Genetic Testing for Hereditary Pancreatitis

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.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASR Sequencing</td>
<td>81405</td>
</tr>
<tr>
<td>CFTR Deletion/Duplication Analysis</td>
<td>81222</td>
</tr>
<tr>
<td>CFTR Known Familial Mutation Analysis</td>
<td>81221</td>
</tr>
<tr>
<td>CFTR Sequencing</td>
<td>81223</td>
</tr>
<tr>
<td>CFTR Targeted Mutation Analysis</td>
<td>81479</td>
</tr>
<tr>
<td>CLDN2 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>CPA1 Sequencing</td>
<td>81479</td>
</tr>
<tr>
<td>CTRC Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>CTRC Sequencing</td>
<td>81405</td>
</tr>
<tr>
<td>PRSS1 Deletion/Duplication Analysis</td>
<td>81479</td>
</tr>
<tr>
<td>PRSS1 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>PRSS1 Sequencing</td>
<td>81404</td>
</tr>
<tr>
<td>PRSS1 Targeted Mutation Analysis</td>
<td>81401</td>
</tr>
<tr>
<td>SPINK1 Deletion/Duplication Analysis</td>
<td>81479</td>
</tr>
<tr>
<td>SPINK1 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>SPINK1 Sequencing</td>
<td>81404</td>
</tr>
</tbody>
</table>
What is pancreatitis

Definition

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

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

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

Chronic pancreatitis is defined as an irreversible fibro-inflammatory process which leads to permanent changes in the pancreatic parenchyma and function. It may be documented by one of the following:¹,²

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

Idiopathic sporadic pancreatitis is 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, acute recurrent, and chronic pancreatitis. It is defined as a personal history of pancreatitis and pancreatitis diagnosed in two first-degree relatives or in three second degree relatives spanning at least two generations. Beginning with the first report of PRSS1 mutation in a family with HP, it has been shown that multiple genetic risk factors are associated with this disease.³

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

- PRSS1 mutations are the most common cause of hereditary pancreatitis.¹,² They follow autosomal dominant inheritance and have a penetrance of approximately 80%. Since 1996, more than 35 mutations in PRSS1 have been found to be associated with hereditary pancreatitis.⁴
- SPINK1 mutations have been associated with a risk for autosomal recessive HP. There is evidence that heterozygous SPINK1 mutations increase the severity of
acute recurrent and chronic pancreatitis due to mutations in PRSS1, CFTR, CASR, or CTRC.\textsuperscript{1,4}  

- CFTR mutations follow autosomal recessive inheritance, and individuals with biallelic CFTR pathogenic variants may have atypical cystic fibrosis (CF), putting them at risk for additional manifestations such as lung disease, male infertility, and chronic sinusitis. All CFTR mutations that cause CF are also risk factors for pancreatitis; however, mutations that do not cause classic CF may still be risk factors for pancreatitis.\textsuperscript{1}  

- CTRC mutations have been identified in individuals with acute recurrent 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.\textsuperscript{5}  

- CASR mutations may be a predisposing genetic factor for pancreatitis either in isolation or as modifying risk when other genetic causes are present.\textsuperscript{5}  

- 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.  

- While single pathogenic variants in SPINK1, CFTR, and CTRC may be associated with an increased risk of pancreatitis, additional unidentified modifying factors may contribute to the disease. Double heterozygotes appear to have a further increased risk.\textsuperscript{1}  

- 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).\textsuperscript{1}  

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 people are discouraged from smoking and drinking alcohol.  

About 5% of patient with chronic pancreatitis develop pancreatic cancer. The efficacy of pancreatic cancer screening has not been proven, and this screening is typically recommended to take place in a research setting.\textsuperscript{7}
Test information

Introduction

Gene mutations and variants have been detected in the CFTR, CTRC, PRSS1, and SPINK1 genes in people with hereditary pancreatitis (HP). Most testing laboratories perform sequence analysis using next generation sequencing (NGS).

The mutation detection rate for PRSS1 sequencing is 60-100%, and deletion/duplication analysis is at least 6%. N29I (p.Asn29Ile) and R122H (p.Arg122His) variants account for approximately 90% of cases of pathogenic variants observed in PRSS1-related HP. The majority of SPINK1 mutations are sequence variants, with deletions having been reported in a very small number of cases. The frequency of CFTR deletions in HP has not been investigated; however they occur rarely in cystic fibrosis (approximately 1%).

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. However, genetic testing cannot predict the age of onset or disease severity.

Identifying a mutation in an affected individual can be used to test at-risk family members with familial mutation analysis.

Guidelines and evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to genetic testing for hereditary pancreatitis.

United European Gastroenterology

United European Gastroenterology (2017) guidelines on chronic pancreatitis state:

• “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)...The recommended investigations for ruling out a diagnosis of cystic fibrosis should follow national and international guidelines. Note, this does not imply a complete sequencing of the CFTR gene but only of known hotspot variants. Moreover, if no further clinical signs of cystic fibrosis are present (for example, no pulmonary symptoms, no male infertility) the diagnostic workup should be restricted to sweat chloride iontophoresis.”

• “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.”

2017 Expert authored review

A 2017 expert authored review on pediatric acute recurrent and chronic pancreatitis concluded that:9

• “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)

• “Mutation analysis of the genes SPINK1, CFTR and CTRC may identify risk factors for ARP or CP.” (Strong consensus, definitely yes).

2016 Expert authored review

A 2016 expert-authored review on hereditary pancreatitis states:10

• “[…] targeted genetic testing of members of an established HP family may be considered in cases of unexplained recurrent acute pancreatitis 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.”

American College of Gastroenterology

American College of Gastroenterology (ACG, 2015) guidelines on genetic testing for hereditary gastrointestinal cancer syndromes state 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.”11
American Pancreatic Association

American Pancreatic Association (2014) guidelines state “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)\(^1\)

2014 Expert authored review

A 2014 expert-authored review on pancreatitis recommends molecular genetic testing in a proband with pancreatitis and at least 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 25 years”
- “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.

American College of Gastroenterology

The American College of Gastroenterology (ACG, 2013) guideline on management of acute pancreatitis states: “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).”\(^13\)

2010 Expert authored review

A 2010 expert-authored review on genetic testing in pancreatitis states: \(^14\)

- "Because of the high penetrance (80%) of the more common PRSS1 mutations, especially R112H and N29I, testing is generally accepted for diagnostic purposes in symptomatic individuals. The confirmation of a genetic etiology of pancreatitis provides a valid explanation for both symptoms and/or disease, and may be helpful to predict a lack of efficacy with various endoscopic or operative procedures."
- "[T]here is currently no clinical indication for the routine use of SPINK1 mutation testing for either diagnostic or screening purposes and has no implications in altering the management of patients with pancreatitis."
• "[T]he CTRC gene that is the most recently identified pancreatitis susceptibility gene, should be approached in a similar fashion to SPINK1 as it is also associated with a very low penetrance."

• Regarding testing for CFTR mutations, "In subjects presenting with pancreatitis, the overwhelming rationale for further testing is to exclude or confirm the diagnosis of CF [cystic fibrosis]. The traditional sweat test remains the primary diagnostic test for CF disease in the genomic age. In any symptomatic individual, diagnostic testing should include sweat testing as the primary test and referral to a CF clinic made if sweat chloride concentration is borderline (40-59 mmol/L) or abnormal (>60 mmol/L). CFTR mutation analysis in isolation, as the first-line clinical diagnostic test, is unlikely to change management but may instead give false reassurance of the absence of CF if CFTR genotyping fails to identify mutations or alternatively be inappropriately thought to be diagnostic of CF... [T]here is currently no rationale for CFTR mutation screening for risk of pancreatitis alone."

Fourth International Symposium of Inherited Diseases of the Pancreas

The Fourth International Symposium of Inherited Diseases of the Pancreas (2007) recommended that 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:15

- “≥2 attacks of acute pancreatitis of unknown etiology"
- “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.”

2007 Expert authored review

A 2007 expert-authored guideline on nonsyndromic pancreatitis states that genetic testing should be considered when an affected patient fulfills at least one of the following criteria:16

- “A family history of recurrent acute pancreatitis, idiopathic chronic pancreatitis, or childhood pancreatitis without a known cause”
- “Relatives known to carry mutations associated with pancreatitis”
- “A series of recurrent acute attacks of pancreatitis for which there is no other explanation”
• “An unexplained documented episode of pancreatitis as a child”
• “Idiopathic chronic pancreatitis (especially when onset of pancreatitis precedes age 25)”
• “Patients eligible for approved research protocols”
• “[…] symptomatic family members at risk of inheriting a PRSS1 mutation may wish to be tested after a mutation has been identified in the family…Testing asymptomatic individuals for CFTR and SPINK1 mutations is not recommended because a large fraction of those who carry mutations in these genes never develop pancreatitis. CFTR carrier testing should be offered to unaffected relatives of a CFTR mutation that is capable of causing classic CF.”

2007 Expert authored review

A 2007 expert-authored review on hereditary pancreatitis recommends PRSS1 and SPINK1 mutation testing in symptomatic patients with one of the following:  
• “recurrent unexplained attacks of acute pancreatitis and positive family history”
• “unexplained chronic pancreatitis and a positive family history”
• “unexplained chronic pancreatitis without a positive family history after exclusion of other causes”
• “unexplained pancreatitis episode in children”

CASR, CLDN2, and CPA1 genes

Pathogenic variants in the CASR, CLDN2, and CPA1 genes may result in an increased risk of developing pancreatitis, and/or act as modifiers of disease severity. However, current data remains limited and the clinical utility of screening for these genetic variants is uncertain.

Criteria

Introduction

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

PRSS1, SPINK1, CFTR, and CTRC Known Familial Mutation Analysis

• Genetic Counseling:
  o 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 for known familial mutation, and
- Pathogenic PRSS1, SPINK1, CFTR, or CTRC mutation(s) in a 1st degree biologic relative, AND

- Member is symptomatic (at least one documented episode of acute pancreatitis or a diagnosis of acute recurrent or chronic pancreatitis)

**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
  - Acute recurrent 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.

**SPINK1, CFTR, and CTRC 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 genetic testing of requested gene, AND
Previous PRSS1 sequence analysis was performed and no mutations were found, AND

- Diagnostic Testing for Symptomatic Individuals:
  - An unexplained, documented episode of acute pancreatitis in an individual less than 18 years of age, OR
  - Acute recurrent 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.

CASR, CLDN2, and CPA1 Analysis

This test is considered investigational and/or experimental.

- Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

- In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

Note: This guideline applies to testing for nonsyndromic hereditary pancreatitis. This guideline does not apply to genetic testing for syndromes that may include pancreatitis as part of a more complex phenotype (e.g. Schwachman-Diamond syndrome, CEL-related MODY, mitochondrial DNA deletion disorders, Johanson-Blizzard syndrome).
Testing for those disorders should be guided by any test-specific guidelines, if available (e.g. Maturity-Onset Diabetes of the Young (MODY) Testing and Mitochondrial DNA Deletion Syndromes), or applicable clinical use guidelines. This guideline does not address CFTR analysis for individuals suspected of having Cystic Fibrosis. For this indication, see the guideline Cystic Fibrosis Testing.

**Benefit exclusion**

**Exclusions and other considerations**

Testing unaffected individuals (e.g. carrier testing, predictive testing, presymptomatic testing, etc) is a BCBSAZ benefit exclusion and, therefore, not eligible for reimbursement.

**References**

**Introduction**

This guideline cites the following references.

8. Lohr JM, Dominguez-Munoz E, Rosendahl J et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of


