EVIDENCE SUMMARY

About 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, rather than having one of the well-described familial breast/ovarian cancer syndromes (eg, \textit{BRCA1}, \textit{BRCA2}). \textit{PALB2}, \textit{CHEK2}, and \textit{ATM} variants are considered to be of moderate penetrance and carriers have an approximately 2- to 4-fold increased risk of developing breast cancer compared with the general population. Risk estimates may be higher in patients with a family history of breast cancer or for a specific variant.

The objective of this review is to synthesize evidence on the analytic validity, clinical validity, and clinical utility of testing for \textit{PALB2, CHEK2, and ATM} variants in women with risk of hereditary breast/ovarian cancer.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: With risk of hereditary breast/ovarian cancer</td>
<td>Interventions of interest are: Genetic testing for a \textit{PALB2} variant</td>
<td>Comparators of interest are: No genetic testing</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival, Test accuracy, Test validity</td>
</tr>
<tr>
<td>Individuals: With risk of hereditary breast/ovarian cancer</td>
<td>Interventions of interest are: Genetic testing for a \textit{CHEK2} variant</td>
<td>Comparators of interest are: No genetic testing</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival, Test accuracy, Test validity</td>
</tr>
<tr>
<td>Individuals: With risk of hereditary breast/ovarian cancer</td>
<td>Interventions of interest are: Genetic testing for a \textit{ATM} variant</td>
<td>Comparators of interest are: No genetic testing</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival, Test accuracy, Test validity</td>
</tr>
</tbody>
</table>

Based on the available evidence, the Blue Cross Blue Shield Association Medical Advisory Panel made the following judgments about the level of evidence and level of benefit associated with Indication 1 in September 2016.

**Overview by Evidence Review Indications**

**Indication 1:** Individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a \textit{PALB2} variant.

The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Indication 2: Individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a CHEK2 variant.

The evidence is insufficient to determine the effects of the technology on health outcomes.

Indication 3: Individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for an ATM variant.

The evidence is insufficient to determine the effects of the technology on health outcomes.

**BACKGROUND**

**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% (seeer.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 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. In addition, specific pathogenic variants within a gene may confer somewhat different risks.

In contrast, about 3% to 5% of women presenting for hereditary breast/ovarian cancer risk assessment have sequence variants in a moderate penetrance gene.


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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 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 between 0.5% to 1.4%; the allele is less frequent in North America and virtually absent in Spain and India.

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a Short (p) arm of chromosome 16 at position 12.2.
b Fanconi anemia is a rare disorder, primarily affecting children, that causes bone marrow failure. Affected individuals also carry a risk of cancers including leukemia.
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.\(^\text{12}\)

**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. 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.\(^\text{13}\) A family history of breast cancer confers between a 2- and a 4-fold increased risk varying according to the number and closeness of affected relatives, age at which cancers developed, whether breast cancers were bilateral, and if other cancers occurred (eg, ovarian).\(^\text{14}\) 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),\(^\text{15}\) screening tools (eg, BRCAPRO,\(^\text{16}\) Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen\(^\text{17,18}\)), or by referring to guidelines that define specific family history criteria (see Table 1). For women with breast cancer, family history also affects the likelihood of carrying a pathogenic variant, although somewhat different criteria are applied (see Table 2) as is risk assessment from a pedigree.\(^\text{15}\)

**Table 1. NCCN Criteria for Genetic Risk Evaluation of an Individual Without a History of Breast Cancer**\(^\text{2}\)

<table>
<thead>
<tr>
<th>Individual Without a History of Breast Cancer</th>
<th></th>
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<tbody>
<tr>
<td>**“A close relative with any of the following:****</td>
<td></td>
</tr>
<tr>
<td>A known mutation in a cancer susceptibility gene within the family</td>
<td></td>
</tr>
<tr>
<td>≥2 breast cancer primaries in a single individual</td>
<td></td>
</tr>
<tr>
<td>≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 years</td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td></td>
</tr>
<tr>
<td>Male breast cancer</td>
<td></td>
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<tr>
<td><strong>First- or second-degree relative with breast cancer ≤45 years</strong></td>
<td></td>
</tr>
<tr>
<td>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*</td>
<td></td>
</tr>
</tbody>
</table>

GI: gastrointestinal; NCCN: National Comprehensive Cancer Network.

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**Current Review Date:** January 2017

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Table 2. NCCN Criteria for Genetic Risk Evaluation of an Individual With Breast Cancer

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;A known sequence variant in a cancer susceptibility gene within the family:&quot;</td>
<td></td>
</tr>
<tr>
<td>Early-age-onset breast cancer</td>
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<tr>
<td>Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 years</td>
<td></td>
</tr>
<tr>
<td>Two breast cancer primaries in a single individual</td>
<td></td>
</tr>
<tr>
<td>Breast cancer at any age, and</td>
<td></td>
</tr>
<tr>
<td>≥1 close blood relative with breast cancer ≤50 years, or</td>
<td></td>
</tr>
<tr>
<td>≥1 close blood relative with invasive ovarian cancer at any age, or</td>
<td></td>
</tr>
<tr>
<td>≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or</td>
<td></td>
</tr>
<tr>
<td>From a population at increased risk</td>
<td></td>
</tr>
<tr>
<td>Male breast cancer</td>
<td></td>
</tr>
<tr>
<td>An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age</td>
<td></td>
</tr>
<tr>
<td>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.“</td>
<td></td>
</tr>
<tr>
<td>An individual with an ovarian cancer</td>
<td></td>
</tr>
</tbody>
</table>

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

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.

Additionally, if a familial pathogenic variant is identified, asymptomatic at-risk family members may benefit from cascade testing for the known variant. If that variant is identified in an at-risk relative, then risk-reducing management options could be offered; if the familial variant is not identified, then the relative may be considered near population risk and could avoid increased surveillance for breast cancer and risk reducing options would not be considered.

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REGULATORY STATUS
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 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
This evidence review was originally created in January 2015, with an evaluation of PALB2 and has been updated most recently with an Evidence Street Assessment from September 2016 (see Appendix Table 1 for genetic testing categories).

In November 2016, the evidence review was expanded to include evidence review 2.04.133 (genetic testing for CHEK2 mutations for breast cancer), and the portions of evidence review 2.04.93 (genetic cancer susceptibility panels using next-generation sequencing) relevant to the use of ATM testing for breast cancer testing risk assessment.

ANALYTIC VALIDITY
Analytic validity is the accuracy of a test for detecting a variant that is present or not detecting a variant that is absent. Assuming testing is performed using next-generation sequencing (NGS) methods, techniques used have generally 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 sequencing 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 guidelines outline the documentation of test performance measures that should be evaluated for NGS platforms, and 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 recent study suggests 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.
PALB2 AND BREAST CANCER RISK ASSESSMENT

Clinical Validity

Individual Clinical Validity Studies: Breast Cancer

Nine studies (see Tables 3 and 4) reporting relative risks or odds ratios (ORs) were included (2 reported penetrance estimates).9-11,24-28 Study designs included family segregation,24 kin-cohort,8 family-based case-control,10,26 and population-based or multicenter case-control.9,11,25,27,28 The 2 multinational studies included individuals from up to 5 of the single country studies.8,28 The number of pathogenic variants identified varied from 1 (founder variants examined) to 48 (see Table 3). 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.24 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.26 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 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. 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.10 Using conventional sequencing, pathogenic PALB2 variants were detected in 31 (3.2%) women with breast cancer and none in controls. Compared with their female relatives without PALB2 variants, the risk of breast cancer increased 2.3-fold (95% CI, 1.5 to 4.2) by age 55 and 3.4-fold (95% CI, 2.4 to 5.9) by age 85. Mean age at diagnosis was not associated with the presence of a variant (50.0 years with vs 50.2 years without). The study 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.26 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.25 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 were 183 BRCA4 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% versus 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 ratio for women with family histories was substantial, but 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.9 In Milan, 9 different pathogenic PALB2 variants were detected in 12 of 575 cases and none in 784 controls (blood donor); in Bergamo PALB2 c.1027C→T variants were detected in 6 of 113 cases and in 2 of 477 controls (OR=13.4; 95% CI, 2.7 to 67.4). Performed in 2 distinct populations, the combined sample size was small and uncertainty in the effect estimate large.

Thompson et al (2015) evaluated Australian women with breast cancer (n=1996) referred for genetic evaluation from 1997 to 2014.27 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 6 not previously described—in 26 (1.3%) cases and in 4 (0.2%) controls—with an odds ratio for breast cancer of 6.58 (95% CI, 2.3 to 18.9). In addition, 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 odds ratio 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.11 From 12,529 genotyped women, a PALB2 variant was identified in 116 (0.93%) cases (95% CI, 0.76% to 1.09%) versus 10 (0.21%, 95% CI, 0.08% to 0.34%) of 4702 controls (OR=4.39; 95% CI, 2.30 to 8.37). A BRCA1 variant was identified in 3.47% of women with breast cancer and in 0.47% of controls (OR=7.65; 95% CI: 4.98 to 11.75). Authors estimated that a PALB2 sequence variant conferred a 24% cumulative risk of breast cancer by age 75 (in the a setting of age-adjusted breast cancer rates slightly more than half that in the U.K.29 or the U.S.30). A PALB2 variant was also associated with a poorer prognosis—10-year survival of 48.0% versus 74.7% when the variant was absent (HR=2.27; 95% CI, 1.64 to 3.15; adjusted


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

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 (VUS) 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 variants identified, 2 were most common (c.1592delT in 44 families, c.3113G>A in 25 families); 39 of the 48 pathogenic variants were found in just 1 or 2 families.

Carriers of *PALB2* variants (men and women) had a 9.47-fold increased risk for breast cancer (95% CI, 7.16 to 12.57) compared with the U.K. population under a single-gene model and age-constant 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 50, by age 50 she would have a 27% (95% CI, 21% to 33%) estimate 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<.01). 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 the study design and low carrier prevalence. The lower estimates obtained following exclusion of those selected based on

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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 variants 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 is 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 conflicting interpretation—3 (6%) had pathogenic, VUS, 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 VUS 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: Clinical Validity**

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 3. Included Association Studies of Pathogenic *PALB2* Variants

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>N</th>
<th>Families</th>
<th>Cases</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls</th>
<th>Pathogenic Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erkkoa,b</td>
<td>2008</td>
<td>Finland</td>
<td>Family segregation</td>
<td>213</td>
<td>17&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17</td>
<td>?</td>
<td>1094</td>
<td>923</td>
<td>1 (c.1592delT)</td>
</tr>
<tr>
<td>Rahmana,b</td>
<td>2007</td>
<td>U.K.</td>
<td>Family-based CC</td>
<td>2007</td>
<td>923</td>
<td>10</td>
<td>0</td>
<td>923</td>
<td>1084</td>
<td>5</td>
</tr>
<tr>
<td>Casadeia,b</td>
<td>2011</td>
<td>U.S.</td>
<td>Family-based CC&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1042</td>
<td>31</td>
<td>0</td>
<td>959</td>
<td>83</td>
<td>13</td>
<td>3.2%</td>
</tr>
<tr>
<td>Heikkinena,b</td>
<td>2009</td>
<td>Finland</td>
<td>Population-based CC</td>
<td>2026</td>
<td>19</td>
<td>2</td>
<td>947</td>
<td>1079</td>
<td>1 (c.1592delT)</td>
<td>2.0%</td>
</tr>
<tr>
<td>Catucci&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>2014</td>
<td>Italy</td>
<td>Population-based CC</td>
<td>590&lt;sup&gt;e&lt;/sup&gt;</td>
<td>6</td>
<td>2</td>
<td>113</td>
<td>477</td>
<td>1 (c.1027C&gt;T)</td>
<td>5.3%</td>
</tr>
<tr>
<td>Thompson</td>
<td>2015</td>
<td>Australia</td>
<td>Population-based CC</td>
<td>3994</td>
<td>26</td>
<td>4</td>
<td>1996</td>
<td>1998</td>
<td>19</td>
<td>1.3%</td>
</tr>
<tr>
<td>Cybulski</td>
<td>2015</td>
<td>Poland</td>
<td>Population-based CC&lt;sup&gt;f&lt;/sup&gt;</td>
<td>17,231</td>
<td>116</td>
<td>10</td>
<td>12,529</td>
<td>4702</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Antoniou</td>
<td>2014</td>
<td>Multinationa l Kin-cohort</td>
<td>2980</td>
<td>154</td>
<td>229</td>
<td>82</td>
<td>542</td>
<td>2438</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Southey</td>
<td>2016</td>
<td>Multinationa l Multicenter CC</td>
<td>84,835</td>
<td>35</td>
<td>6</td>
<td>42,671</td>
<td>42,164</td>
<td>1 (c.1592delT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southey</td>
<td>2016</td>
<td>Multinationa l Multicenter CC</td>
<td>84,835</td>
<td>44</td>
<td>8</td>
<td>42,671</td>
<td>42,164</td>
<td>1 (c.3113G&gt;A)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CC: case-control.

<sup>a</sup> All or selected families included in Antoniou (2014).

<sup>b</sup> Participants included in Southey (2016).

<sup>c</sup> 10 with a family history.

<sup>d</sup> Non-Ashkenazi Jewish descent, males excluded.

<sup>e</sup> Bergamo sample, Milan sample 0 controls with *PALB2* variants

<sup>f</sup> Study primary survival outcome was obtained as part of a prospective cohort. The analysis and sampling to assess breast cancer risk was as a case-control study.
### Table 4. Relative Risks and Penetration Estimates for Breast Cancer Associated With Pathogenic *PALB2* Variants, and Proportions of Triple-Negative Tumors

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

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

\(^a\) Using an “augmented” dataset assuming no cases among families without recorded histories. Analyses limited to those with recorded histories yielded a 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, RR=3.0 (95% CI, 1.4 to 3.9); for women >50 years, RR=1.9 (95% CI, 0.8 to 3.7).

\(^f\) At age 85 years, RR=3.4 (95% CI, 2.4 to 5.9).

\(^g\) In sporadic and familial cancers without *PALB2* variants
**Clinical Utility**

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 were reviewed 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 [MRI] to mammography, and annually), chemoprevention, prophylactic mastectomy, and prophylactic oophorectomy. In women with breast cancer, contralateral prophylactic mastectomy (CPM) is of interest; other treatment decisions are dictated by clinical, pathologic, and other prognostic factors. A concise review of evidence for these interventions follows and all are addressed in guidelines. Lifestyle modifications including weight loss, exercise, limiting alcohol consumption, and avoiding long-term hormone therapy are also recommended, but evidence demonstrating efficacy is indirect and based on observational studies.

**Screening High-Risk Women**

In addition to mammography, annual MRI screening is recommended beginning at an early age for asymptomatic women at high risk (eg, by National Comprehensive Cancer Network [NCCN] at age 25\(^{31} \)) when the lifetime breast cancer risk exceeds 20\%, by the National Institute for Health and Care Excellence at age 30 in women with a known \( BRCA1 \) or \( BRCA2 \) variant or with >30\% risk of being a carrier\(^{23,33} \). We identified a recent meta-analysis of screening MRI in \( BRCA1 \) and \( BRCA2 \) carriers, 2 systematic reviews, and an observational study examining survival.

Phi et al (2016) compared performance characteristics of MRI with mammography or the 2 modalities combined in an individual patient data meta-analysis of 6 high-risk screening trials.\(^{34} \) Among 1219 women with \( BRCA1 \) and 732 with \( BRCA2 \) variants, the sensitivity of MRI was better than mammography (see Table 5), but increased false positives by 8 to 10 per 100 screens.

**Table 5. Screening Performance Characteristics of Mammography and Magnetic Resonance Imaging in \( BRCA1 \) and \( BRCA2 \) Carriers From Individual Patient Data (Phi et al, 2016)\(^{34} \)**

<table>
<thead>
<tr>
<th>Variant Status</th>
<th>Cancers Detected, n</th>
<th>Sensitivity (95% CI), %</th>
<th>Specificity (95% CI), %</th>
<th>Cancers Detected, n</th>
<th>Sensitivity (95% CI), %</th>
<th>Specificity (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>( BRCA1 ) (n=112)</td>
<td>39</td>
<td>35.7</td>
<td>93.8</td>
<td>92</td>
<td>88.6</td>
<td>84.4</td>
</tr>
<tr>
<td>( BRCA2 ) (n=72)</td>
<td>31</td>
<td>44.6</td>
<td>93.4</td>
<td>53</td>
<td>80.1</td>
<td>85.3</td>
</tr>
</tbody>
</table>

Cl: confidence interval.

A 2014 review supported by the Australia Medical Services Advisory Committee provided similar conclusions\(^{35} \): “MRI offers a 2.3-fold increase in the detection of breast cancer in younger high-risk women over mammography alone.” “Breast MRI increases by 3-fold the rate of investigations for false-positive findings.” In addition, evidence for a favorable stage shift with MRI screening was noted.

A prospective matched-cohort study, the MRI Screening Study (MRISC), enrolling 2308 participants, found adding annual MRI to mammography improved metastasis-free survival in \( BRCA1 \) carriers (HR=0.30; 95% CI, 0.08 to 1.13; p=0.055) and in women with a family history of breast cancer (HR=0.21; 95% CI, 0.04 to 0.95; p=0.024).\(^{36} \) No benefit was observed in \( BRCA2 \) carriers. The study was...
limited by its observational design and small subgroups. The 2014 U.S. Preventive Services Task Force (USPSTF) report on testing for \textit{BRCA}-related cancer noted a lack of randomized controlled screening trials in women with \textit{BRCA} variants\textsuperscript{17,18}

The evidence is consistent that MRI screening in a high-risk population can identify more breast cancers than mammography with an increase in false positives. Indirect evidence and limited observational data suggest potential benefit from MRI screening.

\textbf{Chemoprevention}

Guidelines consider risk-reducing agents appropriate for women at risk of hereditary breast cancer. For example, NCCN recommends tamoxifen, raloxifene, anastrozole, and exemestane as potential options in women 35 years or older.\textsuperscript{31} The 2014 USPSTF BRCA review failed to identify trials limited to \textit{BRCA} carriers, but concluded that tamoxifen and raloxifene decreased invasive breast cancer incidence compared with placebo (by 30\% and 68\%, respectively).\textsuperscript{17,18} Phillips et al (2013) pooled results from 3 observational chemoprevention studies of \textit{BRCA1} (n=1583) and \textit{BRCA2} (n=881) carriers with breast cancer.\textsuperscript{31} Women receiving tamoxifen following an initial breast cancer diagnosis had a decreased risk of contralateral breast cancer (in \textit{BRCA1} carriers: HR=0.58; 95\% CI, 0.29 to 1.13; in \textit{BRCA2} carriers: HR=0.48; 95\% CI, 0.22 to 1.05). Adverse effects (hot flashes, thromboembolism, endometrial cancer) accompany these agents and may limit acceptability to some women.

\textbf{Prophylactic Oophorectomy}

In studies limited to \textit{BRCA1} and \textit{BRCA2}-positive women, prophylactic oophorectomy is accompanied by a 50\% to 60\% reduction in breast cancer risk.\textsuperscript{36-40} However, the lack of data obtained from a broader set of women with lower penetrance variants limits generalizability (consistent with current NCCN guidelines\textsuperscript{3}). Accordingly, there is no evidence to support benefit in women outside those with high penetrance variants.

\textbf{Prophylactic Mastectomy}

Hartmann and Lindor (2016)\textsuperscript{41} reviewed 5 nonrandomized studies (8 publications) of bilateral prophylactic risk reduction mastectomy in women with family histories consistent with hereditary breast cancer, including those with \textit{BRCA1} and \textit{BRCA2} variants.\textsuperscript{42-49} Four studies found a 90\% or greater reduction in subsequent breast cancer risk while 1 small study\textsuperscript{42} found no statistically significant risk reduction (RR=0.39; 95\% CI, 0.12 to 1.36). The 2014 USPSTF BRCA screening review concluded: “In high-risk \textit{BRCA}-related cancer women and women who are variant carriers, risk-reducing mastectomy reduced breast cancer by 85\% to 100\% and breast cancer mortality by 81\% to 100\%.... Some women experienced physical complications of surgery, postsurgical symptoms, or changes in body image; some had decreased anxiety.”\textsuperscript{17,18} A 2010 Cochrane reviewed prophylactic mastectomy, but did not pool results.\textsuperscript{50} Twenty studies of bilateral prophylactic mastectomy (BPM), 12 studies of CPM, and 6 studies examining either procedure were included. Reviewers concluded that bilateral prophylactic mastectomy “should be considered only among those at very high risk of disease.” And that “BPM was effective in reducing both the incidence of, and death from, breast cancer, [though] more rigorous prospective studies (ideally randomized trials) are needed.”

Fayenu et al (2014) conducted a systematic review and meta-analysis of studies reporting outcomes following CPM.\textsuperscript{51} Four observational studies were identified including women at increased “familial/genetic risk” — 2 studies limited to \textit{BRCA} carriers\textsuperscript{52,53} and 2 studies in women with a family
history of breast cancer. There was no apparent impact on overall survival (RR=1.09; 95% CI, 0.97 to 1.24; 3 studies, n=1936) and a lower but not significantly decreased risk of breast cancer mortality (RR=0.66; 95% CI, 0.27 to 1.64; 2 studies, n=918); there were decreased risks of metachronous cancers (RR=0.04; 95% CI, 0.02 to 0.09; 7 studies, n=2418) and distant metastases (RR=0.71; 95% CI, 0.51 to 0.81; 2 studies, n=918).

However, 3 recent retrospective studies not included in the meta-analysis suggested improved survival in BRCA carriers following CPM.56,57,58 Evans et al (2013) compared survival in BRCA-positive women with unilateral breast cancer (n=105) undergoing CPM to women (n=593) having either unilateral mastectomy or local excision and radiotherapy.54 Diagnoses were made between 1985 and 2010. Women undergoing CPM were followed a median of 8.6 years from CPM and others a median of 8.6 years from surgery. After adjusting for risk-reducing bilateral salpingo-oophorectomy, CPM was associated with improved survival (HR=0.43; 95% CI, 0.20 to 0.95). Metcalfe et al (2014) followed 390 BRCA-positive women with stage I or II breast cancers undergoing a unilateral mastectomy or additional CPM (n=181); overall mean follow-up was 13 years and an average 2.3 years from diagnosis to CPM.55 CPM was associated with a decreased risk of breast cancer death (HR=0.52; 95% CI, 0.29 to 0.93) adjusting for potential confounders. A propensity-match analysis of 79 pairs yielded a lesser and nonsignificant reduction in risk (HR=0.60; 95% CI, 0.34 to 1.06). Heemskerk-Gerritsen et al (2007) studied 583 BRCA-positive women with breast cancer diagnosed between 1980 and 2011 (11.4 years median follow-up from diagnosis).46 During follow-up, 342 (42%) chose to have CPM, which was accompanied by improved overall survival (HR=0.49; 95% CI, 0.29 to 0.82). These recent studies suggest that CPM may be accompanied by improved survival in BRCA carriers56 implying that those at highest risk of contralateral cancers choosing CPM may benefit.

Prophylactic mastectomy can be accompanied by harms. For example, Silva et al (2015) examined outcomes of 20,501 women with unilateral breast cancer from the American College of Surgeons National Surgery Quality Improvement Program (NSQIP) database.57 A total of 13,268 (64.7%) women underwent unilateral mastectomy and 7233 (35.3%) bilateral procedures. Whether women were at increased risk of hereditary cancers was not reported. Although all had breast reconstruction, autologous reconstructions were more common following unilateral (19.5%) than bilateral mastectomy (8.9%); others underwent implant-based reconstruction. Some complication rates were higher following bilateral mastectomy, regardless of reconstruction type. After implant reconstruction complications occurred in 10.1% after bilateral mastectomy and in 8.8% after unilateral mastectomy. With autologous reconstruction, complications occurred in 21.2% after bilateral mastectomy and in 14.7% after unilateral mastectomy. Transfusion rates were also higher after bilateral mastectomy but with implant reconstruction were low (0.3% after unilateral and 0.8% bilateral mastectomy). Medical complications were relatively infrequent—in about 1% following implant reconstructions and about 3% after autologous reconstructions. The Cochrane review reported complication rates varying from 4% without reconstruction to 49% with reconstruction.50

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.59,60 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 6). 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 6. Model Results of the Effects of Bilateral Prophylactic Mastectomy Compared With Surveillance on Life Expectancy in BRCA Carriers According to Penetrence (Schrag et al 1997)

<table>
<thead>
<tr>
<th>Age of Carrier (y)</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% risk of breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>2.9</td>
<td>2.0</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Mastectomy delayed 10 y</td>
<td>1.8</td>
<td>0.8</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>60% risk of breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>4.1</td>
<td>2.9</td>
<td>1.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Mastectomy delayed 10 y</td>
<td>2.4</td>
<td>1.1</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>85% risk of breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mastectomy</td>
<td>5.3</td>
<td>3.7</td>
<td>2.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Mastectomy delayed 10 y</td>
<td>2.6</td>
<td>1.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Section Summary: Clinical Utility

Evidence concerning preventive interventions in women with PALB2 variants is indirect, relying on studies of high-risk women and BRCA carriers. Compared with other screening modalities, MRI detects more cancers when high-risk women are screened. There is limited evidence that chemoprevention can decrease the risk of invasive cancers in high-risk women; the USPSTF report and NCCN support a chemoprevention option. In high-risk women, prophylactic mastectomy (BPM or CPM) reduces the risk of breast cancer and BPM appears to decrease breast cancer mortality. Decision models project increased life-expectancy, but mastectomy is accompanied by risks of potential harms. Studies have reported that a minority of BRCA carriers choose to undergo BPM. There is a rationale for the impact of prophylactic mastectomy applying to women with PALB2 variants given penetrance approaching a BRCA variant, albeit with lesser benefit-to-risk calculus. 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 tradeoffs involved.

CHEK2 AND BREAST CANCER RISK ASSESSMENT

Clinical Validity

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 risk of breast cancer associated with CHEK2 are population- and family-based case-control studies.

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 2012 meta-analysis by Yang et al examined the risk of breast cancer in whites with the CHEK2 c.1100delC variant. A total of 25 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 5302 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 significant (OR=2.75; 95% CI, 2.25 to 3.36). By subgroup, odds ratios 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 variants. 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 odds ratio 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 odds ratio 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.

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

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 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 variants 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 to 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 to 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 124 (27%) early deaths, 100 (22%) breast cancer–specific deaths, and 40 (9%) second breast cancers among CHEK2 c.1100delC variant carriers were observed. Corresponding numbers among noncarriers were 4864 (19%), 2732 (11%), and 607 (2%), respectively. At the time of diagnosis, CHEK2-variant carriers versus noncarriers were on average 4 years younger (p<0.001) and more often had a positive family history of cancer (p<0.001). Multifactorially adjusted hazard ratios for CHEK2 versus 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: Clinical Validity

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.

Clinical Utility

Risk of Developing Breast Cancer in an Individual With a CHEK2 Sequence Variant

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 (e.g., starting at an early age, addition of MRI to mammography, and annually), chemoprevention, prophylactic mastectomy, and prophylactic oophorectomy. The evidence for those interventions is outlined in the Clinical Utility section for PALB2 and Breast Cancer Risk Assessment.

Following the logic applied in the case of PALB2, there is limited evidence that chemoprevention can decrease the risk of invasive cancers in high-risk women; the USPSTF report and NCCN support a chemoprevention option. In high-risk women, prophylactic mastectomy (BPM or CPM) reduces the risk of breast cancer and BPM appears to decrease breast cancer mortality. Decision models project increased life-expectancy, but mastectomy is accompanied by risks of potential harms. Studies have reported that a minority of BRCA carriers choose to undergo BPM.41 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 women with a CHEK2 variant making a decision about a prophylactic mastectomy. It is unclear that the relative risk associated with CHEK2 variants would increase risk enough beyond that already conferred by familial risk to change screening behavior.

Prognosis of Breast Cancer in an Individual With a CHEK2 Sequence 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 Validity

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 mutations.56 The meta-analysis included 19 studies, which were heterogeneous in terms of population, study design, and baseline breast cancer risk. The estimated cumulative 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%).

Individual studies have also reported on the association between breast cancer development and pathogenic ATM variants, which are summarized in Table 7.

Table 7. Relative Risks Breast Cancer Associated With Pathogenic ATM Variants

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Analysis</th>
<th>RR (Constant) (95% CI)</th>
<th>RR Below Age 50 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson et al</td>
<td>2005</td>
<td>Relative risk</td>
<td>2.23 (1.16 to 4.28)</td>
<td></td>
</tr>
<tr>
<td>Renwick et al</td>
<td>2006</td>
<td>Standard CC</td>
<td>2.37 (1.52 to 3.78)</td>
<td>2.50 (1.41 to 4.17)</td>
</tr>
</tbody>
</table>

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

Clinical Validity

ATM heterozygotes appear to have a relative risk of breast cancer from 2% to 6% of that of the general population, similar to that of CHEK2.
Clinical Utility
The chain of evidence supporting the clinical utility for testing for ATM variants in individuals with risk of hereditary breast/ovarian cancer follows that for testing for CHEK2 variants.

SUMMARY OF EVIDENCE
For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a PALB2 variant, the evidence include studies of analytic validity, variant prevalence, and multiple studies of breast cancer risk, including 1 meta-analysis. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The reported evidence supporting analytic validity is not substantial, but given current next-generation sequencing techniques with variant confirmation by conventional methods, high analytic sensitivity such as reported by Judkins et al (2015) is expected in a laboratory certified by the Clinical Laboratory Improvement Amendments meeting standards for high-complexity molecular diagnostics. Evidence supporting clinical validity was obtained from 9 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 variants) 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. Compared with other screening modalities, magnetic resonance imaging (MRI) has a higher sensitivity, but increased false positives when high-risk women are screened. Screening recommendations for high-risk asymptomatic women include beginning at an earlier age and addition of MRI to mammography. However, there is no direct evidence and limited observational data suggesting improved outcomes. There is limited observational evidence that chemoprevention can decrease the risk of invasive cancers in high-risk women; the U.S. Preventive Services Task Force (USPSTF) report and National Comprehensive Cancer Network (NCCN) support a chemoprevention option. In high-risk women, prophylactic mastectomy (bilateral or contralateral) reduces the risk of breast cancer and breast cancer mortality and decision analytic models project increased life-expectancy. Prophylactic mastectomy can be accompanied by a significant risk of adverse effects and studies have found a minority of asymptomatic BRCA carriers choose to undergo a bilateral prophylactic 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 tradeoffs involved for 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 of for a CHEK2 variant or 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 both CHEK2 and ATM2 variants are of moderate penetrants, 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 or ATM variants in individuals with risk of hereditary breast/ovarian cancer was not identified. 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 MRI to mammography, and annually), chemoprevention, prophylactic mastectomy, and prophylactic oophorectomy. Following the logic applied in the case of PALB2, there is limited evidence that chemoprevention can decrease the risk of invasive cancers in high-risk women; the USPSTF report and NCCN support a chemoprevention option. 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 women with a CHEK2 variant making a decision about a prophylactic mastectomy. It is unclear that the relative risk associated with the moderate penetrance variants 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.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

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

National Comprehensive Cancer Network
Based on expert consensus opinion, National Comprehensive Cancer Network (NCCN) guidelines on breast cancer screening and diagnosis (v.1.2016) and on genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2017) recommend:

- Annual mammogram
- Annual breast magnetic resonance imaging if patient has >20% risk of breast cancer based on gene and/or risk level, including ATM, CDH1, CHEK2, PALB2, PTEN, and TP53
- Consideration of a risk reducing mastectomy based on family history.

NCCN guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2017) state that there is insufficient evidence for increased ovarian cancer risk in women with PALB2 variants.

NCCN guidelines for pancreatic cancer (v.2.2016) note that the presence of PALB2 variants has been identified as increasing pancreatic cancer susceptibility; however, testing for this variant is not discussed.
U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
No U.S. Preventive Services Task Force recommendations for PALB2, CHEK2, or ATM variant testing have been identified.

MEDICARE NATIONAL COVERAGE
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
A search of ClinicalTrials.gov in October 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

REFERENCES
34. Seil E, Jack B. Breast magnetic resonance imaging (MRI) for screening of high-risk women. MSAC application no 10981. Assessment report. 2014.

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Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.126

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td>X</td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
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Current Review Date: January 2017
5a. Carrier testing: preconception
5b. Carrier testing: prenatal
5c. In utero testing: aneuploidy
5d. In utero testing: mutations
5e. In utero testing: other
5f. Preimplantation testing with in vitro fertilization