Genetic Testing for Hereditary Pancreatitis

**Description of Procedure or Service**

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 (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 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 twenty percent 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. Individuals with hereditary pancreatitis have an estimated 40% to 50% lifetime risk of developing pancreatic cancer.

**Genetic Determinants of Hereditary Pancreatitis**

**PRSS1 Variants**

In 1996, Whitcomb and colleagues discovered that disease-associated variants of protease, serine, 1(trypsin 1) (PRSS1) on chromosome 7q35 cause hereditary pancreatitis. PRSS1 encodes cationic trypsinogen. Gain of function variants 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 disease-associated PRSS1 variant will experience pancreatitis in their lifetimes; 30% to 40% will develop chronic pancreatitis. Most, but not all, individuals 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 or spontaneous variant of PRSS1 is unknown. In families with two or more affected individuals in two or more generations, genetic testing shows that most have a demonstrable disease-associated PRSS1 variant. In 60-100%, 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 percent. Two PRSS1 point variants (p.Arg122His and p.Asn29lle) 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 chronic pancreatitis.

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
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for PRSS1 testing and emphasis on pre- and posttest genetic counseling have remained central features of 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) 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 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 heterozygous variants of the CFTR gene (CF carriers) have a 3 to 4-fold increased risk for chronic pancreatitis. Individuals with two CFTR pathogenic 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 chronic pancreatitis, 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.

**CTRC Variants**
CTRC is important for the degradation of trypsin and trypsinogen, and two variants (p.R254W and p.K247_R254del) are associated with increased risk for idiopathic chronic pancreatitis (Odds Ratio [OR] 4.6), alcoholic pancreatitis (OR 4.2), and tropical pancreatitis (OR 13.6).

**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 variants in CLDN2 have been associated with CP.

**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.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

**Policy**

BCBSNC will cover Genetic Testing for Hereditary Pancreatitis when it is considered medically necessary because the medical criteria and guidelines shown below are met.

Genetic Testing for Hereditary Pancreatitis is considered investigational for all patients 19 years of age and above. BCBSNC does not provide coverage for investigational services or procedures.
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Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When it is covered
Genetic Testing for hereditary pancreatitis may be considered medically necessary for patients aged 18 years and under with a confirmed diagnosis of acute or chronic pancreatitis.

When it is not covered
Genetic testing for hereditary pancreatitis is considered investigational for all patients over 19 years of age.

Policy Guidelines
The evidence for the use of genetic testing for genes associated with hereditary pancreatitis (HP) among patients with chronic pancreatitis (CP) or recurrent acute pancreatitis in adulthood or childhood, includes cohort studies on variant detection rates. 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 enroll patients with known hereditary pancreatitis; those that have reported detection rates for disease-associated variants of 52% and 62%. For other studies that tested patients with chronic pancreatitis or ARP; the disease-associated variant detection rate varied widely across studies. Overall, there is a lack of direct evidence that testing for HP improves health outcomes, and insufficient chain of evidence that, in individuals 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.

The evidence for the use of testing for known familial variant associated with HP among asymptomatic individuals with family members with HP, 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 that compared 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 such as diet, smoking, and alcohol use, and this may delay or prevent the onset of CP. 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.

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, despite 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) is most appropriate for those with recurrent acute pancreatitis (>1 episode) or chronic pancreatitis. Genetic testing for HP is considered investigational over the age of 19 years.

Billing/Coding/Physician Documentation Information
This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative
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Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81401, 81404

ICD-10 Diagnosis Codes: K85.0 (K85.00, K85.01, K85.02); K85.8 (K85.80, K85.81, K85.82); K85.9 (K85.90, K85.91, K85.92); K86.1

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Specialty Matched Consultant Advisory Panel review 8/014

Medical Director review 8/2014


Senior Medical Director review 1/2014
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Specialty Matched Consultant Advisory Panel review 8/2015
Medical Director review 8/2015
Medical Director review 7/2016
Medical Director review 2/2017
Specialty Matched Consultant Advisory Panel review 7/2017
Medical Director review 7/2017

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Details</th>
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<tbody>
<tr>
<td>10/1/13</td>
<td>New policy developed. Genetic testing for hereditary pancreatitis is considered investigational. Medical Director review 9/2013. Notice given 10/1/13 for effective dated 12/10/13. (mco)</td>
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<tr>
<td>12/30/14</td>
<td>References updated. Description section updated. Policy Statement revised to include this statement, “Genetic Testing for Hereditary Pancreatitis is considered investigational for all patients over 18 years of age”. When Covered and When Not Covered sections updated to reflect Policy Statement intent. Policy Guidelines section updated. (td)</td>
</tr>
<tr>
<td>2/10/15</td>
<td>Revised Policy Statement and When Not Covered sections to state genetic testing for hereditary pancreatitis as investigational for age 19 years old and above. Medical Director review 1/2015. (td)</td>
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<tr>
<td>8/30/16</td>
<td>Specialty Matched Consultant Advisory Panel review 7/2016. Medical Director review 7/2016. (jd)</td>
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<tr>
<td>3/31/17</td>
<td>Minor revisions with updated genetic terminology. References updated. Medical Director review 2/2017. (jd)</td>
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<tr>
<td>5/26/17</td>
<td>Code section updated with current ICD-10 codes. (jd)</td>
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational
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purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.