Coverage Guidelines

Genetic Testing and Counseling for
Ehlers-Danlos Syndrome (EDS)

Disclaimer:
Please note that Baptist Health Plan Coverage Guidelines may be updated throughout
the year. A printed version may not be most up to date version available. The health
plan reserves the right to review and update this policy as needed. Refer to the website
to ascertain that you are utilizing the most current available version. Clinical guideline
policies are not intended to serve as treatment guidelines or treatment recommendation.
Treating providers must use their own clinical judgment in rendering care to their patient
population.

DEFINITION

Ehlers–Danlos syndrome (EDS) is a group of inherited connective tissue disorders caused by a
defect in the synthesis of collagen. EDS symptoms vary depending on the type and severity of
disease, which can range from mild to life-threatening. There is no cure, but palliative treatment
is available focusing on symptom relief and lifestyle modification as a means of preventing
injury.

There are currently six different sub groups or classifications of EDS:

- Class I/II describes Classic EDS and is characterized by recurrent joint dislocations,
  musculoskeletal abnormalities, easy bruising, hernias, rectal prolapse cervical insufficiency,
  and premature rupture of the amniotic membranes during pregnancy. Classic EDS is
  caused by mutations of the collagen genes COL5A1 and COL5A2 and is both inherited as
  an autosomal dominant disorder and occurs due to de novo mutations.

- Class III is more commonly referred to as the Hypermobility type EDS. It includes chronic or
debilitating musculoskeletal pain and ongoing joint hypermobility. Severe arthritis and other
physical limitations are common as well as fatigue, fibromyalgia, migraines, and irritable
bowel syndrome. Hypermobility is diagnosed clinically based on the presence of
characteristic symptoms. The genetic cause of this type of EDS has not been identified.

- Class IV is often referred to as Vascular and represents the most severe form of EDS,
  accounting for 5-10% of all cases. Vascular EDS poses a strong risk for arterial,
gastrointestinal, and uterine ruptures. Thin skin that bruises easily and facial features such
as thin lips and nose, a small chin and prominent eyes are common and complications
including but not limited to varicose veins, acrogeria, clubfeet, or tendon or muscle rupture.
Vascular EDS is caused by mutations of \textit{COL3A1} and is both inherited as an autosomal dominant disorder and occurs due to de novo mutations.\textsuperscript{1,2}

- Class VI is also referred to as Kyphoscoliosis is caused by a deficiency in the collagen-modifying enzyme lysis hydroxylase.
- Class VIIA/B is also known as Athrochalasia, which is characterized by abnormally weak collagen caused by a loss of exon 6.
- Class VIIIC is Dermatosparaxis is caused by a deficiency in pro-collagen I N-terminal peptidase.

EDS is a rare condition and most cases can be classified into the first three subgroups, as classes VI through VII are considered extremely rare.\textsuperscript{3,4}

**COVERAGE CRITERIA**

Genetic testing for \textbf{EDS Class I/II} performed through DNA sequencing of the \textit{COL5A1} and \textit{COL5A2} genes is medically necessary when the following criteria are met:

- Member demonstrates characteristic clinical features, which includes all the following:
  - Generalized joint hypermobility involving both small and large joints; and
  - Skin hyperextensibility; and
  - Widened atrophic papyraceous and poor wound healing; and\textsuperscript{5,6}

- Member has minor characteristics which include any of the following criteria:
  - Smooth velvety skin, or
  - Molluscoid pseudotumors, or
  - Subcutaneous spheroids, or
  - Complications of joint hypermobility, or
  - Muscle hypotonia, or
  - Delayed development, or
  - Hernias, or
  - Anal prolapse, or
  - Cervical insufficiency, or
  - Positive family history.

- Test results will directly impact treatment, and
- Member’s history, physical exam, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies does not produce a definitive diagnosis.

Genetic testing for \textbf{EDS Class III} is not currently considered medically necessary or is considered experimental / investigational because genetic testing for this classification is not proven.\textsuperscript{7,8}
Genetic testing for **EDS IV** performed through DNA sequencing of the *COL3A1* gene is **medically necessary** when the following criteria are met:

- Member is at a direct risk of inheriting syndrome or member has a family history of unexplained sudden death that is potentially consistent with catastrophic internal organ rupture in a first-degree relative, multiple second-degree relatives, and/or at <50 years of age, and

- Member demonstrates characteristic clinical features, which includes any two of the following:
  - Arterial rupture, and/or
  - Intestinal rupture, and/or
  - Uterine rupture.

- Member has minor characteristics which include **two** of the following criteria:
  - Translucent skin, and/or
  - Characteristic facial appearance including thin face, lips, and nose along with large appearing eyes, and/or
  - Acrogeria, and/or
  - Hypermobility of small joints, and/or
  - Tendon and muscle rupture, and/or
  - Talipes equinovarus, and/or
  - Early onset varicosities, and/or
  - Pneumothorax, and/or
  - Gingival recession.

- Test results will directly impact treatment, and

- Member’s history, physical exam, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies does not produce a definitive diagnosis.

Genetic testing for **EDS Class VI, Class VIIA/B, Class VIIC** is **not medically necessary** as testing methodology is unproven or unavailable given the rarity of these conditions.

**Prenatal** genetic testing for **EDS IV** is **not medically necessary** for any indication. It is considered experimental and/or investigational and knowledge of the results will not impact treatment or health outcomes.

**MEDICAL BACKGROUND**

Ehlers-Danlos syndrome (EDS) comprises a group of genetic disorders characterized by abnormalities of the connective tissues. EDS is classified into 6 different subtypes characterized by an inheritance pattern and clinical signs and symptoms. The three most common EDS types are EDS I/II, EDS IV and EDS III. The remaining EDS types are extremely rare.

Classic EDS, or EDS I/II, is an autosomal dominant genetic condition for which the cause has
been isolated to the COL5A1 and COL5A2 genes. Several studies have been published demonstrating a relationship between EDS I/II and a variant in 1 of 2 collagen type V genes: COL5A1 on the ninth chromosome and COL5A2 on the second chromosome. Mutations of these genes undermine the amount of collagen produced by the body or undermine the process of healthy collagen production. The prevalence of EDS I/II is approximately 1 in 20,000 and an estimated half of these cases have a detectable variant in either the COL5A1 or COL5A2 genes. COL5A1 or COL5A2 genes mutations can be identified as having been inherited from a parent in only half of these cases, which equates to 25% of all cases. The other half of cases seem to develop the mutation as a result of a de novo sequence variant. In other cases, no variant is detected in the COL5A1 or COL5A2 genes, indicating that another undiscovered etiology exists. More research is needed to establish a genetic cause in these cases. The current body of peer-reviewed literature demonstrates a well-described relationship between the COL5A1 and COL5A2 genes, and the use of DNA sequence testing offers diagnostic support. However, very little is available on alternative genetic etiology as well as the efficacy and clinical utility of prenatal testing. Instead, current literature focuses on case reports of unique syndrome presentation, symptom management, and pedigree analysis of families in which the disease epidemiology is prevalent.

EDS III is most commonly referred to as the Hypermobility type EDS, or EDS-HT. EDS-HT is characterized by chronic and often debilitating musculoskeletal pain as well as ongoing joint hypermobility. Severe arthritis and other physical limitations are common complications of EDS-HT. Specific diagnostic criteria known as the Beighton scale has been used as a clinical support tool for diagnosing the condition for several years. Diagnoses are made based on a score of 5 or greater on a 9-point hypermobility scale. Emerging literature has identified additional complications that may also be associated with the disease that are not included on the Beighton scale which include fatigue, fibromyalgia, migraines, and irritable bowel syndrome, which may have contributed to the under diagnosis of this disease. There is currently no objective imaging or laboratory study that provides a definitive diagnosis for EDS-HT. In fact, the genetic etiology of EDS III has not been identified.

EDS IV is the disease type universally acknowledged as the most severe, which accounts for 5-10% of all EDS cases. Also known as vascular EDS, EDS IV poses a strong risk for arterial and gastrointestinal rupture. Uterine rupture is common in pregnant women with EDS IV. The clinical features of EDS IV include thin or transparent skin with an increased susceptibility of bruising. Also, those with EDS IV often demonstrate characteristic facial features such as thin lips, thin nose, small chin, and prominent eyes. Common complications of EDS IV include varicose veins, hypermobility of the small joints, acrogeria, clubfeet, tendon or muscle rupture, spontaneous pneumothorax or hemothorax, and gingival recession. Less frequent complications include rupture of the spleen, liver, and heart. EDS IV is diagnosed clinically, and medical management includes the treatment of symptoms along with lifestyle modification to undermine the risk of vascular and organ injury. EDS IV has also been associated with the COL3A1 gene. Genetic testing for EDS IV involves the direct sequence analysis of COL3A1 coding exons and splice junctions. Negative results may be explained by further testing analyzing additional or the omission of genetic material associated with the COL3A1 gene through microarray analysis. Genetic testing might be appropriate for the diagnosis of EDS IV and at risk family relative given the life-threatening nature of the disease. EDS IV is also been evaluated as a prenatal test, although more research is needed on prenatal testing for EDS IV before the clinical value can be established.

Other rare forms of EDS include Kyphoscoliosis (Class VI), Athrochalasia (Class VIIA/B), and Dermatosparaxis (Class VIIC). These types of EDS represent extremely rare forms of the syndrome. Research demonstrating the efficacy of genetic diagnostic tests for these EDS types
is experimental and investigational given the rarity of these conditions and the unavailability of data.

REGULATORY INFORMATION

No legislative mandates were found for coverage of Hepatitis C testing in either Kentucky or Indiana. Baptist Health Plan Coverage Guidelines are created to provide members and providers with peer-reviewed, current medical information.

State and federal laws/mandates and contract language have priority over Coverage Guidelines and must be taken into consideration before eligibility for coverage is determined.

Baptist Health Plan Coverage Guidelines may or may not mirror Centers for Medicare & Medicaid Services benefits or coverage offered by any other health insurance company.

For self-funded plans, consult individual plan documents. If there is a conflict between this policy and a self-funded plan document, the provisions of the plan document will govern. In addition, coverage for Medicare Advantage members may differ. This is a result of applicable coverage statements by the Center for Medicare & Medicaid Services (CMS). The National Coverage Determinations, Local Coverage Determinations, and Local Medical Review Policies may be found at the CMS website: http://www.cms.gov. Please note that for all plans, the member’s health plan benefits that are in effect on the rendered date of service must be used in coverage determinations.

COVERAGE DETAIL

CODES INCLUDE BUT MAY NOT BE LIMITED TO THE FOLLOWING:

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<td>Unlisted molecular pathology procedure</td>
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**REFERENCES**


**SEARCH TERMS**

Arthritis
Athrochalasia
Birth
*COL3A1 gene*
*COL5A1 gene*
*COL5A2 gene*
Collagen
Counseling
Danlos
Defects
Dermatosparaxis
Ehlers
Genetics
Hereditary
Hypermobility
Inherited
Joints
Kyphoscoliosis
Musculoskeletal
Pathology
Prenatal Syndromes