

2.04.148 Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes (ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53)			
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Section:	2.0 Medicine	Page:	Page 1 of 28

Policy Statement

- I. Genetic testing for *BRCA1*, *BRCA2*, and *PALB2* or a small panel (such as CPT 81432) containing these gene variants to guide selection for treatment with [platinum-based chemotherapy](#)* may be considered **medically necessary** in previously untreated individuals with locally advanced or metastatic pancreatic cancer.
- II. Genetic testing for *BRCA1* and *BRCA2* variants to guide selection for treatment with olaparib ([Lynparza](#))** may be considered **medically necessary** in individuals with pancreatic cancer.
- III. 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](#).
- IV. 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](#).

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Platinum based chemotherapy includes the drugs **cisplatin**, **carboplatin** and **oxaliplatin**

**Lynparza is a PARP inhibitor (stops the function of the protein PARP that helps repair DNA damage in cells so cancer cells die) that is also used for advanced ovarian, fallopian tube, primary peritoneal, HRR prostate and breast cancer. This policy is limited to use for pancreatic cancer, but similar testing is indicated for the other noted cancers.

Related Policies on Hereditary Cancer Syndromes

- Genetic testing for *BRCA1*, *BRCA2*, and *PALB2* variants
 - See Blue Shield of California Medical Policy: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
- Genetic testing for *ATM* gene variants
 - See Blue Shield of California Medical Policy: Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)
- Genetic testing for *EPCAM*, *MMR* (*MLH1*, *MSH2*, *MSH6*, *PMS2*), and *STK11* gene variants
 - See Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Genetic testing for *CDKN2A* gene variants
 - See Blue Shield of California Medical Policy: Genetic Testing for Familial Cutaneous Malignant Melanoma
- Genetic cancer susceptibility panel testing
 - See Blue Shield of California Medical Policy: 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, 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(s) 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.

Description

Pancreatic cancer is the fourth leading cause of cancer death in the United States, accounting for 7.8% of all cancer deaths in 2020. 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.

Related Policies

- Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- Genetic Testing for Familial Cutaneous Malignant Melanoma
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

- Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)
- Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 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

Background

Pancreatic Cancer Epidemiology

Pancreatic cancer is the fourth leading cause of cancer death in the U.S., accounting for 7.9% of all cancer deaths in 2021.¹ The disease has a poor prognosis, with only 10.8% of patients surviving to 5 years. Five-year survival for localized pancreatic cancer is 41.6% but most symptomatic patients have advanced, incurable disease at diagnosis.

Genetics and Pancreatic Cancer

Approximately 10%-15% of patients with pancreatic cancer are thought to have a hereditary susceptibility to the disease.² Multiple genetic syndromes, including hereditary breast and ovarian cancer syndrome, are associated with an increased risk for pancreatic cancer. Five percent to 9% of pancreatic ductal adenocarcinomas (PDACs) develop in patients with a germline *BRCA* or *PALB2* variant, with higher rates observed in those with a family or personal history of pancreatic cancer or

other *BRCA*-related malignancies.³ The incidence of germline *PALB2* variants³ in persons with PDAC is estimated to be between 0.6% and 2.1%.⁴

Having a first-degree relative with pancreatic cancer increases an individual's risk of developing pancreatic cancer, and the degree of risk increases depending on the number of affected relatives (Table 1).⁵ 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. In 80% of pancreatic cancer patients with a family history of pancreatic cancer, the genetic basis of the inherited predisposition is unknown.⁶

Table 1. Family History and Pancreatic Cancer Risk

<https://seer.cancer.gov/statfacts/html/pancreas.html>

Number of First Degree Relatives (FDR) with Pancreatic Cancer	Increased Risk
1 affected FDR	4.6-fold
2 affected FDR	6.4-fold
3 affected FDR	32-fold

Sources: American Society of Clinical Oncology,² American College of Gastroenterology⁷
FDR: first-degree relative.

Germline genetic testing for pancreatic cancer susceptibility genes has several proposed purposes. In patients with pancreatic cancer, the purpose of genetic testing would be to guide treatment decisions (e.g., selection of platinum-based chemotherapy for first-line treatment, targeted treatment with a poly *ADP* ribose polymerase [PARP] inhibitor). In asymptomatic patients at high risk of pancreatic cancer (e.g., due to family history or other clinical factors), the purpose of genetic testing would be to inform decisions about surveillance for early detection of pancreatic cancer. Because the incidence of pancreatic cancer in the general population is low, with a lifetime risk of approximately 1.6%, screening is not recommended for patients who are not at high-risk, but patients with a family history of pancreatic cancer or a syndrome associated with increased risk of pancreatic cancer are potential targets for surveillance.

Literature Review

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Genetic Testing for a *BRCA1*, *BRCA2*, or *PALB2* Variant to Select First-Line Treatment Clinical Context and Test Purpose

The purpose of genetic testing for a *BRCA1*, *BRCA2*, or *PALB2* variant in individuals with pancreatic cancer is to identify patients who might benefit from a platinum-containing chemotherapy regimen. The following PICO was used to select literature to inform this review.

Population

The relevant population of interest is individuals with previously untreated, locally advanced or metastatic pancreatic cancer.

Interventions

The test being considered is genetic testing for a *BRCA1*, *BRCA2*, or *PALB2* 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 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.

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).

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

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 (e.g., summaries from professional societies).

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 Validity

Multiple observational studies have demonstrated that testing patients with pancreatic cancer can identify individuals with *BRCA1*, *BRCA2*, and *PALB2* variants.

Clinical Utility

There is no direct evidence from RCTs of the clinical utility of germline testing for *BRCA* or *PALB2* variants in patients with pancreatic cancer. Several retrospective observational studies and an uncontrolled subgroup analysis from a randomized controlled trial of veliparib have reported a survival advantage for pancreatic cancer patients with *BRCA* or *PALB2* pathogenic variants who received platinum-containing chemotherapy (Tables 2 and 3).

Golan et al (2014) analyzed survival data and clinical characteristics from databases of pancreatic cancer patients treated at 3 institutions between 1994 and 2012, including 71 patients with *BRCA1* or *BRCA2* variants.⁹ Longer median overall survival was observed in patients with *BRCA* variants who received platinum-based chemotherapy compared to those who received non-platinum-based chemotherapies (22 months [range 6–27] vs. 9 months [range 4–12]; $p=.039$).

Three retrospective cohort studies used similar methods to compare survival outcomes in patients with or without *BRCA* or *PALB2* variants who were treated with platinum-based these studies, patients with a pathogenic variant were matched to control patients on prognostic factors such as age at diagnosis, sex, and stage of disease. All of these studies reported a survival advantage when variant-positive patients were treated with platinum versus non-platinum-based regimens, while there was no advantage for platinum-based therapy in patients who did not harbor a *BRCA* or *PALB2* variant (See Table 3).

Limitations of these studies are summarized in Tables 4 and 5. Major limitations include the studies' small sample sizes and retrospective designs. The timing of genetic testing varied within the patient cohorts (e.g. some patients were tested before and others after their pancreatic cancer diagnosis). It is possible that patients who survived their PDAC diagnosis longer were more likely to undergo genetic testing. Because many control patients were not tested, some may have been variant-positive. However, this is less of a concern because this would have biased results toward the null. There was also heterogeneity in the timing and type of chemotherapy regimens patients received. Although the studies attempted to control for confounding by matching patients on important prognostic factors or using statistical analysis methods, the potential for unmeasured confounding decreases confidence in the results. Despite these limitations, consistency in the magnitude and direction of results across studies suggest that a strategy of testing for these variants to aid in decision-making about first-line treatment is a reasonable approach.

O'Reilly et al (2020) conducted a RCT of platinum-based chemotherapy with or without the PARP inhibitor veliparib in patients with previously untreated, locally advanced or metastatic pancreatic cancer and a *BRCA* or *PALB2* germline variant. Two-year OS rate for the entire cohort was 30.6% (95%CI, 17.8% to 44.4%), and 3-year OS rate for the entire cohort was 17.8% (95% CI, 8.1% to 30.7%). Overall survival did not differ significantly when veliparib was added to the platinum-based regimen. The trial was not designed to compare platinum-based versus standard chemotherapy, but it does provide uncontrolled evidence of the effectiveness of platinum-containing chemotherapy in patients with germline pathogenic *BRCA* or *PALB2* variants. The major limitation of this analysis was the lack of a control group of patients who did not receive platinum-based chemotherapy.

Table 2. Platinum-based Chemotherapy for Pancreatic Cancer Treatment in Patients with a *BRCA1*, *BRCA2*, or *PALB2* Variant: Study Characteristics

Study	Study Type	Location	Dates	Participants	Pancreatic Cancer Treatment Regimen
Golan et al (2014) ⁹	Retrospective cohort	Canada and Israel, 3 sites	Patients diagnosed between January 1994 and December 2012	71 patients with PDAC and <i>BRCA1</i> (n=21), <i>BRCA2</i> (n=49), or both (n=1) variants Stage 1 (1.4%), stage 2 (27%), stage 3 (23%), stage 4 (48%); 1 missing data on stage	22 patients in the stage 3/4 group received platinum-based treatment. The majority of platinum-treated patients received gemcitabine and cisplatin, 1 patient received gemcitabine and oxaliplatin and 3 patients received FOLFIRINOX
O'Reilly et al (2020) ³	RCT (platinum-based chemotherapy + veliparib vs. platinum-based chemotherapy alone)	US, Canada, Israel, 6 sites	Patients enrolled between 2014 and 2018	52 patients with untreated locally advanced or metastatic PDAC and germline pathogenic variants in <i>BRCA</i> or <i>PALB2</i>	Arm A: cisplatin, gemcitabine, and veliparib Arm B: cisplatin and gemcitabine

Study	Study Type	Location	Dates	Participants	Pancreatic Cancer Treatment Regimen
Reiss et al (2018)⁴	Retrospective cohort	US, single site	Patients diagnosed between 1995 and 2016	29 patients diagnosed with either locally advanced or metastatic PDAC with a known pathogenic germline <i>BRCA1</i> , <i>BRCA2</i> , or <i>PALB2</i> variant. 58 controls were either confirmed variant noncarriers or had not been tested. Cohorts matched by age at diagnosis, year of diagnosis, stage at diagnosis, and sex	Of the 87 patients, 4 variant-positive patients (13.8%) and 12 control patients (20.7%) received no systemic treatment of any kind. Treatment history for 1 control patient was unknown. Patients who were variant-positive and did receive systemic therapy: 18 of 25 (72.0%) received platinum-based therapy 48.0% oxaliplatin, 12.0% received cisplatin, 8.0% received both oxaliplatin and cisplatin, and the exact regimen was unknown for 1 patient. Control patients, 60.8% received platinum-based therapy (96.4% oxaliplatin, 1 cisplatin (3.5%), regimen unknown for 1 patient..
Yu et al (2019)¹¹	Retrospective cohort	US, single site	Patients diagnosed between January 1, 1995 and March 31, 2018	32 patients with nonmetastatic PDAC who had undergone curative intent surgical resection and had a known pathogenic germline variant in <i>BRCA1</i> , <i>BRCA2</i> , or <i>PALB2</i> 64 control patients who were either confirmed variant noncarriers or had not been tested. Cohorts matched by age at diagnosis, year of diagnosis, sex, and disease stage.	42% in the variant-positive group and 17% in the variant-negative group received perioperative platinum chemotherapy (p=.01). Of these, 3 patients in the variant-positive group and 10 in the variant-negative group received perioperative FOLFIRINOX, the remaining patients received other platinum-containing regimens. 12 patients in the variant-positive group and 23 in the variant-negative group received palliative platinum chemotherapy upon recurrence.
Wattenberg et al (2020)¹⁰	Retrospective cohort	US, single site	Patients diagnosed between July 2011 and March 2018	26 patients with locally advanced or metastatic PDAC and pathogenic germline variants in <i>BRCA1</i> (n=5), <i>BRCA2</i> (n=17) or <i>PALB2</i> (n=4) who had received platinum-based therapy 52 control patients who were either confirmed non-carriers or had not been tested Cohorts matched by age at diagnosis, sex, and race.	Variant-positive patients: FOLFIRINOX (n=10; 38.5%), FOLFOX (n=10; 38.5%) and cisplatin plus gemcitabine (n=6; 23.0%). 1 patient received FOLFIRINOX followed by cisplatin plus gemcitabine. Control patients: FOLFIRINOX (n=39; 75%), FOLFOX (n=11; 21.1%), cisplatin plus gemcitabine (n=1; 1.9%) and cisplatin plus gemcitabine plus nab-paclitaxel (n=1; 1.9%). Platinum therapy was most

Study	Study Type	Location	Dates	Participants	Pancreatic Cancer Treatment Regimen
					commonly received in the first-line setting regardless of cohort 80.7% of variant-positive patients 67.3% of control patients (p=.21). Significantly more control patients received FOLFIRINOX (75% vs. 38.5%; p=.0016) and significantly more variant-positive patients received cisplatin plus gemcitabine (23.1% vs. 1.9%; p=0.0021)

FOLFIRINOX: folinic acid, fluorouracil, irinotecan and oxaliplatin; FOLFOX: folinic acid, fluorouracil and oxaliplatin, or cisplatin/gemcitabine; PDAC: pancreatic ductal adenocarcinoma

Table 3. Platinum-based Chemotherapy for Pancreatic Cancer Treatment in Patients with a BRCA1, BRCA2, or PALB2 Variant: Study Results

Study	Overall Survival	Median Overall Survival	Median Progression-Free Survival
Golan et al (2014)⁹	Probability of survival, platinum-based (n=22) vs. non-platinum-based (n=21) therapy: 12 months: 0.70 (0.44–0.85) vs. 0.26 (0.08–0.48) 36 months: 0.16 (0.01–0.46) vs. 0.07 (0.01–0.26)	Stage 3/4 patients treated with platinum-based chemotherapy vs. non-platinum-based chemotherapy (N=43): 22 months (6–27) vs. 9 months (4–12); p=.039	(Disease-free survival) Patients with stage 1 or 2 disease (n=20): 13 months (95% CI 6-19 months) Probability of remaining disease free: 1 year: 0.54 (95% CI, 0.29 to 0.74) 5 years: 0.27 (95% CI, 0.09 to 0.5)
O'Reilly et al (2020)³	9/50 (18%) alive at final data cutoff 2-year OS: 30.6% (95%CI, 17.8% to 44.4%) 3-year OS: 17.8% (95% CI, 8.1% to 30.7%)	Arm A: 15.5 months (95% CI, 12.2 to 24.3 months) Arm B: 16.4 months (95% CI, 11.7 to 23.4)	Arm A: 10.1 months (95% CI, 6.7 to 11.5 months) Arm B: 9.7 months (95% CI, 4.2 to 13.6)
Reiss et al (2018)⁴	1-year OS: 94% Control: 60% HR, 0.25; 95% CI, 0.1 to 0.61; p=.002 In patients not treated with platinum, there was no significant difference in OS between groups (HR, 0.54; 95% CI, 0.25 to 1.17; p=.12).	BRCA-or PALB2 variant-positive: Undefined at a median follow-up of 20.1 months Control: 15.5 months	
Yu et al (2019)¹¹		Variant-positive group vs. control (all patients): 46.6 months vs. 23.2 months; HR, 0.49; 95% CI, 0.27 to 0.88 Subgroup who received platinum treatment at any time, variant-positive vs. control: 47.7 months vs. 23.1 months (HR, 0.30; 95% CI, 0.13 to 0.70) Subgroup who did not receive platinum treatment, variant-positive	

Study	Overall Survival	Median Overall Survival	Median Progression-Free Survival
		vs. control: HR, 0.52; 95% CI, 0.12 to 2.24	
Wattenberg et al (2020)¹⁰		Variant-positive group vs. control: 24.6 months vs. 18.8 months (p=.0467) No difference in outcomes between groups when platinum was administered in the second line or later.	10.1 months vs 6.9 months

CI: confidence interval; HR: hazard ratio; OS: overall survival.

Table 4. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Golan et al (2014)⁹	stage of disease varied	3. timing of testing varied			
O'Reilly et al (2020)³			No variant-negative control group		
Reiss et al (2018)⁴	stage of disease varied	3. timing of testing varied			
Yu et al (2019)¹¹	stage of disease varied	3. timing of testing varied			
Wattenberg et al (2020)¹⁰	stage of disease varied	3. timing of testing varied			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Golan et al (2014)⁹	1. not randomized	1. not blinded				
O'Reilly et al (2020)³						
Reiss et al (2018)⁴	1. not randomized	1. not blinded		1. missing data on chemotherapy regimen received		
Yu et al (2019)¹¹	1. not randomized	1. not blinded				
Wattenberg et al (2020)¹⁰	1. not randomized	1. not blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed

by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Genetic Testing for a *BRCA1*, *BRCA2*, or *PALB2* Variant to Select First-Line Treatment

Retrospective cohort studies and an uncontrolled analysis from a randomized controlled trial 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.

Genetic Testing for a *BRCA1* or *BRCA2* Variant to Select Targeted Treatment

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.

Population

The relevant population of interest is individuals with metastatic or recurrent pancreatic cancer.

Interventions

The test being considered is genetic testing for a *BRCA1* or *BRCA2* variant to select targeted treatment with PARP inhibitors such as olaparib.

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.

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).

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

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 (e.g., summaries from professional societies).

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.

Review of 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). 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 observational studies have demonstrated that testing patients with pancreatic cancer can identify individuals with *BRCA1* and *BRCA2* variants.

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 6 and 7).¹² Of 3315 patients screened, 247 (7.5%) had a germline BRCA variant. Median progression-free survival was longer in the olaparib group, but there was no difference in OS.

Table 6. RCT of Targeted Treatment in Patients With Pancreatic Cancer: Study Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Golan et al (2019) ¹² NCT02184195	Multiple	119	2014-2019	N=144	Olaparib	Placebo
				Patients with a germline <i>BRCA</i> variant and metastatic pancreatic adenocarcinoma that had not progressed during first-line platinum-based chemotherapy		

RCT: randomized controlled trial; NCT: National Clinical Trial 02184195, Multicentre Study of Maintenance Olaparib Monotherapy in Patients With gBRCA Mutated Metastatic Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy; N: sample size.

Table 7. RCT of Targeted Treatment in Patients With Pancreatic Cancer: Results

Study	Median Progression-free Survival	Median Overall Survival	Serious Adverse Events
Golan et al (2019) ¹²			
Olaparib	7.4 mos	18.9 mos	24%
Placebo	3.8 mos	18.1 mos	15%

HR (95% CI)	0.53 (0.35 to 0.82); p=.004	0.91 (0.56 to 1.46) p=.68
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RCT: randomized controlled trial; CI: confidence interval; HR: hazard ratio.

Section Summary: Genetic Testing for a *BRCA1* or *BRCA2* Variant to Select Targeted Treatment

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 [HR], 0.53; 95% CI 0.35 to 0.82; P=0.04).

Genetic Testing for *ATM*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *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.

Population

The relevant population of interest is individuals with pancreatic cancer.

Interventions

The test being considered is genetic testing for *ATM*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *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.

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).

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

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 (e.g., summaries from professional societies).

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).

Direct Evidence

There are no direct outcome data on the clinical usefulness of genetic testing for ATM, CDKN2A, 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 observational studies have demonstrated that testing patients with pancreatic cancer can identify individuals with disease-associated variants; some recent studies are summarized in Table 8. A case-control analysis conducted by Hu et al (2018) compared the association of germline pathogenic variations in 3030 patients with pancreatic cancer to 176,241 controls from 2 public genome databases.¹³ 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.¹³ Shindo et al (2017) reported that pathogenic variants were identified in 3.9% of a cohort of 854 patients with pancreatic adenocarcinoma.¹⁴ Of those with an identified pathogenic variant, only 3 (9.0%) reported a family history of pancreatic cancer.

Table 8. Study Characteristics: Clinical Validity of Genetic Tests in Patients with Pancreatic Cancer

Study	Study Population	Pathogenic Variants Identified, overall and by specific genes
Hu et al (2018) ¹³	3030 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	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)
Brand et al (2018) ¹⁵	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%
Mandelker et al (2017) ¹⁶	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	44/176 (25%) Pathogenic variants by gene BRCA1: 6 BRCA2: 11 CDKN2A: 3 PALB2: 1

Study	Study Population	Pathogenic Variants Identified, overall and by specific genes
Shindo et al (2017) ¹⁴	854 patients with pancreatic ductal adenocarcinoma;	ATM: 5 CHEK2: 7 APC: 7 MUTYH: 3 FH (recessive): 1 33/854 (3.9%; 95% CI, 3.0% to 5.8%)
	Control groups: 288 patients with other pancreatic and periampullary neoplasms, and 51 patients with nonneoplastic diseases who underwent pancreatic resection	Number of patients with deleterious variants in specific genes: BRCA2: 12 ATM: 10 BRCA1 3 PALB2: 2 MLH1: 2 CDKN2A: 1 TP53: 1
Grant et al (2015) ¹⁷	708 individuals with pancreatic cancer consenting to be in a province-wide population-based registry, with available blood or saliva samples	3/33 patients had reported a family history of pancreatic cancer 11/290 (3.8%)
		Number of pathogenic variants by gene: ATM: 3 BRCA1: 1 BRCA2: 2 MLH1: 1 MSH2: 2 MSH6: 1 TP53: 1

CI: confidence interval.

Clinical Utility

There are currently no targeted treatments for pancreatic cancer based on germline testing for *ATM*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *STK11*, or *TP53*. It is unclear what management changes would be implemented based on results of such testing.

Section Summary: Genetic Testing for *ATM*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *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 these variants. There are no targeted treatments for pancreatic cancer based on these variants.

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

Population

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 variants in genes associated with pancreatic cancer, including *ATM*, *BRCA1*, *BRCA2*, *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.

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).

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

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 (e.g., summaries from professional societies). 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.

Chain of 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.

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

Indirect Evidence: Clinical Validity of Genetic Testing in Asymptomatic Patients at High Risk for Hereditary Pancreatic Cancer

Multiple genetic syndromes, including hereditary breast and ovarian cancer syndrome, are associated with an increased risk for pancreatic cancer (Table 9). 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 1 of these syndromes.

Table 9. Pancreatic Cancer Susceptibility Genes and Associated Syndromes

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

Sources: American Society of Clinical Oncology;² American College of Gastroenterology⁷.
NA: not available.

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 10).¹⁸ In addition, 66 variants of unclear significance were identified. The cumulative incidence of pancreatic cancer in the germline variant 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 10. Clinical Validity of Genetic Testing in Asymptomatic Individuals at High Risk for Hereditary Pancreatic Cancer

Study	Study Population	Prevalence of Pancreatic Cancer	Pathogenic Variants Identified, overall and by specific genes
Abe et al (2019)¹⁸	464 individuals enrolled in a high-risk pancreatic cancer surveillance program	PDAC: 13/462 (2.8%) PDAC or HGD:19/462 (4.1%) PDAC or HGD or worrisome features on imaging: 42/446 (9.4%)	For patients with germline variants (n=134) compared to those with family history only with no known variant (n=330): PDAC: HR, 2.85 (95% CI, 1-8.18, p=.05) PDAC or HGD: HR, 2.81 (95% CI, 1.17-6.76, p=.02) PDAC or HGD or worrisome features on imaging: HR, 3.27 (95% CI, 1.8-5.96, p<.001)

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

Surveillance in Asymptomatic Individuals at High Risk for Hereditary Pancreatic Cancer

Recent prospective observational studies have reported the yield of screening and outcomes in high-risk individuals enrolled in pancreatic cancer surveillance programs (Table 11). 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).¹⁹ 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* variant carriers detected most pancreatic adenocarcinomas at a resectable stage.²⁰ 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.

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).²¹ Survival rate was significantly poorer for individuals with advanced pancreatic cancer compared with those who had surgery (40% vs. 83% respectively, p=.050; mean survival 9.5 vs. 54.3 months, p<.001).

Dbouk et al (2022) published results of the CAPS5 cohort, consisting of 1461 individuals who were determined to be at high risk for PDAC based either on presence of a germline pathogenic variant (48.5%) or family history without a known germline pathogenic variant (51.5%).²² A total of 9 individuals were diagnosed with a screen-detected pancreatic adenocarcinoma. The study authors concluded that their results "support current CAPS surveillance recommendations and argue against the notion of limiting pancreatic surveillance to those high-risk individuals with known pathogenic mutations."

In a cohort of 366 Dutch individuals at high risk of PDAC followed for 63 months (standard deviation, 43.2 months), Overbeek et al (2022) reported a 9.3% incidence of PDAC in the subset of individuals with a germline pathogenic variant and no PDAC in those with family history but no pathogenic variant.²³ Three out of 10 (30%) individuals with PDAC were detected at an early stage. The resectability rate was 60% (6/10) overall and 50% (4/8) for incident cases.

Although these 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 (lead-time bias) and not the effects of early intervention and treatment.

Table 11. Studies of Surveillance in Individuals at High Risk of Pancreatic Cancer

Study	Study Populations	Surveillance Methods	Results
Canto et al (2018) ¹⁹ (CAPS1, CAPS2, CAPS3, CAPS4)	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 <ul style="list-style-type: none"> Patients who met clinical criteria for Peutz-Jeghers syndrome, or who had a 	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	Overall detection rate over 16 yrs was 7%; 9/10 cancers detected were resectable.

Study	Study Populations	Surveillance Methods	Results
	variant in the <i>STK11</i> gene, at least 30 yrs old <ul style="list-style-type: none"> • Individuals from an <i>FPC</i> kindred (at least 1 FDR with pancreatic cancer, at least 50 yrs old (CAPS 1-3) or at least 55 yrs old (CAPS 4), or 10 yrs younger than youngest pancreatic cancer in the family • Individuals with confirmed germline variants in <i>BRCA1</i>, <i>BRCA2</i>, <i>PALB2</i>, <i>PRSS1</i>, <i>CDKN2A</i>, or <i>MLH1</i>, <i>MSH2</i>, <i>MSH6</i>, <i>PMS2</i> (Lynch syndrome), with at least 1 affected first- or second-degree relative, and at least 50 yrs old, or 10 yrs younger than the youngest pancreatic cancer in the family 	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 months for those without a mural nodule or dilated pancreatic duct and every 3-6 months 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.	
Dbouk et al (2022)²², CAPS5 NCT02000089	1461 individuals with estimated elevated risk of developing PDAC. Eligibility criteria: Hereditary syndromes or germline variant carriers (<i>BRCA2</i> , <i>ATM</i> , <i>BRCA1</i> , <i>PALB2</i> , or Lynch syndrome-associated genes with family history of PDAC, FAMMM [<i>CDKN2A</i>], Peutz-Jeghers [<i>STK11</i>]). Family history of at least 1 first-degree and 1 second-degree relative with PDAC. Met age criteria for surveillance. Participants: 48.5% had a pathogenic germline variant; 51.5% had family history without known pathogenic germline variant; 31.1% had a personal history of cancer	Annual surveillance with EUS and/or MRI/MRCP, often alternating between the 2 methods (surveillance interval was modified when concerning lesions were detected)	9 patients were diagnosed with a screen-detected PDAC (either at baseline or at subsequent surveillance visits). 1 additional patient presented with symptomatic metastatic PDAC 4 years after their baseline and only surveillance. 7/9, (77.8%) were stage I by surgical pathology (4 stage IA, 3 stage IB); 1 patient had stage IIB cancer (case 8), and one (case 9) had a stage III cancer (clinically staged) with superior mesenteric artery involvement. Overall, 8/9 (88.9%) of the screen-detected PDACs were resectable. Two of the stage I PDACs were surgically staged after neoadjuvant chemotherapy (their stages at diagnosis by imaging, before neoadjuvant therapy were stage IA and IIA). Among 7 of 9 patients

Study	Study Populations	Surveillance Methods	Results
			diagnosed with a screen-detected PDAC still alive, median overall survival is 3.84 years.
Overbeek et al 2022²³	366 asymptomatic individuals with an estimated 10% or greater lifetime risk of PDAC ²⁰¹ with family history and no known germline pathogenic variant, 165 with a PDAC susceptibility gene	Annual surveillance with both EUS and MRI/MRCP at each visit, surveillance after 3 or 6 months when a concerning lesion detected.	9.3% in PDAC susceptibility gene carriers (cumulative incidence 6.5% at 5 years and 9.3% at 10 years). No cases identified in germline pathogenic variant-negative FPC kindreds. Median survival was 18 months (range, 1 to 32).
Vasen et al (2016)²⁰	<ul style="list-style-type: none"> • 178 individuals with a <i>CDKN2A</i> variant • 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 <i>BRCA1/2</i> or <i>PALB2</i> variant 	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 months later. In cases where there was serious suspicion of pancreatic adenocarcinoma, additional endoscopic ultrasound and CT scanning was performed.	Individuals with a <i>CDKN2A</i> variant: <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • 3/214 (1.4%) Individuals with a <i>BRCA1/2</i> or <i>PALB2</i> variant <ul style="list-style-type: none"> • 1/19 (3.8%)

CAPS: Cancer of the Pancreas Screening; CT: computed tomography; EUS: endoscopic ultrasound; FAMMM: familial atypical multiple mole melanoma; FDR: first-degree relative; FPC: familial pancreatic cancer; MRCP, magnetic resonance cholangiopancreatography; MRI: magnetic resonance imaging; PDAC: pancreatic ductal adenocarcinoma.

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 9). 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 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 (lead-time bias) 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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, 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 (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 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 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.1.2023) 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.2.2022) 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, most Lynch syndrome genes (MLH1, MSH2, MSH6, EPCAM), PALB2, 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 BRCA 1/2 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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12.

Table 12. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT03060720	Systematic Hereditary Pancreatic Cancer Risk Assessment and Implications for Personalized Therapy	271	Feb 2023
NCT00835133	Biospecimen Resource for Familial Pancreas Research, a Data and Tissue Registry (Also Known as a Bio-repository, Bio-bank, Data and Tissue Database, Data and Tissue Bank, Etc.) to Help Advance Research in Familial Pancreas Disease	7,500	Sep 2023
NCT02206360	Observational Study to Analyze the Outcomes of Subjects Who - Based Upon Their Sufficiently Elevated Risk for the Development of Pancreatic Adenocarcinoma- Elect to Undergo Early Detection Testing	100	Mar 2024
NCT00526578	Pancreatic Cancer Genetic Epidemiology (PACGENE) Study	4,770	Jun 2025
NCT05287347	Prospective Multicenter Observational Study for Validation of a Pancreatic Cancer Risk Model and Assessment of the Predictive Value of Blood Biomarkers in a High-risk Cohort	4,000	Mar 2026

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
 - Clinical findings (i.e., pertinent symptoms and duration)
 - Family history, if applicable
 - Reason for test including particular genetic mutations and potential drug therapies of interest
 - Pertinent past procedural and surgical history
 - Past and present applicable diagnostic testing and results
 - Treatment plan (i.e., drug selection for treatment) if known
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram) if applicable
- Laboratory results including but not limited to cancer diagnosis or genetic testing

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s) if applicable

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0129U	Hereditary breast cancer-related disorders (e.g., 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)
	0342U	Oncology (pancreatic cancer), multiplex immunoassay of C5, C4, cystatin C, factor B, osteoprotegerin (OPG), gelsolin, IGFBP3, CA125 and multiplex electrochemiluminescent immunoassay (ECLIA) for CA19-9, serum, diagnostic algorithm reported qualitatively as positive, negative, or borderline
	81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)

Type	Code	Description
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81201	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
	81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81298	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81299	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81300	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

Type	Code	Description
	81318	PMS2 (postmeiotic segregation increased 2 [<i>S. cerevisiae</i>]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81319	PMS2 (postmeiotic segregation increased 2 [<i>S. cerevisiae</i>]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81403	Molecular Pathology Procedure Level 4
	81404	Molecular Pathology Procedure Level 5
	81405	Molecular Pathology Procedure Level 6
	81406	Molecular Pathology Procedure Level 7
	81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
	81433	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
	81435	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
	81436	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
	81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis. <i>(Code revision effective 01/01/2024)</i>
	81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis <i>(Code revision effective 01/01/2024)</i>
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
05/01/2021	New policy.
07/01/2022	Annual review. No change to policy statement. Literature review updated.
12/01/2022	Coding update.
04/01/2023	Annual review. Policy statement and literature review updated. Policy title changed from Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes to current one.

Effective Date	Action
03/01/2024	Coding update,.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT

(No changes)

BEFORE

AFTER

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

Policy Statement:

- I. Genetic testing for *BRCA1*, *BRCA2*, and *PALB2* or a small panel (such as CPT 81432) containing these gene variants to guide selection for treatment with [platinum-based chemotherapy](#)* may be considered **medically necessary** in previously untreated individuals with locally advanced or metastatic pancreatic cancer.
- II. Genetic testing for *BRCA1* and *BRCA2* variants to guide selection for treatment with olaparib ([Lynparza](#))** may be considered **medically necessary** in individuals with pancreatic cancer.
- III. 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](#).
- IV. 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](#).

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

Policy Statement:

- I. Genetic testing for *BRCA1*, *BRCA2*, and *PALB2* or a small panel (such as CPT 81432) containing these gene variants to guide selection for treatment with [platinum-based chemotherapy](#)* may be considered **medically necessary** in previously untreated individuals with locally advanced or metastatic pancreatic cancer.
- II. Genetic testing for *BRCA1* and *BRCA2* variants to guide selection for treatment with olaparib ([Lynparza](#))** may be considered **medically necessary** in individuals with pancreatic cancer.
- III. 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](#).
- IV. 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](#).