Genetic Testing for Hereditary Pancreatitis

Policy # 00394
Original Effective Date: 11/20/2013
Current Effective Date: 11/20/2013

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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for hereditary pancreatitis to be investigational.*

Background/Overview
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.

Acute and chronic pancreatitis is caused by trypsin activation within the pancreas, resulting in autodigestion, inflammation, elevation of pancreatic enzymes in serum, and abdominal pain. Chronic pancreatitis 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 chronic pancreatitis, which has a peak incidence in the 4th and 5th decades of life. Gallstones, hypercalcemia, inflammatory bowel disease, autoimmune pancreatitis, and peptic ulcer disease can also cause chronic pancreatitis. About 20% of chronic pancreatitis is idiopathic. A small percentage of chronic pancreatitis is categorized as HP, which usually begins with recurrent episodes of acute pancreatitis in childhood and evolves into chronic pancreatitis 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 chronic pancreatitis and hereditary pancreatitis, especially early in the course of the disease. HP is rare disorder, in 1997 there were about 1,000 individuals with HP in the United States.

Genetic determinants of hereditary pancreatitis
In 1996, Whitcomb and colleagues discovered that mutations of protease, serine, 1 (trypsin 1) (PRSS1) on chromosome 7q35 cause hereditary pancreatitis. 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. Up to 4% of individuals with chronic pancreatitis have a deleterious mutation of PRSS1. Between 60% and 80% of individuals who have a PRSS1 mutation will experience pancreatitis in their lifetimes; 30% to 40% will develop chronic pancreatitis. Most, but not all, individuals with a mutation of PRSS1 will have inherited it from one of their parents. The proportion of HP
caused by a spontaneous mutation of \textit{PRSS1} is unknown. In families with two or more affected individuals in two or more generations, genetic testing shows that the majority have a demonstrable \textit{PRSS1} mutation. In 60-100\%, the mutation 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 mutations (p.Arg122His and p.Asn29Ile) are most common, accounting for 90\% of mutations in affected individuals. Over 40 other \textit{PRSS1} sequence variants have been found, but their clinical significance is uncertain. Pathogenic \textit{PRSS1} mutations are present in 10\% or less of individuals with chronic pancreatitis.

Targeted analysis of exons 2 and 3, where the common mutations are found, or \textit{PRSS1} sequencing, are first-line tests, followed by duplication analysis. The general indications and emphasis on pre- and post-test genetic counseling have remained central features of subsequent reviews and guidelines. However, several other genes have emerged as significant contributors to both HP and chronic pancreatitis. These include cystic fibrosis transmembrane conductance regulator (CFTR), serine peptidase inhibitor, Kazal type 1 (SPINK1), and chymotrypsin C (CTRC).

Autosomal recessive mutations of \textit{CFTR} cause cystic fibrosis (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 chronic pancreatitis. Individuals with homozygous mutations of the \textit{CFTR} gene (CF carriers) have a 3- to 4-fold increased risk for chronic pancreatitis. Individuals with 2 \textit{CFTR} mutations (homozygotes or compound heterozygotes) will benefit from CF-specific evaluations, therapies, and genetic counseling.

The \textit{SPINK} gene encodes a protein that binds to trypsin and thereby inhibits its activity. Mutations in \textit{SPINK} are not associated with acute pancreatitis but are found, primarily as modifiers, in recurrent acute pancreatitis and seem to promote the development of chronic pancreatitis, including for individuals with compound heterozygous mutations of the \textit{CFTR} gene. Fink et al. in 2007 did not recommend testing asymptomatic individuals for \textit{CFTR} and \textit{SPINK} because of the poor predictive value. Loss of function mutations in \textit{SPINK} are also associated with tropical and alcoholic pancreatitis. Autosomal recessive familial pancreatitis may be caused by homozygous or compound heterozygous \textit{SPINK} mutations.

\textit{CTRC} is important for the degradation of trypsin and trypsinogen, and 2 mutations (p.R254W and p.K247_R254del) are associated with increased risk for idiopathic chronic pancreatitis (OR 4.6), alcoholic pancreatitis (OR 4.2), and tropical pancreatitis (OR 13.6).

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
Genetic testing for chronic pancreatitis is available as a laboratory-developed service, subject only to the general laboratory operational regulation under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. Laboratories performing clinical tests must be certified for high complexity testing under CLIA. The U.S. FDA has not regulated these tests to date.
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Centers for Medicare and Medicaid Services (CMS)
None

Rationale/Source

Analytic Validity
Testing for mutations in the protease, serine 1 (trypsin 1) (PRSS1), serine peptidase inhibitor (SPINK), and cystic fibrosis transmembrane conductance regulator (CTFR) genes is usually done by direct sequence analysis, which is the gold 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 is defined as 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 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>
</thead>
<tbody>
<tr>
<td>Ceppa 2013 (U.S.)</td>
<td>87 patients (pts) with hereditary pancreatitis, defined by known genetic mutation or family history</td>
<td>PRSS1, SPINK, CTFR</td>
<td>62% (54/87)</td>
<td>NR</td>
</tr>
<tr>
<td>Sultan 2012 (U.S.)</td>
<td>29 children with recurrent acute or chronic pancreatitis</td>
<td>PRSS1, SPINK, CTFR</td>
<td>79% (23/29)</td>
<td>NR</td>
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<tr>
<td>Gasiorowska 2011 (Poland)</td>
<td>14 pts with idiopathic chronic pancreatitis. 46 control pts without pancreatitis</td>
<td>PRSS1, SPINK</td>
<td>50% (7/14)</td>
<td>11% (5/46)</td>
</tr>
<tr>
<td>Joergensen 2010 (Denmark)</td>
<td>122 pts with idiopathic pancreatitis</td>
<td>PRSS1, SPINK, CTFR</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</td>
<td>68% (136/200)</td>
<td>NR</td>
</tr>
<tr>
<td>Keiles 2006 (U.S.)</td>
<td>389 pts with recurrent or chronic pancreatitis referred for genetic testing</td>
<td>PRSS1, SPINK, CTFR</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 (U.S.)</td>
<td>115 pts with hereditary pancreatitis defined clinically</td>
<td>PRSS1</td>
<td>52% (60/115)</td>
<td>13% (46/349)</td>
</tr>
</tbody>
</table>

These data on clinical validity demonstrate that genetic mutations are common in patients with chronic pancreatitis. A very limited amount of evidence reports that genetic mutations are found in a small percentage of patients without pancreatitis. However, the true clinical sensitivity and specificity 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 hereditary pancreatitis. The populations are from different geographic regions, in which the prevalence of genetic mutations may vary. Finally, mutations tested for in these studies differ, with many studies not including all of the known genes that are associated with HP.
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 is no direct outcome data regarding the clinical utility of testing for confirmation of HP, i.e. 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 chronic pancreatitis. 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. This trial included patients 6 years or older who had CP 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 the 4 patients had improved scores on the SF (Short Form)-36 outcome instrument. There were no differences before and after treatment in blood pressure, laboratory tests, or physical exam.

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. 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 and that surgical intervention is required less often for patients with HP. However, one
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. 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.

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

Section summary. 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 to other etiologies of CP.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
None

Summary
HP is a form of CP that is associated with mutations in several genes. Numerous studies demonstrate that genetic mutations are found in a large percentage of patients with idiopathic CP. However, these studies are limited by wide variations 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. 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. As a result, genetic testing for hereditary pancreatitis is considered investigational.

References
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
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<th>Code Type</th>
<th>Code</th>
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<td>81401, 81404</td>
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<tr>
<td>HCPCS</td>
<td>No code</td>
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<tr>
<td>ICD-9 Diagnosis</td>
<td>577.1</td>
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<tr>
<td>ICD-9 Procedure</td>
<td>No code</td>
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11/07/2013 Medical Policy Committee review
Next Scheduled Review Date: 11/2014

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
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