Policy Statement

Testing for PALB2 variants for breast cancer risk assessment in adults who meet all of the following criteria may be considered medically necessary:

- The individual meets criteria for genetic risk evaluation (see Policy Guidelines section)
- The individual has undergone testing for sequence variants in BRCA1 and BRCA2 (see Policy Guidelines section) with negative results

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

Testing for CHEK2 and ATM variants in the assessment of breast cancer risk is considered investigational.

Policy Guidelines

Criteria for Genetic Risk Evaluation

The National Comprehensive Cancer Network (NCCN) guidelines provide criteria for genetic risk evaluation for individuals without and with breast cancer. Updated versions of the criteria are available on the NCCN website.

The recommended testing strategy for BRCA1 and BRCA2 is described in Blue Shield of California Medical Policy: Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1 or BRCA2).

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

There is no specific CPT code for PALB2 testing, but it is included in the CPT tier 2 molecular pathology:

- **81406**: Molecular Pathology Procedure Level 7 – which includes PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer), full gene sequence.

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 Hereditary Breast/Ovarian Cancer Syndrome (BRCA1 or BRCA2)
- 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 testing 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 2016, researchers estimated breast cancer would be diagnosed in 252,710 women and 40,610 would die from the disease; a woman’s lifetime risk is 12.4%.2 Breast cancers can be classified as sporadic, familial, or hereditary.3 Most breast cancers, however, 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. Pathogenic
BRCA1 and BRCA2 variants appear responsible for 20% to 25% of hereditary breast cancers, while small proportions are attributed to pathogenic variants in other highly penetrant genes (e.g., TP53, CDH1, PTEN, STK11).

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). 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 roughly a 75% lifetime risk of developing breast cancer and a relative risk of 11 to 12 compared with the general population. 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. The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines. Still, distinctions between a variant of uncertain significance and a pathogenic one from different laboratories may not always be identical.

Genes Associated With a Moderate Penetrance of Breast Cancer

**PALB2 Gene**
The PALB2 gene (partner and localizer of BRCA2) encodes for a protein first described in 2006. The gene is located at 16p12.2 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. Most pathogenic PALB2 variants are truncating frameshift or stop codons, and are found throughout the gene. Pathogenic PALB2 variants are uncommon in unselected populations and prevalence varies by ethnicity and family history. For example, Antoniou et al (2014) assumed a prevalence of 8 per 10,000 in the general population when modeling breast cancer risks. 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). In women with a family history of breast cancer, the prevalence of pathogenic PALB2 variants ranges between 0.9% and 3.9% 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, and in populations with founder mutations cause 0.5% to 1% of all breast cancers.

**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

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1. **Short (p) arm of chromosome 16 at position 12.2.**
2. **Fanconi anemia is a rare disorder, primarily affecting children, that causes bone marrow failure. Affected individuals also carry a risk of cancers including leukemia.**
Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk

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.14

**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 heterozygote 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.15 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).16 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),17 screening tools (e.g., BRCAPRO,18 Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen19,20), 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.17

**Patient 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. Potential benefit derives from interventions (screening, chemoprevention, risk-reducing surgery) that can prevent a first breast cancer, a 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), the effectiveness and the harms of interventions. Assessing the net health outcome requires:

1. that a test accurately identifies variants and pathogenicity can be determined;
2. 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
3. management changes informed by testing can lead to improved health outcomes.

**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 individuals at high-risk of breast cancer 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 PALB2 variants improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest is patients who are undergoing assessment for hereditary breast and/or ovarian cancer syndrome who tested negative for BRCA1 or BRCA2.

**Interventions**

The intervention of interest is PALB2 variant testing.

**Comparators**

The comparator of interest is no genetic testing.

**Outcomes**

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

**Timing**

Testing for PALB2 variants is conducted as part of a genetic risk assessment for hereditary breast and ovarian cancer syndrome.

**Setting**

These tests are offered commercially through various laboratories and institutions.

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

A number of studies (see Tables 1 and 2) reporting relative risks (RR) or odds ratios (ORs) for the association between PALB2 and breast cancer were identified (2 reported penetrance estimates). Study designs included family segregation, kin-cohort, family-based case-control, and population-based or multicenter case-control. The 2 multinational
studies included individuals from up to 5 of the single-country studies. The number of pathogenic variants identified varied from 1 (founder mutations examined) to 48 (see Table 1). Studies conducted from single-country samples are described first followed by the 2 multinational collaborative efforts.

**Single-Country Samples**

Erkko et al (2008) studied Finnish women with BRCA1- or BRCA2-negative familial breast cancer. A total of 17 PALB2 (c.1592delT) probands were examined: in 10 (mean age onset, 54.3 years), a family history of breast cancer was known while, in 7, family history was unknown (mean age of onset, 59.3 years). From a segregation analysis, the RR of breast cancer was 6.1 (95% confidence interval [CI], 2.2 to 17.2), decreasing with increasing age. The cumulative risk at age 70 years was 40% (95% CI, 17% to 77%). Limitations of the study included a small number of carriers and missing family history data contributing to uncertainty in the estimated RR.

Rahman et al (2007) conducted a family-based case-control study enrolling cases (mean age, 49 years) identified at U.K. Cancer Genetics clinics. Controls, aged 48 years living in geographic regions similar to cases, were selected from the 1958 Birth Cohort Collection study. Protein-truncating PALB2 variants were identified in 10 of 923 individuals with a family history of breast cancer but none in 1084 controls. In a segregation analysis, the RR of breast cancer associated with a PALB2 variant was 2.3 (95% CI, 1.4 to 3.9), but modified by age with a RR of 3.0 for women less than 50 years (95% CI, 1.4 to 3.9) and 1.9 (95% CI, 0.8 to 3.7) for women over 50 years of age. This study was limited by its sample size and possibly analytic sensitivity of the sequencing employed.

Casadei et al (2011) studied 959 U.S. women (non-Ashkenazi Jewish descent) with a family history of BRCA1- or BRCA2-negative breast cancer and 83 female relatives using a family-based case-control design. Using conventional sequencing, pathogenic PALB2 variants were detected in 31 (3.2%) women with breast cancer and none in controls. Compared with their female relatives without PALB2 variants, the risk of breast cancer increased 2.3-fold (95% CI, 1.5 to 4.2) by age 55 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 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. 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 the 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=0.041; hazard ratio [HR], 2.94, p=0.047). A PALB2 variant was also associated with triple-negative tumors—54.5% vs 12.2% with familial disease and 9.4% in sporadic cancers.

Catucci et al (2014) performed population-based case-control studies in Italy (Milan or Bergamo) among women at risk for hereditary breast cancer and no BRCA1 or BRCA2 variant. In Milan, 9 different pathogenic PALB2 variants were detected in 12 of 575 cases and none in 784 controls (blood donor); in Bergamo, PALB2 c.1027C>T variants were detected in 6 of 113
cases and in 2 of 477 controls (OR=13.4; 95% CI, 2.7 to 67.4). Performed in 2 distinct populations, the combined sample size was small, and uncertainty as indicated by the large effect estimate.

Thompson et al (2015) evaluated Australian women with breast cancer (n=1996) referred for genetic evaluation from 1997 to 2014.24 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.13 From 12,529 genotyped women, a PALB2 variant was identified in 116 (0.93%) cases (95% CI, 0.76% to 1.09%) vs 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.26 or the U.S.2). A PALB2 variant was also associated with a poorer prognosis—10-year survival of 48.0% vs 74.7% when the variant was absent (HR=2.27; 95% CI, 1.64 to 3.15; adjusted for prognostic factors).

Multinational Samples

Antoniou et al (2014) analyzed data from 362 members of 154 families with deleterious PALB2 variants.10 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, two 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=0.08). 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....”

Southey et al (2016) examined the association of 3 PALB2 variants (2 protein-truncating: c.1592delTand c.3113G>A; 1 missense c.2816T>G) with breast, prostate, and ovarian cancers.27 The association with breast cancer was examined among participants in the Breast Cancer Association Consortium (BCAC; 42,671 cases and 42,164 controls). 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-control with some oversampling cases with family histories or bilateral disease. A custom array was used for genotyping at 4 centers, with 2%
duplicate samples. Odds ratios 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<0.001); 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<0.001) 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) 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.

**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 agreement in variant classification by different laboratories from tests for inherited cancer susceptibility from individuals undergoing panel testing. The Prospective Registry of Multiplex Testing registry 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 at least moderate and approach the range for a highly penetrant variant.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>N</th>
<th>Families</th>
<th>PALB2 Variants</th>
<th>Totals</th>
<th>Pathogenic Variants Identified</th>
<th>N</th>
<th>Prevalence Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erkko21,a,b</td>
<td>2008</td>
<td>Finland</td>
<td>Family segregation</td>
<td>213</td>
<td>17c</td>
<td>17</td>
<td>17</td>
<td>923</td>
<td>10</td>
<td>(c.1592delT)</td>
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<tr>
<td>Rahman23,a,b</td>
<td>2007</td>
<td>U.K.</td>
<td>Family-based CC</td>
<td>2007</td>
<td>923</td>
<td>10</td>
<td>0</td>
<td>923</td>
<td>1084</td>
<td>5</td>
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<tr>
<td>Casadei22,a</td>
<td>2011</td>
<td>U.S.</td>
<td>Family-based CCd</td>
<td>1042</td>
<td>31</td>
<td>31</td>
<td>0</td>
<td>959</td>
<td>83</td>
<td>13</td>
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<tr>
<td>Heikkinen22,a,b</td>
<td>2009</td>
<td>Finland</td>
<td>Population-based CC</td>
<td>2026</td>
<td>19</td>
<td>19</td>
<td>2</td>
<td>947</td>
<td>1079</td>
<td>(c.1592delT)</td>
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<tr>
<td>Catucci11,a,b</td>
<td>2014</td>
<td>Italy</td>
<td>Population-based CC</td>
<td>590</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>113</td>
<td>477</td>
<td>(c.1027C&gt;T)</td>
</tr>
<tr>
<td>Cybulski13</td>
<td>2015</td>
<td>Poland</td>
<td>Population-based CC</td>
<td>17,231</td>
<td>116</td>
<td>116</td>
<td>10</td>
<td>12,529</td>
<td>4702</td>
<td>2</td>
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<tr>
<td>Antoniou10</td>
<td>2014</td>
<td>Multinational</td>
<td>Kin-cohort</td>
<td>2980</td>
<td>154</td>
<td>229</td>
<td>82</td>
<td>542</td>
<td>2438</td>
<td>48</td>
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<tr>
<td>Southey27</td>
<td>2016</td>
<td>Multinational</td>
<td>Multicenter CC</td>
<td>84,835</td>
<td>35</td>
<td>35</td>
<td>6</td>
<td>42,671</td>
<td>42,164</td>
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</tbody>
</table>

CC: case-control.

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

### Table 2. Measures of Association and Penetrance for Breast Cancer and PALB2

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Analysis</th>
<th>RR or (95% CI)</th>
<th>Penetrance at Age 70 (95% CI), %</th>
<th>Mean (Median) Age Onset, y</th>
<th>Triple-Negative Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erkko21</td>
<td>2008</td>
<td>Segregation</td>
<td>6.1 (2.2 to 17.2)a</td>
<td>40 (17 to 77)</td>
<td>54.3 (+FH); 59.3 (FH unavailable)</td>
<td>PALB2+</td>
</tr>
<tr>
<td>Rahman23</td>
<td>2007</td>
<td>Segregationb</td>
<td>2.3 (1.4 to 3.9)c</td>
<td>46 (IQR, 40-51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casadei22</td>
<td>2011</td>
<td>Relative risk</td>
<td>2.3 (1.5 to 4.2)d</td>
<td>50.0 (SD=11.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heikkinen22</td>
<td>2009</td>
<td>Standard CC</td>
<td>11.0 (2.6 to 97.8)</td>
<td>53.1 (95% CI, 33.4 to 79.9)</td>
<td>54.5%</td>
<td>9.4%, 12.2%</td>
</tr>
<tr>
<td>Catucci11</td>
<td>2014</td>
<td>Standard CC</td>
<td>13.4 (2.7 to 67.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson24</td>
<td>2015</td>
<td>Standard CC</td>
<td>6.6 (2.3 to 18.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cybulski13</td>
<td>2015</td>
<td>Standard CC</td>
<td>4.4 (2.3 to 8.4)</td>
<td>53.3</td>
<td>34.4%</td>
<td>14.4%</td>
</tr>
<tr>
<td>Antoniou10</td>
<td>2014</td>
<td>Segregationb</td>
<td>6.6 (4.6 to 9.2)c</td>
<td>47.5 (38.6 to 57.4)d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Analysis</td>
<td>RR or (95% CI)</td>
<td>Penetrance at Age 70 (95% CI), %</td>
<td>Mean (Median) Age Onset, y</td>
<td>Triple-Negative Tumors</td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
<td>-------------------</td>
<td>-------------------------</td>
<td>----------------------------------</td>
<td>----------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Southey²⁷ 2016 Standard CC</td>
<td>4.5 (1.9 to 10.8)</td>
<td>5.9 (2.8 to 12.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c.1592delT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c.3113G&gt;A)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CC: case-control; CI: confidence interval; FH: family history; IQR: interquartile range; OR: odds ratio; RR: relative risk.

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 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%).
e 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).
f At age 85 years, RR of 3.4 (95% CI, 2.4 to 5.9).
g In sporadic and familial cancers without PALB2 variants.
Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

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.

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 screening29 (e.g., starting at an early age, the addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention,30 and prophylactic mastectomy.31 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 that the impact on breast cancer incidence extends life in high, but not average risk,32 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.33,34 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 (see Table 3).33 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 CPM.34

Table 3. Model Results of the Effects of Bilateral Risk-Reducing Mastectomy vs Surveillance on Life Expectancy in BRCA Carriers According to Penetrance

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

Adapted from Schrag et al (1997).33

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 breast cancer 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?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is patients who are undergoing assessment for hereditary breast and/or ovarian cancer syndrome who tested negative for BRCA1 or BRCA2.

**Interventions**
The intervention of interest is CHEK2 variant testing.

**Comparators**
The comparator of interest is no genetic testing.

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

**Timing**
Testing for CHEK2 variants is conducted as part of an assessment for hereditary breast and ovarian syndrome.

**Setting**
These tests are offered commercially through various laboratories and institutions.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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

**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. 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 4 and results are shown in Table 5.

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.35 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 multiple cancer 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 vs 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.

A meta-analysis by Yang et al (2012) examined the risk of breast cancer in whites with the CHEK2 c.1100delC variant.36 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.

An article by Schmidt et al (2016) evaluated data on CHEK2 variant status and breast cancer risk from BCAC.37 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).

Table 4. Characteristics of Systematic Reviews of CHEK2 and Risk of Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Population</th>
<th>Designs included</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>Pathogenic Variants Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weischer et al</td>
<td>Up to Mar 2007</td>
<td>Unilateral breast cancer, Northern or Eastern European descent, BRCA1- or BRCA2-negative or -unknown, and breast cancer-free controls</td>
<td>Prospective cohort and case-control</td>
<td>16</td>
<td>26,488</td>
<td>c.1100delC</td>
</tr>
<tr>
<td>Yang et al</td>
<td>Up to May 2012</td>
<td>Mixed</td>
<td>Case-control</td>
<td>16</td>
<td>66,218</td>
<td>c.1100delC</td>
</tr>
<tr>
<td>Schmidt et al</td>
<td>NR</td>
<td>European women in the Breast Cancer Association Consortium</td>
<td>Case-control</td>
<td>33</td>
<td>87,754</td>
<td>c.1100delC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR: not reported</td>
</tr>
</tbody>
</table>

Table 5. Results of Systematic Reviews of CHEK2 and Risk of Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk/Odds Ratio (95% CI)</th>
<th>Penetrance at Age 70 (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weischer et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unselected for family history</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pooled estimate (95% CI)</td>
<td>2.4 (1.8 to 3.2)</td>
</tr>
<tr>
<td></td>
<td>Early-onset breast cancer</td>
<td></td>
</tr>
</tbody>
</table>
### Table 6. Characteristics of Individuals Studies of CHEK2 and Risk of Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Population</th>
<th>No. of Participants</th>
<th>Pathogenic Variants Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naslund-Koch et al (2016)</td>
<td>2003-2010</td>
<td>Copenhagen General Population Study; White participants and those of Danish descent from certain areas of Copenhagen</td>
<td>86,975</td>
<td>c.1100delC</td>
</tr>
<tr>
<td>Hauke et al (2018)</td>
<td>NR</td>
<td>Met inclusion criteria of the German Consortium for Hereditary Breast and Ovarian Cancer for germ-line testing</td>
<td>5589</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

NR: not reported.

### 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 6 and 7. The number of included patients ranged from over 5500 to almost 87,000. 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 family history of breast cancer.
## Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Duration of FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Cybulski et al (2011)</td>
<td>Case-control population of breast cancer patients (and controls), likely overestimated risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; NR: not reported.

Design and conduct gaps are shown in Tables 8 and 9. Only one 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 9. Study Design and Conduct Gaps of Individuals Studies of CHEK2 and Risk of Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Blinding</th>
<th>Delivery of Test</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Statistical</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Duration of FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cybulski et al (2011)14</td>
<td>1. No description of how cases or controls were selected</td>
<td>1. Registration not reported</td>
<td>1. No description of disposition of eligible patients/samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decker et al (2017)38</td>
<td>1. No description of how cases or controls were selected</td>
<td>1. Registration not reported</td>
<td>1. No description of disposition of eligible patients/samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Couch et al (2017)39</td>
<td>1. Incomplete description of how controls were selected</td>
<td>1. Registration not reported</td>
<td>1. Registration not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naslund-Koch et al (2016)40</td>
<td>1. Registration not reported</td>
<td>1. Registration not reported</td>
<td>1. Registration not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
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.

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. 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 hazard ratio comparing carriers of the missense variant with noncarriers was similar, as was the hazard ratio 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. 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 BCAC conducted in 12 countries. 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 a 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 vs noncarriers were
on average 4 years younger (p<0.001); additionally, CHEK2-variant carriers were more likely to have a family history of cancer (p<0.001). Multifactorially adjusted hazard ratios for CHEK2 vs noncarriers were 1.43 (95% CI, 1.12 to 1.82; p=0.004) for early death and 1.63 (95% CI, 1.24 to 2.15; p<0.001) 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 that 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, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

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.

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.

**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. 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 breast cancer 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?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is patients who are undergoing assessment for hereditary breast and/or ovarian cancer syndrome who tested negative for BRCA1 or BRCA2.

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

**Comparators**
The comparator of interest is no genetic testing.

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

**Timing**
Testing for ATM variants is conducted as part of an assessment for hereditary breast and ovarian syndrome.

**Setting**
These tests are offered commercially through various laboratories and institutions.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

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.45 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%).

In another meta-analysis, van Os et al (2016) included 7 studies and found that ATM variants were associated with an increased risk of developing breast cancer in women (RR=3.0; 95% CI, 2.1 to 4.5) and a decreased life expectancy (RR=1.7; 95% CI, 1.2 to 2.4).46

Individual studies published after the meta-analyses have also reported on the association between breast cancer development and pathogenic ATM variants. The study characteristics as well as gaps of Decker (2017), Couch (2017), and Hauke (2018) were included in the previous section on CHEK2 (see Tables 6, 8, and 9). Study results are shown in Table 10.
Table 10. Risk of Breast Cancer Associated With Pathogenic ATM Variants

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Prevalence of ATM variants</th>
<th>RR/ORS (95% CI)</th>
<th>Penetrance at Age 70 (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decker et al (2017)</td>
<td>2017</td>
<td>• 0.6% in breast cancer patients • 0.2% in controls</td>
<td>3.26 (1.82 to 6.46)</td>
<td>NR</td>
</tr>
<tr>
<td>Couch et al (2017)</td>
<td>2017</td>
<td>• 0.9% in breast cancer patients referred for testing • 0.3% in controls</td>
<td>2.78 (2.22 to 3.62)</td>
<td>NR</td>
</tr>
<tr>
<td>Hauke et al (2018)</td>
<td>2018</td>
<td>• 1.3% in breast cancer cases • 0.4% and 0.2% in control samples</td>
<td>3.63 (2.67 to 4.94)</td>
<td>NR</td>
</tr>
</tbody>
</table>

CI: confidence interval; NR: not reported; OR: odds ratio; RR: relative risk.

Section Summary: Clinically Valid
ATM heterozygotes appear to have a RR of breast cancer from 2 to 3 times that of the general population, with an estimated absolute risk of 6% by age 50 and 33% by age 80, although estimates come from the population- and family-based case-controls, which are subject to bias and overestimation.

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

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

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

Section Summary: ATM and Breast Cancer Risk Assessment
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 risk of hereditary breast/ovarian cancer 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 overall survival, disease-specific survival, and test accuracy and validity. Evidence supporting clinical validity was obtained from numerous studies reporting relative risks or odds ratios (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. Relative risks 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 on 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 a meaningful improvement in the net health outcome.

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a CHEK2 variant, the evidence includes studies of variant prevalence, and studies of breast cancer risk. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The available studies on clinical validity have demonstrated that CHEK2 variants are of moderate penetrance, with lower relative risks 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 hereditary breast/ovarian cancer was not identified. It is unclear the relative risk 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 the effects of the technology on health outcomes.

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for an ATM variant, the evidence includes studies of variant prevalence, and studies of breast cancer risk. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The available studies on clinical validity have demonstrated that ATM variants are of moderate penetrance, with lower relative risks 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 hereditary breast/ovarian cancer was not identified. It is unclear the relative risk 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 the effects of the technology on health outcomes.

**Supplemental Information**

**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. 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**

**American Society of Clinical Oncology**
In a 2015 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. 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 National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2018) review single-gene tests for PALB2, CHEK2, or ATM. The guidelines state that a number of genes, including but not limited to PALB2, CHEK2, and ATM, “could potentially” be included in a multigene test, and that there are limited data on the degree of cancer risk associated with some genes in multigene panels.

The National Comprehensive Cancer Network guidelines on breast cancer screening and diagnosis (v.1.2018) and on genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2018) 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 that there is insufficient evidence to draw conclusions on risk-reducing mastectomy in individuals with PALB2, CHEK2, or ATM and that patients should be managed based on family history.

**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 11.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<tbody>
<tr>
<td>NCT02620852</td>
<td>Enabling a Paradigm Shift: A Preference-Tolerant RCT of Personalized vs. Annual Screening for Breast Cancer (Wisdom Study)</td>
<td>100,000</td>
<td>Dec 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
## References

2.04.126 Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk
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2014;160(4):255-266. PMID 24366442


mutation PALB2 1592delT is associated with an aggressive tumor phenotype. Clin Cancer Res. May
1 2009;15(9):3214-3222. PMID 19383810

17200668

26283626

25. Southey MC, Goldgar DE, Winqvist R, et al. PALB2, CHEK2 and ATM rare variants and

26248842

27. Southey MC, Goldgar DE, Winqvist R, et al. PALB2, CHEK2 and ATM rare variants and
26283626

and cancer risk by commercial laboratories as assessed by the prospective registry of

screening in BRCA mutation carriers by BRCA status and age: individual patient data

27269948

31. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in
1637. PMID 11698567

32. Portschy PR, Kuntz KM, Tuttle TM. Survival outcomes after contralateral prophylactic

mastectomy and oophorectomy on life expectancy among women with BRCA1 or

34. Schrag D, Kuntz KM, Garber JE, et al. Life expectancy gains from cancer prevention
strategies for women with breast cancer and BRCA1 or BRCA2 mutations. JAMA. Feb 2
2000;283(5):617-624. PMID 10665701

35. Weischer M, Bojesen SE, Ellervik C, et al. CHEK2*1100delC genotyping for clinical
assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000

Caucasians: a meta-analysis based on 25 studies with 29,154 cases and 37,064 controls.

2760. PMID 27269948

38. Decker B, Allen J, Lucchini C, et al. Rare, protein-truncating variants in ATM, CHEK2 and
PALB2, but not XRCC2, are associated with increased breast cancer risks. J Med Genet. Nov
2017;54(11):732-741. PMID 28779002

panel genes and breast cancer. JAMA Oncol. Sep 1 2017;3(9):1190-1196. PMID 28418444

40. Naslund-Koch C, Nordestgaard BG, Bojesen SE. Increased risk for other cancers in
addition to breast cancer for CHEK2*1100delC heterozygotes estimated from the


**Documentation for Clinical Review**

**Please provide the following documentation (if/when requested):**

- 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/BRCA2 mutation 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**

- 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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT®</td>
<td>81406</td>
<td>Molecular pathology procedure, Level 7</td>
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<tr>
<td>CPT®</td>
<td>81408</td>
<td>Molecular pathology procedure, Level 9</td>
</tr>
<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
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**Policy History**

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>05/29/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>04/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2017</td>
<td>Policy title change from Genetic Testing for PALB2 Mutations Policy revision with position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>09/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
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</tbody>
</table>

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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. Please call (800) 541-6652 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.