Genetic Testing for Hereditary Pancreatitis

Policy # 00394
Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider genetic testing for hereditary pancreatitis (HP) for patients aged 18 years and younger with unexplained acute recurrent (>1 episode) or chronic pancreatitis (CP) with documented elevated amylase or lipase levels to be eligible for coverage.

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 (HP) in all other situations to be investigational.*

Background/Overview

PANCREATITIS
Acute and CP are caused by trypsin activation within the pancreas, resulting in autodigestion, inflammation, elevation of pancreatic enzymes in serum, and abdominal pain. CP is defined as a state of ongoing inflammation associated with chronic or 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 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Genetic Determinants

**PRSS1 Variants**

Whitcomb et al discovered that disease-associated variants of protease, serine, 1 (trypsin 1) (PRSS1) on chromosome 7q35 cause HP. PRSS1 encodes cationic trypsinogen. 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 have 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.

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 posttest genetic counseling have remained central features of reviews and guidelines. 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. Individuals with heterozygous variants of the CFTR gene (CF carriers) have a 3- to 4-fold increased risk for CP. Individuals with 2 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 acute recurrent 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.
Genetic Testing for Hereditary Pancreatitis

Policy # 00394
Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018

**CTRC Variants**
CTRC is important for the degradation of trypsin and trypsinogen, and 2 variants (p.R254W, p.K247_R254del) are associated with increased risk for idiopathic CP (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.

**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. Prevention Genetics (Marshfield, WI) offers a Chronic Pancreatitis Sequencing Panel, which includes NGS of 5 genes: CASR, CFTR, CTRC, PRSS1, and SPINK1. Ambry Genetics (Aliso Viejo, CA) offers a Pancreatitis Panel, which includes NGS of PRSS1, SPINK1, CTRC, and CFTR. Ambry’s PancNext™ panel consists of NGS of 13 genes: APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53.

**FDA or Other Governmental Regulatory Approval**
U.S. Food and Drug Administration (FDA)
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. FDA has chosen not to require any regulatory review of this test.

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

**Rationale/Source**
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess

©2018 Blue Cross and Blue Shield of Louisiana
the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

TESTING FOR HEREDITARY PANCREATITIS IN PATIENTS WITH CHRONIC PANCREATITIS OR RECURRENT ACUTE PANCREATITIS

Clinical Context and Test Purpose
The purpose of genetic testing of patients who have CP or acute recurrent pancreatitis (ARP) is to confirm a diagnosis and inform management decisions.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals with CP or ARP?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with chronic pancreatitis or recurrent acute pancreatitis.

Interventions
Genetic testing for HP.

Comparators
Standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are test accuracy, symptoms, change in disease status, morbid events and hospitalizations.

Timing
The time frame for outcome measurement varies from short-term development of symptoms to long-term survival outcomes. There are no clear established frameworks to use for outcome timeframes.

Setting
Patients are generally referred by a family practice physician or gastroenterologist to a medical geneticist. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:
Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). The clinical validity of genetic testing for HP refers to the variant detection rate in patients who have known HP.

There is a lack of published evidence on the percentage of patients who are first identified as having clinically defined HP and then tested for genetic variants. Most studies that examined disease-associated variant detection rates 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 variants or family history, which therefore may include patients with genetic variants who do not have a family history of CP.

A summary of representative studies reporting rates of detecting disease-associated variants in patients with symptoms of pancreatitis is included in Table 1.

**Table 1. Summary of Studies Reporting the Clinical Validity of HP Gene Testing**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Population</th>
<th>Genes Tested</th>
<th>Detection Rate</th>
</tr>
</thead>
</table>

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Genetic Testing for Hereditary Pancreatitis

Policy # 00394
Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018

<table>
<thead>
<tr>
<th>Studies</th>
<th>Population</th>
<th>Genes Tested</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with HP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Applebaum-Shapiro et al (2001) (U.S.)</td>
<td>115 patients with HP defined clinically</td>
<td>PRSS1</td>
<td>52% (60/115)</td>
</tr>
<tr>
<td>Ceppa et al (2013) (U.S.)</td>
<td>87 patients with HP, defined by known pathogenic variant or family history</td>
<td>PRSS1, SPINK, CFTR</td>
<td>62% (54/87)</td>
</tr>
<tr>
<td><strong>Patients with CP and/or ARP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vue et al (2016) (U.S.)</td>
<td>91 children with ARP (n=77) or CP (n=14)</td>
<td>SPINK, CFTR, PRSS1</td>
<td>33/69 (48%) tested had at least 1 disease-associated variant</td>
</tr>
<tr>
<td>Saito et al (2016) (Japan)</td>
<td>128 children with CP or ARP</td>
<td>PRSS1, SPINK, CTRC, CPA1</td>
<td>39.1% (50/128) had at least 1 abnormal variant</td>
</tr>
<tr>
<td>Koziel et al (2015) (Poland)</td>
<td>221 patients with AP and 345 healthy controls</td>
<td>SPINK, CFTR, CTRC</td>
<td></td>
</tr>
<tr>
<td>Schwarzenberg et al (2015) (international)</td>
<td>170 children, 76 with CP and 94 with ARP</td>
<td>PRSS1, SPINK, CFTR, CTRC</td>
<td>67% (51/76) with CP</td>
</tr>
<tr>
<td>Poddar et al (2015) (India)</td>
<td>68 children with pancreatitis (35.3% AP, 32.3% ARP, 32.3% CP); 25 healthy controls</td>
<td>PRSS1, SPINK, CFTR</td>
<td>44% (38/86)</td>
</tr>
<tr>
<td>Masson et al (2013) (France)</td>
<td>253 patients with idiopathic CP</td>
<td>PRSS1, SPINK, CFTR, CTRC</td>
<td>23.7% (60/253) “causal” variant</td>
</tr>
<tr>
<td>Wang et al (2013) (China)</td>
<td>75 children with idiopathic CP</td>
<td>PRSS1, SPINK, CFTR, CTRC</td>
<td>66.7% (50/75) (with PRSS1 or SPINK variants)</td>
</tr>
<tr>
<td>Sultan et al (2012) (U.S.)</td>
<td>29 children with ARP or CP</td>
<td>PRSS1, SPINK, CFTR</td>
<td>79% (23/29)</td>
</tr>
<tr>
<td>Gasiorowska et al (2011) (Poland)</td>
<td>14 patients with idiopathic CP; 46 healthy controls</td>
<td>PRSS1, SPINK</td>
<td>50% (7/14)</td>
</tr>
<tr>
<td>Joergensen et al (2010) (Denmark)</td>
<td>122 patients with idiopathic pancreatitis</td>
<td>PRSS1, SPINK, CFTR</td>
<td>40% (49/122)</td>
</tr>
<tr>
<td>Rebours et al (2009) (France)</td>
<td>200 patients with CP</td>
<td>PRSS1</td>
<td>68% (136/200)</td>
</tr>
</tbody>
</table>

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Genetic Testing for Hereditary Pancreatitis

Policy # 00394
Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018

<table>
<thead>
<tr>
<th>Studies</th>
<th>Population</th>
<th>Genes Tested</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keiles et al (2006)</td>
<td>389 patients with recurrent or CP</td>
<td>PRSS1,</td>
<td>49% (185/381)</td>
</tr>
<tr>
<td>(U.S.)</td>
<td></td>
<td>SPINK,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CFTR</td>
<td></td>
</tr>
<tr>
<td>Truninger et al (2001)</td>
<td>104 patients with CP</td>
<td>PRSS1</td>
<td>8% (8/104)</td>
</tr>
<tr>
<td>(Germany)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AP: acute pancreatitis; ARP: acute recurrent pancreatitis; CP: chronic pancreatitis; HP: hereditary pancreatitis.

Only 2 studies were identified that evaluated patients with known HP. Applebaum-Shapiro et al (2001) identified protease, serine, 1 (trypsin 1) (PRSS1) variants in 52% of patients with HP; other patients might have had different disease-associated variants not addressed in this study. Ceppa et al (2013) identified PRSS1, serine peptidase inhibitor (SPINK), or CF transmembrane conductance regulator (CFTR) disease-associated variants in 62% of patients with HP. Again, other patients may have had different, rarer, variants. The true clinical sensitivity and specificity for genetic testing in cases of HP are uncertain for a number of reasons. First, the populations in published studies have been defined differently, with most not consisting of patients with clinically defined HP. The populations were from different geographic regions, in which the prevalence of genetic variants may vary. Some of the studies assessed mixed adult and pediatric populations, while others reported on either adults or children. Finally, genes tested for differed, with many studies not including all of the known genes associated with HP.

Culetto et al (2015) found that the proportion of patients with acute pancreatitis attributable to genetic causes is higher among younger patients. In a group of 309 subjects with acute pancreatitis, patients ages 35 and younger (n=66) were more likely to have a genetic cause of pancreatitis identified (10%) than older patients (1.5%; p=0.003).

Section Summary: Clinically Valid
A number of studies have reported variant detection rates in various populations of patients with CP, but few have enrolled a population of patients with known HP. Studies that tested patients with known HP reported variant detection rates between 52% and 62%; studies might not have tested for all relevant genetic variants. For other studies that tested patients with CP or ARP, disease-associated variant detection rates varied widely across studies.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.
There are no direct outcome data on the clinical usefulness of testing for confirmation of HP (ie, no studies have reported outcomes data for patients tested and not tested for HP).

**Indirect Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence would demonstrate that genetic testing can identify individuals with HP who would not otherwise be identified, that treatments are available for these patients that would not otherwise be given to patients with CP or ARP, and that these treatments improve health outcomes.

There is some evidence that testing patients with HP, or patients with CP or ARP, can identify individuals with disease-associated variants (see Clinically Valid section). However, it is unclear whether patient management would differ for patients with CP depending on whether or not a variant associated with HP is found. Conservative therapy for CP includes 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 with other etiologies of CP.

Moreover, there is a lack of evidence that treatments (eg, for CP-related pain) would differ depending on whether patients had HP. Total pancreatectomy with islet cell transplantation (or total pancreatectomy with islet autotransplantation [TP-IAT]) has been investigated in CP or ARP, 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. Chinnakotla et al (2014) retrospectively compared outcomes after TP-IAT for patients who had HP or familial pancreatitis with other causes of CP among 484 patients treated at a single institution from 1977 to 2012, 80 of whom had HP. Genetic testing was not available for all patients with suspected HP. Multiple causes of HP or familial pancreatitis were included: 38 with PRSS1 variants; 9 with SPINK1 variants; 14 with CFTR variants; and 19 with familial pancreatitis without a variant 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.

Several studies were identified that examined whether the severity and/or natural history of CP differs in patients with and without disease-associated variants. A 2008 review article reported that patients with HP have an earlier age of onset compared with patients with other etiologies of CP. Other studies have reported data from an observational cohort and a registry that disease progression is slower in patients with HP and that surgical intervention is required less often for patients with HP. The registry study also reported that the cumulative risk for exocrine failure was more than twice as high for patients with disease-
associated variants compared with patients without disease-associated variants. A small case series (1998) compared the clinical course of patients who had HP with those who had alcoholic CP. Most clinical manifestations were similar, but patients with HP had a higher rate of pseudocysts.

A 2017 systematic review and meta-analysis by Hu et al investigated the association between the p.R122H variant in the PRSS1 gene and the risk of CP. Eight case-control studies in which patients had CP, whether hereditary or of another cause, were included. Analysis of all 8 reviewed studies (n=1733 patients with CP of all etiologies combined; n=2415 controls) showed an overall pooled odds ratio (OR) of 4.78 (95% confidence interval [CI] 1.13 to 20.20); heterogeneity was low ($I^2=32.2\%$). A subgroup analysis compared hereditary CP with nonhereditary CP in 4 studies (n=225 patients, n=2214 controls). There was low heterogeneity between the studies ($p=0.235$, $I^2=29.5\%$), with a pooled OR for an association between the p.R122H variant and the risk of hereditary CP of 65.52 (95% CI 9.09 to 472.48). By comparison, the pooled OR for an association between the p.R122H variant, and an increased risk of nonhereditary CP was 2.79 (95% CI 0.68 to 1.55).

**Section Summary: Clinically Useful Testing for Variants Associated With HP**

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 direct evidence that genetic testing leads to management changes. A chain of evidence does not indicate that treatment would differ for patients with HP compared with other patients with CP. In addition, the evidence to date is insufficient to determine whether patients with HP respond differently to treatments such as TP-IAT than other patients with CP. However, there is a suggestion that patients with HP have earlier onset of disease and inconsistent evidence on disease severity in patients with HP vs other types of CP. A systematic review and meta-analysis identified eight studies that included patients with CP of several etiologies and found an increased association between the presence of the p.R122H variant in both hereditary and nonhereditary CP.

**TARGETED TESTING OF ASYMPTOMATIC RELATIVES OF PATIENTS WITH HP**

**Clinical Context and Test Purpose**

The purpose of genetic testing of asymptomatic relatives of patients with HP is to determine the likelihood that the individual will develop CP.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in asymptomatic relatives of patients with HP?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest is patients who are asymptomatic with a relative or relatives who have been diagnosed with HP.
Interventions
The test being considered is genetic testing for HP.

Comparators
The following practice is currently being used: standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are test accuracy, symptoms, change in disease status, morbid events, and hospitalizations.

Timing
There are no clinical guidelines with recommendations for testing asymptomatic relatives of patient with HP or for monitoring asymptomatic individuals if found to have variants associated with HP. The timeframe for outcome measurement varies from short-term development of symptoms to long-term survival outcomes. There are no clear established frameworks to use for outcome timeframes.

Setting
Asymptomatic patients might be referred by a family practice physician to a medical geneticist. Referral for genetic counseling is important for explanation of genetic disease, heritability, and genetic risk.

Technical Reliability
See the previous section for patients with CP or ARP.

Clinically Valid
See the previous section for patients with CP or ARP.

Clinically Useful
Predictive testing can be performed in asymptomatic relatives of patients with known HP to determine the likelihood of CP. For this population, no direct evidence was identified that compared outcomes in patients who did and did not undergo genetic testing. It is possible that at-risk relatives who are identified with disease-associated variants might alter lifestyle factors (e.g., diet, smoking, alcohol use), and this might delay or prevent CP onset. However, evidence on this question is lacking, so that conclusions cannot be made on whether genetic testing of asymptomatic family members of patients with HP improves outcomes.

Section Summary: Targeted Testing of Asymptomatic Relatives of Patients With HP
There is a lack of evidence that genetic testing of asymptomatic relatives of patients with HP leads to interventions that delay or prevent pancreatitis onset. It is possible that lifestyle interventions might alter the risk of subsequent pancreatitis, but such studies are lacking.
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.

References


©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
 Genetic Testing for Hereditary Pancreatitis

Policy # 00394
Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018


©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.

Page 12 of 14
Genetic Testing for Hereditary Pancreatitis

Policy # 00394
Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018


Policy History

Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018
11/07/2013 Medical Policy Committee review
11/06/2014 Medical Policy Committee review
11/21/2014 Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. Added “Based on review of available data, the Company may consider genetic testing for hereditary pancreatitis for patients aged 18 years and younger with unexplained recurrent (>1 episode) acute or chronic pancreatitis with documented elevated amylase or lipase to be eligible for coverage.”
11/03/2016 Medical Policy Committee review
11/16/2016 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017 Medical Policy Committee review
11/15/2017 Medical Policy Implementation Committee approval. No change to coverage.
11/08/2018 Medical Policy Committee review
11/21/2018 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 11/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current
Genetic Testing for Hereditary Pancreatitis

Policy # 00394
Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018

Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81222, 81223, 81401, 81404, 81405, 814799</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>K86.0-K86.1</td>
</tr>
</tbody>
</table>

*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. 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);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

† Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.