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Genetic Testing for Hereditary Pancreatitis

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Line(s) of Business: HMO; PPO; QUEST Integration; Medicare; FEP	**Precertification:** Refer to the GTM Utilization Review Matrix

I. Policy Description

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 et al., 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 et al., 2012).

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) For individuals under 20 years of age, genetic testing for hereditary pancreatitis (see Note 1) **MEETS COVERAGE CRITERIA** when at least **one** of the following conditions is met:
   a) For individuals with recurrent (two separate, documented episodes with hyperlipasemia) attacks of acute pancreatitis for which there is no identifiable cause.
   b) For individuals with unexplained chronic pancreatitis.
   c) For individuals with a first- or second-degree relative (see Note 2) with a history of recurrent acute pancreatitis, idiopathic chronic pancreatitis, **or** childhood pancreatitis without a known cause.
   d) For individuals with an unexplained episode of pancreatitis that required hospitalization.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

2) For all other situations not described above, genetic testing for hereditary pancreatitis **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement Policy.

Note 2: First-degree relatives include parents, full siblings, and children of the individual. Second-degree relatives include grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings of the individual.

III. Table of Terminology

Term	Definition
ACG	American College of Gastroenterology
AP	Acute pancreatitis
ARP	Acute recurrent pancreatitis
ARUP	Associated Regional and University Pathologists, Inc.
ASCO	American Society of Clinical Oncology
CASR	*Calcium sensing receptor*
CEL	Carboxyl ester lipase
CF	Cystic fibrosis
CFTR	*Cystic fibrosis transmembrane conductance regulator*
CLDN2	*Claudin-2*
CP	Chronic pancreatitis
CPA1	Carboxypeptidase A1
CTRC	*Chymotrypsin C*
DNA	Deoxyribonucleic acid
DNA2	*Deoxyribonucleic acid replication helicase/nuclease 2*
DNAJC21	*Deoxyribonucleic acid J heat shock protein family (Hsp40) member C21*
EFL1	*Elongation factor like-1*
EPC	European Pancreatic Club
HP	Hereditary pancreatitis
HPSG	Hungarian Pancreatic Study Group
IAP	Idiopathic acute pancreatitis
INSPPIRE	International Study Group of Pediatric Pancreatitis
KSS	Kearns-Sayre syndrome
MAGI2	*Membrane-associated Guanylate Kinase Inverted-2*
MODY	Maturity-onset diabetes of the young
MT	Mitochondrial
MYO9B	Myosin IXB
NAPS2	North American Pancreatitis Study 2

NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
OPA1	*Mitochondrial dynamin*
OR	Odds ratio
PARD3	Partitioning defective 3
PEO	Progressive external ophthalmoplegia
POLG	*DNA polymerase subunit gamma*
PRSS1	*Cationic* trypsinogen
RAP	Recurrent acute pancreatitis
RRM2B	*Ribonucleotide-diphosphate reductase subunit M2*
SBDS	Shwachman-Bodian-Diamond syndrome
SCP	Smoking-associated chronic pancreatitis
SLC25A4	*Solute carrier family 25 member 4*
SPINK1	Serine protease inhibitor
SRP54	*Pancreatic secretory trypsin inhibitor Kazal type 1*
TIGAR-O	Toxic-Metabolic; Idiopathic; Genetic; Autoimmune; Recurrent and Severe Acute Pancreatitis; Obstructive
TWNK	Twinkle mitochondrial deoxyribonucleic acid helicase
TYMP	Thymidine phosphorylase
UEG	United European Gastroenterology
WES	Whole exome sequencing

IV. Scientific 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; 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 resulting in the impairment of both exocrine and endocrine functions (Brock et al., 2013). The annual incidence of the disease has been estimated to be 5-10 per 100,000 persons (Molven et al., 2015). The main symptom of CP is pain; however, it is highly variable in character, frequency, and severity (Mullady et al., 2011; 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). Genetic risk factors play a larger role in early-onset CP as opposed to late-onset CP. Older adults have a host of

environmental and genetic factors that contribute to CP development while hereditary pancreatitis is postulated to make up less than 4% of CP in late-onset groups (Wertheim-Tysarowska et al., 2021).

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* (Whitcomb, 2019).

Hereditary pancreatitis (HP) presents as an autosomal dominant chronic pancreatitis with variable penetrance. It mainly develops in childhood (Wertheim-Tysarowska et al., 2021). 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. HP is recognized when pathogenic gene variants of the *PRSS1* gene are found or when acute or chronic pancreatitis develops with a distinct family history (Wertheim-Tysarowska et al., 2021). 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 (Schwarzenberg, 2023).

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 et al., 2008), causing autosomal dominant pancreatitis in 60%-100% of families with hereditary pancreatitis (LaRusch & Whitcomb, 2011). "The age of onset for *PRSS-1* related HP ranges from 10 to 12 years" (Hasan et al., 2018).

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 (Whitcomb, 2004).

CFTR encodes 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; mutated 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).

TRPV6 is a potential novel susceptibility gene for CP that plays a role in epithelial calcium absorption and reabsorption. Variants of this gene also co-occur with pathogenic variants of genes such as *SPINK1* and *CFTR* (Wertheim-Tysarowska et al., 2021).

Syndromes that Include Pancreatitis or Pancreatic Insufficiency

Disorder(s)	Genetic Cause(s)	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 et al., 2013)
Johanson-Blizzard syndrome	*UBD1*	protein synthesis	(Kniffin & McKusick, 2012)

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

As the number of genes and mutations involved in the onset and progression of pancreatitis becomes higher (Ooi et al., 2010; Walker et al., 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, 2023). Other firms offering proprietary panels include ARUP Laboratories (4 genes), LabCorp (3 genes), and Ambry (6 genes) (Ambry, 2023; ARUP, 2023; LabCorp, 2023). Still other firms evaluate as many as 12 genes and more (Schwarzenberg, 2023).

Clinical Utility and Validity

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 et al., 2015; Sultan et al., 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).

Grabarczyk et al. (2017) 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. (2015) 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. (2018) 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).

Nabi et al. (2020) evaluated 239 children in a prospective study from January 2015 to May 2018 to examine genetic risk factors in children with idiopathic acute recurrent pancreatitis (IARP). Among the enrollees, 85.35% children had IARP, and found that family history of pancreatitis was found among 4.6% of participants. For specific genes, "mutations/polymorphisms in at least 1 gene were identified in 89.5% (129/144) children including *SPINK1* in 41.9%, *PRSS1* (rs10273639) in 58.2%, *CTRC* in 25.6%, *CTSB* in 54.9%, *CLDN2* in 72.9%, and *CFTR* in 2.3%." This conveys the overlapping genetic nature of IARP with related genes in HP, making genetic testing important for managing potential disease progression.

Suzuki et al. (2020) investigated the currently understood genetic abnormalities in pancreatitis, and found that "patients with these genetic predispositions [*PRSS1* and *SPINK1* genes], both children and adults, have often been initially diagnosed with idiopathic acute pancreatitis, in approximately 20-50% pediatric cases and 28-0% of adult cases… Patients with chronic pancreatitis (CP) due to *SPINK1* gene mutation and HP patients have a potentially high risk of pancreatic exocrine insufficiency, diabetes mellitus, and of particular importance, pancreatic cancer." This conveys the continuously emphasized clinical utility of genetic testing to pursue opportunities for counselling and symptom management with disease progression, despite not having gene therapy options for directly targeting HP causing and associated genes (Suzuki et al., 2020).

Weiss et al. (2020) discussed the potential pitfalls from using next generation sequencing (NGS) to diagnose *PRSS1* mutations in chronic pancreatitis. Due to the "high degree of DNA sequence homology (>91%) between *PRSS1* and other members of the trypsinogen multigene family," there may be erroneous diagnoses of pathologic chronic pancreatitis among patients with benign variants of other *PRSS1*- related genes, like *PRSS2* or *PRSS3P2*. The researchers concluded that sequence homology "can confound the mapping of short NGS reads to a reference genome and lead to technical artefacts." They recommend "careful clinical evaluation, pretest and post-test genetic counselling and confirmation of NGS test results by Sanger sequencing" to confirm a diagnosis of genetically mutated chronic

pancreatitis. This presented the precautions that must be accounted for when utilizing genetic testing for hereditary pancreatitis (Weiss et al., 2020).

Zou et al. (2020) performed whole genome sequencing on a population of 464 Chinese CP patients and on a group of 504 control participants. The *Transient receptor potential cation channel, Subfamily V, Member 6 (TRPV6)* gene was identified as a gene significantly associated with chronic pancreatitis through a "burden test of aggregated rare nonsynonymous variants with a combined annotation dependent depletion score > 20 (p = .020)." In another phase of the study, Sanger sequencing was used to analyze the entire coding sequence and exon/intron boundaries of the *TPRV6* gene. Combining the two phases of the study, the authors identified 25 distinct variants of *TPRV6* and noted that loss-of-function variants were over-represented in the chronic pancreatitis group. The authors concluded that *TPRV6* is likely a novel susceptibility gene for chronic pancreatitis.

V. Guidelines and Recommendations

Consensus Committees of the European Registry of Hereditary Pancreatic Diseases, the Midwest Multi-Center Pancreatic Study Group and the International Association of Pancreatology

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 et al., 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 and fully informed decision (Ellis et al., 2001).

American Society of Clinical Oncology (ASCO)

The 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." However, the authors note that "it is unknown if mutations in these genes cause an increased risk of pancreatic cancer. The authors believe that other genes may be associated with HP, and studies are ongoing to learn more about this condition" (ASCO, 2021). It is also noted that "Screening for pancreatic cancer is suggested for people known to have HP beginning at age 40, 20 years after the onset of pancreatitis, or 10 years before the youngest pancreatic cancer diagnosis in the family, whichever is earliest. However, the effectiveness of current screening techniques for the early diagnosis

of pancreatic cancer is not proven." Nevertheless, the most commonly used screening tests include magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) (ASCO, 2021).

American College of Gastroenterology (ACG)

In 2013, the ACG 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)." 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).

In 2020, the ACG published clinical guidelines on chronic pancreatitis. There, they state that "In patients with clinical features of CP, a comprehensive review of all risk factors should be performed. This provides information on the underlying mechanisms, identifies both fixed and modifiable risk factors, identifies potential targets for therapies, and provides clinically relevant prognostic information." As part of that initial approach, 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 (UEG)

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

"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 (EPC) and Hungarian Pancreatic Study Group (HPSG)

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 the following:

"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". The authors go further to mention that "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" (Parniczky et al., 2018).

"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).

Regarding the etiological factors in childhood onset CP, the authors assert that "Genetic variations are the most common risk factors for development of pediatric CP. *(GRADE 1/A, full agreement)* However, other risk factors such as obstruction, autoimmune and toxic and metabolic factors also need to be examined. *(GRADE 2/B, full agreement)*". Moreover, as "There is an association between CP and cystic fibrosis (CF), therefore a sweat test should be performed to screen for CF as a possible etiological factor in children. *(GRADE 1/A, strong agreement)*" (Parniczky et al., 2018).

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

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)

The NCCN notes familial pancreatitis and non-hereditary forms of pancreatitis are both linked with an increased risk of pancreatic cancer. Additionally, chronic pancreatitis is another risk factor for pancreatic cancer. The NCCN specifically lists *PRSS1*, *SPINK1*, and *CFTR* as contributing genes to familial pancreatitis. The approximate increase in risk of pancreatic cancer is somewhere between 26-fold and 87-fold in those with the *PRSS1*, *SPINK1*, and *CFTR* gene mutations (NCCN, 2023).

International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, and European Pancreatic Club

In 2020, the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club released a set of international consensus guidelines on surveillance for pancreatic cancer in the setting of chronic pancreatitis. Though the working group did not explicitly endorse or oppose genetic testing, it was clear that due to the recommendations separated by genetic variants within chronic pancreatitis, genetic testing would become critical for surveillance. With regards to the conditions by which hereditary pancreatitis would warrant surveillance for cancer, the working group stated:

- "The risk of pancreatic cancer in affected individuals with an autosomal dominant history of hereditary pancreatitis due to inherited *PRSS1* mutations is high enough to justify surveillance. *Quality assessment: high; recommendation: strong*"
- "The risk of pancreatic cancer in affected individuals with an autosomal dominant history of hereditary pancreatitis but without *PRSS1* mutations is high enough to justify surveillance. *Quality assessment: moderate; recommendation: weak*"
- "The risk of pancreatic cancer in patients with chronic pancreatitis associated with *SPINK1* p. N34S is not high enough to justify screening or surveillance. *Quality assessment: moderate; recommendation: strong*"
- "The risk of pancreatic cancer in patients with chronic pancreatitis associated with other germline mutations including those of *CFTR, CTRC, CPA1, and CEL*, is not high enough to justify screening or surveillance. *Quality assessment: moderate; recommendation: conditional*" (Greenhalf et al., 2020).

National Institute for Health and Care Excellence (NICE)

NICE updated their guidelines on pancreatitis in December 2020. With regards to genetic testing for hereditary pancreatitis (acute) and patient information, NICE stated the following:

> "Give people with pancreatitis, and their family members or carers (as appropriate), written and verbal information on the following, where relevant, as soon as possible after diagnosis:
>
> - pancreatitis and any proposed investigations and procedures, using diagrams
> - hereditary pancreatitis, and pancreatitis in children, including specific information on genetic counselling, genetic testing, risk to other family members, and advice on the impact of their pancreatitis on life insurance and travel
> - the long-term effects of pancreatitis, including effects on the person's quality of life

- the harm caused to the pancreas by smoking or alcohol."

For an individual with chronic pancreatitis, NICE recognizes that the cause may not be alcohol-related, but can include "genetic factors; autoimmune disease, in particular IgG4 disease; metabolic causes; [and] structural or anatomical factors" (NICE, 2020).

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VIII. Evidence-based Scientific References

Ambry. (2023). Pancreatitis panel. https://www.ambrygen.com/clinician/genetic-testing/69/exome-and-general-genetics/pancreatitis-panel

Applebaum-Shapiro, S. E., Finch, R., Pfutzer, R. H., Hepp, L. A., Gates, L., Amann, S., Martin, S., Ulrich, C. D., 2nd, & Whitcomb, D. C. (2001). Hereditary pancreatitis in North America: the Pittsburgh-Midwest Multi-Center Pancreatic Study Group Study. *Pancreatology*, *1*(5), 439-443. https://doi.org/10.1159/000055844

ARUP. (2023). *Pancreatitis Panel (CFTR, CTRC, PRSS1, SPINK1), Sequencing*. https://ltd.aruplab.com/Tests/Pub/3004788

ASCO. (2021). *Hereditary Pancreatitis*. https://www.cancer.net/cancer-types/hereditary-pancreatitis

Ballard, D. D., Flueckiger, J. R., Fogel, E. L., McHenry, L., Lehman, G. A., Watkins, J. L., Sherman, S., & Cote, G. A. (2015). Evaluating Adults With Idiopathic Pancreatitis for Genetic Predisposition: Higher Prevalence of Abnormal Results With Use of Complete Gene Sequencing. *Pancreas*, *44*(1), 116-121. https://doi.org/10.1097/mpa.0000000000000225

Brock, C., Nielsen, L. M., Lelic, D., & Drewes, A. M. (2013). Pathophysiology of chronic pancreatitis. *World J Gastroenterol*, *19*(42), 7231-7240. https://doi.org/10.3748/wjg.v19.i42.7231

Ceppa, E. P., Pitt, H. A., Hunter, J. L., Leys, C. M., Zyromski, N. J., Rescorla, F. J., Sandrasegaran, K., Fogel, E. L., McHenry, L. W., Watkins, J. L., Sherman, S., & Lehman, G. A. (2013). Hereditary pancreatitis: endoscopic and surgical management. *J Gastrointest Surg*, *17*(5), 847-856; discussion 856-847. https://doi.org/10.1007/s11605-013-2167-8

Durie, P. R. (1996). Inherited and congenital disorders of the exocrine pancreas. *Gastroenterologist*, *4*(3), 169-187. https://www.ncbi.nlm.nih.gov/pubmed/8891682

Ellis, I., Lerch, M. M., & Whitcomb, D. C. (2001). Genetic testing for hereditary pancreatitis: guidelines for indications, counselling, consent and privacy issues. *Pancreatology*, *1*(5), 405-415. https://www.karger.com/Article/PDF/55840

Etemad, B., & Whitcomb, D. C. (2001). Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology*, *120*(3), 682-707. https://doi.org/10.1053/gast.2001.22586

Gardner, T. B., Adler, D. G., Forsmark, C. E., Sauer, B. G., Taylor, J. R., & Whitcomb, D. C. (2020). ACG Clinical Guideline: Chronic Pancreatitis. *American Journal of Gastroenterology*, *115*(3). https://doi.org/10.14309/ajg.0000000000000535

Gariepy, C. E., Heyman, M. B., Lowe, M. E., Pohl, J. F., Werlin, S. L., Wilschanski, M., Barth, B., Fishman, D. S., Freedman, S. D., Giefer, M. J., Gonska, T., Himes, R., Husain, S. Z., Morinville, V. D., Ooi, C. Y., Schwarzenberg, S. J., Troendle, D. M., Yen, E., & Uc, A. (2017). Causal Evaluation of Acute Recurrent and Chronic Pancreatitis in Children: Consensus From the INSPPIRE Group. *J Pediatr Gastroenterol Nutr*, *64*(1), 95-103. https://doi.org/10.1097/mpg.0000000000001446

Goldstein, A., & Falk, M. (2003, 01/31/2019). *Mitochondrial DNA Deletion Syndromes*. University of Washington, WA. https://www.ncbi.nlm.nih.gov/books/NBK1203/

Grabarczyk, A. M., Oracz, G., Wertheim-Tysarowska, K., Kujko, A. A., Wejnarska, K., Kolodziejczyk, E., Bal, J., Koziel, D., Kowalik, A., Gluszek, S., & Rygiel, A. M. (2017). Chymotrypsinogen C Genetic Variants, Including c.180TT, Are Strongly Associated With Chronic Pancreatitis in Pediatric Patients. *J Pediatr Gastroenterol Nutr*, *65*(6), 652-657. https://doi.org/10.1097/mpg.0000000000001767

Greenhalf, W., Lévy, P., Gress, T., Rebours, V., Brand, R. E., Pandol, S., Chari, S., Jørgensen, M. T., Mayerle, J., Lerch, M. M., Hegyi, P., Kleeff, J., Castillo, C. F., Isaji, S., Shimosegawa, T., Sheel, A., Halloran, C. M., Garg, P., Takaori, K., . . . Neoptolemos, J. (2020). International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. *Pancreatology*, *20*(5), 910-918. https://doi.org/10.1016/j.pan.2020.05.011

Grendell, J. H. (2003). Genetic factors in pancreatitis. *Curr Gastroenterol Rep*, *5*(2), 105-109. https://doi.org/10.1007/s11894-003-0078-7

Hasan, A., Moscoso, D. I., & Kastrinos, F. (2018). The Role of Genetics in Pancreatitis. *Gastrointest Endosc Clin N Am*, *28*(4), 587-603. https://doi.org/10.1016/j.giec.2018.06.001

Invitae. (2023). Invitae Chronic Pancreatitis Panel. https://www.invitae.com/en/physician/tests/01745/#info-panel-disorders_tested

Kniffin, C., & McKusick, V. (2012, 09/15/2016). *JOHANSON-BLIZZARD SYNDROME; JBS*. Johns Hopkins University. https://omim.org/entry/243800

Kumar, S., Ooi, C. Y., Werlin, S., Abu-El-Haija, M., Barth, B., Bellin, M. D., Durie, P. R., Fishman, D. S., Freedman, S. D., Gariepy, C., Giefer, M. J., Gonska, T., Heyman, M. B., Himes, R., Husain, S. Z., Lin, T. K., Lowe, M. E., Morinville, V., Palermo, J. J., . . . Uc, A. (2016). Risk Factors Associated With Pediatric Acute Recurrent and Chronic Pancreatitis: Lessons From INSPPIRE. *JAMA Pediatr*, *170*(6), 562-569. https://doi.org/10.1001/jamapediatrics.2015.4955

LabCorp. (2023). Pancreatitis: Three-gene Profile (PRSS1, SPINK1, CFTR) (Full Gene Sequencing). https://www.labcorp.com/tests/252794/pancreatitis-three-gene-profile-i-prss1-spink1-cftr-i-full-gene-sequencing

LaRusch, J., Barmada, M. M., Solomon, S., & Whitcomb, D. C. (2012). Whole exome sequencing identifies multiple, complex etiologies in an idiopathic hereditary pancreatitis kindred. *Jop*, *13*(3), 258-262. https://pubmed.ncbi.nlm.nih.gov/22572128/

LaRusch, J., Solomon, S., & Whitcomb, D. C. (2014). Pancreatitis Overview [Text]. *GEneReviews*. https://www.ncbi.nlm.nih.gov/books/NBK190101/

LaRusch, J., & Whitcomb, D. C. (2011). Genetics of pancreatitis. *Curr Opin Gastroenterol*, *27*(5), 467-474. https://doi.org/10.1097/MOG.0b013e328349e2f8

Lerch, M. M., & Gorelick, F. S. (2000). Early trypsinogen activation in acute pancreatitis. *Med Clin North Am*, *84*(3), 549-563, viii. https://doi.org/10.1016/S0025-7125(05)70239-X

Lerch, M. M., Zenker, M., Turi, S., & Mayerle, J. (2006). Developmental and metabolic disorders of the pancreas. *Endocrinol Metab Clin North Am*, *35*(2), 219-241, vii. https://doi.org/10.1016/j.ecl.2006.02.004

Li, Z. S., Wang, W., Liao, Z., Zou, D. W., Jin, Z. D., Chen, J., Wu, R. P., Liu, F., Wang, L. W., Shi, X. G., Yang, Z., & Wang, L. (2010). A long-term follow-up study on endoscopic management of children

and adolescents with chronic pancreatitis. *Am J Gastroenterol*, *105*(8), 1884-1892. https://doi.org/10.1038/ajg.2010.85

Lohr, J. M., Dominguez-Munoz, E., Rosendahl, J., Besselink, M., Mayerle, J., Lerch, M. M., Haas, S., Akisik, F., Kartalis, N., Iglesias-Garcia, J., Keller, J., Boermeester, M., Werner, J., Dumonceau, J. M., Fockens, P., Drewes, A., Ceyhan, G., Lindkvist, B., Drenth, J., . . . Bruno, M. (2017). United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). *United European Gastroenterol J*, *5*(2), 153-199. https://doi.org/10.1177/2050640616684695

Masson, E., Le Marechal, C., Delcenserie, R., Chen, J. M., & Ferec, C. (2008). Hereditary pancreatitis caused by a double gain-of-function trypsinogen mutation. *Hum Genet*, *123*(5), 521-529. https://doi.org/10.1007/s00439-008-0508-6

Molven, A., Njolstad, P. R., & Weiss, F. U. (2015). Lipase gene fusion: a new route to chronic pancreatitis. In *Oncotarget* (Vol. 6, pp. 30443-30444). https://doi.org/10.18632/oncotarget.5454

Mullady, D. K., Yadav, D., Amann, S. T., O'Connell, M. R., Barmada, M. M., Elta, G. H., Scheiman, J. M., Wamsteker, E. J., Chey, W. D., Korneffel, M. L., Weinman, B. M., Slivka, A., Sherman, S., Hawes, R. H., Brand, R. E., Burton, F. R., Lewis, M. D., Gardner, T. B., Gelrud, A., . . . Anderson, M. A. (2011). Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. *Gut*, *60*(1), 77-84. https://doi.org/10.1136/gut.2010.213835

Nabi, Z., Talukdar, R., Venkata, R., Aslam, M., Shava, U., & Reddy, D. N. (2020). Genetic Evaluation of Children with Idiopathic Recurrent Acute Pancreatitis. *Dig Dis Sci*, *65*(10), 3000-3005. https://doi.org/10.1007/s10620-019-06026-2

NCCN. (2023, December 13, 2023). *NCCN Clinical Practice Guidelines in Oncology - Pancreatic Adenocarcinoma Version 1.2024 - December 13, 2023*. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

Nelson, A., & Myers, K. (2008, 10/18/2018). *Shwachman-Diamond Syndrome*. University of Washington, Seattle. https://www.ncbi.nlm.nih.gov/books/NBK1756/

NICE. (2020, December 16). *Pancreatitis*. Retrieved April 22 from https://www.nice.org.uk/guidance/ng104/chapter/Recommendations

Nijmeijer, R. M., van Santvoort, H. C., Zhernakova, A., Teller, S., Scheiber, J. A., de Kovel, C. G., Besselink, M. G., Visser, J. T., Lutgendorff, F., Bollen, T. L., Boermeester, M. A., Rijkers, G. T., Weiss, F. U., Mayerle, J., Lerch, M. M., Gooszen, H. G., Akkermans, L. M., & Wijmenga, C. (2013). Association analysis of genetic variants in the myosin IXB gene in acute pancreatitis. *PLoS One*, *8*(12), e85870. https://doi.org/10.1371/journal.pone.0085870

O'Neill, M., Stumpf, A., & McKusick, V. (2013, 09/10/2013). *MATURITY-ONSET DIABETES OF THE YOUNG, TYPE 8, WITH EXOCRINE DYSFUNCTION; MODY8*. Johns Hopkins University. https://omim.org/entry/609812

Ooi, C. Y., Gonska, T., Durie, P. R., & Freedman, S. D. (2010). Genetic testing in pancreatitis. *Gastroenterology*, *138*(7), 2202-2206, 2206.e2201. https://doi.org/10.1053/j.gastro.2010.04.022

Palermo, J. J., Lin, T. K., Hornung, L., Valencia, C. A., Mathur, A., Jackson, K., Fei, L., & Abu-El-Haija, M. (2016). Genophenotypic Analysis of Pediatric Patients With Acute Recurrent and Chronic Pancreatitis. *Pancreas*, *45*(9), 1347-1352. https://doi.org/10.1097/mpa.0000000000000655

Parniczky, A., Abu-El-Haija, M., Husain, S., Lowe, M., Oracz, G., Sahin-Toth, M., Szabo, F. K., Uc, A., Wilschanski, M., Witt, H., Czako, L., Grammatikopoulos, T., Rasmussen, I. C., Sutton, R., & Hegyi, P.

(2018). EPC/HPSG evidence-based guidelines for the management of pediatric pancreatitis. *Pancreatology*, *18*(2), 146-160. https://doi.org/10.1016/j.pan.2018.01.001

Poddar, U., Yachha, S. K., Mathias, A., & Choudhuri, G. (2015). Genetic predisposition and its impact on natural history of idiopathic acute and acute recurrent pancreatitis in children. *Dig Liver Dis*, *47*(8), 709-714. https://doi.org/10.1016/j.dld.2015.04.012

Ravi Kanth, V., & Nageshwar Reddy, D. (2014). Genetics of acute and chronic pancreatitis: An update. *World J Gastrointest Pathophysiol*, *5*(4), 427-437. https://doi.org/10.4291/wjgp.v5.i4.427

Schwarzenberg, S. J. (2023, September 13, 2023). *Pancreatitis associated with genetic risk factors*. UpToDate, Inc. https://www.uptodate.com/contents/pancreatitis-associated-with-genetic-risk-factors

Schwarzenberg, S. J., Bellin, M., Husain, S. Z., Ahuja, M., Barth, B., Davis, H., Durie, P. R., Fishman, D. S., Freedman, S. D., Gariepy, C. E., Giefer, M. J., Gonska, T., Heyman, M. B., Himes, R., Kumar, S., Morinville, V. D., Lowe, M. E., Nuehring, N. E., Ooi, C. Y., . . . Uc, A. (2015). Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. *J Pediatr*, *166*(4), 890-896.e891. https://doi.org/10.1016/j.jpeds.2014.11.019

Sultan, M., Werlin, S., & Venkatasubramani, N. (2012). Genetic prevalence and characteristics in children with recurrent pancreatitis. *J Pediatr Gastroenterol Nutr*, *54*(5), 645-650. https://doi.org/10.1097/mpg.0b013e31823f0269

Sun, C., Liu, M. Y., Liu, X. G., Hu, L. H., Xia, T., Liao, Z., & Li, Z. S. (2015). Serine Protease Inhibitor Kazal Type 1 (SPINK1) c.194+2T > C Mutation May Predict Long-term Outcome of Endoscopic Treatments in Idiopathic Chronic Pancreatitis. *Medicine (Baltimore)*, *94*(47), e2046. https://doi.org/10.1097/md.0000000000002046

Suzuki, M., Minowa, K., Nakano, S., Isayama, H., & Shimizu, T. (2020). Genetic Abnormalities in Pancreatitis: An Update on Diagnosis, Clinical Features, and Treatment. *Diagnostics (Basel, Switzerland)*, *11*(1), 31. https://doi.org/10.3390/diagnostics11010031

Szmola, R., & Sahin-Toth, M. (2007). Chymotrypsin C (caldecrin) promotes degradation of human cationic trypsin: identity with Rinderknecht's enzyme Y. *Proc Natl Acad Sci U S A*, *104*(27), 11227-11232. https://doi.org/10.1073/pnas.0703714104

Tandan, M., & Nageshwar Reddy, D. (2013). Endotherapy in chronic pancreatitis. *World J Gastroenterol*, *19*(37), 6156-6164. https://doi.org/10.3748/wjg.v19.i37.6156

Tenner, S., Baillie, J., DeWitt, J., & Vege, S. S. (2013). American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol*, *108*(9), 1400-1415; 1416. https://doi.org/10.1038/ajg.2013.218

Walker, N. F., Warren, O. J., Gawn, L., & Jiao, L. R. (2013). The role of genetic testing in management of hereditary chronic pancreatitis. *JRSM Short Rep*, *4*(1), 6. https://doi.org/10.1258/shorts.2012.012071

Weiss, F. U., Laemmerhirt, F., & Lerch, M. M. (2020). Next generation sequencing pitfalls in diagnosing trypsinogen (PRSS1) mutations in chronic pancreatitis. *Gut*. https://doi.org/10.1136/gutjnl-2020-322864

Werlin, S., Konikoff, F. M., Halpern, Z., Barkay, O., Yerushalmi, B., Broide, E., Santo, E., Shamir, R., Shaoul, R., Shteyer, E., Yaakov, Y., Cohen, M., Kerem, E., Ruszniewski, P., Masson, E., Ferec, C., & Wilschanski, M. (2015). Genetic and electrophysiological characteristics of recurrent acute pancreatitis. *J Pediatr Gastroenterol Nutr*, *60*(5), 675-679. https://doi.org/10.1097/mpg.0000000000000623

Wertheim-Tysarowska, K., Oracz, G., & Rygiel, A. M. (2021). Genetic Risk Factors in Early-Onset Nonalcoholic Chronic Pancreatitis: An Update. *Genes*, *12*(5), 785. https://doi.org/10.3390/genes12050785

Whitcomb, D. C. (1999). Early trypsinogen activation in acute pancreatitis. *Gastroenterology*, *116*(3), 770-772. https://www.gastrojournal.org/article/S0016-5085(99)70205-2/fulltext

Whitcomb, D. C. (2004). Mechanisms of disease: Advances in understanding the mechanisms leading to chronic pancreatitis. *Nat Clin Pract Gastroenterol Hepatol*, *1*(1), 46-52. https://doi.org/10.1038/ncpgasthep0025

Whitcomb, D. C. (2019). Pancreatitis: TIGAR-O Version 2 Risk/Etiology Checklist With Topic Reviews, Updates, and Use Primers. *Clin Transl Gastroenterol*, *10*(6), e00027. https://doi.org/10.14309/ctg.0000000000000027

Whitcomb, D. C., Yadav, D., Adam, S., Hawes, R. H., Brand, R. E., Anderson, M. A., Money, M. E., Banks, P. A., Bishop, M. D., Baillie, J., Sherman, S., DiSario, J., Burton, F. R., Gardner, T. B., Amann, S. T., Gelrud, A., Lo, S. K., DeMeo, M. T., Steinberg, W. M., . . . Barmada, M. M. (2008). Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). *Pancreatology*, *8*(4-5), 520-531. https://doi.org/10.1159/000152001

Witt, H., Beer, S., Rosendahl, J., Chen, J. M., Chandak, G. R., Masamune, A., Bence, M., Szmola, R., Oracz, G., Macek, M., Jr., Bhatia, E., Steigenberger, S., Lasher, D., Buhler, F., Delaporte, C., Tebbing, J., Ludwig, M., Pilsak, C., Saum, K., . . . Sahin-Toth, M. (2013). Variants in CPA1 are strongly associated with early onset chronic pancreatitis. *Nat Genet*, *45*(10), 1216-1220. https://doi.org/10.1038/ng.2730

Zou, W. B., Tang, X. Y., Zhou, D. Z., Qian, Y. Y., Hu, L. H., Yu, F. F., Yu, D., Wu, H., Deng, S. J., Lin, J. H., Zhao, A. J., Zhao, Z. H., Wu, H. Y., Zhu, J. H., Qian, W., Wang, L., Xin, L., Wang, M. J., Wang, L. J., . . . Liao, Z. (2018). SPINK1, PRSS1, CTRC, and CFTR Genotypes Influence Disease Onset and Clinical Outcomes in Chronic Pancreatitis. *Clin Transl Gastroenterol*, *9*(11), 204. https://doi.org/10.1038/s41424-018-0069-5

Zou, W. B., Wang, Y. C., Ren, X. L., Wang, L., Deng, S. J., Mao, X. T., Li, Z. S., & Liao, Z. (2020). TRPV6 variants confer susceptibility to chronic pancreatitis in the Chinese population. *Hum Mutat*, *41*(8), 1351-1357. https://doi.org/10.1002/humu.24032

IX. Policy History

Action Date	Action
June 01, 2023	Policy created
December 03, 2024	Policy approved by Medical Directors
December 20, 2024	Policy approved at UMC
February 01, 2025	Policy effective date following notification period