Policy Statement

Testing for PALB2 variants for breast cancer risk assessment in adults who meet both 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 of PALB2, CHEK2, ATM, or other genes that are included in a limited panel that meets criteria for medical necessity under another policy (such as 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) may be considered medically necessary.

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 cancer risk is considered investigational.

Policy Guidelines

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

<table>
<thead>
<tr>
<th>Individual without a History of Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>First- or second-degree relative with any of the following:</td>
</tr>
<tr>
<td>o Breast cancer less than or equal to 45 years</td>
</tr>
<tr>
<td>o Ovarian cancer</td>
</tr>
<tr>
<td>o Male breast cancer</td>
</tr>
<tr>
<td>o Pancreatic cancer</td>
</tr>
<tr>
<td>o Metastatic prostate cancer</td>
</tr>
<tr>
<td>o Greater than or equal to 2 breast cancer primaries in a single individual</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>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):</td>
</tr>
<tr>
<td>o Breast cancer, sarcoma, adenocortical carcinoma, brain tumor, leukemia</td>
</tr>
<tr>
<td>o Colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, macrocephaly, hamartomatous polyps of gastrointestinal tract</td>
</tr>
<tr>
<td>o Lobular breast cancer, diffuse gastric cancer</td>
</tr>
<tr>
<td>o Breast cancer, gastrointestinal cancer or hamartomatous polyps, ovarian sex chord tumors, pancreatic cancer, testicular sertoli cell tumors, or childhood skin pigmentation</td>
</tr>
</tbody>
</table>
Table PG2. NCCN Criteria for Genetic Risk Evaluation of an Individual with Breast Cancer

<table>
<thead>
<tr>
<th>Individual with Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 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</td>
</tr>
<tr>
<td>• An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene found on tumor testing</td>
</tr>
<tr>
<td>• An individual diagnosed at any age with any of the following:</td>
</tr>
<tr>
<td>o Ovarian cancer</td>
</tr>
<tr>
<td>o Pancreatic cancer</td>
</tr>
<tr>
<td>o Metastatic prostate cancer</td>
</tr>
<tr>
<td>o Breast cancer or high-grade (Gleason score greater than or equal to 7) prostate cancer and of Ashkenazi Jewish ancestry</td>
</tr>
<tr>
<td>• An individual with a breast cancer diagnosis meeting any of the following:</td>
</tr>
<tr>
<td>o Breast cancer diagnosed age less than or equal to 50 years</td>
</tr>
<tr>
<td>o Triple-negative (ER-, PR-, HER2-) breast cancer diagnosed less than or equal to 60 years</td>
</tr>
<tr>
<td>o Two breast cancer primaries</td>
</tr>
<tr>
<td>o Breast cancer at any age and:</td>
</tr>
<tr>
<td>▪ Greater than or equal to 1 close blood relative with breast cancer age less than or equal to 50 years, or</td>
</tr>
<tr>
<td>▪ Greater than or equal to 1 close blood relative with invasive ovarian cancer, or</td>
</tr>
<tr>
<td>▪ Greater than or equal to 1 close blood relative with male breast cancer, or</td>
</tr>
<tr>
<td>▪ Greater than or equal to 1 close blood relative with pancreatic cancer, or</td>
</tr>
<tr>
<td>▪ 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</td>
</tr>
<tr>
<td>▪ Greater than or equal to 2 close blood relatives with breast cancer at any age</td>
</tr>
<tr>
<td>• 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):</td>
</tr>
<tr>
<td>o Breast cancer, sarcoma, adrenocortical carcinoma, brain tumor, leukemia</td>
</tr>
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<td>o Colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, macrocephaly, hamartomatous polyps of gastrointestinal tract</td>
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</tr>
</tbody>
</table>

ER: estrogen receptor; HER2: human epithelial 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

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 BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers
- 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 252710 women and 40610 would die from the disease; a woman’s lifetime risk is 12.4%. Breast cancers can be classified as sporadic, familial, or hereditary. 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 10000 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 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 one and four 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.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 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), 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.

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 PICOs were used to select literature to inform this review.

**Patients**

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 who tested negative for BRCA1 or BRCA2.

**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
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires a 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).

Systematic Reviews

Suszynska et al (2019) reported a systematic review of variants identified in panels of breast and ovarian cancer-related genes. Results were reported for PALB2, CHEK2, and ATM. CHEK2 and ATM results will be discussed in the following sections. The systematic review included studies published through July 2017 reporting on genetic test results of breast and ovarian cancer patients who were referred for evaluation by a multi-gene panel. Given that the Suszynska et al (2019) report included only studies reporting on test results from a panel, it does not substantially overlap with the studies described in the following section including other PALB2 association studies. The studies of panel results were used to calculate mutation frequencies by the gene. As a control, population mutation frequencies were extracted from the Genome Aggregation Database. Forty-three studies included panels in breast cancer patients. In the breast cancer studies, 95853 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 CI, 4.1 to 5.6).

Observational Studies

A number of studies (see Tables 1 and 2) reporting relative risks (RR) or ORs for the association between PALB2 and breast cancer were identified (two reported penetrance estimates). Study designs included family segregation, kin-cohort, family-based case-control, and population-based or multicenter case-control. The two multinational studies included individuals from up to five 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 two multinational collaborative efforts.

Single-Country Samples

Lu et al (2019) included analysis of 11416 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. Whole-exome sequencing was used for sequencing 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 95561 women tested clinically for hereditary cancer risk using a multi-gene panel that included PALB2, CHEK2 and ATM. Although the country is not stated, the patients underwent testing between Laboratory Improvement Amendments 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 were OR = 3.39 (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. 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% confidence interval [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. From 12529 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. or the U.S.). A PALB2 variant was also associated with poorer prognosis-10-year survival of 48.0% vs 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. 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 two distinct populations, the combined sample size was small, and uncertainty as indicated by the large effect estimate.

Casadei et al (2011) studied 959 U.S. women (non-Ashkenazi Jewish descent) with a family history of BRCA1- or BRCA2-negative breast cancer and 83 female relatives using a family-based case-control design. Using conventional sequencing, pathogenic PALB2 variants were detected in 31 (3.2%) women with breast cancer and none in controls. Compared with their female relatives without PALB2 variants, the risk of breast cancer increased 2.3-fold (95% CI, 1.5 to 4.2) by age 55 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. 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; 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.

**Multinational Samples**

Southey et al (2016) examined the association of 3 PALB2 variants (2 protein-truncating: c.1592delT and c.3113G>A; 1 missense c.2816T>G) with breast, prostate, and ovarian cancers. The association with breast cancer was examined among participants in the Breast Cancer Association Consortium (BCAC; 42671 cases and 42164 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 four 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 (37039 cases, 38260 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=0.003). The c.3113G>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<0.001). There was no association between the c.2816T>G missense variant and breast cancer (found in 150 cases and 145 controls).

These results, derived from a large sample, used a different analytic approach than Antoniou et al (2014), described next, and examined only 2 pathogenic variants. The magnitude of the estimated RR approaches that of a high penetrance gene but is accompanied by wide CIs owing to the study design and low carrier prevalence. The lower estimates obtained following exclusion of those selected based on family history or bilateral disease are consistent with the importance of carefully considering the risk of hereditary disease prior to genetic testing. Antoniou et al (2014) analyzed data from 362 members of 154 families with deleterious PALB2 variants. Individuals with benign variants or variants of uncertain significance were excluded. Families were recruited at 14 centers in 8 countries (U.S., U.K., Finland, Greece, Australia, Canada, Belgium, Italy) and had at least 1 member with a BRCA1- or BRCA2-negative PALB2-positive breast cancer. There were 311 women with PALB2 variants—229 had breast cancer; 51 men also had PALB2 variants (7 had breast cancer). Of the 48 pathogenic (loss-of-function) variants identified, 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....”
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.31 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 Families</th>
<th>PALB2 Variants</th>
<th>Totals</th>
<th>Pathogenic Variants Identified</th>
<th>N Prevalence Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu</td>
<td>2019</td>
<td>U.S.</td>
<td>Multicenter CC</td>
<td>15,404</td>
<td>61 NR</td>
<td>155 32</td>
<td>3988 NR</td>
<td>0.4%</td>
</tr>
<tr>
<td>Thompson</td>
<td>2015</td>
<td>Australia</td>
<td>Population-based CC</td>
<td>399 4</td>
<td>26 4</td>
<td>199 6</td>
<td>1998 19</td>
<td>1.3</td>
</tr>
<tr>
<td>Cybulski</td>
<td>2015</td>
<td>Poland</td>
<td>Population-based CC</td>
<td>17,231</td>
<td>116 10</td>
<td>12,529</td>
<td>4702 2</td>
<td>0.9</td>
</tr>
<tr>
<td>Catucci</td>
<td>2014</td>
<td>Italy</td>
<td>Population-based</td>
<td>590</td>
<td>6 2</td>
<td>113 477</td>
<td>1 (c.1027 C&gt;T)</td>
<td>5.3</td>
</tr>
</tbody>
</table>
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 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>Lu27.</td>
<td>2019</td>
<td>Standard CC</td>
<td>5.5 (2.2 to 17.7)</td>
<td>53.1 (95% CI, 33.4 to 79.9)</td>
<td>54.5 (IQR; 40-51)</td>
<td>30</td>
</tr>
<tr>
<td>Antoniou10,</td>
<td>2014</td>
<td>Segregation(^a)</td>
<td>6.6 (4.6 to 9.2)</td>
<td>47.5 (38.6 to 57.4)</td>
<td>54.3 (+FH); 59.3</td>
<td></td>
</tr>
<tr>
<td>Erkko22,</td>
<td>2008</td>
<td>Segregation</td>
<td>6.1 (2.2 to 17.2)</td>
<td>40 (17 to 77)</td>
<td>54.3 (-FH); 59.3</td>
<td></td>
</tr>
<tr>
<td>Rahman24,</td>
<td>2007</td>
<td>Segregation(^a)</td>
<td>2.3 (1.4 to 3.9)</td>
<td>46 (IQR); 40-51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casadei12</td>
<td>2011</td>
<td>Relative risk</td>
<td>2.3 (1.5 to 4.2)</td>
<td>50.0 (SD=11.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson25</td>
<td>2015</td>
<td>Standard CC</td>
<td>6.6 (2.3 to 18.9)</td>
<td>55.3</td>
<td>34.4</td>
<td>14.4</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></td>
<td></td>
</tr>
<tr>
<td>Catucci11</td>
<td>2014</td>
<td>Standard CC</td>
<td>13.4 (2.7 to 67.4)</td>
<td>53.1 (95% CI, 33.4 to 79.9)</td>
<td>54.5</td>
<td>9.4, 12.2(^a)</td>
</tr>
<tr>
<td>Heikkinen23</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></td>
</tr>
<tr>
<td>Southey30</td>
<td>2016</td>
<td>Standard CC</td>
<td>4.5 (1.9 to 10.8)</td>
<td>(c.1592delT)</td>
<td>5.9 (2.8 to 12.7)</td>
<td></td>
</tr>
<tr>
<td>Kuriann 28,</td>
<td>2017</td>
<td>Standard CC</td>
<td>3.39 (2.79 to 4.12)</td>
<td>5.9 (2.8 to 12.7)</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; SD: standard deviation.
Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk

2.04.126

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.

The purpose of limitations tables (see Tables 3 and 4) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

### Table 3. Relevance Limitations of Individuals Studies of Pathogenic PALB2 Variants

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Duration of FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu27,</td>
<td>4. Case-control population of breast cancer patients (and controls), likely overestimated risk</td>
<td>1: Not clear which variants were included</td>
<td>Control chosen from patients being tested for hereditary cancer; unclear how many developed cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurian28,</td>
<td>4. Case-control population of breast cancer patients (and controls), likely overestimated risk</td>
<td>1: Not clear which variants were included</td>
<td>Control chosen from patients being tested for hereditary cancer; unclear how many developed cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southey et al (2016)30,</td>
<td>4. Case-control population of breast cancer patients (and controls), likely overestimated risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson et al (2015)25,</td>
<td>4. Case-control population of breast cancer patients (and controls), likely overestimated risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cybulski et al (2015)13,</td>
<td>4. Case-control population of breast cancer patients (and controls), likely overestimated risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catucci et al (2014)11,</td>
<td>4. Case-control population of breast cancer patients referred for genetic testing (and controls), likely overestimated risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antoniou et al (2014)10,</td>
<td>4. Case-control population of breast cancer patients (and controls), likely overestimated risk; only kin-cohort included</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casadei et al (2011)12,</td>
<td>4. Case-control population of breast cancer patients (and controls), likely overestimated risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Heikkinen et al (2009)\textsuperscript{23}. 4. Case-control population of breast cancer patients referred for genetic testing (and controls), likely overestimated risk

Erkko et al (2008)\textsuperscript{22}. 4. No case-control group

Rahman et al (2007)\textsuperscript{24}. 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 limitations assessment.

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.

\(d\) Outcome 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection(a)</th>
<th>Blinding(b)</th>
<th>Delivery of Test(c)</th>
<th>Selective Reporting(d)</th>
<th>Data Completeness(e)</th>
<th>Statistical(f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu\textsuperscript{27}.</td>
<td>1. Incomplete description of how controls selected</td>
<td></td>
<td></td>
<td>1. Registration not reported</td>
<td>1. No description of disposition of eligible patients/samples</td>
<td></td>
</tr>
<tr>
<td>Kurian\textsuperscript{28}.</td>
<td></td>
<td></td>
<td></td>
<td>1. Registration not reported</td>
<td>1. No description of disposition of eligible patients/samples</td>
<td></td>
</tr>
<tr>
<td>Southey et al (2016)\textsuperscript{30}.</td>
<td></td>
<td></td>
<td></td>
<td>1. Registration not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thompson et al (2015)\textsuperscript{25}.</td>
<td>1. Incomplete description of how controls selected</td>
<td></td>
<td></td>
<td>1. Registration not reported</td>
<td>1. No description of disposition of eligible patients/samples</td>
<td></td>
</tr>
<tr>
<td>Cybulski et al (2015)\textsuperscript{13}.</td>
<td>1. Incomplete description of how controls selected</td>
<td></td>
<td></td>
<td>1. Registration not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catucci et al (2014)\textsuperscript{11}.</td>
<td>1. Incomplete description of how controls selected</td>
<td></td>
<td></td>
<td>1. Registration not reported</td>
<td>1. No description of disposition of eligible patients/samples</td>
<td></td>
</tr>
<tr>
<td>Antoniou et al (2014)\textsuperscript{10}.</td>
<td>2. Kin-cohort-controls not randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Casadei et al (2011)\textsuperscript{12}  
2. Family groups: controls not randomized  
1. Registration not reported

Heikkinen et al (2009)\textsuperscript{23}  
1. Incomplete description of how controls selected  
1. Registration not reported

Erkko et al (2008)\textsuperscript{22}  
2. Family groups: selection not randomized  
1. Registration not reported; number of controls unknown

Rahman et al (2007)\textsuperscript{24}  
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 limitations assessment.

\textsuperscript{a} Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

\textsuperscript{b} Blinding key: 1. Not blinded to results of reference or other comparator tests.

\textsuperscript{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.

\textsuperscript{d} Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

\textsuperscript{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.

\textsuperscript{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, 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.

Rosenthal et al (2017) reported an analysis of the impact of testing for genes other than BRCA1/2 and by calculating whether carriers of these gene variants would have been identified as candidates for enhanced screening based family history alone.\textsuperscript{32} The database included 194107 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
A moderate penetrance variant but did not have 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 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 (e.g., starting at an early age, the addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention, and prophylactic mastectomy. 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, 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. 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 5). A 50-year-old female BRCA carrier with node-negative breast cancer and a 24% risk of contralateral breast cancer by age 70 would anticipate 0.9 years in improved life expectancy (0.6 years for node-negative disease) following a prophylactic contralateral mastectomy.

Table 5. 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>
<th>40% Risk of Breast Cancer</th>
<th>60% Risk of Breast Cancer</th>
<th>85% Risk of Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td></td>
<td>4.1</td>
<td>2.4</td>
<td>5.3</td>
</tr>
<tr>
<td>40</td>
<td></td>
<td>2.9</td>
<td>1.1</td>
<td>2.6</td>
</tr>
<tr>
<td>50</td>
<td></td>
<td>1.0</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>60</td>
<td></td>
<td>0.2</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Mastectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy delayed 10 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td></td>
<td>1.6</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Mastectomy delayed 10 y</td>
<td></td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td></td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy delayed 10 y</td>
<td></td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Schrag et al (1997).37

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 PICOs were used to select literature to inform this review.

**Patients**
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 are 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 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 met the eligibility criteria outlined for indication 1 were considered.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires a 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 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. 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.
Liang et al (2018) conducted a meta-analysis to investigate the link between CHEK2 and breast cancer. Two researchers independently searched 7 online databases and selected for analysis 26 published studies representing a pooled sample of 118735 cancer patients and 195807 controls, all case-control studies conducted in Europe or the Americas. The meta-analysis revealed that CHEK2 variants are more common in patients with breast cancer (OR=2.89; 95% CI, 2.63 to 3.16), with variants 5.9% more likely in female patients with breast cancer than in male patients with breast cancer. Limitations of the study included a study population that might not represent the general population, inaccurate control sampling methods in some original studies, selection biases, and unclear criteria for breast cancer diagnoses.

An article by Schmidt et al (2016) evaluated data on CHEK2 variant status and breast cancer risk from BCAC.39,40, The analysis included 44777 breast cancer patients and 42997 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.39 Twenty-five case-control studies conducted in Europe and North and South America published in 16 articles were analyzed, with a total of 29154 breast cancer cases and 37064 controls. Of the cases, 13875 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.41, 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 multicaner 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 26488 patient cases and 27402 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.

<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>Suszynska et al (2019)</td>
<td>To Jul 2017</td>
<td>Cases: Patients with breast and/or ovarian cancer referred for evaluation by a multi-gene panel</td>
<td>Studies reporting prevalence of genetic variants</td>
<td>48 (overall) 43 (breast cancer)</td>
<td>94845 included in CHEK2 analysis</td>
<td>37 CHEK2 variants</td>
</tr>
</tbody>
</table>
Schmidt et al (2016)\(^{39,40,39,}\) with breast cancer) European women in the Breast Cancer Association Consortium Case-control 33 87,754 c.1100delC

Yang et al (2012)\(^{39,}\) To May 2012 Mixed Case-control 16 66,218 c.1100delC

Weischer et al (2008)\(^{41,}\) 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>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk/Odds Ratio (95% CI)</th>
<th>Penetration at Age 70 (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suszynska et al (2019)(^{21,})</td>
<td>1.73 (95% CI, 1.58 to 1.89(^{a}))</td>
<td>NR</td>
</tr>
<tr>
<td>Schmidt et al (2016)(^{40,}) Overall</td>
<td>1.73 (95% CI, 1.58 to 1.89(^{a}))</td>
<td>NR</td>
</tr>
<tr>
<td>Total N</td>
<td>81,700</td>
<td></td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>2.4 (2.1 to 2.9)</td>
<td>»17</td>
</tr>
<tr>
<td>Non-BRCA1 or BRCA2 Total N</td>
<td>72,334</td>
<td></td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>2.3 (2.0 to 2.8)</td>
<td>NR</td>
</tr>
<tr>
<td>Yang et al (2012)(^{39,}) Unselected for family history Total N</td>
<td>50,939</td>
<td></td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>2.3 (1.8 to 3.1)</td>
<td></td>
</tr>
<tr>
<td>Early-onset breast cancer Total N</td>
<td>42,866</td>
<td></td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>2.8 (2.3 to 3.4)</td>
<td></td>
</tr>
<tr>
<td>Familial breast cancer Total N</td>
<td>45,009</td>
<td></td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>3.7 (2.6 to 5.3)</td>
<td></td>
</tr>
<tr>
<td>Weischer et al (2008)(^{41,}) Unselected for family history Total N</td>
<td>45,009</td>
<td></td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>2.4 (1.8 to 3.2)</td>
<td></td>
</tr>
<tr>
<td>Early-onset breast cancer Total N</td>
<td>42,866</td>
<td></td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>2.7 (1.3 to 5.6)</td>
<td></td>
</tr>
<tr>
<td>Familial breast cancer Total N</td>
<td>37 (26 to 56)</td>
<td></td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>4.6 (3.1 to 6.8)</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; 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 8 and 9. The number of included patients ranged from over 5500 to over 95000. The prevalence of CHEK2 variants was approximately 2% to 3% in breast cancer patients.

Table 7. 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>Penetration at Age 70 (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suszynska et al (2019)(^{21,})</td>
<td>1.73 (95% CI, 1.58 to 1.89(^{a}))</td>
<td>NR</td>
</tr>
</tbody>
</table>

Excluding variants c.470T>C and c.1283C>T
HR, or RR ranged from approximately two to three, although it was higher in subgroups of women with a family history of breast cancer.

**Table 8. Characteristics of 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>Lu et al (2019)</td>
<td>2014-2015</td>
<td>Cases with breast and/or ovarian cancer referred for genetic testing and controls referred for genetic testing for noncancer conditions</td>
<td>15,404</td>
<td>Known breast or ovarian cancer gene*</td>
</tr>
<tr>
<td>Kurian et al (2017)</td>
<td>2013-2015</td>
<td>Cases and controls referred for testing for hereditary cancer. Control were those without cancer at the time of testing</td>
<td>95,561</td>
<td>Unclear</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>
<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>
</tbody>
</table>

NR: not reported.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence of CHEK2 Variants</th>
<th>OR (95% CI)</th>
<th>Penetrance at Age 70 (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu et al (2019)</td>
<td>0.8% in breast or ovarian cancer cases 0.3% in controls</td>
<td>2.19 (1.40 to 3.56)</td>
<td>NR</td>
</tr>
<tr>
<td>Kurian et al (2017)</td>
<td>1.2% in breast cancer patients 1.1% in patients without breast or ovarian cancer</td>
<td>1.99 (1.70 to 2.33)</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Fan et al (2018)**

<table>
<thead>
<tr>
<th>Overall</th>
<th>Total N</th>
<th>7657</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate (95% CI)</td>
<td>0.34% in breast cancer patients</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

**Hauke et al (2018)**

<table>
<thead>
<tr>
<th>Overall</th>
<th>Total N</th>
<th>5589</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate (95% CI)</td>
<td>1.8% in breast cancer patients 0.6% and 0.4% in control datasets</td>
<td>2.9 (2.3 to 3.8)</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Decker et al (2017)**

<table>
<thead>
<tr>
<th>Overall</th>
<th>Total N</th>
<th>18,575</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate (95% CI)</td>
<td>c.1100delC plus 14 rare truncating variants</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>
Total N
Estimate (95% CI)  
18,575
- 1.6% in breast cancer patients
- 0.5% in controls

Couch et al (2017)\textsuperscript{44}.

Overall
Total N
Estimate (95% CI)  
54,305
- 1.5% in breast cancer patients
- 0.7% in controls

Naslund-Koch et al (2016)\textsuperscript{45}.

Overall
Total N
Estimate (95% CI)  
86,975
- 0% homozygotes
- 0.8% heterozygotes

Cybulski et al (2011)\textsuperscript{14}.

Overall
Total N
Estimate (95% CI)  
11,842
- 3.0% in breast cancer patients
- 0.8% in controls

Without family history of breast cancer
Total N
Estimate (95% CI)  
10,391
- 2.8% in breast cancer patients
- 0.8% in controls

First- or second-degree relative with breast cancer
Total N
Estimate (95% CI)  
5797
- 4.7% in breast cancer patients
- 0.8% in controls

<table>
<thead>
<tr>
<th>Study</th>
<th>Population\textsuperscript{a}</th>
<th>Intervention\textsuperscript{b}</th>
<th>Comparator\textsuperscript{c}</th>
<th>Outcomes\textsuperscript{d}</th>
<th>Duration of FU\textsuperscript{e}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu\textsuperscript{27}</td>
<td>4. Case-control population of breast cancer patients (and controls), likely overestimated risk</td>
<td>1: Not clear which variants were included</td>
<td>1: Control chosen from patients being tested for hereditary cancer; unclear how many developed cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurian\textsuperscript{28}</td>
<td>4. Case-control population of breast cancer patients (and controls), likely overestimated risk</td>
<td>1: Not clear which variants were included</td>
<td>1: Control chosen from patients being tested for hereditary cancer; unclear how many developed cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fan et al (2018)</td>
<td>4. Case-control population of breast cancer patients (and controls), likely overestimated risk; only included Chinese patients</td>
<td>1: Not clear which variants were included</td>
<td>1: Control chosen from patients being tested for hereditary cancer; unclear how many developed cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Study design and conduct limitations are shown in Tables 10 and 11. 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 10. Relevance Limitations 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>
</tr>
</thead>
<tbody>
<tr>
<td>Lu27,</td>
<td>1. Incomplete description of how controls 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>
</tr>
<tr>
<td>Kurian28,</td>
<td></td>
<td></td>
<td>Registration not reported</td>
<td>1. No description of disposition of eligible patients/samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fan et al (2018)</td>
<td>1. Incomplete description of how controls 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>
</tr>
<tr>
<td>Hauke et al (2018)42.</td>
<td>1. Incomplete description of how controls 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>
</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.

Fan et al (2018) investigated the clinical relevance of CHEK2 variants in breast cancer patients. 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 ($p=0.022$) 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. 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 four 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 six 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 25571 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.48 The 22 studies included 30056 controls. Data were reported on early death in 25571 women, breast cancer-specific death in 24345, and a diagnosis of second breast cancer in 25094. Of the 25571 women, 459 (1.8%) were CHEK2 c.1100delC heterozygous and 25112 (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 four 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 two to four 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, 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 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 PICOs were used to select literature to inform this review.

**Patients**
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 are patients who are undergoing assessment for HBOC syndrome who tested negative for BRCA1 or BRCA2.

**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 met the eligibility criteria outlined for indication 1 were considered.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires a 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).

Systematic Reviews
The Suszynska et al (2019) systematic review described previously also included association estimates for ATM variants. In the 43 breast cancer studies included in the review, 94787 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. 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).

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 Lu et al (2019), Kurian et al (2017), Decker et al (2017), Couch et al (2017), Hauke et al (2018), were included in the previous section on CHEK2 (see Tables 8, 10, and 11). Study results are shown in Table 12.

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence of ATM Variants</th>
<th>RR OR (95% CI)</th>
<th>Penetrance at Age 70 (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu et al (2019)</td>
<td>0.7% in breast and ovarian cancer cases 0.2% in controls</td>
<td>2.97 (1.67 to 5.68)</td>
<td>NR</td>
</tr>
<tr>
<td>Hauke et al (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>
<tr>
<td>Decker et al (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>• 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>Kurian et al (2017)</td>
<td>• 0.92% in breast cancer patients referred for testing • 1% in patients referred for testing without breast or ovarian cancer</td>
<td>1.74 (1.46 to 2.07)</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 an 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.

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.

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 a 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. The relevant outcomes are OS, disease-specific survival, and test validity. Evidence supporting clinical validity was obtained from numerous studies reporting RR or ORs (two 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 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. The 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 two to four 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 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 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. The 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 two to four 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 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 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. 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

American Society of Clinical Oncology
In a policy statement update on genetic and genomic testing for cancer susceptibility, the American Society of Clinical Oncology (2015) 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 (v.3.2019) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer 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 guidelines state that the panel recommends an annual mammogram for women with mutated PALB2 gene beginning at age 30 and with mutated ATM or CHEK2 gene beginning at age 40 with consideration of annual breast MRI.
The National Comprehensive Cancer Network guidelines on breast cancer screening and diagnosis (v.1.2019)\textsuperscript{52} and on genetic/familial high-risk assessment for breast and ovarian cancer (v.3.2019)\textsuperscript{3} 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 \textit{PALB2}, \textit{CHEK2}, or \textit{ATM} and that patients should be managed based on family history.

\textbf{U.S. Preventive Services Task Force Recommendations}

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

\textbf{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.

\textbf{Ongoing and Unpublished Clinical Trials}

Some currently unpublished trials that might influence this review are listed in Table 13.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{NCT No.} & \textbf{Trial Name} & \textbf{Planned Enrollment} & \textbf{Completion Date} \\
\hline
Ongoing & NCT02620852 & Enabling a Paradigm Shift: A Preference-Tolerant RCT of Personalized vs. Annual Screening for Breast Cancer (Wisdom Study) & 100,000 & Dec 2020 \\
\hline
\end{tabular}
\caption{Summary of Key Trials}
\end{table}

NCT: national clinical trial.

\textbf{References}


**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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<tbody>
<tr>
<td>CPT®</td>
<td>0102U</td>
<td>Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [17 genes (sequencing and deletion/duplication)] <em>(Code effective 7/1/2019)</em></td>
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<td>Type</td>
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<tr>
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<td>0129U</td>
<td>Hereditary breast cancer-related disorders (eg, 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) (Code effective 10/1/2019)</td>
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<tr>
<td></td>
<td>0131U</td>
<td>Hereditary breast cancer-related disorders (eg, 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) (Code effective 10/1/2019)</td>
</tr>
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<td>81406</td>
<td>Molecular pathology procedure, Level 7</td>
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<tr>
<td></td>
<td>81408</td>
<td>Molecular pathology procedure, Level 9</td>
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<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
<td></td>
<td>HCPCS</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>
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<tbody>
<tr>
<td>05/29/2015</td>
<td>BCBSA Medical Policy adoption</td>
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<tr>
<td>04/01/2016</td>
<td>Policy revision without position change</td>
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<tr>
<td>03/01/2017</td>
<td>Policy title change from Genetic Testing for PALB2 Mutations</td>
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<tr>
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<td>Policy revision with position change</td>
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<tr>
<td>02/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>09/01/2018</td>
<td>Policy revision without position change</td>
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<tr>
<td>03/01/2019</td>
<td>Policy revision without position change</td>
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<tr>
<td>05/01/2019</td>
<td>Policy revision without position change/Coding update</td>
</tr>
<tr>
<td>11/01/2019</td>
<td>Coding update</td>
</tr>
<tr>
<td>01/01/2020</td>
<td>Annual review. No change to policy statement. Literature review updated.</td>
</tr>
</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 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.