MAYO CLINIC LABORATORIES

Test Definition: CDHZ

CDH1 Full Gene Analysis

Overview

Useful For

Evaluation for patients with a personal or family history suggestive of hereditary diffuse gastric cancer (HDGC) syndrome

Establishing a diagnosis of HDGC syndrome allowing for targeted cancer surveillance based on associated risks

Identifying genetic variants associated with increased risk for HDGC syndrome allowing for predictive testing of at-risk family members

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in one gene associated with hereditary diffuse gastric cancer (HDGC) syndrome: *CDH1*. See Method Description for additional details.

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

Special Instructions

- Molecular Genetics: Inherited Cancer Syndromes Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)

Method Name

Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

For a comprehensive hereditary cancer panel that includes the *CDH1* gene, consider ordering 1 of the following tests:

-CRCGP / Hereditary Gastrointestinal Cancer Panel, Varies

-BRGYP / Hereditary Breast/Gynecologic Cancer Panel, Varies

Testing for *CDH1* gene as part of a customized panel is available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for this gene. For more information see FMTT / Familial Mutation, Targeted Testing, Varies.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

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.

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

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

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 in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing (Spanish) (T826)

2. Molecular Genetics: Inherited Cancer Syndromes Patient Information Sheet (T519) in Special Instructions

3. If not ordering electronically, complete, print, and send a Oncology Test Request (T729) with the specimen.

Reject Due To

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

Specimen Minimum Volume

See Specimen Required

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies (preferred)		

Clinical & Interpretive

Clinical Information

Germline variants in the *CDH1* gene are associated with hereditary diffuse gastric cancer (HDGC) syndrome, a rare autosomal dominant hereditary cancer syndrome representing 30% to 50% of all diffuse gastric cancer cases. HDGC syndrome is characterized by increased risk to develop diffuse (signet ring cell) gastric cancer and lobular breast cancer, with overall penetrance of this condition approaching 80%.(1-5) Colorectal cancer has been reported in individuals with germline *CDH1* variants, however, the specific lifetime risk for colorectal cancer is unknown.(1,5)

The National Comprehensive Cancer Network and the International Gastric Cancer Linkage Consortium provide recommendations regarding the medical management of individuals with hereditary diffuse gastric cancer syndrome.(1,4-5)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

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

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of further testing options, or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Insertions/deletions (indels) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller indels.

Deletion/Duplication Analysis: This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If

there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent heterologous blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants**:**
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages health care providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation:
Evaluation and categorization of variants is performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

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 periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgement.

Clinical Reference

1. Kaurah P, Huntsman DG, Adam MP, et al: Hereditary diffuse gastric cancer. In: Adams MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews (Internet). University of Washington, Seattle; 2002. Updated March 22, 2018. Accessed May 18, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1139/

2. Lindor NM, McMaster ML, Lindor CJ, Greene MH: Concise handbook of familial cancer susceptibility syndromes - second edition. J Natl Cancer Inst Monogr. 2008;(38):1-93. doi: 10.1093/jncimonographs/lgn001

3. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2020. CA Cancer J Clin. 2020 Jan;70(1):7-30

4. Blair VR, McLeod M, Carneiro F, et al: Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol. 2020 Aug;21(8):e386-e397

5. Ajani JA, D'Amico TA, Almhanna K, et al: Gastric Cancer, Version 3.2016. NCCN clinical practice guidelines in Oncology. J Natl Compr Canc Netw. 2016 Oct;14(10):1286-1312

6. 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

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions and intron/exon boundaries of the *CDH1* gene analyzed, as well as some other regions that have known pathogenic variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for insertions/deletions (indels) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the gene analyzed.

There may be regions of gene that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. The reference transcript for *CDH1* gene is NM_004360.5. Reference transcript numbers may be updated due to transcript re-versioning. Always refer to the final patient report for gene transcript information referenced at the time of testing.

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.(Unpublished Mayo method)

PDF Report

Supplemental

Specimen Retention Time

Whole Blood: 2 weeks (if available); Extracted DNA: 3 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

81406

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
CDHZ	CDH1 Full Gene Analysis	94240-9

Result ID	Reporting Name	LOINC®
614671	Test Description	62364-5
614672	Specimen	31208-2
614673	Source	31208-2
614674	Result Summary	50397-9
614675	Result	82939-0
614676	Interpretation	69047-9
614677	Resources	99622-3
614678	Additional Information	48767-8
614679	Method	85069-3
614680	Genes Analyzed	48018-6
614681	Disclaimer	62364-5
614682	Released By	18771-6