Genetic Testing for Hereditary Pancreatitis

Policy # 00394
Original Effective Date: 11/20/2013
Current Effective Date: 12/14/2020

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.****

When 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.***

Policy Guidelines

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was 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 Organisation, and by the Human Genome Variation Society itself.

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The American College of Medical Genetics and Genomics and the Association for Molecular Pathology 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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.

Background/Overview

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 2 or more affected individuals in 2 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.

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 post-test 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, 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. 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.

CTRC Variants

The *CTRC* gene 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). Tropical pancreatitis is a disease almost exclusively occurring in the setting of tropical climate and malnutrition.

CLDN2 Variants

The *CLDN2* gene 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.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 (CLIA). Genetic testing for HP is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Rationale/Source

In 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. 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 1 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 and a systematic review. 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.

Clinical input has 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 (≤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 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 as having 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 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, input was received from 2 specialty medical societies (1 of which provided 2 responses) and 4 academic medical centers (1 of which provided 2 responses) when this policy was under review in 2014. Input was specific to testing children. There was a consensus among reviewers that genetic testing for HP is medically necessary for children.

Practice Guidelines and Position Statements

American College of Gastroenterology

In 2013, the American College of Gastroenterology 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)."

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In 2015, the American College of Gastroenterology Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes 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 HP-associated genes should be considered if personal and/or family history criteria are met for the syndrome.

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

American College of Medical Genetics and Genomics
In 2001 (updated in 2004; reaffirmed in 2013), the American College of Medical Genetics and Genomics issued a policy statement on laboratory standards and guidelines for population-based cystic fibrosis carrier screening. These guidelines provided recommendations on specific variant testing in cystic fibrosis but did not specifically address genetic testing for suspected HP.

European Consensus Conference
In 2001, a European Consensus Conference developed guidelines for genetic testing of the *PRSS1* gene, genetic counseling, and consent for genetic testing for HP. The indications recommended for symptomatic patients included the following:

"(1) Recurrent (2 or more separate, documented episodes with hyperamylasemia) 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,]" be over 16 years old and capable of making an independent and informed decision, and able to "understand the (autosomal dominant) mode of inheritance and incomplete penetrance of HP mutations."

International Consensus Guidelines for Chronic Pancreatitis
In 2018, the working group for the International Consensus Guidelines for Chronic Pancreatitis, in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, Pancreas Fest Working Group, and the European Pancreatic Club, published consensus statements on the diagnosis and management of early CP. 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
In 2017, the International Study Group of Pediatric Pancreatitis INSPPIRE (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. There was a strong consensus that search for a genetic cause of acute recurrent pancreatitis or CP should include *PRSS1, SPINK1, CFTR,* and *CTRC* gene mutation testing.

American Society of Clinical Oncology
In 2018, the American Society of Clinical Oncology (ASCO) published "Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion". 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. 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 germline variant in genes associated with predisposition to pancreatic cancer.

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

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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 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

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Policy History

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11/07/2013 Medical Policy Committee review

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11/20/2013	Medical Policy Implementation Committee approval. New policy.
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.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. No change to coverage.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 11/2021

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 2019 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.

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

Code Type	Code
CPT	81222, 81223, 81401, 81404, 81405, 81479
HCPCS	No codes
ICD-10 Diagnosis	K86.0-K86.1

*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. Food and Drug Administration (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.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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