Idiopathic and Hereditary Pancreatitis Testing

Pancreatitis is a relatively common disorder with many etiologies that causes inflammation in the pancreas. Acute pancreatitis (AP) is a result of acute inflammation, and patients 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 uncover 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
- Idiopathic chronic pancreatitis is more common than previously thought

<table>
<thead>
<tr>
<th>Symptoms/Presentation</th>
<th>Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td></td>
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<tr>
<td>Sudden onset of pain in the upper abdomen, fever, nausea and vomiting, rapid pulse</td>
<td>Common</td>
</tr>
<tr>
<td>Increased concentrations of pancreatic enzymes: lipase, amylase</td>
<td>Gallstone passage or obstruction; chronic, heavy alcohol use</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Abdominal trauma, medications, infections, tumors, genetic abnormalities, vascular abnormalities</td>
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Tests to Consider

Pancreatitis, Panel (CFTR, CTRC, PRSS1, SPINK1) Sequencing 2010876
Method: Polymerase Chain Reaction/Sequencing
Preferred test for individuals with history of idiopathic pancreatitis

Pancreatitis (CTRC) Sequencing 2010703
Method: Polymerase Chain Reaction/Sequencing
For adults with idiopathic pancreatitis if other components of panel (CFTR, PRSS1, SPINK1) have been sequenced without providing a complete explanation for the pancreatitis

Pancreatitis (PRSS1) Sequencing and Deletion/Duplication 3001768
Method: Polymerase Chain Reaction/Sequencing and Multiplex Ligation Dependent Probe Amplification
Preferred test for individuals with idiopathic pancreatitis who
- Are <20 years of age OR
- Have two affected first-degree relatives

Pancreatitis (SPINK1) Sequencing 2002012
Method: Polymerase Chain Reaction/Sequencing
For adults with idiopathic pancreatitis if other components of panel (CFTR, CTRC, PRSS1) have been sequenced without providing a complete explanation for the pancreatitis
Genetics

Genes

- **CFTR, CTRC, PRSS1, SPINK1**
- Other genes have been reported to be associated with CP but are not currently included in the ARUP test menu

Inheritance

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

Penetranve

80% in the U.S. for **PRSS1** variants R122H (p.Arg122His) and N29I (p.Asn29Ile)

Test Interpretation

Sensitivity/Specificity in Idiopathic Pancreatitis

- Clinical sensitivity for contributory or causative variants

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<tbody>
<tr>
<td>Abdominal pain, nausea, vomiting, weight loss, diarrhea, oily stools</td>
<td>Alcohol related</td>
</tr>
<tr>
<td>At advanced stages, pain often decreases, and malabsorption and diabetes may occur</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Patients with CP have up to a 40% lifetime risk for pancreatic cancer&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Other</td>
</tr>
</tbody>
</table>

Cystic Fibrosis (CFTR) Sequencing 0051110

**Method**: Polymerase Chain Reaction/Sequencing

May be used to test for variants causative for mild cystic fibrosis in individuals with idiopathic pancreatitis

Related Tests

Familial Mutation, Targeted Sequencing 2001961

**Method**: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known

Pancreatitis (PRSS1) Deletion/Duplication 3001760

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

- Second-tier test when previous full gene sequencing of **PRSS1** has been performed and is negative in individuals with idiopathic pancreatitis <20 years of age and/or two affected first-degree relatives.
- Appropriate test to order with **PRSS1** full gene sequencing for most comprehensive coverage of **PRSS1** gene.

Pancreatitis (SPINK1) Deletion/Duplication 3001764

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

Appropriate test for adults with idiopathic pancreatitis:

- When previous full gene sequencing of **SPINK1** has been performed and is negative or detects one variant
- If other components of the pancreatitis panel (**CTRC, CFTR**, and **PRSS1** genes) have been
Pancreatitis panel (CFTR, CTRC, PRSS1, SPINK1) sequencing: ~48%.
Pancreatitis (CFTR) sequencing: ~28%
Pancreatitis (SPINK1) sequencing: ~16%
Pancreatitis (PRSS1) sequencing: ~ 9%
Pancreatitis (CTRC) sequencing: ~4%
Pancreatitis (PRSS1) deletion/duplication analysis: ~6%
Pancreatitis (SPINK1) deletion/duplication analysis: unknown
Analytical sensitivity/specificity: 99%

Results

<table>
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<tr>
<th>Positive</th>
<th>Negative</th>
<th>Inconclusive</th>
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<tbody>
<tr>
<td>Single gain-of-function PRSS1 gene variant detected, OR copy number variant in PRSS1 detected</td>
<td>No pathogenic variants detected in CFTR, CTRC, PRSS1, or SPINK1 genes</td>
<td>Gene variant detected, but whether variant is pathogenic or benign is unknown</td>
</tr>
<tr>
<td>2 pathogenic CFTR, SPINK1, or CTRC gene variants detected, OR 1 pathogenic variant detected in 2 different genes (digenic inheritance) is causative for pancreatitis</td>
<td>• No genetic etiology for pancreatitis determined, but genetic etiology is not excluded</td>
<td>Consider additional testing if suspicions remain</td>
</tr>
<tr>
<td>Single pathogenic CFTR, SPINK1, or CTRC gene variant detected (increases risk for pancreatitis, but is not causative)</td>
<td></td>
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</table>

Limitations

• Large deletions/duplications, regulatory region variants, and deep intronic variants will not be detected
• Diagnostic errors can occur due to rare sequence variations
• Variants in currently unknown genes may be associated with pancreatitis

References


Related Information

Chronic Pancreatitis

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