2.04.02	Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)		
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Section:	2.0 Medicine	**Page:**	Page 1 of 39

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 (see Policy Guidelines) 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
   D. Personal history of **one or more** of the following at any age:
      1. Male breast cancer
      2. Epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer)
      3. Exocrine pancreatic cancer
      4. Metastatic or intraductal/cribriform histology prostate cancer or high-risk group or very-high-risk group prostate cancer
      5. Prostate cancer with **one or more** of the following:
         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
         b. Two or more close blood relatives with breast or prostate cancer (any grade) at any age
         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.

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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 *BRCA*1, *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

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- 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.

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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.

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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)

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- **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:** BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
- **81216:** BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
- **81217:** BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
- **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

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- 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).[21,]

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

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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).

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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).[22,] 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.[23,] 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.[24,] 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.[25,] 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*.[8,11,26,27,] However, a genotyping study of Ashkenazi

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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).[27,] 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.[28,] 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.[29,] 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%.30, 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*.[23,] Table 1 lists the results from several additional studies measuring the presence of *BRCA* variants among patients with ovarian cancer.[31,32,33,34,35,] One study noted that variant prevalence was higher for women in their 40s (24%) and for women with serous ovarian cancer (18%).[31,] Ethnicity was another risk factor for *BRCA*, with higher rates seen in women of Italian (43.5%), Jewish (30%), and Indo-Pakistani (29.4%) origin.[31,]

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

Study	Population	N	*BRCA* Variant, n (%)	
			BRCA1	*BRCA2*
Harter et al (2017)[35,]	Patients with invasive ovarian cancer across 20 medical centers	523	81 (15.5)	29 (5.5)
Kurian et al (2017)[32,]	Patients with invasive ovarian cancer tested for hereditary cancer risk from a commercial laboratory database	5020[a]	255 (15.5)	199 (5.5)
Langer et al (2016)[33,]	Patients with ovarian cancer tested for hereditary cancer risk from a commercial laboratory database	3088	153 (4.9)	124 (4.0)
Norquist et al (2016)[34,]	Patients with invasive ovarian cancer, from 2 phase 3 clinical trials and a gynecologic oncology tissue bank	1915	182 (9.5)	98 (5.1)
Zhang et al (2011)[31,]	Patients with invasive ovarian cancer	1342	107 (8.0)	67 (5.0)

[a] 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.[36,] 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.[37,] Among 15 women with invasive carcinoma

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(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.[38,] Table 2 lists the results from several studies measuring the presence of BRCA variants among patients with pancreatic adenocarcinoma.[39,40,41,42,43,44,] 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 2. *BRCA* Variant Rates in Patients With Pancreatic Cancer

Study	Population	N	*BRCA* Variant, n (%)	
			BRCA1	*BRCA2*
Hu et al (2018)[44,a]	Patients with pancreatic adenocarcinoma from a prospective pancreatic cancer registry	3030	18 (0.6)	59 (1.9)
Yurgelun et al (2018)[43,]	Patients with pancreatic adenocarcinoma from 3 medical centers	289	3 (1.0)	4 (1.4)
Shindo et al (2017)[42,]	Patients with pancreatic adenocarcinoma from 1 medical center	854	3 (0.3)	12 (1.4)
Holter et al (2015)[41,]	Patients with pancreatic adenocarcinoma from a large academic health care complex	306	3 (1.0)	11 (3.6)
Ferrone et al (2009)[40,]	Jewish patients with pancreatic adenocarcinoma from 1 hospital	145	2 (1.3)	6 (4.1)
Couch et al (2007)[39,]	Probands from high-risk families identified through pancreatic cancer clinics and a pancreatic tumor registry	180		10 (5.5)

[a] Case-control study; rates for *BRCA1* and *BRCA2* variants in controls were 0.2 and 0.3, respectively.

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.[45,46,47,]

Table 3. *BRCA* Variant Rates in Patients With Prostate Cancer

Study	Population	N	*BRCA* Variant, n (%)	
			BRCA1	*BRCA2*
Abida et al (2017)[47,]	Patients with prostate cancer from 1 clinical practice	221	2 (1)	20 (9)
Pritchard et al (2016)[46,]	Patients with metastatic prostate cancer from 7 case series across multiple centers	692	6 (0.9)	37 (5.3)
Edwards et al (2003)[45,]	Patients with prostate cancer diagnosed before age 56 from 2 cancer study groups	263		6 (2.3)

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*.[48,] 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*.

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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%.[49,] 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.[50,]

Knowledge of variant status in individuals at potentially increased risk of a *BRCA* variant may impact health care decisions to reduce risk.[51,52,53,54,55,56,57,] 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%.[52,] Prophylactic oophorectomy significantly reduces the risk of ovarian cancer by 80% or more[55,56,58,] and reduces the risk of breast cancer by approximately 50%.[56,] In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse.[42,] Prophylactic oophorectomy or salpingo-oophorectomy in women with *BRCA1* or *BRCA2* reduced the risk of all-cause mortality by 60% to 77%.[58,59,] 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.[60,]

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.[61,62,63,] Studies have indicated that the results of genotyping significantly influenced treatment choices.[53,64,57,]
In a systematic review for the USPSTF, Nelson et al (2019) assessed the efficacy of risk-reducing surgery in *BRCA*-positive women.[50,] 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

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unknown whether *BRCA* 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 *BRCA* variant carriers and 95 control patients.[65,] 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.

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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.[66,] 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.[18,17,19,20,67,68,69,70,71,72,73,] Study designs included family segregation[67,74,], kin-cohort,[17,] family-based case-control,[19,69,75,] and population-based or multicenter case-control.[18,20,68,70,71,72,73,] The 2 multinational studies included individuals from up to 5 of the single-country studies.[17,71,] 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.

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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).

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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.[18,] 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.[19,] 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 thier 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.[68,] 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.[74,] 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.[71,] 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

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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.[17] 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

Study	Year	Country	Design	N	Families	*PALB2* Variants		Totals		Pathogenic Variants Identified	
						Cases	Controls	Cases	Controls	N	Prevalence Cases, %
Woodward et al[73,]	2021	U.K.	Single-center CC	4694		35	3	3127	1567	NR	1.12
Li et al (BEACCON)[75,]	2021	Australia	Family-based CC	3892		144	98	1990	1902	NR	2.49
Yang et al[74,]	2020	Multinational	Multicenter family segregation	17,906	524	976	NR	NR	NR	976	5.5
Lu et al[72,]	2019	U.S.	Multicenter CC	15,404		61	NR	15,532	3988	NR	0.4
Thompson et al[70,]	2015	Australia	Population-based CC	3994		26	4	1996	1998	19	1.3
Cybulski et al[20,]	2015	Poland	Population-based CC[f]	17,231		116	10	12,529	4702	2	0.9
Catucci et al[18,a,b]	2014	Italy	Population-based CC	590[e]		6	2	113	477	1 (c.1027C>T)	5.3
Heikkinen et al[68,,a,b]	2009	Finland	Population-based CC	2026		19	2	947	1079	1 (c.1592delT)	2.0
Casadei et al[19,a]	2011	U.S.	Family-based CC[d]	1042		31	0	959	83	13	3.2

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Study	Year	Country	Design	N	Families	*PALB2* Variants		Totals		Pathogenic Variants Identified	
Rahman et al[69,a,b]	2007	U.K.	Family-based CC	2007	923	10	0	923	1084	5	1.1
Erkko et al[67,a,b]	2008	Finland	Family segregation	213	17[c]	17	?			1 (c.1592delT)	
Antoniou et al[17,]	2014	Multinational	Kin-cohort	2980	154	229	82	542	2438	48	
Southey et al[71,]	2016	Multinational	Mutlicenter CC	84,835		35	6	42,671	42,164	1 (c.1592delT)	
						44	8			1 (c.3113G>A)	
Kurian et al[32,]	2017	U.S.	CC	95,561		257	NR	26,384	Unclear	NR	0.97

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*

Study	Year	Analysis	RR or OR (95% CI)	Penetrance at Age 70 years (95% CI), %	Mean (Median) Age Onset, y	Triple-Negative Tumors, %	
						PALB2+	*PALB2*-
Woodward et al[73,]	2021	Standard CC	5.90 (1.92 to 18.36)				
Li et al (BEACCON)[75,]	2021	Standard CC	3.47 (1.92 to 6.65)			27.6	
Yang et al[74,]	2019	Segregation	7.18 (5.82 to 8.85)	52.8 (43.7 to 62.7)[d]	NR	NR	NR
Lu et al[72,]	2019	Standard CC	5.5 (2.2 to 17.7)				
Antoniou et al[17,]	2014	Segregation[b]	6.6 (4.6 to 9.2)[c]	47.5 (38.6 to 57.4)[e]		30	
Erkko et al[67,]	2008	Segregation	6.1 (2.2 to 17.2)[a]	40 (17 to 77)	54.3 (+FH); 59.3 (FH unavailable)		
Rahman et al[69,]	2007	Segregation[b]	2.3 (1.4 to 3.9)[f]		46 (IQR, 40 to 51)		
Casadei et al[19,]	2011	Relative risk	2.3 (1.5 to 4.2)[g]		50.0 (SD, 11.9)		
Thompson et al[70,]	2015	Standard CC	6.6 (2.3 to 18.9)				
Cybulski et al[20,]	2015	Standard CC	4.4 (2.3 to 8.4)		53.3	34.4	14.4
Catucci et al[18,]	2014	Standard CC	13.4 (2.7 to 67.4)				
Heikkinen et al[68,]	2009	Standard CC	11.0 (2.6 to 97.8)		53.1 (95% CI, 33.4 to 79.9)	54.5	9.4, 12.2[h]
Southey et al[71,]	2016	Standard CC	4.5 (1.9 to 10.8) (c.1592delT)				
			5.9 (2.8 to 12.7) (c.3113G>A)				
Kurian et al[32,]	2017	Standard CC	3.39 (2.79 to 4.12)				

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.

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[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

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Woodward et al (2021)[73],	4. Case-control population of breast cancer patients referred for genetic testing (and controls), likely overestimated risk				
Li et al (2021) (BEACCON)[75],	4. Case-control population of familial BRCA 1/2 negative breast cancer patients (and controls)				
Yang et al (2019)[74],	4. No case-control group	1. Not clear which variants were included			
Lu et al (2019)[72],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk	1. Not clear which variants were included			
Kurian et al (2017)[32],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk	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)[71],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk				
Thompson et al (2015)[70],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk				
Cybulski et al (2015)[20],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk				
Catucci et al (2014)[18],	4. Case-control population of breast cancer patients referred for genetic testing (and controls), likely overestimated risk				
Antoniou et al (2014)[17],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk; only kin-cohort included				

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Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Casadei et al (2011)[19],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk				
Heikkinen et al (2009)[68],	4. Case-control population of breast cancer patients referred for genetic testing (and controls), likely overestimated risk				
Erkko et al (2008)[67],	4. No case-control group				
Rahman et al (2007)[69],	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.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Table 7. Study Design and Conduct Limitations of Individuals Studies of Pathogenic *PALB2* Variants

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Woodward et al (2021)[73],	1. Incomplete description of how controls selected					
Li et al (2021) (BEACCON)[75],				1. Registration not reported	1. No description of disposition of eligible patients/samples	
Yang et al (2019)[74],	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)[72],	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Kurian et al (2017)[32],				1. Registration not reported	1. No description of disposition of eligible patients/samples	
Southey et al (2016)[71],				1. Registration not reported		
Thompson et al (2015)[70],	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Cybulski et al (2015)[20],	1. Incomplete description of how controls selected			1. Registration not reported		

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Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Catucci et al (2015)[18,]	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Antoniou et al (2014)[17,]	2. Kin-cohort-controls not randomized					
Casadei et al (2011)[19,]	2. Family groups: controls not randomized			1. Registration not reported		
Heikkinen et al (2009)[68,]	1. Incomplete description of how controls selected			1. Registration not reported		
Erkko et al (2008)[67,]	2. Family groups: selection not randomized			1. Registration not reported; number of controls unknown		
Rahman et al (2007)[69,]	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.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] 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.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] 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.
[f] 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.[78,] 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

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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[79,] (e.g., starting at an early age, the addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention,[80,] and prophylactic mastectomy.[81,] 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,[82,] 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.[83,84,] Compared with surveillance, a 30-year-old *BRCA* 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).[83,] 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.[84,]

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

Risk Level and Strategy	Age of Carrier, years			
	30	40	50	60
40% risk of breast cancer				
Mastectomy	2.9	2.0	1.0	0.2
Mastectomy delayed 10 years	1.8	0.8	0.1	0.0
60% risk of breast cancer				
Mastectomy	4.1	2.9	1.6	0.3
Mastectomy delayed 10 years	2.4	1.1	0.1	0.0
85% risk of breast cancer				
Mastectomy	5.3	3.7	2.3	0.5
Mastectomy delayed 10 years	2.6	1.1	0.1	0.1

Adapted from Schrag et al (1997).[83,]

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 *BRCA* 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 cancer by age 70 years, increasing to 28.7% if she carries a *PALB2* variant.

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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

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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,]

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,]

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,] 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

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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.[92,] 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)[93,] 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

NCT No.	Trial Name	Planned Enrollment	Completion Date (status if beyond Completion Date)
Ongoing			
NCT04009148	Cascade Testing in Families With Newly Diagnosed Hereditary Breast and Ovarian Cancer Syndrome	300	Mar 2025
NCT03246841	Investigation of Tumour Spectrum, Penetrance and Clinical Utility of Germline Mutations in New Breast and Ovarian Cancer Susceptibility Genes (TUMOSPEC)	500	Dec 2024
NCT02321228	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)	510	Jan 2035
NCT05420064	Effective Familial OutReach Via Tele-genetics (EfFORT): A Sustainable Model to Expand Access to MSK's Genetic Services	896	Nov 2026

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

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Ethnicity/Ancestry
  - Personal and/or family history of cancer (if applicable) including:

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        - 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.

Type	Code	Description
CPT®	0102U	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])
	0103U	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])
	0129U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
	0131U	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)
	0132U	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)

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Type	Code	Description
	0135U	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)
	0138U	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)
	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
	81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
	81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81307	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence
	81308	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic 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);

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Type	Code	Description
		duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
	81479	Unlisted molecular pathology proceduregermlin
HCPCS	None	

Policy History

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

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

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Effective Date	Action
11/01/2019	Administrative Update
04/01/2020	Annual review. No change to policy statement. Literature review updated.
06/01/2020	Administrative update. Policy statement and guidelines updated. Coding Update.
07/01/2020	Administrative update. Policy statement and guidelines updated.
08/01/2020	Coding Update
01/01/2021	Annual review. Policy statement, guidelines and literature updated.
02/01/2021	Administrative update.
04/01/2021	Annual review. Policy statement and guidelines updated.
01/01/2022	Annual review. Policy statement, guidelines and literature updated. Policy title changed from Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers to current one.
03/01/2022	Annual review. Policy statement, guidelines and literature updated.
10/01/2022	Annual review. Policy statement, guidelines and literature updated. Policy title changed from Germline Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers to current one.
12/01/2022	Annual review. Policy statement, guidelines and literature updated.
11/01/2023	Annual review. No change to policy statement. Literature review updated.

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.

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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.

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Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER**
Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2) 2.04.02 **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)*** **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)	**Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2) 2.04.02** **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)

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POLICY STATEMENT	
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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 (see Policy Guidelines) 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 D. Personal history of **one or more** of the following at any age: 1. Male breast cancer 2. Epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer)	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 (see Policy Guidelines) 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 D. Personal history of **one or more** of the following at any age: 1. Male breast cancer 2. Epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer)

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3. Exocrine pancreatic cancer 4. Metastatic or intraductal/cribriform histology prostate cancer or high-risk group or very-high-risk group prostate cancer 5. Prostate cancer with **one or more** of the following: 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 b. Two or more close blood relatives with breast or prostate cancer (any grade) at any age 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.	3. Exocrine pancreatic cancer 4. Metastatic or intraductal/cribriform histology prostate cancer or high-risk group or very-high-risk group prostate cancer 5. Prostate cancer with **one or more** of the following: 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 b. Two or more close blood relatives with breast or prostate cancer (any grade) at any age 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	**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

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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.	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 *BRCA*1, *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**.	III. Genetic testing for *BRCA*1, *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**.	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).	**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**.	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**.

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