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
  - Prevalence: ~37-42/100,000

Symptoms and Etiology

<table>
<thead>
<tr>
<th>Symptoms/Presentation</th>
<th>Etiologies</th>
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<tbody>
<tr>
<td>AP</td>
<td>Sudden onset of pain in the upper abdomen, nausea and vomiting, orthostatic hypotension, confusion, and shortness of breath</td>
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<tr>
<td></td>
<td>Duration is &lt;6 months</td>
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<tr>
<td></td>
<td>Increased concentrations of pancreatic enzymes (ie, lipase, amylase)</td>
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<td></td>
<td>Characteristic findings of pancreatic inflammation on abdominal imaging</td>
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<tr>
<td>RAP</td>
<td>&gt;1 episode of acute pancreatitis, separated by ≥3 months</td>
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<tr>
<td>CP</td>
<td>Abdominal pain, nausea, vomiting, weight loss, diarrhea, oily stools</td>
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<tr>
<td></td>
<td>Duration is &gt;6 months</td>
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<tr>
<td></td>
<td>At advanced stages, pain often decreases, and malabsorption and diabetes may occur</td>
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<td></td>
<td>Patients with CP have an increased risk of pancreatic cancer after age 50</td>
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</tbody>
</table>

Nonhereditary RAP and CP are typically associated with ≥1 risk factor, divided into the following TIGAR-O categories:

- Toxic-metabolic
- Idiopathic
- Autoimmune
- Recurrent or severe acute pancreatitis
- Obstructive

44-65% of CP cases are alcohol-related; alcohol use and smoking are independent risk factors but together have a multiplicative effect on risk

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)
  - Other genes (**CLDN2, CPA1, CASR, CEL, TRPV6**) have been reported to be associated with CP but are not currently assessed at ARUP Laboratories.

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

Familial Targeted Sequencing 3005867

**Method:** Massively Parallel Sequencing

- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member’s test result documenting the familial gene variant is REQUIRED.
- Not all common CFTR variants are covered by this test; please see the Targeted Sequencing Gene List for detailed information regarding the limitations of sequencing.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.
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%

#### Analytical Sensitivity

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate (and 95% Credibility Region) (%)</th>
<th>Analytical Specificity (NPA) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>&gt;99 (96.9-99.4)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Deletions 1-10 bp</td>
<td>93.8 (84.3-98.2)</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Insertions 1-10 bp</td>
<td>94.8 (86.8-98.5)</td>
<td>&gt;99.9</td>
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</table>

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

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

<table>
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<tr>
<th>Result</th>
<th>Interpretation</th>
</tr>
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</table>
| Positive | One of the following:
  - One **PRSS1** pathogenic variant or copy number variant detected
  - Two pathogenic **CFTR, SPINK1, or CTRC** gene variants detected
  - Two pathogenic variants detected, one in each of two different genes (digenic inheritance)
  - 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


Additional Resources


Related Information

Acute Pancreatitis
Chronic Pancreatitis