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Corporate Medical Policy

Genetic Testing for Hereditary Pancreatitis AHS – M2079

File Name:	genetic_testing_for_hereditary_pancreatitis
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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) (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 (LaRusch, Barmada, Solomon, & Whitcomb, 2012).

Related Policies
Pancreatic Enzyme Testing for Acute Pancreatitis AHS-G2153
General Genetic Testing, Germline Disorders AHS-M2145
General Genetic Testing, Somatic Disorders AHS-M2146

******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 the medical criteria or reimbursement guidelines 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 (Note 1) 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

c. A 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

Note 1: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing, please refer to the Laboratory Procedures Reimbursement Policy AHS – R2162

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).

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 the structural integrity of the pancreas, changes in arrangement and composition of the islets, and deformation of the large ducts, eventually leading to the impairment of both exocrine and endocrine functions ((Brock, Nielsen, Lelic, & Drewes, 2013). The annual incidence of the disease has been estimated to 5-10 per 100,000 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 (Etemad & Whitcomb, 2001; Sun et al., 2015). The genetic factors listed in TIGAR-O are *PRSS1* (listed as "cationic trypsinogen"), *CFTR*, *SPINK1*, and alpha-1-antitrypsin (listed as "possible") (Etemad & Whitcomb, 2001). TIGAR-O Version 2 was published in 2019, and lists *PRSS1*, *CFTR*, *SPINK1*, *CTRC*, *CASR*, and *CEL* as genetic factors, as well as some modifier genes such as *CLDN2* (D. C. Whitcomb, 2019).

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 genes associated with HP 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 (D.C. Whitcomb, 2019).

Genes Linked to Hereditary Pancreatitis

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 (LaRusch et al., 2012; Masson, Le Marechal, Delcenserie, Chen, & Ferec, 2008)causing autosomal dominant pancreatitis in 60%-100% of families with hereditary pancreatitis (LaRusch & Whitcomb, 2011).

SPINK1 encodes serine protease inhibitor, Kazel-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).

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

***CFTR* e**ncodes the cystic fibrosis transmembrane conductance protein. Mutations are associated with recurrent acute and chronic pancreatitis since dysfunctional CFTR can result in retention of zymogens that can become active and result in pancreatitis (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, CLDN2 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).

CPA1 encodes carboxypeptidase A1, mutation CPA1 is associated with nonalcoholic chronic pancreatitis, especially with an early age of onset (Witt et al., 2013). Risk for chronic pancreatitis unrelated to trypsin activation appears to be related to endoplasmic reticulum stress from pathogenic CPA1 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, and CEL 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).

Disorders	Genetic Causes	Consequence(s)	Source Citation
Shwachman-Diamond syndrome	SBDS, DNAJC21, EFL1, and SRP54	affect RNA function	(Nelson & Myers, 2008)
Mitochondrial(mt)DNA deletion syndromes, including Kearns-Sayre syndrome (KSS), Pearson syndrome, and progressive external ophthalmoplegia (PEO)	Multiple possible mitochondrial genetic etiologies, including SLC25A4, TWNK, POLG, TYMP, OPA1, RRM2B, DNA2, and MT-TL1	defective oxidative phosphorylation	(Goldstein & Falk 2003)
Carboxyl ester lipase (CEL-MODY)	CEL	pancreatic exocrine, endocrine dysfunction, and chronic pancreatitis	(O'Neill, Stumpf, & McKusick, 2013)
Johanson-Blizzard syndrome	UBD1	protein synthesis	(Kniffin & McKusick, 2012)

As the number of genes and mutations involved in the onset and progression of pancreatitis becomes higher (Ooi, Gonska, Durie, & Freedman, 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 (LaRusch et al., 2012). In response to this accelerating development of sequencing techniques, several firms have created genetic panels focusing on hereditary pancreatitis. For example, Invitae offers a six-gene panel (*CASR, CFTR, CPA1, CTRC, PRSS1, SPINK1*) for chronic pancreatitis (Invitae). Other firms offering proprietary panels include LabCorp (3 genes) and Ambry (6 genes) (Ambry, 2020; LabCorp, 2020). Still other firms evaluate as many as 12 genes and more (D.C. Whitcomb, 2019).

Clinical Validity and Utility

Testing for mutations in the *PRSS1*, *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, & 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 acute recurrent pancreatitis (ARP) and CP in childhood in a multinational cross-sectional study (INSPPIRE). The authors analyzed 301 children with ARP or CP. 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. Children with PRSS1 or SPINK1 mutations were more likely to present with CP compared with ARP (PRSS1: OR = 4.20 and SPINK1: OR = 2.30). Obstructive risk factors presented in 33% in both groups, but toxic/metabolic risk factors were more common in children with ARP (21% overall; 26% ARP, 15% CP). They concluded that "The high disease burden in pediatric CP underscores the importance of identifying predisposing factors for progression of ARP to CP in children (Kumar et al., 2016)."

Gabarczyk (2017) et al also found that CTRC variants are strong CP risk factors in pediatric patients. The authors investigated 136 pediatric patients with CP and compared them to 401 controls. 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). The c.180TT genotype of common p.Gly60Gly variant was found to be a strong and independent CP risk factor (OR=23; 95% CI 7.7-70; P<0.001) with effect size comparable to p.Arg254Trp mutation (Grabarczyk et al., 2017).

Schwarzenberg et al evaluated the genetic spectrum of CP. 76 CP patients were examined, and 51 were found to have a genetic risk factor for CP. Of these 51 mutations, 33 were a PRSS1 mutation, 14 were a SPINK1 mutation, 11 were a CFTR mutation, and 2 were a CTRC mutation. The final 25 patients were found to have an obstructive risk factor (Schwarzenberg et al., 2015).

Zou et al evaluated the prevalence of four CP-related genes (*SPINK1, PRSS1, CTRC, CFTR*) in Han Chinese patients. The authors performed next-generation sequencing on 1061 patients and 1196 controls. The 1061 patients were further divided into three categories, idiopathic CP (ICP, 715 patients), alcoholic CP (ACP, 206), and smoking-associated CP (SCP, 140). The impact of rare pathogenic variants on age of onset and clinical outcomes was evaluated. Rare pathogenic variants were found in 535 CP patients compared to 71 controls. Mutation positive patients were found to have earlier age of onset as well additional clinical features such as pancreatic stones and diabetes mellitus compared to mutation negative ICP patients. Overall, pathogenic variants were found in 57.1% of ICP patients, compared to 39.8% of ACP patients and 32.1% of SCP patients. The authors concluded that rare pathogenic variants "significantly" influenced age of onset and clinical outcomes of CP (Zou et al., 2018).

Guidelines and Recommendations

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).

American Society of Clinical Oncology (ASCO)

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 (ASCO, 2018)."

American College of Gastroenterology (ACG)

In 2013, the ACGissued 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)". 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, Baillie, DeWitt, & Vege, 2013).

In 2020, the ACG published an update on chronic pancreatitis. In it, they recommend genetic testing in patients "with clinical evidence of a pancreatitis-associated disorder or possible CP [chronic pancreatitis] in which the etiology is unclear, especially in younger patients (strong recommendation, low quality of evidence)". The guideline goes on to state that "at minimum, patients with idiopathic CP should be evaluated for *PRSS1*, *SPINK1*, *CFTR*, and *CTRC* gene mutation analysis…" The guideline mentions that assessment of germline mutations is primarily for prognostic and therapeutic purposes, rather than diagnostic (Gardner et al., 2020).

United European Gastroenterology (2017)

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."

"In patients with alcoholic CP, routine genetic testing cannot be recommended."

The working group also noted that "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" (Lohr et al., 2017).

European Pancreatic Club/ Hungarian Pancreatic Study Group (EPC/HPSG, 2018)

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 state (Parniczky et al., 2018):

"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 (Parniczky et al., 2018)."

International Study Group of Pediatric Pancreatitis: In search for a cuRE (INSPPIRE) Consortium (2017)

This group was formed "to collect detailed information on a cohort of children with ARP and CP with the aim to fill gaps in knowledge and improve clinical care". Their genetic testing-related guidelines are listed below:

- "The search for a genetic cause of ARP or CP should include a sweat chloride test (even if newborn screening for cystic fibrosis (CF) is negative) and PRSS1 gene mutation testing. Genetic testing for CF should be considered if a sweat test is unable to be performed."

- "Mutation analysis of the genes SPINK1, CFTR and CTRC may identify risk factors for ARP or CP."

- "Patients with ARP or CP and a sweat test <=60 mmol/L should have expanded CFTR mutation testing done if there is no other identified cause of their pancreatic disease (such as a PRSS1 mutation or a clear obstructive etiology) (Gariepy et al., 2017)."

National Comprehensive Cancer Network (NCCN, 2019)

The NCCN lists chronic pancreatitis as a risk factor for pancreatic adenocarcinoma and specifically lists PRSS1, SPINK1, and CFTR as contributing genes to CP (familial pancreatitis) (NCCN, 2019).

Applicable Federal Regulations

A search on the FDA website on March 24, 2020 for "pancreatitis" yielded no genetic results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (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). 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.

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

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

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Specialty Matched Consultant Advisory Panel review 7/2019

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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)
8/13/2019	Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2019. (jd)
9/10/2019	Reviewed by Avalon 2nd Quarter 2019 CAB. Related Policies added to Description section. Minor revision to When Covered section; removed "Unexplained pancreatitis with" from item 1c. Policy guidelines and references updated. Code table removed from Billing/Coding section. Medical Director review 8/2019. (jd)
10/29/19	Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)
7/28/20	Reviewed by Avalon 2nd Quarter 2020 CAB. Note 1 added to When Covered section. Policy guidelines and references updated. Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)