Policy Statement

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

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

Policy Guidelines

Genetics Nomenclature Update
The Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td></td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Familial variant</td>
<td></td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling
Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Coding
CPT code 81401 (Molecular Pathology Procedure Level 2) includes the following testing for hereditary pancreatitis:
- PRSS1 (protease, serine, 1 [trypsin 1]) (e.g., hereditary pancreatitis), common variants (e.g., N29I, A16V, R122H)

CPT code 81404 (Molecular Pathology Procedure Level 5) includes the following testing for hereditary pancreatitis:
- PRSS1 (protease, serine, 1 [trypsin 1]) (e.g., hereditary pancreatitis), full gene sequence
- SPINK1 (serine peptidase inhibitor, Kazal type 1) (e.g., hereditary pancreatitis), full gene sequence

CPT code 81405 (Molecular Pathology Procedure Level 6) includes the following testing for hereditary pancreatitis (effective 01/01/18):
- CTRC (chymotrypsin C) (e.g., hereditary pancreatitis), full gene sequence

CPT code 81222 and/or 81223 might be reported for CFTR testing for hereditary pancreatitis:
- 81222: CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; duplication/deletion variants
- 81223: CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; full gene sequence

Testing for duplication or deletion variants for PRSS1 and SPINK1 would be reported with the unlisted molecular pathology code 81479.

There is no mention CLDN2 testing in CPT, so the unlisted molecular pathology code 81479 would be reported.

Description
In chronic pancreatitis (CP), recurrent attacks of acute pancreatitis evolve into a chronic inflammatory state with exocrine insufficiency, endocrine insufficiency manifested as diabetes and increased risk for pancreatic cancer. Hereditary pancreatitis (HP) is a subset of CP defined clinically as a familial pattern of CP. Variants of several genes are associated with HP. Demonstration of a pathogenic variant 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.

Related Policies
- N/A

Benefit Application
Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
Regulatory Status

Testing for variants associated with HP is typically done by direct sequence analysis or next-generation sequencing. A number of laboratories offer to test for the relevant genes, either individually or as panels.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic testing for HP is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale

Background
Pancreatitis

Acute and chronic pancreatitis (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. Gallstones, 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 hereditary pancreatitis (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 associated with a markedly increased risk of pancreatic cancer, although HP patients account for only a small fraction of all cases of pancreatic cancer and are only a subset of the 10% of pancreatic cancers that are considered to have a genetic or familial predisposition. Individuals with HP have an estimated 40% to 55% lifetime risk of developing pancreatic cancer.

Genetic Determinants
PRSS1 Variants

Whitcomb (2001) discovered that disease-associated variants of protease, serine, 1 (trypsin 1) (PRSS1) on chromosome 7q35 cause HP. PRSS1 encodes cationic trypsinogen. The 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 two or more affected individuals in two or more generations, genetic testing has 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.2.

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 has remained central features of reviews and guidelines.3,4 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, a serine protease inhibitor, Kazal type 1 (SPINK1) gene, chymotrypsin C (CTRC) gene, and claudin-2 (CLDN2) 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.3 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.5

**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, 4.6), alcoholic pancreatitis (odds ratio=4.2), and tropical pancreatitis (odds ratio=13.6).5 Tropical pancreatitis is a disease almost exclusively occurring in the setting of tropical climate and malnutrition.

**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.

**Literature Review**
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 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 Acute Recurrent Pancreatitis

Clinical Context and Test Purpose
The purpose of genetic testing of patients who have CP or 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 are patients with CP or ARP.

Interventions
The test being considered is genetic testing for hereditary pancreatitis (HP).

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

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

Timing
The timeframe for outcomes measurement varies from the short-term development of symptoms to long-term survival outcomes. There are no clearly 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 the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Study Selection Criteria
For the evaluation of clinical validity of genetic testing for variants associated with HP, methodologically credible studies were selected using the following principles:

For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from the development cohort.

Simplifying Test Terms
There are three core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.
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 the presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a timeframe. 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 an adverse response. The term predictive test is often used to refer to the response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predict response to therapy.

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires a 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 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.

**Observational Studies**

A summary of representative observational 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 Hereditary Pancreatitis Gene Testing**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Population</th>
<th>Genes Tested</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applebaum-Shapiro et al (2001)</td>
<td>115 patients with HP defined clinically</td>
<td>PRSS1</td>
<td>52% (60/115)</td>
</tr>
<tr>
<td>Ceppa et al (2013)</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>
</tbody>
</table>
| Weiss et al (2018)          | 1462 patients with AP 3999 controls                                         | PRSS1-PRSS2, RIPPLY, MORC4   | PRSS1-PRSS2: OR 0.88; 95% CI 0.81-0.97; p = 0.01.  
RIPPLY: OR 1.27, 95% CI 1.07-1.5, p = 0.005.  
MORC4: OR 1.32, 95% CI 1.12-1.56, p = 0.001. |
| Zou et al (2018)            | 1061 idiopathic CP patients and 1196 controls                               | SPINK1, PRSS1, CTRC, CFTR     | CP group: 50.42% (535/1061)  
Control group: 5.94% (71/1196)  
OR: 16.12; p < 0.001 (CI NR)    |
Table 1: Studies of Genetic Testing in Pancreatitis

<table>
<thead>
<tr>
<th>Studies</th>
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<th>Genes Tested</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vue et al (2016)</td>
<td>91 children with ARP (n=77) or CP (n=14)</td>
<td>SPINK, CFTR, PRSS1, PRESS1, CTRC</td>
<td>33/69 (48%) had at least 1 disease-associated variant</td>
</tr>
<tr>
<td>Saito et al (2016)</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)</td>
<td>221 patients with AP and 345 healthy controls</td>
<td>SPINK, CTRC</td>
<td>Variants identified: SPINK (6.3% of AP, 3.2% controls)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CFTR (2.3% of AP, 3.8% of controls)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CTRC (1.8% of AP, 1.2% of controls)</td>
</tr>
<tr>
<td>Schwarzenberg et al (2015)</td>
<td>170 children, 76 with CP and 94 with ARP</td>
<td>PRSS1, SPINK, CTRC, CTRC</td>
<td>67% (51/76) with CP</td>
</tr>
<tr>
<td>Poddar et al (2015)</td>
<td>68 children with pancreatitis (35.3% AP, 32.3% ARP, 32.3% CP); 25 healthy controls</td>
<td>PRSS1, SPINK, CTRC</td>
<td>44% (38/86)</td>
</tr>
<tr>
<td>Masson et al (2013)</td>
<td>253 patients with idiopathic CP</td>
<td>PRSS1, SPINK, CTRC, CTRC</td>
<td>23.7% (60/253) “causal” variant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24.5% (62/253) “contributory” variant</td>
</tr>
<tr>
<td>Wang et al (2013)</td>
<td>75 children with idiopathic CP</td>
<td>PRSS1, SPINK, CTRC, CTRC, CLDN2</td>
<td>66.7% (50/75) (with PRSS1 or SPINK variants)</td>
</tr>
<tr>
<td>Sultan et al (2012)</td>
<td>29 children with ARP or CP</td>
<td>PRSS1, SPINK, CTRC</td>
<td>79% (23/29)</td>
</tr>
<tr>
<td>Gasiorowska et al (2011)</td>
<td>14 patients with idiopathic CP; 46 healthy controls</td>
<td>PRSS1, SPINK, CTRC</td>
<td>50% (7/14)</td>
</tr>
<tr>
<td>Joergensen et al (2010)</td>
<td>122 patients with idiopathic pancreatitis</td>
<td>PRSS1, SPINK, CTRC</td>
<td>40% (49/122)</td>
</tr>
<tr>
<td>Rebours et al (2009)</td>
<td>200 patients with CP</td>
<td>PRSS1</td>
<td>68% (136/200)</td>
</tr>
<tr>
<td>Kelles et al (2006)</td>
<td>389 patients with recurrent or CP</td>
<td>PRSS1, SPINK, CTRC</td>
<td>49% (185/381)</td>
</tr>
<tr>
<td>Truninger et al (2001)</td>
<td>104 patients with CP</td>
<td>PRSS1</td>
<td>8% (8/104)</td>
</tr>
</tbody>
</table>

AP: acute pancreatitis; ARP: acute recurrent pancreatitis; CI: confidence interval; CP: chronic pancreatitis; HP: hereditary pancreatitis; NR: not reported.

Only two 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 cystic fibrosis 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).

Weiss et al (2018) used genetic testing to analyze associations between common variants and AP; 1462 patients with AP and 3999 healthy controls were evaluated. For all AP patients, significant associations were found for PRSS1-PRSS2 variant (rs10273639) (odds ratio [OR] 0.88,
95% confidence interval [CI]: 0.81-0.97, p=0.01), RIPPLY variant (rs7057398) (OR 1.27, 95% CI: 1.07-1.5, p=0.005), and MORC4 (rs12688220) (OR 1.32, 95% CI: 1.12-1.56, p=0.001). Patients were included with AP of all etiologies and did not specifically have a history of recurrent episodes. The population was drawn from four European countries and the variant identification varied in the different populations. The results confirmed that PRSS1-PRSS2 is protective. The other two variants are being investigated for a pathogenic phenotype.

Zou et al (2018) analyzed 1196 controls and 1061 Han Chinese patients with idiopathic CP tested with targeted next-generation sequencing of four CP-associated genes (SPINK1, PRSS1, CTRC, CFTR). The objective of the study was to focus on rare variants defined as <1% frequency in the control population. Variants were identified in 535 (50.42%; OR=16.12; p<0.001) patients with CP compared to 71 (5.94%) controls. There was also an interest in assessing the influence of a variant on clinical presentation and disease onset. Median age at disease onset differed between mutation-positive (29.7±14.84 years) and mutation-negative patients (43.01±15.97; p<0.001). When patients were divided into idiopathic (n=715), alcoholic (n=206), and smoking-associated (n=140) CP subgroups, the rates of pathogenic genotypes were 57.1%, 39.8%, and 32.1%, respectively. The study did not assess the variants more commonly encountered which are associated with a more defined phenotype.

Section Summary: Clinically Valid
A number of studies have reported variant detection rates in various populations of patients with CP, but there is limited frequency information on populations of patients with known HP. Studies that tested patients with known HP reported variant detection rates between 52% and 62%. Genotype-phenotype studies have attempted to characterize rarer variants as well as determine the influence of variant status on clinical presentation and disease onset. Multiple observational studies that tested patients with AP or ARP with variant detection rates varying widely. These studies have added information to the variant frequency differences in populations and subgroups.

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 (i.e., 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.

There is a lack of evidence that treatments (e.g., 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 treatments have failed. However, questions remain about the best timing of surgery, selection of candidates, evaluation of outcomes, and follow-up.25 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.26 Genetic testing was not available for all patients with suspected HP. Multiple causes of HP or familial pancreatitis were included: 38 with \textit{PRSS1} variants; 9 with \textit{SPINK1} variants; 14 with \textit{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 long 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.27 Other studies have reported data from an observational cohort and a registry that disease progression is slower in patients with HP27,28,29, and that surgical intervention is required less often for patients with HP.28 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.29 A small case series (1998) compared the clinical course of patients who had HP with those who had alcoholic CP.30 Most clinical manifestations were similar, but patients with HP had a higher rate of pseudocysts.

A systematic review and meta-analysis by Hu et al (2017) investigated the association between the p.R122H variant in the \textit{PRSS1} gene and the risk of CP.31 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 OR of 4.78 (95% 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).

There is an increased risk for pancreatic cancer in individuals with CP caused by HP. Individuals with HP have an estimated 40% to 55% lifetime risk of developing pancreatic cancer.1 The risk estimates are primarily derived from the study of populations diagnosed with clinical evaluation and family history and antedate characterizations based on genetic variant status. These risk estimates may also represent populations with higher smoking prevalence rates. Smoking increases the likelihood of developing pancreatic cancer in all populations. In general, pancreatic cancer is diagnosed at late stages and has very-low, five-year survival rates. The lack of specificity of premalignant signs and symptoms and uncertainties about the most appropriate imaging or diagnostic studies to assess pancreatic lesions limit the opportunity to make an earlier diagnosis. However, evidence-informed consensus guidelines and opinions have recently appeared to screen for pancreatic cancer in individuals at high-risk. (See Supplemental Information)
Section Summary: Clinically Useful Testing for Variants Associated With HP
The published 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 an 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 PRSS1 gene 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 are 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 symptoms, change in disease status, morbid events, and hospitalizations.

Timing
There are no clinical guidelines with recommendations for testing asymptomatic relatives of a patient with HP or for monitoring asymptomatic individuals if found to have variants associated with HP. The timeframe for outcome measurement varies from the short-term development of symptoms to long-term survival outcomes. There are no clearly 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 the 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 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. The relevant outcomes are 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 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. The relevant outcomes are 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 (e.g., diet, smoking, alcohol use), and this might delay or prevent CP onset. However, studies evaluating behavioral changes and the impact on disease are lacking. The evidence is insufficient to determine the effects of technology on health outcomes.

Supplemental Information
Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 2 specialty medical societies (one of which provided 2 responses) and 4 academic medical centers (one of which provided 2 responses) in 2014. Input was specific to testing children. There was a consensus among reviewers that genetic testing for hereditary pancreatitis is medically necessary for children.

Practice Guidelines and Position Statements
American College of Gastroenterology
The American College of Gastroenterology (2013) guidelines on management of acute pancreatitis included the following statement: “genetic testing may be considered in young patients (<30 years old) if no cause [of acute pancreatitis] is evident, and a family history of pancreatic disease is present (conditional recommendation, low quality of evidence).”32.
The American College of Gastroenterology Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes (2015) recommended genetic testing of patients with suspected familial pancreatic cancer to include analysis of BRCA1/2, CDKN2A, PALB2, and ATM. Evaluation for Peutz-Jeghers Syndrome, Lynch Syndrome, and hereditary pancreatitis-associated genes should be considered if personal and/or family history criteria are met for the syndrome.33

American Pancreatic Association
The American Pancreatic Association (2014) published Practice Guidelines in Chronic Pancreatitis: Evidence-Based Report on Diagnostic Guidelines.34 A classification guideline for the etiology of CP includes genetic mutations in PRSS1, CFTR, SPINK1, and others.

American College of Medical Genetics and Genomics
The American College of Medical Genetics and Genomics (2001)35 issued a policy statement on laboratory standards and guidelines for population-based cystic fibrosis carrier screening which were updated in 200436 and reaffirmed in 2013.36 These guidelines have provided recommendations on specific variant testing in cystic fibrosis, but have not specifically addressed genetic testing for suspected hereditary pancreatitis (HP).

European Consensus Conference
A European Consensus Conference (2001) developed guidelines for genetic testing of the PRSS1 gene, genetic counseling, and consent for genetic testing for HP.37 The indications recommended for symptomatic patients included:

“…(1) Recurrent (2 or more separate, documented episodes with hyper-amylasemia) attacks of acute pancreatitis for which there is no explanation... or (2) unexplained... chronic pancreatitis, or (3) a family history of pancreatitis in a first-degree... or second-degree...relative, or (4) ... unexplained ...pancreatitis occurring in a child that has required 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 “must have a first-degree relative with a well-defined HP gene mutation [pathogenic variant]...” capable of informed consent, and able to “understand the (autosomal dominant) mode of inheritance and incomplete penetrance of HP mutations...”

International Consensus Guidelines for Chronic Pancreatitis
The working group for the International Consensus Guidelines for Chronic Pancreatitis (2018), in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group, and the European Pancreatic Club, published consensus statements on the diagnosis and management of early chronic pancreatitis.38 It included the following recommendation:

“Genetic variants are important risk factors for Early CP and can add specificity to the likely etiology, but they are neither necessary nor sufficient to make a diagnosis. (Quality assessment: moderate; Recommendation: strong; Agreement: strong)”

International Study Group of Pediatric Pancreatitis
The International Study Group of Pediatric Pancreatitis INSPIRE (The International Study Group of Pediatric Pancreatitis: In search for a cure) consortium developed an expert consensus opinion on the evaluation of children with acute recurrent and chronic pancreatitis.39 There was a strong consensus that search for a genetic cause of ARP or CP should include PRSS1, SPINK1, CFTR, and CTRC gene mutation testing.

American Society of Clinical Oncology
The ASCO (2018) published “Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion”.40 The ASCO reported that cancer-unaffected individuals should be offered
genetic risk evaluation if they are: members of families with an identified pathogenic cancer susceptibility gene variant, from families that meet criteria for genetic evaluation for known hereditary syndromes that are linked to pancreatic cancer and, from families that meet criteria for familial pancreatic cancer. The ASCO further considered what surveillance strategies should be used for individuals with a predisposition to pancreatic ductal adenocarcinoma to screen for pancreatic and other cancers. Surveillance can be considered for individuals who are first-degree relatives of individuals with familial pancreatic cancer and/or individuals with a family history of pancreatic cancer who carry a pathogenic germ line variant in genes associated with predisposition to pancreatic cancer.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in December 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

References


**Documentation for Clinical Review**

**Please provide the following documentation (if/when requested):**

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history, if applicable
- Reason for procedure/test/device, when applicable
- Pertinent past procedural and surgical history
- Past and present diagnostic testing and results
- Prior conservative treatments, duration, and response
- Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (i.e., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management), when applicable

**Post Service**

- Results/reports of tests performed
- Procedure report(s)
Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions.
but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.