FEP 2.04.99 Genetic Testing for Hereditary Pancreatitis

Effective Date: July 15, 2018

Related Policies: None

Genetic Testing for Hereditary Pancreatitis

Description

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

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 for HP. This review does not address individuals who have a familial risk (See benefit application).

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for HP is available under the auspices of the Clinical Laboratory Improvement Amendments. Exome or genome sequencing tests as a clinical service are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by 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.

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 is being 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—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	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

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.

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

RATIONALE

Summary of Evidence

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

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Gastroenterology

The American College of Gastroenterology's 2013 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)."[34]

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics issued a policy statement on laboratory standards and guidelines for population-based cystic fibrosis carrier screening in 2001,[35] which were updated in 2004[36] and reaffirmed in 2013.[36] These guidelines have provided recommendations on specific variant testing in cystic fibrosis, but have not specifically addressed genetic testing for suspected hereditary pancreatitis (HP).

European Consensus Conference

A 2001 European Consensus Conference developed guidelines for genetic testing of the *PRSS1* gene, genetic counseling, and consent for genetic testing for HP.[37] The indications recommended for symptomatic patients included:

> "…(1) Recurrent (2 or more separate, documented episodes with hyper-amylasemia) attacks of *acute* pancreatitis for which there is no explanation… or (2) unexplained … *chronic* pancreatitis, or (3) a family history of pancreatitis in a first- degree … or second-degree … relative, or (4) … unexplained … pancreatitis occurring in a child that has required hospitalization.…"

Predictive genetic testing, defined as genetic testing in an asymptomatic "at-risk" relative of an individual proven to have HP, was considered more complex. Candidates for predictive testing "must have a first-degree relative with a well-defined HP gene mutation [pathogenic variant],…" capable of informed consent, and able to "understand the (autosomal dominant) mode of inheritance and incomplete penetrance of HP mutations…"

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

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POLICY HISTORY

Date	Action	Description
December 2013	New Policy	Genetic testing for hereditary pancreatitis is considered investigational.
March 2015	Update Policy	Policy updated and policy statements changed to indicate that genetic testing for hereditary pancreatitis may be considered medically necessary for children.
June 2018	Update 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”.