



## MASSACHUSETTS

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# Medical Policy

## Genetic Testing for Hereditary Pancreatitis

### Table of Contents

- [Policy: Commercial](#)
- [Policy: Medicare](#)
- [Authorization Information](#)
- [Coding Information](#)
- [Description](#)
- [Policy History](#)
- [Information Pertaining to All Policies](#)
- [References](#)

### Policy Number: 516

BCBSA Reference Number: 2.04.99

NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

### Related Policies

None

### Policy

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

Genetic testing for hereditary pancreatitis may be considered **MEDICALLY NECESSARY** for patients aged 18 years and younger with unexplained acute recurrent (>1 episode) or chronic pancreatitis with documented elevated amylase or lipase.

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

#### Medicare HMO Blue<sup>SM</sup> and Medicare PPO Blue<sup>SM</sup> Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

[Local Coverage Determination \(LCD\): Molecular Pathology Procedures \(L35000\)](#)

For medical necessity criteria and coding guidance for **Medicare Advantage members living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at <https://www.cms.gov>.

### Prior Authorization Information

#### Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

#### Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	<b>Outpatient</b>
<b>Commercial Managed Care (HMO and POS)</b>	Prior authorization is <b>not required</b> .
<b>Commercial PPO and Indemnity</b>	Prior authorization is <b>not required</b> .
<b>Medicare HMO Blue<sup>SM</sup></b>	Prior authorization is <b>not required</b> .
<b>Medicare PPO Blue<sup>SM</sup></b>	Prior authorization is <b>not required</b> .

## CPT Codes / HCPCS Codes / ICD Codes

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

**The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

### CPT Codes

<b>CPT codes:</b>	<b>Code Description</b>
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

## Description

### 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. 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 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. Individuals with HP have an estimated 40% to 55% lifetime risk of developing pancreatic cancer.<sup>1</sup>

### 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.<sup>2</sup>

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.<sup>3,4</sup> 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 (*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.<sup>3</sup> 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.<sup>5</sup>

#### ***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).<sup>6</sup>

#### ***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*.<sup>7</sup> Prevention Genetics (Marshfield, WI) offers a Chronic Pancreatitis Sequencing Panel, which includes NGS of 5 genes: *CASR*, *CFTR*, *CTRC*, *PRSS1*, and *SPINK1*.<sup>8</sup> 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*.<sup>9</sup>

## Summary

In chronic pancreatitis (CP), recurrent attacks of acute pancreatitis evolve into a chronic inflammatory state with exocrine insufficiency, 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.

For individuals who have CP or acute recurrent pancreatitis (ARP) who receive testing for genes associated with HP, the evidence 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 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 chain of 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.

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 testing in the setting of a genetically determined HP diagnosis. As a result, genetic testing for HP in children ( $\leq 18$  years) with ARP ( $>1$  episode) or CP may be considered medically necessary.

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 co. 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 may 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.

## Policy History

Date	Action
3/2018	New references added from BCBSA National medical policy.
4/2017	BCBSA National medical policy review. Policy clarified. Policy statements unchanged. 4/1/2017
11/2015	New references added from BCBSA National medical policy.
6/2015	Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.
4/2015	BCBSA National medical policy review. New medically necessary and investigational indications described. Effective 4/1/2015.
2/2014	New medical policy describing investigational indications. Effective 2/1/2014.

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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