# Pancreatitis Panel

Pancreatitis is a relatively common disorder with multiple etiologies that causes inflammation in the pancreas. Acute pancreatitis (AP) is a result of sudden inflammation, and patients may present with increased pancreatic enzyme concentrations. Chronic pancreatitis (CP) is a syndrome of progressive inflammation that may lead to permanent damage to pancreatic structure and function. Genetic testing can be utilized to determine a genetic cause of idiopathic or hereditary AP or CP and/or to assess risk of disease in family members.

## Disease Overview

### Incidence/Prevalence

- Chronic pancreatitis
  - Incidence: ~4-12/100,000 per year[1]
  - Prevalence: ~37-42/100,000[1]

### Symptoms and Etiology

| | Symptoms/Presentation | Etiologies |
|---|---|---|
| AP | Sudden onset of pain in the upper abdomen, nausea and vomiting, orthostatic hypotension, confusion, and shortness of breath<br>Duration is <6 months<br>Increased concentrations of pancreatic enzymes (ie, lipase, amylase)<br>Characteristic findings of pancreatic inflammation on abdominal imaging | Most acute pancreatitis is caused by gallstones, alcohol use, hypertriglyceridemia, or is idiopathic |
| RAP | >1 episode of acute pancreatitis, separated by ≥3 months | Nonhereditary RAP and CP are typically associated with ≥1 risk factor, divided into the following TIGAR-O categories:<br>• Toxic-metabolic<br>• Idiopathic<br>• Autoimmune<br>• Recurrent or severe acute pancreatitis<br>• Obstructive<br>44-65% of CP cases are alcohol-related[1]; alcohol use and smoking are independent risk factors but together have a multiplicative effect on risk[1] |
| CP | Abdominal pain, nausea, vomiting, weight loss, diarrhea, oily stools<br>Duration is >6 months<br>At advanced stages, pain often decreases, and malabsorption and diabetes may occur<br>Patients with CP have an increased risk of pancreatic cancer after age 50 | |

RAP, recurrent acute pancreatitis

Source: Conwell, 2014[1]; Shelton, 2020[2]; Shelton, 2019[3]

## Tests to Consider

### Pancreatitis Panel (CFTR, CTRC, PRSS1, SPINK1), Sequencing 3004788

**Method:** Massively Parallel Sequencing/Sequencing

- Use for individuals with a personal history of idiopathic pancreatitis
- Use to detect sequence variants in the *CFTR*, *CTRC*, *PRSS1*, and *SPINK1* genes

**Related Tests**

### Familial Mutation, Targeted Sequencing 2001961

**Method:** Polymerase Chain Reaction/Sequencing

- Recommended test for a known familial sequence variant previously identified in a family member
- A copy of the family member's test result documenting the familial variant is required.

### Deletion/Duplication Analysis by MLPA 3003144

**Method:** Multiplex Ligation-dependent Probe Amplification

- A copy of the family member's test result is required and a control sample from the affected family member is highly recommended.
- May be ordered to assess for large deletions/duplications in a gene of interest when a previous sequencing result was not diagnostic

# Genetics

## Genes

- *CFTR* (NM_000492), *CTRC* (NM_007272), *PRSS1* (NM_002769), *SPINK1* (NM_003122)
  - 90% of individuals affected with *PRSS1*-related hereditary pancreatitis have the *PRSS1* sequence variant R122H (p.Arg122His)[4]
  - Other genes (*CLDN2*, *CPA1*, *CASR*, *CEL*, *TRPV6*) have been reported to be associated with CP but are not currently assessed at ARUP Laboratories.[2]

## Inheritance

- *PRSS1*: autosomal dominant with gain-of-function variants
- *CFTR*, *CTRC*, *SPINK1:* autosomal recessive/digenic

# Test Interpretation

## Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline.
- Sanger sequencing is performed as necessary to fill in regions of low coverage or known low quality, and in certain other situations to confirm variant calls.

## Sensitivity/Specificity

### Clinical Sensitivity

*CFTR*, *CTRC*, *PRSS1*, and *SPINK1* pathogenic variants which contribute to or explain idiopathic pancreatitis: ~48%[5]

### Analytical Sensitivity

| Variant Class | Analytical Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%) | Analytical Specificity (NPA) (%) |
|---|---|---|
| SNVs | >99 (96.9-99.4) | >99.9 |
| Deletions 1-10 bp[b] | 93.8 (84.3-98.2) | >99.9 |
| Insertions 1-10 bp[b] | 94.8 (86.8-98.5) | >99.9 |

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

[b]Variants greater than 10 bp may be detected, but the analytical sensitivity may be reduced.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

## Results

| Result | Interpretation |
|---|---|

| Result | Interpretation |
|---|---|
| Positive | One of the following:<br>• One *PRSS1* pathogenic variant or copy number variant detected<br>• Two pathogenic *CFTR*, *SPINK1*, or *CTRC* gene variants detected<br>• Two pathogenic variants detected, one in each of two different genes (digenic inheritance)<br>• One pathogenic variant detected in *CFTR*, *CTRC*, or *SPINK1* genes (may increase the risk for pancreatitis but is not causative) |
| Negative | No pathogenic variants detected in any of the genes; reduces the risk for hereditary pancreatitis but genetic etiology is not excluded |
| Uncertain | Variant(s) of uncertain clinical significance detected; may be disease-causing or benign |

## Limitations

- A negative result does not exclude a genetic etiology for pancreatitis.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted genes
  - Regulatory region and deep intronic variants other than 5T (IVS8), c.1680-886A>G (c.1679+1.6kbA>G), and c.3718-2477C>T in the *CFTR* gene
  - Large deletions/duplications in any of the tested genes
  - Variants in currently unknown genes that may be associated with pancreatitis
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Noncoding transcripts
  - Low-level somatic variants
  - Certain other variants due to technical limitations in the presence of pseudogenes or repetitive/homologous regions

## References


1. Conwell DL, Lee LS, Yadav D, et al. American Pancreatic Association practice guidelines in chronic pancreatitis: evidence-based report on diagnostic guidelines. *Pancreas*. 2014;43(8):1143-1162.

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3. Shelton C, Solomon S, LaRusch J, et al. *PRSS1*-related hereditary pancreatitis. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington, Seattle; 1993-2020. [Last Update: Apr 2019; Accessed: Feb 2022]

4. Rebours V, Boutron-Ruault MC, Schnee M, et al. The natural history of hereditary pancreatitis: a national series. *Gut*. 2009;58(1):97-103.

5. Masson E, Chen JM, Audrézet MP, et al. A conservative assessment of the major genetic causes of idiopathic chronic pancreatitis: data from a comprehensive analysis of PRSS1, SPINK1, CTRC and CFTR genes in 253 young French patients. *PLoS One*. 2013;8(8):e73522.


# Additional Resources


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LaRusch J, Whitcomb DC. Genetics of pancreatitis. *Curr Opin Gastroenterol*. 2011;27(5):467-474.

Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013;144(6):1252-1261.


# Related Information

Acute Pancreatitis
Chronic Pancreatitis

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