Hereditary Pancreatitis Genetic Testing

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Introduction

Genetic testing for hereditary pancreatitis is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
CFTR deletion/duplication analysis	81222
CFTR known familial mutation analysis	81221
CFTR sequencing	81223
Hereditary pancreatitis gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Hereditary pancreatitis multigene panel	81479

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Criteria

Introduction

Requests for genetic testing for hereditary pancreatitis are reviewed using the following criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation, and
  - Pathogenic pancreatitis-associated mutation(s) in a 1st degree biologic relative, AND
- Diagnostic Testing in Symptomatic Individuals:
  - Member is symptomatic (at least one documented episode of acute pancreatitis or a diagnosis of recurrent acute or chronic pancreatitis), OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - Age 16 years or older

PRSS1 Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous PRSS1 analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
  - An unexplained, documented episode of acute pancreatitis in an individual less than 18 years of age, or
  - Recurrent acute pancreatitis (2 or more documented episodes) or chronic pancreatitis, and
    - Symptom onset prior to age 25 years, and/or

        - A first degree biologic relative with recurrent acute pancreatitis, idiopathic chronic pancreatitis, or childhood pancreatitis (less than 18 years of age) without a known cause, and
    - No known etiology for the member's pancreatitis (e.g. alcoholism, gallstones, known genetic disorder), and
    - Absence of extra-pancreatic features suggestive of a complex genetic syndrome or cystic fibrosis (e.g. chronic sinopulmonary disease, failure-to-thrive, obstructive azoospermia due to congenital absence of the vas deferens, etc.), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Pancreatitis Multi-Gene Panel

When a multi-gene panel is being requested and will be billed with the appropriate CPT panel code, the panel will be considered medically necessary when the following criteria are met:

- Genetic Counseling:
    - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
    - No previous multi-gene analysis, and
    - PRSS1 analysis, if previously performed, was negative, AND
- Diagnostic Testing for Symptomatic Individuals:
    - An unexplained, documented episode of acute pancreatitis in an individual less than 18 years of age, or
    - Recurrent acute pancreatitis (2 or more documented episodes) or chronic pancreatitis, and
        - Symptom onset prior to age 25 years, or
        - A first degree biologic relative with recurrent acute pancreatitis, idiopathic chronic pancreatitis, or childhood pancreatitis (less than 18 years of age) without a known cause, and
    - No known etiology for the member's pancreatitis (e.g., alcoholism, gallstones, known genetic disorder), and
    - Absence of extra-pancreatic features suggestive of a complex genetic syndrome or cystic fibrosis (e.g., chronic sinopulmonary disease, failure-to-thrive, obstructive azoospermia due to congenital absence of the vas deferens, etc.), AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CLDN2, PNLIP, and CEL Analysis

Individual testing of these genes for the purpose of diagnosing hereditary pancreatitis is not medically necessary.

Other considerations

Broad gastrointestinal disease panels may not be medically necessary when a narrower panel is available and more appropriate based on the clinical findings.

This guideline addresses testing for non-syndromic hereditary pancreatitis. For information on testing for syndromes that may include pancreatitis as part of a more complex phenotype (e.g. Schwachman-Diamond syndrome, CEL-related MODY, mitochondrial disorders, Johanson-Blizzard syndrome) please refer to appropriate guidelines (e.g. *Maturity-Onset Diabetes of the Young (MODY) Genetic Testing* or *Mitochondrial Disorders Genetic Testing*) or applicable clinical use guidelines, if available. For information on CFTR analysis for individuals suspected of having Cystic Fibrosis please refer to the guideline *Cystic Fibrosis Testing*, as this is not addressed here.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- CLDN2, PNLIP, and CEL Analysis are not separately reimbursable.
- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
    - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81479*).
    - When use of a panel code is not possible, each billed component procedure will be assessed independently.

- In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
- When the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement in a tiered fashion:
  - PRSS1
  - SPINK1
  - CFTR
  - CTRC

Note *The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is pancreatitis?

Definition

Pancreatitis is inflammation of the pancreas that may be acute, recurrent acute, or chronic.[1]

Prevalence

PRSS1 mutations are identified in 5-7% of individuals with chronic pancreatitis.[2] In one US study of children, PRSS1 mutations were identified in 46% of those diagnosed with chronic pancreatitis and 17% of those with recurrent acute pancreatitis.[2]

Symptoms

Acute pancreatitis is defined as two of the three following findings:[2]

- Abdominal pain
- Elevated serum amylase or lipase (greater than 3x the upper limit of normal)
- Findings consistent with pancreatic inflammation on abdominal imaging.

Recurrent acute pancreatitis is defined as multiple (2 or more), discrete episodes of acute pancreatitis without any evidence of chronic pancreatitis.[2] There must be complete resolution of clinical and laboratory findings between episodes.

Chronic pancreatitis (CP) is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.[3] Common features of established and advanced CP include:

- Pancreatic exocrine dysfunction
- Pancreatic endocrine dysfunction and dysplasia.

Up to 5% of patients with chronic pancreatitis may develop pancreatic cancer.[4] The efficacy of pancreatic cancer screening has not been proven, and this screening is typically recommended to take place in a research setting.[4]

Cause

Idiopathic sporadic pancreatitis occurs when a single individual in a family is affected, and the etiology is unknown despite comprehensive investigations.

Familial pancreatitis is pancreatitis of any cause (genetic or non-genetic) that occurs in a family with a greater incidence than would be expected by chance alone.[1]

Hereditary pancreatitis (HP) is a rare cause of acute, recurrent acute, and chronic pancreatitis. It is defined as a personal history of pancreatitis with diagnosis in either two first-degree relatives or three second degree relatives spanning at least two generations. Beginning with the first report of a PRSS1 mutation in a family with HP, it has been shown that multiple genetic risk factors are associated with this disease.[5]

Mutations in the following genes contribute to the development of recurrent acute and chronic pancreatitis:[1]

- PRSS1 mutations are the most common cause of hereditary pancreatitis.[1,2] Mutations in this gene follow autosomal dominant inheritance and have a penetrance of approximately 40-93%, depending on the variant.[1,2]
    - The mutation detection rate for PRSS1 sequencing is approximately 94%, and deletion/duplication analysis is at least 6%.[2] N29I (p.Asn29Ile) and R122H (p.Arg122His) variants account for approximately 90% of cases of pathogenic variants observed in PRSS1-related HP.[2] Test results particularly for the PRSS1 gene, may offer prognostic information since the risk of pancreatic cancer in those with chronic pancreatitis is significantly increased.
- SPINK1 mutations may increase the severity of recurrent acute and chronic pancreatitis due to mutations in PRSS1, CFTR, CASR, or CTRC.[1,6] The majority of SPINK1 mutations are sequence variants, with deletions having been reported in a very small number of cases.[1]
- CFTR mutations are risk factors for pancreatitis. Individuals with biallelic CFTR mutations may have atypical cystic fibrosis (CF), putting them at risk for additional manifestations such as lung disease, male infertility, and chronic sinusitis.[1] The frequency of CFTR deletions in HP has not been investigated; however they occur rarely in cystic fibrosis (approximately 1%).[1]
- CTRC mutations have been identified in individuals with recurrent acute and chronic pancreatitis. These variants were initially thought to be modifier genes, however, they have been shown to be sufficient to cause disease without other identifiable genetic or environmental risk factors.[7]

- CASR mutations may be a predisposing genetic factor for pancreatitis either in isolation or as modifying risk when other genetic causes are present.[8]
- CLDN2, CPA1, and GGT1 variants have been implicated as risk factors or modifiers for chronic pancreatitis, but less is known about the utility of screening for these mutations compared to the others mentioned above.[1,8]
- TRPV6 mutations have been reported in patients with early-onset CP not associated with alcohol consumption.[1] In a recent study, 20% patients with functionally defective TRPV6 variants also had the SPINK1 p.N34S variant.[9]
- CEL and PNLIP variants may result in an increased risk of developing pancreatitis as mutations in these genes are enriched in chronic pancreatitis patient populations. However, current data remains limited and the clinical utility of screening for these genetic variants is uncertain.[1,9]
- Rare disorders that include pancreatitis/pancreatic insufficiency as part of a more complex syndrome include Schwachman-Diamond syndrome (SBDS), mitochondrial DNA deletions, CEL-associated maturity-onset diabetes of the young (MODY), and Johanson-Blizzard syndrome (UBR1).[1]

Genes included on hereditary pancreatitis multi-gene panels may not be causative or associated with high risk for pancreatitis (e.g.: CLDN2).[1]

Inheritance

While single pathogenic variants in SPINK1, CFTR, and CTRC are associated with an increased risk of recurrent acute or chronic pancreatitis, additional unidentified modifying factors may contribute to the disease.[1] These include alcohol use, smoking, chronic kidney disease, autoimmune factors, and anatomic issues.[1] Individuals with multiple risk factors (including multiple gene mutations) have a higher risk for pancreatitis.[1]

Biallelic variants of SPINK1 have been reported to result in early onset pancreatitis, suggesting an autosomal recessive pattern of inheritance with reduced penetrance.[1]

The rare disorders of which pancreatitis is a feature have varying patterns of inheritance.

Diagnosis

Pancreatitis is diagnosed by one of the following:[1-3]

- Abdominal imaging
- Functional studies (e.g. pancreatic exocrine insufficiency or pancreatic endocrine insufficiency with diabetes mellitus)
- Histology

Genetic testing results provide important early information about the etiology of pancreatitis-related disorders.[3] Determining the etiology of a pancreatitis-related

disorder may not lead to immediate treatment in some cases, but it often ends exhaustive, invasive, and expensive diagnostic testing for advanced disease. Understanding the genetic etiology also informs decisions about therapy for persistent or severe disease, such as total pancreatectomy with islet autotransplantation.[3] However, genetic testing cannot predict the age of onset or disease severity.[1,4]

Management

Treatment of HP focuses on longitudinal monitoring of endocrine and exocrine pancreatic function, enzyme and nutritional supplementation, pain management and monitoring for complications (such as decreased bone mineral density and fat-soluble vitamin deficiencies). Endoscopic and surgical therapies may be necessary in some cases. Affected individuals are discouraged from smoking and drinking alcohol.[1]

Survival

In a relatively small study of PRSS1 mutation carriers, overall survival did not differ significantly from that of the general US Caucasian population.[10] Pancreatic cancer rates were higher and contributed to mortality.

Test information

Introduction

Testing for hereditary pancreatitis may include known familial mutation analysis, next generation sequencing, and/or multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and evidence

American College of Gastroenterology

The American College of Gastroenterology (ACG, 2013) guideline on management of acute pancreatitis stated: “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).” [11]

The ACG (2015) guidelines on genetic testing for hereditary gastrointestinal cancer syndromes stated that having a history of hereditary pancreatitis is a risk factor for familial pancreatic adenocarcinoma, and genetic testing for pancreatitis-associated genes should be considered for pancreatic cancer patients with “a personal history of at least 2 acute attacks of acute pancreatitis of unknown etiology, a family history of pancreatitis, or early-age onset chronic pancreatitis.”[12]

The ACG (2020) guideline on chronic pancreatitis recommended genetic testing in patients with clinical evidence of a pancreatitis-associated disorder or possible CP in which the etiology is unclear, especially in younger patients.[3]

American Pancreatic Association

American Pancreatic Association (APA, 2014) guidelines stated: “Several genetic variations have been associated with pancreatitis including PRSS1, PRSS2, SPINK1, CTRC, CASR, and CFTR. The role of these gene mutations in CP is becoming increasingly recognized and better understood.” It is also noted that “knowledge of gene, gene-environment interactions may translate into new diagnostic and treatment paradigms” (Strong recommendation, level of evidence – moderate).[13]

Fourth International Symposium of Inherited Diseases of the Pancreas

The Fourth International Symposium of Inherited Diseases of the Pancreas (2007) recommended symptomatic patients be referred for genetic counseling to consider PRSS1 testing when at least one of the following conditions are met, in order to determine if they may be candidates for pancreatic cancer surveillance:[14]

- “≥2 attacks of acute pancreatitis of unknown aetiology”

- "Idiopathic chronic pancreatitis, particularly if disease onset occurs <25 years of age"
- "One first-degree or second-degree relative with pancreatitis"
- "Unexplained documented episode of childhood pancreatitis that required hospitalization and where there is concern that HP should be excluded."
- "Asymptomatic people should be referred for genetic counseling to consider testing for a PRSS1 mutation when the patient has one first-degree relative with a defined HP gene mutation."

United European Gastroenterology

United European Gastroenterology (UEG, 2018) guidelines on chronic pancreatitis stated:[15]

- "A diagnosis of cystic fibrosis needs to be ruled out in all patients with CP onset before the age of 20 years as well as in patients with so-called 'idiopathic' CP (regardless of the age of onset). (GRADE 1B, strong agreement)"
- "All patients with a family history or early onset disease (less than 20 years) should be offered genetic testing for associated variants. (GRADE 2C, strong agreement)"
- "Genetic testing was recommended to include PRSS1, SPINK1, CPA1, CTRC, CEL, and "may include screening for variants in CFTR. (GRADE 2C, strong agreement)"

Select Relevant Publications

2016 Expert Authored Review

A 2016 expert-authored review on hereditary pancreatitis stated:[16]

- "[…] targeted genetic testing of members of an established HP family may be considered in cases of unexplained [recurrent acute pancreatitis] and/or [chronic pancreatitis], an affected individual with a first or second-degree relative with pancreatitis, unexplained pancreatitis in a child requiring hospitalization and/or when there is a known mutation in the family."
- "[…] next generation sequencing approaches such as whole exome sequencing or whole genome sequencing should not be used for PRSS1 testing because of challenges in sequence alignment. If a mutation is not identified from sequencing or targeted mutation analysis, deletion/duplication analysis can be considered."
- "In families where a deleterious variant has been identified, predictive genetic testing may be considered in close family members…Genetic testing of asymptomatic family members in a family without an identifiable mutation is uninformative."

- "Genetic testing may be indicated in a child with diagnosed or suspected pancreatitis…Predictive genetic testing for asymptomatic patients less than 16 years of age is not recommended and does not have clear benefits."

2017 Expert Authored Review

A 2017 expert authored review on pediatric acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) concluded:[17]

- "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." (Strong consensus, definitely yes, 1A)
- "Mutation analysis of the genes SPINK1, CFTR and CTRC may identify risk factors for ARP or CP." (Strong consensus, definitely yes, 1B)

2020 Expert Authored Review

A 2020 expert-authored review on pancreatitis recommended molecular genetic testing in a proband with pancreatitis and at least of one of the following:[1]

- "An unexplained documented episode of acute pancreatitis in childhood"
- "Recurrent acute attacks of pancreatitis of unknown cause"
- "Chronic pancreatitis of unknown cause, particularly with onset before age 35 years without a history of heavy alcohol use (>5 drinks per day)"
- "A history of at least one relative with recurrent acute pancreatitis, chronic pancreatitis of unknown cause, or childhood pancreatitis of unknown cause"
- PRSS1 sequencing is recommended, followed by deletion/duplication analysis if sequencing is negative. Alternatively, a multi-gene panel that includes PRSS1, SPINK1, CFTR, and CTRC may be appropriate.

Note This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for hereditary pancreatitis genetic testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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