Ehlers-Danlos Syndrome Testing

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.

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<thead>
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<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
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<td>COL1A2 Sequencing</td>
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<td>COL1A2 Deletion/Duplication Analysis</td>
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<tr>
<td>COL12A1 Sequencing</td>
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<td>COL3A1 Sequencing</td>
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<td>COL3A1 Deletion/Duplication Analysis</td>
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<td>COL5A1 Sequencing</td>
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<td>COL5A1 Deletion/Duplication Analysis</td>
<td>81479</td>
</tr>
<tr>
<td>COL5A2 Sequencing</td>
<td>81479</td>
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</tbody>
</table>
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

- 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. 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).”

- 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.
- Six types of EDS were originally delineated in 1997. In 2017, clinical criteria were updated and revised to include thirteen EDS types:
  - Classical EDS
  - Classical-like EDS
  - Cardiac-valvular EDS
  - Vascular EDS
  - Hypermobile EDS
  - Arthrochalasia EDS
  - Dermatosparaxis EDS
  - Kyphoscoliotic EDS
  - Brittle cornea syndrome
  - Spondylodysplastic EDS
  - Musculocontractural type
  - Myopathic EDS
  - Periodontal EDS

**Genetics of Ehlers-Danlos Syndrome**

Genetics of EDS (summarized in the table below):

- Some EDS types follow an autosomal dominant pattern, meaning only one mutation is required to cause disease. In these cases, children, siblings, and parents of an affected person each have a 50% chance of having the same disease-causing mutation.
- Other types are autosomal recessive. Two mutations are required to cause recessive types, and usually only siblings are at risk for also being affected. There is rarely parent-to-child transmission.
<table>
<thead>
<tr>
<th>EDS Type</th>
<th>Inheritance</th>
<th>Genetic basis</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical EDS</td>
<td>Autosomal dominant</td>
<td>Major: COL5A1, COL5A2 Rare: COL1A1 c.934C&gt;T</td>
<td>Type V collagen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type I collagen</td>
</tr>
<tr>
<td>Classical-like EDS</td>
<td>Autosomal recessive</td>
<td>TNXB</td>
<td>Tenascin XB</td>
</tr>
<tr>
<td>Cardiac valvular EDS</td>
<td>Autosomal recessive</td>
<td>COL1A2 (biallelic mutations that lead to COL1A2 NMD &amp; absence of pro α2(I) collagen chains)</td>
<td>Type I collagen</td>
</tr>
<tr>
<td>Vascular EDS</td>
<td>Autosomal dominant</td>
<td>Major: COL3A1 Rare: COL1A1 c.934C&gt;T, c.1720C&gt;T, c.3227C&gt;T</td>
<td>Type III collagen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type I collagen</td>
</tr>
<tr>
<td>Hypermobile EDS</td>
<td>Autosomal dominant</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Arthrochalasia EDS</td>
<td>Autosomal dominant</td>
<td>COL1A1 COL1A2</td>
<td>Type I collagen</td>
</tr>
<tr>
<td>Dermatosparaxis EDS</td>
<td>Autosomal recessive</td>
<td>ADAMTS2</td>
<td>ADAMTS-2</td>
</tr>
<tr>
<td>Kyphoscoliotic EDS</td>
<td>Autosomal recessive</td>
<td>PLOD1 FKBP14</td>
<td>LH1 FKBP22</td>
</tr>
<tr>
<td>Brittle cornea syndrome</td>
<td>Autosomal recessive</td>
<td>ZNF469 PRDM5</td>
<td>ZNF469 PRDM5</td>
</tr>
<tr>
<td>Spondylodysplastic EDS</td>
<td>Autosomal recessive</td>
<td>B4GALT7 B3GALT6 SLC9A13</td>
<td>β4GalT7 β3GalT6 ZIP13</td>
</tr>
<tr>
<td>Musculocontractual EDS</td>
<td>Autosomal recessive</td>
<td>CHST14 DSE</td>
<td>D4ST1 DSE</td>
</tr>
<tr>
<td>Myopathic EDS</td>
<td>Autosomal recessive or dominant</td>
<td></td>
<td>COL12A1</td>
</tr>
<tr>
<td>Periodontal type</td>
<td>Autosomal dominant</td>
<td>C1R C1S</td>
<td>C1r C1s</td>
</tr>
</tbody>
</table>
Test information

- 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.\(^4\)
  - Hypermobile EDS (hEDS) continues to require a clinical diagnosis, since the genetic etiology of this type is not yet known.\(^4,8\)
- **Single gene analysis** — EDS genetic testing may be performed with Sanger sequencing or next generation sequencing (NGS). Deletion/duplication analysis may be considered. Mutation detection rates vary by type:
  - >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.
- **Multi-gene 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. Panel testing is addressed in the guideline: Hereditary Connective Tissue Disorder Testing.

Guidelines and evidence

- An expert-authored review (updated in 2018)\(^8\) states 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.”
- 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.

**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.

<table>
<thead>
<tr>
<th>Major criteria for cEDS</th>
<th>Minor criteria for cEDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Skin hyperextensibility and atrophic scarring</td>
<td>1. Easy bruising</td>
</tr>
<tr>
<td>2. Generalized joint hypermobility</td>
<td>2. Soft, doughy skin</td>
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<td></td>
<td>3. Skin fragility (or traumatic splitting)</td>
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<td></td>
<td>4. Molluscoid pseudotumors</td>
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<td></td>
<td>5. Subcutaneous spheroids</td>
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<td></td>
<td>6. Hernia (or history thereof)</td>
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<td>7. Epicanthal folds</td>
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<td></td>
<td>8. Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot)</td>
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<td></td>
<td>9. Family history of a first-degree relative who meets clinical criteria</td>
</tr>
</tbody>
</table>

**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 cIEDS

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

### Minor criteria for cIEDS

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

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### 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

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)

### Minor criteria for cvEDS

1. Inguinal hernia
2. Pectus deformity (especially pectus excavatum)
3. Joint dislocations
4. Foot deformities: pes planus, pes planovalgus, hallux valgus

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### 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

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

### Minor criteria for vEDS

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.

<table>
<thead>
<tr>
<th>Feature A</th>
<th>Feature B</th>
<th>Feature C</th>
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</thead>
<tbody>
<tr>
<td>A total of 5 must be present:</td>
<td>Positive family history, with one or more first degree relatives independently meeting the current diagnostic criteria for hEDS.</td>
<td>Must have at least one</td>
</tr>
<tr>
<td>1. Unusually soft or velvety skin</td>
<td></td>
<td>1. Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months.</td>
</tr>
<tr>
<td>2. Mild skin hyperextensibility</td>
<td></td>
<td>2. Chronic, widespread pain for ≥ 3 months</td>
</tr>
<tr>
<td>3. Unexplained striae</td>
<td></td>
<td>3. Recurrent joint dislocations or frank joint instability, in the absence of trauma:</td>
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<tr>
<td>4. Bilateral piezogenic papules of the heel</td>
<td></td>
<td>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</td>
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<tr>
<td>5. Recurrent or multiple abdominal hernia(s)</td>
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<td>b. Medical confirmation of joint instability at two or more sites not related to trauma</td>
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<tr>
<td>6. Atrophic scarring involving at least two sites</td>
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<tr>
<td>7. Pelvic floor, rectal, and/or uterine prolapses in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition</td>
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<td>8. Dental crowding and high or narrow palate</td>
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<td>9. Arachnodactyly</td>
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<td>10. Arm span-to-height ≥ 1.05</td>
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<td>11. Mitral valve prolapse (MVP)</td>
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<td>12. Aortic root dilatation with Z-score &gt; +2</td>
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</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Major criteria for aEDS</th>
<th>Minor criteria for aEDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Congenital bilateral hip dislocation</td>
<td>1. Muscle hypotonia</td>
</tr>
<tr>
<td>2. Severe generalized joint hypermobility, with multiple dislocations/subluxations</td>
<td>2. Kyphoscoliosis</td>
</tr>
<tr>
<td>3. Skin hyperextensibility</td>
<td>3. Radiologically mild osteopenia</td>
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<tr>
<td></td>
<td>4. Tissue fragility, including atrophic scars</td>
</tr>
<tr>
<td></td>
<td>5. Easy bruisable skin</td>
</tr>
</tbody>
</table>

**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  | 1. Soft and doughy skin texture  
2. Characteristic craniofacial features, which are evident at birth or early infancy, or evolve later in childhood  | 2. Skin hyperextensibility  
3. Redundant, almost lax skin, with excessive skin folds at the wrist and ankles  | 3. Atrophic scars  
4. Increased palmar wrinkling  | 4. Generalized joint hypermobility  
5. Severe bruising with a risk of subcutaneous hematomas and hemorrhage  | 5. Complications of visceral fragility (e.g., bladder rupture, diaphragmatic rupture, rectal prolapse)  
6. Umbilical hernia  | 6. Delayed motor development  
7. Postnatal growth retardation  | 7. Osteopenia  
8. Short limbs, hands and feet  | 8. Hirsutism  
9. Perinatal complications due to connective tissue fragility  | 9. Tooth abnormalities  
10. Refractive errors (myopia, astigmatism)  | 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
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)

### Minor criteria for kEDS
1. Skin hyperextensibility
2. Easy bruising 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)

### Gene-specific minor criteria for kEDS
- **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.

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### Major 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

### Minor criteria for BCS
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).
<table>
<thead>
<tr>
<th>Major criteria for spEDS</th>
<th>Minor criteria for spEDS</th>
<th>Gene-specific minor criteria for spEDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Short stature (progressive in childhood)</td>
<td>1. Skin hyperextensibility, soft, doughy skin, thin translucent skin</td>
<td>B4GALT7</td>
</tr>
<tr>
<td>2. Muscle hypotonia (ranging from severe congenital, to mild later-onset)</td>
<td>2. Pes planus</td>
<td>1. Radioulnar synostosis</td>
</tr>
<tr>
<td>3. Bowing of limbs</td>
<td>3. Delayed motor development</td>
<td>2. Bilateral elbow contractures or limited elbow movement</td>
</tr>
<tr>
<td></td>
<td>4. Osteopenia</td>
<td>3. Generalized joint hypermobility</td>
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<td></td>
<td>5. Delayed cognitive development</td>
<td>4. Single transverse palmar curve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Characteristic craniofacial features</td>
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<tr>
<td></td>
<td></td>
<td>6. Characteristic radiographic findings</td>
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<tr>
<td></td>
<td></td>
<td>7. Severe hypermetropia</td>
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<td>8. Clouded cornea</td>
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<tr>
<td></td>
<td></td>
<td>SLC39A13</td>
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<tr>
<td></td>
<td></td>
<td>1. Protuberant eyes with bluish sclerae</td>
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<tr>
<td></td>
<td></td>
<td>2. Hands with finely wrinkled palms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Atrophy of the thenar muscles, tapering fingers</td>
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<tr>
<td></td>
<td></td>
<td>4. Hypermobility of distal joints</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Characteristic radiologic findings</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Major criteria for spEDS</th>
<th>Minor criteria for spEDS</th>
<th>Gene-specific minor criteria for spEDS</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>B3GALT6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Kyphoscoliosis (congenital or early onset, progressive)</td>
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<tr>
<td></td>
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<td>2. Joint hypermobility, generalized or restricted to distal joints, with joint dislocations</td>
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<td>3. Joint contractures (congenital or progressive) (especially hands)</td>
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<td>4. Peculiar fingers (slender, tapered, arachnodactyly, spatulate, with broad distal phalanges)</td>
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<td>5. Talipes equinovarus</td>
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<td></td>
<td>6. Characteristic craniofacial features</td>
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<td></td>
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<td>7. Tooth discoloration, dysplastic teeth</td>
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<td>8. Characteristic radiographic findings</td>
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<td></td>
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<td>9. Osteoporosis with multiple spontaneous fractures Ascending aortic aneurysm</td>
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<td>10. Lung hypoplasia, restrictive lung disease</td>
</tr>
</tbody>
</table>

### 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.

<table>
<thead>
<tr>
<th>Major criteria for mcEDS</th>
<th>Minor criteria for mcEDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Congenital multiple contractures, characteristically adduction-flexion contractures, and/or talipes equinovarus (clubfoot)</td>
<td>1. Recurrent/chronic dislocations</td>
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<tr>
<td>2. Characteristic craniofacial features, which are evident at birth or in early infancy</td>
<td>2. Pectus deformities (flat, excavated)</td>
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<tr>
<td>3. Characteristic cutaneous features including skin hyperextensibility, easy bruisability, skin fragility with atrophic scars, increased palmar wrinkling</td>
<td>3. Spinal deformities (scoliosis, kyphoscoliosis)</td>
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<tr>
<td></td>
<td>4. Peculiar fingers (tapering, slender, cylindrical)</td>
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<td></td>
<td>5. Progressive talipes deformities (valgus, planus, cavum)</td>
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<td></td>
<td>6. Large subcutaneous hematomas</td>
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<td></td>
<td>7. Chronic constipation</td>
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<td>8. Colonic diverticula</td>
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<td></td>
<td>9. Pneumothorax/pneumohemothorax</td>
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<td></td>
<td>10. Nephrolithiasis/cystolithiasis</td>
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<td>11. Hydronephrosis</td>
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<td></td>
<td>12. Cryptorchidism in males</td>
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<td></td>
<td>13. Strabismus</td>
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<td>14. Refractive errors (myopia, astigmatism)</td>
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<td>15. Glaucoma/eleaved intraocular pressure</td>
</tr>
</tbody>
</table>

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 | 1. Soft, doughy skin
2. Proximal joint contractures (knee, hip, and elbow) | 2. Atrophic scarring
3. Hypermobility of distal joints | 3. Motor developmental delay
4. Myopathy on muscle biopsy | 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) | 1. Easy bruising
2. Lack of attached gingiva | 2. Joint hypermobility, mostly distal joints
3. Pretibial plaques | 3. Skin hyperextensibility and fragility, abnormal scarring (wide or atrophic)
4. Family history of a first-degree relative who meets clinical criteria | 4. Increased rate of infections
5. Hernias | 5. Hernias
7. Acrogeria | 7. Acrogeria
8. Prominent vasculature

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 of the requested gene, 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

- 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 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

  o For COL1A2* analysis: criteria met for one of the following EDS types:
    - Cardiac valvular EDS, or
    - Arthrochalasia EDS, or
  
  o For COL3A1* analysis: criteria for vascular EDS met, or
    - Member displays one or more of the following:\(^4\)
      - 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

  o For ADAMTS2 analysis: criteria for dermatosparaxis EDS met, or
  o For PLOD1 and/or FKBP14 analysis: criteria for kyphoscoliotic EDS met, or
  o For ZNF469 and/or PRDM5 analysis: criteria for brittle cornea syndrome met, or
  o For B3GALT6, B4GALT7, and/or SLC39A13 analysis: criteria for spondylodysplastic EDS met, or
  o For CHST14 and/or DSE analysis: criteria for musculocontractural EDS met, or
  o For COL12A1 analysis: criteria for myopathic EDS met, or
  o 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).

Panel testing is addressed in the guideline: *Hereditary Connective Tissue Disorder Testing*.

**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**


