MAYO CLINIC LABORATORIES

Test Definition: HPGLP

Hereditary Paraganglioma/Pheochromocytoma Panel, Varies

Overview

Useful For

Evaluating patients with a personal or family history suggestive of a hereditary paraganglioma and pheochromocytoma (PGL/PCC) syndrome

Establishing a diagnosis of a hereditary PGL/PCC, allowing for targeted surveillance based on associated risks

Identifying genetic variants associated with increased risk for PGL/PCC, 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 11 genes associated with hereditary paraganglioma and/or pheochromocytoma (PGL/PCC): *FH*, *MAX*, *NF1*, *RET*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, and *VHL*. For more information see Method Description and Targeted Genes and Methodology Details for Hereditary Paraganglioma/Pheochromocytoma Panel.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for hereditary PGL/PCC.

Special Instructions

- Molecular Genetics: Inherited Cancer Syndromes Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes and Methodology Details for Hereditary Paraganglioma/Pheochromocytoma Panel

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

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 Mutation, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

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 whole blood 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:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
2. Molecular Genetics: Inherited Cancer Syndromes Patient Information Sheet (T519)
3. If not ordering electronically, complete, print, and send a Oncology Test Request (T729) with the specimen.

Specimen Minimum Volume

1 mL

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

Paragangliomas (PGL)and pheochromocytomas (PCC) are rare neuroendocrine tumors that arise from autonomous ganglia. Tumors located within the adrenal medulla (the largest sympathetic ganglion) are called pheochromocytomas, while those that stem from either parasympathetic or sympathetic ganglia are designated paragangliomas.

PGL/PCC have a germline genetic basis in up to 30% of cases.(1) The genes implicated in hereditary PGL/PCC syndrome include *MAX*, *TMEM127, FH,* and the *SDH*x genes.

The genes most frequently associated with hereditary PGL/PCC syndromes 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.(2)

TMEM127 variants are associated most commonly with PCC and rarely PGL.(1) Alterations of *TMEM127* account for approximately 2% of individuals with hereditary PGL/PCC.(2)

Recent evidence suggests that disease-causing variants in *FH* also increase risk for PGL/PCC.(3,4) Individuals with disease-causing *FH* variants carry a significantly increased risk for cutaneous or uterine leiomyomata and renal tumors.(5)

Alterations in *VHL, NF1,* and *RET* also increase risk for PGL/PCC, in addition to other types of tumors.(6)

Disease-causing variants in the *VHL* gene are associated with a syndrome called von Hippel Lindau (VHL) syndrome. In addition to PGL/PCC, individuals with VHL syndrome are at increased risk for hemangioblastomas, renal cell carcinoma, pancreatic cysts, neuroendocrine tumors, endolymphatic sac and epididymal tumors.(7)

NF1 gene variants are associated with neurofibromatosis type I (NF1). Individuals with NF1 are at increased risk for pheochromocytomas in addition to neurofibromas and central nervous system gliomas, such as optic nerve gliomas. NF1 is also characterized by other features such as cafe-au lait macules, axillary/inguinal freckling and Lisch nodules.(8)

Disease-causing *RET* variants result in a syndrome called multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid cancer (FMTC). In addition to an increased risk for PGL/PCC, individuals with MEN2/FMTC have a very high risk of developing medullary thyroid cancer. Individuals with MEN2 may also have other features, such as primary hyperparathyroidism, mucosal neuromas, ganglioneuromatosis, and distinctive facial features.(9)

The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with hereditary PGL/PCC syndromes.(10)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(11) 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.

This test is not designed to detect low levels of mosaicism or 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 Targeted Genes and Methodology Details for Hereditary Paraganglioma/Pheochromocytoma 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.(11) 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. Else T, Greenberg S, Fishbein L: In: Adam MP, Everman DB, Mirzaa GM, et al, eds. Hereditary paraganglioma-pheochromocytoma syndromes. GeneReviews [Internet]. University of Washington, Seattle; 2008. Updated October 4, 2018. Accessed November 8, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1548/
2. 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 Sep 1;3(9):1204-1212
3. Udager AM, Magers MJ, Goerke DM, et al: The utility of *SDHB* and *FH* immunohistochemistry in patients evaluated for hereditary paraganglioma-pheochromocytoma syndromes. Hum Pathol. 2018 Jan;71:47-54
4. Castro-Vega LJ, Buffet A, De Cubas AA, et al: Germline mutations in *FH* confer predisposition to malignant pheochromocytomas and paragangliomas. Hum Mol Genet. 2014 May 1;23(9):2440-2446. doi: 10.1093/hmg/ddt639
5. Kamihara J, Schultz KA, Rana HQ: *FH* tumor predisposition syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated August 13, 2020. Accessed November 7, 2022 Available at www.ncbi.nlm.nih.gov/books/NBK1252/
6. Shah MH, Goldner WS, Halfdanarson TR et al: NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. J Natl Compr Canc Netw. 2018 Jun;16(6):693-702
7. van Leeuwaarde RS, Ahmad S, Links TP, et al: Von Hippel-Lindau syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2000. Updated September 6, 2018. Accessed

November 7, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1463/
8. Friedman JM: Neurofibromatosis 1. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated April 21, 2022. Accessed November 7, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1109/
9. Eng C: Multiple Endocrine Neoplasia Type 2. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated August 15, 2019. Accessed November 7, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1257/
10. Benn DE, Gimenez-Roqueplo AP, Reilly JR, et al: Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. J Clin Endocrinol Metab. 2006 Mar;91(3):827-836
11. 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 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-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 Targeted Genes and Methodology Details for Hereditary Paraganglioma/Pheochromocytoma.(Unpublished Mayo method)

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

Genes analyzed: *FH*, *MAX*, *NF1*, *RET*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, and *VHL*

PDF Report

Supplemental

Day(s) Performed

Varies

Test Definition: HPGLP

Hereditary Paraganglioma/Pheochromocytoma Panel, Varies

Report Available
21 days to 28 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location
Rochester

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. This test 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
HPGLP	Hereditary PGL/PCC Panel	In Process

Result ID	Test Result Name	Result LOINC® Value
614731	Test Description	62364-5
614732	Specimen	31208-2
614733	Source	31208-2
614734	Result Summary	50397-9
614735	Result	82939-0
614736	Interpretation	69047-9
614737	Resources	99622-3
614738	Additional Information	48767-8
614739	Method	85069-3
614740	Genes Analyzed	48018-6
614741	Disclaimer	62364-5
614742	Released By	18771-6