

Corporate Medical Policy

Genetic Testing for Hereditary Pancreatitis AHS – M2079

File Name: genetic_testing_for_hereditary_pancreatitis
Origination: 01/01/2019
Last CAP Review: N/A
Next CAP Review: 01/01/2020
Last Review: 01/01/2019

Description of Procedure or Service

Pancreatitis is defined as inflammation of the pancreas that progresses from acute (AP) (sudden onset; duration <6 months) to recurrent acute (RAP) (>1 episode of acute pancreatitis) to chronic (CP) (duration >6 months) (Jessica LaRusch, Solomon, & Whitcomb, 2014). This recurrent inflammation can lead to total destruction of the pancreas with subsequent pancreatic insufficiency, secondary diabetes, increased risk for pancreatic cancer and severe unrelenting pain (Ravi Kanth & Nageshwar Reddy, 2014).

Hereditary pancreatitis is the early onset form of chronic pancreatitis that is carried in an autosomal dominant pattern with variable penetrance (J. LaRusch, Barmada, Solomon, & Whitcomb, 2012).

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for genetic testing for hereditary pancreatitis when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Hereditary Pancreatitis is covered

Genetic testing for hereditary pancreatitis is considered medically necessary in symptomatic patients <20 years old and the individual is presenting with one of the following situations:

- A. Recurrent (two separate, documented episodes with hyperlipasemia) attacks of acute pancreatitis for which there is no identifiable cause
- B. Unexplained chronic pancreatitis (define)
- C. Unexplained pancreatitis with family history of recurrent acute pancreatitis, idiopathic chronic pancreatitis, or childhood pancreatitis without a known cause in a first- or second-degree relative
- D. Unexplained episode of pancreatitis in a child that required hospitalization

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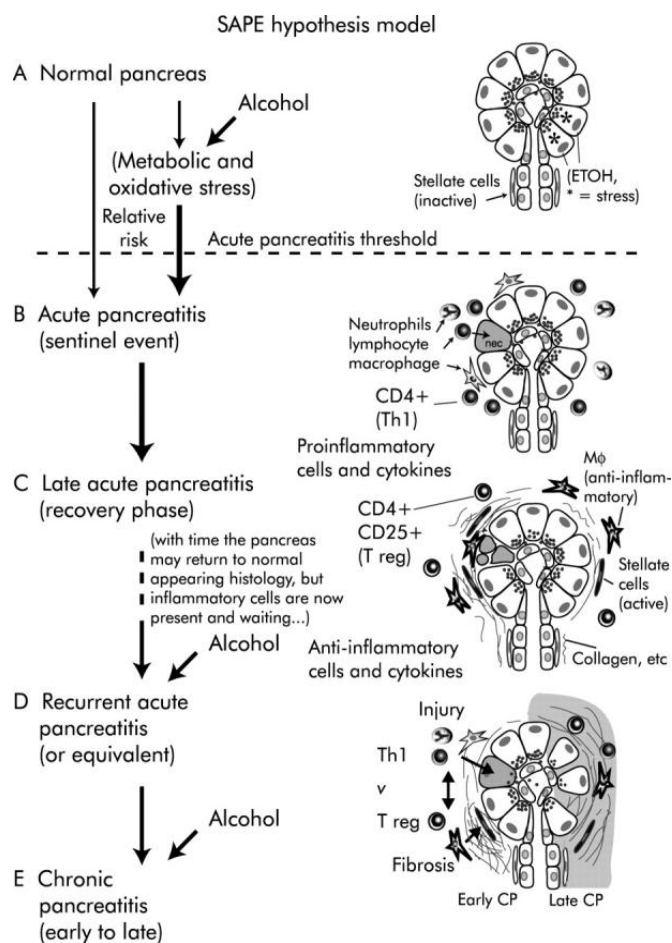
When Genetic Testing for Hereditary Pancreatitis is not covered

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

Policy Guidelines

Background

Pancreatitis is caused by unregulated trypsin activity within the pancreatic acinar cell or pancreatic duct that leads to pancreatic autodigestion, and pancreatic inflammation (Lerch & Gorelick, 2000; D. C. Whitcomb, 1999). Under acinar cell stress (e.g., hyperstimulation, intracellular hypercalcemia), intracellular trypsinogen is likely converted to trypsin, which activates other digestive enzymes causing injury. Injury releases immune system-activating molecules that cause an initial acute inflammatory response, followed by recruitment of tissue macrophages and activated pancreatic stellate cells. Recurrent injury leads to chronic pancreatitis and fibrosis, mediated by pancreatic stellate cells (Werlin et al., 2015).



from: (D. C. Whitcomb, 2004b)

Chronic pancreatitis (CP) is a progressive inflammatory disease in which the pancreatic tissue is destroyed over time and replaced by fibrous tissue. The process of fibrosis usually leads to progressive worsening in structure of pancreas, changes in arrangement and composition of the islets and deformation of the large ducts (Brock, Nielsen, Lelic, & Drewes, 2013), eventually leading to the impairment of both exocrine and endocrine functions (Braganza, Lee, McCloy, & McMahon, 2011). The annual incidence of the disease has been estimated to 5-10 per 100,000

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persons. (Molven, Njolstad, & Weiss, 2015) The main symptom of CP is pain, however it is highly variable in character, frequency, and severity (Mullady et al., 2011; D. C. Whitcomb et al., 2008). Therapeutic efforts are mostly aimed at extracting stones and decompressing pancreatic ducts to achieve ideal drainage of the pancreatic duct (Li et al., 2010; Tandan & Nageshwar Reddy, 2013).

The etiologies of chronic pancreatitis are classified by the TIGAR-O system into alcoholism, hyperlipidemia, obstructive damage caused by trauma or congenital anomalies, hereditary pancreatitis, autoimmune pancreatitis, and idiopathic (Etamad & Whitcomb, 2001; Sun et al., 2015) The most common by far being alcohol abuse, accounting for around 70% of all cases.

Hereditary pancreatitis (HP) presents as an autosomal dominant chronic pancreatitis with variable penetrance. This variability has been attributed to a genetic predisposition to chronic pancreatitis, with the additive effects of environmental and inherited factors. Most pancreatitis genes either directly encode components of the trypsin system of the exocrine pancreas or are likely to perturb this system indirectly.

The phenotype of HP is increased susceptibility to acute pancreatitis, resulting in chronic pancreatitis (including pancreatic fibrosis, chronic pain, maldigestion and diabetes mellitus) occurring in at least 50%. The risk of pancreatic cancer is also increased.

Genes associated with Hereditary Pancreatitis from: (Ooi, Gonska, Durie, & Freedman, 2010; Vue, McFann, & Narkewicz, 2016)

Gene	Gene Name	Consequence	Prevalence, %		Other genetic and environmental factors	Gene	Key features
			General Population	CP			
<i>PRSS1</i>	Cationic trypsinogen	Increased trypsinogen activation, decreased trypsin degradation	<0.01	2-3		<i>PRSS1</i>	<ul style="list-style-type: none"> Autosomal dominant High penetrance
<i>SPINK1</i>	Pancreatic secretory trypsin inhibitor	Failure of trypsin degradation	3-8	8		<i>SPINK1</i>	<ul style="list-style-type: none"> High frequency in general population but low penetrance (N34S mutation) Disease modifying rather than disease causing
<i>CTRC</i>	Chymotrypsin C	Failure of trypsin degradation	≤1	3-4		<i>CFTR</i>	<ul style="list-style-type: none"> May be associated with CF disease Majority of the >1600 CFTR mutations have unknown functional and clinical significance; only a minority are disease-causing mutations
<i>CASR</i>	Calcium sensing receptor	Increased extracellular ionized calcium; increased trypsin activation and failed trypsin degradation	10	18			
<i>CFTR</i>	Cystic fibrosis transmembrane conductance receptor	Impaired flushing of pancreatic ducts leading to trypsin activation	2-3 (ΔF508)	6	5 (other)	8-9	

PRSS1 encodes trypsin-1 (cationic trypsinogen) a major pancreatic digestive enzyme. Mutations in *PRSS1* typically result in a trypsin protein that is either prematurely activated or resistant to degradation (J. LaRusch et al., 2012; Masson, Le Marechal, Delcenserie, Chen, & Ferec, 2008) causing autosomal dominant pancreatitis in 60%-100% of families with hereditary pancreatitis (J. LaRusch & Whitcomb, 2011).

SPINK1 encodes serine protease inhibitor, Kazal-type 1, a trypsin inhibitor that is upregulated by inflammation (Grendell, 2003). It is not a typical susceptibility gene for acute pancreatitis, but rather a susceptibility gene for the chronic pancreatitis that follows acute pancreatitis

CTRC encodes chymotrypsin C, Prematurely activated trypsin is destroyed by *CTRC* by acting on the molecule within the calcium-binding loop in the absence of calcium and therefore is a crucial candidate gene in the pathogenesis of pancreatitis (Szmola & Sahin-Toth, 2007).

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CASR encodes calcium sensing receptor, mutations of which can cause increased calcium ion levels increasing trypsin activation and failed trypsin degradation (D. C. Whitcomb, 2004a).

CFTR encodes the cystic fibrosis transmembrane conductance protein. Mutations are associated with recurrent acute and chronic pancreatitis as dysfunctional CFTR results in retention of zymogens which can become active and result in pancreatitis (J. LaRusch & Whitcomb, 2011).

CLDN2 encodes claudin-2, a tight-junction protein that seals the space between epithelial cells, normally expressed in the proximal pancreatic duct, and is thought to facilitate the transport of water and sodium into the duct to match the chloride and bicarbonate that are actively secreted by pancreatic duct cells through CFTR. It is strongly associated with alcohol-related chronic pancreatitis rather than recurrent acute pancreatitis (Ravi Kanth & Nageshwar Reddy, 2014).

CPAI encodes carboxypeptidase A1, mutation is associated with nonalcoholic chronic pancreatitis, especially with an early age of onset (Witt et al., 2013). Risk for chronic pancreatitis (which is unrelated to trypsin activation) appears to be related to endoplasmic reticulum stress from pathogenic variants that alter protein folding, triggering the unfolded protein response. **MYO9B** gene and the two tight-junction adaptor genes, PARD3 and MAGI2, have been linked to gastrointestinal permeability. Impairment of the mucosal barrier plays an important role in the pathophysiology of acute pancreatitis. (Nijmeijer et al., 2013).

CEL encodes carboxyl-ester lipase, mutations can cause an autosomal dominant syndrome of maturity-onset diabetes of the young (MODY) and exocrine pancreatic dysfunction (Molven et al., 2015).

Syndromes that Include Pancreatitis or Pancreatic Insufficiency

Several genes are associated with rare disorders in which pancreatitis or pancreatic insufficiency is part of their phenotype (Durie, 1996; Lerch, Zenker, Turi, & Mayerle, 2006).

Disease	Gene	Consequence
Shwachman-Diamond syndrome	SBDS	affect RNA function
Mitochondrial(mt)DNA deletions		defective oxidative phosphorylation
carboxyl ester lipase (CEL-MODY)	CEL	pancreatic exocrine, endocrine dysfunction, and chronic pancreatitis
Johanson-Blizzard syndrome	UBD1	protein synthesis

As the number of genes and mutations involved in the onset and progression of pancreatitis becomes higher (Ooi et al., 2010; Walker, Warren, Gawn, & Jiao, 2013), the time and cost of screening and sequencing specific genes continues to increase. However, massive parallel sequencing or next generation sequencing (NGS) is becoming standardized (Ballard et al., 2015), and the cost per patient is rapidly dropping (Palermo et al., 2016). NGS includes whole genome sequencing, whole exome sequencing (WES) and other methods. Because the cost of WES is now less than the cost of sequencing **CFTR** use of this technology is becoming an attractive alternative to classic targeted gene sequencing or mutation specific genotyping for a genetic counseling workup (J. LaRusch et al., 2012).

Clinical Validity and Utility

Testing for mutations in the **PRSSI**, **SPINK**, and **CFTR** genes is usually done by either direct sequence analysis or next generation sequencing, both of which have high analytic validity. Several studies have evaluated the clinical validity of genetic testing (Applebaum-Shapiro et al., 2001; Ceppa et al., 2013; Poddar, Yachha, Mathias, & Choudhuri, 2015; Sultan, Werlin, &

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Venkatasubramani, 2012). One limitation with some studies was lack of inclusion of patients with clinically defined hereditary pancreatitis. Hence, the true clinical sensitivity and specificity of genetic testing in hereditary pancreatitis cannot be accurately determined and needs to be further researched. Similarly, there is a lack of published literature on the clinical utility of testing. Further research is required to evaluate how genetic testing will impact patient management decision and clinical outcomes.

Kumar et al (2016) sought to characterize and identify risk factors associated with ARP and CP in childhood in a multinational cross sectional study (INSPPIRE). They found that “At least 1 gene mutation in pancreatitis-related genes was found in 48% of patients with ARP vs 73% of patients with CP ($P < .001$). Children with *PRSS1* or *SPINK1* mutations were more likely to present with CP compared with ARP (*PRSS1*: OR = 4.20; 95% CI, 2.14-8.22; $P < .001$; and *SPINK1*: OR = 2.30; 95% CI, 1.03-5.13; $P = .04$). Obstructive risk factors did not differ between children with ARP or CP (33% in both the ARP and CP groups), but toxic/metabolic risk factors were more common in children with ARP (21% overall; 26% in the ARP group and 15% in the CP group; OR = 0.55; 95% CI, 0.31-0.99; $P = .046$).” They conclude that “Genetic mutations are common in both ARP and CP. Ethnicity and mutations in *PRSS1* or *SPINK1* may influence the development of CP. The high disease burden in pediatric CP underscores the importance of identifying predisposing factors for progression of ARP to CP in children.”

Gabarczyk (2017) et al also found that *CTRC* variants are strong CP risk factors in pediatric patients. They showed that p.Arg254Trp (4.6%) and p.Lys247_Arg254del (5.3%) heterozygous mutations are frequent and significantly associated with CP risk in pediatric patients (odds ratio [OR]=19.1; 95% CI 2.8-160; $P=0.001$ and OR=5.5; 95% CI 1.6-19.4; $P=0.001$, respectively) and that the c.180TT genotype of common p.Gly60Gly variant is strong, an independent CP risk factor (OR=23; 95% CI 7.7-70; $P<0.001$) with effect size comparable to p.Arg254Trp mutation.

According to Whitcomb (2017), genetic testing for pancreatitis susceptibility genes (*PRSS1*, *CFTR*, *SPINK1*, and *CTRC*) in symptomatic patients should be considered in patients who meet any of the following criteria:

- An unexplained documented episode of pancreatitis as a child
- Idiopathic chronic pancreatitis, particularly when the onset of pancreatitis occurs before age 25
- A family history of recurrent acute pancreatitis, idiopathic chronic pancreatitis, or childhood pancreatitis without a known cause
- Relatives known to carry mutations associated with hereditary pancreatitis (ie, *PRSS1* mutations)
- Recurrent acute attacks of pancreatitis for which there is no identifiable cause
- Patients eligible for approved research protocols

For asymptomatic patients, predictive testing can be considered for individuals who have a first-degree relative with a known *PRSS1* mutation, but is generally not recommended for individuals under 16 years of age (D. Whitcomb, 2017). Additionally, predictive testing of *SPINK1* or *CFTR* mutations in asymptomatic individuals is of minimal value, because mutations are common and most patients with these mutations do not develop disease (D. Whitcomb, 2017).

Applicable Federal Regulations

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA'88).

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As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Practice Guidelines and Position Statements

A Consensus Committees of the **European Registry of Hereditary Pancreatic Diseases**, the **Midwest Multi-Center Pancreatic Study Group** and the **International Association of Pancreatology** developed guidelines for genetic testing of the *PRSS1* gene and genetic counseling for HP (Ellis, Lerch, & Whitcomb, 2001). The recommended indications for symptomatic patients included:

- Recurrent (two separate, documented episodes with hyperlipasemia) attacks of acute pancreatitis for which there is no explanation (anatomical anomalies, ampullary or main pancreatic strictures, trauma, viral infection, gallstones, alcohol, drugs, hyperlipidaemia, etc.)
- Unexplained chronic pancreatitis
- A family history of pancreatitis in a first- or second-degree relative
- Unexplained episode of pancreatitis in a child that required hospitalization

Predictive (presymptomatic) genetic testing of unaffected relatives is considered more complex. Predictive testing is recommended only for individuals with a first-degree relative with a defined HP gene mutation, and who are over 16 years of age and capable of making an independent a fully informed decision (Ellis et al., 2001).

The **American Society of Clinical Oncology (ASCO)** states that “genetic testing is sometimes considered for patients who develop recurrent pancreatitis at young ages. Genetic testing is available for mutations in the *PRSS1*, *SPINK1*, and *CFTR* genes”(“American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility," 2003).

In 2013, the **American College of Gastroenterology** issued guidelines for the management of acute pancreatitis. They include the following recommendation: “genetic testing may be considered in young patients (< 30 years old) if no cause is evident and a family history of pancreatic disease is present (conditional recommendation, low quality of evidence)”(Tenner, Baillie, DeWitt, & Vege, 2013). ACG also states that “the role of genetic testing in AP has yet to be determined, but may be useful in patients with more than one family member with pancreatic disease. Individuals with IAP and a family history of pancreatic diseases should be referred for formal genetic counseling” (Tenner et al., 2013).

United European Gastroenterology

The United European Gastroenterology published evidence based guidelines (Lohr et al., 2017) for the diagnosis and therapy of chronic pancreatitis which recommend:

All patients with a family history or early onset disease (<20 years) should be offered genetic testing for associated variants.

Genetic screening for every CP patient cannot be recommended since alcohol abuse is the predominant cause of the disease in up to 60% of adult cases. In patients with early onset CP, genetic screening can be offered after informed consent (see Statement 1-2). Note, the genetic test results will neither change the medical treatment offered to the patient nor alter the disease course. However, it might enable some patients to understand their disease better and might even

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impact family planning. In patients with alcoholic CP, routine genetic testing cannot be recommended. Variants in SPINK1 and CTRC, and to a lesser extent, common single-nucleotide polymorphisms (SNPs) in the PRSS1 and CLDN2-MORC4 loci, are associated with alcoholic CP.

European Pancreatic Club/ Hungarian Pancreatic Study Group

The European Pancreatic Club, in collaboration with the Hungarian Pancreatic Study Group organized a consensus guideline meeting on the diagnosis and management of pancreatitis in the pediatric population which recommend:

Pediatric AP and RAP often develop in the background of genetic susceptibility and genetic testing is warranted in patients with a second episode of idiopathic AP or first episode of idiopathic AP and a family history of AP or CP, full sequence analysis of PRSS1, SPINK1, CTRC, CPA1 and CFTR gene exons and exon-intron boundaries and testing for the pathogenic CEL hybrid allele are recommended. Variants in the PRSS1 and CPA1 genes may be associated with a family history of pancreatitis or even autosomal dominant hereditary pancreatitis. Children with a single episode of AP are at risk for developing a second episode. However, genetic testing is cumbersome and expensive. There is usually no therapeutic consequence, but it may assist in long term prognosis.

The presence of mutations in the above mentioned genes increases the risk of ARP and CP. Hereditary pancreatitis associated with mutations in *PRSS1*, especially p.R122H that could considerably increase the risk of pancreatic adenocarcinoma. Knowing the genetic risk factors may not alter the therapy, but it helps to understand the disease's etiological background for the disease and may lead to future targeted investigation.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81222, 81223, 81224, 81401, 81404, 81405, 81479

Code Number	PA Required	PA Not Required	Not Covered
81222	X		
81223	X		
81224	X		
81401	X		
81404	X		
81405	X		
81479	X		

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. (2003). *J Clin Oncol*, 21(12), 2397-2406. doi:10.1200/jco.2003.03.189

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Policy Implementation/Update Information

1/1/2019 BCBSNC will provide coverage for genetic testing for hereditary pancreatitis when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.