joint hypermobility, with multiple dislocations/subluxations 3. Skin hyperextensibility	1. Muscle hypotonia 2. Kyphoscoliosis 3. Radiologically mild osteopenia 4. Tissue fragility, including atrophic scars 5. 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
1. Extreme skin fragility with congenital or postnatal skin tears 2. Characteristic craniofacial features, which are evident at birth or early infancy, or evolve later in childhood 3. Redundant, almost lax skin, with excessive skin folds at the wrist and ankles 4. Increased palmar wrinkling 5. Severe bruisability with a risk of subcutaneous hematomas and hemorrhage 6. Umbilical hernia 7. Postnatal growth retardation 8. Short limbs, hands and feet 9. Perinatal complications due to connective tissue fragility	1. Soft and doughy skin texture 2. Skin hyperextensibility 3. Atrophic scars 4. Generalized joint hypermobility 5. Complications of visceral fragility (e.g., bladder rupture, diaphragmatic rupture, rectal prolapse) 6. Delayed motor development 7. Osteopenia 8. Hirsutism 9. Tooth abnormalities 10. Refractive errors (myopia, astigmatism) 11. 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
1. Congenital muscle hypotonia 2. Congenital or early onset kyphoscoliosis (progressive or non-progressive) 3. Generalized joint hypermobility with dislocations/subluxations (shoulders, hips, and knees in particular)	1. Skin hyperextensibility 2. Easy bruisable skin 3. Rupture/aneurysm of a medium-sized artery 4. Osteopenia/ osteoporosis 5. Blue sclerae 6. Hernia (umbilical or inguinal) 7. Pectus deformity 8. Marfanoid habitus 9. Talipes equinovarus 10. Refractive errors (myopia, hypermetropia)	PLOD1 1. Skin fragility (easy bruising, friable skin, poor wound healing), widened atrophic scarring 2. Scleral and ocular fragility/rupture 3. Microcornea 4. Facial dysmorphology FKBP14 1. Congenital hearing impairment (any type) 2. Follicular hyperkeratosis 3. Muscle atrophy 4. 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
1. Thin cornea, with or without rupture (central corneal thickness often <400 µm) 2. Early onset progressive keratoconus 3. Early onset progressive keratoglobus 4. Blue sclerae	1. Enucleation or corneal scarring as a result of previous rupture 2. Progressive loss of corneal stromal depth, especially in central cornea 3. High myopia, with normal or moderately increased axial length 4. Retinal detachment 5. Deafness (often mixed, progressive, higher frequencies often more severely affected) 6. Hypercompliant tympanic membranes 7. Developmental dysplasia of the hip 8. Hypotonia in infancy, usually mild if present 9. Scoliosis 10. Arachnodactyly 11. Hypermobility of distal joints 12. Pes planus, hallux valgus 13. Mild contractures of fingers (especially fifth) 14. 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
1. Short stature (progressive in childhood) 2. Muscle hypotonia (ranging from severe congenital, to mild later-onset) 3. Bowing of limbs	1. Skin hyperextensibility, soft, doughy skin, thin translucent skin 2. Pes planus 3. Delayed motor development 4. Osteopenia 5. Delayed cognitive development	B4GALT7 1. Radioulnar synostosis 2. Bilateral elbow contractures or limited elbow movement 3. Generalized joint hypermobility 4. Single transverse palmar curve 5. Characteristic craniofacial features 6. Characteristic radiographic findings 7. Severe hypermetropia 8. Clouded cornea
		SLC39A13 1. Protuberant eyes with bluish sclerae 2. Hands with finely wrinkled palms 3. Atrophy of the thenar muscles, tapering fingers 4. Hypermobility of distal joints 5. Characteristic radiologic findings

Major criteria for spEDS	Minor criteria for spEDS	Gene-specific minor criteria for spEDS
		B3GALT6 1. Kyphoscoliosis (congenital or early onset, progressive) 2. Joint hypermobility, generalized or restricted to distal joints, with joint dislocations 3. Joint contractures (congenital or progressive) (especially hands) 4. Peculiar fingers (slender, tapered, arachnodactyly, spatulate, with broad distal phalanges) 5. Talipes equinovarus 6. Characteristic craniofacial features 7. Tooth discoloration, dysplastic teeth 8. Characteristic radiographic findings 9. Osteoporosis with multiple spontaneous fractures Ascending aortic aneurysm 10. 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
1. Congenital multiple contractures, characteristically adduction-flexion contractures, and/or talipes equinovarus (clubfoot) 2. Characteristic craniofacial features, which are evident at birth or in early infancy 3. Characteristic cutaneous features including skin hyperextensibility, easy bruisability, skin fragility with atrophic scars, increased palmar wrinkling	1. Recurrent/chronic dislocations 2. Pectus deformities (flat, excavated) 3. Spinal deformities (scoliosis, kyphoscoliosis) 4. Peculiar fingers (tapering, slender, cylindrical) 5. Progressive talipes deformities (valgus, planus, cavum) 6. Large subcutaneous hematomas 7. Chronic constipation 8. Colonic diverticula 9. Pneumothorax/pneumohemothorax 10. Nephrolithiasis/cystolithiasis 11. Hydronephrosis 12. Cryptorchidism in males 13. Strabismus 14. Refractive errors (myopia, astigmatism) 15. 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
1. Congenital muscle hypotonia, and/or muscle atrophy, that improves with age 2. Proximal joint contractures (knee, hip, and elbow) 3. Hypermobility of distal joints	1. Soft, doughy skin 2. Atrophic scarring 3. Motor developmental delay 4. 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
1. Severe and intractable periodontitis of early onset (childhood or adolescence) 2. Lack of attached gingiva 3. Pretibial plaques 4. Family history of a first-degree relative who meets clinical criteria	1. Easy bruising 2. Joint hypermobility, mostly distal joints 3. Skin hyperextensibility and fragility, abnormal scarring (wide or atrophic) 4. Increased rate of infections 5. Hernias 6. Marfanoid facial features 7. Acrogeria 8. Prominent vasculature

Selected Relevant Publications

An expert-authored review in 2024 stated the following regarding hEDS:[9]

"No underlying genetic etiology has been identified for hEDS, and thus molecular genetic testing cannot be used to establish the diagnosis."

Recently, the Paediatric Working Group of the International Consortium on EDS and HSD developed a pediatric diagnostic framework that includes four components: generalized joint hypermobility (GJH), skin and tissue abnormalities, musculoskeletal complications, and core comorbidities. The framework supports categorization of hypermobile children into a group describing their phenotypic and symptomatic presentation. The authors do not recommend genetic testing on all children with GJH, HSD or hEDS.[10]

Note This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Ehlers-Danlos syndrome testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924