Introduction

The pancreas is an important organ behind and below the stomach. It releases enzymes to help us digest our food and also releases hormones (insulin and glucagon) to help the body control how it uses the food for energy. If the pancreas becomes inflamed, it is called pancreatitis. In some people, pancreatitis may have come on suddenly and only lasts for a short time (acute pancreatitis). Other people may have been sick with pancreatitis for a long time (chronic pancreatitis). Chronic pancreatitis may seem to run in some families, and as a result these cases may be caused by genetic problems. Genetic testing has sometimes been done to see if a person has hereditary pancreatitis. This policy discusses when genetic testing for hereditary pancreatitis may be medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Testing | Medical Necessity
--- | ---
Genetic testing for hereditary pancreatitis | Genetic testing for hereditary pancreatitis may be considered medically necessary for patients aged 18 years and younger with unexplained recurrent (greater than 1 episode) acute or chronic pancreatitis with documented elevated amylase or lipase levels.

Testing | Investigational
--- | ---
Genetic testing for hereditary pancreatitis | Genetic testing for hereditary pancreatitis is considered investigational in all other situations.

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT 81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence</td>
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| 81401 | Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant (typically using nonsequencing target variant analysis), or detection of a dynamic mutation disorder/triplet repeat)  
Includes the following tests: PRSS1 (protease, serine, 1 [trypsin 1]) (eg, hereditary pancreatitis), common variants (eg, N29I, A16V,R122H) |
| 81404 | Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)  
Includes the following tests: PRSS1 (protease, serine, 1 [trypsin 1]) (eg, hereditary pancreatitis), full gene sequence, SPINK1 (serine peptidase inhibitor, Kazal type 1) (eg, hereditary pancreatitis), full gene sequence |
| 81479 | Unlisted molecular pathology |

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Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Consideration of Age

The age described in this policy for medical necessity of genetic testing for hereditary pancreatitis is age 18 and younger. Having recurrent pancreatitis in children is not very common. The literature regarding genetic testing for hereditary pancreatitis in children is sparse. Although there is a lot of evidence, there is consensus opinion from physician medical societies that, in children with more than one episode of pancreatitis, a positive result of this genetic testing may make additional invasive testing unnecessary. See the Evidence Review section below for more detail.

Evidence Review

Description

In chronic pancreatitis (CP), recurrent attacks of acute pancreatitis evolve into a chronic inflammatory state with exocrine insufficiency, diabetes mellitus, 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 genetic variant in one or several of these genes can potentially be used to confirm the diagnosis
Background

Pancreatitis

Acute and chronic pancreatitis (CP) is caused by the premature activation of trypsinogen into trypsin within the pancreas, resulting in autodigestion, inflammation, increased levels of pancreatic enzymes in the serum, and abdominal pain. CP is defined as an ongoing inflammatory state associated with chronic/recurrent symptoms and progression to exocrine and endocrine pancreatic insufficiency.

Alcohol is the major etiologic factor in 80% of CP, which has a peak incidence in the fourth and fifth decades of life. Gall stones, hypercalcemia, inflammatory bowel disease, autoimmune pancreatitis, and peptic ulcer disease can also cause CP. About 20% of CP is idiopathic.

A small percentage of CP is categorized as hereditary pancreatitis (HP), which usually begins with recurrent episodes of acute pancreatitis in childhood and evolves into CP by age 20 years. Multiple family members may be affected over several generations, and pedigree analysis often reveals an autosomal dominant pattern of inheritance. Clinical presentation and family history alone are sometimes insufficient to distinguish between idiopathic CP and HP, especially early in the course of the disease. Individuals with HP have an estimated 40% to 55% lifetime risk of developing pancreatic cancer.¹

Genetic Determinants of Hereditary Pancreatitis (HP)

PRSS1 Variant

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 PRSS1 gene 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 2 or more affected individuals in 2 or more
generations, genetic testing has shown that most have a demonstrable disease-associated PRSS1 variant. In 60% to 100%, the variant is detected by sequencing technology (Sanger or next-generation), and duplications of exons or the whole PRSS1 gene are seen in about 6%. Two PRSS1 point variants (p.Arg122His, p.Asn29Ile) are most common, accounting for 90% of disease-associated variants in affected individuals. Over 40 other PRSS1 sequence variants have been found, but their clinical significance is uncertain. Pathogenic PRSS1 variants are present in 10% or less of individuals with CP.²

Targeted analysis of exons 2 and 3, where the common disease-associated variants are found, or PRSS1 sequencing, are first-line tests, followed by duplication analysis. The general indications for PRSS1 testing and emphasis on pre- and post-test genetic counseling have remained central features of reviews and guidelines.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 (CFTR) gene, serine peptidase inhibitor, Kazal type 1 (SPINK1) gene, chymotrypsin C (CTRC) gene, and claudin-2 (CLDN-2) gene.

**CFTR Variants**

Autosomal recessive variants of 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.³ Individuals with heterozygous variants of the CFTR gene (CF carriers) have a 3- to 4-fold increased risk for CP. Individuals with 2 CFTR variants (homozygotes or compound heterozygotes) will benefit from CF-specific evaluations, therapies, and genetic counseling.

**SPINK Variants**

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

CTRC is important for the degradation of trypsin and trypsinogen, and 2 variants (p.R254W and p.K247_R254del) are associated with an increased risk for idiopathic CP (odds ratio [OR], 4.6), alcoholic pancreatitis (OR =4.2), and tropical pancreatitis (OR =13.6).6

**CLDN2 Variants**

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 polymorphisms in CLDN2 have been associated with CP.

**Genetic Testing for Variants**

Testing for variants associated with HP is typically done by direct sequence analysis or next-generation sequencing (NGS). A number of laboratories offer testing for the relevant genes, either individually or as panels. For example, ARUP Laboratories (Salt Lake City, UT) offers a Pancreatitis Panel, which includes direct (Sanger) sequencing of CFTR, CTRC, PRSS1, and SPINK.7 Prevention Genetics (Marshfield, WI) offers a Chronic Pancreatitis Sequencing Panel, which includes NGS of 5 genes: CASR, CFTR, CTRC, PRSS1, and SPINK1.8 Ambry Genetics (Aliso Viejo, CA) offers a Pancreatitis Panel, which includes NGS of PRSS1, SPINK1, CTRC, and CFTR.8 Ambry’s PancNext™ panel for variants associated with increased risk of pancreatic cancer consists of NGS of 13 genes: APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53.10

**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. Relevant outcomes are test accuracy, 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 the technology on health outcomes.

For individuals who are asymptomatic with family members with HP who receive testing for a known familial variant associated with HP, the evidence includes a very limited number of studies. Relevant outcomes are test accuracy, symptoms, change in disease status, morbid events, and hospitalizations. No direct evidence was identified comparing outcomes in patients tested or not tested for a familial variant. It is possible that at-risk relatives who are identified with a familial variant may alter lifestyle factors (eg, diet, smoking, alcohol use), and this might delay or prevent CP onset. However, studies evaluating behavioral changes and impact on disease are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in December 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 academic medical centers (one of which provided 2 responses) and 2 specialty medical societies (one of which provided 2 responses) when this policy was under review in 2014, with specific focus on testing in children. There was consensus among reviewers that genetic testing for HP is medically necessary in children.
Practice Guidelines and Position Statements

American College of Gastroenterology

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

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics issued a policy statement on laboratory standards and guidelines for population-based cystic fibrosis (CF) carrier screening in 2001, which were updated in 2004 and reaffirmed in 2013. These guidelines have provided recommendations on specific variant testing in CF, but have not specifically addressed genetic testing for suspected hereditary pancreatitis (HP).

European Consensus Conference

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

- Recurrent (2 or more separate, documented episodes with hyperamylasemia) attacks of acute pancreatitis for which there is no explanation
- Unexplained chronic pancreatitis
- A family history of pancreatitis in a first- or second-degree relative
- Unexplained pancreatitis in a child – if recurrent or requiring 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 should be a first-degree relative of an individual with a well-defined HP gene variant, capable of informed consent, and able to demonstrate an understanding of autosomal dominant inheritance, incomplete penetrance, variable expressivity, and the natural history of HP. Written informed consent must be documented before the genetic test is performed.
Medicare National Coverage

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

Regulatory Status

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

References


History

<table>
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<td>10/14/13</td>
<td>New Policy. Policy created with literature review through June 30th, 2013. Genetic testing for hereditary pancreatitis is considered investigational.</td>
</tr>
<tr>
<td>12/08/14</td>
<td>Annual Review. Policy statement added for medically necessary genetic testing for patients 18 years and younger with recurrent acute or chronic pancreatitis; all other indications remain investigational. Policy updated with clinical input. References 6-7, 16, 18-19, and 27-28 added. Policy statement added as noted. CPT code 81222 removed; it does not apply to this policy. CPT codes 81223, 81401, and 81479 added.</td>
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<td>11/10/15</td>
<td>Annual Review. Policy updated with literature review through July 8, 2015; references 6-9 and 20-22 added. Appendix Table 1 added. Policy statements unchanged.</td>
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<tr>
<td>11/01/16</td>
<td>Annual Review, approved October 11, 2016. Policy updated with literature review; reference 39 added. Policy statements unchanged. Supportive language added for application of this policy to those aged 18 and younger.</td>
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<tr>
<td>05/01/17</td>
<td>Annual Review, approved April 11, 2017. Policy updated with literature review through December 20, 2016. References 1, 9, 12-14, and 32 added. The policy revised with updated genetics nomenclature. Appendix table removed. Policy statements unchanged.</td>
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<tr>
<td>09/22/17</td>
<td>Policy moved into new format. No changes to policy statements.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with literature review through December 2017; reference 10 and 33 added; references 3, 9, and 36 updated. Policy statements unchanged.</td>
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Office for Civil Rights Complaint Portal, available at
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