DRAFT

BlueCross BlueShield of Alabama

Name of Policy:

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

Policy #: 609
Category: Laboratory

Latest Review Date: October 2018
Policy Grade: C

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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.*

Description of Procedure or Service:

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. PALB2, CHEK2, and ATM variants are considered to be of moderate penetrance. Carriers of PALB2 have an approximately 2- to 13- fold increased risk of developing breast cancer compared with the general population, and risk for CHEK2 and ATM carriers is increased approximately 2- to 4-fold. Risk estimates may be higher in patients with a family history of breast cancer or for a specific variant.

Breast Cancer and Genetics

In 2016, researchers estimated breast cancer would be diagnosed in 252,710 women and 40,610 would die from the disease; a woman's lifetime risk is 12.4%. Breast cancers can be classified as sporadic, familial, or hereditary. Most breast cancers are sporadic, (70% to 75%), occurring in women without a family history of 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.

Determining Variant Pathogenicity

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

Genes Associated with a Moderate Penetrance of Breast Cancer

PALB2 Gene

The PALB2 gene (partner and localizer of BRCA2) encodes for a protein first described in 2006. The gene is located at 16p12.2 (short (p) arm of chromosome 16 at position 12.2) and has 13 exons. 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 (e.g., Finns, French Canadians, Poles), while infrequently found in others (e.g., in Ashkenazi Jews). In women with a family history of breast cancer, the prevalence of pathogenic PALB2 variants ranges between 0.9% and 3.9%, or substantially higher than in an unselected general population. Depending on population prevalence, PALB2 may be responsible for as much as 2.4% of hereditary breast cancers; and in populations with founder variants cause 0.5% to 1% of all breast cancers.

CHEK2 Gene

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

In 2002, a single recurrent truncating 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 mutated), located on chromosome 11q22.3, is associated with the autosomal recessive condition ataxia-telangiectasia. This condition is characterized by progressive cerebellar ataxia with onset between the ages of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition. Female ATM heterozygotes carriers have a risk of breast cancer about twice as high as that of the general population; however, they do not appear to have an elevated ovarian cancer risk.

Identifying Women at Risk of an Inherited Susceptibility to Breast Cancer
Breast cancer risk can be affected by genetic and nongenetic factors. 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 two- and a four-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 (e.g., ovarian). For a woman without breast cancer, the probability of detecting a pathogenic variant can be estimated from a detailed multigenerational pedigree (e.g., Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), screening tools (e.g., BRCAPRO, Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen), or by referring to guidelines that define specific family history criteria. 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 (e.g., triple-negative disease, young age) increase the likelihood that the breast cancer is hereditary. Testing may also be considered for women from families with known variants. Potential benefit derives from interventions (screening, chemoprevention, risk reducing surgery) that can prevent a first breast cancer, a contralateral breast cancer, or cancer in a different organ caused by the same variant. Whether benefit outweighs harms depends on the risk of developing breast cancer (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;
3. and of a magnitude that management changes informed by testing can lead to improved health outcomes.

Policy:

Effective for dates of service on or after November 1, 2018:

Testing for *PALB2* variants for breast cancer risk assessment in adults who meet the following criteria **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage

1. The individual meets criteria for genetic risk evaluation (see Policy Guidelines section)

AND

2. The individual has undergone testing for sequence variants in *BRCA1* and *BRCA2* (see Policy Guidelines section) with *negative* results.

Testing for *PALB2* sequence variants in individuals who do not meet the criteria outlined above **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Testing for *CHEK2* and *ATM* variants in the assessment of breast cancer risk **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Policy Guidelines

Criteria For Genetic Risk Evaluation:

The NCCN provides criteria for genetic risk evaluation for individuals with no history or breast cancer and for those with a breast cancer. Updated versions of the criteria are available on the NCCN website.

The recommended testing strategy for BRCA1 and BRCA2 can be found in ***MP 513: Genetic Testing for Hereditary and Breast/Ovarian Cancer Syndrome (BRCA1 and BRCA2),*** and below:

I. Patients With Cancer or With Personal History of Cancer:

Genetic testing for *BRCA1* and *BRCA2* variants in **cancer-affected individuals meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage for any of the following circumstances:

- Individual from a family with a known *BRCA1* or *BRCA2* variant
- Personal history of breast cancer **AND** one or more of the following:
    - o Diagnosed at age ≤45 years
    - o Two primary breast cancers when 1st breast cancer diagnosis occurred age at ≤50 years
    - o Diagnosed at age ≤50 years **AND**:
        - One or more 1st-, 2nd-, or 3rd-degree relative(s)[a] with breast cancer at any age, pancreatic cancer or prostate cancer[b] , **or**
        - Unknown or limited family history[c]
    - o Diagnosed at age ≤60 years with a triple-negative (estrogen receptor–negative, progesterone receptor–negative, human epidermal growth factor receptor 2–negative) breast cancer
    - o Diagnosed at any age **AND** 1 or more 1st-, 2nd-, or 3rd-degree relative[a] with breast cancer diagnosed at ≤50 years
    - o Diagnosed at any age **AND** 2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast cancer at any age
    - o Diagnosed at any age **AND** 1 or more 1st-, 2nd-, or 3rd-degree relative[a] with epithelial ovarian, fallopian tube, or primary peritoneal cancer
    - o Diagnosed at any age **AND** 2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with pancreatic cancer or prostate cancer[b] at any age
    - o 1st-, 2nd-, or 3rd-degree male relative with breast cancer
    - o Ethnicity associated with deleterious founder mutations (e.g., Ashkenazi Jewish descent[d])

- Personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer or prostate cancer[c] at any age **AND** 1 or more 1st-, 2nd-, or 3rd-degree relatives[a] with **either** of the following:
    - o Breast cancer ≤50
    - o Ovarian, fallopian tube, or primary peritoneal cancer at any age
- Personal history of pancreatic cancer or prostate cancer[b] at any age **AND** 2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast, pancreatic or prostate cancer[b] at any age.
- For pancreatic cancer, if Ashkenazi Jewish ancestry (no additional affected relative is needed).

II. Patients Without Cancer or Without History of Cancer:
Genetic testing for *BRCA1* and *BRCA2* variants of **cancer-unaffected individuals meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage for any of the following circumstances:

- Individual from a family with a known *BRCA1* or *BRCA2* variant
- 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients With Cancer
- 3rd-degree blood relative with breast cancer and/or ovarian, fallopian tube, or primary peritoneal cancer **AND** 2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast cancer (≥1 at age ≤50 years) and/or ovarian, fallopian tube, or primary peritoneal cancer.

[a]For familial assessment, 1st-, 2nd-, and 3rd-degree relatives are blood relatives on the same side of the family (maternal or paternal).

- 1st-degree relatives are parents, siblings, and children.
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

[b]For familial assessment, prostate cancer is defined as Gleason score ≥7.
[c]For example, fewer than 2 first- or second-degree female relatives having lived beyond age 45 in either lineage. In families with a large number of unaffected female relatives, the likelihood of variant detection may be very low.
[d]Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first

Genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals or of cancer-unaffected individuals with a family history of cancer when criteria above are not met **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Genetic testing in **minors** for *BRCA1* and *BRCA2* variants **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Effective for dates of service January 19, 2018 through October 31, 2018:

Genetic testing for *PALB2* variants for breast cancer risk assessment in adults with or without a history of breast cancer who meet **either of t**he following applicable criteria meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

I. Individual WITHOUT a History of Breast

1. The individual has **any** of the following:

a. Documentation of a close relative with:
    i. A known sequence variant in a cancer susceptibility gene within the family; **or**
    ii. ≥2 breast cancer primaries in a single individual; **or**
    iii. ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 years; **or**
    iv. Ovarian cancer; **or**
    v. Male breast cancer; **OR**
b. Documentation of first- or second-degree relative with breast cancer ≤45 years; **OR**
c. 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"

AND

2. The individual has undergone testing for sequence variants in *BRCA1* and *BRCA2* with **negative** results

OR

II. Individual WITH Breast Cancer

1. The individual has documentation of **ANY** of the following:
    a. Breast cancer ≤50 years ; or
    b. Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 years; or
    c. Two breast cancer primaries in a single individual; or
    d. 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, prostate cancer (Gleason score ≥7 or metastatic) and/or pancreatic cancer at any age, or from a population at increased risk; or
    e. Male breast cancer; or
    f. Metastatic prostate cancer; or
    g. An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age; or
    h. 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."; or
    i. An individual with an ovarian cancer

AND

2. The individual has undergone testing for sequence variants in BRCA1 and BRCA2

with negative results

Genetic testing for *PALB2* sequence variants in individuals who do not meet the criteria outlined above **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Genetic testing for other variants, including but not limited to, *CHEK2* and *ATM*, in the assessment of breast cancer risk **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Effective for dates of service March 17, 2017 through January 18, 2018:

Genetic testing for *PALB2* variants for breast cancer risk assessment in adults with or without a history of breast cancer who meet the following applicable criteria **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

I. Individual WITHOUT a History of Breast

2. The individual has **any** of the following:
    a. Documentation of a close relative with:
        i. A known sequence variant in a cancer susceptibility gene within the family; **or**
        ii. ≥2 breast cancer primaries in a single individual; **or**
        iii. ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 years; **or**
        iv. Ovarian cancer; **or**
        v. Male breast cancer; **OR**
    b. Documentation of first- or second-degree relative with breast cancer ≤45 years; **OR**
    c. 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

    AND
3. The individual has undergone testing for sequence variants in *BRCA1* and *BRCA2* with **negative** results

II. Individuals WITH Breast Cancer

1. The individual has documentation of **ANY** of the following:
    a. Early-age-onset breast cancer; or
    b. Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 years; or
    c. Two breast cancer primaries in a single individual; or
    d. 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; or

e. Male breast cancer; or
f. An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age; or
g. 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; or
h. An individual with an ovarian cancer

Genetic testing for *PALB2* sequence variants in individuals who do not meet the criteria outlined above **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Genetic testing for other variants, including but not limited to, *CHEK2* and *ATM*, in the assessment of breast cancer risk **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Effective for dates of service prior to March 17, 2017:
Genetic testing for *PALB2* mutations in patients with breast or pancreatic cancer or for cancer risk assessment in patients with or without a family history of breast or pancreatic cancer **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Genetic testing for *CHEK2* mutations in patients with breast cancer or for cancer risk assessment in patients with or without a family history of breast cancer **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
This evidence review was updated with a literature review through May 7, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That

is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

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

PALB2 and Breast Cancer Risk Assessment

Clinical Context and Test Purpose

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

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

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

Patients

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

Interventions

The intervention of interest is PALB2 variant testing.

Comparators

The comparator of interest is no genetic testing.

Outcomes

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

Timing

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

Setting

These tests are offered commercially through various laboratories and institutions.

Technically Reliable

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

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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

Single-Country Samples

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 ten (mean age onset, 54.3 years), a family history of breast cancer was known while, in seven, 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. Protein-truncating PALB2 variants were identified in ten 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. This study was limited by its sample size and possibly analytic sensitivity of the sequencing employed.

Casadei et al (2011) studied 959 U.S. women (non-Ashkenazi Jewish descent) with a family history of BRCA1- or BRCA2-negative breast cancer and 83 female relatives using a family-based case-control design. Using conventional sequencing, pathogenic PALB2 variants were detected in 31 (3.2%) women with breast cancer and none in controls. Compared with their female relatives without PALB2 variants, the risk of breast cancer increased 2.3-fold (95% CI, 1.5 to 4.2) by age 55 and 3.4-fold (95% CI, 2.4 to 5.9) by age 85. Mean age at diagnosis was not associated with the presence of a variant (50.0 years with vs 50.2 years without). The study provided few details of analyses. Additionally, participants reported over 30 ancestries and, given intermarriage in the U.S. population, stratification may have had an impact on results. Generalizability of the relative risk estimate is therefore unclear.

Heikkinen et al (2009) conducted a population-based case-control study at a Finnish university hospital employing two 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, were 183 BRCA carriers. PALB2 variant prevalence varied with family history—2.6% when three 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 (ten-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.

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, nine 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 six of 113 cases and in two of 477 controls (OR=13.4; 95% CI, 2.7 to 67.4). Performed in two distinct populations, the combined sample size was small and uncertainty as indicated by the large effect estimate.

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 (next generation sequencing) and novel variants verified by Sanger sequencing. Large deletions or rearrangements were not evaluated. 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 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).

Cybulski et al (2015) examined two 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%) versus 10 (0.21%, 95% CI, 0.08% to 0.34%) of 4702 controls (OR=4.39; 95% CI, 2.30 to 8.37). A BRCA1 variant was identified in 3.47% of women with breast cancer and in 0.47% of controls (OR=7.65; 95% CI: 4.98 to 11.75). Authors estimated that a PALB2 sequence variant conferred a 24% cumulative risk of breast cancer by age 75 (in the setting of age-adjusted breast cancer rates slightly more than half that in the U.K. or the U.S.). A PALB2 variant was also associated with a poorer prognosis— ten-year survival of 48.0% versus 74.7% when the variant was absent (HR=2.27; 95% CI, 1.64 to 3.15; adjusted for prognostic factors).

Multinational Samples
Antoniou et al (2014) analyzed data from 362 members of 154 families with deleterious PALB2 variants. Individuals with benign variants or variants of uncertain significance (VUS) were excluded. Families were recruited at 14 centers in eight countries (U.S., U.K., Finland, Greece, Australia, Canada, Belgium, Italy) and had at least one 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 (seven 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 one or two 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...."

Southey et al (2016) examined the association of three PALB2 variants (two protein truncating: c.1592delT and c.3113G>A; one 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 four 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 six controls (from four 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 eight controls (nine 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 two 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 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, nine (18%) had at least one conflicting interpretation—three (6%) had pathogenic, VUS (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 VUS (variants of uncertain significance) or other uncertainty in interpretation. In addition, discrepancies were confined to missense variants. It is therefore difficult to draw conclusions concerning the frequency of discrepant conclusions among all tested women.

Section Summary: Clinically Valid
Identified studies differed in populations, designs, sample sizes, analyses, and variants examined. While estimates of the magnitude of the association between PALB2 and breast cancer risk varied across studies, their magnitudes are at least moderate and approach the range for a highly penetrant variant.

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

Finally, of interest is how variant detection affects penetrance estimates compared with family history alone. As with BRCA variants, model-based estimates allow estimating risks for individual patient and family characteristics. To illustrate using the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm model, a woman age 30 whose mother had breast cancer at age 35 has an estimated 14.4% risk of breast cancer at age 70; if she carries a PALB2 variant, the risk increases to 51.1%. A woman age 50 with breast cancer whose mother had breast cancer at age 50, has an estimated 11.7% risk of 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

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

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

Author	Year	Analysis	RR/OR (95% CI)	Penetrance at Age 70 (95% CI)	Mean (Median) Age Onset, y	Triple-Negative Tumors	
						PALB2+	*PALB2-*
Erkko	2008	Segregation	6.1 (2.2 to 17.2)[a]	40% (17% to 77%)	54.3 (+FH); 59.3 (FH unavailable)		
Rahman	2007	Segregation[b]	2.3 (1.4 to 3.9)[e]		46 (IQR, 40-51)		
Casadei	2011	Relative risk	2.3 (1.5 to 4.2)[f]		50.0 (SD=11.9)		
Heikkinen	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	2014	Standard CC	13.4 (2.7 to 67.4)				
Thompson	2015	Standard CC	6.6 (2.3 to 18.9)				
Cybulski	2015	Standard CC	4.4 (2.3 to 8.4)		53.3	34.4%	14.4%
Antoniou	2014	Segregation[b]	6.6 (4.6 to 9.2)[c]	47.5% (38.6% to 57.4%)[d]		30%	
Southey	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; 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.

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

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

Evidence of clinical utility limited to women with PALB2 variants was not identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Studies of women at high risk based on family history alone or in those with BRCA1 and BRCA2 variants are relevant to the clinical utility of PALB2 testing given the penetrance estimates for PALB2 and related molecular mechanism ("BRCA-ness"). Interventions to decrease breast cancer risk in asymptomatic high-risk women include screening (e.g., starting at an early age, addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention, and prophylactic mastectomy. In women with breast cancer, contralateral prophylactic mastectomy is of interest; other treatment decisions are dictated by clinical, pathologic, and other prognostic factors.

In women at high risk of hereditary breast cancer, including BRCA1 and BRCA2 carriers, evidence supports a reduction in subsequent breast cancer after 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 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 Risk-Reducing Mastectomy vs Surveillance on Life Expectancy in *BRCA* Carriers According to Penetrance

Risk Level and Strategy	Age of Carrier (y)			
	30	**40**	**50**	**60**
40% risk of breast cancer				
Mastectomy	2.9	2.0	1.0	0.2
Mastectomy delayed 10 y	1.8	0.8	0.1	0.0
60% risk of breast cancer				
Mastectomy	4.1	2.9	1.6	0.3

Mastectomy delayed 10 y	2.4	1.1	0.1	0.0
85% risk of breast cancer				
Mastectomy	5.3	3.7	2.3	0.5
Mastectomy delayed 10 y	2.6	1.1	0.1	0.1

Adapted from Schrag et al (1997).

Section Summary: Clinically Useful

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

CHEK2 and Breast Cancer Risk Assessment

Clinical Context and Test Purpose

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

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

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

Patients

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

Interventions

The intervention of interest is CHEK2 variant testing.

Comparators

The comparator of interest is no genetic testing.

Outcomes

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

Timing

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

Setting

These tests are offered commercially through various laboratories and institutions.

Technically Reliable

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

Clinically Valid

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

Risk of Developing Breast Cancer

For genetic susceptibility to cancer, clinical validity can be established if the variants that the test is intended to identify are associated with disease risk, and if so, if these risks are well quantified. Most studies assessing risk of breast cancer associated with CHEK2 are population- and family-based case-control studies.

Systematic Reviews

Systematic reviews of CHEK2 and breast cancer risk have been reported. Characteristics are shown in Table 4 and results are shown in Table 5.

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 versus non-carriers, 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.

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 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 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.

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).

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

Study	Dates	Population	Designs included	No. of Studies	No. of Participants	Pathogenic Variants Identified
Weischer et al (2008)	Up to Mar 2007	Unilateral breast cancer, Northern or Eastern European descent, *BRCA1*- or *BRCA2*-negative or -unknown, and breast cancer-free controls	Prospective cohort and case-control	16	26,488	c.1100delC
Yang et al (2012)	Up to May 2012	Mixed	Case-control	16	66,218	c.1100delC
Schmidt et al (2016)	NR	European women in the Breast Cancer Association Consortium	Case-control	33	87,754	c.1100delC

NR: not reported.

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

Study	Relative Risk/Odds Ratio (95% CI)	Penetrance at Age 70 (95% CI), %
Weischer et al (2008)		
Unselected for family history		
Total N		
Pooled estimate (95% CI)	2.4 (1.8 to 3.2)	
Early-onset breast cancer		
Total N		
Pooled estimate (95% CI)	2.7 (1.3 to 5.6)	
Familial breast cancer		
Total N		
Pooled estimate (95% CI)	4.6 (3.1 to 6.8)	37 (26 to 56)
Yang et al (2012)		NR
Unselected for family history		
Total N	50,939	
Pooled estimate (95% CI)	2.3 (1.8 to 3.1)	
Early-onset breast cancer		
Total N	42,866	
Pooled estimate (95% CI)	2.8 (2.3 to 3.4)	
Familial breast cancer		
Total N	45,009	
Pooled estimate (95% CI)	3.7 (2.6 to 5.3)	
Schmidt et al (2016)		
Overall		
Total N	81,700	
Pooled estimate (95% CI)	2.4 (2.1 to 2.9)	~17
Non-BRCA1 or BRCA2		
Total N	72,334	
Pooled estimate (95% CI)	2.3 (2.0 to 2.8)	NR

CI: confidence interval; NR: not reported.

Individual Studies Not Included in Systematic Reviews

Individual studies not included in the previous meta-analyses have also reported on the association between breast cancer development and CHEK2 variants; they are summarized in Tables 6 and 7. The number of included patients ranged from over 5500 to almost 87,000. The prevalence of CHEK2 variants was approximately 2% to 3% in breast cancer patients. The OR, HR, or RR ranged from approximately 2 to 3, although it was higher in subgroups of women with family history of breast cancer.

Table 6. Characteristics of Individuals Studies of CHEK2 and Risk of Breast Cancer

Study	Dates	Population	No. of Participants	Pathogenic Variants Identified
Cybulski et al (2011)	1996-2006	Poland; *BRCA1*-negative breast cancer patients unselected for family history and controls from 4 sources	11,840	del5395, IVS21GA, I157T, 1100delC
Decker et al (2017)	After 1991	U.K.; diagnosed with invasive breast cancer from SEARCH study and controls from 3 population-based studies	18,575	c.1100delC plus 14 rare truncating variants
Couch et al (2017)	2012-2016	Women with breast cancer referred for hereditary cancer genetic testing by Ambry Genetics and matched controls from Exome Aggregation Consortium reference	54,305	Unclear
Naslund - Koch et al (2016)	2003-2010	Copenhagen General Population Study: White participants and those of Danish descent from certain areas of Copenhagen	86,975	c.1100delC
Hauke et al (2018)	NR	Met inclusion criteria of the German Consortium for Hereditary Breast and Ovarian Cancer for germ-line testing	5589	Unclear

NR: not reported.

Table 7. Results of Individuals Studies of CHEK2 and Risk of Breast Cancer

Study	Prevalence of CHEK2 Variants	OR (95% CI)	Penetrance at Age 70 (95% CI) %
Cybulski et al (2011)			
Overall			
Total N		11,842	
Estimate (95% CI)	• 3.0% in breast cancer patients • 0.8% in controls	3.6 (2.6 to 5.1)	
Without family history of breast cancer			
Total N		10,391	
Estimate (95% CI)	• 2.8% in breast cancer patients • 0.8% in controls	3.3 (2.3 to 4.7)	20
First- or second-degree relative with breast cancer			
Total N		5797	
Estimate (95% CI)	• 4.7% in breast cancer patients • 0.8% in controls	5.0 (3.3 to 7.6)	
Decker et al (2017)			
Overall			
Total N		18,575	
Estimate (95% CI)	• 1.6% in breast cancer	3.1 (2.2 to 4.7)	NR

	patients • 0.5% in controls		
Couch et al (2017)			
Overall			
Total N		54,305	
Estimate (95% CI)	• 1.5% in breast cancer patients • 0.7% in controls	2.3 (1.9 to 2.7)	NR
Naslund-Koch et al (2016)			
Overall			
Total N		86,975	
Estimate (95% CI)	• 0% homozygotes • 0.8% heterozygotes	2.1 (1.5 to 2.9)	~17
Hauke et al (2018)			
Overall			
Total N		5589	
Estimate (95% CI)	• 1.8% in breast cancer patients • 0.6% and 0.4% in control datasets	2.9 (2.3 to 3.8)	NR

CI: confidence interval; NR: not reported.

Design and conduct gaps are shown in Tables 8 and 9. Only one study included population-based sampling in a prospective cohort. The remaining studies were case-control studies. Several studies did not adequately describe the selection of cases and/or controls. A complete disposition of patients or samples eligible for inclusion and those appearing in the analysis was also not provided in several studies.

Table 8. Study Design and Conduct Gaps of Individuals Studies of CHEK2 and Risk of Breast Cancer

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Cybulski et al (2011)	Case-control population of breast cancer patients (and controls), likely overestimated risk				
Decker et al (2017)	Case-control population of breast cancer patients (and controls), likely overestimated risk				
Couch et al (2017)	Case-control population of breast cancer patients referred to genetic testing (and controls), likely overestimated risk				

Naslund-Koch et al (2016)	Includes only White participants and those of Danish descent
Hauke et al (2018)	Case-control population of breast cancer patients (and controls), likely overestimated risk; only included participants of European ancestry

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. FU: follow-up.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 9. Study Design and Conduct Gaps of Individuals Studies of CHEK2 and Risk of Breast Cancer

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

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.

[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same;
3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Breast Cancer Prognosis in an Individual with a CHEK2 Sequence Variant

Studies of survival between breast cancer patients with and without CHEK2 variants have shown differing results. Breast cancer patients with CHEK2 variants may have worse prognosis than non-carriers.

A 2014 study by Huzarski et al estimated the ten-year survival rate for patients with early-onset breast cancer, with and without CHEK2 variants. Patients were consecutively identified women with invasive breast cancer diagnosed at or below the age of 50, between 1996 and 2007, in 17 hospitals throughout Poland. Patients were tested for four founder 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 non-carriers was similar, as was the hazard ratio for carriers of a truncating variant and non-carriers.

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 non-carriers. Distant disease-free survival and breast cancer–specific survival were similar in the first six years after diagnosis. After six 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 non-carriers 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 non-carriers. 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 non-carriers were 4864 (19%), 2732 (11%), and 607 (2%), respectively. At the time of diagnosis, CHEK2-variant carriers versus non-carriers were on average four 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 non-carriers were

1.43 (95% CI, 1.12 to 1.82; p=0.004) for early death and 1.63 (95% CI, 1.24 to 2.15; p<0.001) for breast cancer–specific death.

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

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

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

Direct evidence of clinical utility for genetic testing in individuals with CHEK2 variants was not identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

As outlined in the section on PALB2, for women with high-risk hereditary cancer syndromes, interventions to decrease breast cancer risk in high-risk women include screening (e.g., starting at an early age, addition of MRI 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.

Section Summary: CHEK2 and Breast Cancer Risk Assessment
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 and/or ovarian cancer syndrome who tested negative for BRCA1 or BRCA2.

Interventions

The intervention of interest is ATM variant testing.

Comparators

The comparator of interest is no genetic testing.

Outcomes

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

Timing

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

Setting

These tests are offered commercially through various laboratories and institutions.

Technically Reliable

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

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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. 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%).

Another 2016 meta-analysis, by van Os et al included seven 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 published after the meta-analyses have also reported on the association between breast cancer development and pathogenic ATM variants. The study characteristics as well as gaps of Decker (2017), Couch (2017), and Hauke (2018) were included in the previous section on CHEK2 (see Tables 6, 8, and 9). Study results are shown in Table 10.

Table 10. Relative Risks Breast Cancer Associated With Pathogenic ATM Variants

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

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

Section Summary: Clinically Valid

ATM heterozygotes appear to have a relative risk of breast cancer from two to three times that of the general population, with an estimated absolute risk of 6% by age 50 and 33% by age 80, although estimates come from the population- and family-based case-controls, which are subject to bias and overestimation.

Clinically Useful

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

Direct Evidence

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

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

Direct Evidence

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

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 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.

Section Summary: ATM and Breast Cancer Risk Assessment

No evidence is available to support the clinical utility of genetic testing for ATM variants in breast cancer patients to guide patient management, and there is no strong chain of evidence supporting ATM testing in breast cancer patients.

Summary of Evidence

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a PALB2 variant, the evidence includes studies of clinical validity and studies of breast cancer risk, including a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Evidence supporting clinical validity was obtained from numerous studies reporting relative risks or odds ratios (two studies estimated penetrance). Study designs included family segregation, kin-cohort, family-based case-control, and population-based case-control. The number of pathogenic variants identified in studies varied from one (founder mutations) to 48. Relative risks for breast cancer associated with a PALB2 variant ranged from 2.3 to 13.4, with the two family-based studies reporting the lowest values. Evidence on preventive interventions in women with PALB2 variants is indirect, relying on studies of high-risk women and BRCA carriers. These interventions include screening with magnetic resonance imaging, chemoprevention, and risk-reducing mastectomy. Given the penetrance of PALB2 variants, the outcomes following bilateral and contralateral risk-reducing mastectomy examined in women with a family history consistent with hereditary breast cancer (including BRCA1 and BRCA2 carriers) can be applied to women with PALB2 variants—with the benefit-to-risk balance affected by penetrance. In women at high risk of hereditary breast cancer who would consider risk-reducing interventions, identifying a PALB2 variant provides a more precise estimated risk of developing breast cancer compared with family history alone and can offer women a more accurate understanding of benefits and potential harms of any intervention. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a CHEK2 variant, the evidence includes studies of variant prevalence, and studies of breast cancer risk. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and

validity. The available studies on clinical validity have demonstrated that CHEK2 variants are of moderate penetrance, with lower relative risks for breast cancer than PALB2, and confer a risk of breast cancer two to four times that of the general population. Direct evidence for the clinical utility of genetic testing for CHEK2 variants in individuals with risk of hereditary breast/ovarian cancer was not identified. In contrast to the case of PALB2, where the penetrance approaches that of a BRCA variant, there is unlikely to be a similar benefit-to-risk calculus for risk-reducing mastectomy in women with a CHEK2 variant. 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 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 two to four times that of the general population. Direct evidence for the clinical utility of genetic testing for ATM variants in individuals with risk of hereditary breast/ovarian cancer was not identified. 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. In contrast to the case of PALB2, where the penetrance approaches that of a BRCA variant, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with an ATM variant. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 (ASCO) stated that testing for high-penetrance mutations in appropriate populations has clinical utility in that they inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes. The update notes: "Clinical utility remains the fundamental issue with respect to testing for mutations 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 mutation. There is insufficient evidence at the present time to conclusively demonstrate the clinical utility of testing for moderate-penetrance mutations, and no guidelines exist to assist oncology providers."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2018) review single-gene tests for PALB2, CHEK2, or ATM. The guidelines state that a number of genes, including but not limited to PALB2, CHEK2, and ATM "could potentially" be included in a multigene test. They note that

there are limited data on the degree of cancer risk associated with some genes in multigene panels.

The National Comprehensive Cancer Network guidelines on breast cancer screening and diagnosis (v.1.2018) and on genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2018) recommend the following:

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

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

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for PALB2 mutation testing have been identified

Key Words:

PALB2, pancreatic cancer, breast cancer, genetic testing, cancer risk assessment, Myriad, Panexia test, CHEK2 mutation, checkpoint kinase 2, ATM gene, ovarian cancer

Approved by Governing Bodies:

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 [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 intermediate- and high-penetrant genes. Refer to medical policy #532, *Genetic Cancer Susceptibility Panels Using Next Generation Sequencing* for information on the inclusion of *PALB2* in these types of panels.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.

FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

81406	PALB2 (partner and localizer of BRCA2) (e.g. breast and pancreatic cancer), full gene sequence
81408	ATM (ataxia telangiectasia mutated) (e.g., ataxia telangiectasia), full gene sequence

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

81479	Unlisted molecular pathology procedure

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Policy History:

Medical Policy Panel, January 2015 (*PALB2*)
Medical Policy Panel, June 2015 (*CHEK2*)
Medical Policy Group, July 2015 (**3**): New policy created (*CHEK2*)
Medical Policy Administration Committee, July 2015 (*CHEK2*)
Available for comment July 17 through August 20, 2015 (*CHEK2*)
Medical Policy Panel, August 2015 (*CHEK2*)
Medical Policy Group, August 2015 **(3)**: Updates to Description & Key Points; no change in policy statement (*CHEK2*)
Medical Policy Group, August 2015 **(3)**: newly adopted policy (*PALB2*)
Medical Policy Administration Committee, August 2015 (*PALB2*)
Available for comment August 19 through October 2, 2015 (*PALB2*)
Medical Policy Panel, January 2016 (*PALB2*)
Medical Policy Group, January 2016 **(3)**: 2016 Updates to Description, Key Points & References; no change in policy statement (*PALB2*)
Medical Policy Panel, July 2016 (*CHEK2*)
Medical Policy Group, July 2016 **(3)**: 2016 Updates to Description, Key Points, & References; no change in policy statement (*CHEK2*)
Medical Policy Panel, October 2016: Tabled by MPP in order to combine policies on intermediate-penetrance mutations for breast cancer risk assessment rather than having multiple policies (*PALB2*)
Medical Policy Panel, December 2016 (*PALB2, CHEK2, ATM*)
Medical Policy Group, March 2016 **(3)**: Major updates to all sections including Title; combined medical policy #605 *Genetic Testing for CHEK2 Mutations for Breast Cancer* into this policy

and archived #605; added information on *ATM* variant testing; updated policy statement to reflect adding coverage criteria for genetic testing for *PALB2* variants for breast cancer risk assessment in adults with or without a history of breast cancer who meet the certain criteria; genetic testing of *CHEK2* and *ATM* variants remains investigational.
Medical Policy Administration Committee, April 2017
Available for comment March 17 through April 30, 2017
Medical Policy Panel, December 2017
Medical Policy Group, January 2018 **(3)**: 2017 Updates to Description, Key Points & References; policy statements updated to reflect clarifications and additional criteria for coverage of *PALB* testing
Available for comment January 18 through March 4, 2018
Medical Policy Panel, July 2018
Medical Policy Group, July 2018 **(9)**: 2018 Updates to Description, Key Points, & References. Policy statement updated to reflect current NCCN recommendations, no change to intent; Key Words added: ATM gene, ovarian cancer.
Available for comment October 29, 2018 through December 13, 2018.
