Medical Policy

Genetic Testing for Hereditary Pancreatitis

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Policy Number: 516
BCBSA Reference Number: 2.04.99

Related Policies
None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Genetic testing for hereditary pancreatitis is INVESTIGATIONAL.

Prior Authorization Information

Commercial Members: Managed Care (HMO and POS)
This is NOT a covered service.

Commercial Members: PPO, and Indemnity
This is NOT a covered service.

Medicare Members: HMO BlueSM
This is NOT a covered service.

Medicare Members: PPO BlueSM
This is NOT a covered service.

CPT Codes / HCPCS Codes / ICD-9 Codes
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.
Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

<table>
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<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tr>
<td>81401</td>
<td>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)</td>
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<tr>
<td>81404</td>
<td>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)</td>
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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 an autosomal dominant disorder that results in a familiar 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 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. Gall stones, 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 hereditary pancreatitis (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. (1)

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 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 PRSS1 mutation. In 60-100%, 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 and emphasis on pre- and post-test genetic counseling have remained central features of subsequent reviews and guidelines. (1, 3) 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 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. (1) Individuals with heterozygous mutations of the CFTR gene (CF carriers) have a 3- to 4-fold increased risk for chronic pancreatitis. (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 chronic pancreatitis, 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 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). (4)

Summary
Hereditary pancreatitis (HP) is a form of chronic pancreatitis (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.

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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
References