FEP Medical Policy Manual

FEP 2.04.148 Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes (ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53)

Annual Effective Policy Date: July 1, 2024

Original Policy Date: July 2020

Related Policies:

2.04.02 - Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
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 - Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)
2.04.44 - Germline Genetic Testing for Familial Cutaneous Malignant Melanoma (CDKN2A, CDK4)
2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
2.04.99 - Genetic Testing for Hereditary Pancreatitis

Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes (ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53)

Description

Description

Pancreatic cancer is the fourth leading cause of cancer death in the United States, accounting for 8.3% of all cancer deaths in 2023. Multiple genetic syndromes are associated with an increased risk for pancreatic cancer, and approximately 10% to 15% of patients with pancreatic cancer are thought to have a hereditary susceptibility to the disease. Germline genetic testing for pancreatic cancer susceptibility genes is proposed to guide treatment decisions in patients with pancreatic cancer, and to inform decisions about surveillance in asymptomatic patients at high risk of pancreatic cancer.

OBJECTIVE

The objective of this evidence review is to evaluate the clinical validity and clinical utility of germline genetic testing of individuals with or at high-risk of pancreatic cancer and to determine if its use improves the net health outcome.

POLICY STATEMENT

Genetic testing for *BRCA1, BRCA2*, and *PALB2* variants to guide selection for treatment with platinum-based chemotherapy in previously untreated individuals with locally advanced or metastatic pancreatic cancer may be considered **medically necessary**.

Genetic testing for *BRCA1* and *BRCA2* variants to guide selection for treatment with olaparib (Lynparza) in individuals with pancreatic cancer may be considered **medically necessary.**

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

Genetic testing for *ATM, BRCA1, BRCA2, CDK2NA, EPCAM*, *MMR* genes (*MLH1*, *MSH2*, *MSH6, PMS2), PALB2, STK11, and TP53* in asymptomatic individuals at high risk for hereditary pancreatic cancer is considered **investigational** unless the individual meets criteria for testing as specified in another policy (see policy guidelines).

POLICY GUIDELINES

Related Policies on Hereditary Cancer Syndromes

- Genetic testing for BRCA1 and BRCA2 variants
  - 2.04.02 Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
- Genetic testing for *ATM* and *PALB2* gene variants
  - Policy 2.04.126 Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk
- Genetic testing for *EPCAM*, *MMR* (*MLH1*, *MSH2*, *MSH6, PMS2),* and *STK11* gene variants
  - Policy 2.04.08 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Genetic testing for *CDKN2A* gene variants
  - Policy 2.04.044 Genetic Testing for Familial Cutaneous Malignant Melanoma
- Genetic testing for *TP53* gene variants
  - 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

Testing At-Risk Relatives

Individuals are considered at high risk for hereditary pancreatic cancer if they have:

- 2 close relatives with pancreatic adenocarcinoma where 1 is a first-degree relative, OR
- have 3 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.

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 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 individuals 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 individuals ; 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

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

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

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

FDA REGULATORY STATUS

Testing for variants associated with 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). 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 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. Also in 2019, BRACAnalysis CDx received expanded FDA approval for use as a companion diagnostic for Lynparza (olaparib) in pancreatic cancer patients.[8,]

RATIONALE

Summary of Evidence

For individuals who have pancreatic cancer who receive testing for a *BRCA1, BRCA2, or PALB2* variant to guide selection for first-line treatment, the evidence includes observational studies. Multiple observational studies have demonstrated that testing patients with pancreatic cancer can identify individuals with *BRCA1*, *BRCA2,* and *PALB2* variants, including among those who do not have a family history of pancreatic cancer. Observational studies have reported a survival advantage when patients with a BRCA or PALB2 variant were treated with platinum-based chemotherapy regimens compared to non-platinum-based regimens. Although these studies are limited by their small sample sizes and retrospective designs, the consistency and magnitude of benefit across studies suggests that genetic testing for these variants to aid in treatments decisions is a reasonable approach. The evidence is sufficient 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 1 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* variants 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=.04). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with pancreatic cancer who receive genetic testing for *ATM, CDK2NA, EPCAM*, *MMR* genes (*MLH1*, *MSH2*, *MSH6, PMS2), STK11, and TP53* to guide treatment, 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. Additionally, there are no targeted treatments for pancreatic cancer based on these genes, and management changes that would result from testing these genes are unclear. The evidence is insufficient 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. There is no direct evidence comparing health outcomes in patients tested or not tested for a variant. There is indirect evidence from 2 comparative observational studies of high-risk individuals under surveillance that the risk of progression to pancreatic cancer is higher among individuals with a known pathogenic variant than in individuals 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 be due to earlier identification of the disease (downstaging) and not the effects of early intervention and treatment. Additionally, evidence is too limited to determine if selecting patients for surveillance based on genetic testing leads to better outcomes than using criteria such as family history alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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

American College of Gastroenterology

In 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:[7,]

- 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 [Peutz-Jeghers syndrome], LS [Lynch syndrome], 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 (ASCO) opinion statement addressed the identification and management of patients and family members with a possible predisposition to pancreatic adenocarcinoma and made the following recommendations:[2,]

- PCO [provisional clinical opinion] 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 3e 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).

In 2020, ASCO published a guideline update on recommendations for second-line therapy options for metastatic pancreatic cancer.[24,] In patients who have a germline *BRCA1* or *BRCA2* mutation and who have received first-line platinum based chemotherapy without disease progression for at least 16 weeks, options for continued treatment include chemotherapy or the poly *ADP* ribose polymerase (PARP) inhibitor olaparib.

International Cancer of the Pancreas Screening Consortium

In 2020, 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.[25,] The panel recommended pancreatic cancer surveillance performed in a research setting 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

Two National Comprehensive Cancer Network (NCCN) guidelines address germline genetic testing in individuals with or at high risk for pancreatic cancer.[26,6,]

The Guidelines on Genetic/Familial High-risk Assessment: Breast, Ovarian, and Pancreatic (v.2.2024) recommend germline testing for all individuals with exocrine pancreatic cancer, and specify that testing of first-degree relatives should only be done only if it is impossible to test the individual who has pancreatic cancer.[26,]

The Guideline on Treatment of Pancreatic Adenocarcinoma (v.1.2024) recommends germline testing for any patient with confirmed pancreatic cancer using comprehensive gene panels for hereditary cancer syndromes.[6,] The guideline specifies the following genes as those typically tested for pancreatic cancer risk: *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*,), PALB2, *PMS2, STK11*, and TP53.

For patients with locally advanced disease, preferred first-line therapy regimens include gemcitabine + cisplatin for patients with *BRCA1/2* or *PALB2* variants For patients with metastatic disease who have received previous platinum-based chemotherapy, olaparib is preferred only for patients with germline *BRCA1/2* variants.

Genetic counseling is recommended for patients who test positive for a pathogenic variant, or for patients with a positive family history of pancreatic cancer, regardless of test results. The guidelines also recommend genetic counseling for patients who test positive for a pathogenic variant or for patients with a positive family history of pancreatic cancer, regardless of variant status.

U.S. Preventive Services Task Force Recommendation

The 2019 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.[5,] 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.

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

Date	Action	Description
June 2020	New policy	Policy created with literature review through August 26, 2019. Genetic 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.
June 2021	Replace policy	Policy updated with literature review through December 16, 2020; references added. New indication and medically necessary statement added for BRCA1, BRCA2, and PALB2 variant testing to select first-line treatment with platinum chemotherapy. PALB2 testing removed from indication 3. Title changed to "Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes."
June 2022	Replace policy	Policy updated with literature review through January 3, 2022; no references added. Policy statements unchanged.
June 2023	Replace policy	Policy updated with literature review through January 6, 2023; references added. Minor editorial refinements to policy statements; intent unchanged. Policy title changed to include gene names (ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53).
June 2024	Replace policy	Policy updated with literature review through January 3, 2024; no references added. Policy statements unchanged.