BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.99 Genetic Testing for Hereditary Pancreatitis

Effective Policy Date: July 1, 2022

Original Policy Date: December 2013

Related Policies:

None

Genetic Testing for Hereditary Pancreatitis

Description

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In chronic pancreatitis (CP), recurrent attacks of acute pancreatitis evolve into a chronic inflammatory state with exocrine insufficiency, endocrine insufficiency manifested as diabetes, and increased risk for pancreatic cancer. Hereditary pancreatitis (HP) is a subset of CP defined clinically as a familial pattern of CP. Variants of several genes are associated with HP. Demonstration of a pathogenic variant in 1 or several of these genes can potentially be used to confirm the diagnosis of HP, provide information on prognosis and management, and/or determine the risk of CP in asymptomatic relatives of patients with HP.

OBJECTIVE

The objective of this evidence review is to evaluate whether genetic testing improves the net health outcome for individuals with chronic or recurrent pancreatitis or who have a familial risk for hereditary pancreatitis. This review does not address individuals who have familial risk (See benefit application).

POLICY STATEMENT

Genetic testing for hereditary pancreatitis may be considered **medically necessary** for patients aged 18 years and younger with unexplained acute recurrent (>1 episode) or chronic pancreatitis with documented elevated amylase or lipase levels.

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

POLICY GUIDELINES

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology<97>"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"<97>to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

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

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

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

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

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

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Testing for variants associated with HP is typically done by direct sequence analysis or next-generation sequencing. A number of laboratories offer to test for the relevant genes, either individually or as panels.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for HP is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who have chronic pancreatitis (CP) or acute recurrent pancreatitis (ARP) who receive testing for genes associated with Hereditary pancreatitis (HP), the evidence includes cohort studies on variant detection rates and a systematic review. Relevant outcomes are symptoms, change in disease status, morbid events, and hospitalizations. There are studies on the detection rate of HP-associated genes in various populations. Few studies have enrolled patients with known HP; those doing so have reported detection rates for disease-associated variants between 52% and 62%. For other studies that tested patients with CP or ARP, disease-associated variant detection rates varied widely across studies. There is a lack of direct evidence that testing for HP improves health outcomes and insufficient indirect evidence that, in patients with CP or ARP, management would change after genetic testing in a manner likely to improve health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology

In 2013, the American College of Gastroenterology guidelines on management of acute pancreatitis included the following statement: "Genetic testing may be considered in young patients (<30 years old) if no cause [of acute pancreatitis] is evident, and a family history of pancreatic disease is present (conditional recommendation, low quality of evidence)."[32,]

In 2015, the American College of Gastroenterology Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes recommended genetic testing of patients with suspected familial pancreatic cancer to include analysis of *BRCA1/2, CDKN2A, PALB2*, and *ATM*. Evaluation for Peutz-Jeghers Syndrome, Lynch Syndrome, and HP-associated genes should be considered if personal and/or family history criteria are met for the syndrome.[33,]

American Pancreatic Association

In 2014, the American Pancreatic Association published Practice Guidelines in Chronic Pancreatitis: Evidence-Based Report on Diagnostic Guidelines.[34,] A classification guideline for the etiology of chronic pancreatitis (CP) includes genetic mutations in *PRSS1*, *CFTR*, *SPINK1*, and others.

American College of Medical Genetics and Genomics

In 2001[35,] (updated in 2004[36,]; reaffirmed in 2013[37,]), the American College of Medical Genetics and Genomics (ACMG) issued a policy statement on laboratory standards and guidelines for population-based cystic fibrosis carrier screening. These guidelines provided recommendations on specific variant testing in cystic fibrosis but did not specifically address genetic testing for suspected HP. In 2020, a technical standard on *CFTR* variant testing by the ACMG was released.[38,] The standard stated that indications for *CFTR* variant testing included diagnosis and carrier testing for individuals with idiopathic pancreatitis.

International Consensus Guidelines for Chronic Pancreatitis

In 2018, the working group for the International Consensus Guidelines for Chronic Pancreatitis, in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group, and the European Pancreatic Club, published consensus statements on the diagnosis and management of early CP.[39,] It included the following recommendation:

"Genetic variants are important risk factors for Early CP and can add specificity to the likely etiology, but they are neither necessary nor sufficient to make a diagnosis. (Quality assessment: moderate; Recommendation: strong; Agreement: strong)"

There was an update to the guideline in 2020, and it included the following statement: [40,]

" In idiopathic disease, full sequence analysis of the CFTR, CPA1, CTRC, PRSS1 and SPINK1 gene exons and exon-intron boundaries and testing for the CEL gene pathogenic hybrid allele is recommended in order to explore the genetic background. (Quality assessment: low; Recommendation: conditional; Agreement: conditional)"

International Study Group of Pediatric Pancreatitis

In 2017, the International Study Group of Pediatric Pancreatitis INSPPIRE (The International Study Group of Pediatric Pancreatitis: In search for a cuRE) consortium developed an expert consensus opinion on the evaluation of children with acute recurrent and chronic pancreatitis.[41,] There was a strong consensus that search for a genetic cause of acute recurrent pancreatitis or CP should include *PRSS1, SPINK1, CFTR,* and *CTRC* gene mutation testing.

American Society of Clinical Oncology

In 2018, the American Society of Clinical Oncology (ASCO) published "Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion".[42,] The ASCO reported that cancer-unaffected individuals should be offered genetic risk evaluation if they are members of families with an identified pathogenic cancer susceptibility gene variant, from families that meet criteria for genetic evaluation for known hereditary syndromes that are linked to pancreatic cancer, and from families that meet criteria for familial pancreatic cancer. ASCO further considered what surveillance strategies should be used for individuals with a predisposition to pancreatic ductal adenocarcinoma to screen for pancreatic and other cancers. Surveillance can be considered for individuals who are first-degree relatives of individuals with familial pancreatic cancer and/or individuals with a family history of pancreatic cancer who carry a pathogenic germline variant in genes associated with predisposition to pancreatic cancer.

National Comprehensive Cancer Network

In 2021, the National Comprehensive Cancer Network (NCCN) released guidelines (version 1.2021) on genetic/familial high-risk assessment for breast, ovarian, and pancreatic cancers. [43,] The NCCN recommends "germline testing for PRSS1, SPINK1, and other pancreatitis genes in individuals with a personal and/or family history of exocrine pancreatic cancer only if there is a personal and/or family history suggestive of hereditary pancreatitis".

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Whitcomb DC. Value of genetic testing in the management of pancreatitis. Gut. Nov 2004; 53(11): 1710-7. PMID 15479696
2. Solomon S, Whitcomb DC, LaRusch J. PRSS1-Related Hereditary Pancreatitis. In: Adam MP, Ardinger HH, Pagon RAW, S.E., et al., eds. GeneReviews. Seattle, WA: University of Washington; 2012.
3. Fink EN, Kant JA, Whitcomb DC. Genetic counseling for nonsyndromic pancreatitis. Gastroenterol Clin North Am. Jun 2007; 36(2): 325-33, ix. PMID 17533082
4. Whitcomb DC. Framework for interpretation of genetic variations in pancreatitis patients. Front Physiol. 2012; 3: 440. PMID 23230421
5. Rosendahl J, Witt H, Szmola R, et al. Chymotrypsin C (CTRC) variants that diminish activity or secretion are associated with chronic pancreatitis. Nat Genet. Jan 2008; 40(1): 78-82. PMID 18059268
6. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. Jun 2013; 144(6): 1252-61. PMID 23622135
7. Applebaum-Shapiro SE, Finch R, Pfutzer RH, et al. Hereditary pancreatitis in North America: the Pittsburgh-Midwest Multi-Center Pancreatic Study Group Study. Pancreatology. 2001; 1(5): 439-43. PMID 12120221
8. Ceppa EP, Pitt HA, Hunter JL, et al. Hereditary pancreatitis: endoscopic and surgical management. J Gastrointest Surg. May 2013; 17(5): 847-56; discussion 856-7. PMID 23435738
9. Weiss FU, Hesselbarth N, Parniczky A, et al. Common variants in the CLDN2-MORC4 and PRSS1-PRSS2 loci confer susceptibility to acute pancreatitis. Pancreatology. Jul 2018; 18(5): 477-481. PMID 29884332
10. Zou WB, Tang XY, Zhou DZ, et al. SPINK1, PRSS1, CTRC, and CFTR Genotypes Influence Disease Onset and Clinical Outcomes in Chronic Pancreatitis. Clin Transl Gastroenterol. Nov 12 2018; 9(11): 204. PMID 30420730
11. Vue PM, McFann K, Narkewicz MR. Genetic Mutations in Pediatric Pancreatitis. Pancreas. Aug 2016; 45(7): 992-6. PMID 26692446
12. Saito N, Suzuki M, Sakurai Y, et al. Genetic Analysis of Japanese Children With Acute Recurrent and Chronic Pancreatitis. J Pediatr Gastroenterol Nutr. Oct 2016; 63(4): 431-6. PMID 27409067
13. Koziel D, Gluszek S, Kowalik A, et al. Genetic mutations in SPINK1, CFTR, CTRC genes in acute pancreatitis. BMC Gastroenterol. Jun 23 2015; 15: 70. PMID 26100556
14. Schwarzenberg SJ, Bellin M, Husain SZ, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. J Pediatr. Apr 2015; 166(4): 890-896.e1. PMID 25556020
15. Poddar U, Yachha SK, Mathias A, et al. Genetic predisposition and its impact on natural history of idiopathic acute and acute recurrent pancreatitis in children. Dig Liver Dis. Aug 2015; 47(8): 709-14. PMID 25981744
16. Masson E, Chen JM, Audrezet MP, et al. A conservative assessment of the major genetic causes of idiopathic chronic pancreatitis: data from a comprehensive analysis of PRSS1, SPINK1, CTRC and CFTR genes in 253 young French patients. PLoS One. 2013; 8(8): e73522. PMID 23951356
17. Wang W, Sun XT, Weng XL, et al. Comprehensive screening for PRSS1, SPINK1, CFTR, CTRC and CLDN2 gene mutations in Chinese paediatric patients with idiopathic chronic pancreatitis: a cohort study. BMJ Open. Sep 03 2013; 3(9): e003150. PMID 24002981
18. Sultan M, Werlin S, Venkatasubramani N. Genetic prevalence and characteristics in children with recurrent pancreatitis. J Pediatr Gastroenterol Nutr. May 2012; 54(5): 645-50. PMID 22094894
19. Gasiorowska A, Talar-Wojnarowska R, Czupryniak L, et al. The prevalence of cationic trypsinogen (PRSS1) and serine protease inhibitor, Kazal type 1 (SPINK1) gene mutations in Polish patients with alcoholic and idiopathic chronic pancreatitis. Dig Dis Sci. Mar 2011; 56(3): 894-901. PMID 20676769
20. Joergensen MT, Brusgaard K, Cruger DG, et al. Genetic, epidemiological, and clinical aspects of hereditary pancreatitis: a population-based cohort study in Denmark. Am J Gastroenterol. Aug 2010; 105(8): 1876-83. PMID 20502448
21. Rebours V, Boutron-Ruault MC, Schnee M, et al. The natural history of hereditary pancreatitis: a national series. Gut. Jan 2009; 58(1): 97-103. PMID 18755888
22. Keiles S, Kammesheidt A. Identification of CFTR, PRSS1, and SPINK1 mutations in 381 patients with pancreatitis. Pancreas. Oct 2006; 33(3): 221-7. PMID 17003641
23. Truninger K, Kock J, Wirth HP, et al. Trypsinogen gene mutations in patients with chronic or recurrent acute pancreatitis. Pancreas. Jan 2001; 22(1): 18-23. PMID 11138965
24. Culetto A, Bournet B, Haennig A, et al. Prospective evaluation of the aetiological profile of acute pancreatitis in young adult patients. Dig Liver Dis. Jul 2015; 47(7): 584-9. PMID 25861839

25. Bellin MD, Freeman ML, Gelrud A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. Pancreatology. Jan-Feb 2014; 14(1): 27-35. PMID 24555976
26. Chinnakotla S, Radosevich DM, Dunn TB, et al. Long-term outcomes of total pancreatectomy and islet auto transplantation for hereditary/genetic pancreatitis. J Am Coll Surg. Apr 2014; 218(4): 530-43. PMID 24655839
27. Teich N, Mossner J. Hereditary chronic pancreatitis. Best Pract Res Clin Gastroenterol. 2008; 22(1): 115-30. PMID 18206817
28. Mullhaupt B, Truninger K, Ammann R. Impact of etiology on the painful early stage of chronic pancreatitis: a long-term prospective study. Z Gastroenterol. Dec 2005; 43(12): 1293-301. PMID 16315124
29. Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol. Mar 2004; 2(3): 252-61. PMID 15017610
30. Paolini O, Hastier P, Buckley M, et al. The natural history of hereditary chronic pancreatitis: a study of 12 cases compared to chronic alcoholic pancreatitis. Pancreas. Oct 1998; 17(3): 266-71. PMID 9788540
31. Hu C, Wen L, Deng L, et al. The Differential Role of Human Cationic Trypsinogen (PRSS1) p.R122H Mutation in Hereditary and Nonhereditary Chronic Pancreatitis: A Systematic Review and Meta-Analysis. Gastroenterol Res Pract. 2017; 2017: 9505460. PMID 29118810
32. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. Sep 2013; 108(9): 1400-15; 1416. PMID 23896955
33. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. Feb 2015; 110(2): 223-62; quiz 263. PMID 25645574
34. Conwell DL, Lee LS, Yadav D, et al. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines. Pancreas. Nov 2014; 43(8): 1143-62. PMID 25333398
35. Grody WW, Cutting GR, Klinger KW, et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. Genet Med. Mar-Apr 2001; 3(2): 149-54. PMID 11280952
36. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med. Sep-Oct 2004; 6(5): 387-91. PMID 15371902
37. Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Genet Med. Jun 2013; 15(6): 482-3. PMID 23619275
38. Deignan JL, Astbury C, Cutting GR, et al. CFTR variant testing: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. Aug 2020; 22(8): 1288-1295. PMID 32404922
39. Whitcomb DC, Shimosegawa T, Chari ST, et al. International consensus statements on early chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group and European Pancreatic Club. Pancreatology. Jul 2018; 18(5): 516-527. PMID 29793839
40. Hegyi P, Parniczky A, Lerch MM, et al. International Consensus Guidelines for Risk Factors 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. Jun 2020; 20(4): 579-585. PMID 32376198
41. Gariepy CE, Heyman MB, Lowe ME, et al. Causal Evaluation of Acute Recurrent and Chronic Pancreatitis in Children: Consensus From the INSPPIRE Group. J Pediatr Gastroenterol Nutr. Jan 2017; 64(1): 95-103. PMID 27782962
42. Stoffel EM, McKernin SE, Brand R, et al. Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol. Jan 10 2019; 37(2): 153-164. PMID 30457921
43. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2021. 2020 Sep 8; National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2013	New Policy	Genetic testing for hereditary pancreatitis is considered investigational.
March 2015	Replace policy	Policy updated and policy statements changed to indicate that genetic testing for hereditary pancreatitis may be considered medically necessary for children.
June 2018	Replace policy	Policy updated with literature review through December 11, 2017; references 6-9, 10, 12-14, 20-22 and 32-33 added; references 3, and 36 updated. Policy statements unchanged. Objective statement added: The objective of this evidence review is to evaluate whether genetic testing improves the net health outcome for individuals with chronic or recurrent pancreatitis for HP. This review does not address individuals who have a familial risk (See benefit application). Summary of evidence updated to reflect policy objective/FEP benefit application for "existing medical condition€.
June 2019	Replace policy	Policy updated with literature review through January 7, 2019; references 9-10, 33, 38-40 added. Policy statements unchanged.
June 2020	Replace policy	Policy updated with literature review through December 9, 2019; no references added. Policy statements unchanged.
June 2021	Replace policy	Policy updated with literature review through December 10, 2020; no references added. Policy statements unchanged.
June 2022	Replace policy	Policy updated with literature review through December 14, 2021; references added. Practice guidelines updated. Policy statements unchanged.