Moderate Penetrance Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider testing for *PALB2* variants for breast cancer risk assessment in adults to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility will be met in individuals with the following:

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

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers testing for *PALB2* sequence variants in individuals who do not meet the criteria outlined above to be **investigational.***

Based on review of available data, the Company considers testing for *CHEK2* and *ATM* variants in the assessment of breast cancer risk to be **investigational.***

Policy Guidelines

Criteria from National Comprehensive Cancer Network (NCCN) guidelines for genetic risk evaluation of women without and with breast cancer are listed in Tables PG1 and PG2.

Table PG1. 2016 NCCN Criteria for Genetic Risk Evaluation of an Individual Without a History of Breast Cancer

Individual Without a History of Breast Cancer
"A close relative (includes 1st, 2nd, 3rd degree relative) with any of the following:
A known sequence variant in a cancer susceptibility gene within the family

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≥2 breast cancer primaries in a single individual(includes bilateral disease or 2 or more separate ipsilateral primary tumors either diagnosed synchronously or asynchronously)
≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 years
Ovarian cancer (includes fallopian tube and primary peritoneal cancers)
Male breast cancer
First- or second-degree relative with breast cancer ≤45 years
Family history of three or more of the following (especially if early onset and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, and/or macrocephaly, hamartomatous polyps of GI tract”

GI: gastrointestinal; NCCN: National Comprehensive Cancer Network.

Table PG2. 2016 NCCN Criteria for Genetic Risk Evaluation of an Individual With Breast Cancer

Individual With Breast Cancer
“A known sequence variant in a cancer susceptibility gene within the family
Early-age-onset breast cancer (clinically use age =/< (equal to or less than) 50 years)
Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 years
Two breast cancer primaries in a single individual(includes bilateral disease or 2 or more separate ipsilateral primary tumors either diagnosed synchronously or asynchronously)
Breast cancer at any age, and
≥1 close blood relative with breast cancer ≤50 years, or
≥1 close blood relative with invasive ovarian cancer at any age, or
≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or
From a population at increased risk
Male breast cancer
An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age
An individual with a personal and/or family history of three or more of the following (especially if early onset and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract.”
An individual with an ovarian cancer (includes fallopian tube and primary peritoneal cancers)

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; NCCN: National Comprehensive Cancer Network; PR: progesterone receptor.

A Recommended Testing Strategy

Patients who meet criteria for genetic testing as outlined in the policy statements above should be tested for sequence variants in *BRCA1* and *BRCA2*.

- In patients with a known familial *BRCA* sequence variant, targeted testing for the specific sequence variant is recommended.
- In patients with unknown familial *BRCA* sequence variant:
  - Non-Ashkenazi Jewish descent

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- To identify clinically significant variants, NCCN advises testing a relative who has breast or ovarian cancer, especially with early-onset disease, bilateral disease, multiple primaries, or ovarian cancer, because that individual has the highest likelihood for a positive test result.
- If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1* or *BRCA2* sequence variants (eg, prostate cancer, pancreatic cancer, melanoma).
- If no familial sequence variant can be identified, 2 possible testing strategies are:
  - Full sequencing followed by testing for common large genomic rearrangements (deletions/duplications) only if sequencing detects no sequence variant (negative result).
    - More than 90% of BRCA sequence variants will be detected by full sequencing.
  - Alternatively, simultaneous full sequencing and testing for common large genomic rearrangements (also known as comprehensive BRCA testing; see the Comprehensive Variant Analysis section below) may be performed as is recommended by NCCN.
    - Comprehensive testing can detect 92.5% of *BRCA1* and *BRCA2* sequence variants.
- If comprehensive BRCA testing is negative, testing for uncommon large genomic rearrangements (eg, BART™)[‡] may be done.
  - Testing for uncommon large rearrangements should not be done unless both sequencing and testing for common large rearrangements have been performed and are negative.
    - Among patients with negative comprehensive testing, BART identified a deleterious sequence variant (positive result) in less than 1%.

o Ashkenazi Jewish descent
- In patients of known Ashkenazi Jewish descent, NCCN recommends testing for the 3 known founder sequence variants (185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*) first.
- If testing is negative for founder sequence variants, comprehensive genetic testing may be considered (see the Comprehensive Variant Analysis section below).

Comprehensive Variant Analysis

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

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High-Risk Ethnic Groups
Testing in eligible individuals who belong to ethnic populations in which there are well-characterized founder sequence variants should begin with tests specifically for these variants. For example, founder variants account for approximately three-quarters of the *BRCA* sequence variants found in Ashkenazi Jewish populations (see Rationale section). When testing for founder sequence variants is negative, comprehensive variant analysis should then be performed.

Testing Unaffected Individuals
In unaffected family members of potential BRCA sequence variant families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an affected family member be tested first whenever possible to adequately interpret the test. Should a *BRCA* variant be found in an affected family member(s), DNA from an unaffected family member can be tested specifically for the same variant of the affected family member without having to sequence the entire gene. Interpreting test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated variant but leads to difficulties in interpreting negative test results (uninformative negative) or variants of uncertain significance because the possibility of a causative *BRCA* variant is not ruled out.

Prostate Cancer
Patients with *BRCA* sequence variants have an increased risk of prostate cancer, and patients with known *BRCA* sequence variants may therefore consider more aggressive screening approaches for prostate cancer. However, the presence of prostate cancer in an individual, or in a family, is not itself considered sufficient justification for BRCA testing.

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.

Background/Overview

BREAST CANCER AND GENETICS
In 2016, researchers anticipate breast cancer will be diagnosed in 246,660 women and 40,450 will die from the disease; a woman's lifetime risk is 12.3% (seer.cancer.gov/statfacts/html/breast.html). Breast cancers can be classified as sporadic, familial, or hereditary. Most are sporadic (70% to 75%), occurring in women without a family history of disease. Familial cancers (15% to 25%) aggregate within families but lack clearly discernable patterns of inheritance and are likely polygenic. Hereditary cancers have discernable

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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 (eg, *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 <1.53). 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. In addition, specific pathogenic variants within a gene may confer somewhat different risks.

DETERMINING VARIANT PATHOGENICITY

Determining the pathogenicity of variants in a cancer-susceptibility gene most commonly detected (eg, founder sequence variants) 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 (www.omim.org/entry/610355). The PALB2 protein assists *BRCA2* in DNA repair and tumor suppression. Heterozygous pathogenic *PALB2* variants increase the risk of developing breast and pancreatic cancers; homozygous variants are found in Fanconi anemia. Most pathogenic *PALB2* variants are truncating frameshift or stop codons, and are found throughout the gene. Pathogenic *PALB2* variants are uncommon in unselected populations and prevalence varies by ethnicity and family history. For example, Antoniou et al (2014) assumed a prevalence of 8 per 10,000 in the general population when modeling breast cancer risks. Variants are more prevalent in ethnic populations where founder variants have persisted (eg, Finns, French Canadians, Poles), while infrequently found in others (eg, 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

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population. Depending on population prevalence, *PALB2* may be responsible for as much as 2.4% of hereditary breast cancers; and in populations with founder variants cause 0.5% to 1% of all breast cancers.

Protein-truncating *PALB2* variants appear responsible for some cases of familial pancreatic cancers, but the proportion is unclear. Whether screening asymptomatic high-risk patients for pancreatic cancer can improve health outcomes is uncertain.

***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 mutation 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 variant, 3 other founder variants of *CHEK2* (IVS2+1G>A, del5395, I157T) have been associated with breast cancer in Eastern Europe. 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.

***ATM* Gene**
ATM (ataxia-telangiectasia [AT] mutated), located on chromosome 11q22.3, is associated with the autosomal recessive condition AT. This condition is characterized by progressive cerebellar ataxia with onset between the ages of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition. Female *ATM* heterozygotes carriers have a risk of breast cancer about twice as high as that of the general population, but 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. A family history of breast cancer confers between a 2- and 4-fold increased risk varying according to several factors: the number and closeness of affected relatives, age at which cancers developed, whether breast cancers were bilateral, and if other cancers occurred (eg, ovarian). For a woman without breast cancer, the probability of detecting a pathogenic variant can be estimated from a detailed multigenerational pedigree (eg, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), screening tools (eg, BRCAPRO, Ontario Family History Assessment Tool, Manchester Scoring

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System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen), or by referring to guidelines that define specific family history criteria (see section on Practice Guidelines and Position Statements below). For women with breast cancer, family history also affects the likelihood of carrying a pathogenic variant.

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). *PALB2, CHEK2,* and *ATM* testing are available under the auspices of CLIA (a list of laboratories offering testing is available at NCBI's Genetic Testing Registry (GTR [https://www.ncbi.nlm.nih.gov/htr/). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the FDA 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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

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

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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.

PALB2 AND BREAST CANCER RISK ASSESSMENT

Clinical Context and Test Purpose

The purpose of testing for *PALB2* variants in individuals at high-risk of breast cancer is to evaluate whether an abnormal variant is present and, if so, to determine whether the variant conveys a sufficiently high risk that changes in surveillance and/or treatment likely to decrease the risk of mortality from breast and/or ovarian cancer are warranted.

The question addressed in this evidence review is: Does genetic testing for *PALB2* variants improve the net health outcome?

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

Patients

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

Interventions

The intervention of interest is *PALB2* variant testing.

Comparators

The comparator of interest is no genetic testing.

Outcomes

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

Timing

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

Setting

These tests are offered commercially through various laboratories and institutions.

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Technically Reliable
The technical reliability of a test is its accuracy in detecting a variant that is present or not detecting a variant that is absent. Assuming testing is performed using NGS methods, all of the techniques that have been used have generally maintained high analytic accuracy for variant identification. However, NGS platforms differ in terms of the depth of sequence coverage, methods for base calling and read alignment, and other factors. NGS accuracy can vary by genomic region and affected by region complexity. These factors contribute to variability across the platforms and procedures used by different clinical laboratories. The American College of Medical Genetics and Genomics has clinical laboratory standards for NGS. The laboratory standards outline the documentation of test performance measures that should be evaluated for NGS platforms; moreover, the standards note that typical definitions of analytic sensitivity and specificity do not apply for NGS. Verification of detected sequence variants by Sanger sequencing is generally standard practice and conclusions of a 2016 study suggested it may be required for hereditary cancer testing.

Mu et al (2016) examined results from 20,000 hereditary cancer NGS panels (including *PALB2*) and found an overall 1.3% false-positive NGS rate (0.66% for *PALB2*) compared with Sanger sequencing. Other published results specific to *PALB2* testing are limited. According to a large reference laboratory, the analytic validity of NGS testing detects 99% of described *PALB2* gene sequence variants. Judkins et al (2015) reported analytic sensitivity exceeding 99.9% (Sanger sequencing referent) for all genes in a 25-gene panel that includes *PALB2* and *CHEK2*.

Clinically Valid
Individual Clinical Validity Studies: Breast Cancer
A number of studies (see Tables 1 and 2) reporting relative risks or odds ratios (ORs) 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 2 multinational studies included individuals from up to 5 of the single country studies. The number of pathogenic variants identified varied from 1 (founder mutations examined) to 48 (see Table 1). Studies conducted from single country samples are described first followed by the 2 multinational collaborative efforts. Finally, pooled results are reported minimizing any overlap of samples.

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

Rahman et al (2007) conducted a family-based case-control study enrolling cases (mean age, 49 years) identified at U.K. Cancer Genetics clinics. Controls, aged 48 years living in geographic regions similar to cases, were selected from the 1958 Birth Cohort Collection study. Variants were identified by Sanger

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sequencing, with a detection rate of 90% assumed for analysis. Protein-truncating *PALB2* variants were identified in 10 of 923 individuals with a family history of breast cancer but none in 1084 controls. In a segregation analysis, the relative risk of breast cancer associated with a *PALB2* variant was 2.3 (95% CI, 1.4 to 3.9), but modified by age with a relative risk of 3.0 for women less than 50 years (95% CI, 1.4 to 3.9) and 1.9 (95% CI, 0.8 to 3.7) for women over 50 years of age. In addition, 50 non-protein-truncating variants were identified without evidence for increasing breast cancer risk. This study, likely the first to report an association between *PALB2* and breast cancer, was limited by its sample size and possibly analytic sensitivity of the sequencing employed. Casadei et al (2011) studied 959 U.S. women (non-Ashkenazi Jewish descent) with a family history of *BRCA1*- or *BRCA2*-negative breast cancer and 83 female relatives using a family-based case-control design. Using conventional sequencing, pathogenic *PALB2* variants were detected in 31 (3.2%) women with breast cancer and none in controls. Compared with their female relatives without *PALB2* variants, the risk of breast cancer increased 2.3-fold (95% CI, 1.5 to 4.2) by age 55 and 3.4-fold (95% CI, 2.4 to 5.9) by age 85. Mean age at diagnosis was not associated with the presence of a variant (50.0 years with vs 50.2 years without). Casadei reported a lower relative risk estimate than all but Rahman et al and provided few details of analyses, and the prevalence of pathogenic *PALB2* variants in women with breast cancer was higher than in all but 1 other study. 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 relative risk estimate is therefore unclear.

Heikkinen et al (2009) conducted a population-based case-control study at a Finnish university hospital employing 2 case groups (947 familial and 1274 sporadic breast cancers) and 1079 controls. The study sample was obtained from 542 patients with familial breast cancer, a series of 884 oncology patients (79% of consecutive new cases), and 986 surgical patients (87% of consecutive new cases); 1706 were genotyped for the *PALB2* c.1592delT variant. All familial cases were *BRCA1*- and *BRCA2*-negative—but among controls, there were 183 *BRCA* carriers. *PALB2* variant prevalence varied with family history—2.6% when 3 or more family members were affected and 0.7% in all breast cancer patients. Variant prevalence was 0.2% among controls. In women with hereditary disease, a *PALB2* c.1592delT variant was associated with an increased risk of breast cancer (OR=11.0; 95% CI, 2.65 to 97.78), and was higher in women with the strongest family histories (women with sporadic cancers OR=4.19; 95% CI, 1.52 to 12.09). Although data were limited, survival was lower among *PALB2*-associated cases (10-year survival, 66.5% [95% CI, 44.0% to 89.0%] vs 84.2% [95% CI, 83.1% to 87.1%] in women without a variant, p=0.041; hazard ratio [HR], 2.94, p=0.047). A *PALB2* variant was also associated with triple-negative tumors—54.5% vs 12.2% with familial disease and 9.4% in sporadic cancers. The study was large as required for a population-based design. The magnitude of the odds for women with family histories was substantial, but those odds were accompanied by substantial uncertainty (wide confidence interval).

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;

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95% CI, 2.7 to 67.4). Performed in 2 distinct populations, the combined sample size was small, and uncertainty as indicated by the large effect estimate.

Thompson et al (2015) evaluated Australian women with breast cancer (n=1996) referred for genetic evaluation from 1997 to 2014. 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 NGS and novel variants verified by Sanger sequencing. Large deletions or rearrangements were not evaluated. Five bioinformatics computational tools were used to assess pathogenicity of novel variants. Nineteen distinct pathogenic variants were identified, including six not previously described—in 26 (1.3%) cases and in 4 (0.2%) controls—with an odds for breast cancer of 6.58 (95% CI, 2.3 to 18.9). Moreover, 54 missense variants identified were slightly more common in cases (OR=1.15; 95% CI, 1.02 to 1.32). This large population-based case-control study used contemporary NGS methods and informatics approaches. The reported OR is consistent with other studies examining multiple pathogenic variants.

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 12,529 genotyped women, a *PALB2* variant was identified in 116 (0.93%) cases (95% CI, 0.76% to 1.09%) vs 10 (0.21%, 95% CI, 0.08% to 0.34%) of 4702 controls (OR=4.39; 95% CI, 2.30 to 8.37). A *BRCA1* variant was identified in 3.47% of women with breast cancer and in 0.47% of controls (OR=7.65; 95% CI: 4.98 to 11.75). Authors estimated that a *PALB2* sequence variant conferred a 24% cumulative risk of breast cancer by age 75 (in the a 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 a poorer prognosis—10-year survival of 48.0% vs 74.7% when the variant was absent (HR=2.27; 95% CI, 1.64 to 3.15; adjusted for prognostic factors). This population-based case-control study was largest and the relative risk estimate in the lower range of study estimates.

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 relative risk; 30% of tumors were triple-negative. For a woman ages 50 to 54, the estimated relative risk was 6.55 (95% CI, 4.60 to 9.18). The relative risk 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

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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...." Still, the number of individuals with *PALB2* variants and breast cancer was not large, and many variants were examined.

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; 42,671 cases and 42,164 controls). BCAC (part of the larger Collaborative Oncological Gene-environment Study) included 48 separate studies with participants of multiple ethnicities, but mainly European, Asian, and African American. Most studies were population- or hospital-based case-control with some oversampling cases with family histories or bilateral disease. A custom array was used for genotyping at 4 centers, with 2% duplicate samples. Odds ratios were estimated adjusting for study among all participants, and excluding those studies selecting patients based on family history or bilateral disease (37,039 cases and 38,260 controls). The c.1592delT variant was identified in 35 cases and 6 controls (from 4 studies in the U.K., Australia, U.S., Canada; OR=4.52; 95% CI, 1.90 to 10.8; p<0.001); in those with no family history or bilateral disease (OR=3.44; 95% CI, 1.39 to 8.52; p=.003). The c3113G>A variant was identified in 44 cases and 8 controls (9 studies from Finland and Sweden; OR=5.93; 95% CI, 2.77 to 12.7; p<0.001) and in those with no family history or bilateral disease (OR=4.21; 95% CI, 1.84 to 9.60; p<.001). There was no association between the c2816T>G missense variant and breast cancer (found in 150 cases and 145 controls).

These results derived from a large sample, used a different analytical approach than Antoniou et al, and examined only 2 pathogenic variants. The magnitude of the estimated relative risks approaches that of a high penetrance gene, but is accompanied by wide confidence intervals 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 risk of hereditary disease prior to genetic testing.

Variant Interpretation

Valid variant classification is required to assess penetrance and is of particular concern for low prevalence variants including *PALB2*. Although the more common founder mutations were identified in many patients in the clinical validity studies, some specific variants were infrequent in the samples. While there are guidelines for variant classification, the consistency of interpretation among laboratories is of interest. Balmaña et al (2016) examined agreement of variant classification by different laboratories from tests for inherited cancer susceptibility from individuals undergoing panel testing. The Prospective Registry of Multiplex Testing (PROMPT) registry is a volunteer sample of patients who were 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

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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 a 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

The overall number of women with breast cancer and *PALB2* variants included in these studies is modest owing to the low carrier rates and is consistent with the penetrance estimates. Identified studies differed in populations, designs, sample sizes, analyses, and variants examined. While relative risk estimates 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 a contralateral cancer by age 70, increasing to 28.7% if she carries a *PALB2* variant.

Table 1. Included Association Studies of Pathogenic *PALB2* Variants

						PALB2 Variants		Totals		Pathogenic Variants Identified	
Author	**Year**	**Country**	**Design**	**N**	**Families**	**Cases**	**Controls**	**Cases**	**Controls**	**N**	**Prevalence Cases, %**
Erkko[26,a,b]	2008	Finland	Family segregation	213	17[c]	17	?			1 (c.1592delT)	
Rahman[28,a,b]	2007	U.K.	Family-based CC	2007	923	10	0	923	1084	5	1.1
Casadei[12,a]	2011	U.S.	Family-based CC[d]	1042		31	0	959	83	13	3.2
Heikkinen[27,a,b]	2009	Finland	Population-based CC	2026		19	2	947	1079	1 (c.1592delT)	2.0
Catucci[11,a,b]	2014	Italy	Population-based CC	590[e]		6	2	113	477	1 (c.1027C>T)	5.3
Thompson[29]	2015	Australia	Population-based CC	3994		26	4	1996	1998	19	1.3
Cybulski[13]	2015	Poland	Population-based CC[f]	17,231		116	10	12,529	4702	2	0.9
Antoniou[10]	2014	Multinational	Kin-cohort	2980	154	229	82	542	2438	48	
Southey[32]	2016	Multinational	Mutlicenter CC	84,835		35	6	42,671	42,164	1 (c.1592delT)	
						44	8			1 (c.3113G>A)	

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

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Table 2. Relative Risks and Penetrance Estimates for Breast Cancer Associated With Pathogenic *PALB2* Variants, and Proportions of Triple-Negative Tumors

Author	Year	Analysis	Relative Risk (Constant) (95% CI)	Penetrance at Age 70 (95% CI), %	Mean (<u>Median</u>) Age Onset, y	Triple-Negative Tumors	
						PALB2+	*PALB2-*
Erkko[26]	2008	Segregation	6.1 (2.2 to 17.2)[a]	40 (17 to 77)	54.3 (+FH); 59.3 (FH unavailable)		
Rahman[28]	2007	Segregation[b]	2.3 (1.4 to 3.9)[e]		<u>46</u> (IQR, 40-51)		
Casadei[12]	2011	Relative risk	2.3 (1.5 to 4.2)[f]		50.0 (SD=11.9)		
Heikkinen[27]	2009	Standard CC	11.0 (2.6 to 97.8)		53.1 (95% CI, 33.4 to 79.9)	54.5%	9.4%, 12.2%[g]
Catucci[11]	2014	Standard CC	13.4 (2.7 to 67.4)				
Thompson[29]	2015	Standard CC	6.6 (2.3 to 18.9)				
Cybulski[13]	2015	Standard CC	4.4 (2.3 to 8.4)		53.3	34.4%	14.4%
Antoniou[10]	2014	Segregation[b]	6.6 (4.6 to 9.2)[c]	47.5 (38.6 to 57.4)[d]		30%	
Southey[32]	2016	Standard CC	4.5 (1.9 to 10.8) (c.1592delT)				
			5.9 (2.8 to 12.7) (c.3113G>A)				

CC: case-control; CI: confidence interval; FH: family history; IQR: interquartile range.
[a] Using an "augmented" dataset assuming no cases among families without recorded histories. Analyses limited to those with recorded histories yielded a relative risk 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, relative risk of 3.0 (95% CI, 1.4 to 3.9); for women >50 years, relative risk of 1.9 (95% CI, 0.8 to 3.7).
[f] At age 85 years, relative risk of 3.4 (95% CI, 2.4 to 5.9).
[g] In sporadic and familial cancers without *PALB2* variants.

Clinically Useful

Evidence of clinical utility limited to women with *PALB2* variants was not identified. Studies of women at high risk based on family history alone or in those with *BRCA1* and *BRCA2* variants are relevant to the clinical utility of *PALB2* testing given the penetrance estimates for *PALB2* and related molecular mechanism ("BRCA-ness"). Interventions to decrease breast cancer risk in asymptomatic high-risk women include screening (eg, starting at an early age, addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention, and prophylactic mastectomy.[36] 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 BPM or CPM. Decision analyses have also concluded that 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

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with surveillance, a 30-year-old *BRCA* carrier with an expected 40% risk of breast cancer and 5% risk of ovarian cancer by age 70 would gain an expected 2.9 years following a prophylactic mastectomy alone and an additional 0.3 years with a prophylactic oophorectomy (see Table 3). A 50-year-old female *BRCA* carrier with node-negative breast cancer and a 24% risk of contralateral breast cancer at age 70 would anticipate 0.9 years in improved life expectancy (0.6 years for node-negative disease) following a CPM.

Table 3. Model Results of the Effects of Bilateral Prophylactic Mastectomy Compared With Surveillance on Life Expectancy in *BRCA* Carriers According to Penetrance

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

Adapted from Schrag et al (1997).

Section Summary: Clinically Useful

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

CHEK2 AND BREAST CANCER RISK ASSESSMENT

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Does genetic testing for *CHEK2* variants improve the net health outcome?

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

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

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

Comparators
The comparator of interest is no genetic testing.

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

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

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

Technically Reliable
See the discussion of technical reliability in the *PALB2* section.

Clinically Valid

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.

In 2008 Weischer et al 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. The analysis identified prospective cohort and case-control studies on *CHEK2* c.1100delC and the risk of breast cancer published before March 2007. Inclusion criteria were women with unilateral breast cancer who did not have a known multicancer syndrome, Northern or Eastern European descent, availability for *CHEK2* genotyping, *BRCA1* and *BRCA2* sequence variant–negative or unknown status, and breast cancer–free women as controls. The meta-analysis included 16 studies with 26,488 patient cases and 27,402 controls. Presenting both fixed and random-effect models, for *CHEK2* c.1100delC heterozygotes vs noncarriers, the aggregated ORs for breast cancer were

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2.7 (95% CI, 2.1 to 3.4) and 2.4 (95% CI, 1.8 to 3.2) in studies of unselected breast cancer, 2.6 (95% CI, 1.3 to 5.5) and 2.7 (95% CI, 1.3 to 5.6) in studies of early-onset breast cancer, and 4.8 (95% CI, 3.3 to 7.2) and 4.6 (95% CI, 3.1 to 6.8) in studies of familial breast cancer, respectively.

A 2012 meta-analysis by Yang et al examined the risk of breast cancer in whites with the *CHEK2* c.1100delC variant. Twenty-five case-control studies conducted in Europe and North and South America published in 16 articles were analyzed, with a total of 29,154 breast cancer cases and 37,064 controls. Of the cases, 13,875 patients had unselected breast cancer, 7945 had familial breast cancer, and 5802 had early-onset breast cancer. In total, 391 (1.3%) of the cases had a *CHEK2* c.1100delC variant and 164 (0.4%) of the controls. The association between *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.

In 2011, Cybulski et al reported on the risk of breast cancer in women with a *CHEK2* variant with and without a family history of breast cancer. A total of 7494 *BRCA1*-negative breast cancer patients and 4346 controls were genotyped for the 4 *CHEK2* founder mutations. A truncating variant was present in 227 (3.0%) patients and in 37 (0.8%) controls (OR=3.6; 95% CI, 2.6 to 5.1). The OR was higher for women with a first- or second-degree relative with breast cancer (OR=5.0; 95% CI, 3.3 to 7.6) than for women with no family history (OR=3.3; 95% CI, 2.3 to 4.7), and if both a first- and second-degree relative were affected with breast cancer, the OR was 7.3 (95% CI, 3.2 to 16.8). Authors estimated the lifetime risk of breast cancer for carriers of *CHEK2*-truncating variants to be 20% for a woman with no affected relative, 28% for a woman with 1 second-degree relative affected, 34% for a woman with 1 first-degree relative affected, and 44% for a woman with both a first- and second-degree relative affected.

A 2015 article by Easton et al reported that the magnitude of relative risk of breast cancer associated with *CHEK2*-truncating variants is likely to be moderate and unlikely to be high. On the basis of 2 large case-control analyses, authors calculated an estimated relative risk of breast cancer associated with *CHEK2* variants of 3.0 (90% CI, 2.6 to 3.5) and an absolute risk of 29% by age 80 years.

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

In 2017, Decker et al published an analysis from the U.K. of genetic testing results in 13,087 breast cancer cases, and 5488 controls. Truncating variants in *CHEK2* were associated with a significantly increased risk of breast cancer (OR=3.11; 95% CI, 2.15 to 4.69).

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Breast Cancer Prognosis in an Individual With a CHEK2 Sequence Variant

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

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

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

In 2012, Weischer et al reported on breast cancer associated with early death, breast cancer–specific death, and the increased risk of a second breast cancer (defined as a contralateral tumor) in *CHEK2*-variant carriers and noncarriers in 25,571 white women of Northern and Eastern European descent who had invasive breast cancer, using data from 22 studies participating in the Breast Cancer Association Consortium conducted in 12 countries. The 22 studies included 30,056 controls. Data were reported on early death in 25,571 women, breast cancer–specific death in 24,345, and a diagnosis of a second breast cancer in 25,094. Of the 25,571 women, 459 (1.8%) were *CHEK2* c.1100delC heterozygous and 25,112 (98.2%) were noncarriers. Median follow-up was 6.6 years, over which time the following was observed: 124 (27%) early deaths occurred, 100 (22%) breast cancer–specific deaths occurred, and 40 (9%) second breast cancers among *CHEK2* c.1100delC variant carriers were observed. Corresponding numbers among noncarriers were 4864 (19%), 2732 (11%), and 607 (2%), respectively. At the time of diagnosis, *CHEK2*-variant carriers vs noncarriers were on average 4 years younger (p<0.001); additionally, *CHEK2*-variant carriers were more likely to have a family history of cancer (p<0.001). Multifactorially adjusted hazard ratios for *CHEK2* vs noncarriers were 1.43 (95% CI, 1.12 to 1.82; p=0.004) for early death and 1.63 (95% CI, 1.24 to 2.15; p<0.001) for breast cancer–specific death.

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Section Summary: Clinically Valid
Studies have shown that a *CHEK2* variant is of moderate penetrance and confers a risk of breast cancer 2 to 4 times that of the general population; this risk appears to be higher in patients who also have a strong family history of breast cancer. Although the *CHEK2* variant appears to account for approximately one-third of variants identified in *BRCA1*- and *BRCA2*-negative patients, it is relatively rare, and risk estimates, which have been studied in population- and family-based case controls, are subject to bias and overestimation. 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
Direct evidence of clinical utility for genetic testing in individuals with *CHEK2* 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 (eg, starting at an early age, addition of magnetic resonance imaging to mammography, and 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.

Despite some studies showing potentially poorer outcomes of breast cancer patients who have *CHEK2* variants, it is unclear how such knowledge would be used to alter the treatment of such a patient. No evidence is available to support the clinical utility of genetic testing for *CHEK2* variants in breast cancer patients to guide patient management. There is no strong chain of evidence supporting *CHEK2* testing in breast cancer patients.

***ATM* AND BREAST CANCER RISK ASSESSMENT**

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

The question addressed in this evidence review is: Does genetic testing for *ATM* variants improve the net health outcome?

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

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

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

Comparators
The comparator of interest is no genetic testing.

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

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

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

Technically Reliable
See the discussion of technical reliability in the *PALB2* section.

Clinically Valid
In 2016, Marabelli et al reported on a meta-analysis of the penetrance of *ATM* gene 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%).

Another 2016 meta-analysis, by van Os et al included 7 studies and found that *ATM* variants were associated with an increased risk of developing breast cancer in women (relative risk [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).

Individual studies have also reported on the association between breast cancer development and pathogenic *ATM* variants; they are summarized in Table 4.

Table 4. Risk of Breast Cancer Associated With Pathogenic *ATM* Variants

Author	Year	Analysis	RR/OR (95% CI)	RR<Age 50 (95 % CI)
Thompson et al	2005	RR	2.23 (1.16 to 4.28)	
Renwick et al	2006	Standard CC	2.37 (1.52 to 3.78)	2.50 (1.41 to 4.17)
Goldgar et al	2011	CC, OR	2.55 (0.54 to 1.20)	

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Decker et al	2017	CC, OR	3.26 (1.82 to 6.46)

CC: case control; CI: confidence interval; OR: odds ratio; RR: relative risk.

Section Summary: Clinically Valid
ATM heterozygotes appear to have a relative risk 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.

Clinically Useful
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 (eg, starting at an early age, addition of magnetic resonance imaging to mammography, and 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. No evidence is available to support the clinical utility of genetic testing for *ATM* variants in breast cancer patients to guide patient management, and there is no strong chain of evidence supporting *ATM* testing in breast cancer patients.

SUMMARY OF EVIDENCE
For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a *PALB2* variant, the evidence includes studies of analytic and clinical validity and studies of breast cancer risk, including a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Evidence supporting clinical validity was obtained from numerous studies reporting relative risks or odds ratios (2 studies estimated penetrance). Study designs included family segregation, kin-cohort, family-based case-control, and population-based case-control. The number of pathogenic variants identified in studies varied from 1 (founder mutations) to 48. Relative risks for breast cancer associated with a *PALB2* variant ranged from 2.3 to 13.4, with the 2 family-based studies reporting the lowest values. Evidence on preventive interventions in women with *PALB2* variants is indirect, relying on studies of high-risk women and *BRCA* carriers. These interventions include screening with magnetic resonance imaging, chemoprevention, and risk reduction mastectomy. Given the penetrance of *PALB2* variants, the outcomes following bilateral and contralateral prophylactic 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 preventive 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 analytic validity, variant prevalence, and studies of breast cancer risk. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The

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available studies on clinical validity have demonstrated that *CHEK2* variants are of moderate penetrance, with lower relative risks for breast cancer than *PALB2*, and confer a risk of breast cancer 2 to 4 times that of the general population. Direct evidence for the clinical utility of genetic testing for *CHEK2* variants in individuals with risk of hereditary breast/ovarian cancer was not identified. 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. It is unclear that the relative risk associated with the moderate penetrance variants other than *PALB2* would increase risk enough beyond that already conferred by familial risk to change screening behavior. 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 analytic validity, variant prevalence, and studies of breast cancer risk. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The available studies on clinical validity have demonstrated that *ATM* variants are of moderate penetrance, with lower relative risks for breast cancer than *PALB2*; moreover, *ATM* variants confer a risk of breast cancer 2 to 4 times that of the general population. Direct evidence for the clinical utility of genetic testing for *ATM* variants in individuals with risk of hereditary breast/ovarian cancer was not identified. 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. It is unclear that the relative risk associated with the moderate penetrance variants—other than *PALB2*—would increase risk enough beyond that already conferred by familial risk to change screening behavior. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 07/20/2016
Current Effective Date: 02/21/2018
06/30/2016 Medical Policy Committee review
07/20/2016 Medical Policy Implementation Committee approval. New Policy.

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Policy # 00504
Original Effective Date: 07/20/2016
Current Effective Date: 02/21/2018

01/01/2017	Coding update: Removing ICD-9 Diagnosis codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. Added coverage statement with criteria for PALB2 variants, added CHEK2 and ATM to the policy. Added policy guidelines section and updated rationale and references. Title change.
06/08/2017	Removed colons from NCCN guideline sections.
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 02/2019

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81406, 81408, 81479
HCPCS	No codes
ICD-10 Diagnosis	C25.0-C25.9, C50.01-C50.929, Z15.01, Z80.0, Z80.3

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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