Most Recent Updates

Medical Policy

MP 2.04.148
Genetic Testing for Hereditary Pancreatic Cancer

Related Policies
2.04.02 - Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
2.04.08 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
2.04.101 - Genetic Testing for Li-Fraumeni Syndrome
2.04.126 - Moderate Penetrance Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk
2.04.44 - Genetic Testing for Familial Cutaneous Malignant Melanoma
2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
2.04.99 - Genetic Testing for Hereditary Pancreatitis
2.04.570 Genetic Counseling

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POLICY

Genetic testing for BRCA1 and BRCA2 variants to guide selection for treatment in patients with pancreatic cancer may be considered medically necessary.

Genetic testing for ATM, CDK2NA, EPCAM, MMR genes (MLH1, MSH2, MSH6, PMS2), PALB, STK11, and TP53 in patients with pancreatic cancer is considered investigational unless the individual meets criteria for testing as specified in another policy (see policy guidelines).

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Genetic testing for \textit{ATM}, \textit{BRCA1}, \textit{BRCA2}, \textit{CDK2NA}, \textit{EPCAM}, \textit{MMR} genes (\textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}), \textit{PALB}, \textit{STK11}, and \textit{TP53} in asymptomatic individuals at high risk for hereditary pancreatic cancer is considered \textbf{investigational} unless the individual meets criteria for testing as specified in another policy (see policy guidelines).

**Genetic Counseling**

Documentation of individualized genetic counseling is required, before any genetic testing will be considered medically necessary. See MP 2.04.570.

**POLICY GUIDELINES**

\textit{Related Policies on Hereditary Cancer Syndromes}

- Genetic testing for \textit{BRCA1} and \textit{BRCA2} variants
  - Policy 2.04.02 Genetic Testing for \textit{BRCA1} or \textit{BRCA2} for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
- Genetic testing for \textit{ATM} and \textit{PALB2} gene variants
  - Policy 2.04.126 Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk
- Genetic testing for \textit{EPCAM}, \textit{MMR} (\textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}), and \textit{STK11} gene variants
  - Policy 2.04.08 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Genetic testing for \textit{CDKN2A} gene variants
  - Policy 2.04.044 Genetic Testing for Familial Cutaneous Malignant Melanoma
- Genetic testing for \textit{TP53} gene variants
  - Policy 2.04.101 Genetic Testing for Li-Fraumeni Syndrome
- Genetic cancer susceptibility panel testing
  - Policy 2.04.93 Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

\textit{Testing At-Risk Relatives}

Individuals are considered at high risk for hereditary pancreatic cancer if they have two close relatives with pancreatic adenocarcinoma where one is a first-degree relative, have three or more close relatives with pancreatic cancer, or have a history of hereditary pancreatitis.

For familial assessment, 1st-, 2nd-, and 3rd-degree relatives are blood relatives on the same side of the family (maternal or paternal).

- 1st-degree relatives are parents, siblings, and children.
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

At-risk relatives primarily refer to first-degree relatives. However, some judgment must be permitted, e.g., in the case of a small family pedigree, when extended family members may need to be included in the testing strategy.

\textit{Targeted Variant Testing}

It is recommended that, when possible, initial genetic testing for variants associated with hereditary pancreatic cancer be performed in an affected family member so that testing in unaffected family members can focus on the pathogenic variant found in the affected family member. In unaffected family members of potential hereditary pancreatic cancer families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an affected family member be tested first.
Genetic Testing for Hereditary Pancreatic Cancer

whenever possible to adequately interpret the test. Should a variant be found in an affected family member(s), DNA from an unaffected family member can be tested specifically for the same variant of the affected family member without having to sequence the entire gene.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

BlueCard/National Account Issues

Some Plans may have contract or benefit exclusions for genetic testing.

BACKGROUND

Pancreatic Cancer Epidemiology

Pancreatic cancer is the fourth leading cause of cancer death in the U.S., accounting for 7.5% of all cancer deaths in 2019. The disease has a poor prognosis, with only 9.3% of patients surviving to 5 years. In 80% of pancreatic cancer patients with a family history of pancreatic cancer, the genetic basis of the inherited predisposition is unknown. Individuals are considered at high-risk for hereditary pancreatic cancer if they have 2 relatives with pancreatic cancer where 1 is a first-degree relative, have 3 or more relatives with pancreatic cancer or have a history of hereditary pancreatitis.

Table 1. Risk of Developing Pancreatic Cancer

<table>
<thead>
<tr>
<th>Number of First Degree Relatives (FDR) with Pancreatic Cancer</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 affected FDR</td>
<td>4.6-fold</td>
</tr>
<tr>
<td>2 affected FDR</td>
<td>6.4-fold</td>
</tr>
<tr>
<td>3 affected FDR</td>
<td>32-fold</td>
</tr>
</tbody>
</table>

Sources: American Society of Clinical Oncology, American College of Gastroenterology
**Regulatory Status**

Testing for variants associated with pancreatic cancer 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). Lab Test X 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 (FDA) has chosen not to require any regulatory review of this test.

In December 2019, the FDA approved olaparib (LYNPARZA, AstraZeneca Pharmaceuticals LP) for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) metastatic pancreatic adenocarcinoma, as detected by an FDA-approved test, whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

**RATIONALE**

This evidence review was created in February 2020 with a search of the MEDLINE database through August 26, 2019.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition. The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Genetic Testing for ATM, CDK2NA, EPCAM, MLH1, MSH2, MSH6, PMS2, PALB, STK11, and TP53 to Guide Treatment in Individuals with Pancreatic Cancer**

**Clinical Context and Test Purpose**

The purpose of genetic testing for genes associated with pancreatic cancer in individuals with pancreatic cancer is to guide treatment for pancreatic cancer.

The following PICO was used to select literature to inform this review.

**Patients**

The relevant population of interest is individuals with pancreatic cancer.

**Interventions**

The test being considered is genetic testing for ATM, CDK2NA, EPCAM, MLH1, MSH2, MSH6, PMS2, PALB, STK11, and TP53

**Comparators**

Alternatives to genetic testing would be treatment as usual without genetic testing.
Outcomes
The potential beneficial outcomes of primary interest would be improvements in overall survival (OS) and disease-specific survival in individuals with pancreatic cancer.

Potential harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to unnecessary clinical management changes or unnecessary cascade testing for other cancers. False-negative test results can lead to the absence of clinical management changes.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Study Selection Criteria
For the evaluation of the clinical validity of the genetic test, studies that reported on the sensitivity and specificity and/or diagnostic yield of the test were considered, including curated sources of information on genes associated with increased risk of pancreatic cancer (eg, summaries from professional societies).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Study Selection Criteria
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Clinical Utility
Direct Evidence
There are no direct outcome data on the clinical usefulness of genetic testing for ATM, CDK2NA, EPCAM, MLH1, MSH2, MSH6, PMS2, PALB, STK11, and TP53 (ie, no studies have reported outcomes data for patients tested and not tested).

Indirect Evidence
A chain of indirect evidence would demonstrate that genetic testing can identify individuals with pathogenic variants associated with pancreatic cancer who would not otherwise be identified, that treatments are available for these patients that would not otherwise be given to patients with pancreatic cancer, and that these treatments improve health outcomes.
Clinical Validity

Multiple genetic syndromes, including hereditary breast and ovarian cancer syndrome, are associated with an increased risk for pancreatic cancer (Table 2). Most of these are also associated with increased risk of other cancers. However, individual genes associated with the syndromes have been identified as increasing risk of pancreatic cancer, even in the absence of one of these syndromes.

Table 2. Pancreatic Cancer Susceptibility Genes and Associated Syndromes

<table>
<thead>
<tr>
<th>Genes</th>
<th>Associated Syndromes</th>
<th>Absolute Risk of Pancreatic Cancer</th>
<th>Relative Risk of Pancreatic Cancer</th>
<th>Other Associated Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Ataxia-telangiectasia</td>
<td>1%-5%</td>
<td>3-fold</td>
<td>Breast, ovarian</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Hereditary breast and ovarian</td>
<td>1.2%</td>
<td>3-fold</td>
<td>Breast, ovarian, prostate</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Hereditary breast and ovarian</td>
<td>2%-5%</td>
<td>3.5 to 10-fold</td>
<td>Breast, ovarian, prostate, melanoma</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Familial atypical multiple mole melanoma</td>
<td>10%-30%</td>
<td>13- to 39-fold</td>
<td>Melanoma</td>
</tr>
<tr>
<td>MLH1, MSH2, MSH6, EPCAM</td>
<td>Lynch</td>
<td>5%-10%</td>
<td>9- to 11-fold</td>
<td>Ovarian, colon, uterine, others</td>
</tr>
<tr>
<td>PALB2</td>
<td>Hereditary breast and ovarian</td>
<td>5%-10%?</td>
<td>Unknown</td>
<td>Breast, ovarian</td>
</tr>
<tr>
<td>PRSS1, SPINK1</td>
<td>Hereditary pancreatitis</td>
<td>40%-45%</td>
<td>53-fold</td>
<td>NA</td>
</tr>
<tr>
<td>STK11/LKB1</td>
<td>Peutz–Jeghers</td>
<td>10%-30%</td>
<td>Up to 132-fold</td>
<td>Breast, ovarian, colorectal</td>
</tr>
<tr>
<td>Tp53</td>
<td>Li-Fraumeni</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Breast</td>
</tr>
</tbody>
</table>

Sources: American Society of Clinical Oncology, American College of Gastroenterology

NA: not available.

Multiple observational studies have demonstrated that testing patients with pancreatic cancer can identify individuals with disease-associated variants; some recent studies are summarized in Table 3. A case-control analysis conducted by Hu et al (2018) compared the association of germline pathogenic variations in 3030 patients with pancreatic cancer to 176241 controls from 2 public genome databases. There were significant associations between pancreatic cancer and pathogenic variations in 6 genes associated with pancreatic cancer (ATM, BRCA1, BRCA2, CDKN2A, MLH1, and TP53). Overall, pathogenic variants were identified in 5.5% of patients with pancreatic cancer.

Observational studies have reported that pathogenic variants are found in patients with pancreatic cancer who do not have a family history of the disease. In Hu et al. (2018), pancreatic cancer associated variants were found in 7.9% of patients with a family history of pancreatic cancer and 5.2% of those without a family history of pancreatic cancer. Shindo et al. (2017) reported that pathogenic variants were identified in 3.9% of a cohort of 854 patients with pancreatic adenocarcinoma. Of those with an identified pathogenic variant, only 3 (9.0%) reported a family history of pancreatic cancer.
Table 3. Study Characteristics: Clinical Validity of Genetic Tests in Patients with Pancreatic Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Pathogenic Variants Identified, overall and by specific genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al. (2018)</td>
<td>3,030 adults with pancreatic cancer enrolled in a registry 123,136 controls from the Genome Aggregation Database and 53,105 controls from the Exome Aggregation Consortium Database</td>
<td>Odds ratios (95% CI): CDKN2A: 12.33 (5.43-25.61) TP53: 6.70 (2.52-14.95) MLH1: 6.66 (1.94-17.53) BRCA2: 6.20 (4.62-8.17) ATM: 5.71 (4.38-7.33) BRCA1: 2.58 (1.54-4.05)</td>
</tr>
<tr>
<td>Brand et al. (2018)</td>
<td>298 patients with newly diagnosed with pancreatic ductal adenocarcinoma 9.7% Rate of pathogenic variants in specific genes: ATM: 3.3% BRCA1/2: 2.7% CHEK2: 1.7%</td>
<td>44/176 (25%) Pathogenic variants by gene BRCA1: 6 BRCA2: 11 CDKN2A: 3 PALB2: 1 ATM: 5 CHEK2: 7 APC: 7 MUTYH: 3 FH (recessive): 1</td>
</tr>
<tr>
<td>Mandelker et al. (2017)</td>
<td>1040 patients with advanced cancer (predominantly prostate, renal, pancreatic, breast and colon) referred for germline testing for hereditary cancer, who also had tumor DNA sequenced</td>
<td>33/854 (3.9%; 95% CI 3.0% to 5.8%) Number of patients with deleterious mutations in specific genes: BRCA2: 12 ATM: 10 BRCA1 3 PALB2: 2 MLH1: 2 CDKN2A: 1 TP53: 1 3/33 patients had reported a family history of pancreatic cancer</td>
</tr>
<tr>
<td>Shindo et al. (2017)</td>
<td>854 patients with pancreatic ductal adenocarcinoma; Control groups: 288 patients with other pancreatic and periampullary neoplasms, and 51 patients with nonneoplastic diseases who underwent pancreatic resection</td>
<td>11/290 (3.8%) Number of pathogenic variants by gene: ATM: 3 BRCA1: 1 BRCA2: 2</td>
</tr>
<tr>
<td>Grant et al. (2015)</td>
<td>708 individuals with pancreatic cancer consenting to be in a province-wide population-based registry, with available blood or saliva samples</td>
<td>11/290 (3.8%) Number of pathogenic variants by gene: ATM: 3 BRCA1: 1 BRCA2: 2</td>
</tr>
</tbody>
</table>
Genetic Testing for Hereditary Pancreatic Cancer

Section Summary: Genetic Testing for ATM, CDK2NA, EPCAM, MLH1, MSH2, MSH6, PMS2, PALB, STK11, and TP53 in Individuals with Pancreatic Cancer

Multiple observational studies have demonstrated that testing patients with pancreatic cancer can identify individuals with disease-associated variants, including among those who do not have a family history of the disease. However, there is no direct evidence comparing health outcomes in patients tested or not tested for a variant. There are no targeted treatments for pancreatic cancer based on these genes.

Genetic Testing for a BRCA1 or BRCA2 Variant to Guide Treatment in Individuals with Pancreatic Cancer

Clinical Context and Test Purpose

The purpose of genetic testing for a BRCA1 or BRCA2 variant in individuals with pancreatic cancer is to guide selection of targeted treatment for pancreatic cancer.

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is individuals with pancreatic cancer.

Interventions

The test being considered is genetic testing for a BRCA1 or BRCA2 variant.

Comparators

Alternatives to genetic testing would be treatment as usual without genetic testing.

Outcomes

The potential beneficial outcomes of primary interest would be improvements in OS and disease-specific survival in individuals with pancreatic cancer.

Potential harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to unnecessary clinical management changes or unnecessary cascade testing for other cancers. False-negative test results can lead to the absence of clinical management changes.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).
**Study Selection Criteria**

For the evaluation of the clinical validity of the genetic test, studies that reported on the sensitivity and specificity and/or diagnostic yield of the test were considered, including curated sources of information on genes associated with increased risk of pancreatic cancer (eg, summaries from professional societies).

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Study Selection Criteria**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

**Clinical Utility**

**Direct Evidence**

There are no direct outcome data on the clinical usefulness of testing for confirmation of a BRCA1 or BRCA2 variant in patients with pancreatic cancer (ie, no studies have reported outcomes data for patients tested and not tested for a variant).

**Indirect Evidence**

A chain of indirect evidence would demonstrate that genetic testing can identify individuals with pathogenic variants associated with pancreatic cancer who would not otherwise be identified, that treatments are available for these patients that would not otherwise be given to patients with pancreatic cancer, and that these treatments improve health outcomes.

**Clinical Validity**

Studies of the clinical validity of genetic testing in patients with pancreatic cancer are summarized in the previous section.

**Clinical Utility**

Golan et al. (2019) conducted a placebo-controlled RCT of olaparib as maintenance therapy in patients with germline BRCA1 or BRCA2 variants and metastatic pancreatic cancer (Tables 4 and 5). Of 3315 patients screened, 247 (7.5%) had a germline BRCA mutation. Median progression-free survival was longer in the olaparib group, but there was no difference in OS.

### Table 4. RCT of Targeted Treatment in Patients With Pancreatic Cancer: Study Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Active Comparator</td>
</tr>
</tbody>
</table>
Multiple observational studies have demonstrated that testing patients with pancreatic cancer can identify individuals with \textit{BRCA1} or \textit{BRCA2} variants, including among those who do not have a family history of pancreatic cancer. A placebo-controlled trial of olaparib as maintenance therapy in patients with germline \textit{BRCA1} or \textit{BRCA2} mutations and metastatic pancreatic adenocarcinoma that had not progressed during first-line platinum-based chemotherapy found longer progression-free survival with olaparib (7.4 months vs. 3.8 months; Hazard Ratio, HR 0.53; 95% CI 0.35 to 0.82; \(P=0.04\)).

### Genetic Testing in Asymptomatic Individuals who are at Risk for Hereditary Pancreatic Cancer

#### Clinical Context and Test Purpose
The purpose of genetic testing of asymptomatic individuals who are at high-risk for hereditary pancreatic cancer is to inform decisions about surveillance for early detection of pancreatic cancer. Given that most symptomatic pancreatic cancer is detected at an advanced stage and has a poor prognosis, targeted surveillance of high-risk individuals has the potential to identify tumors at an earlier stage that are more amenable to treatment.

The question addressed in this evidence review is: Does genetic testing improve the net health outcome in individuals who are asymptomatic and at high-risk for hereditary pancreatic cancer?

The following PICO was used to select literature to inform this review.

<table>
<thead>
<tr>
<th>Study</th>
<th>Median Progression-free Survival</th>
<th>Median Overall Survival</th>
<th>Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golan et al. (2019)</td>
<td>Olaparib 7.4 mos</td>
<td>18.9 mos</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>Placebo 3.8 mos</td>
<td>18.1 mos</td>
<td>15%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>(0.53 (0.35 to 0.82); P = 0.004)</td>
<td>(0.91 (0.56 to 1.46); P = 0.68)</td>
<td></td>
</tr>
</tbody>
</table>
**Patients**

Individuals are considered at high-risk for hereditary pancreatic cancer if they have 2 relatives with pancreatic cancer where 1 is a first-degree relative, have 3 or more relatives with pancreatic cancer, or have a history of hereditary pancreatitis.

**Interventions**

The test being considered is testing for genes associated with pancreatic cancer, including ATM, BRCA1/2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, STK11, and TP53.

For individuals without cancer who are at high-risk for hereditary pancreatic cancer, surveillance may be performed by endoscopic ultrasonography, magnetic resonance imaging (MRI), and/or computed tomography.

**Comparators**

Alternatives to genetic testing include risk assessment using criteria other than genetic testing (eg, family history)

**Outcomes**

The potential beneficial outcomes of primary interest would be improvements in OS and disease-specific survival.

Potential harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to unnecessary clinical management changes or unnecessary cascade testing for asymptomatic family members. False-negative test results can lead to the absence of clinical management changes or a lack of testing for asymptomatic family members.

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Study Selection Criteria**

For the evaluation of the clinical validity of the genetic test, studies that reported on the sensitivity and specificity and/or diagnostic yield of the test were considered, including curated sources of information on genes associated with increased risk of pancreatic cancer (eg, summaries from professional societies).

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.
Direct Evidence

There is no direct evidence comparing health outcomes in asymptomatic patients tested or not tested for genes associated with hereditary pancreatic cancer.

Indirect Evidence

A chain of indirect evidence would demonstrate that genetic testing can identify individuals with pathogenic variants associated with hereditary pancreatic cancer who would not otherwise be identified, that treatments or increased surveillance are available for these patients that would not otherwise be given to patients with hereditary pancreatic cancer, and that these interventions improve health outcomes.

Clinical Validity

A prospective observational study of individuals under surveillance for pancreatic cancer on the basis of a family history of pancreatic cancer identified a known pathogenic variant in a pancreatic cancer susceptibility gene in 4.3% (15/345) (Table 6). In addition, 66 variants of unclear significance were identified. The cumulative incidence of pancreatic cancer in the germline mutation group was higher than in the familial risk group, adjusted for age and sex and accounting for death as a competing event (HR, 2.85; 95% CI, 1.0 to 8.18; P = .05).

Table 6. Study Characteristics: Clinical Validity of Genetic Tests in Patients With Pancreatic Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Prevalence of Pancreatic Cancer</th>
<th>Pathogenic Variants Identified, overall and by specific genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abe et al. (2019)</td>
<td>464 individuals enrolled in a high-risk pancreatic cancer surveillance program</td>
<td>PDA: 13/462 (2.8%) PDA or HGD: 19/462 (4.1%) PDA or HGD or worrisome features on imaging: 42/446 (9.4%)</td>
<td>For patients with germline mutations (n=134) compared to those with family history only with no known mutation (n=330): PDA: HR 2.85 (95% CI 1-8.18, p=0.05) PDA or HGD: HR 2.81 (95% CI 1.17-6.76, p=0.02) PDA or HGD or worrisome features on imaging: HR 3.27 (95% CI, 1.8-5.96, p&lt;0.001)</td>
</tr>
</tbody>
</table>

PDA: pancreatic ductal adenocarcinoma; HGD: high-grade dysplasia; HR: hazard ratio; CI: confidence interval.

Prospective Observational Studies

Recent prospective observational studies have reported the yield of screening and outcomes in high-risk individuals enrolled in pancreatic cancer surveillance programs (Table 7). Surveillance protocols varied somewhat and evolved over time, but typically included annual MRI and/or endoscopic ultrasound, with more frequent follow-up when a suspicious lesion was identified.

A 16-year follow-up study of surveillance in individuals at high-risk of pancreatic cancer due to family history or genetic factors was reported by Canto et al. (2018). The overall detection rate over 16 years
was 7%, including incident and prevalent neoplasms. Of 354 individuals under surveillance, 10 pancreatic cancers were detected, and 9 of 10 were resectable. Among these, 85% survived for 3 years.

Vasen et al. (2016) found that surveillance of CDKN2A mutation carriers detected most pancreatic adenocarcinomas at a resectable stage. In patients at risk for familial pancreatic cancer (those from families with 2 or 3 first-degree relatives with pancreatic cancer), however, the yield of screening was low.

Table 7. Studies of Surveillance in Individuals at High Risk of Pancreatic Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Populations</th>
<th>Surveillance Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canto et al. (2018) 13,(CAPS 1, CAPS2, CAPS3, CAPS4)</td>
<td>354 individuals at high-risk for pancreatic cancer enrolled in Cancer of the Pancreas Screening cohort studies at tertiary care academic centers from 1998 through 2014</td>
<td>EUS, MRI, and/or CT baseline screening with EUS intervals depended on the presence or absence of neoplastic-type pancreatic lesions. Normal pancreas or EUS features of chronic pancreatitis were followed annually. Those with pancreatic cysts or indeterminate radiologic lesions underwent more frequent imaging with EUS and/or MRI or CT, according to published international guidelines: every 6-12 mos for those without a mural nodule or dilated pancreatic duct and every 3-6 mos</td>
<td>Overall detection rate over 16 yrs was 7%; 9/10 cancers detected were resectable.</td>
</tr>
</tbody>
</table>
mos for larger cysts or cysts with worrisome features. Stable or improved appearance of pancreatic lesions resulted in decreased surveillance imaging frequency to every 12 mos. Median follow-up 5.6 yrs.

Vasen et al. (2016)\textsuperscript{15}  
- 178 individuals with a CDKN2A mutation  
- 214 Individuals at high-risk for familial pancreatic cancer (from families with 2 or 3 first-degree relatives with pancreatic cancer)  
- 19 individuals with a BRCA1/2 or PALB2 mutation

Annual MRI. Beginning in 2012, endoscopic ultrasound was also offered as an option in addition to annual MRI. In the event of a small lesion, MRI was repeated 3 to 6 mos later. In cases where there was serious suspicion of pancreatic adenocarcinoma, additional endoscopic ultrasound and CT scanning was performed.

Individuals with a CDKN2A mutation:  
- 13/178 (7.3%)  
- Cumulative incidence of pancreatic cancer was 14% by the age of 70 yrs

Individuals at high-risk for familial pancreatic cancer  
- 3/214 (1.4%)  
- Individuals with a BRCA1/2 or PALB2 mutation  
- 1/19 (3.8%)

EUS: endoscopic ultrasound; CT: computed tomography; CAPS: Cancer of the Pancreas Screening; FDR: first-degree relative; FPC: familial pancreatic cancer; MRI: magnetic resonance imaging.

Konings et al. (2019) published a report of outcomes on 76 high-risk individuals from CAPS surveillance programs in 4 countries (U.S., the Netherlands, Israel, and Italy) who had either undergone pancreatic surgery because of the detection of a suspicious pancreatic lesion (n=71) or progressed to advanced unresectable malignant disease (n=5).\textsuperscript{15} Survival rate was significantly poorer for individuals with
advanced pancreatic cancer compared with those who had surgery (40% vs. 83% respectively, $P = 0.050$; mean survival 9.5 vs. 54.3 months, $P < 0.001$).

Although observational studies have demonstrated that surveillance can identify pancreatic cancer and precursor lesions in asymptomatic individuals, it is not possible to conclude from this body of evidence that surveillance improves survival. Longer survival time observed in individuals undergoing surveillance could simply be due to earlier identification of the disease (lead-time bias) and not the effects of early intervention and treatment.

**Screening and Surveillance for Other Cancers in Asymptomatic Patients at High-Risk for Hereditary Pancreatic Cancer**

Genes that are associated with pancreatic cancer are also associated with increased risk of other cancers and genetic cancer syndromes (see Table 2). For this reason, genetic testing in patients with pancreatic cancer has been proposed to identify patients who are candidates for surveillance, early treatment, and prevention of cancers such as breast, ovarian, colon, and melanoma. A review of the evidence in other cancers is beyond the scope of this review, and is addressed in the following policies:

- 2.04.02 - Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1 or BRCA2)
- 2.04.08 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- 2.04.44 - Genetic Testing for Familial Cutaneous Malignant Melanoma
- 2.04.93 - Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- 2.04.101 - Genetic Testing for Li-Fraumeni Syndrome
- 2.04.126 - Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk

**Section Summary: Genetic Testing in Asymptomatic Individuals who are at Risk for Hereditary Pancreatic Cancer**

There is no direct evidence comparing health outcomes in patients tested or not tested for a variant. There is indirect evidence from one comparative observational study of high-risk patients under surveillance that the risk of progression to pancreatic cancer is higher among individuals with a known pathogenic variant than in patients identified as at-risk based on family history alone. There is also evidence from prospective observational studies that surveillance of high-risk individuals can identify pancreatic cancer and precursor lesions. In 1 analysis of 76 high-risk individuals under surveillance, survival was better in those who had surgery due to detection of either low- or high-risk neoplastic precursor lesions (n=71) compared to those who had advanced to unresectable disease (n=5). Although observational studies have demonstrated that surveillance can identify pancreatic cancer and precursor lesions in asymptomatic individuals, it is not possible to conclude from this body of evidence that surveillance improves survival. Longer survival time observed in individuals undergoing surveillance could simply be due to earlier identification of the disease (lead-time bias) and not the effects of early intervention and treatment.

**Summary of Evidence**

For individuals with pancreatic cancer who receive genetic testing for ATM, CDK2NA, EPCAM, MMR genes (MLH1, MSH2, MSH6, PMS2), PALB, STK11, and TP53, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Multiple observational studies have demonstrated that testing patients with pancreatic cancer can identify individuals with disease-associated variants, including
among those who do not have a family history of the disease. However, there is no direct evidence comparing health outcomes in patients tested or not tested for a variant. There are no targeted treatments for pancreatic cancer based on these genes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have pancreatic cancer who receive testing for a BRCA1 or BRCA2 variant to guide selection for targeted treatment, the evidence includes observational studies and one randomized controlled trial. Multiple observational studies have demonstrated that testing patients with pancreatic cancer can identify individuals with BRCA1 or BRCA2 variants, including among those who do not have a family history of pancreatic cancer. A placebo-controlled trial of olaparib as maintenance therapy in patients with germline BRCA1 or BRCA2 mutations and metastatic pancreatic cancer found longer progression-free survival with olaparib (7.4 months vs. 3.8 months; hazard ratio 0.53; 95% confidence interval 0.35 to 0.82; P=0.04). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic and at high-risk for hereditary pancreatic cancer who receive testing for genes associated with hereditary pancreatic cancer, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. There is no direct evidence comparing health outcomes in patients tested or not tested for a variant. There is indirect evidence from one comparative observational study of high-risk patients under surveillance that the risk of progression to pancreatic cancer is higher among individuals with a known pathogenic variant than in patients identified as at-risk based on family history alone. There is also evidence from prospective observational studies that surveillance of high-risk individuals can identify pancreatic cancer and precursor lesions. In 1 analysis of 76 high-risk individuals under surveillance, survival was better in those who had surgery due to detection of either low- or high-risk neoplastic precursor lesions (n=71) compared to those who had advanced to unresectable disease (n=5). Although observational studies have demonstrated that surveillance can identify pancreatic cancer and precursor lesions in asymptomatic individuals, it is not possible to conclude from this body of evidence that surveillance improves survival. Longer survival time observed in individuals undergoing surveillance could simply be due to earlier identification of the disease (lead-time bias) and not the effects of early intervention and treatment. 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

American College of Gastroenterology

In 2015, the American College of Gastroenterology Clinical Guideline on Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes includes the following recommendations on genetic testing for pancreatic cancer: 5

- Individuals should be considered to be at risk for familial pancreatic adenocarcinoma if they (i) have a known genetic syndrome associated with pancreatic cancer, including hereditary breast-ovarian cancer syndrome, familial atypical multiple melanoma, and mole syndrome, PJS, LS, or other gene mutations associated with an increased risk of pancreatic adenocarcinoma; or (ii) have 2 relatives with pancreatic adenocarcinoma, where 1 is a first-degree relative; (iii) have 3 or more relatives with pancreatic cancer; or (iv) have a history of hereditary pancreatitis.
- Genetic testing of patients with suspected familial pancreatic cancer should include analysis of BRCA1/2, CDKN2A, PALB2, and ATM. Evaluation for PJS, LS, and hereditary pancreatitis-associated genes should be considered if other component personal and/or family history criteria are met for the syndrome.
American Society of Clinical Oncology

In 2019, an American Society of Clinical Oncology opinion statement published, addressed the identification and management of patients and family members with a possible predisposition to pancreatic adenocarcinoma and made the following recommendations:1

- PCO 1.2 Individuals with a family history of pancreatic cancer affecting 2 first-degree relatives meet the criteria for familial pancreatic cancer. Individuals whose family history meets criteria for familial pancreatic cancer, those with 3 or more diagnoses of pancreatic cancer in the same side of the family, and individuals meeting criteria for other genetic syndromes associated with increased risk for pancreatic cancer have an increased risk for pancreatic cancer and are candidates for genetic testing (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

- PCO 1.3 Genetic risk evaluation should be conducted in conjunction with health care providers familiar with the diagnosis and management of hereditary cancer syndromes to determine the most appropriate testing strategy and discuss implications of the findings for family members. Germline genetic testing for patients with pancreatic cancer should be offered in the context of shared decision making. (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

- PCO 2.1 All patients diagnosed with pancreatic adenocarcinoma should undergo an assessment of risk for hereditary syndromes known to be associated with an increased risk for pancreatic adenocarcinoma. Assessment of risk includes obtaining a personal cancer history and family history of cancers in first- and second-degree relatives. However, recent data demonstrate that many individuals who develop pancreatic cancer in the setting of genetic predisposition lack clinical features or family cancer history typically associated with the corresponding hereditary syndrome. Therefore, germline genetic testing may be discussed with patients with a personal history of pancreatic cancer, even if family history is unremarkable (Type: informal consensus; benefits outweigh harms; Strength of statement: strong).

International Cancer of the Pancreas Screening Consortium

In 2019, the International Cancer of the Pancreas Screening Consortium published an updated consensus document on the management of patients with increased risk for familial pancreatic cancer.16 The panel recommended pancreatic cancer surveillance for the following individuals:

- All patients with Peutz-Jeghers syndrome (carriers of a germline LKB1/STK11 gene mutation)
- All carriers of a germline CDKN2A mutation
- Carriers of a germline BRCA2, BRCA1, PALB2, ATM, MLH1, MSH2, or MSH6 gene mutation with at least 1 affected first-degree blood relative
- Individuals who have at least 1 first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer (familial pancreatic cancer kindred)

The preferred surveillance tests are endoscopic ultrasound and magnetic resonance imaging (MRI). The recommended age to initiate surveillance depends on an individual’s gene mutation status and family history, but no earlier than age 50 or 10 years earlier than the youngest relative with pancreatic cancer. There was no consensus on the age to end surveillance.

National Comprehensive Cancer Network

In v.1.2020, National Comprehensive Cancer Network guidelines for genetic/familial high-risk assessment: breast, ovarian, and pancreatic cancer recommend germline testing for all individuals with exocrine pancreatic cancer.13 The guidelines list the following genes as those typically tested for pancreatic cancer risk: ATM, BRCA1, BRCA2, CDKN2A, most Lynch syndrome genes (MLH1, MSH2, MSH6, EPCAM), PALB2, STK11, and TP53.
In v.1.2020, the National Comprehensive Cancer Network guidelines on pancreatic adenocarcinoma recommend germline testing for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes, and genetic counseling for patients who test positive for a pathogenic mutation or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status.  

**U.S. Preventive Services Task Force Recommendation**

In 2019, the U.S. Preventive Services Task Force recommendation on screening for pancreatic cancer applies to asymptomatic adults not known to be at high-risk of pancreatic cancer. The recommendation does not apply to persons at high-risk of pancreatic cancer due to an inherited genetic syndrome or due to a history of hereditary pancreatic cancer.

**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.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 8.

**Table 8. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Ongoing</strong></td>
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<tr>
<td>NCT02790944</td>
<td>Utilizing a Multi-gene Testing Approach to Identify Hereditary Pancreatic</td>
<td>300</td>
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<td>Cancer in Consecutive Cases Unselected for Family History</td>
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<td>NCT03060720</td>
<td>Systematic Hereditary Pancreatic Cancer Risk Assessment and Implications</td>
<td>375</td>
<td>Feb 2022</td>
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<td></td>
<td>for Personalized Therapy</td>
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<td>NCT00835133</td>
<td>Biospecimen Resource for Familial Pancreas Research, a Data and Tissue</td>
<td>4000</td>
<td>Sep 2022</td>
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<td></td>
<td>Registry (Also Known as a Bio-repository, Bio-bank, Data and Tissue</td>
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<tr>
<td></td>
<td>Database, Data and Tissue Bank, Etc.) to Help Advance Research in Familial</td>
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<td></td>
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<td></td>
<td>Pancreas Disease</td>
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<td>NCT02206360</td>
<td>Observational Study to Analyze the Outcomes of Subjects Who - Based Upon</td>
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<td>Their Sufficiently Elevated Risk for the Development of Pancreatic</td>
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<td>Adenocarcinoma- Elect to Undergo Early Detection Testing</td>
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<td>NCT00526578</td>
<td>Pancreatic Cancer Genetic Epidemiology (PACGENE) Study</td>
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<td>Jun 2025</td>
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<td><strong>Unpublished</strong></td>
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<td>NCT03982446</td>
<td>Prevalence of Germline Pathogenic Mutations in Patients with Pancreatic</td>
<td>500</td>
<td>Dec 2019</td>
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<td></td>
<td>Adenocarcinoma</td>
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</table>

NCT: national clinical trial.

Denotes industry-sponsored or cosponsored trial.
ESSENTIAL HEALTH BENEFIT

The Affordable Care Act (ACA) requires fully insured non-grandfathered individual and small group benefit plans to provide coverage for ten categories of Essential Health Benefits (“EHBs”), whether the benefit plans are offered through an Exchange or not. States can define EHBs for their respective state.

States vary on how they define the term small group. In Idaho, a small group employer is defined as an employer with at least two but no more than fifty eligible employees on the first day of the plan or contract year, the majority of whom are employed in Idaho. Large group employers, whether they are self-funded or fully insured, are not required to offer EHBs, but may voluntarily offer them.

The Affordable Care Act requires any benefit plan offering EHBs to remove all dollar limits for EHBs.

REFERENCES


CODES

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<th>Codes</th>
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<th>Description</th>
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<td>There is no test specifically for pancreatic cancer. Genes associated with pancreatic cancer include BRCA1, BRCA2, PALB2, ATM, APC, MLH1, MLH2, MSH6, PMS2, EPCAM, CDKN2A, TP53, STK11. Tests or panels that include these genes may be reported and are listed below</td>
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<td>CPT</td>
<td>0129U</td>
<td>Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)</td>
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<td>BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)</td>
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### Genetic Testing for Hereditary Pancreatic Cancer

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<tr>
<th>Service Description</th>
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<th>ICD10-CM Code(s)</th>
<th>PCS Code(s)</th>
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<td>C25.0-C25.9</td>
<td>Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests.</td>
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<td>Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed</td>
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**HCPCS** No code

**ICD10-CM**

- C25.0-C25.9 Malignant neoplasm of the pancreas code range
- C25.0-C25.9 Carcinoma in situ of other specified digestive organs (pancreas)
- Z12.89 Encounter for screening for malignant neoplasm of other sites
- Z15.09 Genetic susceptibility to other malignant neoplasm
- Z80.0 Family history of malignant neoplasm of digestive organs
- Z85.07 Personal history of malignant neoplasm of pancreas

**PCS** Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests.

**TOS** Laboratory

**POS** Outpatient

### POLICY HISTORY

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<th>Action</th>
<th>Description</th>
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<tr>
<td>02/19/20</td>
<td>New policy -added to medicine section</td>
<td>Blue Cross of Idaho adopted policy effective 05/20/2020. Policy created with literature review through August 26, 2019. Genetic</td>
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testing for BRCA1 and BRCA2 variants in patients with pancreatic cancer may be considered medically necessary. Genetic testing for other genes in patients with pancreatic cancer is considered investigational unless the individual meets testing criteria specified in another policy. Genetic testing for genes associated with pancreatic cancer in asymptomatic individuals is considered investigational unless the individual meets testing criteria specified in another policy.