Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Germline Genetic Testing for BRCA1, BRCA2, and PALB2 for Hereditary Breast/Ovarian Cancer Syndrome and Associated High-Risk Cancers

Description/Background

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Several genetic syndromes with an autosomal dominant pattern of inheritance that increase the risk of breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary site-specific breast cancer have in common causative variants in *BRCA* (**Br**east **Ca**ncer susceptibility) genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma and laryngeal cancer occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early onset breast cancer with or without male cases, but without ovarian cancer. For this policy, both will be referred to collectively as hereditary breast and/or ovarian cancer.

Germline variants in the *BRCA1* and *BRCA2* genes are responsible for the cancer susceptibility in the majority of HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, *BRCA* variants are responsible for only a proportion of affected families. *BRCA* gene variants are inherited in an autosomal dominant fashion through either the maternal or the paternal lineage. It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases, and to identify family members with increased cancer risk. Family members without existing cancer who are found to have BRCA variants can consider preventive interventions for reducing risk and mortality.

Evidence suggests that genetic services are not equitably applied. Chapman-Davis et al (2021) found that non-Hispanic Whites and Asians were more likely to be referred for genetic services based solely on family history than were non-Hispanic Blacks and Hispanics. [1] In addition, non-Hispanic Black patients and Hispanic patients were more likely to have advanced cancer when referred for genetic services than non-Hispanic Whites and Asians.

Clinical Features Suggestive of BRCA Variant

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for *BRCA1* variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30.[2] In several studies, *BRCA* variants were independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years).[2-5] In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s.[6] In the Ashkenazi Jewish population, Frank et al (2002) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had *BRCA* variants.[3] In a similar study by Gershoni-Baruch et al (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had *BRCA* variants.[6] Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of *BRCA* variants in the absence of family history in this population.[8,9,10]

As in the general population, a family history of breast or ovarian cancer, particularly of early age onset, is a significant risk factor for a *BRCA* variant in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12% to 31% will have a *BRCA* variant depending on the extent and nature of the family history.[5] Several other studies have documented the significant influence of family history.[7,8,9,10,11]

In patients with “triple-negative” breast cancer (i.e., negative for expression of estrogen, progesterone, and overexpression of human epidermal growth factor receptor 2 receptors), there is an increased prevalence of *BRCA* variants. Pathophysiologic research has suggested that the physiologic pathway for the development of triple-negative breast cancer is similar to that for *BRCA*-associated breast cancer.[12] In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, Kandel et al (2006) reported that there was a greater than 3-fold increase in the expected rate of *BRCA* variants.[13] *BRCA1* variants were found in 39.1% of patients and *BRCA2* variants in 8.7%. Young et al (2009) studied 54 women with high-grade, triple-negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for *BRCA* testing.[14] Six *BRCA* variants (5 *BRCA1*, 1 *BRCA2*) were found, for a variant rate of 11%. Finally, Gonzalez-Angulo et al (2011) in a study of 77 patients with triple-negative breast cancer, reported that 15 patients (19.5%) had *BRCA* variants (12 in *BRCA1*, 3 in *BRCA2*).[15]

PALB2 Gene

The *PALB2* gene (partner and localizer of *BRCA2*) encodes for a protein first described in 2006.[16] The gene is located at 16p12.2 [Short (p) arm of chromosome 16 at position 12.2.] and has 13 exons. PALB2 protein assists *BRCA2* in DNA repair and tumor suppression. Heterozygous pathogenic *PALB2* variants increase the risk of developing breast and pancreatic cancers; homozygous variants are found in Fanconi anemia. Fanconi anemia is a rare disorder, primarily affecting children, that causes bone marrow failure. Affected individuals also carry a risk of cancers including leukemia. Most pathogenic *PALB2* variants are truncating

frameshift or stop codons, and are found throughout the gene. Pathogenic *PALB2* variants are uncommon in unselected populations and prevalence varies by ethnicity and family history. For example, Antoniou et al (2014) assumed a prevalence of 8 per 10,000 in the general population when modeling breast cancer risks. [17] Variants are more prevalent in ethnic populations where founder mutations have persisted (eg, Finns, French Canadians, Poles), while infrequently found in others (eg, Ashkenazi Jews). [18,19] In women with a family history of breast cancer, the prevalence of pathogenic *PALB2* variants ranges between 0.9% and 3.9%, [17] or substantially higher than in an unselected general population. Depending on population prevalence, *PALB2* may be responsible for as much as 2.4% of hereditary breast cancers [17]; and in populations with founder mutations cause 0.5% to 1% of all breast cancers. [20]

Possible Testing Strategies (Not to be used as strict guidelines)
Individuals who meet criteria for genetic testing as outlined in this policy should be tested for variants in *BRCA1, BRCA2, and PALB2.* Testing strategies than can be used 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 for a positive test result. Unless the affected individual is a member of an ethnic group for which particular founder pathogenic or likely pathogenic variants are known, comprehensive genetic testing (*i.e.,* full sequencing of the genes and detection of large gene rearrangements) should be performed.
    - If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1*/*BRCA2* variants (e.g., prostate cancer, pancreatic cancer, melanoma).
    - If no familial variant can be identified, two possible testing strategies are:
        - Full sequencing followed by testing for large genomic rearrangements (deletions/duplications) only if sequencing detects no variant (negative result).
            - More than 90% of *BRCA* variants will be detected by full sequencing.
        - Alternatively, simultaneous full sequencing and testing for large genomic rearrangements (also known as comprehensive *BRCA* testing; see Comprehensive Variant Analysis, below) may be performed as is recommended by NCCN.
            - Comprehensive testing can detect 92.5% of *BRCA1/BRCA2* variants.

- Ashkenazi Jewish descent
    - In individuals of known Ashkenazi Jewish descent, one approach is to test for the 3 known founder mutations (185delAG and 5182insC in BRCA1; 6174delT in BRCA2) first; if testing is negative for founder mutations and if the individual's ancestry also included non-Ashkenazi ethnicity (or if other BRCA1/2 testing criteria are met), comprehensive genetic testing should be considered.

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

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

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.

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 may be given 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 patients with known *BRCA or PALB2* variants may therefore consider more aggressive screening approaches for prostate cancer.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

REGULATORY STATUS

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.

MEDICAL POLICY STATEMENT

Simultaneous or individual testing for inherited *BRCA1*, *BRCA2, and PALB2* variants have been established. It is considered a useful option when criteria are met.

The following multi-gene panels represented by BreastNext, OvaNext, BRCAPlus, and BROCA tests are experimental/investigational. There is insufficient data on the analytical and clinical validity as well as clinical utility of these tests on individual management and outcomes.

Inclusionary and Exclusionary Guidelines

The National Comprehensive Cancer Network (NCCN) provides criteria for genetic risk evaluation for individuals with no history or breast cancer and for those with a breast cancer. Updated versions of the criteria are available on the NCCN website.

The framework for using the inclusionary guidelines below are as follow:

- For the purpose of this policy close blood relatives include 1st-, 2nd-, and 3rd-degree relatives that are blood relatives on the same side of the family (maternal or paternal), such as:
  - 1st-degree relatives, which are parents, siblings, and children.
  - 2nd-degree relatives, which are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
  - 3rd-degree relatives, which are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.
- For the purpose of this policy high-risk and very-high-risk prostate cancer groups are defined as follows:
  - 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.

Inclusions:

For purposes of this policy invasive and ductal carcinoma in situ breast cancers should be included.

Testing for BRCA1 or BRCA2 or PALB2 is clinically indicated in the following scenarios:

- Individuals with any close blood relative with any one of the known pathogenic/likely pathogenic gene variant.
- Individuals meeting the criteria below but who tested negative with previous limited testing (*e.g.*, single gene and/or absent deletion duplication analysis) who are interested in multi-gene testing.

- A pathogenic or likely pathogenic (P/LP) variant identified on tumor genomic testing that has clinical implications if also identified in the germline.
- To aid in systemic therapy and surgical decision-making (e.g., PARP inhibitors for ovarian cancer, prostate cancer, pancreatic cancer, and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer and pancreatic cancer; and risk-reducing surgery).

Genetic testing for *BRCA1*, *BRCA2, and PALB2* variants in individuals may be considered appropriate under any of the following circumstances:

- History of **epithelial ovarian cancer** and **ANY** of the following:
  - Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
  - Family history of epithelial ovarian cancer only:
    - An individual unaffected with ovarian cancer with a first- or second-degree blood relative with epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age.

      OR
    - An individual unaffected with ovarian cancer who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* P/LP variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk).

- Personal history of **pancreatic cancer** and **ANY** of the following:
  - Diagnosis of exocrine pancreatic cancer and **one** of the following
    - All individuals diagnosed with exocrine pancreatic cancer; **OR**
    - First-degree relatives of individuals diagnosed with exocrine pancreatic cancer.

      OR
  - Diagnosis of neuroendocrine pancreatic tumor where a mutation is identified on tumor genomic testing that has clinical implications if also identified in the germline (e.g., BRCA1, BRCA2, and PALB2 testing).

- Personal history of **breast cancer** and **ANY** of the following:
  - Diagnosed age ≤50 years; **OR**
  - Diagnosed at any age with **ANY** of the following:
    - Treatment indications:
      - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting; **OR**
      - To aid in adjuvant treatment decisions with Olaparib for high-risk, HER2-negative breast cancer.

    - Pathology/histology:
      - Triple-negative breast cancer; **OR**
      - Multiple primary breast cancers (synchronous or metachronous); **OR**
      - Lobular breast cancer with personal or family history of diffuse gastric cancer.
    - Male breast cancer
    - Ancestry: Ashkenazi Jewish ancestry
    - Family history of **ANY** of the following:

- ≥1 close blood relative with **ANY**:
  - Breast cancer diagnosed ≤50 years; **OR**
  - Male breast cancer any age; **OR**
  - Ovarian cancer any age; **OR**
  - Prostate cancer with metastatic, or high- or very high-risk group any age, **OR**
  - Pancreatic cancer any age**.**

OR

- ≥3 diagnoses of breast cancer and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer.

OR

- Family history of breast cancer only:
  - Individuals affected with breast cancer (not meeting the criteria above) or unaffected individual with breast cancer with a 1st - or 2nd -degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).

OR

  - Individuals affected or unaffected with breast cancer who otherwise do not meet the criteria above but have a probability >5% of a BRCA1/2 pathogenic/likely pathogenetic variant based on prior probability testing models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk).

Genetic testing for BRCA1 and BRCA2 variants in individuals may be considered appropriate under any of the following circumstances:

- Personal history of **prostate cancer** and **ANY** of the following:
  - By tumor characteristics (any age)
    - Metastatic (Stage IVB) or node-positive (Stage IVA) prostate cancer; **OR**
    - Histology
      – high- or very-high-risk group.

OR

  - By family history and ancestry
    - ≥1 close blood relative with **ANY**:
      – Breast cancer at age ≤50 years; **OR**
      – Triple-negative breast cancer at any age; **OR**
      – Male breast cancer at any age; **OR**
      – Ovarian cancer at any age; **OR**
      – Pancreatic cancer at any age; **OR**
      – Metastatic, node positive, high-, or very-high-risk prostate cancer at any age.

OR

    - ≥3 close blood relatives with prostate cancer (any grade) and/or breast cancer on the same side of the family including the patient with prostate cancer; **OR**
    - Ashkenazi Jewish ancestry

OR

- Family history of prostate cancer only:

- An affected (not meeting testing criteria listed above) or unaffected individual with a first-degree blood relative meeting any of the criteria listed (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).

It is highly recommended that genetic testing should be performed in a setting that has suitably trained healthcare providers who can give appropriate pre- and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments (CLIA)-licensed laboratory that offers comprehensive variant analysis.

Exclusions:

- Patients not meeting any of the above criteria.
- Genetic testing for *BRCA1*, *BRCA2, and PALB2* variants in minors (under 18 years of age).
- BRCA testing as a screening test for cancer in women in the general population.
- BRCA testing for unaffected individuals of high-risk populations (e.g., Ashkenazi Jewish descendant) *who have no relatives* with a history of breast, ovarian, fallopian tube or primary peritoneal cancer at any age.
- Multi-gene panels represented by BreastNext, OvaNext, BRCAPlus, and BROCA tests.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81162	81163	81164	81165	81166	81167
81212	81215	81216	81217	81307	81308
81432	81479**				

Other codes (investigational, not medically necessary, etc.):

81479**	0102U	0103U	0129U

*** 81479 is established when used to report only duplication/deletion analysis panel for hereditary breast cancer-related disorders. 81479 is experimental/investigational in all other situations including when used to represent BROCA testing or any other panel testing not represented by 81432.*

Note: Complete sequencing analyses, represented by the codes above for either BRCA1 or BRCA 2 alone are seldom done in the clinical setting.

RATIONALE

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

This review was informed by a TEC Assessment (1997). [21]

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.

TESTING FOR BRCA1 AND BRCA2 VARIANTS IN INDIVIDUALS AT RISK FOR HEREDITARY BREAST/OVARIAN CANCER SYNDROME AND ASSOCIATED 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 are individuals with cancer (i.e., breast cancer, epithelial ovarian, fallopian tube, primary peritoneal cancer), or individuals with a personal or family history of cancer, or patients who meet certain criteria that might suggest they are at risk of hereditary breast/ovarian cancer 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.

Comparator

The comparator of interest is the withholding of genetic testing for HBOC syndrome

Outcomes

The outcomes of interest are overall survival, disease-specific (breast and ovarian cancer) survival, test accuracy and validity, and quality of life (e.g., anxiety).

Study Selection Criteria

For the evaluation of clinical validity, studies of variant prevalence and cancer risk were included. For the evaluation of clinical utility, studies that represent the intended clinical use of the technology in the intended population were included. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings.

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

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). Studies have focused on identifying the population.

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. 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 *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 overall survival 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=0.034).[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-analysis estimates of the prevalence and penetrance of *BRCA* variants; in order to update the U.S. Preventive Services Task Force (USPSTF) recommendation for risk assessment, genetic counseling, and genetic testing for BRCA-related cancer.[23] The authors selected 70 articles to address five key questions. *BRCA* prevalence and penetrance were estimated to assess clinical validity of variant testing. 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 is tested, and 70% for *BRCA1* and 71% for *BRCA2* when multiple family members are tested; cumulative risks for developing ovarian cancer by age 70 years were 41% for *BRCA1* and 17% for *BRCA2* when a single family member is tested, and 46% for *BRCA1* and 23% for *BRCA2* when multiple family members are 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 included meta-analytic estimates of *BRCA* prevalence in their 2013 systematic 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 extensive history of disease, have been as high as 85%. For example, Kuchenbaecher 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 variants in

ethnic populations (e.g., Ashkenazi Jewish, Polish, and Icelandic populations) unselected for family history indicated lower penetrance estimates, in the range of 40–60% for *BRCA1* and 25–40% for *BRCA2*.[8,11,26,27] However, a genotyping study of Ashkenazi Jewish women with incident, invasive breast cancer, selected regardless of family history of cancer, and their family members resulted in an 82% lifetime risk of breast cancer for carriers of any of 3 *BRCA* founder variants (185delAG, 5382insC, and 6174delT).[27] Importantly, the risk of cancer in variant carriers from families with little history of cancer (≈50% of all carriers) was not significantly different. Lifetime risks 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 one prospective study by Metcalfe et al (2004) the risk was 29.5% at 10 years for women with initial stage I or II disease.[28] In a 2013 prospective study (EMBRACE), the cumulative risk of contralateral breast cancer by age 70 years was 83% in *BRCA1* variant carriers and 62% for *BRCA2* variant carriers.[29] These investigators also reported cumulative risks of breast cancer by age 70 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 results from several additional studies measuring the presence of BRCA variants among patients with ovarian cancer.[31-35] 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	2088	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 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%) were found to have fallopian tube malignancies. The authors noted that this supports 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 to14 years]) followed 32 *BRCA* variant carriers with occult malignancy (4 ovarian, 23 fallopian tube, and 5 ovarian and fallopian tube) diagnosed at prophylactic salpingo-oophorectomy.[37] Among 15 women with invasive carcinoma (median age 50 years), 7 (47%) experienced recurrence at a median of 33 months, and overall survival was 73%. Among 17 women with noninvasive neoplasia (median age, 53 years), 4 (24%) received chemotherapy, none of whom experienced recurrence. One patient (6%) who did not receive chemotherapy experienced recurrence at 43 months. Overall survival 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 Associated with Pancreatic Cancer

Unaffected individuals may also 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- to10-fold over the general population.[38] Table 2 lists results from several studies measuring the presence of BRCA variants among patients with pancreatic adenocarcinoma.[39-44] 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
Hue 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 different 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.[45-47]

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 one of these genes. For example, in 2006 Walsh and colleagues 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*.[46] These patients underwent screening with additional multiple DNA-based and RNA-based methods. Of these 300 patients, 17% carried previously undetected variants, including 35 (12%) with genomic rearrangement of *BRCA1* or *BRCA2*.

A 2008 study by Palma et al evaluated 251 patients with an estimated *BRCA* variant using the Myriad II model of 10% or greater.[49] In the 136 non-Ashkenazi Jewish probands, 36 (26%) had *BRCA* point variants and 8 (6%) had genomic rearrangements, 7 in *BRCA1* and 1 in *BRCA2*. No genomic rearrangements were identified in the 115 Ashkenazi Jewish probands, but 47 of the 115 (40%) had point variants. In this population genomic rearrangements constituted 18% of all identified *BRCA* variants. The authors also indicated that the estimated prevalence of a variant was not predictive of 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. 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.[51-57] 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 to observation in women with *BRCA1* and *BRCA2* variants demonstrate contralateral prophylactic mastectomy in women with breast cancer are associated with significantly lower all-cause mortality while bilateral prophylactic mastectomy was not associated with all-cause mortality.[61-63] Studies have indicated that the results of genotyping has a significant influence on treatment choices.[53,64,57]

In a systematic review for USPSTF, Nelson et al (2019) assessed efficacy of risk-reducing surgery in *BRCA*-positive women.[50] 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% and 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 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 the authors observed whether *BRCA* variant testing reduces cause-specific or all-cause mortality and improves quality of life is currently unknown. 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 IMPACT study (2011) evaluated the results of screening in 205 men 40-69 years of age who were *BRCA* variant carriers and 95 control patients.[65] At the baseline screen, biopsies were performed in 7.0% of patients with a prostate-specific antigen (PSA) greater than 3.0, 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 normal risk men. In addition, 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/Ovarian Cancer Syndrome and Associated 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.

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 (eg, triple-negative disease, young age) increase the likelihood that the breast cancer is hereditary. Testing may also be considered for women from families with known variants.

The relevant population of interest for this review are individuals who are undergoing assessment for HBOC syndrome.

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

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

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

Study Selection Criteria

For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Included a suitable reference standard
- Patient/sample clinical characteristics were described with women at high breast cancer risk
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Systematic Reviews
Suszynska et al (2019) reported a systematic review of variants identified in panels of breast and ovarian cancer-related genes. [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, 95,853patients 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 (RR) 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 from1 (founder mutations examined) to 48 (Table 4). Studies conducted from single-country samples are described first followed by the 2 multinational collaborative efforts.

Single-Country Samples

Woodward et al (2021) assessed the contribution of *PALB2* gene variants to familial breast and ovarian cancer. [73] A total of3127 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 Life Pool 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 (ie, 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 Life Pool study (n=1998) who were recruited for a mammography screening program. All *PALB2* coding exons were sequenced by next-generation sequencing and novel variants verified by Sanger sequencing. Large deletions or rearrangements were not evaluated. Nineteen distinct pathogenic variants were identified, including 6 not previously described in 26 (1.3%) cases and in 4 (0.2%) controls with an odds for breast cancer of 6.58 (95% CI, 2.3 to 18.9). Moreover, 54 missense variants identified were slightly more common in cases (OR, 1.15; 95% CI, 1.02 to 1.32).

Cybulski et al (2015) examined 2 loss-of-function *PALB2* variants (c.509_510delGA, c.172_175delTTGT) in women with invasive breast cancer diagnosed between 1996 and 2012 in Poland. [20] From 12,529 genotyped women, a *PALB2* variant was identified in 116 (0.93%) cases (95% CI, 0.76% to 1.09%) versus 10 (0.21%, 95% CI, 0.08% to 0.34%) of 4702 controls (OR, 4.39; 95% CI, 2.30 to 8.37). A *BRCA1* variant was identified in 3.47% of women with breast cancer and in 0.47% of controls (OR, 7.65; 95% CI, 4.98 to 11.75). Authors estimated that a *PALB2* sequence variant conferred a 24% cumulative risk of breast cancer by age 75 years (in the setting of age-adjusted breast cancer rates slightly more than half that in the U.K. [76] or the U.S. [77]). A *PALB2* variant was also associated with poorer prognosis: 10-year survival of 48.0% versus 74.7%when the variant was absent (HR adjusted for prognostic factors, 2.27; 95% CI, 1.64 to 3.15).

Catucci et al (2014) performed population-based case-control studies in Italy (Milan or Bergamo) among women at risk for hereditary breast cancer and no *BRCA1* or *BRCA2* variant. [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 of113 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 to4.2) by age 55 years and 3.4-fold (95% CI, 2.4 to 5.9) by age 85 years. Mean age at diagnosis was not associated with the presence of a variant (50.0 years with vs. 50.2 years without). Casadei et al (2011) provided few details of their analyses. Additionally, participants reported over 30 ancestries and, given intermarriage in the U.S. population, stratification may have had an impact on results. Generalizability of the risk estimate is therefore unclear.

Heikkinen et al (2009) conducted a population-based case-control study at a Finnish university hospital employing 2 case groups (947 familial and 1274 sporadic breast cancers) and 1079 controls. [68] The study sample was obtained from 542patients 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; 1missense 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 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 and145 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 50years, 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
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. 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				
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		
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 (ie, convenience).b Blinding key: 1. Not blinded to results of reference or other comparator tests. cTest 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 2013and 2016. The women were referred by their health care providers for clinical suspicion of hereditary cancer. It is unclear what proportion of the women met professional society criteria for genetic testing for breast cancer risk; baseline information regarding family history was not reported. Of the women in the database, 893 had *PALB2* variants and were eligible for Claus assessment to estimate the risk of breast cancer. Approximately 27% of women with *PALB2* variants would have had an estimated risk of breast cancer of 20% or higher based on the Claus model. The report did not include health outcomes and it is unclear whether enhanced screening in women who had a moderate penetrance variant but did not have an estimated risk of breast cancer of 20% or greater based on the Claus model would have improved health outcomes from enhanced surveillance.

Studies of women at high-risk based on family history alone or in those with *BRCA1* and *BRCA2* variants are relevant to the clinical utility of *PALB2* testing given the penetrance estimates for *PALB2* and related molecular mechanism ("BRCA-ness"). Interventions to decrease breast cancer risk in asymptomatic high-risk women include screening [79] (eg, 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 2.9years 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 age70 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 50years, has an estimated 11.7% risk of contralateral cancer by age 70 years, increasing to 28.7% if she carries a *PALB2* variant.

Evidence concerning preventive interventions in women with *PALB2* variants is indirect, relying on studies of high-risk women and *BRCA* carriers. In women at high-risk of hereditary breast cancer who would consider preventive interventions, identifying a *PALB2* variant provides a more accurate estimated risk of developing breast cancer compared with family history alone and can offer a better understanding of benefits and potential harms of interventions.

SUMMARY OF EVIDENCE

For individuals who have cancer or a personal or family cancer history and meet criteria suggesting a risk of hereditary breast and ovarian cancer syndrome (HBOC) syndrome who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes a TEC Assessment and studies of variant prevalence and cancer risk. Relevant outcomes are overall survival (OS), disease-specific survival, test validity and quality of life (QOL). The accuracy of

variant testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a *BRCA* variant have shown a risk as high as 85%. Knowledge of *BRCA* variant status in individuals at risk of a *BRCA* variant may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. In individuals with *BRCA1* or *BRCA2* variants, prophylactic mastectomy and oophorectomy have been found to significantly increase disease-specific survival and overall survival. Knowledge of BRCA variant status in individuals diagnosed with breast cancer may impact treatment decisions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have associated high-risk cancers (e.g., cancers of the fallopian tube, pancreas, prostate) who receive genetic testing for a BRCA1 or BRCA2 variant, the evidence includes studies of variant prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. The accuracy of variant testing has been shown to be high. Knowledge of BRCA variant status in individuals with associated high-risk cancers can inform decisions regarding genetic counseling, chemotherapy, and enrollment in clinical trials. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a risk of HBOC syndrome who receive genetic testing for a *PALB2* variant, the evidence includes studies of clinical validity and studies of breast cancer risk, including a meta-analysis. Relevant outcomes are OS, disease-specific survival, and test validity. Evidence supporting clinical validity was obtained from numerous studies reporting relative risks (RRs) or odds ratios (ORs). Study designs included family segregation, kin-cohort, family-based case-control, and population-based case-control. The number of pathogenic variants identified in studies varied from 1 (founder mutations) to 48. The relative risk for breast cancer associated with a *PALB2* variant ranged from 2.3 to 13.4, with the 2 family-based studies reporting the lowest values. Evidence of preventive interventions in women with *PALB2* variants is indirect, relying on studies of high-risk women and *BRCA* carriers. These interventions include screening with magnetic resonance imaging, chemoprevention, and risk-reducing mastectomy. Given the penetrance of *PALB2* variants, the outcomes following bilateral and contralateral risk-reducing mastectomy examined in women with a family history consistent with hereditary breast cancer (including *BRCA1*and *BRCA2* carriers) can be applied to women with *PALB2* variants, with the benefit-to-risk balance affected by penetrance. In women at high-risk of hereditary breast cancer who would consider risk-reducing interventions, identifying a *PALB2* variant provides a more precise estimated risk of developing breast cancer compared with family history alone and can offer women a more accurate understanding of benefits and potential harms of any intervention. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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
Ongoing			
NCT04009148	Cascade Testing in Families With Newly Diagnosed Hereditary Breast and Ovarian Cancer Syndrome	120	Oct 2025

NCT03246841	Investigation of tumour spectrum, penetrance and clinical utility of germline mutations in new breast and ovarian cancer susceptibility genes	500	Dec 2024
NCT02321228	Early salpingectomy (tubectomy) with delayed 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	2590	Nov 2026

NCT: national clinical trial

SUPPLEMENTAL INFORMATION

Clinical Input Received through 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 through three physician specialty societies (5 reviewers) and three academic medical centers (5 reviewers) while this policy was under review for January 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 additional 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.

American Society of Clinical Oncology

In 2024, the American Society of Clinical Oncology (ASCO) published a guideline on germline testing in patients with breast cancer.[85] The guideline recommends BRCA1 and BRCA2 testing for all patients with breast cancer who are younger than 65 years of age, and some patients over age 65 years (including those who are eligible for poly-ADP ribose polymerase [PARP] inhibitor therapy). Patients with a history of breast cancer may also be candidates for BRCA1 and BRCA2 testing if it would help determine their personal and family risk. Testing for other high-penetrance genes (i.e., PALB2, TP53, PTEN, STK11, and CDH1) may be appropriate for some patients.

In 2024, ASCO also published a guideline on germline genetic testing in patients with cancer. Genes with a strong testing recommendation are those that confer a higher cancer risk or are highly actionable. For breast cancer, the more strongly recommended genes for testing and inclusion in multigene panels are: BRCA1, BRCA2, PALB2, CDH1, PTEN, STK11, and TP53. Of these, CDH1, PTEN, STK11, and TP53 are associated with specific syndromes and can be excluded from testing if personal or family history do not suggest an increased risk of the syndrome.[86] For epithelial ovarian cancer, the more strongly recommended genes are: BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, RAD51C, and RAD51D. Testing for BRCA1 and BRCA2 is also strongly recommended for pancreatic adenocarcinoma and prostate cancer, and testing for PALB2 is strongly recommended for pancreatic adenocarcinoma. The authors note including BRCA1, BRCA2, and Lynch syndrome genes (i.e., MLH1, MSH2, MSH6, PMS2, and EPCAM) in multigene panels for any patient with cancer is reasonable due to their importance and prevalence.

National Comprehensive Cancer Network

Breast Cancer and Ovarian Cancer
Current National Comprehensive Cancer Network (NCCN) guidelines on genetic and familial high-risk assessment of breast, ovarian, and pancreatic cancers (v.2.2025) include criteria for identifying individuals who should be referred for further risk assessment, and separate criteria for genetic testing.[87] 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,STK11, and TP53. Use of "tailored panels that are disease-focused and include clinically actionable cancer susceptibility genes is preferred over large panels that include genes of uncertain clinical relevance".

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

BRCA1 and *BRCA2* somatic variants are uncommon. The National Comprehensive Cancer Network 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.3.2024) recommend tumor molecular testing prior to initiation of therapy for persistent/recurrent disease (OV-6) and describe in multiple algorithms that testing should include at least *BRCA1/2* and microsatellite instability or DNA mismatch repair, and evaluation of homologous recombination deficiency can be considered (OV-6, OV-7, OV-B Principles of Pathology, OV-C Principles of Systemic Therapy).[88]

Pancreatic Adenocarcinoma and Pancreatic Neuroendocrine Tumors
Current NCCN guidelines for pancreatic adenocarcinoma (v.3.2024) 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 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.”[89]

The NCCN guidelines for genetic and familial high-risk assessment of breast, ovarian, and pancreatic cancers (v.2.2025) includes that germline testing is clinically indicated for individuals with neuroendocrine pancreatic cancers per the NCCN guidelines on neuroendocrine and adrenal tumors. The NCCN guidelines for neuroendocrine and adrenal tumors (v.2.2024) 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." [90]

Prostate Cancer
The current NCCN guidelines for prostate cancer are version 4.2024.[91] 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. [92] 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 National Comprehensive Cancer Network (NCCN) guideline criteria. The guidelines also note that variants of uncertain significance are not clinically actionable.

Society of Gynecologic Oncology
In 2015, Society of Gynecologic Oncology (SGO) published an evidence-based consensus statement on risk assessment for inherited gynecologic cancer.[93] The statement includes criteria for recommending genetic assessment (counseling with or without testing) to patients who may be genetically predisposed to breast or ovarian cancer. Overall, SGO and NCCN recommendations align. Differences are: exclusion of women with breast cancer onset at age 50 years or younger who have one or more first-, second-, or third-degree relatives with breast cancer at any age; women with breast cancer of 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. SGO additionally recommends genetic assessment for unaffected women who have a male relative with breast cancer. SGO allows that some patients who do not satisfy criteria may still benefit from genetic assessment, e.g., few female relatives, hysterectomy or oophorectomy at a young age in multiple family members, or adoption in the lineage.

American College of Obstetricians and Gynecologists
The American College of Obstetricians and Gynecologists published a practice bulletin in 2017 (reaffirmed 2021) on hereditary breast and ovarian cancer syndrome.[94] The following recommendation was based primarily on consensus and expert opinion (level C): “Genetic testing is recommended when the results of a detailed risk assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management.”

U.S. Preventive Services Task Force
Current U.S. Preventative Services Task Force (USPSTF) recommendations (2019) for genetic testing of *BRCA1* and *BRCA2* variants in women state: [95]

“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 designed to identify a family history that may be associated with an increased risk for potentially harmful variants in *BRCA1* or *BRCA2* include:

- 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

Government Regulations
National:
There is no CMS National Coverage Determination (NCD) for genetic testing for breast cancer.

Local:
LCD L36813 **Retired on 8/20/2022**.

Wisconsin Physicians Service Insurance Corporation MolDx Program has determined that *BRCA1*/*BRCA2* targeted mutation analysis (familial or founder mutation), sequencing with common deletion/duplication analysis, and uncommon deletion/duplication analysis meets Medicare criteria for a covered service.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing-Assays of Genetic Expression in Tumor Tissue as a Technique to Help Guide Decision-Making in Patients with Breast Cancer
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
- Genetic Testing- NGS of Multiple Genes (Panel) for Solid and Hematolymphoid Malignant Conditions
- Genetic Testing for CHEK2 Mutations for Breast Cancer retired 1/1/20 and replaced with policy Moderate Penetrance Variants associated with Breast Cancer in Individuals at High Breast Cancer Risk. This policies title changed to Germline Genetic Testing for Gene Variants Associated with Breast Cancer in Individuals at Moderate and High Breast Cancer Risk (e.g., CHEK2, ATM, BARD1, etc.)
- Genetic Testing for Li-Fraumeni Syndrome
- Genetic Testing for PTEN Hamartoma Tumor Syndrome
- Germline Genetic Testing for Gene Variants Associated with Breast Cancer in Individuals at Moderate and High Breast Cancer Risk (e.g., CHEK2, ATM, BARD1, etc.)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
6/23/03	6/23/03	7/7/03	Joint medical policy established
7/20/04	7/20/04	8/5/04	Routine maintenance
9/7/05	9/7/05	9/1/05	Routine maintenance
5/1/07	2/10/07	2/1/07	Routine maintenance
11/1/08	8/19/08	9/23/08	Routine maintenance
5/1/09	2/10/09	2/10/09	Updated policy to reflect the fact that S3818 and S3819 are never done individually and are thus considered not medically necessary.
5/1/11	2/15/11	3/3/11	Combined the policy on "Genetic Testing for BRAC Analysis Rearrangement (BART)" into this policy; added information on CHEK2 testing. Updated references and added NOC code for BART testing. Policy title changed from "Genetic Testing for Hereditary Breast and/or Ovarian Cancer (BRCA Testing)" to "Genetic Testing for Inherited Breast and/or Ovarian Cancer"
11/1/11	8/16/11	8/16/11	Clarified inclusionary guidelines for BRCA testing for affected individuals. Genetic counseling changed from "required" to "strongly recommended." Added criteria for non-affected women with breast cancer at an early age but no high risk family history.
5/1/12	2/21/12	2/21/12	New codes added, 81211-81217
5/1/12	5/1/12	7/9/12	Corrected inclusionary guidelines to indicate that BRCA testing is appropriate in cancer-affected individuals with ovarian cancer of any age, without a family history consistent with being "high-risk." Maintained last effective date.
5/1/13	2/19/13	3/4/13	Routine update. Guidelines and rationale updated to mirror BCBSA.

7/1/14	4/8/14	4/15/14	Routine update. Title changed from "Genetic Testing for Inherited Breast and/or Ovarian Cancer" to "Genetic Testing for Hereditary Breast and/or Ovarian Cancer, Including Multigene Panels." Updated NCCN guidelines.
1/1/16	10/13/15	10/27/15	Policy title changed from "Genetic Testing for Hereditary Breast and/or Ovarian Cancer, Including Multigene Panels" to "Genetic Testing for Hereditary Breast and/or Ovarian Cancer **Syndrome (*BRCA1*/*BRCA2*)** Including Multigene Panels."
1/1/17	10/11/16	10/11/16	Removed all materials related to CHEK2. Routine policy maintenance.
3/1/17	12/13/16	12/13/16	Added codes 81662, 81432 and 81433.
3/1/18	12/12/17	12/12/17	Rationale updated, few references removed, added # 3, 12, 45 and 46. Policy statement updated to reflect changes to NCCN recommendation.
3/1/19	12/11/18		• "mutation(s)" changed to "variant(s)" throughout document • Policy Inclusion/Exclusion section updated to reflect changes to NCCN recommendation and BCBSA update. • An indication was added for "individuals with other high-risk cancers such as cancers of the ovary, fallopian tubes, pancreas and prostate". • Policy title was changed to fit the other changes. • Medicaid section deleted • References 28-31, 34-37, 40-42, 67 and 69 added. • Codes (81163-81167) added. Codes (81212, 81215-81217) revised and codes 81211, 81213 and 81214 deleted.
3/1/20	12/17/19		Routine policy maintenance, no change in policy status.

3/1/21	12/15/20		Rationale updated, references added, created a separate indication for the previous content on use of BRCA1 and BRCA2 variant testing in individuals with HBOC Syndrome or other high-risk cancers considering systemic therapy options. NCCN guidelines updated. Minor edits made to policy statements and policy guidelines to reflect current NCCN guidelines. 11/3/21: correction added bullet “personal history of ovarian cancer” under inclusions as this was inadvertently left off.
3/1/22	12/14/21		Inclusion statement regarding genetic testing for systemic therapy options updated to include individuals with high-risk, early stage breast cancer. • Personal history of cancer and to aid in systemic therapy decision-making, such as for PARP-inhibitors for human epidermal receptor 2 (HER2)-**negative early stage, high-risk breast cancer,** ovarian cancer, prostate cancer, pancreatic cancer; platinum therapy for prostate cancer and pancreatic cancer Other minor edits made to policy statements and policy guidelines to reflect current NCCN guidelines. 11/3/21, added in bullet “personal history of ovarian cancer” under inclusions as this was inadvertently left off. Updated this statement to reflect what is in BCBSA’s policy: • Personal history of epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer) at any age References updated Updates made to the Inclusions section under - Patients with Cancer

			or With A Personal History of Cancer (affected patients) based BCBSA updates and on NCCN guideline Version 1.2022 – August 11, 2021.
3/1/23	12/20/22		• Routine maintenance • Inclusion statement updated based on NCCN Guidelines V1.2023 – September 7, 2022 Hereditary Cancer Testing Criteria. • Added the below about NCCN guideline under the Inclusionary/Exclusionary Guidelines section: • Criteria for Genetic Risk Evaluation • The National Comprehensive Cancer Network (NCCN) provides criteria for genetic risk evaluation for individuals with no history or breast cancer and for those with a breast cancer. Updated versions of the criteria are available on the NCCN website. • Per BCBSA's update from 1/13/22: Section on BRCA1 and BRCA2 Variants to Guide Systemic Therapy Decisions in Individuals with HBOC Syndrome or Other High-Risk Cancers removed this JUMP policy. BCBSA added this section to BCBSA's policy 2.04.151 - Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer. • Per BCBSA's update from 8/1/22: Revised and added PALB2 PICO previously found in BCBSA's Policy 2.04.126 and JUMP policy: GENE VARIANTS ASSOCIATED WITH BREAST CANCER IN

			INDIVIDUALS AT HIGH BREAST CANCER RISK eff 5.1.22. • Added the codes 81307, 81308, 81406 under EST from the above JUMP policy. • Title changed to "Germline Genetic Testing for BRCA1, BRCA2, and PALB2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers from Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers. " Policy statements updated to include PALB2 information. • Per BCBSA's update on 10/13/22: Removed content on use of BRCA1 and BRCA2 testing in prostate and ovarian cancer-affected individuals considering systemic therapy. This content is addressed separately in evidence reviews 2.04.155 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, Microsatellite Instability/Mismatch Repair, Tumor Mutational Burden) and 2.04.156 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, Tumor Mutational Burden, Microsatellite

			Instability/Mismatch Repair). (ky)
3/1/24	1/5/24		Routine maintenance Inclusion section updated based on NCCN Guidelines V2.2024 – September 27, 2023 Hereditary Cancer Testing Criteria under the Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Removed Chek2 from code 81479. Vendor: N/A (ky) Post JUMP changes: • Per discussion at JUMP, moved codes 81432 and 81433 from E/I to EST. • Updated MPS to read: The following multi-gene panels represented by BreastNext, OvaNext, BRCAPlus, and BROCA tests are experimental/investigational. There is insufficient data on the analytical and clinical validity as well as clinical utility of these tests on patient management and outcomes. • Updated Exclusions to read: Multi-gene panels represented by BreastNext, OvaNext, BRCAPlus, and BROCA tests. • Added 18 years of age to the below exclusion: o Genetic testing for BRCA1, BRCA2, and PALB2 variants in minors (under 18 years of age). • Updated asterisk to read: **81479 is experimental/investigational when used to bill BROCA testing or any other panel testing not represented by 81432 or 81433. • Removed (Use for OvaNext, BreastNext, BRCAplus, or BROCA testing) after code 81479 nomenclature.

			• Added codes BreastNext (0102U), OvaNext (0103U), and BRCAPlus (0129U) under E/I. These codes are on the PLA policy under E/I. (ky)
3/1/25	12/17/24		• Routine Maintenance • Code 81432 revised EFD 1/1/25. • Added Associated and deleted other to title of policy. New title now called: Germline Genetic Testing for BRCA1, BRCA2, and PALB2 for Hereditary Breast/Ovarian Cancer Syndrome and Associated High-Risk Cancers • Inclusions section personal history of prostate cancer updated based on NCCN Guidelines V2.2025 – November 7, 2024 Hereditary Cancer Testing Criteria under the Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate except for statement regard triple-negative breast cancer. NCCN removed we will keep this statement as the support for it still remains in NCCN. • Updated MPS to read as follow: Simultaneous testing for inherited BRCA1, BRCA2, and PALB2 variants have been established. It is considered a useful option when criteria are met. • Testing for genomic rearrangements of BRCA 1 and BRCA2 genes discussed in Comprehensive Variant Analysis under Description/Background section. Removed MPS: Testing for genomic rearrangements of the BRCA1 and BRCA2 genes [e.g., the BRACAnalysis Large

			Rearrangement (BART) testing] may be considered established in patients who meet criteria for BRCA1 and BRCA2 testing and whose testing for point variants is negative. • Removed BART from the exclusion statements as BART testing is now part of the immediate testing as standard of care. • Vendor: N/A Post JUMP changes/comments: • Remove code 81406 from the policy representing PALB2 as there is a code for PALB2. •Added or individuals to first MPS bullet. •Under Inclusions updated and to or in the first set of inclusionary guidelines: BRCA1 or BRCA2 or PALB2. • Code 81433 was removed from the policy as this code will be deleted effective 1/1/25. • Added code 81479** under established. • Updated ** 81479 is established when used to report only duplication/deletion analysis panel for hereditary breast cancer-related disorders. 81479 is experimental/investigational in all other situations including when used to represent BROCA testing or any other panel testing not represented by 81432. (ky)

Next Review Date: 4th Qtr. 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: 10/12/98	Revised: 5/8/01
BCBSM: N/A	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GERMLINE GENETIC TESTING FOR BRCA1, BRCA2, AND PALB2 FOR HEREDITARY BREAST/OVARIAN CANCER SYNDROME AND ASSOCIATED HIGH-RISK CANCERS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service. Codes 81432 & 81433 are listed under “non-covered genomic sequencing procedures and other molecular analyte assays”. These codes are considered not medically necessary.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member’s certificate and is not guaranteed. Please consult the individual member’s certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.