Genetic Testing for Hereditary Pancreatitis

Description

In chronic pancreatitis (CP), recurrent attacks of acute pancreatitis evolve into a chronic inflammatory state with exocrine insufficiency, endocrine insufficiency manifested as diabetes and increased risk for pancreatic cancer. Hereditary pancreatitis (HP) is a subset of CP defined clinically as a familial pattern of CP. Variants of several genes are associated with HP. Demonstration of a pathogenic variant in one or several of these genes can potentially be used to confirm the diagnosis of HP or provide information on prognosis and management.

Genetic Determinants

PRSS1 Variants

Whitcomb (2001) discovered that disease-associated variants of protease, serine, 1 (trypsin 1) (PRSS1) on chromosome 7q35 cause HP. PRSS1 encodes cationic trypsinogen. The gain of function variants of the PRSS1gene cause HP by prematurely and excessively converting trypsinogen to trypsin, which results in pancreatic autodigestion. Between 60% and 80% of people who have a disease-associated PRSS1 variant will experience pancreatitis in their lifetimes; 30% to 40% will develop CP. Most, but not all, people with a disease-associated variant of PRSS1 will have inherited it from one of their parents. The proportion of HP caused by a de novo variant of PRSS1 is unknown. In families with two or more affected individuals in two or more generations,
genetic testing has shown that most have a demonstrable disease-associated \textit{PRSS1} variant. In 60\% to 100\%, the variant is detected by sequencing technology (Sanger or next-generation), and duplications of exons or the whole \textit{PRSS1} gene are seen in about 6\%. Two \textit{PRSS1} point variants (p.Arg122His, p.Asn29Ile) are most common, accounting for 90\% of disease-associated variants in affected individuals. Over 40 other \textit{PRSS1} sequence variants have been found, but their clinical significance is uncertain. Pathogenic \textit{PRSS1} variants are present in 10\% or less of individuals with CP.\textsuperscript{2}

Targeted analysis of exons 2 and 3, where the common disease-associated variants are found, or \textit{PRSS1} sequencing, are first-line tests, followed by duplication analysis. The general indications for \textit{PRSS1} testing and emphasis on pre- and posttest genetic counseling has remained central features of reviews and guidelines.\textsuperscript{3,4} However, several other genes have emerged as significant contributors to both HP and CP. They include the cystic fibrosis (CF) transmembrane conductance regulator (\textit{CFTR}) gene, a serine protease inhibitor, Kazal type 1 (\textit{SPINK1}) gene, chymotrypsin C (\textit{CTRC}) gene, and claudin-2 (\textit{CLDN2}) gene.

**CFTR Variants**

Autosomal recessive variants of \textit{CFTR} cause CF, a chronic disease with onset in childhood that causes severe sinopulmonary disease and numerous gastrointestinal abnormalities. The signs and symptoms of CF can vary widely. On rare occasions, an affected individual may have mild pulmonary disease, pancreatic exocrine sufficiency, and may present with acute, recurrent acute, or CP.\textsuperscript{3} Individuals with heterozygous variants of the \textit{CFTR} gene (CF carriers) have a 3- to 4-fold increased risk for CP. Individuals with 2 \textit{CFTR} pathogenic variants (homozygotes or compound heterozygotes) will benefit from CF-specific evaluations, therapies, and genetic counseling.

**SPINK Variants**

The \textit{SPINK} gene encodes a protein that binds to trypsin and thereby inhibits its activity. Variants in \textit{SPINK} are not associated with acute pancreatitis but are found, primarily as modifiers, in acute recurrent pancreatitis and seem to promote the development of CP, including for individuals with compound heterozygous variants of the \textit{CFTR} gene. Autosomal recessive familial pancreatitis may be caused by homozygous or compound heterozygous \textit{SPINK} variants.\textsuperscript{5}

**CTRC Variants**

\textit{CTRC} is important for the degradation of trypsin and trypsinogen, and 2 variants (p.R254W, p.K247\_R254del) are associated with increased risk for idiopathic CP (odds ratio, 4.6), alcoholic pancreatitis (odds ratio=4.2), and tropical pancreatitis (odds ratio=13.6).\textsuperscript{6} Tropical pancreatitis is a disease almost exclusively occurring in the setting of tropical climate and malnutrition.

**CLDN2 Variants**

\textit{CLDN2} encodes a member of the claudin protein family, which acts as an integral membrane protein at tight junctions and has tissue-specific expression. Several single nucleotide variants in \textit{CLDN2} have been associated with CP.
OBJECTIVE

The objective of this evidence review is to evaluate whether genetic testing improves the net health outcome for individuals with chronic or recurrent pancreatitis.

POLICY STATEMENT

Genetic testing for hereditary pancreatitis may be considered medically necessary for patients aged 18 years and younger with unexplained acute recurrent (>1 episode) or chronic pancreatitis with documented elevated amylase or lipase levels.

Genetic testing for hereditary pancreatitis is considered investigational in all other situations.

POLICY GUIDELINES

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td></td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Familial variant</td>
<td></td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).
FDA REGULATORY STATUS

Testing for variants associated with HP is typically done by direct sequence analysis or next-generation sequencing. A number of laboratories offer to test for the relevant genes, either individually or as panels.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic testing for HP is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who have CP or ARP who receive testing for genes associated with HP, the evidence includes cohort studies on variant detection rates and a systematic review. The relevant outcomes are symptoms, change in disease status, morbid events, and hospitalizations. There are studies on the detection rate of HP-associated genes in various populations. Few studies have enrolled patients with known HP; those doing so have reported detection rates for disease-associated variants between 52% and 62%. For other studies that tested patients with CP or ARP, disease-associated variant detection rates varied widely across studies. There is a lack of direct evidence that testing for HP improves health outcomes and insufficient indirect evidence that, in patients with CP or ARP, management would change after genetic testing in a manner likely to improve health outcomes. The evidence is insufficient to determine the effects of technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Gastroenterology

The American College of Gastroenterology (2013) guidelines on management of acute pancreatitis included the following statement: “genetic testing may be considered in young patients (<30 years old) if no cause [of acute pancreatitis] is evident, and a family history of pancreatic disease is present (conditional recommendation, low quality of evidence).”

The American College of Gastroenterology Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes (2015) recommended genetic testing of patients with suspected familial pancreatic cancer to include analysis of BRCA1/2, CDKN2A, PALB2, and ATM. Evaluation for Peutz-Jeghers Syndrome, Lynch Syndrome, and hereditary pancreatitis-associated genes should be considered if personal and/or family history criteria are met for the...
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syndrome.33

**American Pancreatic Association**

The American Pancreatic Association (2014) published Practice Guidelines in Chronic Pancreatitis: Evidence-Based Report on Diagnostic Guidelines.34 A classification guideline for the etiology of CP includes genetic mutations in PRSS1, CFTR, SPINK1, and others.

**American College of Medical Genetics and Genomics**

The American College of Medical Genetics and Genomics (2001)35 issued a policy statement on laboratory standards and guidelines for population-based cystic fibrosis carrier screening which were updated in 200436 and reaffirmed in 2013.36 These guidelines have provided recommendations on specific variant testing in cystic fibrosis, but have not specifically addressed genetic testing for suspected hereditary pancreatitis (HP).

**European Consensus Conference**

A European Consensus Conference (2001) developed guidelines for genetic testing of the PRSS1 gene, genetic counseling, and consent for genetic testing for HP.37 The indications recommended for symptomatic patients included:

“…(1) Recurrent (2 or more separate, documented episodes with hyper-amylasemia) attacks of acute pancreatitis for which there is no explanation… or (2) unexplained …chronic pancreatitis, or (3) a family history of pancreatitis in a first- degree … or second-degree …relative, or (4) … unexplained …pancreatitis occurring in a child that has required hospitalization….”

Predictive genetic testing, defined as genetic testing in an asymptomatic “at-risk” relative of an individual proven to have HP, was considered more complex. Candidates for predictive testing “must have a first-degree relative with a well-defined HP gene mutation [pathogenic variant]…” capable of informed consent, and able to “understand the (autosomal dominant) mode of inheritance and incomplete penetrance of HP mutations…”

**International Consensus Guidelines for Chronic Pancreatitis**

The working group for the International Consensus Guidelines for Chronic Pancreatitis (2018), in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group, and the European Pancreatic Club, published consensus statements on the diagnosis and management of early chronic pancreatitis.38 It included the following recommendation:

“Genetic variants are important risk factors for Early CP and can add specificity to the likely etiology, but they are neither necessary nor sufficient to make a diagnosis. (Quality assessment: moderate; Recommendation: strong; Agreement: strong)”
International Study Group of Pediatric Pancreatitis

The International Study Group of Pediatric Pancreatitis INSPIRE (The International Study Group of Pediatric Pancreatitis: In search for a cure) consortium developed an expert consensus opinion on the evaluation of children with acute recurrent and chronic pancreatitis. There was a strong consensus that search for a genetic cause of ARP or CP should include PRSS1, SPINK1, CFTR, and CTRC gene mutation testing.

American Society of Clinical Oncology

The ASCO (2018) published “Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion”. The ASCO reported that cancer-unaffected individuals should be offered genetic risk evaluation if they are: members of families with an identified pathogenic cancer susceptibility gene variant, from families that meet criteria for genetic evaluation for known hereditary syndromes that are linked to pancreatic cancer and, from families that meet criteria for familial pancreatic cancer. The ASCO further considered what surveillance strategies should be used for individuals with a predisposition to pancreatic ductal adenocarcinoma to screen for pancreatic and other cancers. Surveillance can be considered for individuals who are first-degree relatives of individuals with familial pancreatic cancer and/or individuals with a family history of pancreatic cancer who carry a pathogenic germline variant in genes associated with predisposition to pancreatic cancer.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


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### POLICY

**HISTORY - THIS POLICY WAS APPROVED BY THE FEP®**

**PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>December 2013</td>
<td>New Policy</td>
<td>Genetic testing for hereditary pancreatitis is considered investigational.</td>
</tr>
<tr>
<td>March 2015</td>
<td>Replace Policy</td>
<td>Policy updated and policy statements changed to indicate that genetic testing for hereditary pancreatitis may be considered medically necessary for children.</td>
</tr>
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</table>
| June 2018   | Replace Policy   | Policy updated with literature review through December 11, 2017; references 6-9, 10, 12-14, 20-22 and 32-33 added; references 3, and 36 updated. Policy statements unchanged. Objective statement added: The objective of this evidence review is to evaluate whether genetic testing improves the net health outcome for individuals with chronic or recurrent pancreatitis for HP. This review does not address individuals who have a familial risk (See benefit application). Summary of evidence updated to reflect policy objective/FEP benefit application for “existing

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June 2019

Replace Policy

Policy updated with literature review through January 7, 2019; references 9-10, 33, 38-40 added. Policy statements unchanged.

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