

## Overview

### Useful For

Confirmation of a clinical diagnosis of Ehlers-Danlos Syndrome (EDS)

Differentiating between the different subtypes of EDS for diagnosis and management purposes

Ascertaining carrier status of family members of individuals diagnosed with EDS for genetic counseling purposes

### Genetics Test Information

This test includes next-generation sequencing with deletion/duplication (copy number variation) analysis and supplemental Sanger sequencing to evaluate for variants in the *ADAMTS2*, *ATP7A*, *CHST14*, *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, *FKBP14*, *FLNA*, *PLOD1*, and *SLC39A13* genes.

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

### Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Marfan and Related Disorders Patient Information](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

### Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing or qPCR if needed

### NY State Available

Yes

## Specimen

### Specimen Type

Varies

### Ordering Guidance

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[Targeted testing for familial variants \(also called site-specific or known mutations testing\) is available for the genes on this panel. See FMTT / Familial Mutation, Targeted Testing, Varies.](#)

**Shipping Instructions**

Specimen preferred to arrive within 96 hours of collection.

**Necessary Information**

1. [Marfan and Related Disorders Patient Information \(T636\)](#) is strongly recommended, but not required, to be filled out and sent with the specimen. This information aids in providing a more thorough interpretation of test results. Ordering providers are strongly encouraged to complete the form and send it with the specimen.

2. Include physician name and phone number with specimen.

**Specimen Required**

**Patient Preparation:** A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

**Submit only 1 of the following specimens:**

**Specimen Type:** Whole blood

**Container/Tube:** Lavender top (EDTA)

**Specimen Volume:** 3 mL

**Collection Instructions:**

1. Invert several times to mix blood.
2. Send specimen in original tube. **Do not** aliquot.

**Specimen Stability Information:** Ambient (preferred) 4 days/Refrigerated 14 days

**Specimen Type:** Extracted DNA

**Container/Tube:** 2 mL screw top tube

**Specimen Volume:** 100 mcL (microliters)

**Collection Instructions:**

1. The preferred volume is 100 mL at a concentration of 250 ng/mL.
2. Include concentration and volume on tube.

**Specimen Stability Information:** Frozen (preferred)/Ambient/Refrigerated**Forms**

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:

-[Informed Consent for Genetic Testing](#) (T576)

-[Informed Consent for Genetic Testing \(Spanish\)](#) (T826)

2. [Marfan and Related Disorders Patient Information](#) (T636) is recommended

3. If not ordering electronically, complete, print, and send a [Cardiovascular Test Request Form](#) (T724) with the specimen.

**Reject Due To**

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

**Specimen Minimum Volume**

Whole blood: 1 mL

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Varies	Varies (preferred)		

**Clinical & Interpretive****Clinical Information**

The Ehlers Danlos syndromes (EDS) are a clinically and genetically diverse group of heritable connective tissue disorders. An EDS classification system proposed by the International EDS Consortium identifies 13 subtypes of EDS, with an overall estimated prevalence of EDS between 1:5000 and 1:25,000. Over 90% of cases are either classic or hypermobile EDS (cEDS or hEDS), while less than 5% of cases are vascular EDS (vEDS). Other, rarer, subtypes of EDS also exist and are listed in the table below.

The clinical hallmarks of EDS are joint hypermobility, skin hyperextensibility, and tissue fragility. However, a variety of skin, ligament, joint, and cardiovascular features are seen across the spectrum of EDS. A clinical diagnosis of a specific subtype of EDS may be suspected based on a combination of major (a symptom present in the majority of affected individuals) and minor (a symptom of lesser diagnostic specificity that supports the diagnosis) clinical criteria. However, due to the clinical overlap between EDS subtypes and other heritable connective tissue disorders (eg, Marfan syndrome and Loeys-Dietz syndrome), a definitive diagnosis of all EDS subtypes (except EDS hypermobility type) relies on the identification of a causative variant in the appropriate gene.

Genetic variants in collagen-encoding or collagen-modifying genes have been identified as the cause of EDS in the majority of subtypes. These variants result in defects in collagen structure, processing, folding, and cross-linking. One notable exception to this is hypermobile EDS (hEDS). Hypermobile EDS is inherited in an autosomal dominant inheritance pattern, similar to cEDS and vEDS, however, the molecular basis of this condition is unknown, and a diagnosis is based on clinical criteria.

This panel also tests for variants in the *ATP7A* and *FLNA* genes, which result in X-linked conditions. Some patients with these conditions have clinical overlap with EDS.

**Table1. Genes included in this gene panel**

Gene symbol	Protein	Inheritance*	EDS Classification
<i>ADAMTS2</i>	Procollagen I N-proteinase (NPI)	AR	Dermatosparaxis EDS (dEDS) / human dermatosparaxis EDS VIIC
<i>ATP7A</i>	Copper-transporting ATPase 1	XL	Occipital horn syndrome
<i>CHST14</i>	Dermatan-4-sulfotransferase-1 (D4ST1)	AR	Musculocontractural EDS (mcEDS- <i>CHST14</i> )
<i>COL1A1</i>	Collagen alpha-1(I) chain	AD	Classical EDS (cEDS)
		AD	Vascular EDS (vEDS)
		AD	Arthrochalasia EDS (aEDS)
<i>COL1A2</i>	Collagen alpha-2(I) chain	AD	Arthrochalasia EDS (aEDS)
		AR	Cardiac valvular EDS (cvEDS)
<i>COL3A1</i>	Collagen alpha-1(III) chain	AD	Vascular EDS (vEDS)
<i>COL5A1</i>	Collagen alpha-1(V) chain	AD	Classical EDS (cEDS)
<i>COL5A2</i>	Collagen alpha-2(V) chain	AD	Classical EDS (cEDS)

<i>FKBP14</i>	Peptidyl-prolyl cis-trans isomerase FKBP14 (FK506 binding protein 14)	AR	Kyphoscoliotic EDS (kEDS- <i>FKBP14</i> )
<i>FLNA</i>	Filamin A	XL	Filamin A related EDS with periventricular nodular heterotopia
<i>PLOD1</i>	Procollagen-lysine 5-dioxygenase	AR	Kyphoscoliotic EDS (kEDS – <i>PLOD1</i> )
<i>SLC39A13</i>	Zinc transporter ZIP13	AR	Spondylodysplastic EDS (spEDS- <i>SLC39A13</i> )

\*Abbreviations: Autosomal dominant (AD), autosomal recessive (AR), X-linked (XL), Ehlers-Danlos syndrome (EDS)

### Reference Values

An interpretive report will be provided.

### Interpretation

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

### Cautions

Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a variation that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of disease.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

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For predictive testing of asymptomatic individuals, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual allows for more informative testing of at-risk individuals.

**Technical Limitations:**

Next-generation sequencing (NGS) may not detect all types of genetic variants. Additionally, rare alteration (ie, polymorphisms) may be present that could lead to false negative or positive results. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing.

If the patient has had an allogeneic blood or bone marrow transplant or a recent (ie, <6 weeks from time of sample collection) heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

**Reclassification of Variants Policy:**

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time. Consultation with a genetics professional should be considered for interpretation of this result.

A list of benign and likely benign variants detected for this patient is available from the laboratory upon request.

Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of the patient's results.

**Clinical Reference**

- [Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17\(5\):405-424](#)
- Malfait F, Francomano C, Byers P, et al: The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):8-26. doi: 10.1002/ajmg.c.31552
- Meester JAN, Verstraeten A, Schepers D, et al: Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome. Ann Cardiothorac Surg. 2017;6(6):582-594. doi: 10.21037/acs.2017.11.03
- Brady AF, Demirdas S, Fournel-Gigleux S, et al: The Ehlers-Danlos syndromes, rare types. Am J Med Genet C Semin

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Med Genet. 2017;175(1):70-115. doi: 10.1002/ajmg.c.31550

5. Bowen JM, Sobey GJ, Burrows NP, et al: Ehlers-Danlos syndrome, classical type. Am J Med Genet C Semin Med Genet. 2017;175(1):27-39. doi: 10.1002/ajmg.c.31548

6. Bursztejn AC, Baumann M, Lipsker D: Ehlers-Danlos syndrome related to FKBP14 mutations: detailed cutaneous phenotype. Clin Exp Dermatol 2017;42(1):64-67. doi: 10.1111/ced.12983

## Performance

### Method Description

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline for sequence variants and the presence of large intragenic deletions and duplications. Supplemental Sanger sequencing or qPCR may be performed occasionally in regions where NGS is insufficient for data capture or not specific enough to correctly identify a variant. Sanger sequencing or qPCR may also be used for confirmatory testing. (Unpublished Mayo method)

Genes analyzed: *ADAMTS2*, *ATP7A*, *CHST14*, *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, *FKBP14*, *FLNA*, *PLOD1*, *SLC39A13*

### PDF Report

No

### Specimen Retention Time

Extracted DNA: 2 months

### Performing Laboratory Location

Rochester

## Fees & Codes

### Test Classification

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

**CPT Code Information**

81479

81408 x 2

**LOINC® Information**

Test ID	Test Order Name	Order LOINC Value
EDSGP	Ehlers-Danlos Syndrome Gene Panel	93200-4

Result ID	Reporting Name	LOINC®
601731	Gene(s) Evaluated	48018-6
601732	Result Summary	47997-2
601733	Result Details	82939-0
601734	Interpretation	69047-9
601735	Additional Information	48767-8
601736	Method	85069-3
601737	Disclaimer	62364-5
601738	Reviewed By	18771-6