Policy Statement

Individuals With Cancer or With a Personal History of Cancer

I. Full sequence and duplication/deletion analysis genetic testing for BRCA1, BRCA2, and PALB2 gene variants (including when part of an approved small panel such as 81432) in cancer-affected individuals age 18 or over may be considered medically necessary under any of the following circumstances:

A. Individuals meeting the criteria for medically necessary testing below but with previous limited testing (e.g., single gene and/or absent deletion duplication analysis)

B. Individuals (with or without a history of cancer) with any close blood relative with a known BRCA1, BRCA2, or PALB2 pathogenic/likely pathogenic variant (see Policy Guidelines for definitions and for testing strategy).

C. Personal history of breast cancer (including invasive and ductal carcinoma in situ) and one or more of the following:
   1. Diagnosed at age 45 or younger
   2. Diagnosed 46 to 50 years of age and one or more of the following:
      a. An additional breast cancer primary at any age
      b. One or more close relative (see Policy Guidelines) with breast, ovarian, pancreatic, or prostate cancer at any age
      c. An unknown or limited family history
   3. Diagnosed on or before 60 years of age with triple-negative breast cancer (estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor 2-negative)
   4. Diagnosed at any age with one or more of the following:
      a. One or more close blood relative with one or more of the following:
         i. Breast cancer diagnosed on or before 50 years of age
         ii. Ovarian carcinoma
         iii. Metastatic or intraductal/cribriform prostate cancer, or high-risk group or very-high-risk group prostate cancer
         iv. Pancreatic cancer
      b. Three or more total diagnoses of breast cancer in individual and/or close blood relatives
      c. Ashkenazi Jewish ancestry
   6. Any cancer and a mutation identified on somatic tumor genomic testing that has clinical implications if also identified in the germline.
E. An affected or unaffected individual with a first or second degree blood relative meeting any of the criteria above as documented by the requesting provider.

Individuals Without Cancer or With any Other Personal History of Cancer (not noted above)
(See Policy Guidelines section: Testing Unaffected Individuals.)

II. Genetic testing for BRCA1, BRCA2, and PALB2 variants of individuals either without cancer or any other type of cancer not noted above (including cancer related to hereditary breast ovarian cancer syndrome but not meeting above criteria, or cancers unrelated to hereditary breast ovarian cancer syndrome) may be considered medically necessary under any of the following circumstances:

A. Has a probability of greater than 5% of a BRCA1/2 or PALB2 pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, PennII) as documented by the requesting provider.

B. Individuals (with or without a history of cancer) with any close blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene (included in the small panel).

C. An affected or unaffected individual with a first or second degree blood relative meeting any of the criteria in the “Individuals with cancer..” section above and as documented by the requesting provider.

III. Genetic testing for BRCA1, BRCA2, and PALB2 variants in cancer-affected individuals or of cancer-unaffected individuals with or without a family history of cancer when criteria above are not met (including genetic screening in the general population) is considered investigational.

IV. Genetic testing in minors (younger than age 18) for BRCA1, BRCA2, and PALB2 variants is considered investigational.

Confirmatory BRCA Testing

V. Confirmatory BRCA testing may be considered medically necessary for individuals who underwent over-the-counter (OTC) U.S. Food and Drug Administration (FDA) approved genetic screening and were found to have a pathogenic BRCA1 or BRCA2 mutation (including one of the three Ashkenazi founder mutations).

VI. Large multi-gene panels including multiple genes that are not highly associated with hereditary breast and ovarian cancer (see Policy Guidelines) are considered investigational.

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

Policy Guidelines

Genetic testing should be performed in a setting that has suitably trained health care providers who can give appropriate pre- and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments-licensed laboratory that offers comprehensive variant analysis. As other genes have become associated with hereditary breast and ovarian cancer, small panels (using CPT code 81432) are now the preferred tests (rather than just testing for BRCA1 and BRCA2, such as 81162).

Genetic testing for BRCA1 and BRCA2 variants in breast cancer-, pancreatic cancer-, prostate cancer-, or ovarian cancer-affected individuals who are considering systemic therapy is addressed separately in the following Blue Shield of California Medical Policies:

- Germline and Somatic Biomarker Testing for Targeted Treatment and Immunotherapy in Breast Cancer
- Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes
• Germline and Somatic Biomarker Testing for Targeted Treatment and Immunotherapy in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, Microsatellite Instability/Mismatch Repair, Tumor Mutational Burden)

• Germline and Somatic Biomarker Testing for Targeted Treatment and Immunotherapy in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, Tumor Mutational Burden, Microsatellite Instability/Mismatch Repair)

When criteria are met, small panel testing using CPT code 81432 is the preferred testing for breast and ovarian cancer risk. As an alternative, 81162 is allowed for BRCA 1 and 2 testing. If BRCA testing in 81162 is negative, PALB2 (81406 molecular pathology procedure level 7) testing can also be allowed (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)). After 81162 is performed, the remaining genes in the 81432 or similar panels (with the exception of PALB2) are considered investigational and are not covered if requested at a later time.

Testing related to hereditary colorectal cancer, see Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes.

Panel testing related to cancers other than breast, ovarian, colorectal, and non-small-cell lung cancer, see Blue Shield of California Medical Policy: Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing.

Current U.S. Preventive Services Task Force guidelines recommend screening women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene mutation. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing (B recommendation).

Recommended screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful variants in BRCA1 or BRCA2 are:

• Ontario Family History Assessment Tool (FHAT)
• Manchester Scoring System
• Referral Screening Tool (RST)
• Pedigree Assessment Tool (PAT)
• Family History Screen (FHS-7)
• International Breast Cancer Intervention Study instrument (Tyrer-Cuziak)
• Brief versions of the BRCAPRO

Close Relatives
Close relatives are blood related family members including 1st-, 2nd-, and 3rd-degree 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.

Prostate Cancer Risk Groups
Risk groups for prostate cancer in this policy include high-risk groups and very-high-risk groups.
High-risk group: no very-high-risk features and are T3a (American Joint Committee on Cancer staging T3a = tumor has extended outside of the prostate but has not spread to the seminal vesicles); OR Grade Group 4 or 5; OR prostate specific antigen of 20 ng/mL or greater.

Very-high-risk group: T3b-T4 (tumor invades seminal vesicle(s); or tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall); OR Primary Gleason Pattern 5; OR 2 or 3 high-risk features; OR greater than 4 cores with Grade Group 4 or 5.

**Recommended Testing Strategies**

As other genes have become associated with hereditary breast and ovarian cancer and as ethnicity becomes more mixed, small panels (using CPT code 81432) are now the preferred tests (rather than just testing for BRCA1 and BRCA2, such as 81162), or testing for founder mutations in those of Ashkenazi descent). Complete testing includes at a minimum: Full sequence and duplication/deletion analysis of *BRCA1*, *BRCA2*, and *PALB2*.

Individuals who meet criteria for genetic testing as outlined in the policy statements above should be tested for variants in *BRCA1*, *BRCA2*, and *PALB2*.

Recommended strategies are listed below.

- In individuals with a known familial *BRCA* or *PALB2* variant, targeted testing for the specific variant is recommended.
- In individuals with unknown familial *BRCA* or *PALB2* variant:
  - To identify clinically significant variants, NCCN advises testing a relative who has early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood of obtaining a positive test result.

Testing strategy may also include testing individuals not meeting the above criteria who are adopted and have limited medical information on biological family members, individuals with small family structure, and individuals with presumed paternal transmission.

**Comprehensive Variant Analysis**

Standard Comprehensive variant analysis currently includes sequencing the coding regions and intron and exon splice sites, as well as testing to detect large deletions and rearrangements that can be missed with sequence analysis alone. In addition, before August 2006, testing for large deletions and rearrangements was not performed, thus some individuals with familial breast cancer who had negative *BRCA* testing before this time may consider repeat testing for the rearrangements (see Policy section for criteria).

- More than 90% of BRCA variants will be detected by full sequencing alone
- Adding common deletions and duplications will detect another 2.5%
- Adding uncommon large deletions and duplications (e.g., previously known as BART or BRCA Analysis Rearrangement Test) detects less than 1% more
- Standard comprehensive testing will detect 93.5% of BRCA related variants

**High-Risk Ethnic Groups**

Testing of eligible individuals who belong to ethnic populations in which there are well-characterized founder mutations should begin with tests specifically for these variants. For example, founder mutations account for approximately three-quarters of the *BRCA* variants found in Ashkenazi Jewish populations (see Rationale section). When testing for founder mutations is negative, a comprehensive variant analysis should then be performed. However, as ethnicities become more mixed and harder to identify, standard small panel testing is preferred.
Testing Unaffected Individuals
In unaffected family members of potential BRCA or PALB2 variant 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 BRCA or PALB2 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. Interpreting test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated variant but leads to difficulties in interpreting negative test results (uninformative negative) or variants of uncertain significance because the possibility of a causative BRCA or PALB2 variant is not ruled out.

Note: If the individual with cancer has pancreatic cancer or prostate cancer (metastatic or intraductal/cribriform or high-risk group or very-high-risk group) then only first-degree relatives should be offered testing unless there are other family history indications for testing.

Testing for known variants of BRCA or PALB2 genes in an unaffected reproductive partner may be indicated as carrier screening for rare autosomal recessive conditions.

Confirmatory Testing
Consideration might be given at the local level for confirmatory germline testing of a BRCA or PALB2 pathogenic/likely pathogenic variant found on tumor genomic analyses, direct-to-consumer testing, or research testing.

Testing Minors
The use of genetic testing for BRCA1, BRCA2, or PALB2 variants for identifying hereditary breast ovarian cancer syndrome has limited or no clinical utility in minors, because there is no change in management for minors as a result of knowledge of the presence or absence of a deleterious variant. In addition, there are potential harms related to stigmatization and discrimination.

Prostate Cancer
Individuals with BRCA or PALB2 variants have an increased risk of prostate cancer, and individuals with known BRCA or PALB2 variants may, therefore, consider more aggressive screening approaches for prostate cancer. However, the presence of prostate cancer in an individual, or in a family, is not itself considered sufficient justification for BRCA or PALB2 testing outside of guiding therapy.

Panel Testing
Limited genetic panels (such as CPT code 81432, including but not limited to: BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, STK11, PTEN, and TP53), when they include both full sequence and deletion/duplication analysis, may be considered medically necessary as an alternative to serial testing of individual genes when criteria are met for genetic testing of hereditary breast and ovarian cancer.

Coding
The following CPT codes may be used for genetic testing for BRCA1 and BRCA2 variants:

- **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)
  
  Note: This code includes both 81163 and 81164 (and previously 81211 and 81213).

- **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)
2.04.02 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

- **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)
- **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**: BRCA2 (BRCA2, 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
- **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

The following test is not used for hereditary BRCA testing and this policy does not apply to it. It represents the myChoice test by Myriad. It is done as a companion test (related to drug use) on tumor tissue (not blood) to see if there is a mutation present that would make the tumor susceptible to either Zejula (ovarian cancer) or Lynparza (prostate cancer). Since somatic (tumor) mutations can occur independent of inherited (germline) genetics, it is indicated even if prior BRCA hereditary testing is negative, and to confirm the presence of the mutation in the tumor when germline testing was positive:
- **0172U**: Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score

### Description

Hereditary breast and ovarian cancer syndrome describe the familial cancer syndromes related to variants in the BRCA genes (BRCA1 located on chromosome 17q21, BRCA2 located on chromosome 13q12-13). The PALB2 gene is located at 16p12.2 and has 13 exons. PALB2 protein assists BRCA2 in DNA repair and tumor suppression. Families with hereditary breast and ovarian cancer syndrome have an increased susceptibility to the following types of cancer: breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer (at any age), cancer of the fallopian tube, primary peritoneal cancer, prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

### Related Policies

- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
- Germline and Somatic Biomarker Testing for Targeted Treatment and Immunotherapy in Breast Cancer
• Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

• Germline and Somatic Biomarker Testing for Targeted Treatment and Immunotherapy in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, Microsatellite Instability/Mismatch Repair, Tumor Mutational Burden)

• Germline and Somatic Biomarker Testing for Targeted Treatment and Immunotherapy in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, Tumor Mutational Burden, Microsatellite Instability/Mismatch Repair)

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

• Risk-Reducing Mastectomy

**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**

**FDA:**
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. Genetic tests reviewed in this evidence review are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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.

**State:**
Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

**Rationale**

This review was informed by a TEC Assessment (1997). 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.

**Testing for BRCA1 and BRCA2 Variants in Individuals at Risk for Hereditary Breast/Ovarian Cancer Syndrome or Other High-Risk Cancers**

**Clinical Context and Test Purpose**

The purpose of testing for BRCA1 and BRCA2 variants in individuals at high-risk for hereditary breast and ovarian cancer (HBOC) syndrome is to evaluate whether variants are present and if so, to determine the appropriate surveillance and treatment to decrease the risk of mortality from breast and/or ovarian cancer.

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

**Populations**
The relevant population of interest is individuals with cancer (i.e., breast cancer, epithelial ovarian, fallopian tube, primary peritoneal cancer), or individuals with a personal or family history of cancer and criteria that might suggest they are at risk for HBOC syndrome.

**Interventions**
The intervention of interest is BRCA1 and BRCA2 variant testing.

For patients without a cancer diagnosis who are assessing cancer risk, results may guide potential prophylactic measures such as surveillance, chemoprevention, or prophylactic mastectomy, and/or oophorectomy.

For patients with a cancer diagnosis, results may guide treatment decisions.

Testing for BRCA1 and BRCA2 variants is conducted in adults when appropriate treatment and/or prophylactic treatment options are available.

**Comparators**
The following practice is currently being used to manage HBOC syndrome or other high-risk cancers: standard of care without genetic testing.

**Outcomes**
The outcomes of interest are overall survival (OS), disease-specific (breast and ovarian cancer) survival, test validity, and quality of life (QOL; e.g., anxiety).
Study Selection Criteria
For the evaluation of clinical validity, studies of variant prevalence and cancer risk were included. For the evaluation of clinical utility, studies that represent the intended clinical use of the technology in the intended population were included. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings.

Evidence for the 2 indications is presented together because there is overlap in the evidence base for the 2 populations: (1) patients at risk for HBOC syndrome, and (2) patients with other high-risk cancers such as cancers of the fallopian tube, pancreas, and prostate.

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).

Review of Evidence
Prevalence of BRCA Variants and Risks of Cancer and Survival
The prevalence of BRCA variants is approximately 0.1% to 0.2% in the general population. The prevalence may be much higher for particular ethnic groups with characterized founder mutations (e.g., 2.5% [1/40] in the Ashkenazi Jewish population). A family history of breast and ovarian cancer is an important risk factor for the BRCA variant; additionally, age and ethnicity could be independent risk factors.

Systematic Reviews
A systematic review published by Zhu et al (2016) found a significantly lower risk of OS in breast cancer patients with BRCA1 (pooled hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.35 to 2.12) and with BRCA2 (pooled HR, 1.50; 95% CI, 1.02 to 2.09; p = .034). However, in patients with breast cancer, BRCA1 and BRCA2 were not associated with a lower breast cancer-specific survival.

Nelson et al (2013) conducted a systematic review that included meta-analytic estimates of the prevalence and penetrance of BRCA variants; this review was used to update the U.S. Preventive Services Task Force (USPSTF) recommendation for risk assessment, genetic counseling, and genetic testing for BRCA-related cancer. In high-risk women with positive test results, cumulative risks for developing breast cancer by age 70 years were 46% for BRCA1 and 50% for BRCA2 when a single family member was tested, and 70% for BRCA1 and 71% for BRCA2 when multiple family members were tested; cumulative risks for developing ovarian cancer by age 70 years were 41% for BRCA1 and 17% for BRCA2 when a single family member was tested; and 46% for BRCA1 and 23% for BRCA2 when multiple family members were tested. For Ashkenazi Jewish women with positive test results, cumulative risks for developing breast or ovarian cancer by age 75 years were 34% and 21%, respectively. Nelson et al (2013) included meta-analytic estimates of BRCA prevalence in their review for USPSTF. In unselected women, BRCA variant prevalence estimates were 0.2% to 0.3%; in women with breast cancer, 1.8% for BRCA1 and 1.3% for BRCA2; in women with breast cancer onset at age 40 years or younger, 6%; in women from high-risk families, 13.6% for BRCA1, 7.9% for BRCA2, and 19.8% for BRCA1 or BRCA2; in unselected Ashkenazi Jewish women, 2.1%; and in Ashkenazi Jewish women from high-risk families, 10.2%.

Estimates of lifetime risk of cancer for BRCA variant carriers (penetrance), based on studies of families with an extensive history of the disease, have been as high as 85%. For example, Kuchenbaecker et al (2017) found that the cumulative risk of breast cancer up to age 80 years was 72% in BRCA1 carriers and 69% in BRCA2 carriers. Because other factors that influence risk may be present in families with extensive breast and ovarian cancer histories, early penetrance estimates may have been biased upward. Studies of founder mutations in ethnic populations (e.g., Ashkenazi Jewish, Polish, Icelandic populations) unselected for family history have indicated lower penetrance estimates, in the range of 40% to 60% for BRCA1 and 25% to 40% for BRCA2. However, a genotyping study of Ashkenazi
Jewish women with incident invasive breast cancer, selected regardless of family history of cancer and their family members, resulted in an 82% lifetime risk of breast cancer for carriers of any of 3 BRCA founder mutations (185delAG, 5382insC, 6174delT). Importantly, the risk of cancer in variant carriers from families with little history of cancer (>50% of all carriers) did not differ significantly. Lifetime risk estimates of ovarian cancer were 54% for BRCA1 and 23% for BRCA2 variant carriers.

**Prospective Studies**

Women with a history of breast cancer and a BRCA variant have a significant risk of contralateral breast cancer. In a prospective study by Metcalfe et al (2004), the 10-year risk was 29.5% for women with initial stage I or II diseases. In a prospective study, Epidemiological Study of Familial Breast Cancer, Mavaddat et al (2013) reported that the cumulative risk of contralateral breast cancer by age 70 years was 83% in the BRCA1 variant carriers, and 62% for BRCA2 variant carriers. These investigators also reported cumulative risks of breast cancer by age 70 years in women without previous cancer (60% in BRCA1 carriers, 55% in BRCA2 carriers). Similarly, the cumulative risk estimates of ovarian cancer by age 70 years in women without previous ovarian cancer were 59% for BRCA1 carriers and 17% for BRCA2 carriers.

**BRCA Variant Rates Associated With Ovarian Cancer**

Women with a personal history of ovarian cancer have an increased rate of BRCA variants. In a systematic review of 23 studies, Trainer et al (2010) estimated the rate of BRCA variants among women with ovarian cancer to be 3% to 15%. In this review, 3 U.S. studies tested for both BRCA1 and BRCA2; incidences of BRCA variants were 11.3%, 15.3%, and 9.5%. In the systematic review for USPSTF by Nelson et al (2013), meta-analytic estimates of BRCA prevalence among women with ovarian cancer were 4.4% for BRCA1 and 5.6% for BRCA2. Table 1 lists the results from several additional studies measuring the presence of BRCA variants among patients with ovarian cancer. One study noted that variant prevalence was higher for women in their 40s (24%) and for women with serous ovarian cancer (18%). Ethnicity was another risk factor for BRCA, with higher rates seen in women of Italian (43.5%), Jewish (30%), and Indo-Pakistani (29.6%) origin.

**Table 1. BRCA Variant Rates in Patients With Ovarian Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>BRCA Variant, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harter et al (2017)35</td>
<td>Patients with invasive ovarian cancer across 20 medical centers</td>
<td>523</td>
<td>81 (15.5)</td>
</tr>
<tr>
<td>Kurian et al (2017)32</td>
<td>Patients with invasive ovarian cancer tested for hereditary cancer risk from a commercial laboratory database</td>
<td>5020a</td>
<td>255 (15.5)</td>
</tr>
<tr>
<td>Langer et al (2016)33</td>
<td>Patients with ovarian cancer tested for hereditary cancer risk from a commercial laboratory database</td>
<td>3088</td>
<td>153 (4.9)</td>
</tr>
<tr>
<td>Norquist et al (2016)34</td>
<td>Patients with invasive ovarian cancer, from 2 phase 3 clinical trials and a gynecologic oncology tissue bank</td>
<td>1915</td>
<td>182 (9.5)</td>
</tr>
<tr>
<td>Zhang et al (2011)31</td>
<td>Patients with invasive ovarian cancer</td>
<td>1342</td>
<td>107 (8.0)</td>
</tr>
</tbody>
</table>

* Total N was reported as 5020, however, the percentage of BRCA variants as reported in article is inconsistent with 5020 as the denominator.

**BRCA Variant Rates Associated With Fallopian Tube Cancer**

A study by Hirst et al (2009) described the high rate of occult fallopian tube cancers in at-risk women having prophylactic bilateral salpingo-oophorectomy. In this prospective series of 45 women, 4 (9%) had fallopian tube malignancies. Reviewers noted that these findings supported other studies that have demonstrated the fimbrial end of the fallopian tube as an important site of cancer in those with BRCA1 or BRCA2 variants.

A long-term study by Powell et al (2013; median follow-up, 7 years; range, 3 to 14 years) followed 32 BRCA variant carriers with occult malignancy (4 ovarian, 23 fallopian tube, 5 ovarian and fallopian tube) diagnosed of prophylactic salpingo-oophorectomy. Among 15 women with invasive carcinoma...
(median age, 50 years), 7 (47%) experienced recurrence at a median of 33 months, and OS was 73%. Among 17 women with noninvasive neoplasia (median age, 53 years), 4 (24%) received chemotherapy, none of whom experienced recurrence. One (6%) patient who did not receive chemotherapy experienced recurrence at 43 months. OS was 100%. The authors concluded that, in BRCA variant carriers, unsuspected invasive carcinoma has a relatively high rate of recurrence, but noninvasive neoplasms rarely recur and may not require adjuvant chemotherapy.

**BRCA Variant Rates Associated With Pancreatic Cancer**

Unaffected individuals also may be at high-risk due to other patterns of non-breast-cancer malignancies. A personal history of pancreatic cancer is estimated to raise the risk of a BRCA variant by 3.5- to 10-fold over the general population. Table 2 lists the results from several studies measuring the presence of BRCA variants among patients with pancreatic adenocarcinoma. Patients with pancreatic adenocarcinoma of Jewish descent appear to have a higher prevalence of BRCA variants compared with the general population of patients with pancreatic adenocarcinoma.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>BRCA Variant, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al (2018)</td>
<td>Patients with pancreatic adenocarcinoma from a prospective pancreatic cancer registry</td>
<td>3030</td>
<td>18 (0.6) 59 (1.9)</td>
</tr>
<tr>
<td>Yurgelun et al (2018)</td>
<td>Patients with pancreatic adenocarcinoma from 3 medical centers</td>
<td>289</td>
<td>3 (1.0) 4 (1.4)</td>
</tr>
<tr>
<td>Shindo et al (2017)</td>
<td>Patients with pancreatic adenocarcinoma from 1 medical center</td>
<td>854</td>
<td>3 (0.3) 12 (1.4)</td>
</tr>
<tr>
<td>Holter et al (2015)</td>
<td>Patients with pancreatic adenocarcinoma from a large academic health care complex</td>
<td>306</td>
<td>3 (1.0) 11 (3.6)</td>
</tr>
<tr>
<td>Ferrone et al (2009)</td>
<td>Jewish patients with pancreatic adenocarcinoma from 1 hospital</td>
<td>145</td>
<td>2 (1.3) 6 (4.1)</td>
</tr>
<tr>
<td>Couch et al (2007)</td>
<td>Probands from high-risk families identified through prostate cancer clinics and a pancreatic tumor registry</td>
<td>180</td>
<td>10 (5.5)</td>
</tr>
<tr>
<td>^o Case-control study; rates for BRCA1 and BRCA2 variants in controls were 0.2 and 0.3, respectively.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BRCA Variant Rates Associated With Prostate Cancer**

Table 3 lists the results from several studies measuring the presence of BRCA variants among patients with prostate cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>BRCA Variant, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abida et al (2017)</td>
<td>Patients with prostate cancer from 1 clinical practice</td>
<td>221</td>
<td>2 (1) 20 (9)</td>
</tr>
<tr>
<td>Pritchard et al (2016)</td>
<td>Patients with metastatic prostate cancer from 7 case series across multiple centers</td>
<td>692</td>
<td>6 (0.9) 37 (5.3)</td>
</tr>
<tr>
<td>Edwards et al (2003)</td>
<td>Patients with prostate cancer diagnosed before age 56 from 2 cancer study groups</td>
<td>263</td>
<td>6 (2.3)</td>
</tr>
</tbody>
</table>

**Testing for Large BRCA Rearrangements**

A number of studies have shown that a significant percentage of women with a strong family history of breast cancer and negative tests for BRCA variants have large genomic rearrangements (including deletions or duplications) in 1 of these genes. For example, Walsh et al (2006) reported on probands from 300 U.S. families with 4 or more cases of breast or ovarian cancer but with negative (wild-type) commercial genetic tests for BRCA1 and BRCA2. These patients underwent screening with additional multiple DNA-based and RNA-based methods. Of these 300 patients, 17% carried previously undetected variants, including 35 (12%) with genomic rearrangement of BRCA1 or BRCA2.
A study by Palma et al (2008) evaluated 251 patients with an estimated BRCA variant prevalence using the Myriad II model of at least 10%. In 136 non-Ashkenazi Jewish probands, 36 (26%) had BRCA point mutations and 8 (6%) had genomic rearrangements (7 in BRCA1, 1 in BRCA2). Genomic rearrangements comprised 18% of all identified BRCA variants. No genomic rearrangements were identified in the 115 Ashkenazi Jewish probands, but 47 (40%) had point mutations. The authors indicated that the estimated prevalence of a variant did not predict the presence of a genomic rearrangement.

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

**Direct Evidence**
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). In their systematic review for the USPSTF, Nelson et al (2019) confirmed that they identified no studies that compared health outcomes for patients managed with and without BRCA variant testing.

Knowledge of variant status in individuals at potentially increased risk of a BRCA variant may impact health care decisions to reduce risk. Risk-reducing options include intensive surveillance, chemoprevention, prophylactic mastectomy, or prophylactic oophorectomy.

Prophylactic mastectomy reduces the risk of breast cancer in high-risk women (based on family history) by 90%. Prophylactic oophorectomy significantly reduces the risk of ovarian cancer by 80% or more and reduces the risk of breast cancer by approximately 50%. In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse. Prophylactic oophorectomy or salpingo-oophorectomy in women with BRCA1 or BRCA2 reduced the risk of all-cause mortality by 60% to 77%. For patients at risk for both breast and ovarian cancer, a study by Elmi et al (2018), drawing on data from the American College of Surgeon’s National Surgical Quality Improvement Program dataset, found that prophylactic mastectomy with concurrent salpingo-oophorectomy was not associated with significant additional morbidity compared with prophylactic mastectomy alone.

Systematic reviews of observational studies comparing prophylactic surgeries with observation in women who had BRCA1 and BRCA2 variants have demonstrated that contralateral prophylactic mastectomy in women with breast cancer is associated with significantly lower all-cause mortality while bilateral prophylactic mastectomy was not associated with all-cause mortality. Studies have indicated that the results of genotyping significantly influenced treatment choices. In a systematic review for the USPSTF, Nelson et al (2019) assessed the efficacy of risk-reducing surgery in BRCA-positive women. The literature search was conducted through March 2019. A total of 13 observational studies (n=9938) provided consistent and moderate-strength evidence of the benefits of risk-reducing surgery. For high-risk women and variant carriers, bilateral mastectomy reduced breast cancer incidence by 90% to 100% and breast cancer mortality by 81% to 100%; oophorectomy or salpingo-oophorectomy reduced breast cancer incidence by 37% to 83%, ovarian cancer incidence by 69% to 100%. Some women experienced reduced anxiety. Limitations of the studies of benefits included lack of comparison groups, variations in methodology and enrollment criteria, and heterogeneous outcome measures. Additionally, a total of 14 observational studies (n=3073) provided low-strength evidence of the harms of risk-reducing surgery. Adverse events included physical complications of the surgery, postsurgical symptoms, and changes in body image. Studies of harms shared the same limitations as the studies of benefits as noted above, with the addition that their findings were inconsistent and the sample sizes were smaller. As reviewers observed, it is still currently
unknown whether BRCA4 variant testing reduces cause-specific or all-cause mortality, or if it improves the QOL. Harms associated with false-negative results or variants of uncertain significance also are unknown.

Other studies have looked at the results of prostate cancer screening in men with BRCA variants. The Immunotherapy for Prostate Adenocarcinoma Treatment study (2011) evaluated the results of screening in 205 men 40 to 69 years of age who were BRCA4 variant carriers and 95 control patients. At the baseline screen, biopsies were performed in 7.0% of men with a prostate-specific antigen level greater than 3.0 ng/mL, and prostate cancer was identified in 3.3%. This resulted in a positive predictive value of 47.6%, which is considerably higher than that estimated for men at normal risk. Moreover, the grade of tumor identified was intermediate in 67% of cancers and high in 11%. This differs from the expected distribution of cancer grade in average-risk men, with more than 60% expected to have low-grade cancer.

**Section Summary: Testing for BRCA1 and BRCA2 Variants in Individuals at Risk for Hereditary Breast and Ovarian Cancer Syndrome or Other High-Risk Cancers**

Evidence for the clinical validity of BRCA1 and BRCA2 variant testing consists of multiple studies that calculated BRCA1 and BRCA2 variant prevalence among samples of patients with HBOC syndrome, fallopian tube cancer, pancreatic cancer, and prostate cancer.

Regarding clinical utility of BRCA1 and BRCA2 variant testing, current evidence has not directly evaluated management with and without genetic testing. In terms of prophylactic measures (mastectomy and oophorectomy), RCTs would be difficult to conduct. However, retrospective analyses have shown that prophylactic mastectomy and/or oophorectomy greatly reduced the risk of breast cancer (90% to 100%) and ovarian cancer (69% to 100%).

**PALB2 and Breast Cancer Risk Assessment**

**Clinical Context and Test Purpose**

The purpose of testing for PALB2 variants in women at high-risk of HBOC syndrome is to evaluate whether an abnormal variant is present and, if so, to determine whether the variant conveys a sufficiently high-risk such that changes in surveillance and/or treatment that are likely to decrease the risk of mortality from breast cancer are warranted.

Potential benefit derives from interventions (screening, chemoprevention, risk-reducing surgery) that can prevent first breast cancer, contralateral breast cancer, or cancer in a different organ caused by the same variant. Whether benefit outweighs harms depends on the risk of developing breast cancer (first cancer or a contralateral one) and the effectiveness and the harms of interventions.

Assessing the net health outcome requires:

- That a test accurately identifies variants and pathogenicity can be determined;
- That a variant alters (increasing or decreasing) a woman’s risk of developing breast cancer (including contralateral disease in women already diagnosed) sufficient to change decision making, and of a magnitude that
- Management changes informed by testing can lead to improved health outcomes.

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

**Populations**

Genetic testing can be considered for women at increased risk of developing hereditary breast cancer based on their family history or in women with breast cancer whose family history or cancer characteristics (e.g., triple-negative disease, young age) increase the likelihood that the breast cancer is hereditary. Testing may also be considered for women from families with known variants.
The relevant population of interest for this review are individuals who are undergoing assessment for HBOC syndrome.

**Interventions**
The intervention of interest is *PALB2* variant testing.

**Comparators**
The alternative would be to manage women at high-risk of HBOC syndrome with no *PALB2* genetic testing.

**Outcomes**
The outcomes of interest are OS, disease-specific (breast and ovarian cancer) survival, and test validity.

**Study Selection Criteria**
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:
- Included a suitable reference standard
- Patient/sample clinical characteristics were described with women at high breast cancer risk
- Patient/sample selection criteria were described.

**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).

**Review of Evidence**

**Systematic Reviews**
Suszynska et al (2019) reported a systematic review of variants identified in panels of breast and ovarian cancer-related genes. Results were reported for *PALB2*, *CHEK2*, and *ATM*. *CHEK2* and *ATM* results will be discussed in the following sections. The systematic review included studies published through July 2017 reporting on genetic test results of breast and ovarian cancer patients who were referred for evaluation by a multi-gene panel. Given that the Suszynska et al (2019) report included only studies reporting on test results from a panel, it does not substantially overlap with the studies described in the following section including other *PALB2* association studies. The studies of panel results were used to calculate mutation frequencies by the gene. As a control, population mutation frequencies were extracted from the Genome Aggregation Database. Forty-three studies included panels in breast cancer patients. In the breast cancer studies, 95,853 patients were included in the analysis of *PALB2*. *PALB2* variants were identified in 0.9% of breast cancer patients. The meta-analytic estimate odds ratio (OR) of the association between *PALB2* variants and risk of breast cancer was 4.8 (95% CI, 4.1 to 5.6).

**Observational Studies**
A number of studies (Tables 4 and 5) reporting relative risks (RRs) or ORs for the association between *PALB2* and breast cancer were identified. Study designs included family segregation, kin-cohort, family-based case-control, and population-based or multicenter case-control. The 2 multinational studies included individuals from up to 5 of the single-country studies. The number of pathogenic variants identified varied from 1 (founder mutations examined) to 48 (Table 4). Studies conducted from single-country samples are described first followed by the 2 multinational collaborative efforts.
Single-Country Samples
Woodward et al (2021) assessed the contribution of PALB2 gene variants to familial breast and ovarian cancer.73 A total of 3127 women with a histologically confirmed diagnosis of invasive or in situ breast cancer or an epithelial nonmucinous ovarian cancer who had undergone germline testing of BRCA1, BRCA2, PALB2, and CHEK2_c.1100delC were included. Cases were identified from centers in the U.K.

Li et al (2021) assessed the association between 14 known genes associated with HBOC syndrome in a sample of 1990 BRCA 1/2-negative family members with breast cancer and/or ovarian cancer and 1902 older women (>40 years of age) who were cancer free at the time of the study.75 The initial assessment in 3892 women was conducted with targeted gene panel sequencing, followed by assessment of 145 candidate genes and 14 known HBOC syndrome genes in a sample of 3780 BRCA1 and BRCA2-negative families and 3839 controls. Index cases were identified from Familial Cancer Centers and a Pathology center in Australia, and controls were identified from the LifePool mammography screening study.

Lu et al (2019) included an analysis of 11,416 patients with breast cancer and/or ovarian cancer who were referred for genetic testing from 1200 U.S. hospitals and clinics and of 3988 controls referred for genetic testing for noncancer conditions between 2014 and 2015.72 Whole-exome sequencing was used and suspected pathogenic variants in the breast or ovarian cancer-associated genes were confirmed by Sanger sequencing.

Kurian et al (2017) reported the association between pathogenic variants and breast or ovarian cancer using a commercial laboratory database of 95,561 women tested clinically for hereditary cancer risk using a multi-gene panel that included PALB2, CHEK2, and ATM.32 Although the country is not stated, the patients underwent testing between 2013 and 2015 performed at a Clinical Laboratory Improvement Amendments (CLIA) laboratory and, thus, will be assumed to include patients from the U.S. Cases were women with a single diagnosis of breast or ovarian cancer. Controls were women from the same database (i.e., being tested for hereditary cancer) with no cancer history at the time of genetic testing. The multivariable models for breast cancer risk are reported here. Among the breast cancer patients, 244 (0.92%) had a PALB2 variant. The association between PALB2 and breast cancer adjusting for age, ancestry, personal and family cancer histories, and Lynch and adenomatous polyposis colon cancer syndromes had an OR of 3.39 (95% CI, 2.79 to 4.12).

Thompson et al (2015) evaluated Australian women with breast cancer (n=1996) referred for genetic evaluation from 1997 to 2014.70 A control group was accrued from participants in the LifePool study (n=1998) who were recruited for a mammography screening program. All PALB2 coding exons were sequenced by next-generation sequencing and novel variants verified by Sanger sequencing. Large deletions or rearrangements were not evaluated. Nineteen distinct pathogenic variants were identified, including 6 not previously described in 26 (1.3%) cases and in 4 (0.2%) controls with an odds for breast cancer of 6.58 (95% CI, 2.3 to 18.9). Moreover, 54 missense variants identified were slightly more common in cases (OR, 1.15; 95% CI, 1.02 to 1.32).

Cybulski et al (2015) examined 2 loss-of-function PALB2 variants (c.509_510delGA, c.172_175delTTGT) in women with invasive breast cancer diagnosed between 1996 and 2012 in Poland.20 From 12,529 genotyped women, a PALB2 variant was identified in 116 (0.93%) cases (95% CI, 0.76% to 1.09%) versus 10 (0.21% ; 95% CI, 0.08% to 0.34%) of 4702 controls (OR, 4.39; 95% CI, 2.30 to 8.37). A BRCA1 variant was identified in 3.47% of women with breast cancer and in 0.47% of controls (OR, 7.65; 95% CI, 4.98 to 11.75). Authors estimated that a PALB2 sequence variant conferred a 24% cumulative risk of breast cancer by age 75 years (in the setting of age-adjusted breast cancer rates slightly more than half that in the U.K.76, or the U.S.77). A PALB2 variant was also associated with poorer prognosis: 10-year survival of 48.0% versus 74.7% when the variant was absent (HR adjusted for prognostic factors, 2.27; 95% CI, 1.64 to 3.15).
Catucci et al (2014) performed population-based case-control studies in Italy (Milan or Bergamo) among women at risk for hereditary breast cancer and no BRCA1 or BRCA2 variant. In Milan, 9 different pathogenic PALB2 variants were detected in 12 of 575 cases and none in 784 controls (blood donor); in Bergamo, PALB2 c.1027C>T variants were detected in 6 of 113 cases and in 2 of 477 controls (OR, 13.4; 95% CI, 2.7 to 67.4). Performed in 2 distinct populations, the combined sample size was small, and uncertainty existed as indicated by the large effect estimate.

Casadei et al (2011) studied 959 U.S. women (non-Ashkenazi Jewish descent) with a family history of BRCA1- or BRCA2-negative breast cancer and 83 female relatives using a family-based case-control design. Using conventional sequencing, pathogenic PALB2 variants were detected in 31 (3.2%) women with breast cancer and none in controls. Compared with their female relatives without PALB2 variants, the risk of breast cancer increased 2.3-fold (95% CI, 1.5 to 4.2) by age 55 years and 3.4-fold (95% CI, 2.4 to 5.9) by age 85 years. Mean age at diagnosis was not associated with the presence of a variant (50.0 years with vs. 50.2 years without). Casadei et al (2011) provided few details of their analyses. Additionally, participants reported over 30 ancestries and, given intermarriage in the U.S. population, stratification may have had an impact on results. Generalizability of the risk estimate is therefore unclear.

Heikkinen et al (2009) conducted a population-based case-control study at a Finnish university hospital employing 2 case groups (947 familial and 1274 sporadic breast cancers) and 1079 controls. The study sample was obtained from 542 patients with familial breast cancer, a series of 884 oncology patients (79% of consecutive new cases), and 986 surgical patients (87% of consecutive new cases); 1706 were genotyped for the PALB2 c.1592delT variant. All familial cases were BRCA1- and BRCA2-negative, but among controls, there were 183 BRCA carriers. PALB2 variant prevalence varied with family history: 2.6% when 3 or more family members were affected and 0.7% in all breast cancer patients. Variant prevalence was 0.2% among controls. In women with hereditary disease, a PALB2 c.1592delT variant was associated with an increased risk of breast cancer (OR, 11.0; 95% CI, 2.65 to 97.78), and was higher in women with the strongest family histories (women with sporadic cancers; OR, 4.19; 95% CI, 1.52 to 12.09). Although data were limited, survival was lower among PALB2-associated cases (10-year survival, 66.5%; 95% CI, 44.0% to 89.0% vs. 84.2%; 95% CI, 83.1% to 87.1% in women without a variant; p=.041; HR, 2.94; p=.047). A PALB2 variant was also associated with triple-negative tumors: 54.5% versus 12.2% with familial disease and 9.4% in sporadic cancers.

Multinational Samples

Yang et al (2020) performed a complex segregation analysis to estimate relative and absolute risks of breast cancer from data on 524 families with PALB2 pathogenic variants from 21 countries, the most frequent being c.3113G>A. Female breast cancer relative risk (RR was 7.18 (95% CI, 5.82 to 8.85; p=6.5x10-75) when assumed to be constant with age. The age-trend model provided the best fit (p=2x10-3) and demonstrated a pattern of decreasing RR with each increased decade in age. The RR was 4.69 (95% CI, 3.28 to 6.70) in those 75 years of age per the age-trend model.

Southey et al (2016) examined the association of 3 PALB2 variants (2 protein-truncating: c.1592delT and c.3113G>A; 1 missense c.2816T>G) with breast, prostate, and ovarian cancers. The association with breast cancer was examined among participants in the Breast Cancer Association Consortium (BCAC; 42,671 cases and 42,164 controls). The BCAC (part of the larger Collaborative Oncological Gene-environment Study) included 48 separate studies with participants of multiple ethnicities, but mainly European, Asian, and African American. Most studies were population- or hospital-based case-controls with some oversampling cases with family histories or bilateral disease. A custom array was used for genotyping at 4 centers, with 2% duplicate samples. The ORs were estimated adjusting for study among all participants, and excluding those studies selecting patients based on family history or bilateral disease (37,039 cases, 38,260 controls). The c.1592delT variant was identified in 35 cases and 6 controls (from 4 studies in the U.K., Australia, U.S., Canada; OR, 4.52; 95% CI, 1.90 to 10.8; p<.001); in
those with no family history or bilateral disease (OR, 3.44; 95% CI, 1.39 to 8.52; p=.003). The c3113G>A variant was identified in 44 cases and 8 controls (9 studies from Finland and Sweden; OR, 5.93; 95% CI, 2.77 to 12.7; p<.001) and in those with no family history or bilateral disease (OR, 4.21; 95% CI, 1.84 to 9.60; p<.001). There was no association between the c2816T>G missense variant and breast cancer (found in 150 cases and 145 controls). These results, derived from a large sample, used a different analytic approach than Antoniou et al (2014), described next, and examined only 2 pathogenic variants. The magnitude of the estimated RR approaches that of a high penetrance gene but is accompanied by wide CIs owing to the study design and low carrier prevalence. The lower estimates obtained following exclusion of those selected based on family history or bilateral disease are consistent with the importance of carefully considering the risk of hereditary disease prior to genetic testing.

Antoniou et al (2014) analyzed data from 362 members of 154 families with deleterious PALB2 variants. Individuals with benign variants or variants of uncertain significance were excluded. Families were recruited at 14 centers in 8 countries (U.S., U.K., Finland, Greece, Australia, Canada, Belgium, Italy) and had at least 1 member with a BRCA1- or BRCA2-negative PALB2-positive breast cancer. There were 311 women with PALB2 variants: 229 had breast cancer; 51 men also had PALB2 variants (7 had breast cancer). Of the 48 pathogenic (loss-of-function) variants identified, 2 were most common (c.1592delT in 44 families, c.3113G>A in 25 families); 39 of the 48 pathogenic variants were found in just 1 or 2 families. Carriers of PALB2 variants (men and women) had a 9.47-fold increased risk for breast cancer (95% CI, 7.16 to 12.57) compared with the U.K. population under a single-gene model and age-constant RR; 30% of tumors were triple-negative. For a woman aged 50 to 54 years, the estimated RR was 6.55 (95% CI, 4.60 to 9.18). The RR of breast cancer for males with PALB2 variants, compared with the male breast cancer incidence in the general population, was 8.3 (95% CI, 0.77 to 88.5; p=.08). The cumulative risk at age 50 years of breast cancer for female PALB2 carriers without considering family history was 14% (95% CI, 9% to 20%); by age 70 years, it was 35% (95% CI, 26% to 46%). A family history of breast cancer increased the cumulative risk. If a woman with a PALB2 variant has a sister and mother who had breast cancer at age 50 years, by age 50 years she would have a 27% (95% CI, 21% to 33%) estimated risk of developing breast cancer; and by age 70 years, a 58% (95% CI, 50% to 66%) risk. These results emphasize that family history affects penetrance. Authors noted that the study “includes most of the reported families with PALB2 variant carriers, as well as many not previously reported”.

### Table 4. Included Association Studies of Pathogenic PALB2 Variants

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>N</th>
<th>Families</th>
<th>PALB2 Variants</th>
<th>Totals</th>
<th>Pathogenic Variants Identified</th>
<th>Cases</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls</th>
<th>N</th>
<th>Prevalence Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al (BEACCON)[75]</td>
<td>2021</td>
<td>Australia</td>
<td>Family-based CC</td>
<td>3892</td>
<td>144</td>
<td>98</td>
<td>1990</td>
<td>1902</td>
<td>NR</td>
<td>2.49</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al[74]</td>
<td>2020</td>
<td>Multinational</td>
<td>Multicenter family segregation</td>
<td>17,906</td>
<td>976</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>976</td>
<td>5.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lu et al[72]</td>
<td>2019</td>
<td>U.S.</td>
<td>Multicenter CC</td>
<td>15,404</td>
<td>61</td>
<td>NR</td>
<td>15,532</td>
<td>3988</td>
<td>NR</td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cybulski et al[77]</td>
<td>2015</td>
<td>Poland</td>
<td>Population-based CC</td>
<td>17,231</td>
<td>116</td>
<td>10</td>
<td>12,529</td>
<td>4702</td>
<td>2</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catucci et al*[18,ab]</td>
<td>2014</td>
<td>Italy</td>
<td>Population-based CC</td>
<td>590*</td>
<td>6</td>
<td>2</td>
<td>113</td>
<td>477</td>
<td>1</td>
<td>5.3</td>
<td>(c.1027C&gt;T)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heikkinen et al*[18,ab]</td>
<td>2009</td>
<td>Finland</td>
<td>Population-based CC</td>
<td>2026</td>
<td>19</td>
<td>2</td>
<td>947</td>
<td>1079</td>
<td>1</td>
<td>2.0</td>
<td>(c.1592delT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casadei et al*[19,ab]</td>
<td>2011</td>
<td>U.S.</td>
<td>Family-based CC</td>
<td>1042</td>
<td>31</td>
<td>0</td>
<td>959</td>
<td>83</td>
<td>13</td>
<td>3.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Study Year Country Design N Families PALB2 Variants Totals Pathogenic Variants Identified

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>N</th>
<th>Families</th>
<th>PALB2 Variants</th>
<th>Totals</th>
<th>Pathogenic Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahman et al[69,64]</td>
<td>2007</td>
<td>U.K.</td>
<td>Family-based CC</td>
<td>2007</td>
<td>923</td>
<td>10 0</td>
<td>923</td>
<td>1084</td>
</tr>
<tr>
<td>Erkko et al[67,66]</td>
<td>2008</td>
<td>Finland</td>
<td>Family segregation</td>
<td>213</td>
<td>17</td>
<td>17 ?</td>
<td>1</td>
<td>1(c.1592delT)</td>
</tr>
<tr>
<td>Antoniou et al[17]</td>
<td>2014</td>
<td>Multinational</td>
<td>Kin-cohort</td>
<td>2980</td>
<td>154</td>
<td>229 82</td>
<td>542</td>
<td>2438</td>
</tr>
<tr>
<td>Southey et al[71]</td>
<td>2016</td>
<td>Multinational</td>
<td>Multicenter CC</td>
<td>84,835</td>
<td>35</td>
<td>6 42,671</td>
<td>42,164</td>
<td></td>
</tr>
<tr>
<td>Southey et al[71]</td>
<td>2017</td>
<td>U.S.</td>
<td>CC</td>
<td>95,561</td>
<td>257</td>
<td>NR</td>
<td>26,384</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

BEACCON: Hereditary BrEAst Case CONtrol study; CC: case-control; NR: not reported.

a All or selected families included in Antoniou et al (2014).
b Participants included in Southey et al (2016).
c 10 with a family history.
d Non-Ashkenazi Jewish descent, males excluded.
e Bergamo sample, Milan sample 0 controls with PALB2 variants.
f Study primary survival outcome was obtained as part of a prospective cohort. The analysis and sampling to assess breast cancer risk were as a case-control study.

table 5. Measures of Association and Penetrance for Breast Cancer and PALB2

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Analysis</th>
<th>RR or OR (95% CI)</th>
<th>Penetrance at Age 70 years (95% CI), %</th>
<th>Mean (Median) Age Onset, y</th>
<th>Triple-Negative Tumors, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodward et al[73]</td>
<td>2021</td>
<td>Standard CC</td>
<td>5.90 (1.92 to 18.36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al (BEACCON)[75]</td>
<td>2021</td>
<td>Standard CC</td>
<td>3.47 (1.92 to 6.65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al[74]</td>
<td>2019</td>
<td>Segregation</td>
<td>7.18 (5.82 to 8.85)</td>
<td>52.8 (43.7 to 62.7)d</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lu et al[72]</td>
<td>2019</td>
<td>Standard CC</td>
<td>5.5 (2.2 to 17.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antoniou et al[17]</td>
<td>2014</td>
<td>Segregationb</td>
<td>6.6 (4.6 to 9.2)c</td>
<td>47.5 (38.6 to 57.4)e</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Erkko et al[67]</td>
<td>2008</td>
<td>Segregation</td>
<td>6.1 (2.2 to 17.2)a</td>
<td>40 (17 to 77)</td>
<td>54.3 (+FH); 59.3 (FH unavailable)</td>
<td></td>
</tr>
<tr>
<td>Rahman et al[69]</td>
<td>2007</td>
<td>Segregationb</td>
<td>2.3 (1.4 to 3.9)f</td>
<td>46 (IQR, 40 to 51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casadei et al[19]</td>
<td>2011</td>
<td>Relative risk</td>
<td>2.3 (1.5 to 4.2)g</td>
<td>50.0 (SD, 11.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson et al[10]</td>
<td>2015</td>
<td>Standard CC</td>
<td>6.6 (2.3 to 18.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cybulski et al[20]</td>
<td>2015</td>
<td>Standard CC</td>
<td>4.4 (2.3 to 8.4)</td>
<td>53.3</td>
<td>34.4 14.4</td>
<td></td>
</tr>
<tr>
<td>Catucci et al[18]</td>
<td>2014</td>
<td>Standard CC</td>
<td>13.4 (2.7 to 67.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heikkinen et al[69]</td>
<td>2009</td>
<td>Standard CC</td>
<td>11.0 (2.6 to 97.8)</td>
<td>53.1 (95% CI, 33.4 to 79.9)</td>
<td>54.5 9.4 12.2h</td>
<td></td>
</tr>
<tr>
<td>Southey et al[71]</td>
<td>2016</td>
<td>Standard CC</td>
<td>4.5 (1.9 to 10.8)</td>
<td>(c.1592delT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.9 (2.8 to 12.7)</td>
<td>(c.3113G&gt;A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.39 (2.79 to 4.12)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BEACCON: Hereditary BrEAst Case CONtrol study; CC: case-control; CI: confidence interval; FH: family history; IQR: interquartile range; NR: not reported; OR: odds ratio; RR: relative risk; SD: standard deviation.
a Using an “augmented” dataset assuming no cases among families without recorded histories. Analyses limited to those with recorded histories yielded a RR of 14.3 (95% CI, 6.6 to 31.2).
b Modified.
2.04.02  Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

Page 19 of 39

c Estimate for women age 50 years.
d Estimate for women age 80 years.
e Estimates varied according to family history. For women with a mother and sister with breast cancer at age 50 years, cumulative risk was estimated at 58% (95% CI, 50% to 66%); for women with no family history, 33% (95% CI, 26% to 46%).
f For women <50 years, RR of 3.0 (95% CI, 1.4 to 3.9); for women >50 years, RR of 1.9 (95% CI, 0.8 to 3.7).
g At age 85 years, RR of 3.4 (95% CI, 2.4 to 5.9).
h In sporadic and familial cancers without PALB2 variants.

Notable limitations identified in each study are shown in Tables 6 and 7.

Table 6. Study Relevance Limitations of Individuals Studies of Pathogenic PALB2 Variants

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Duration of FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodward et al (2021)</td>
<td>Case-control population of breast cancer patients referred for genetic testing (and controls), likely overestimated risk</td>
<td>4</td>
<td>1. Not clear which variants were included</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al (2021) (BEACCON)</td>
<td>Case-control population of familial BRCA 1/2 negative breast cancer patients (and controls)</td>
<td>4</td>
<td>1. Not clear which variants were included</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al (2019)</td>
<td>No case-control group</td>
<td>4</td>
<td>1. Not clear which variants were included</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lu et al (2019)</td>
<td>Case-control population of breast cancer patients (and controls), likely overestimated risk</td>
<td>4</td>
<td>1. Not clear which variants were included</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Kurian et al (2017)  | Case-control population of breast cancer patients (and controls), likely overestimated risk | 4            | 1. Not clear which variants were included | 1: Control chosen from patients being tested for hereditary cancer; unclear how many developed cancer
| Southey et al (2016) | Case-control population of breast cancer patients (and controls), likely overestimated risk | 4            | 1. Not clear which variants were included |          |                |
| Thompson et al (2015) | Case-control population of breast cancer patients (and controls), likely overestimated risk | 4            | 1. Not clear which variants were included |          |                |
| Cybulski et al (2015) | Case-control population of breast cancer patients (and controls), likely overestimated risk | 4            | 1. Not clear which variants were included |          |                |
| Catucci et al (2014) | Case-control population of breast cancer patients referred for genetic testing (and controls), likely overestimated risk | 4            | 1. Not clear which variants were included |          |                |
| Antoniou et al (2014) | Case-control population of breast cancer patients (and controls), likely overestimated risk; only kin-cohort included | 4            | 1. Not clear which variants were included |          |                |
Study | Population | Intervention | Comparator | Outcomes | Duration of FU
---|---|---|---|---|---
Casadei et al (2011) | 4. Case-control population of breast cancer patients (and controls), likely overestimated risk | | | | 
Heikkinen et al (2009) | 4. Case-control population of breast cancer patients referred for genetic testing (and controls), likely overestimated risk | | | | 
Rahman et al (2007) | 4. Case-control population of breast cancer patients (and controls), likely overestimated risk | | | | 

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

BEACCON: Hereditary BrEAst Case CONtrol study; FU: follow-up.

Study Selection | Blinding | Delivery | Selective Reporting | Data Completeness | Statistical
---|---|---|---|---|---
Woodward et al (2021) | 1. Incomplete description of how controls selected | | | | 
Li et al (2021) (BEACCON) | 1. Registration not reported | 1. No description of disposition of eligible patients/samples | | | 
Yang et al (2019) | 1. Incomplete descriptions of how family groups selected | 1. Registration not reported | 1. No description of disposition of eligible patients/samples | | 
Lu et al (2019) | 1. Incomplete description of how controls selected | 1. Registration not reported | 1. No description of disposition of eligible patients/samples | | 
Kurian et al (2017) | 1. Registration not reported | 1. No description of disposition of eligible patients/samples | | | 
Southey et al (2016) | 1. Registration not reported | | | | 
Thompson et al (2015) | 1. Incomplete description of how controls selected | 1. Registration not reported | 1. No description of disposition of eligible patients/samples | | 
Cybulski et al (2015) | 1. Incomplete description of how controls selected | 1. Registration not reported | | |
Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

Study | Selection | Blinding | Delivery | Selective Reporting | Data Completeness | Statistical |
--- | --- | --- | --- | --- | --- | --- |
Catucci et al (2015) | 1. Incomplete description of how controls selected | 1. Registration not reported | 1. No description of disposition of eligible patients/samples |
Casadei et al (2011) | 2. Family groups: controls not randomized | 1. Registration not reported |
Heikkinen et al (2009) | 1. Incomplete description of how controls selected | | 1. Registration not reported |
Erkko et al (2008) | 2. Family groups: selection not randomized | 1. Registration not reported; number of controls unknown |
Rahman et al (2007) | 2. Family groups: controls not randomized | 1. Registration not reported |

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

BEACCON: Hereditary BrEAst Case CONtrol study.

1. Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
2. Blinding key: 1. Not blinded to results of reference or other comparator tests.
3. Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
5. Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
6. Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

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, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

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.

Evidence of clinical utility limited to women with PALB2 variants was not identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Rosenthal et al (2017) reported an analysis of the impact of testing for genes other than BRCA1/2 and by calculating whether carriers of these gene variants would have been identified as candidates for enhanced screening based on family history alone. The database included 194,107 women who were tested using a hereditary cancer panel between 2013 and 2016. The women were referred by their health care providers for clinical suspicion of hereditary cancer. It is unclear what proportion of the women met professional society criteria for genetic testing for breast cancer risk; baseline information regarding family history was not reported. Of the women in the database, 893 had PALB2 variants and were eligible for Claus assessment to estimate the risk of breast cancer. Approximately 27% of women...
with PALB2 variants would have had an estimated risk of breast cancer of 20% or higher based on the Claus model. The report did not include health outcomes and it is unclear whether enhanced screening in women who had a moderate penetrance variant but did not have an estimated risk of breast cancer of 20% or greater based on the Claus model would have improved health outcomes from enhanced surveillance.

Studies of women at high-risk based on family history alone or in those with BRCA1 and BRCA2 variants are relevant to the clinical utility of PALB2 testing given the penetrance estimates for PALB2 and related molecular mechanism (“BRCA-ness”). Interventions to decrease breast cancer risk in asymptomatic high-risk women include screening\(^7\) (e.g., starting at an early age, the addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention,\(^8\) and prophylactic mastectomy.\(^9\) In women with breast cancer, contralateral prophylactic mastectomy is of interest; other treatment decisions are dictated by clinical, pathologic, and other prognostic factors.

In women at high-risk of hereditary breast cancer, including BRCA1 and BRCA2 carriers, evidence supports a reduction in subsequent breast cancer after bilateral or contralateral prophylactic mastectomy. Decision analyses have also concluded the impact on breast cancer incidence extends life in high, but not average risk,\(^8\) women. For example, Schrag et al (1997, 2000) modeled the impact of preventive interventions in women with BRCA1 or BRCA2 variants and examined penetrance magnitudes similar to those estimated for a PALB2 variant.\(^8\)\(^,\)\(^8\)^ Compared with surveillance, a 30-year-old BRCA4 carrier with an expected 40% risk of breast cancer and 5% risk of ovarian cancer by age 70 years would gain an expected 2.9 years following a prophylactic mastectomy alone and an additional 0.3 years with a prophylactic oophorectomy (Table 8). A 50-year-old female BRCA carrier with node-negative breast cancer and a 24% risk of contralateral breast cancer at age 70 years would anticipate 0.9 years in improved life expectancy (0.6 years for node-negative disease) following a prophylactic contralateral mastectomy.\(^8\)^

### Table 8. Model Results of the Effects of Bilateral Risk-Reducing Mastectomy versus Surveillance on Life Expectancy in BRCA Carriers According to Penetrance

<table>
<thead>
<tr>
<th>Risk Level and Strategy</th>
<th>Age of Carrier, years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>40% risk of breast cancer</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>2.9</td>
</tr>
<tr>
<td>Mastectomy delayed 10 years</td>
<td>1.8</td>
</tr>
<tr>
<td>60% risk of breast cancer</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>4.1</td>
</tr>
<tr>
<td>Mastectomy delayed 10 years</td>
<td>2.4</td>
</tr>
<tr>
<td>85% risk of breast cancer</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>5.3</td>
</tr>
<tr>
<td>Mastectomy delayed 10 years</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Adapted from Schrag et al (1997).\(^8\)

### Section Summary: PALB2 and Breast Cancer Risk Assessment

Identified studies differed by populations, designs, sample sizes, analyses, and variants examined. While estimates of the magnitude of the association between PALB2 and breast cancer risk varied across studies, their magnitudes are of moderate to high penetrance.

Of interest is how variant detection affects penetrance estimates compared with family history alone. As with BRCA4 variants, model-based estimates allow estimating risks for individual patient and family characteristics. To illustrate using the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm model, a woman age 30 years whose mother had breast cancer at age 35 years has an estimated 14.4% risk of breast cancer at age 70 years. If she carries a PALB2 variant, the risk increases to 51.1%. A woman, age 50 years, with breast cancer whose mother had breast cancer at age 50 years, has an estimated 11.7% risk of contralateral breast cancer by age 70 years, increasing to 28.7% if she carries a PALB2 variant.
Evidence concerning preventive interventions in women with PALB2 variants is indirect, relying on studies of high-risk women and BRCA carriers. In women at high-risk of hereditary breast cancer who would consider preventive interventions, identifying a PALB2 variant provides a more accurate estimated risk of developing breast cancer compared with family history alone and can offer a better understanding of benefits and potential harms of interventions.

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.

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2010 Input
In response to requests, input was received for 3 physician specialty societies (5 reviewers) and 3 academic medical centers (5 reviewers) while this policy was under review in 2010. Those providing input were in general agreement with the Policy statements considering testing for genomic rearrangements of BRCA1 and BRCA2 as medically necessary and with adding fallopian tube and primary peritoneal cancer as BRCA-associated malignancies to assess when obtaining the family history.

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.

National Comprehensive Cancer Network
Breast Cancer and Ovarian Cancer
Current National Comprehensive Cancer Network (NCCN) (v.3.2023) guidelines on the genetic and familial high-risk assessment of breast, ovarian, and pancreatic cancers include criteria for identifying individuals who should be referred for further risk assessment and separate criteria for genetic testing.85 Patients who satisfy any of the testing criteria listed in CRIT-1 through CRIT-4 should undergo “further personalized risk assessment, genetic counseling, and often genetic testing and management.” For these criteria, both invasive and in situ breast cancers were included. Maternal and paternal sides of the family should be considered independently for familial patterns of cancer. Testing of unaffected individuals should be considered "when no appropriate affected family member is available for testing."

The recommendations are for testing high penetrance breast cancer susceptibility genes, specifically BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53. Use of "tailored panels that are disease-focused and include clinically actionable cancer susceptibility genes is preferred over large panels that include genes of uncertain clinical relevance."

The panel does not endorse population based testing, stating instead that the panel, "continues to endorse a risk-stratified approach and does not endorse universal testing of all patients with breast cancer due to limitations of this approach, such as low specificity, shortages in trained genetics health
professionals to provide appropriate pre- and post-test genetic counseling, and lack of evidence to support risk management for genes included in many multi-gene panels."

*BRCA1* and *BRCA2* somatic only variants are uncommon. The NCCN recommends if a somatic variant is identified through tumor profiling, then *BRCA1* and *BRCA2* germline testing is recommended. Additionally, the NCCN ovarian cancer guidelines (v.2.2023) recommend tumor molecular testing for persistent/recurrent disease (OV-6) and describe in multiple algorithms that testing should include at least *BRCA1*/2, homologous recombination, microsatellite instability, tumor mutational burden, and neurotrophic tyrosine receptor kinase, (OV-6, OV-7, OV-B Principles of Pathology, OV-C Principles of Systemic Therapy).86,87

**Pancreatic Adenocarcinoma and Pancreatic Neuroendocrine Tumors**

Current NCCN guidelines for pancreatic adenocarcinoma (v.2.2023) refers to the NCCN guidelines on genetic/familial high-risk assessment of breast, ovarian, and pancreatic cancers detailed above, and state: "The panel recommends germline testing in any patient with confirmed pancreatic cancer and in those in whom there is a clinical suspicion for inherited susceptibility." The panel recommends" using comprehensive gene panels for hereditary cancer syndromes."87,88

The NCCN guidelines for genetic and familial high-risk assessment of breast, ovarian, and pancreatic cancers (v.3.2023) includes that germline testing is clinically indicated for individuals with neuroendocrine pancreatic cancers per the NCCN guidelines on neuroendocrine and adrenal tumors.88,89 The NCCN guidelines for neuroendocrine and adrenal tumors (v.2.2022) states, "consider genetic risk evaluation and genetic testing: In a patient with duodenal/pancreatic neuroendocrine tumor at any age", noting, "studies of unselected patients with pancreatic neuroendocrine tumors have identified germline variants in 16%-17% of cases. However, these studies involved relatively small cohorts of patients."

**Prostate Cancer**

The current NCCN guidelines for prostate cancer are version 1.2023.89. The Principles of Genetics and Molecular/Biomarker Analysis section (PROS-C) provides appropriate scenarios for germline genetic testing in individuals with a personal history of prostate cancer.

**American Society of Breast Surgeons**

A consensus guideline on genetic testing for hereditary breast cancer was updated in February 2019.90 The guideline states that genetic testing should be made available to all patients with a personal history of breast cancer and that such testing should include *BRCA1*/*BRCA2* and *PALB2*, with other genes as appropriate for the clinical scenario and patient family history. Furthermore, patients who had previous genetic testing may benefit from updated testing. Finally, genetic testing should be made available to patients without a personal history of breast cancer when they meet NCCN guideline criteria. The guidelines also note that variants of uncertain significance are not clinically actionable.

**Society of Gynecologic Oncology**

In 2015, the Society of Gynecologic Oncology (SGO) published an evidence-based consensus statement on risk assessment for inherited gynecologic cancer.91 The statement included criteria for recommending genetic assessment (counseling with or without testing) to patients who may be genetically predisposed to breast or ovarian cancer. Overall, the SGO and the NCCN recommendations are very similar; the main differences are the exclusion of women with breast cancer onset at age 50 years or younger who have 1 or more first-, second-, or third-degree relatives with breast cancer at any age; women with breast cancer or history of breast cancer who have a first-, second-, or third-degree male relative with breast cancer; and men with a personal history of breast cancer. Additionally, SGO recommended genetic assessment for unaffected women who have a male relative with breast cancer. Moreover, SGO indicated that some patients who do not satisfy criteria may still benefit from genetic
assessment (e.g., few female relatives, hysterectomy, or oophorectomy at a young age in multiple family members, or adoption in the lineage).

American College of Obstetricians and Gynecologists
The American College of Obstetricians and Gynecologists (2017, reaffirmed 2021) published a Practice Bulletin on hereditary breast and ovarian cancer syndrome. The following recommendation was based primarily on consensus and expert opinion (level C): “Genetic testing is recommended when the results of a detailed risk assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management.”

U.S. Preventive Services Task Force
Current U.S. Preventative Services Task Force (USPSTF) recommendations (2019) for genetic testing of BRCA1 and BRCA2 variants in women state:

"The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene mutation with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing (B recommendation). The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful BRCA1/2 gene mutations. (D recommendation)"

Recommended screening tools included the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, 7-Question Family History Screening Tool, International Breast Cancer Intervention Study instrument (Tyrer-Cuziak), and brief versions of the BRCAPRO.

Medicare National Coverage
There are no national coverage determinations. 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 9.

Table 9. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date (status if beyond Completion Date)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT04009148</td>
<td>Cascade Testing in Families With Newly Diagnosed Hereditary Breast and Ovarian Cancer Syndrome</td>
<td>300</td>
<td>Mar 2025</td>
</tr>
<tr>
<td>NCT03246841</td>
<td>Investigation of Tumour Spectrum, Penetrance and Clinical Utility of Germline Mutations in New Breast and Ovarian Cancer Susceptibility Genes (TUMOSPEC)</td>
<td>500</td>
<td>Dec 2024</td>
</tr>
<tr>
<td>NCT02321228</td>
<td>Early Salpingectomy (Tubectomy) With Delayed Oophorectomy to Improve Quality of Life as Alternative for Risk Reducing Salpingo-oophorectomy in BRCA1/2 Gene Mutation Carriers (TUBA)</td>
<td>510</td>
<td>Jan 2035</td>
</tr>
<tr>
<td>NCT054200064</td>
<td>Effective Familial OutReach Via Tele-genetics (EFFORT): A Sustainable Model to Expand Access to MSK’s Genetic Services</td>
<td>896</td>
<td>Nov 2026</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.
References


Reproduction without authorization from Blue Shield of California is prohibited


Documentation for Clinical Review

Please provide the following documentation:

• History and physical and/or consultation notes including:
  o Ethnicity/Ancestry
  o Personal and/or family history of cancer (if applicable) including:
Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

- Family relationship(s): (maternal or paternal), (family member [e.g., sibling, aunt, grandparent]), (living or deceased) (if applicable)
- Site(s) and stage of cancer (if applicable)
- Age at diagnosis (including family members) (if applicable)
- If breast cancer, indicate if bilateral, premenopausal, or triple negative cancer
  - BRCA1/BRCA2 or PALB2 mutation history (if applicable)
- Genetic counseling/professional results (if applicable)
- Laboratory or Pathology reports (if applicable)
- Applicable known family genetic variants and the relationship to the individual being tested

Post Service (in addition to the above, please include the following):
- Procedure report(s)
- Applicable test results

**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.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0102U</td>
<td>Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])</td>
</tr>
<tr>
<td></td>
<td>0103U</td>
<td>Hereditary ovarian cancer (e.g., hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication only])</td>
</tr>
<tr>
<td>CPT*</td>
<td>0129U</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>0131U</td>
<td>Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>0132U</td>
<td>Hereditary ovarian cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>0135U</td>
<td>Hereditary gynecological cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>0138U</td>
<td>BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>0172U</td>
<td>Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score</td>
</tr>
<tr>
<td></td>
<td>81162</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>81163</td>
<td>BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td></td>
<td>81164</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>81165</td>
<td>BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td></td>
<td>81166</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>81167</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>81212</td>
<td>BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants</td>
</tr>
<tr>
<td></td>
<td>81215</td>
<td>BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td></td>
<td>81216</td>
<td>BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td></td>
<td>81217</td>
<td>BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td></td>
<td>81307</td>
<td>PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence</td>
</tr>
<tr>
<td></td>
<td>81308</td>
<td>PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; known familial variant</td>
</tr>
<tr>
<td></td>
<td>81432</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>81433</td>
<td>Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer);</td>
</tr>
</tbody>
</table>

Reproduction without authorization from Blue Shield of California is prohibited
Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology proceduregermlin</td>
</tr>
<tr>
<td>HCPCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

### Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/15/1997</td>
<td>New Policy Adoption</td>
</tr>
<tr>
<td>06/01/1999</td>
<td>BCBSA Medical Policy adoption</td>
</tr>
<tr>
<td>05/01/2001</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>08/01/2005</td>
<td>BCBSA Medical Policy adoption</td>
</tr>
<tr>
<td>10/01/2005</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>01/11/2008</td>
<td>Policy Revision</td>
</tr>
<tr>
<td>12/05/2008</td>
<td>Policy Revision</td>
</tr>
<tr>
<td>05/06/2009</td>
<td>Coding Update</td>
</tr>
<tr>
<td>07/28/2009</td>
<td>Criteria Revised</td>
</tr>
<tr>
<td>11/04/2009</td>
<td>Coding update</td>
</tr>
<tr>
<td>04/02/2010</td>
<td>Policy revision with position change to clarify BART testing</td>
</tr>
<tr>
<td>07/15/2010</td>
<td>Policy Revision with position change adopting 2010 NCCN guidelines</td>
</tr>
<tr>
<td>09/13/2010</td>
<td>Coding Update</td>
</tr>
<tr>
<td>03/30/2012</td>
<td>Title change from BRCA1 and BRCA2 Genetic Testing with position change</td>
</tr>
<tr>
<td>06/13/2012</td>
<td>Coding Update</td>
</tr>
<tr>
<td>08/21/2012</td>
<td>Administrative Update (Clarification of Policy Guideline)</td>
</tr>
<tr>
<td>02/22/2013</td>
<td>Coding Update</td>
</tr>
<tr>
<td>03/29/2013</td>
<td>Policy revision with position change</td>
</tr>
<tr>
<td>10/9/2013</td>
<td>Administrative Update (Clarification of BART testing policy statement)</td>
</tr>
<tr>
<td>12/19/2013</td>
<td>Policy revision with position change</td>
</tr>
<tr>
<td>03/30/2015</td>
<td>Administrative Update (Revision and clarification of the Documentation Required section)</td>
</tr>
<tr>
<td>08/31/2015</td>
<td>Policy title change from Genetic Testing for Hereditary Breast and/or Ovarian Cancer Administrative Update (Formatting changes only)</td>
</tr>
<tr>
<td>02/01/2016</td>
<td>Coding update</td>
</tr>
<tr>
<td>01/01/2017</td>
<td>Policy title change from Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome (BRCA1/BRCAN Cancer) Policy revision without position change.</td>
</tr>
<tr>
<td>09/01/2017</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>01/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>04/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>07/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>05/01/2019</td>
<td>Policy revision without position change. Coding update.</td>
</tr>
<tr>
<td>08/01/2019</td>
<td>Administrative Update</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red font: Verbage removed</td>
<td>Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2) 2.04.02</td>
</tr>
</tbody>
</table>

Policy Statement:

Note: Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review). *(moved to Regulatory status section)*

Genetic testing should be performed in a setting that has suitably trained health care providers who can give appropriate pre- and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments-licensed laboratory that offers comprehensive variant analysis (see Policy Guidelines section: Comprehensive Variant Analysis). As other genes have become associated with hereditary breast and ovarian cancer, small panels (using CPT code 81432) are now the preferred tests (rather than just testing for BRCA1 and BRCA2, such as 81162). *(moved to Policy Guidelines)*

<table>
<thead>
<tr>
<th>Individuals With Cancer or With a Personal History of Cancer</th>
<th>Individuals With Cancer or With a Personal History of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Full sequence and duplication/deletion analysis genetic testing for BRCA1, BRCA2, and PALB2 gene variants (including when part of an approved small panel such as 81432) in cancer-affected individuals age 18 or over may be considered medically necessary under any of the following circumstances:</td>
<td>I. Full sequence and duplication/deletion analysis genetic testing for BRCA1, BRCA2, and PALB2 gene variants (including when part of an approved small panel such as 81432) in cancer-affected individuals age 18 or over may be considered medically necessary under any of the following circumstances:</td>
</tr>
<tr>
<td>A. Individuals meeting the criteria for medically necessary testing below but with previous limited testing (e.g., single gene and/or absent deletion duplication analysis)</td>
<td>A. Individuals meeting the criteria for medically necessary testing below but with previous limited testing (e.g., single gene and/or absent deletion duplication analysis)</td>
</tr>
</tbody>
</table>
### POLICY STATEMENT

#### BEFORE

Red font: Verbiage removed

<table>
<thead>
<tr>
<th>B.</th>
<th>Individuals (with or without a history of cancer) with any close blood relative with a known <em>BRCA1</em>, <em>BRCA2</em>, or <em>PALB2</em> pathogenic/likely pathogenic variant (see Policy Guidelines for definitions and for testing strategy).</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.</td>
<td>Personal history of breast cancer (including invasive and ductal carcinoma in situ) and one or more of the following:</td>
</tr>
<tr>
<td>1.</td>
<td>Diagnosed at age 45 or younger</td>
</tr>
<tr>
<td>2.</td>
<td>Diagnosed 46 to 50 years of age and one or more of the following:</td>
</tr>
<tr>
<td>a.</td>
<td>An additional breast cancer primary at any age</td>
</tr>
<tr>
<td>b.</td>
<td>One or more close relative (see Policy Guidelines) with breast, ovarian, pancreatic, or <em>prostate cancer</em> at any age</td>
</tr>
<tr>
<td>c.</td>
<td>An unknown or limited family history</td>
</tr>
<tr>
<td>3.</td>
<td>Diagnosed on or before 60 years of age with triple-negative breast cancer (estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor 2-negative)</td>
</tr>
<tr>
<td>4.</td>
<td>Diagnosed at any age with one or more of the following:</td>
</tr>
<tr>
<td>a.</td>
<td>One or more close blood relative with one or more of the following:</td>
</tr>
<tr>
<td>i.</td>
<td>Breast cancer diagnosed on or before 50 years of age</td>
</tr>
<tr>
<td>ii.</td>
<td>Ovarian carcinoma</td>
</tr>
<tr>
<td>iii.</td>
<td>Metastatic or intraductal/cribriform <em>prostate cancer</em>, or high-risk group or very-high-risk group (see Policy Guidelines) <em>prostate cancer</em></td>
</tr>
<tr>
<td>iv.</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>b.</td>
<td>Three or more total diagnoses of breast cancer in individual and/or close blood relatives</td>
</tr>
<tr>
<td>c.</td>
<td>Ashkenazi Jewish ancestry</td>
</tr>
<tr>
<td>D.</td>
<td>Personal history of one or more of the following at any age:</td>
</tr>
<tr>
<td>1.</td>
<td>Male breast cancer</td>
</tr>
<tr>
<td>2.</td>
<td>Epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer)</td>
</tr>
</tbody>
</table>

#### AFTER

<table>
<thead>
<tr>
<th>B.</th>
<th>Individuals (with or without a history of cancer) with any close blood relative with a known <em>BRCA1</em>, <em>BRCA2</em>, or <em>PALB2</em> pathogenic/likely pathogenic variant (see Policy Guidelines for definitions and for testing strategy).</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.</td>
<td>Personal history of breast cancer (including invasive and ductal carcinoma in situ) and one or more of the following:</td>
</tr>
<tr>
<td>1.</td>
<td>Diagnosed at age 45 or younger</td>
</tr>
<tr>
<td>2.</td>
<td>Diagnosed 46 to 50 years of age and one or more of the following:</td>
</tr>
<tr>
<td>a.</td>
<td>An additional breast cancer primary at any age</td>
</tr>
<tr>
<td>b.</td>
<td>One or more close relative (see Policy Guidelines) with breast, ovarian, pancreatic, or <em>prostate cancer</em> at any age</td>
</tr>
<tr>
<td>c.</td>
<td>An unknown or limited family history</td>
</tr>
<tr>
<td>3.</td>
<td>Diagnosed on or before 60 years of age with triple-negative breast cancer (estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor 2-negative)</td>
</tr>
<tr>
<td>4.</td>
<td>Diagnosed at any age with one or more of the following:</td>
</tr>
<tr>
<td>a.</td>
<td>One or more close blood relative with one or more of the following:</td>
</tr>
<tr>
<td>i.</td>
<td>Breast cancer diagnosed on or before 50 years of age</td>
</tr>
<tr>
<td>ii.</td>
<td>Ovarian carcinoma</td>
</tr>
<tr>
<td>iii.</td>
<td>Metastatic or intraductal/cribriform <em>prostate cancer</em>, or high-risk group or very-high-risk group (see Policy Guidelines) <em>prostate cancer</em></td>
</tr>
<tr>
<td>iv.</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>b.</td>
<td>Three or more total diagnoses of breast cancer in individual and/or close blood relatives</td>
</tr>
<tr>
<td>c.</td>
<td>Ashkenazi Jewish ancestry</td>
</tr>
<tr>
<td>D.</td>
<td>Personal history of one or more of the following at any age:</td>
</tr>
<tr>
<td>1.</td>
<td>Male breast cancer</td>
</tr>
<tr>
<td>2.</td>
<td>Epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer)</td>
</tr>
<tr>
<td>BEFORE</td>
<td>AFTER</td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Exocrine pancreatic cancer</td>
<td>Exocrine pancreatic cancer</td>
</tr>
<tr>
<td>Metastatic or intraductal/cribriform histology prostate cancer or high-risk group or very-high-risk group prostate cancer</td>
<td>Metastatic or intraductal/cribriform histology prostate cancer or high-risk group or very-high-risk group prostate cancer</td>
</tr>
<tr>
<td>Prostate cancer with one or more of the following:</td>
<td>Prostate cancer with one or more of the following:</td>
</tr>
<tr>
<td>a. One or more close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic or intraductal/cribriform prostate cancer at any age, or breast cancer at age 50 years or younger</td>
<td>a. One or more close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic or intraductal/cribriform prostate cancer at any age, or breast cancer at age 50 years or younger</td>
</tr>
<tr>
<td>b. Two or more close blood relatives with breast or prostate cancer (any grade) at any age</td>
<td>b. Two or more close blood relatives with breast or prostate cancer (any grade) at any age</td>
</tr>
<tr>
<td>c. Ashkenazi Jewish ancestry</td>
<td>c. Ashkenazi Jewish ancestry</td>
</tr>
<tr>
<td>Any cancer and a mutation identified on somatic tumor genomic testing that has clinical implications if also identified in the germline.</td>
<td>Any cancer and a mutation identified on somatic tumor genomic testing that has clinical implications if also identified in the germline.</td>
</tr>
<tr>
<td>E. An affected or unaffected individual with a first or second degree blood relative meeting any of the criteria above as documented by the requesting provider.</td>
<td>E. An affected or unaffected individual with a first or second degree blood relative meeting any of the criteria above as documented by the requesting provider.</td>
</tr>
</tbody>
</table>

**Individuals Without Cancer or With any Other Personal History of Cancer (not noted above)**

*(See Policy Guidelines section: Testing Unaffected Individuals.)*

II. Genetic testing for BRCA1, BRCA2, and PALB2 variants of individuals either without cancer or any other type of cancer not noted above (including cancer related to hereditary breast ovarian cancer syndrome but not meeting above criteria, or cancers unrelated to hereditary breast ovarian cancer syndrome) may be considered medically necessary under any of the following circumstances:

A. Has a probability of greater than 5% of a BRCA1/2 or PALB2 pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, PennII) as documented by the requesting provider.

B. Individuals (with or without a history of cancer) with any close blood relative with a known pathogenic/likely pathogenic
<table>
<thead>
<tr>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POLICY STATEMENT</strong></td>
<td><strong>POLICY STATEMENT</strong></td>
</tr>
<tr>
<td><strong>variant in a cancer susceptibility gene (included in the small panel).</strong></td>
<td><strong>variant in a cancer susceptibility gene (included in the small panel).</strong></td>
</tr>
<tr>
<td><strong>C.</strong> An affected or unaffected individual with a first or second degree blood relative meeting any of the criteria in the “Individuals with cancer…” section above and as documented by the requesting provider.</td>
<td><strong>C.</strong> An affected or unaffected individual with a first or second degree blood relative meeting any of the criteria in the “Individuals with cancer…” section above and as documented by the requesting provider.</td>
</tr>
<tr>
<td><strong>III.</strong> Genetic testing for <em>BRCA1</em>, <em>BRCA2</em>, and <em>PALB2</em> variants in cancer-affected individuals or of cancer-unaffected individuals with or without a family history of cancer when criteria above are not met (including genetic screening in the general population) is considered <strong>investigational</strong>.</td>
<td><strong>III.</strong> Genetic testing for <em>BRCA1</em>, <em>BRCA2</em>, and <em>PALB2</em> variants in cancer-affected individuals or of cancer-unaffected individuals with or without a family history of cancer when criteria above are not met (including genetic screening in the general population) is considered <strong>investigational</strong>.</td>
</tr>
<tr>
<td><strong>IV.</strong> Genetic testing in minors (younger than age 18) for <em>BRCA1</em>, <em>BRCA2</em>, and <em>PALB2</em> variants is considered <strong>investigational</strong>.</td>
<td><strong>IV.</strong> Genetic testing in minors (younger than age 18) for <em>BRCA1</em>, <em>BRCA2</em>, and <em>PALB2</em> variants is considered <strong>investigational</strong>.</td>
</tr>
<tr>
<td><strong>Confirmatory BRCA Testing</strong></td>
<td><strong>Confirmatory BRCA Testing</strong></td>
</tr>
<tr>
<td><strong>V.</strong> Confirmatory BRCA testing may be considered <strong>medically necessary</strong> for individuals who underwent over-the-counter (OTC) U.S. Food and Drug Administration (FDA) approved genetic screening and were found to have a pathogenic <em>BRCA1</em> or <em>BRCA2</em> mutation (including one of the three Ashkenazi founder mutations).</td>
<td><strong>V.</strong> Confirmatory BRCA testing may be considered <strong>medically necessary</strong> for individuals who underwent over-the-counter (OTC) U.S. Food and Drug Administration (FDA) approved genetic screening and were found to have a pathogenic <em>BRCA1</em> or <em>BRCA2</em> mutation (including one of the three Ashkenazi founder mutations).</td>
</tr>
<tr>
<td><strong>VI.</strong> Large multi-gene panels including multiple genes that are not highly associated with hereditary breast and ovarian cancer (see Policy Guidelines) are considered <strong>investigational</strong>.</td>
<td><strong>VI.</strong> Large multi-gene panels including multiple genes that are not highly associated with hereditary breast and ovarian cancer (see Policy Guidelines) are considered <strong>investigational</strong>.</td>
</tr>
</tbody>
</table>