Genetic Testing for Hereditary Pancreatitis

Description

Chronic pancreatitis (CP) is a condition in which 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 chronic pancreatitis, and is defined as an autosomal dominant disorder that results in a familial pattern of CP. Mutations of several genes are associated with HP. Demonstration of a pathogenic genetic mutation in one or several of these genes can potentially be used to confirm the diagnosis of HP, provide information on prognosis and management, and/or determine the risk of CP in asymptomatic relatives of patients with HP.

Background

Acute and CP is caused by trypsin activation within the pancreas, resulting in autodigestion, inflammation, elevation of pancreatic enzymes in 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 4th and 5th 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 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. HP is a rare disorder, in 1997 there were about 1000 individuals with HP in the United States. (1)

Genetic Determinants of HP

In 1996, Whitcomb et al discovered that mutations of protease, serine, 1(trypsin 1) (PRSS1) on chromosome 7q35 cause HP. PRSS1 encodes cationic trypsinogen. Gain of function mutations of the PRSS1 gene cause HP by prematurely and excessively converting trypsinogen to trypsin, which then results in pancreatic autodigestion. Between 60% and 80% of individuals who have a PRSS1 mutation will experience pancreatitis in their lifetimes; 30% to 40% will develop CP. Most, but not all, people with a mutation of PRSS1 will have inherited it from one of their parents. The proportion of HP caused
by a spontaneous mutation of PRSS1 is unknown. In families with 2 or more affected individuals in 2 or more generations, genetic testing shows that the majority have a demonstrable PRSS1 mutation. In 60% to 100%, the mutation 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 mutations (p.Arg122His and p.Asn29Ile) are most common, accounting for 90% of mutations in affected individuals. Over 40 other PRSS1 sequence variants have been found, but their clinical significance is uncertain. Pathogenic PRSS1 mutations are present in 10% or less of individuals with chronic pancreatitis. (2)

Targeted analysis of exons 2 and 3, where the common mutations 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, 1) However, several other genes have emerged as significant contributors to both HP and CP. These include cystic fibrosis (CF) transmembrane conductance regulator (CFTR), serine protease inhibitor, Kazal type 1 (SPINK1), and chymotrypsin C (CTRC).

Autosomal recessive mutations 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. (1) Individuals with heterozygous mutations of the CFTR gene (CF carriers) have a 3 to 4-fold increased risk for CP. (3) Individuals with 2 CFTR mutations (homozygotes or compound heterozygotes) will benefit from CF-specific evaluations, therapies, and genetic counseling.

The SPINK gene encodes a protein that binds to trypsin and thereby inhibits its activity. Mutations 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 mutations of the CFTR gene. Fink et al in 2007 did not recommend testing asymptomatic individuals for CFTR and SPINK because of the poor predictive value. Loss of function mutations in SPINK are also associated with tropical and alcoholic pancreatitis. (4) Autosomal recessive familial pancreatitis may be caused by homozygous or compound heterozygous SPINK mutations. (5)

CTRC is important for the degradation of trypsin and trypsinogen, and two mutations (p.R254W and p.K247_R254del) are associated with increased risk for idiopathic CP (odds ration [OR], 4.6), alcoholic pancreatitis (OR= 4.2), and tropical pancreatitis (OR= 13.6). (4)

**Regulatory Status**

Genetic testing for CP is available as laboratory-developed service, subject only to the general laboratory operational regulation under CLIA. Laboratories performing clinical tests must be certified for high complexity testing under CLIA. FDA has not regulated these tests to date.
Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

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

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

Rationale

Analytic Validity

Testing for mutations in the protease, serine, 1 (trypsin 1) (PRSS1) serine peptidase inhibitor (SPINK), and cystic fibrosis (CF) transmembrane conductance regulator (CFTR) genes is usually done by direct sequence analysis, which is the criterion standard for detecting a mutation that is present and/or excluding a mutation that is absent. Testing can also be done by next generation sequencing, which has an accuracy that approaches that of direct sequencing. In patients who test negative by either of these methods, duplication/deletion analysis may be performed to detect copy number variations. These genetic testing methods are considered to have high analytic validity.

Clinical Validity

The clinical validity of genetic testing for hereditary pancreatitis (HP) refers to the mutation detection rate in patients who have known HP.

There is a lack of published evidence on the percent of patients who are first identified as having clinically defined HP and then tested for genetic mutations. The majority of studies that examine the mutation detection rate use a population of patients with idiopathic chronic pancreatitis (CP), and do not necessarily require that patients have a family history of CP. In other studies, cohorts of patients with HP were defined by the presence of genetic mutations or family history, which therefore may include patients with genetic mutations who do not have a family history of CP.

A summary of available studies is included in the following table:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Genes tested</th>
<th>Clinical sensitivity</th>
<th>Clinical specificity</th>
</tr>
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<tbody>
<tr>
<td>Masson (2014) (France)</td>
<td>253 patients with idiopathic CP</td>
<td>PRSS1, SPINK, CFTR, CTRC</td>
<td>23.7% “causal” mutation (60/253)</td>
<td>24.5% “contributory” mutation (62/253)</td>
</tr>
<tr>
<td>Study</td>
<td>Patient Description</td>
<td>Mutation(s)</td>
<td>Prevalence (Cases/Total)</td>
<td>Study Notes</td>
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<tr>
<td>Wang (2004) (China)</td>
<td>75 children with idiopathic CP</td>
<td>PRSS1, SPINK, CFTR, CTRC, CLDN2</td>
<td>66.7% (50/75) (with PRSS1 or SPINK mutations)</td>
<td>NR</td>
</tr>
<tr>
<td>Ceppa 2013 (US)</td>
<td>87 patients with hereditary pancreatitis, defined by known genetic mutation or family history</td>
<td>PRSS1 SPINK CTRF</td>
<td>62% (54/87)</td>
<td>NR</td>
</tr>
<tr>
<td>Sultan 2012 (US)</td>
<td>29 children with recurrent acute or chronic pancreatitis</td>
<td>PRSS1 SPINK CTRF</td>
<td>79% (23/29)</td>
<td>NR</td>
</tr>
<tr>
<td>Gasiorowska 2011 (Poland)</td>
<td>14 pts with idiopathic CP. 46 control pts without pancreatitis</td>
<td>PRSS1 SPINK</td>
<td>50% (97/194)</td>
<td>11% (5/46)</td>
</tr>
<tr>
<td>Joergensen 2010 (Denmark)</td>
<td>122 pts with idiopathic pancreatitis</td>
<td>PRSS1 SPINK CTRF</td>
<td>40% (49/122)</td>
<td>NR</td>
</tr>
<tr>
<td>Rebours 2009 (France)</td>
<td>200 pts with chronic pancreatitis</td>
<td>PRSS1 SPINK CTRF</td>
<td>68% (136/200)</td>
<td>NR</td>
</tr>
<tr>
<td>Keiles 2006 (US)</td>
<td>389 patients with recurrent or chronic pancreatitis referred for genetic testing</td>
<td>PRSS1 SPINK CTRF</td>
<td>49% (185/381)</td>
<td>NR</td>
</tr>
<tr>
<td>Truninger 2001 (Germany)</td>
<td>104 pts with chronic pancreatitis</td>
<td>PRSS1</td>
<td>8% (8/1040)</td>
<td>NR</td>
</tr>
<tr>
<td>Applebaum-Shapiro 2001 (US)</td>
<td>115 patients with hereditary pancreatitis defined clinically. 349 unaffected family members</td>
<td>PRSS1</td>
<td>52% (60/115)</td>
<td>13% (46/349)</td>
</tr>
</tbody>
</table>

CP, chronic pancreatitis; HP, hereditary pancreatitis

These data on clinical validity demonstrate that genetic mutations are common in patients with CP. A very limited amount of evidence reports that genetic mutations are found in a small percentage of patients without pancreatitis. SPINK mutations have also been associated with acute pancreatitis and recurrent acute pancreatitis. (16) However, the true clinical sensitivity and specificity for genetic testing in cases of HP are uncertain for a number of reasons. First, the populations in these studies are defined differently, with most not consisting of patients with clinically defined HP. The populations are from...
different geographic regions, in which the prevalence of genetic mutations may vary. Some of the studies mix adult and pediatric populations, while others report on either adults or children. In the 2 studies that exclusively enrolled children, the rate of mutation detection was generally higher than other studies (67% and 79%). Finally, mutations tested for in these studies differ, with many studies not including all of the known genes that are associated with HP.

**Section Summary**

Evidence on the clinical sensitivity and specificity of genetic testing for pancreatitis is incomplete, and therefore the true clinical sensitivity and specificity cannot be determined. A number of studies report the mutation detection rate in various populations of patients with CP, but few studies enroll a population of patients with clinically defined HP. In 2 studies that report on children, the detection rates are generally higher than other studies, suggesting that the mutation detection rate may be higher in children than in adults.

**Clinical Utility**

Potential types of clinical utility for PRSS1 genetic testing include confirmation of the diagnosis of HP, predictive testing in asymptomatic relatives, and prognostic testing to determine the course of the disease. In each case, demonstration of clinical utility depends on whether identification of a genetic defect leads to changes in medical and/or surgical management options, and whether these changes lead to improved health outcomes. Preconception (carrier) testing and prenatal (in utero) testing can also be performed, but are not addressed in this literature review.

**Diagnostic testing**

There are no direct outcome data regarding the clinical utility of testing for confirmation of HP that is there are no studies that report outcome data in patients who have been tested for HP compared to patients who have not been tested.

Confirmatory testing can be performed in patients who experience acute pancreatitis that is otherwise unexplained, for recurrent acute pancreatitis of unclear cause, and/or for idiopathic CP. In all of these scenarios, a substantial percentage of patients will be found to have a genetic defect, thereby confirming the diagnosis of HP. Most treatments for the pain, maldigestion, and diabetes caused by HP are fundamentally the same as for other types of CP. Therefore, if a deleterious mutation associated with HP is found, treatment for CP is unlikely to change. Interventions for CP include a low-fat diet with multiple small meals, maintenance of good hydration, use of antioxidants, and avoidance of smoking and alcohol use. While all of these interventions may alter the natural history of the disease, there is no evidence that the impact differs for HP compared to other etiologies of CP.

Calcium channel blockers are currently being investigated as a potential treatment for HP. One small uncontrolled trial of amlodipine in 9 patients was identified in the literature. (17) This trial included patients 6 years or older who had chronic pancreatitis and a known PRSS1 mutation. Treatment was continued for up to 11 weeks and 4 patients successfully completed the full course of treatment. All 4 patients reported decreased symptoms, and 3 of 4 patients had improved scores on the 36-Item Short-Form Health Survey outcome instrument. There were no differences before and after treatment in blood pressure, laboratory tests, or physical exam.
Total pancreatectomy with islet cell transplantation (or total pancreatectomy with islet autotransplantation [TP-IAT]) has been investigated in CP or recurrent acute pancreatitis, particularly as a treatment for intractable pain in patients with impaired quality of life in whom medical, endoscopic, or prior surgical treatment have failed. However, questions remain about the best timing of surgery, selection of candidates, evaluation of outcomes, and follow up. (18) Chinnakotla et al conducted a retrospective study that compared outcomes after TP-IAT for patients with HP or familial pancreatitis compared with other causes of CP among 484 patients treated at a single institution from 1977 to 2012, 80 of whom had HP.19 Genetic testing was not available for all patients with suspected HP. Multiple causes of HP or familial pancreatitis were included: n=38 with PRSS1 mutations; n=9 with SPINK1 mutations; n=14 with CFTR mutations; and 19 with familial pancreatitis without a mutation specified. Patients with HP were younger at the time of TP-IAT (mean age, 21.9 years vs 37.9 years in nonhereditary CP, p<0.001), but had a longer history of pancreatitis (mean, 10.1 years vs 6.4 years in nonhereditary CP, p<0.001). Pain scores significantly improved after TP-IAT (p<0.001), with no significant differences between HP and nonhereditary CP.

Predictive testing
Predictive testing can be performed in asymptomatic relatives of patients with known HP in order to determine the likelihood of CP. For this population, no direct evidence was identified that compared outcomes in patients tested for genetic mutations compared to patients not tested for genetic mutations. It is possible that at-risk relatives who are identified with genetic mutations may alter lifestyle factors such as diet, smoking and alcohol use, and this may delay the onset or prevent CP. However, evidence on this question is lacking, so that conclusions cannot be made on whether testing of asymptomatic family members of patients with HP improves outcomes.

Prognostic testing
Several studies were identified that examined whether the severity and/or natural history of CP differs in patients with and without genetic mutations. A number of studies have reported that patients with HP have an earlier age of onset compared to patients with other etiologies of CP. (20) Other studies have examined whether the severity and natural history differs for patients with HP, but these studies have not reported consistent findings. Some studies have reported that the progression of disease is slower in patients with HP, (21, 20, 22) and that surgical intervention is required less often for patients with HP. (21) However, 1 study also reported that the cumulative risk for exocrine failure was more than twice as high for patients with genetic mutations compared to patients without mutations. (22) In another small study that compared the clinical course of patients with HP to those with alcoholic CP, most clinical manifestations were similar, but patients with HP had a higher rate of pseudocysts. (23)

Individuals with CP due to HP, like others with CP, are at increased risk for pancreatic cancer. In a survey of 246 patients with HP from 10 countries, the cumulative risk of pancreatic cancer by age 70 was estimated to be 40%. (24) In a series of 200 patients with HP from France, the cumulative incidence of pancreatic cancer at 50 years was 11% for men and 85% for women. At 75 years of age, the cumulative risk was 49% for men and 55% for women. There was no evidence identified that the risk of pancreatic cancer differs for patients with HP compared to patients with other forms of CP.

Screening for pancreatic cancer with CT scanning, endoscopic ultrasound and/or endoscopic retrograde cholangiopancreatography (ERCP) has been recommended for patients with CP irrespective
of etiology (25, 26), but close surveillance has not yet been demonstrated to improve long-term survival for any of these methods in patients with CP.

**Section Summary**

The evidence on clinical utility does not support an improvement in health outcomes associated with genetic testing. For diagnostic testing, there is a lack of evidence that genetic testing leads to management changes. Several treatments for CP, including calcium channel blockers and TP-IAT, are under investigation; however, the evidence to date is insufficient to determine whether patients with HP respond differently to such treatments than other patients with CP. For prognostic testing, there have been some differences reported regarding the natural course of CP in patients with and without genetic mutations. The age of onset is consistently younger, and the progression of disease may be slower, but it is not possible to conclude whether the overall severity of disease or need for surgical intervention differs. The risk of pancreatic cancer is high for patients with HP, but no evidence was identified that establishes whether the risk of cancer is greater for patients with HP compared with other etiologies of CP. For testing asymptomatic, at-risk family members, there is a lack of evidence that genetic testing leads to interventions that delay or prevent the onset of pancreatitis.

**Practice Guidelines and Position Statements**

The American College of Medical Genetics issued a policy statement on laboratory standards and guidelines for population-based CF carrier screening in 2001, (27) which were updated in 2004.(28) These guidelines provide recommendations about specific mutation testing in CF, but do not specifically address genetic testing for suspected HP.

A 2001 European Consensus Conference developed guidelines for genetic testing of the PRSS1 gene, genetic counseling, and consent for genetic testing for HP. (29) The recommended indications for symptomatic patients included:

- Recurrent (2 or more separate, documented episodes with hyper-amylasemia) 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 mutation, 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.

**U.S. Preventive Services Task Force Recommendations**

Genetic testing for hereditary pancreatitis is not a preventive service.
Summary

Numerous studies demonstrate that genetic mutations are found in a large percentage of patients with idiopathic CP. However, these studies are limited by wide variation in the patient populations and genes tested; as a result, it is not possible to determine the true prevalence of HP among patients with idiopathic CP, nor the sensitivity and specificity of genetic testing (clinical validity) in patients with a familial pattern of disease. The clinical utility of testing has not been demonstrated empirically. While testing can confirm the diagnosis of HP, there is no evidence that treatment is altered by testing or that health outcomes are improved. Similarly, predictive testing of at-risk relatives and prognostic testing have not been shown to improve outcomes. Predictive testing can better define the risk of developing CP, but there is no evidence that early interventions based on genetic testing alter the prevalence or course of disease. The prognosis of HP may differ from other etiologies of CP, but this evidence is mixed and there are no changes in management that result from refining the prognosis of CP. For children, recurrent acute or chronic pancreatitis is a much less common event, making the yield of genetic testing higher. Clinical input supported the use of genetic testing for HP in children, in spite of a lack of evidence for improvements in outcomes, due to the possibility of reduced diagnostic tests in the setting of a genetically-determined HP diagnosis. As a result, genetic testing for HP in children (≤18 years) with recurrent acute pancreatitis (>1 episode) or chronic pancreatitis may be considered medically necessary. Genetic testing for HP is considered investigational in all other cases.

Medicare National Coverage

There is no national coverage determination (NCD).

References


Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2013</td>
<td>New Policy</td>
<td></td>
</tr>
<tr>
<td>March 2015</td>
<td>Update 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>
</tbody>
</table>

Keywords

Genetic testing, PRSS1
Genetic testing, SPINK1
Genetic testing, chronic pancreatitis

This policy was approved by the FEP Pharmacy and Medical Policy Committee on March 20, 2015 and is effective April 15, 2015.

Signature on file

Deborah M. Smith, MD, MPH