Test Definition: ENDCP

Hereditary Endocrine Cancer Panel, Varies

Overview

Useful For

Evaluating patients with a personal or family history suggestive of a hereditary endocrine tumor syndrome

Establishing a diagnosis of a hereditary endocrine tumor syndrome, allowing for targeted surveillance based on associated risks

Identifying genetic variants associated with increased risk for endocrine tumors, allowing for predictive testing and appropriate screening of at-risk family members

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 24 genes associated with hereditary endocrine cancer syndromes: *AIP, APC* (including promoters 1A and 1B)*, CDC73, CDKN1B, DICER1, FH, MAX, MEN1, NF1, PHOX2B, PRKAR1A*, *PTEN* (including promoter), *RET*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WRN*. For more information, see Method Description and Gene Selection Table.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for hereditary endocrine cancer syndromes.

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 (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Customization of this panel and single gene analysis for any gene present on this panel are 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 the genes on this panel. For more information see FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. For instructions for testing patients who have received a bone marrow transplant, call 800-533-1710.
Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Green top (Sodium heparin)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.
Specimen Stability Information: Ambient 4 days/Refrigerated 4 days/Frozen 4 days
Additional Information:
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for samples received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA are met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies:
DNA Saliva Kit High Yield (T1007)
Saliva Swab Collection Kit (T786)
Container/Tube:
Preferred: High-yield DNA saliva kit
Acceptable: Saliva swab
Specimen Volume: 1 Tube if using T1007 or 2 swabs if using T786
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient (preferred) 30 days/Refrigerated 30 days
Additional Information: Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

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. Molecular Genetics: Inherited Cancer Syndromes Patient Information (T519)
3. If not ordering electronically, complete, print, and send a Oncology Test Request (T729) with the specimen.

Specimen Minimum Volume

Whole blood: 1 mL; Saliva: See Specimen Required

Reject Due To

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

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Tumors occurring within the endocrine and neuroendocrine systems, including thyroid/parathyroid tumors, pituitary tumors, pheochromocytomas (PCC), and paragangliomas (PGL), may occasionally be caused by an underlying hereditary predisposition. Suspicion may be raised for a hereditary cause in families with a strong history of endocrine cancers, patients diagnosed with an endocrine cancer at an early age, patients with multiple primary endocrine cancer diagnoses, and patients with specific histological subtypes, such as medullary thyroid cancer.

The most common endocrine-related malignancy is thyroid cancer, with a lifetime risk of approximately 1.2%.(1,2) Papillary thyroid cancers are typically sporadic but can be seen in individuals or families with familial adenomatous polyposis (FAP) syndrome, caused by variants within the *APC* gene (cribriform-morular variant). Additionally, about 5% of cases of isolated papillary thyroid cancer cluster in a familial pattern; however, in most cases, no underlying genetic predisposition has yet been identified.(3-6)

Follicular and/or papillary thyroid cancers may be seen in families with *PTEN* hamartoma tumor syndrome (PHTS). Individuals with disease-causing *PTEN* variants have a 70-fold increased incidence of thyroid cancer compared to the general population.(7) Thyroid cancers with follicular or papillary features can also be seen in individuals with disease-causing *DICER1* variants, as well as individuals with Carney complex, which is caused by disease-causing variants within the *PRKAR1A* gene.(8,9)

Approximately 25% of cases of medullary thyroid cancer (MTC) are caused by an inherited *RET* variant.(10) Some disease-causing *RET* variants are associated with only familial MTC, while others cause a syndrome called multiple endocrine neoplasia type 2 (MEN2). Individuals with MEN2 have a high risk for MTC and may also have other tumors of the endocrine/neuroendocrine system, including PGL, PCC, and parathyroid tumors.(11)

Parathyroid and pituitary tumors may be caused by disease-causing variants within *MEN1*, *CDKN1B,* and *CDC73.* The *AIP* gene is associated with hereditary predisposition for isolated pituitary adenomas.

PCC and PGL are rare neuroendocrine tumors, 30% of which may have an underlying hereditary predisposition.(12) The genes most frequently associated with increased risk for PGL/PCC are the succinate dehydrogenase-associated genes: *SDHA, SDHAF2, SDHB, SDHC,* and *SDHD.*

Germline alterations in the *MAX* gene are typically associated with increased risk for PCC, although some individuals

have been identified with PGL. *MAX* variants occur in approximately 1% of patients with hereditary PGL/PCC syndromes.(13)

TMEM127 variants are most frequently associated with PCC and rarely PGL.(12) Alterations of *TMEM127* account for approximately 2% of individuals with hereditary PGL/PCC.(13)

Recent evidence suggests that disease-causing variants in *FH* increase risk for PGL/PCC.(14,15) Individuals with disease-causing *FH* variants also have a significantly increased risk for cutaneous or uterine leiomyomata and renal tumors.(16)

Alterations in *VHL, NF1,* and *RET* also increase risk for PGL/PCC in addition to other features and tumor types.(17)

The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with hereditary endocrine tumor syndromes.(17,18)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(19) 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 additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors 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. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

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.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

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.

Genes may be added or removed based on updated clinical relevance. For the most up to date list of genes included in this test or detailed information regarding gene-specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor at 800-533-1710.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent 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:
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare 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 are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(19) 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 judgment.

Clinical Reference

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13. Bausch B, Schiavi F, Ni Y, et al. European-American-Asian Pheochromocytoma-Paraganglioma Registry Study Group. Clinical characterization of the pheochromocytoma and paraganglioma susceptibility genes SDHA, TMEM127, MAX, and SDHAF2 for gene-informed prevention. JAMA Oncol. 2017;3(9):1204-1212
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consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing 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 deletion-insertions (delins) 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 genes analyzed.

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. For details regarding the targeted genes analyzed or specific gene regions not routinely covered see Gene Selection Table.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *AIP, APC* (including promoters 1A and 1B)*, CDC73, CDKN1B, DICER1, FH, MAX, MEN1, NF1, PHOX2B, PRKAR1A*, *PTEN* (including promoter), *RET*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WRN*

PDF Report

No

Day(s) Performed

Varies

Report Available

14 to 21 days

Specimen Retention Time

Whole blood: 2 weeks (if available); Saliva: 1 month; Extracted DNA: 3 months

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

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

CPT Code Information

81437

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
ENDCP	Hereditary Endocrine Cancer Panel	In Process

Result ID	Test Result Name	Result LOINC® Value
614707	Test Description	62364-5
614708	Specimen	31208-2
614709	Source	31208-2
614710	Result Summary	50397-9
614711	Result	82939-0
614712	Interpretation	69047-9
614713	Resources	99622-3
614714	Additional Information	48767-8
614715	Method	85069-3
614716	Genes Analyzed	48018-6
614717	Disclaimer	62364-5
614718	Released By	18771-6