MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HEREDITARY PANCREATITIS
POLICY NUMBER	MP 2.318

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**1/1/2025**

I. POLICY

Genetic testing for hereditary pancreatitis may be considered **medically necessary** for members with any of the following indications:

- An unexplained episode of documented pancreatitis occurring in a child where the diagnosis of hereditary pancreatitis should be excluded; or
- Recurrent (2 or more separate, documented episodes with elevated amylase or lipase) attacks of acute pancreatitis for which there is no explanation (anatomical anomalies, ampullary or main pancreatic strictures, trauma, viral infection, gallstones, alcohol, drugs, hyperlipidemia, etc.); or
- Unexplained (idiopathic) chronic pancreatitis and documented elevated amylase or lipase.

Genetic testing for hereditary pancreatitis is considered **investigational** in all other situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

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 is being implemented for genetic testing medical policy updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

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	Diseased-Assoc.Variant	Disease-associated change in the DNA sequence.
	Variant	Change in 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 of Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

III. DESCRIPTION/BACKGROUND

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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.

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.

HP is associated with a markedly increased risk of pancreatic cancer, although it accounts for only small fraction of all cases of pancreatic cancer and 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.[1]

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, 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.

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).[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.

REGULATORY STATUS

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.

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.

IV. RATIONALE

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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 (e.g., 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.

For individuals who have clinical evidence of a pancreatic-associated disorder or possible CP in which the etiology is unclear, especially in individuals younger than 35 years, ACG Clinical Guidelines: Chronic Pancreatitis 2020, recommends genetic testing. The primary goal of genetic testing is to identify underlying pancreatitis-related disorders that are contributing to the pathogenic process, assist in decision making, and to help prevent the development of irreversible CP.

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V. DEFINITIONS TOP

N/A

VI. BENEFIT VARIATIONS TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER TOP

Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes								
81220	81221	81222	81223	81401	81404	81405	81479	

ICD-10-CM Diagnosis Codes	Description
K85.00	Idiopathic acute pancreatitis without necrosis or infection
K85.01	Idiopathic acute pancreatitis with uninfected necrosis
K85.02	Idiopathic acute pancreatitis with infected necrosis
K85.10	Biliary acute pancreatitis without necrosis or infection
K85.11	Biliary acute pancreatitis with uninfected necrosis

ICD-10-CM Diagnosis Codes	Description
K85.12	Biliary acute pancreatitis with infected necrosis
K85.20	Alcohol induced acute pancreatitis without necrosis or infection
K85.21	Alcohol induced acute pancreatitis with uninfected necrosis
K85.22	Alcohol induced acute pancreatitis with infected necrosis
K85.30	Drug induced acute pancreatitis without necrosis or infection
K85.31	Drug induced acute pancreatitis with uninfected necrosis
K85.32	Drug induced acute pancreatitis with infected necrosis
K85.80	Other acute pancreatitis without necrosis or infection
K85.81	Other acute pancreatitis with uninfected necrosis
K85.82	Other acute pancreatitis with infected necrosis
K85.90	Acute pancreatitis without necrosis or infection, unspecified
K85.91	Acute pancreatitis with uninfected necrosis, unspecified
K85.92	Acute pancreatitis with infected necrosis, unspecified Acute pancreatitis with infected necrosis, unspecified
K86.1	Other chronic pancreatitis

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.318	**02/14/2019 Consensus Review**. No changes to the policy statements. Background and references updated. Rationale revised. Appendix removed.
	04/07/2020 Consensus Review. No changes to policy statements. Coding reviewed, added the following diagnosis codes: K85.90, K85.91, and K85.92.
	04/14/2021 Consensus Review. No change to policy statement. Two new codes added 81220 and 81221. Tables updated to correct format
	06/14/2022 Consensus Review. No changes to policy statement. References updated and coding reviewed.
	01/20/2023 Minor Review. Policy statement changed to include criteria for genetic testing of all ages. Rationale updated. References updated and added. NCCN statement added. Coding reviewed.
	01/22/2024 Consensus Review. No changes to policy statement. References updated and coding reviewed.

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	11/19/2024 Administrative Update. Removed NCCN statement.

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