MAYO CLINIC LABORATORIES

Test Definition: HPANP

Hereditary Pancreatitis Gene Panel, Varies

Overview

Useful For

Confirming a suspected clinical diagnosis of familial or hereditary pancreatitis in patients with chronic pancreatitis

Identifying gene variants contributing to pancreatitis in an individual or family

Identifying gene variants to allow for predictive and diagnostic testing in family members

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 4 genes associated with hereditary pancreatitis (HP): *CFTR, CTRC, PRSS1,* and *SPINK1.* See Targeted Genes and Methodology Details for Hereditary Pancreatitis Gene Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for HP.

Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture testing will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes and Methodology Details for Hereditary Pancreatitis Gene Panel

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

Targeted testing for familial variants (also called site-specific or known variants testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about 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.

Submit only 1 of the following specimens:

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

Specimen Type: Skin biopsy
Supplies: Fibroblast Biopsy Transport Media (T115)
Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.
Specimen Volume: 4-mm punch
Specimen Stability Information: Refrigerated (preferred)/Ambient
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Cultured fibroblasts
Container/Tube: T-25 flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. Cultured cells from a prenatal specimen will not be accepted.
Specimen Stability Information: Ambient (preferred)/Refrigerated (<24 hours)
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic

testing can occur.

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. If not ordering electronically, complete, print, and send a Gastroenterology and Hepatology Test Request (T728) with the specimen.

Specimen Minimum Volume

Blood: 1 mL; Skin biopsy or cultured fibroblasts: 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

Hereditary pancreatitis (HP) is defined as 2 or more individuals in a family affected with pancreatitis involving at least 2 generations.(1) Variants in several genes, including *PRSS1*, *CFTR*, *CTRC*, and *SPINK1* have demonstrated genetic susceptibility to chronic pancreatitis. Disease susceptibility may be monogenic, as is the case with *PRSS1*, digenic or multigenic, and multifactorial in which multiple genes and environmental factors play a role in disease expression.

PRSS1:
The most common monogenic cause of HP is the presence of a variant in the cationic trypsinogen (*PRSS1*) gene. Variants in the *PRSS1* gene are inherited in an autosomal dominant manner. It has been reported that as many as 80% of patients with symptomatic hereditary pancreatitis have a causative *PRSS1* variant.(1) HP cannot be clinically distinguished from other forms of pancreatitis. However, *PRSS1* variants are generally restricted to individuals with a family history of pancreatitis and are infrequently found in patients with alcohol-induced pancreatitis. Although several variants have been identified, the p.R122H, p.N29I, and p.A16V variants are the most common disease-causing variants in *PRSS1* associated with HP.(2) Patients with HP are also at an increased risk for developing pancreatic cancer. Studies have estimated the lifetime risk of developing pancreatic cancer to be as high as 40%.(3)

SPINK1:
Biallelic variants in the *SPINK1* gene have been associated with increased susceptibility to chronic pancreatitis especially in families without *PRSS1* variants; however, it is unknown if biallelic variants alone are sufficient to cause chronic pancreatitis. Additionally, heterozygous *SPINK1* variants appear to modify disease severity when observed in combination with variants in other genes.(1,2,4) Unlike *PRSS1* variants, *SPINK1* variants have been associated with alcohol-induced pancreatitis.(4)

CFTR:
Pancreatitis is a known manifestation of an atypical *CFTR*-related disorder, which results from biallelic disease-causing variants in the *CFTR* gene. However, *CFTR* variants can also cooccur with variants in *CTRC*, *SPINK1*, or *CASR* to confer pancreatitis disease susceptibility.(1-4) When observed in the context of a *SPINK1* variant, for example, heterozygous variants in *CFTR* are associated with a 2- to 5-fold increased risk for pancreatitis as compared to the general population.(4)

CTRC:
Variants in *CTRC* have been observed in individuals with chronic pancreatitis in association with other risk factors, such as variants in *CFTR* or *SPINK1* or specific environmental risk factors. Thus, chronic pancreatitis may be attributable to the presence of *CTRC* variants in the context of other risk factors as opposed to *CTRC* variants alone.(1)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(5) 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 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 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. Refer to the Targeted Genes and Methodology Details for Hereditary Pancreatitis Gene Panel for the most up to date list of genes included in this test. 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 non-leukoreduced 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 health care providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

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.(5) 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.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Raphael KL, Willingham FF: Hereditary pancreatitis: current perspectives. Clin Exp Gastroenterol. 2016 Jul 26;9:197-207. doi: 10.2147/CEG.S84358

2. Suzuki M, Minowa K, Nakano S, Isayama H, Shimizu T: Genetic abnormalities in pancreatitis: An update on diagnosis, clinical features, and treatment. Diagnostics (Basel). 2020 Dec 26;11(1):31. doi: 10.3390/diagnostics11010031
3. Shelton C, LaRusch J, Whitcomb DC: Pancreatitis overview. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2014.Updated July 2, 2020. Accessed January 17, 2023.Available at www.ncbi.nlm.nih.gov/books/NBK190101/
4. Hasan A, Moscoso DI, Kastrinos F. The role of genetics in pancreatitis. Gastrointest Endosc Clin N Am. 2018 Oct;28(4):587-603.
5. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: 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 deletions/insertions (delins) less than 40 base pairs (bp), and 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.(Unpublished Mayo method)

See Targeted Genes and Methodology Details for Hereditary Pancreatitis Gene Panel for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.

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

Genes analyzed: *CFTR, CTRC, PRSS1,* and *SPINK1*

PDF Report

Supplemental

Day(s) Performed

Varies

Report Available

28 to 42 days

Specimen Retention Time

Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Cultured fibroblasts, skin biopsy: 1 month

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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81223
81404 x2
81405
81479 (if appropriate for government payers)
88223- Tissue culture, skin, solid tissue biopsy (if appropriate)
88240- Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
HPANP	Hereditary Pancreatitis Gene Panel	22070-7

Result ID	Test Result Name	Result LOINC® Value
619845	Test Description	62364-5
619846	Specimen	31208-2
619847	Source	31208-2
619848	Result Summary	50397-9
619849	Result	82939-0
619850	Interpretation	69047-9
619851	Additional Results	82939-0
619852	Resources	99622-3
619853	Additional Information	48767-8
619854	Method	85069-3
619855	Genes Analyzed	82939-0
619856	Disclaimer	62364-5
619857	Released By	18771-6