2.04.126	Gene Variants (PALB2, CHEK2 and ATM) Associated with Breast Cancer in Individuals at High Breast Cancer Risk		
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Section:	2.0 Medicine	**Page:**	Page 1 of 41

Policy Statement

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

Individual testing for *PALB2* variants for breast cancer risk assessment in adults who meet **both** of the following criteria may be considered **medically necessary:**

I. The individual meets criteria for genetic risk evaluation
II. The individual has undergone testing for sequence variants in BRCA1 and BRCA2 with negative results

When being initially tested for at the same time as BRCA1 and BRCA2 (and when criteria is met for such testing), the small panel 81432 should be used (see Policy Guidelines) rather than individual or sequential gene testing

Testing for *PALB2* sequence variants in individuals who do not meet the criteria outlined above is considered **investigational**.

Individual or large panel testing for *CHEK2* and *ATM* variants when not included as part of an approved small panel in the assessment of breast cancer risk is considered **investigational.**

NOTE: Germline genetic testing for BRCA1 and BRCA2 is addressed separately in Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers

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

Policy Guidelines

When part of a limited panel that meets criteria for medical necessity under another policy (e.g., 2.04.02 Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers, or 2.04.08 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes), the inclusion of PALB2, CHEK2, ATM, or other genes is allowed.

Criteria for Genetic Risk Evaluation

The National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer provides criteria for genetic risk evaluation for individuals without and with breast cancer. However, the recommended testing strategy for *BRCA1* and *BRCA2* is described in Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers.

Table PG1. NCCN Criteria for Genetic Risk Evaluation of an Individual without a History of Breast Cancer[3]

Individual without a History of Breast Cancer
• First- or second-degree relative with any of the following:

Individual without a History of Breast Cancer
o Breast cancer less than or equal to 45 years o Ovarian cancer o Male breast cancer o Pancreatic cancer o Metastatic prostate cancer o Greater than or equal to 2 breast cancer primaries in a single individual o Greater than or equal to 2 individuals with breast cancer primaries on the same side of family with at least one diagnosed less than or equal to 50 years
• Family history on the same side of the family of three or more of the following (especially if diagnosed age less than or equal to 50 years; can include multiple primary cancers in the same individual): o Breast cancer, sarcoma, adrenocortical carcinoma, brain tumor, leukemia o Colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, macrocephaly, hamartomatous polyps of gastrointestinal tract o Lobular breast cancer, diffuse gastric cancer o Breast cancer, gastrointestinal cancer or hamartomatous polyps, ovarian sex chord tumors, pancreatic cancer, testicular sertoli cell tumors, or childhood skin pigmentation

Table PG2. NCCN Criteria for Genetic Risk Evaluation of an Individual with Breast Cancer[3]

Individual with Breast Cancer
• An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene within the family, including such variants found on research testing
• An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene found on tumor testing
• An individual diagnosed at any age with any of the following: o Ovarian cancer o Pancreatic cancer o Metastatic prostate cancer o Breast cancer or high-grade (Gleason score greater than or equal to 7) prostate cancer and of Ashkenazi Jewish ancestry
• An individual with a breast cancer diagnosis meeting any of the following: o Breast cancer diagnosed age less than or equal to 50 years o Triple-negative (ER-, PR-, HER2-) breast cancer diagnosed less than or equal to 60 years o Two breast cancer primaries o Breast cancer at any age and: ▪ Greater than or equal to 1 close blood relative with breast cancer age less than or equal to 50 years, or ▪ Greater than or equal to 1 close blood relative with invasive ovarian cancer, or ▪ Greater than or equal to 1 close blood relative with male breast cancer, or ▪ Greater than or equal to 1 close blood relative with pancreatic cancer, or ▪ Greater than or equal to 1 close blood relative with high-grade (Gleason score greater than or equal to 7) or metastatic prostate cancer, or ▪ Greater than or equal to 2 close blood relatives with breast cancer at any age
• An individual with a personal and/or family history on the same side of the family of three or more of the following (especially if diagnosed age less than or equal to 50 years; can include multiple primary cancers in the same individual): o Breast cancer, sarcoma, adrenocortical carcinoma, brain tumor, leukemia o Colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, macrocephaly, hamartomatous polyps of gastrointestinal tract o Lobular breast cancer, diffuse gastric cancer o Breast cancer, gastrointestinal cancer or hamartomatous polyps, ovarian sex chord tumors, pancreatic cancer, testicular sertoli cell tumors, or childhood skin pigmentation

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; PR: progesterone receptor.

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.

Coding

The following new CPT codes describe partner and localizer gene analysis for *PALB2* testing:

- **81307**: *PALB2* (partner and localizer of *BRCA2*) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence
- **81308**: *PALB2* (partner and localizer of *BRCA2*) (e.g., breast and pancreatic cancer) gene analysis; known familial variant

Testing for *ATM* variants is included in CPT tier 2 molecular pathology:

- **81408**: Molecular Pathology Procedure Level 9 – which includes *ATM (ataxia telangiectasia mutated)* (e.g., ataxia telangiectasia), full gene sequence

There is no specific CPT code for testing for *CHEK2* variants. It is likely reported using the unlisted molecular pathology code 81479.

Description

It is estimated that 3% to 5% of women presenting for assessment for hereditary breast/ovarian cancer risk have a variant in a gene that moderately increases the risk of cancer. *PALB2, CHEK2*, and *ATM* variants are considered to be of moderate penetrance. Carriers of *PALB2* have an approximately 2- to 13-fold increased risk of developing breast cancer compared with the general population, and risk for *CHEK2* and *ATM* carriers is increased approximately 2- to 4-fold. Risk estimates may be higher in patients with a family history of breast cancer or a family history of a specific variant.

Related Policies

- Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer

Benefit Application

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

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

Regulatory Status

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. *PALB2, CHEK2*, *and ATM* testing are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories offering to test and voluntarily listing is available through the National Center for Biotechnology Genetic Testing Registry. 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 has chosen not to require any regulatory review of this test.

Customized next-generation sequencing panels provide simultaneous analysis of multiple cancer predisposition genes, and typically include both moderate- and high-penetrant genes.

Rationale

Background

Breast Cancer and Genetics

In 2021, researchers estimated breast cancer would be diagnosed in 281550 women and 43600 would die from the disease; a woman's lifetime risk is 12.6%.[1] Breast cancers can be classified as sporadic, familial, or hereditary. Most breast cancers are sporadic (70% to 75%), occurring in women without a family history of the disease. Familial cancers (15% to 25%) aggregate within families but lack clearly discernable patterns of inheritance and are likely polygenic. Hereditary cancers have discernable inheritance patterns, often occur at younger ages, may be bilateral, and comprise between 5% and 10% of breast cancers. For women who inherit a pathogenic *BRCA1* and *BRCA2* variant, 45% to 72% will develop breast cancer by 70-80 years of age.,[2] Pathogenic variants in other highly penetrant genes (e.g., *TP53*, *CDH1*, *PTEN*, *STK11*) contribute to a smaller number of cancer cases.

Testing for *BRCA1/BRCA2* is addressed in Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers.

Testing for mismatch repair genes linked to Lynch syndrome is addressed in Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes.

Penetrance of Pathogenic Variants

Penetrance is the risk conferred by a pathogenic variant or the proportion of individuals with the variant expected to develop cancer. Variant penetrance is considered high, moderate, or low according to lifetime risk: high (>50%), moderate (20% to 50%), and low (<20%) (corresponding relative risks of approximately ≥5, 1.5 to 5, and <1.5).[3] Variants in only a few breast cancer-susceptibility genes (*BRCA1* and *BRCA2* [hereditary breast/ovarian cancer syndrome], *TP53* [Li-Fraumeni syndrome], *PTEN* [Cowden syndrome], *CDH1* [hereditary diffuse gastric cancer], *STK11* [Peutz-Jeghers syndrome]) are considered highly penetrant. For example, a woman with a *BRCA1* or *BRCA2* variant has a relative risk of 11 to 12 compared with the general population.[4] Penetrance can be modified by environmental factors and by family history, which is a particularly important modifier for low and moderate penetrance genes. Moreover, specific pathogenic variants within a gene may confer somewhat different risks.

Determining Variant Pathogenicity

Determining the pathogenicity of variants in a more commonly detected cancer susceptibility gene (e.g., founder sequence mutations) is generally straightforward because associations are repeatedly observed. For uncommonly identified variants, such as those found in a few individuals or families, defining pathogenicity can be more difficult. For example, predicting the pathogenicity of previously unidentified variants typically requires in silico (computational) analysis predicting protein structure/function, evolutionary conservation, and splice site prediction.[5] The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines.[5] Still, distinctions between a variant of uncertain significance and a pathogenic one from different laboratories may not always be identical.[6]

Genes Associated With a Moderate-to-High Penetrance of Breast Cancer

PALB2 Gene

The *PALB2* gene (partner and localizer of *BRCA2*) encodes for a protein first described in 2006.[7] 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 10000 in the general population when modeling breast cancer risks.[8] Variants are more prevalent in ethnic populations where founder mutations have persisted (e.g., Finns, French Canadians, Poles), while infrequently found in others (e.g., in Ashkenazi Jews[9,10]). In women with a family history of breast cancer, the prevalence of pathogenic *PALB2* variants ranges between 0.9% and 3.9%,[8] 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[8]; and in populations with founder mutations cause 0.5% to 1% of all breast cancers.[11]

CHEK2 Gene

The *CHEK2* (checkpoint kinase 2) gene is activated in response to DNA double-strand breakage and plays a role in cell-cycle control, DNA repair, and apoptosis.

In 2002, a single recurrent truncating variant in the *CHEK2* gene (c.1100delC) was first reported as a cause of breast cancer, and studies have since confirmed this. The incidence of *CHEK2* variants varies widely among populations. It is most prevalent in Eastern and Northern Europe, where the population frequency of the c.1100delC allele ranges from 0.5% to 1.4%; the allele is less frequent in North America and virtually absent in Spain and India.

Although most data for truncating *CHEK2* variants are limited to the c.1100delC allele, 3 other founder mutations of *CHEK2* (IVS2+1G>A, del5395, I157T) have been associated with breast cancer in Eastern Europe. Both IVS2+1G>A and del5395 are protein-truncating variants, and I157T is a missense variant. The truncating variants are associated with breast cancer in the Slavic populations of Poland, Belarus, Russia, and the Czech Republic. The I157T variant has a wider geographic distribution and has been reported to be associated with breast cancer in Poland, Finland, Germany, and Belarus.[12]

ATM Gene

ATM (ataxia-telangiectasia mutated), located on chromosome 11q22.3, is associated with the autosomal recessive condition ataxia-telangiectasia syndrome. This condition is characterized by progressive cerebellar ataxia with onset between the ages of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition. Female *ATM* heterozygotes carriers have a risk of breast cancer about twice as high as that of the general population; however, they do not appear to have an elevated ovarian cancer risk.

Identifying Women at Risk of an Inherited Susceptibility to Breast Cancer

Breast cancer risk can be affected by genetic and nongenetic factors. The risk is increased in women experiencing an earlier age at menarche, nulliparity, late age of first pregnancy, fewer births, late menopause, proliferative breast disease, menopausal hormone therapy, alcohol, obesity, inactivity, and radiation.[13] A family history of breast cancer confers between a 2- and 4-fold increased risk varying by several factors: the number and closeness of affected relatives, age at which cancers developed, whether breast cancers were bilateral and if other cancers occurred (e.g., ovarian).[14] For a woman without breast cancer, the probability of detecting a pathogenic variant can be estimated from a detailed multigenerational pedigree (e.g., Breast

and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm),[15] screening tools (e.g., BRCAPRO,[16] Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen[17,18]), or by referring to guidelines that define specific family history criteria (see Supplemental Information section on Practice Guidelines and Position Statements). For women with breast cancer, family history also affects the likelihood of carrying a pathogenic variant.[15]

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

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

***PALB2* and Breast Cancer Risk Assessment**
Clinical Context and Test Purpose
The purpose of testing for *PALB2* variants in women at high-risk of hereditary breast cancer/ ovarian cancer (HBOC) is to evaluate whether an abnormal variant is present and, if so, to determine whether the variant conveys a sufficiently high-risk such that changes in surveillance and/or treatment that are likely to decrease the risk of mortality from breast cancer are warranted.

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

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

The question addressed in this evidence review is: Does genetic testing for *PALB2* variants improve the net health outcome in women at high-risk of HBOC?

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

Populations
Genetic testing can be considered for women at increased risk of developing hereditary breast cancer based on their family history or in women with breast cancer whose family history or cancer characteristics (e.g., triple-negative disease, young age) increase the likelihood that the breast cancer is hereditary. Testing may also be considered for women from families with known variants.

The relevant population of interest for this review are patients 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 with no *PALB2* genetic testing.

Outcomes
The outcomes of interest are overall survival (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.[19] Results were reported for *PALB2, CHEK2,* and *ATM. CHEK2* and *ATM* results will be discussed in the following sections. The systematic review included studies published through July 2017 reporting on genetic test results of breast and ovarian cancer patients who were referred for evaluation by a multi-gene panel. Given that the Suszynska et al (2019) report included only studies reporting on test results from a panel, it does not substantially overlap with the studies described in the following section including other *PALB2* association studies. The studies of panel results were used to calculate mutation frequencies by the gene. As a control, population mutation frequencies were extracted from the Genome Aggregation Database. Forty-three studies included panels in breast cancer patients. In the breast cancer studies, 95,853 patients were included in the analysis of *PALB2. PALB2* variants were identified in 0.9% of breast cancer patients. The meta-analytic estimate odds ratio (OR) of the association between *PALB2* variants and risk of breast cancer was OR=4.8 (95% confidence interval [CI], 4.1 to 5.6).

Observational Studies
A number of studies (Tables 1 and 2) reporting relative risks (RR) or ORs for the association between *PALB2* and breast cancer were identified.[8,9,10,11,20,21,22,23,24,25,] Study designs included family segregation,[20,26,] kin-cohort,[8,] family-based case-control,[10,22,27,]and population-based or multicenter case-control.[9,11,21,23,24,25,] The 2 multinational studies included individuals from up to 5 of the single-country studies.[8,24,] The number of pathogenic variants identified varied from 1 (founder mutations examined) to 48 (Table 1). Studies conducted from single-country samples are described first followed by the 2 multinational collaborative efforts.

Single-Country Samples
Li et al (2021) assessed the association between 14 known genes associated with HBOC 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.[27,] The initial assessment in 3892 women was conducted with targeted gene panel sequencing, followed by assessment of 145 candidate genes and 14 known HBOC genes in a sample of 3780 BRCA 1and BRCA 2-negative families and 3839 controls. Index cases were identified from Familial Cancer Centers and a Pathology center in Australia and controls were identified from the LifePool mammography screening study.

Lu et al (2019) included an analysis of 11,416 patients with breast cancer and/or ovarian cancer who were referred for genetic testing from 1200 U.S. hospitals and clinics and of 3988 controls referred for genetic testing for noncancer conditions between 2014 and 2015.[25] 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.[28] Although the country is not stated, the patients underwent testing between 2013 and 2015 performed at a Clinical Laboratory Improvement Amendments (CLIA) laboratory and thus will be assumed to include patients from the U.S. Cases were women with a single diagnosis of breast or ovarian cancer. Controls were women from the same database (i.e., being tested for hereditary cancer) with no cancer history at the time of genetic testing. The multivariable models for breast cancer risk are reported here. Among the breast cancer patients, 244 (0.92%) had a PALB2 variant. The association between PALB2 and breast cancer adjusting for age, ancestry, personal and family cancer histories, and Lynch and adenomatous polyposis colon cancer syndromes was OR=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.[23] A control group was accrued from participants in the LifePool study (n=1998) who were recruited for a mammography screening program. All *PALB2* coding exons were sequenced by next-generation sequencing and novel variants verified by Sanger sequencing. Large deletions or rearrangements were not evaluated. Nineteen distinct pathogenic variants were identified, including 6 not previously described in 26 (1.3%) cases and in 4 (0.2%) controls with an odds for breast cancer of 6.58 (95% CI, 2.3 to 18.9). Moreover, 54 missense variants identified were slightly more common in cases (OR=1.15; 95% CI, 1.02 to 1.32).

Cybulski et al (2015) examined 2 loss-of-function *PALB2* variants (c.509_510delGA, c.172_175delTTGT) in women with invasive breast cancer diagnosed between 1996 and 2012 in Poland.[11] 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 (in the setting of age-adjusted breast cancer rates slightly more than half that in the U.K.[29] or the U.S.[1]). A *PALB2* variant was also associated with poorer prognosis: 10-year survival of 48.0% versus 74.7% when the variant was absent (hazard ratio [HR]=2.27; 95% CI, 1.64 to 3.15; adjusted for prognostic factors).

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.[9] In Milan, 9 different pathogenic *PALB2* variants were detected in 12 of 575 cases and none in 784 controls (blood donor); in Bergamo, *PALB2* c.1027C>T variants were detected in 6 of 113 cases and in 2 of 477 controls (OR=13.4; 95% CI, 2.7 to 67.4). Performed in 2 distinct populations, the combined sample size was small, and uncertainty existed as indicated by the large effect estimate.

Casadei et al (2011) studied 959 U.S. women (non-Ashkenazi Jewish descent) with a family history of *BRCA1*- or *BRCA2*-negative breast cancer and 83 female relatives using a family-based case-control design.[10] Using conventional sequencing, pathogenic *PALB2* variants were detected in 31 (3.2%) women with breast cancer and none in controls. Compared with their female relatives without *PALB2* variants, the risk of breast cancer increased 2.3-fold (95% CI, 1.5 to 4.2) by age 55 and 3.4-fold (95% CI, 2.4 to 5.9) by age 85. 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 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 RR 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.[21] The study sample was obtained from 542 patients with familial breast cancer, a series of 884 oncology patients (79% of consecutive new cases), and 986 surgical patients (87% of consecutive new cases); 1706 were genotyped for the *PALB2* c.1592delT variant. All familial cases were *BRCA1*- and *BRCA2*-negative, but among controls, there were 183 BRCA carriers. *PALB2* variant prevalence varied with family history: 2.6% when 3 or more family members were affected and 0.7% in all breast cancer patients. Variant prevalence was 0.2% among controls. In women with hereditary disease, a *PALB2* c.1592delT variant was associated with an increased risk of breast cancer (OR=11.0; 95% CI, 2.65 to 97.78), and was higher in women with the strongest family histories (women with sporadic cancers OR=4.19; 95% CI, 1.52 to 12.09). Although data were limited, survival was lower among *PALB2*-associated cases (10-year survival, 66.5% [95% CI, 44.0% to 89.0%] vs. 84.2% [95% CI, 83.1% to 87.1%] in women without a variant, p=.041; HR, 2.94, p=.047). A *PALB2* variant was also associated with triple-negative tumors: 54.5% versus 12.2% with familial disease and 9.4% in sporadic cancers.

Multinational Samples
Yang et al (2019) 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.[26] Female breast cancer RR was found to be 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 found to be 4.69 (95% CI, 3.28 to 6.70) in those 75 years of age per the age-trend model.

Southey et al (2016) examined the association of 3 *PALB2* variants (2 protein-truncating: c.1592delT and c.3113G>A; 1 missense c.2816T>G) with breast, prostate, and ovarian cancers.[24] The association with breast cancer was examined among participants in the Breast Cancer Association Consortium (BCAC; 42,671 cases and 42,164 controls). The BCAC (part of the larger Collaborative Oncological Gene-environment Study) included 48 separate studies with participants of multiple ethnicities, but mainly European, Asian, and African American. Most studies were population- or hospital-based case-controls with some oversampling cases with family histories or bilateral disease. A custom array was used for genotyping at 4 centers, with 2% duplicate samples. The ORs were estimated adjusting for study among all participants, and excluding those studies selecting patients based on family history or bilateral disease (37,039 cases, 38,260 controls). The c.1592delT variant was identified in 35 cases and 6 controls (from 4 studies in the U.K., Australia, U.S., Canada; OR=4.52; 95% CI, 1.90 to 10.8; p<.001); in those with no family history or bilateral disease (OR=3.44; 95% CI, 1.39 to 8.52; p=.003). The c3113G>A variant was identified in 44 cases and 8 controls (9 studies from Finland and Sweden; OR=5.93; 95% CI, 2.77 to 12.7; p<.001) and in those with no family history or bilateral disease (OR=4.21; 95% CI, 1.84 to 9.60; p<.001). There was no association between the c2816T>G missense variant and breast cancer (found in 150 cases and 145 controls).

These results, derived from a large sample, used a different analytic approach than Antoniou et al (2014), described next, and examined only 2 pathogenic variants. The magnitude of the estimated RR approaches that of a high penetrance gene but is accompanied by wide CIs owing to the study design and low carrier prevalence. The lower estimates obtained following exclusion of those selected based on family history or bilateral disease are consistent with the importance of carefully considering the risk of hereditary disease prior to genetic testing.

Antoniou et al (2014) analyzed data from 362 members of 154 families with deleterious *PALB2* variants.[8] 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 ages 50 to 54, 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 of breast cancer for female *PALB2* carriers without considering family history was 14% (95% CI, 9% to 20%); by age 70, it was 35% (95% CI, 26% to 46%). A family history of breast cancer increased the cumulative risk. If a woman with a *PALB2* variant has a sister and mother who had breast cancer at age 50, by age 50 she would have a 27% (95% CI, 21% to 33%) estimated risk of developing breast cancer; and by age 70, 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..."

Variant Interpretation
Valid variant classification is required to assess penetrance and is of particular concern for low prevalence variants including *PALB2*. Although the more common founder mutations were identified in many patients in the clinical validity studies, some specific variants were infrequent in the samples. While there are guidelines for variant classification, the consistency of interpretation among laboratories is of interest. Balmaña et al (2016) examined the agreement in variant classification by different laboratories from tests for inherited cancer susceptibility from individuals undergoing panel testing.[30] The Prospective Registry of Multiplex Testing is a volunteer sample of patients invited to participate when test results were provided to patients from participating laboratories. From 518 participants, 603 variants were interpreted by multiple laboratories and/or found in ClinVar. Discrepancies were most common with *CHEK2* and *ATM*. Of 49 missense *PALB2* results with multiple interpretations, 9 (18%) had at least 1 conflicting interpretation; 3 (6%) had pathogenic variants of uncertain significance or likely benign interpretations from different sources. Given the nature of the sample, there was a significant potential for biased selection of women with either reported variants of uncertain significance or other uncertainty in interpretation. In addition, discrepancies were confined to missense variants. It is therefore difficult to draw conclusions concerning the frequency of discrepant conclusions among all tested women.

Section Summary: Clinically Valid
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.

Errors in missense variant classification have been reported. False-negatives would result in risk determined by family history alone or may offer incorrect reassurance; the consequences of false-positives may have adverse consequences due to incorrect management decisions.

Finally, 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 whose mother had breast cancer at age 35 has an estimated 14.4% risk of breast cancer at age 70. If she carries a *PALB2* variant, the risk increases to 51.1%. A woman, age 50, with breast cancer whose mother had breast cancer at age 50, has an estimated 11.7% risk of contralateral cancer by age 70, increasing to 28.7% if she carries a *PALB2* variant.

Table 1. 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, %
Li[27.] (BEACCON)	2021	Australia	Family-based CC	3892		144	98	1990	1902		2.49
Yang[26.]	2020	Multinational	Multicenter family segregation	17,906	524	976	NR	NR	NR	976	5.5
Lu [25.]	2019	U.S.	Multicenter CC	15,404		61	NR	15532	3988	NR	0.4
Thompson [23.]	2015	Australia	Population-based CC	3994		26	4	1996	1998	19	1.3
Cybulski[11.]	2015	Poland	Population-based CC[f]	17,231		116	10	12,529	4702	2	0.9
Catucci[9.,a,b]	2014	Italy	Population-based CC	590[e]		6	2	113	477	1 (c.1027C>T)	5.3
Heikkinen[21.,a,b]	2009	Finland	Population-based CC	2026		19	2	947	1079	1 (c.1592delT)	2.0
Casadei[10.,a]	2011	U.S.	Family-based CC[d]	1042		31	0	959	83	13	3.2
Rahman[22.,a,b]	2007	U.K.	Family-based CC	2007	923	10	0	923	1084	5	1.1
Erkko[20.,a,b]	2008	Finland	Family segregation	213	17[c]	17	?			1 (c.1592delT)	
Antoniou[8.]	2014	Multinational	Kin-cohort	2980	154	229	82	542	2438	48	
Southey[24.]	2016	Multinational	Mutlicenter CC	84,835		35	6	42,671	42,164	1 (c.1592delT)	
						44	8			1 (c.3113G>A)	
Kurian [28.]	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 2. Measures of Association and Penetrance for Breast Cancer and *PALB2*

Study	Year	Analysis	RR or (95% CI)	Penetrance at Age 70 (95% CI), %	Mean (Median) Age Onset, y	Triple-Negative Tumors, %	
						PALB2+	*PALB2*-
Li[27] (BEACCON)	2021	Standard CC	3.47 (1.92 to 6.65)			27.6	
Yang[26]	2019	Segregation	7.18 (5.82 to 8.85)	52.8 (43.7 to 62.7)[d]	NR	NR	NR
Lu[25]	2019	Standard CC	5.5 (2.2 to 17.7)				
Antoniou[8]	2014	Segregation[b]	6.6 (4.6 to 9.2)[c]	47.5 (38.6 to 57.4)[e]		30	
Erkko[20]	2008	Segregation	6.1 (2.2 to 17.2)[a]	40 (17 to 77)	54.3 (+FH); 59.3 (FH unavailable)		
Rahman[22]	2007	Segregation[b]	2.3 (1.4 to 3.9)[f]		46 (IQR, 40-51)		
Casadei[10]	2011	Relative risk	2.3 (1.5 to 4.2)[g]		50.0 (SD=11.9)		
Thompson[23]	2015	Standard CC	6.6 (2.3 to 18.9)				
Cybulski[11]	2015	Standard CC	4.4 (2.3 to 8.4)		53.3	34.4	14.4
Catucci[9]	2014	Standard CC	13.4 (2.7 to 67.4)				
Heikkinen[21]	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[24]	2016	Standard CC	4.5 (1.9 to 10.8) (c.1592delT)				
			5.9 (2.8 to 12.7) (c.3113G>A)				
Kurian [28]	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.
[d] Estimate for women age 80.
[e] Estimates varied according to family history. For women with a mother and sister with breast cancer at age 50, 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 3 and 4.

Table 3. Study Relevance Limitations of Individuals Studies of Pathogenic *PALB2* Variants

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Li[27] (BEACCON)	4. Case-control population of familial BRCA 1/2 negative breast cancer patients (and controls)				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Yang[26.]	4. No case-control group	1. Not clear which variants were included			
Lu[25.]	4. Case-control population of breast cancer patients (and controls), likely overestimated risk	1. Not clear which variants were included			
Kurian[28.]	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)[24.]	4. Case-control population of breast cancer patients (and controls), likely overestimated risk				
Thompson et al (2015)[23.]	4. Case-control population of breast cancer patients (and controls), likely overestimated risk				
Cybulski et al (2015)[11.]	4. Case-control population of breast cancer patients (and controls), likely overestimated risk				
Catucci et al (2014)[9.]	4. Case-control population of breast cancer patients referred for genetic testing (and controls), likely overestimated risk				
Antoniou et al (2014)[8.]	4. Case-control population of breast cancer patients (and controls), likely overestimated risk; only kin-cohort included				
Casadei et al (2011)[10.]	4. Case-control population of breast cancer				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
	patients (and controls), likely overestimated risk				
Heikkinen et al (2009)[21]	4. Case-control population of breast cancer patients referred for genetic testing (and controls), likely overestimated risk				
Erkko et al (2008)[20]	4. No case-control group				
Rahman et al (2007)[22]	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 4. 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]
Li[27] (BEACCON)				1. Registration not reported	1. No description of disposition of eligible patients/samples	
Yang[26]	1. Incomplete descriptions of how family groups selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Lu[25]	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Kurian[28.]				1. Registration not reported	1. No description of disposition of eligible patients/samples	
Southey et al (2016)[24.]				1. Registration not reported		
Thompson et al (2015)[23.]	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Cybulski et al (2015)[11.]	1. Incomplete description of how controls selected			1. Registration not reported		
Catucci et al (2014)[9.]	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Antoniou et al (2014)[8.]	2. Kin-cohort-controls not randomized					
Casadei et al (2011)[10.]	2. Family groups: controls not randomized			1. Registration not reported		
Heikkinen et al (2009)[21.]	1. Incomplete description of how controls selected			1. Registration not reported		
Erkko et al (2008)[20.]	2. Family groups: selection not randomized			1. Registration not reported; number of controls unknown		
Rahman et al (2007)[22.]	2. Family groups: controls not randomized			1. Registration not reported		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
BEACCON: Hereditary BrEAst Case CONtrol study;
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective

publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

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

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (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 *BRCA*1/2 and by calculating whether carriers of these gene variants would have been identified as candidates for enhanced screening based on family history alone.[31] The database included 194,107 women who were tested using a hereditary cancer panel between 2013 and 2016. The women were referred by their health care providers for clinical suspicion of hereditary cancer. It is unclear what proportion of the women met professional society criteria for genetic testing for breast cancer risk; baseline information regarding family history was not reported. Of the women in the database, 893 had *PALB2* variants and were eligible for Claus assessment to estimate the risk of breast cancer. Approximately 27% of women with *PALB2* variants would have had an estimated risk of breast cancer of 20% or higher based on the Claus model. The report did not include health outcomes and it is unclear whether enhanced screening in women who had a moderate penetrance variant but did not have an estimated risk of breast cancer of 20% or greater based on the Claus model would have improved health outcomes from enhanced surveillance.

Studies of women at high-risk based on family history alone or in those with *BRCA1* and *BRCA2* variants are relevant to the clinical utility of *PALB2* testing given the penetrance estimates for *PALB2* and related molecular mechanism ("BRCA-ness"). Interventions to decrease breast cancer risk in asymptomatic high-risk women include screening[32] (e.g., starting at an early age, the addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention,[33] and prophylactic mastectomy.[34] 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,[35] 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. [36,37] 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 would gain an expected 2.9 years following a prophylactic mastectomy alone and an additional 0.3 years with a prophylactic oophorectomy (Table 5).[36] A 50-year-old female *BRCA* carrier with node-negative breast cancer and a 24% risk

of contralateral breast cancer at age 70 would anticipate 0.9 years in improved life expectancy (0.6 years for node-negative disease) following a prophylactic contralateral mastectomy.[37,]

Table 5. 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, y			
	30	40	50	60
40% risk of breast cancer				
Mastectomy	2.9	2.0	1.0	0.2
Mastectomy delayed 10 y	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 y	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 y	2.6	1.1	0.1	0.1

Adapted from Schrag et al (1997).[36,]

Section Summary: Clinically Useful
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.

CHEK2 and Breast Cancer Risk Assessment

Clinical Context and Test Purpose

The purpose of testing for *CHEK2* variants in individuals at high-risk of HBOC is to evaluate whether an abnormal variant is present and, if so, to determine whether the variant conveys a sufficiently high-risk that changes in surveillance and/or treatment likely to decrease the risk of mortality from breast and/or ovarian cancer are warranted.

The question addressed in this evidence review is: Does genetic testing for *CHEK2* variants improve the net health outcome in women at high-risk of HBOC?

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

Populations

Genetic testing can be considered for women at increased risk of developing hereditary breast cancer based on their family history or in women with breast cancer whose family history or cancer characteristics (e.g., triple-negative disease, young age) increase the likelihood that the breast cancer is hereditary. Testing may also be considered for women from families with known variants.

The relevant population of interest in this review is patients who are undergoing assessment for HBOC syndrome.

Interventions

The intervention of interest is *CHEK2* variant testing.

Comparators

The alternative would be to manage women at high-risk of HBOC with no CHEK2 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
Risk of Developing Breast Cancer
For genetic susceptibility to cancer, clinical validity can be established if the variants that the test is intended to identify are associated with disease risk, and if so, if these risks are well quantified.[4.] Most studies assessing the risk of breast cancer associated with *CHEK2* are population- and family-based case-control studies.

Systematic Reviews
Systematic reviews of *CHEK2* and breast cancer risk have been reported. Characteristics are shown in Table 6 and the results are shown in Table 7.

The Suszynska et al (2019) systematic review described previously also included association estimates for *CHEK2* variants.[19.] In the 43 breast cancer studies included in the review, 94,845 patients contributed to the meta-analysis of *CHEK2* in breast cancer patients. The OR of breast cancer for *CHEK2* variants including variants c.470T>C and c.1283C>T was OR=0.96 (95% CI, 0.90 to 1.03); after excluding variants c.470T>C and c.1283C>T, the association between the remaining *CHEK2* variants and breast cancer was OR=1.73 (95% CI, 1.58 to 1.89). 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 *CHEK2* association studies.

An article by Schmidt et al (2016) evaluated data on *CHEK2* variant status and breast cancer risk from the BCAC.[38,39.] The analysis included 44,777 breast cancer patients and 42,997 controls from 33 studies in which individuals were genotyped for *CHEK2* variants. The estimated odds for invasive breast cancer in patients with and without the *CHEK2* 1100delC variant was 2.26 (95% CI, 1.90 to 3.10).

A meta-analysis by Yang et al (2012) examined the risk of breast cancer in whites with the *CHEK2* c.1100delC variant.[38.] Twenty-five case-control studies conducted in Europe and North and South America published in 16 articles were analyzed, with a total of 29,154 breast cancer cases and 37,064 controls. Of the cases, 13,875 patients had unselected breast cancer, 7945 had familial breast cancer, and 5802 had early-onset breast cancer. In total, 391 (1.3%) of the cases had a *CHEK2* c.1100delC variant and 164 (0.4%) of the controls. The association between the *CHEK2* c.1100delC variant and breast cancer risk was statistically significant (OR=2.75; 95% CI, 2.25 to 3.36). By subgroup, odds were 2.33 (95% CI, 1.79 to 3.05) for unselected, 3.72 (95% CI, 2.61 to 5.31) for familial, and 2.78 (95% CI, 2.28 to 3.39) for early-onset breast cancer.

Weischer et al (2008) performed a meta-analysis of studies on *CHEK2* c.1100delC heterozygosity and the risk of breast cancer among patients with unselected (including the general population), early-onset (<51 years of age), and familial breast cancer.[40.] The analysis identified prospective cohort and case-control studies on *CHEK2* c.1100delC and the risk of breast cancer published before March 2007. Inclusion criteria were women with unilateral breast cancer who did not have a known multicancer syndrome, Northern or Eastern European descent, availability for *CHEK2* genotyping, *BRCA1* and *BRCA2* sequence variant-negative or unknown status, and

breast cancer-free women as controls. The meta-analysis included 16 studies with 26,488 patient cases and 27,402 controls. Presenting both fixed and random-effect models, for *CHEK2* c.1100delC heterozygotes versus noncarriers, the aggregated ORs for breast cancer were 2.7 (95% CI, 2.1 to 3.4) and 2.4 (95% CI, 1.8 to 3.2) in studies of unselected breast cancer, 2.6 (95% CI, 1.3 to 5.5) and 2.7 (95% CI, 1.3 to 5.6) in studies of early-onset breast cancer, and 4.8 (95% CI, 3.3 to 7.2) and 4.6 (95% CI, 3.1 to 6.8) in studies of familial breast cancer, respectively.

Table 6. Characteristics of Systematic Reviews of *CHEK2* and Risk of Breast Cancer

Study	Dates	Population	Designs Included	No. of Studies	No. of Participants	Pathogenic Variants Identified
Suszynska et al (2019)[19.]	To Jul 2017	Cases: Patients with breast and/or ovarian cancer referred for evaluation by a multi-gene panel Controls: Patients from the Genome Aggregation Database	Studies reporting prevalence of genetic variants	48 (overall) 43 (breast cancer)	94,845 included in CHEK2 analysis Unclear how many controls were included from the Genome Aggregation Database	37 *CHEK2* variants
Schmidt et al (2016)[38,39,38.]	NR	European women in the Breast Cancer Association Consortium	Case-control	33	87,754	c.1100delC
Yang et al (2012)[38.]	To May 2012	Mixed	Case-control	16	66,218	c.1100delC
Weischer et al (2008)[40.]	To Mar 2007	Unilateral breast cancer, Northern or Eastern European descent, *BRCA1*- or *BRCA2*-negative or -unknown, and breast cancer-free controls	Prospective cohort and case-control	16	26,488	c.1100delC

NR: not reported.

Table 7. Results of Systematic Reviews of *CHEK2* and Risk of Breast Cancer

Study	Relative Risk/Odds Ratio (95% CI)	Penetrance at Age 70 (95% CI), %
Suszynska et al (2019)[19.]	1.73 (95% CI, 1.58 to 1.89[a]	NR
Schmidt et al (2016)[39.]		
Overall		
Total N	81,700	
Pooled estimate (95% CI)	2.4 (2.1 to 2.9)	≈17
Non-*BRCA1* or *BRCA2*		
Total N	72,334	
Pooled estimate (95% CI)	2.3 (2.0 to 2.8)	NR
Yang et al (2012)[38.]		NR
Unselected for family history		
Total N	50,939	
Pooled estimate (95% CI)	2.3 1.8 to 3.1)	

Study	Relative Risk/Odds Ratio (95% CI)	Penetrance at Age 70 (95% CI), %
Early-onset breast cancer		
Total N	42,866	
Pooled estimate (95% CI)	2.8 (2.3 to 3.4)	
Familial breast cancer		
Total N	45,009	
Pooled estimate (95% CI)	3.7 (2.6 to 5.3)	
Weischer et al (2008)[40.]		
Unselected for family history		
Total N		
Pooled estimate (95% CI)	2.4 (1.8 to 3.2)	
Early-onset breast cancer		
Total N		
Pooled estimate (95% CI)	2.7 (1.3 to 5.6)	
Familial breast cancer		
Total N		
Pooled estimate (95% CI)	4.6 (3.1 to 6.8)	37 (26 to 56)

CI: confidence interval; NR: not reported.
[a]Excluding variants c.470T>C and c.1283C>T.

Individual Studies Not Included in Systematic Reviews

Individual studies not included in the previous meta-analyses have also reported on the association between breast cancer development and *CHEK2* variants; they are summarized in Tables 8 and 9. The number of included patients ranged from 4000 to over 95,000. The prevalence of *CHEK2* variants was approximately 2% to 3% in breast cancer patients. The OR, HR, or RR ranged from approximately 2 to 3, although it was higher in subgroups of women with a family history of breast cancer and in biallelic carriers of *CHEK2* pathogenic variants.

Table 8. Characteristics of Studies of *CHEK2* and Risk of Breast Cancer

Study	Dates	Population	No. of Participants	Pathogenic Variants Identified
Li et al (2021)[27.](BEACON)	-2019	Female patients with breast and/or ovarian cancer from non-*BRCA1* and *BRCA2* hereditary breast and ovarian cancer families. The control population was older women without cancer at the time of the study.	1990 cases 1902 population-matched controls	85% were c.1100delC
Nguyen-Dumont (2021)[41.]	NR	Segregation analysis of cases and controls in 26 families	1476 cases 861 controls	c.1100delC plus 8 rare variants
Rainville et al (2020)[42.]	2013-2019	Monoallelic and biallelic female carriers of *CHEK2* pathogenic variants identified through clinical pan-hereditary cancer panel testing	6515	c.1100delC and unclear
Lu et al (2019) [25.]	2014 -2015	Cases with breast and/or ovarian cancer referred for genetic testing and controls referred for genetic testing for noncancer conditions	15,404	'Known breast or ovarian cancer gene'
Kurian et al (2017)[28.]	2013 - 2015	Cases and controls referred for testing for hereditary cancer; Controls were those without cancer at the time of testing	95,561	Unclear
Fan et al (2018)[43.]	2003-2015	Breast cancer patients at Chinese university cancer hospital who received gene panel sequencing	8085	c.1100delC
Hauke et al (2018)[44.]	NR	Met inclusion criteria of the German Consortium for Hereditary Breast and Ovarian Cancer for germ-line testing	5589	Unclear

Study	Dates	Population	No. of Participants	Pathogenic Variants Identified
Decker et al (2017)[45]	After 1991	U.K.; diagnosed with invasive breast cancer from SEARCH study and controls from 3 population-based studies	18,575	c.1100delC plus 14 rare truncating variants
Couch et al (2017)[46]	2012-2016	Women with breast cancer referred for hereditary cancer genetic testing by Ambry Genetics and matched controls from Exome Aggregation Consortium reference	54,305	Unclear
Naslund-Koch et al (2016)[47]	2003-2010	Copenhagen General Population Study: White participants and those of Danish descent from certain areas of Copenhagen	86,975	c.1100delC
Cybulski et al (2011)[12]	1996-2006	Poland; *BRCA1*-negative breast cancer patients unselected for family history and controls from 4 sources	11,840	del5395, IVS21GA, I157T, 1100delC

BEACCON: Hereditary BrEAst Case CONtrol study; NR: not reported.

Table 9. Results of Individuals Studies of *CHEK2* and Risk of Breast Cancer

Study	Prevalence of *CHEK2* Variants	OR (95% CI)	Penetrance at Age 70 (95% CI), %
Li et al (2021)[27] (BEACON)			
Total N		3892	
Loss of Function	78 (1.35%) familial breast cancer patients 29 (0.51%) population-matched controls	2.70 (1.74 to 4.30)	NR
Missense	122/1900 (2.11%) familial breast cancer patients 71/1902 (1.24%) population-matched controls	1.73 (1.27 to 2.35)	NR
Nguyen-Dumont (2021)[41]	20 (1.4%) case probands 7 (0.8%) control probands		26 (16 to 40)
	For all variants	4.9 (2.5 to 9.5)	
	c.1100delC	3.5 (1.02 to 11.6)	
Rainville et al (2020)[42]			
Monoallelic	6473/6515 (99.4%) monoallelic carriers of *CHEK2* variants 2668/6473 (41.2%) in breast cancer patients 3234 (50.0%) in no personal cancer history	Ductal invasive: 2.02 (1.90 to 2.15) DCIS: 1.82 (1.66 to 2.00)	NR
Biallelic	42/6515 (0.6%) biallelic carriers of *CHEK2* variants (16/42 homozygous for c.1100delC) 25/31 (80.6%) in breast cancer patients 3 (9.7%) in no personal cancer history	Ductal invasive: 8.69 (3.69 to 20.47) DCIS: 4.98 (2.00 to 12.35)	NR
Lu et al (2019) [25]	0.8% in breast or ovarian cancer cases 0.3% in controls	2.19 (1.40 to 3.56)	NR
Kurian et al (2017)[28]	1.2% in breast cancer patients 1% in patients without breast or ovarian cancer	1.99 (1.70 to 2.33)	NR
Fan et al (2018)[43]			
Overall			
Total N	7657		NR
Estimate (95% CI)	0.34% in breast cancer patients	NR	
Hauke et al (2018)[44]			
Overall			
Total N		5589	

Study	Prevalence of *CHEK2* Variants	OR (95% CI)	Penetrance at Age 70 (95% CI), %
Estimate (95% CI)	1.8% in breast cancer patients 0.6% and 0.4% in control datasets	2.9 (2.3 to 3.8)	NR
Decker et al (2017)[45.]			
Overall			
Total N		18,575	
Estimate (95% CI)	1.6% in breast cancer patients 0.5% in controls	3.1 (2.2 to 4.7)	NR
Couch et al (2017)[46.]			
Overall			
Total N		54,305	
Estimate (95% CI)	1.5% in breast cancer patients 0.7% in controls	2.3 (1.9 to 2.7)	NR
Naslund-Koch et al (2016)[47.]			
Overall			
Total N		86,975	
Estimate (95% CI)	0% homozygotes 0.8% heterozygotes	2.1 (1.5 to 2.9)	≈17
Cybulski et al (2011)[12.]			
Overall			
Total N		11,842	
Estimate (95% CI)	3.0% in breast cancer patients 0.8% in controls	3.6 (2.6 to 5.1)	
Without family history of breast cancer			
Total N		10,391	
Estimate (95% CI)	2.8% in breast cancer patients 0.8% in controls	3.3 (2.3 to 4.7)	20
First- or second-degree relative with breast cancer			
Total N		5797	
Estimate (95% CI)	4.7% in breast cancer patients 0.8% in controls	5.0 (3.3 to 7.6)	

BEACCON: Hereditary BrEAst Case CONtrol study; CI: confidence interval; DCIS: ductal carcinoma in situ; NR: not reported; OR: odds ratio.

Study design and conduct limitations are shown in Tables 10 and 11. Only 1 study included population-based sampling in a prospective cohort. The remaining studies were case-control studies. Several studies did not adequately describe the selection of cases and/or controls. A complete disposition of patients or samples eligible for inclusion and those appearing in the analysis was also not provided in several studies.

Table 10. Study Relevance Limitations of Individuals Studies of *CHEK2* and Risk of Breast Cancer

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Li et al (2021)[27.](BEACON)	4. Case-control population of breast cancer patients (and controls), included primarily participants of European ancestry				
Nguyen-Dumont (2021)[41.]	4. Included primarily participants of				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
	European ancestry				
Rainville (2020)[42]	4. No control population, likely overestimated risk	1. Not clear which variants were included			1. Unclear if follow-up duration is sufficient due to retrospective review
Lu et al (2019)[25]	4. Case-control population of breast cancer patients (and controls), likely overestimated risk	1. Not clear which variants were included			
Kurian et al (2017)[28]	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
Fan et al (2018)[43]	4. Case-control population of breast cancer patients (and controls), likely overestimated risk; only included Chinese patients				
Hauke et al (2018)[44]	4. Case-control population of breast cancer patients (and controls), likely overestimated risk; only included participants of European ancestry				
Decker et al (2017)[45]	4. Case-control population of breast cancer patients (and controls), likely overestimated risk				
Couch et al (2017)[46]	4. Case-control population of breast cancer patients				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
	referred to genetic testing (and controls), likely overestimated risk				
Naslund-Koch et al (2016)[47.]	4. Includes only White participants and those of Danish descent				
Cybulski et al (2011)[12.]	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 11. Study Design and Conduct Limitations of Individuals Studies of *CHEK2* and Risk of Breast Cancer

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Li et al (2021)[27.](BEACON)				1. Registration not reported	1. No description of disposition of eligible patients/samples	
Nguyen-Dumont (2021)[41.]				1. Registration not reported		
Rainville (2020)[42.]				1. Registration not reported	1. Only exclusion criteria are provided	
Lu et al (2019)[25.]	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Kurian et al (2017)[28.]				1. Registration	1. No description of disposition of	

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
				not reported	eligible patients/samples	
Fan et al (2018)[43]	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Hauke et al (2018)[44]	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Decker et al (2017)[45]	1. No description of how cases or controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Couch et al (2017)[46]	1. Incomplete description of how controls selected			1. Registration not reported		
Naslund-Koch et al (2016)[47]				1. Registration not reported		
Cybulski et al (2011)[12]				1. Registration not reported	1. No description of disposition of eligible patients/samples	

BEACCON: Hereditary BrEAst Case CONtrol study;
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Breast Cancer Prognosis in an Individual With a *CHEK2* Sequence Variant

Studies of survival between breast cancer patients with and without *CHEK2* variants have shown differing results. Breast cancer patients with *CHEK2* variants may have a worse prognosis than noncarriers.

Fan et al (2018) investigated the clinical relevance of *CHEK2* variants in breast cancer patients.[43] In this observational study, the genomes of 7657 Chinese *BRCA1*- and *BRCA2*-negative breast cancer patients were analyzed. Researchers reported a *CHEK2* germline variant rate of 0.34%, and those with the variants were significantly more likely (p=.022) to have family

histories of cancer and to develop lymph node-positive and progesterone receptor-positive cancers. Limitations include sample homogeneity and retrospective design.

A study by Huzarski et al (2014) estimated the 10-year survival rate for patients with early-onset breast cancer, with and without *CHEK2* variants.[48] Patients were consecutively identified women with invasive breast cancer diagnosed at or below the age of 50, between 1996 and 2007, in 17 hospitals throughout Poland. Patients were tested for 4 founder mutations in the *CHEK2* gene after diagnosis, and their medical records were used to retrieve tumor characteristics and treatments received. Dates of death were retrieved from a national registry. A total of 3592 women were eligible for the study, of whom 487 (13.6%) carried a *CHEK2* variant (140 with truncating variants, 347 with missense variants). Mean follow-up was 8.9 years. Ten-year survival for *CHEK2*-variant carriers (78.8%; 95% CI, 74.6% to 83.2%) was similar to noncarriers (80.1%; 95% CI, 78.5% to 81.8%). After adjusting for other prognostic features, the HR comparing carriers of the missense variant with noncarriers was similar, as was the HR for carriers of a truncating variant and noncarriers.

A study by Kriege et al (2014) compared breast cancer outcomes in patients with and without *CHEK2* variants.[49] Different study cohorts were combined to compare 193 carriers with 4529 noncarriers. Distant disease-free survival and breast cancer-specific survival were similar in the first 6 years after diagnosis. After 6 years, both distant disease-free survival (multivariate HR=2.65; 95% CI 1.79 to 3.93) and breast cancer-specific survival (multivariate HR=2.05; 95% CI, 1.41 to 2.99) were worse in *CHEK2* carriers. No interaction between *CHEK2* status and adjuvant chemotherapy was observed.

Weischer et al (2012) reported on breast cancer associated with early death, breast cancer-specific death, and the increased risk of a second breast cancer (defined as a contralateral tumor) in *CHEK2*-variant carriers and noncarriers in 25,571 white women of Northern and Eastern European descent who had invasive breast cancer, using data from 22 studies participating in the BCAC conducted in 12 countries.[50] The 22 studies included 30,056 controls. Data were reported on early death in 25,571 women, breast cancer-specific death in 24,345, and a diagnosis of second breast cancer in 25,094. Of the 25,571 women, 459 (1.8%) were *CHEK2* c.1100delC heterozygous and 25,112 (98.2%) were noncarriers. Median follow-up was 6.6 years, over which time the following was observed: 124 (27%) early deaths occurred, 100 (22%) breast cancer-specific deaths occurred, and 40 (9%) second breast cancers among *CHEK2* c.1100delC variant carriers were observed. Corresponding numbers among noncarriers were 4864 (19%), 2732 (11%), and 607 (2%), respectively. At the time of diagnosis, *CHEK2*-variant carriers versus noncarriers were on average 4 years younger (p<.001); additionally, *CHEK2*-variant carriers were more likely to have a family history of cancer (p<.001). Multifactorially adjusted HRs for *CHEK2* versus noncarriers were 1.43 (95% CI, 1.12 to 1.82; p=.004) for early death and 1.63 (95% CI, 1.24 to 2.15; p<.001) for breast cancer-specific death.

Section Summary: Clinically Valid
Studies have shown that a *CHEK2* variant is of moderate penetrance and confers a risk of breast cancer 2 to 4 times that of the general population. This risk appears to be higher in patients who also have a strong family history of breast cancer. Although the *CHEK2* variant appears to account for approximately one-third of variants identified in *BRCA1*- and *BRCA2*-negative patients, it is relatively rare with estimates ranging from 1.5 to 4.7% of breast cancer patients in the included studies, and risk estimates, which have been studied in population- and family-based case-controls, are subject to bias and overestimation. One systemic review and 2 studies published since the review estimated the risk of breast cancer by age 70 years in women with *CHEK2* variants was close to 20%. However, another review estimated that it may be as high as 37% (95% CI, 26% to 56%) in women with familial breast cancer. Several studies have suggested that *CHEK2* carriers with breast cancer may have worse breast cancer-specific survival and distant-recurrence free survival, with about twice the risk of early death.

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.

Direct evidence of clinical utility for genetic testing in individuals with *CHEK2* 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.

Weidner et al (2020) conducted a retrospective, consecutive study on 69 *CHEK2* carriers enrolled in the Inherited CAncer REgistry (ICARE) at Vanderbilt University and their relatives.[51] Eligibility for annual breast magnetic resonance imaging surveillance was based on ≥20% lifetime risk of breast cancer based on family cancer history alone as calculated by the BOADICEA predictive model, or family cancer history and proband CHEK2 variant status, utilizing an updated version of the BOADICEA model (BWA v4). Among the *CHEK2* carriers and family history alone, 21 first-degree relatives (FDRs) (14.9%) and 14 second-degree relatives (SDRs) (13.9%) had a lifetime cancer risk ≥20%. Inclusion of the proband's variant status significantly increased identification of FDRs to 78 (55.3%; p<.0001) and SDRs to 22 (21.8%; p=.008), respectively. While the study revealed that family history alone may be insufficient to appropriately identify at-risk FDRs and SDRs of CHEK2 carriers, the study authors note that the expanded BOADICEA predictive model (BWA v4) is not intended for clinical use.[52] Additionally, this version has not been licensed for commercial use. Additional study limitations include the retrospective study design, lack of clarity regarding to what extent study participants met society criteria for genetic testing for breast cancer risk, and no reporting of outcomes associated with enhanced screening for *CHEK2* variant carriers.

As outlined in the section on *PALB2,* for women with high-risk hereditary cancer syndromes, interventions to decrease breast cancer risk in high-risk women include screening (e.g., starting at an early age, the addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention, prophylactic mastectomy, and prophylactic oophorectomy. In contrast to the case of *PALB2,* where the penetrance approaches that of a *BRCA* variant, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a *CHEK2* variant. Surveys assessing adherence to guideline-based recommendations have explored this relationship but are limited in sample size and generally have not reported variant-stratified long-term outcomes of prophylactic or preventative interventions in controlled studies to support standard actionable thresholds for *CHEK2*.[53,54] Findings from other studies point to potential overtreatment through risk-reducing bilateral mastectomy among those with *ATM/CHEK2* variants, with over half of all carriers reporting use of prophylactic surgery independent of family history or personal breast cancer history.[55]

Section Summary: *CHEK2* and Breast Cancer Risk Assessment
Despite some studies showing potentially poorer outcomes for breast cancer patients who have *CHEK2* variants, it is unclear how such knowledge would be used to alter the treatment of such a patient. Furthermore, updated predictive models utilizing information on *CHEK2* status have not been approved for widespread clinical use. No evidence is available to support the clinical utility of genetic testing for *CHEK2* variants in breast cancer patients to guide patient management. There is no strong chain of evidence supporting *CHEK2* testing in breast cancer patients.

ATM and Breast Cancer Risk Assessment

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Does genetic testing for *ATM* variants improve the net health outcome in women at high-risk of HBOC?

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

Populations

Genetic testing can be considered for women at increased risk of developing hereditary breast cancer based on their family history or in women with breast cancer whose family history or cancer characteristics (e.g., triple-negative disease, young age) increase the likelihood that the breast cancer is hereditary. Testing may also be considered for women from families with known variants.

The relevant population of interest in this review is patients who are undergoing assessment for HBOC syndrome.

Interventions

The intervention of interest is *ATM* variant testing.

Comparators

The alternative would be to manage women at high-risk of HBOC with no ATM 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

The Suszynska et al (2019) systematic review described previously also included association estimates for *ATM* variants.[19] In the 43 breast cancer studies included in the review, 94,787 patients contributed to the meta-analysis of *ATM* in breast cancer patients. The OR of breast cancer for *ATM* variants was 2.42 (95% CI, 2.16 to 2.71). 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 *ATM* association studies.

Marabelli et al (2016) reported on a meta-analysis of the penetrance of *ATM* variants in breast cancer, which used a model allowing the integration of different types of cancer risk estimates

to generate a single estimate associated with heterozygous *ATM* gene variants.[56] The meta-analysis included 19 studies, which were heterogeneous in terms of population, study designs, and baseline breast cancer risk. The estimated cumulative absolute risk of breast cancer in heterozygous *ATM* variant carriers was 6.02% by age 50 (95% credible interval, 4.58% to 7.42%) and 32.83% by age 80 (95% credible interval, 24.55% to 40.43%).

Association Studies

Individual studies published after the meta-analyses have also reported on the association between breast cancer development and pathogenic *ATM* variants. The study characteristics of Li et al (2021), Lu et al (2019), Hauke et al (2018), Kurian et al (2017), Decker et al (2017), and Couch et al (2017), were included in the previous section on *CHEK2* (Tables 8, 10, and 11). Study results are shown in Table 12.

Table 12. Risk of Breast Cancer Associated with Pathogenic *ATM* Variants

Study	Prevalence of *ATM* Variants	RR/OR (95% CI)
Li et al (2021)[27] (BEACON)		
Loss of Function	• 0.90% familial breast cancer patients • 0.26% population-matched controls	2.88 (1.60 to 5.45)
Missense	• 5.53% familial breast cancer patients • 3.81% population-matched controls	1.48 (1.23 to 1.77)
Lu et al (2019)[25]	• 0.7% in breast and ovarian cancer cases • 0.2% in controls	2.97 (1.67 to 5.68)
Hauke et al (2018)[44]	• 1.3% in breast cancer cases • 0.4% and 0.2% in control samples	3.63 (2.67 to 4.94)
Decker et al (2017)[45]	• 0.6% in breast cancer patients • 0.2% in controls	3.26 (1.82 to 6.46)
Couch et al (2017)[46]	• 0.9% in breast cancer patients referred for testing • 0.3% in controls	2.78 (2.22 to 3.62)
Kurian et al (2017)[28]	• 0.92% in breast cancer patients referred for testing • 1% in patients referred for testing without breast or ovarian cancer	1.74 (1.46 to 2.07)

BEACCON: Hereditary BrEAst Case CONtrol study; CI: confidence interval; OR: odds ratio; RR: relative risk.

Section Summary: Clinically Valid

ATM heterozygotes appear to have an RR of breast cancer about 2 to 3 times that of the general population, with an estimated absolute risk of 6% by age 50 and 33% by age 80. Estimates come from the population- and family-based case-controls, and are applicable to individuals at high risk of breast and/or ovarian cancer.

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.

Direct evidence of clinical utility for genetic testing in individuals with *ATM* variants was not identified.

Weidner et al (2020) conducted a retrospective, consecutive study on 56 *ATM* carriers enrolled in the Inherited CAncer REgistry (ICARE) at Vanderbilt University and their relatives.[51] Eligibility for annual breast magnetic resonance imaging surveillance was based on ≥20% lifetime risk of breast cancer based on family cancer history alone as calculated by the BOADICEA predictive model, or family cancer history and proband CHEK2 variant status, utilizing an updated version of the BOADICEA model (BWA v4). Among the *ATM* carriers and family history alone, 24 FDRs (22.6%) and 15 SDRs (13.6%) had a lifetime cancer risk ≥20%. Inclusion of the proband's variant status significantly increased identification of FDRs to 60 (56.6%; p<.0001) and SDRs to 31 (28.1%; p<.0001), respectively. While the study revealed that family history alone may be insufficient to appropriately identify at-risk FDRs and SDRs of *ATM* carriers, the study authors note that the expanded BOADICEA predictive model (BWA v4) is not intended for clinical use.[52] Additionally, this version has not been licensed for commercial use. Additional study limitations include the retrospective study design, lack of clarity regarding to what extent study participants met society criteria for genetic testing for breast cancer risk, and no report of outcomes associated with enhanced screening for *ATM* variant carriers.

As outlined in the section on *PALB2,* for women with high-risk hereditary cancer syndromes, interventions to decrease breast cancer risk in high-risk women include screening (e.g., starting at an early age, the addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention, prophylactic mastectomy, and prophylactic oophorectomy. In contrast to the case of *PALB2,* where the penetrance approaches that of a *BRCA* variant, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with an *ATM* variant. Surveys assessing adherence to guideline-based recommendations have explored this relationship but are limited in sample size and generally have not reported variant-stratified long-term outcomes of prophylactic or preventative interventions in controlled studies to support standard actionable thresholds for *ATM*.[53,54] Findings from a study by Cragun et al (2020) point to potential overtreatment through risk-reducing bilateral mastectomy among those with *ATM/CHEK2* variants, with over half of all carriers reporting use of prophylactic surgery independent of family history or personal breast cancer history.[55]

Section Summary: *ATM* and Breast Cancer Risk Assessment
Updated predictive models utilizing information on *ATM* status for enhanced screening have not been approved for widespread clinical use. No evidence is available to support the clinical utility of genetic testing for *ATM* variants in breast cancer patients to guide patient management, and there is no strong chain of evidence supporting *ATM* testing in breast cancer patients.

Summary of Evidence
For individuals with a risk of HBOC 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 RR or ORs (2 studies estimated penetrance). 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 RR 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.

For individuals with risk of HBOC who receive genetic testing for a *CHEK2* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are OS, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *CHEK2* variants are of moderate penetrance, with lower RR for breast cancer than *PALB2*, and confer a risk of breast cancer 2 to 4 times that of the general population. Direct evidence for the clinical utility of genetic testing for *CHEK2* variants in individuals with risk of HBOC was not identified. It is unclear the RR associated with the moderate penetrance variants, other than *PALB2,* would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to the case of *PALB2,* where the penetrance approaches that of a *BRCA* variant, there is unlikely to be a similar benefit-to-risk calculus for risk-reducing mastectomy in women with a *CHEK2* variant. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with risk of HBOC who receive genetic testing for an *ATM* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are OS, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *ATM* variants are of moderate penetrance, with lower RR for breast cancer than *PALB2*; moreover, *ATM* variants confer a risk of breast cancer 2 to 4 times that of the general population. Direct evidence for the clinical utility of genetic testing for *ATM* variants in individuals with risk of HBOC was not identified. It is unclear that the RR associated with the moderate penetrance variants, other than *PALB2*, would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to the case of *PALB2,* where the penetrance approaches that of a *BRCA* variant, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with an *ATM* variant. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome..

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

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

In response to requests from Blue Cross Blue Shield Association, input was received from 5 specialty societies and 2 academic medical centers (total of 7 reviewers) in 2014. The input was limited on whether *PALB2* testing to estimate the risk of developing breast cancer should be medically necessary, and whether testing results alter patient management. Reviewer input on both questions was mixed.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Radiology
The American College of Radiology (ACR) has established Appropriateness Criteria® for breast cancer screening.[57.] This includes high-risk women with a BRCA gene mutation and their

untested first-degree relatives, women with a history of chest irradiation between 10 to 30 years of age, and women with 20% or greater lifetime risk of breast cancer as follows:

Table 13. American College of Radiology Appropriateness Criteria for Breast Cancer Screening in High-Risk Women

Screening Procedure	Appropriateness Category
Mammography	Usually appropriate
DBT	Usually appropriate
Breast MRI without and with IV contrast	May be appropriate
Breast US	May be appropriate
FDG-PEM	Usually not appropriate
Sestamibi MBI	Usually not appropriate
Breast MRI without IV contrast	Usually not appropriate

DBT: digital breast tomosynthesis; FDG-PEM: flurodeoxyglucose positron emission mammography; IV: intravenous; MBI: molecular breast imaging; MRI: magnetic resonance imaging; US: ultrasound.

Specific recommendations for *PALB2*, *CHEK2*, or *ATM* variant carriers are not available.

American Society of Breast Surgeons
A consensus guideline on genetic testing for hereditary breast cancer was updated in February 2019.[58] Guidelines state 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.

For patients with mutations in *ATM* and *CHEK2*, enhanced screening may be recommended, however, the data are not sufficient to support risk-reducing mastectomy in the absence of other factors such as strong family history.

American Society of Clinical Oncology
In 2015, in a policy statement update on genetic and genomic testing for cancer susceptibility, the American Society of Clinical Oncology stated that testing for highly penetrant variants in appropriate populations has clinical utility in that variants inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes.[59] The update noted: "Clinical utility remains the fundamental issue with respect to testing for variants in moderate penetrance genes. It is not yet clear whether the management of an individual patient or his or her family should change based on the presence or absence of a variant. There is insufficient evidence at the present time to conclusively demonstrate the clinical utility of testing for moderate penetrance variants, and no guidelines exist to assist oncology providers."

National Comprehensive Cancer Network
The NCCN (v.1.2021) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer review single-gene tests for *PALB2*, *CHEK2*, or *ATM*.[60] The guidelines state that for those that meet hereditary cancer testing criteria, testing for a specific familial pathogenic/likely pathogenic variant may be recommended for appropriate genes. For patients who meet criteria with no known familial variants, comprehensive testing of a multigene panel may be considered. This testing may consider a number of genes, including but not limited to *PALB2*, *CHEK2*, and *ATM.* However, the inclusion of certain genes in the guideline does not imply the endorsement "for or against multigene testing for moderate-penetrance genes" and there are limited data on the degree of cancer risk associated with some genes in multigene panels. Testing an affected family member first has the highest likelihood of a positive result. The guidelines state that the panel recommends an annual mammogram for women with a mutated PALB2 gene beginning at age 30 and with a mutated ATM or CHEK2 gene beginning at age 40 with consideration of annual breast magnetic resonance imaging.

The NCCN guidelines on breast cancer screening and diagnosis (v.1.2021)[61,] and on genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2021)[60,] recommend the following:

- Annual mammogram.
- Annual breast magnetic resonance imaging if the patient has >20% risk of breast cancer based on models largely dependent on family history.
- Consideration of a risk-reducing mastectomy based on family history.

The guidelines also state there is insufficient evidence to draw conclusions on risk-reducing mastectomy in individuals with *CHEK2* or *ATM* and that patients should be managed based on family history. For patients with *PALB2*, the option of a risk-reducing mastectomy should be discussed.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for *PALB2*, *CHEK2,* or *ATM* variant testing have been identified.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03989258	Implementation of a Model for Personalised Risk-Based Breast Cancer Prevention and Screening	28,389	Dec 2020 (unknown)
NCT02620852	Enabling a Paradigm Shift: A Preference-Tolerant RCT of Personalized vs. Annual Screening for Breast Cancer (Wisdom Study)	100,000	Mar 2025

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Ethnicity/Ancestry
  - Personal and/or family history of cancer (if applicable) including:
    - Family relationship(s): (maternal or paternal), (family member [e.g., sibling, aunt, grandparent]), (living or deceased) ((if applicable)
    - Site(s) of cancer
    - Age at diagnosis (including family members)
    - If breast cancer, indicate if bilateral, premenopausal, or triple negative cancer
    - BRCA1/BRCA2mutation history, multiple primaries, or ovarian cancer, because that individual has the highest likelihood for a positive test result (if applicable)
- Genetic counseling/professional results (if applicable)
- Laboratory or Pathology reports (e.g., BRCA results for BART testing requests, or hormone receptor assay) (if applicable)

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

- Procedure report(s)

Coding

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

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

Type	Code	Description
CPT®	0102U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])
	0129U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
	0131U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure)
	81307	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence
	81308	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; known familial variant
	81406	MOLECULAR PATHOLOGY PROCEDURE LEVEL 7
	81408	MOLECULAR PATHOLOGY PROCEDURE LEVEL 9
	81479	Unlisted molecular pathology procedure

Type	Code	Description
HCPCS	None	

Policy History

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

Effective Date	Action
05/29/2015	BCBSA Medical Policy adoption
04/01/2016	Policy revision without position change
03/01/2017	Policy title change from Genetic Testing for PALB2 Mutations Policy revision with position change
02/01/2018	Policy revision without position change
09/01/2018	Policy revision without position change
03/01/2019	Policy revision without position change
05/01/2019	Policy revision without position change/Coding update
11/01/2019	Coding update
01/01/2020	Annual review. No change to policy statement. Literature review updated.
03/01/2020	Coding update
05/01/2020	Admin update
11/01/2020	Annual review. Policy title changed from Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk to current one. Policy statement, and literature updated.
01/01/2021	Coding update
10/01/2021	Annual review. Policy statement and literature updated. Policy title changed from Gene Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk to current one.
05/01/2022	Administrative update.

Definitions of Decision Determinations

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

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

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

Prior Authorization Requirements (as applicable to your plan)

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

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

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

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Gene Variants (PALB2, CHEK2 and ATM) Associated with Breast Cancer in Individuals at High Breast Cancer Risk 2.04.126	**Gene Variants (PALB2, CHEK2 and ATM) Associated with Breast Cancer in Individuals at High Breast Cancer Risk 2.04.126**
Policy Statement:	**Policy Statement:** **Note:** Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).
Individual testing for *PALB2* variants for breast cancer risk assessment in adults who meet **both** of the following criteria may be considered **medically necessary**: I. The individual meets criteria for genetic risk evaluation II. The individual has undergone testing for sequence variants in BRCA1 and BRCA2 with negative results	Individual testing for *PALB2* variants for breast cancer risk assessment in adults who meet **both** of the following criteria may be considered **medically necessary:** I. The individual meets criteria for genetic risk evaluation II. The individual has undergone testing for sequence variants in BRCA1 and BRCA2 with negative results
When being initially tested for at the same time as BRCA1 and BRCA2 (and when criteria is met for such testing), the small panel 81432 should be used (see Policy Guidelines) rather than individual or sequential gene testing	When being initially tested for at the same time as BRCA1 and BRCA2 (and when criteria is met for such testing), the small panel 81432 should be used (see Policy Guidelines) rather than individual or sequential gene testing
Testing for *PALB2* sequence variants in individuals who do not meet the criteria outlined above is considered **investigational**.	Testing for *PALB2* sequence variants in individuals who do not meet the criteria outlined above is considered **investigational**.
Individual or large panel testing for *CHEK2* and *ATM* variants when not included as part of an approved small panel in the assessment of breast cancer risk is considered **investigational.**	Individual or large panel testing for *CHEK2* and *ATM* variants when not included as part of an approved small panel in the assessment of breast cancer risk is considered **investigational.**
NOTE: Germline genetic testing for BRCA1 and BRCA2 is addressed separately in Blue Shield of California Medical Policy: Genetic Testing for	**NOTE**: Germline genetic testing for BRCA1 and BRCA2 is addressed separately in Blue Shield of California Medical Policy: Genetic Testing for

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers	BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers