2.04.148 Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes			
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Policy Statement

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 patients with locally advanced or metastatic pancreatic cancer.

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

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

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 and BRCA2 variants
  - See Blue Shield of California Medical Policy: 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
  - See Blue Shield of California Medical Policy: Gene 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
  - 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 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

- Gene Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk
- Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
- Genetic Testing for Familial Cutaneous Malignant Melanoma
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

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 7.8% of all cancer deaths in 2020.[1] The disease has a poor prognosis, with only 10.0% of patients surviving to 5 years. Five-year survival for localized pancreatic cancer is 39.4% 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* variants 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

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 Gastroenterology [7]
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.

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 chemotherapy. [10,11,4.] In 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 vs 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 vs 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 *BRCA1* (n=21), *BRCA2* (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 2014-2018	52 patients with untreated locally advanced or metastatic PDAC and germline pathogenic variants in *BRCA* or *PALB2*	Arm A: cisplatin, gemcitabine, and veliparib Arm B: cisplatin and gemcitabine
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 *BRCA1*, *BRCA2*, or *PALB2* 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,

Study	Study Type	Location	Dates	Participants	Pancreatic Cancer Treatment Regimen
					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 *BRCA1*, *BRCA2*, or *PALB2* 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 *BRCA1* (n = 5), *BRCA2* (n = 17) or *PALB2* (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 commonly received in the first-line setting regardless of cohort 80.7% of variant-positive patients 67.3% of control patients (p = 0.21). Significantly more control patients received FOLFIRINOX (75% vs. 38.5%; p = 0.0016) and significantly more variant-positive patients received cisplatin plus gemcitabine

Study	Study Type	Location	Dates	Participants	Pancreatic Cancer Treatment Regimen
					(23.1% vs. 1.9%; p = 0.0021)

FOLFIRINOX: folinic acid, fluorouracil, irinotecan and oxaliplatin; FOLFOX: folinic acid, fluorouracil andoxaliplatin), 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 (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 v 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 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			

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
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 (i.e., 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 3,315 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 Patients with a germline *BRCA* variant and metastatic pancreatic adenocarcinoma that had not progressed during first-line platinum-based chemotherapy	Olaparib	Placebo

RCT: randomized controlled trial; NCT: National Clinical Trial 02184195, Multicentre Study of Maintenance Olaparib Monotherapy in Patients With g BRCA 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 = 0.004	0.91 (0.56 to 1.46) P = 0.68	

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, CDK2NA, 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*, *CDK2NA*, *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, CDK2NA, EPCAM, MLH1*, *MSH2*, *MSH6, PMS2, PALB, STK11, and TP53* (i.e., 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 176241 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]	3,030 adults with pancreatic cancer enrolled in a registry 123,136 controls from the Genome Aggregation Database and 53,105 controls from the Exome Aggregation Consortium Database	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 ATM: 5 CHEK2: 7 APC: 7 MUTYH: 3 FH (recessive): 1
Shindo et al. (2017)[14]	854 patients with pancreatic ductal adenocarcinoma; Control groups: 288 patients with other pancreatic and periampullary neoplasms, and 51 patients with nonneoplastic diseases who underwent pancreatic resection	33/854 (3.9%; 95% CI 3.0% to 5.8%) Number of patients with deleterious variants in specific genes: BRCA2: 12 ATM: 10 BRCA1 3 PALB2: 2 MLH1: 2 CDKN2A: 1 TP53: 1 3/33 patients had reported a family history of pancreatic cancer
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	11/290 (3.8%) Number of pathogenic variants by gene: ATM: 3 BRCA1: 1 BRCA2: 2 MLH1: 1

Study	Study Population	Pathogenic Variants Identified, overall and by specific genes
		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, CDK2NA, 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, CDK2NA, 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 question addressed in this evidence review is: Does genetic testing improve the net health outcome in individuals who are asymptomatic and at high-risk for hereditary pancreatic cancer?

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

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 (e.g., 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
ATM	Ataxia-telangiectasia	1%-5%	3-fold	Breast, ovarian
BRCA1	Hereditary breast and ovarian	1.2%	3-fold	Breast, ovarian, prostate
BRCA2	Hereditary breast and ovarian	2%-5%	3.5 to 10-fold	Breast, ovarian, prostate, melanoma
CDKN2A	Familial atypical multiple mole melanoma	10%-30%	13- to 39-fold	Melanoma
MLH1, *MSH2*, *MSH6*, *EPCAM*	Lynch	5%-10%	9- to 11-fold	Ovarian, colon, uterine, others
PALB2	Hereditary breast and ovarian	5%-10%?	Unknown	Breast, ovarian
PRSS1, *SPINK1*	Hereditary pancreatitis	40%-45%	53-fold	NA
STK11/LKB1	Peutz–Jeghers	10%-30%	Up to 132-fold	Breast, ovarian, colorectal
Tp53	Li-Fraumeni	Unknown	Unknown	Breast

Sources: American Society of Clinical Oncology,[2] American College of Gastroenterology[7]
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=0.05) PDAC or HGD: HR 2.81 (95% CI 1.17-6.76, p=0.02) PDAC or HGD or worrisome features on imaging: HR 3.27 (95% CI, 1.8-5.96, p<0.001)

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 CDNK2A 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.

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 • 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 pancreatic cysts or indeterminate radiologic	Overall detection rate over 16 yrs was 7%; 9/10 cancers detected were resectable.

Study	Study Populations	Surveillance Methods	Results
	variant in the *STK11* gene, at least 30 yrs old • Individuals from an *FPC* 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 *BRCA1, BRCA2, PALB2.PRSS1, CDKN2A, or MLH1, MSH2, MSH6, PMS2* (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	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	
Vasen et al. (2016)[20]	• 178 individuals with a *CDKN2A* 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 *BRCA1/2* or *PALB2* 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 *CDKN2A* variant: • 13/178 (7.3%) • Cumulative incidence of pancreatic cancer was 14% by the age of 70 yrs Individuals at high-risk for familial pancreatic cancer • 3/214 (1.4%) Individuals with a *BRCA1/2* or *PALB2* variant • 1/19 (3.8%)

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

Konings et al. (2019) published a report of outcomes on 76 high-risk individuals from CAPS surveillance programs in 4 countries (U.S., the Netherlands, Israel, and Italy) who had either undergone pancreatic surgery because of the detection of a suspicious pancreatic lesion (n=71) or progressed to advanced unresectable malignant disease (n=5).[21] Survival rate was significantly poorer for individuals with advanced pancreatic cancer compared with those who had surgery (40% vs. 83% respectively, P =0.050; mean survival 9.5 vs. 54.3 months, P <0.001).

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

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

Genes that are associated with pancreatic cancer are also associated with increased risk of other cancers and genetic cancer syndromes (see Table 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:

- Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
- Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Blue Shield of California Medical Policy: Genetic Testing for Familial Cutaneous Malignant Melanoma
- Blue Shield of California Medical Policy: Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- Blue Shield of California Medical Policy: Gene 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 1 comparative observational study of high-risk patients under surveillance that the risk of progression to pancreatic cancer is higher among individuals with a known pathogenic variant than in patients identified as at-risk based on family history alone. There is also evidence from prospective observational studies that surveillance of high-risk individuals can identify pancreatic cancer and precursor lesions. In 1 analysis of 76 high-risk individuals under surveillance, survival was better in those who had surgery due to detection of either low- or high-risk neoplastic precursor lesions (n=71) compared to those who had advanced to unresectable disease (n=5). Although observational studies have demonstrated that surveillance can identify pancreatic cancer and precursor lesions in asymptomatic individuals, it is not possible to conclude from this body of evidence that surveillance improves survival. Longer survival time observed in individuals undergoing surveillance could 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.

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=0.04). 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 1 comparative observational study of high-risk patients under surveillance that the risk of progression to pancreatic cancer is higher among individuals with a known pathogenic variant than in patients identified as at-risk based on family history alone. There is also evidence from prospective observational studies that surveillance of high-risk individuals can identify pancreatic cancer and precursor lesions. In 1 analysis of 76 high-risk individuals under surveillance, survival was better in those who had surgery due to detection of either low- or high-risk neoplastic precursor lesions (n=71) compared to those who had advanced to unresectable disease (n=5). Although observational studies have demonstrated that surveillance can identify pancreatic cancer and precursor lesions in asymptomatic individuals, it is not possible to conclude from this body of evidence that surveillance improves survival. Longer survival time observed in individuals undergoing surveillance could 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
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.[22,]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.[23,] 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.[24,6,]

The Guidelines on Genetic/Familial High-risk Assessment: Breast, Ovarian, and Pancreatic (v.2.2021) 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.[24,]

The Guideline on Treatment of Pancreatic Adenocarcinoma (v.1.2021) 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
Ongoing			
NCT03140670	A Phase 2, Open Label Study of Rucaparib in Patients With Advanced Pancreatic Cancer and a Known Deleterious Germline or Somatic BRCA or PALB2 Mutation	50	Jun 2022
NCT02790944[a]	Utilizing a Multi-gene Testing Approach to Identify Hereditary Pancreatic Cancer in Consecutive Cases Unselected for Family History	300	May 2021
NCT03060720	Systematic Hereditary Pancreatic Cancer Risk Assessment and Implications for Personalized Therapy	375	Feb 2022
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	4,000	Sep 2022
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

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT00526578	Pancreatic Cancer Genetic Epidemiology (PACGENE) Study	4,770	Jun 2025

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

1. NIH National Cancer Institute: Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Pancreatic Cancer. 2019. https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed January 15, 2021.
2. Stoffel EM, McKernin SE, Khorana AA. Evaluating Susceptibility to Pancreatic Cancer: ASCO Clinical Practice Provisional Clinical Opinion Summary. J Oncol Pract. Feb 2019; 15(2): 108-111. PMID 30589608
3. O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, Multicenter, Phase II Trial of Gemcitabine and Cisplatin With or Without Veliparib in Patients With Pancreas Adenocarcinoma and a Germline BRCA/PALB2 Mutation. J Clin Oncol. May 01 2020; 38(13): 1378-1388. PMID 31976786
4. Reiss KA, Yu S, Judy R, et al. Retrospective Survival Analysis of Patients With Advanced Pancreatic Ductal Adenocarcinoma and Germline BRCA or PALB2 Mutations. JCO Precision Oncology. Published online January 19, 2018. DOI: 10.1200/PO.17.00152.
5. Owens DK, Davidson KW, Krist AH, et al. Screening for Pancreatic Cancer: US Preventive Services Task Force Reaffirmation Recommendation Statement. JAMA. Aug 06 2019; 322(5): 438-444. PMID 31386141
6. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 15, 2021.
7. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. Feb 2015; 110(2): 223-62; quiz 263. PMID 25645574
8. Food & Drug Administration. Premarket Approval: BRACAnalysis CDx. 2019. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P140020S019. Accessed January 18, 2021.
9. Golan T, Kanji ZS, Epelbaum R, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer. Sep 09 2014; 111(6): 1132-8. PMID 25072261
10. Wattenberg MM, Asch D, Yu S, et al. Platinum response characteristics of patients with pancreatic ductal adenocarcinoma and a germline BRCA1, BRCA2 or PALB2 mutation. Br J Cancer. Feb 2020; 122(3): 333-339. PMID 31787751
11. Yu S, Agarwal P, Mamtani R, et al. Retrospective survival analysis of patients with resected pancreatic ductal adenocarcinoma and a Germline BRCA or PALB2 mutation. JCO Precision Oncol. Published online March 28, 2019. DOI: 10.1200/PO.18.00271
12. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA -Mutated Metastatic Pancreatic Cancer. N Engl J Med. Jul 25 2019; 381(4): 317-327. PMID 31157963
13. Hu C, Hart SN, Polley EC, et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA. Jun 19 2018; 319(23): 2401-2409. PMID 29922827
14. Shindo K, Yu J, Suenaga M, et al. Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma. J Clin Oncol. Oct 20 2017; 35(30): 3382-3390. PMID 28767289
15. Brand R, Borazanci E, Speare V, et al. Prospective study of germline genetic testing in incident cases of pancreatic adenocarcinoma. Cancer. Sep 01 2018; 124(17): 3520-3527. PMID 30067863

16. Mandelker D, Zhang L, Kemel Y, et al. Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing. JAMA. Sep 05 2017; 318(9): 825-835. PMID 28873162
17. Grant RC, Selander I, Connor AA, et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. Mar 2015; 148(3): 556-64. PMID 25479140
18. Abe T, Blackford AL, Tamura K, et al. Deleterious Germline Mutations Are a Risk Factor for Neoplastic Progression Among High-Risk Individuals Undergoing Pancreatic Surveillance. J Clin Oncol. May 01 2019; 37(13): 1070-1080. PMID 30883245
19. Canto MI, Almario JA, Schulick RD, et al. Risk of Neoplastic Progression in Individuals at High Risk for Pancreatic Cancer Undergoing Long-term Surveillance. Gastroenterology. Sep 2018; 155(3): 740-751.e2. PMID 29803839
20. Vasen H, Ibrahim I, Ponce CG, et al. Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers. J Clin Oncol. Jun 10 2016; 34(17): 2010-9. PMID 27114589
21. Konings ICAW, Canto MI, Almario JA, et al. Surveillance for pancreatic cancer in high-risk individuals. BJS Open. Oct 2019; 3(5): 656-665. PMID 31592073
22. Sohal DPS, Kennedy EB, Cinar P, et al. Metastatic Pancreatic Cancer: ASCO Guideline Update. J Clin Oncol. Aug 05 2020: JCO2001364. PMID 32755482
23. Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. Jan 2020; 69(1): 7-17. PMID 31672839
24. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed January 16, 2021.
25. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.148 (February 2021).

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)
- 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)
	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)
	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

Type	Code	Description
	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
	81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (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 adenomatosis 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 adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
	81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN,

Type	Code	Description
		RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
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.

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 (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.

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	
BEFORE	**AFTER**
New Policy **Policy Statement:** N/A	**Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes 2.04.148** **Policy Statement:** 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 patients with locally advanced or metastatic pancreatic cancer. Genetic testing for *BRCA1* and *BRCA2* variants to guide selection for treatment with olaparib (Lynparza)** may be considered **medically necessary** in patients with pancreatic cancer. Genetic testing for *ATM, CDK2NA, EPCAM*, *MMR* genes *(MLH1, MSH2, MSH6, PMS2), STK11, and TP53* in patients with pancreatic cancer is considered **investigational** unless the individual meets criteria for testing as specified in another policy. 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.