2.04.126	Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)		
Original Policy Date:	May 29, 2015	**Effective Date:**	December 1, 2022
Section:	2.0 Medicine	**Page:**	Page 1 of 31

Policy Statement

I. Individual or large panel testing for *CHEK2, ATM, and BARD1* variants when not included as part of an approved small panel in the assessment of breast cancer risk is considered **investigational.**

NOTE: Germline genetic testing for BRCA1, BRCA2 and PALB2 is addressed separately in Blue Shield of California Medical Policy: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

When part of a limited panel that meets criteria for medical necessity under another policy (e.g., 2.04.02 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2), or 2.04.08 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes), the inclusion of PALB2, CHEK2, ATM, or other genes is allowed.

Criteria for Genetic Risk Evaluation

The National Comprehensive Cancer Network (NCCN) provides criteria for genetic risk evaluation for individuals with no history of 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, BRCA2,* and *PALB2* is described in Blue Shield of California Medical Policy: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2).

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

The following new CPT codes describe partner and localizer gene analysis for *PALB2* testing:

- **81307**: *PALB2* (partner and localizer of *BRCA2*) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence
- **81308**: *PALB2* (partner and localizer of *BRCA2*) (e.g., breast and pancreatic cancer) gene analysis; known familial variant

Testing for *ATM* variants is included in CPT tier 2 molecular pathology:

- **81408**: Molecular Pathology Procedure Level 9 – which includes *ATM (ataxia telangiectasia mutated)* (e.g., ataxia telangiectasia), full gene sequence

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

Description

It is estimated that 3% to 5% of women presenting for assessment for hereditary breast/ovarian cancer risk have a variant in a gene that moderately increases the risk of cancer. *CHEK2, ATM,* and *BARD1* variants are considered to be of moderate penetrance. Female carriers of *CHEK2, ATM* and *BARD1* 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 a family history of a specific variant.

Germline genetic testing for *BRCA1, BRCA2,* and *PALB2* is addressed separately Blue Shield of California Medical Policy: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2).

Related Policies

- Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
- Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. *CHEK2, ATM,* and *BARD1* testing are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories offering to test and voluntarily listing is available through the National Center for Biotechnology Genetic Testing Registry. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Customized next-generation sequencing panels provide simultaneous analysis of multiple cancer predisposition genes, and typically include both moderate- and high-penetrant genes.

Rationale

Background

Breast Cancer and Genetics

The National Cancer Institute estimated there would be 287,850 new cases of female breast cancer (FBC) and 2,710 cases of male breast cancer (MBC) diagnosed in 2022, with an expected 43,250 deaths due to FBC and 530 deaths due to MBC.[1,] Although non-Hispanic, white women are more likely to be diagnosed with breast cancer than non-Hispanic Black, Asian/Pacific Islander, American Indian/Alaska Native and Hispanic women, non-Hispanic Black women have the highest risk of breast cancer mortality.[2,] Breast cancers can be classified as sporadic, familial, or hereditary. Most breast cancers are sporadic (70% to 75%), occurring in individuals without a family history of the disease. Familial cancers (15% to 25%) aggregate within families but lack clearly discernable patterns of inheritance and are likely polygenic. Hereditary cancers have discernable inheritance patterns, often occur at younger ages, may be bilateral, and comprise between 5% and 10% of breast cancers. Most inherited autosomal dominant breast cancer can be attributed to the *BRCA1* and *BRCA2* variants. For women who inherit a pathogenic *BRCA1* and *BRCA2* variant, 45% to 72% will develop breast cancer by 70 to 80 years of age; risk in men with *BRCA1* and *BRCA2* variants is much lower (1% and 7%, respectively).[3,4,] Pathogenic variants in other highly penetrant genes (e.g., *TP53*, *CDH1*, *PTEN*, *STK11*) contribute to a smaller number of cancers. *CHEK2 and ATM* are believed to be moderately penetrant[5,]and *BARD1* has alternatively been described as moderate, low/moderate, and low penetrance.[6,7,8,]

Testing for *BRCA1, BRCA2, and PALB2* is addressed in Blue Shield of California Medical Policy: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2).

Testing for mismatch repair genes linked to Lynch syndrome is addressed in Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes.

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).[9,] 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], and *STK11* [Peutz-Jeghers syndrome]) are considered highly penetrant. For example, a woman with a *BRCA1* or *BRCA2* variant has a relative risk of 11 to 12 compared with the general population.[10,] Penetrance can be modified by environmental factors and by family history, which is a particularly important modifier for low and moderate penetrance genes. Moreover, specific pathogenic variants within a gene may confer somewhat different risks.

Determining Variant Pathogenicity

Determining the pathogenicity of variants in a more commonly detected cancer susceptibility gene (e.g., founder sequence mutations) is generally straightforward because associations are repeatedly observed. For uncommonly identified variants, such as those found in a few individuals or families, defining pathogenicity can be more difficult. For example, predicting the pathogenicity of previously unidentified variants typically requires in silico (computational) analysis predicting protein structure/function, evolutionary conservation, and splice site prediction.[11,] The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines.[11,] Still, distinctions between a variant of uncertain significance and a pathogenic one from different laboratories may not always be identical.[12,]

Genes Associated With a Moderate Penetrance of Breast Cancer

CHEK2 Gene

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

In 2002, a single recurrent truncating variant in the *CHEK2* gene (c.1100delC) was first reported as a cause of breast cancer, and studies have since confirmed this. The incidence of *CHEK2* variants varies widely among populations. It is most prevalent in Eastern and Northern Europe, where the population frequency of the c.1100delC allele ranges from 0.5% to 1.4%; the allele is less frequent in North America and virtually absent in Spain and India. When compared with non-Hispanic, white individuals, prevalence appears to be lower in Black (odds ratio [OR] 0.17; 95% CI, 0.07 to 0.33), Asian (OR 0.14; 95% CI, 0.04 to 0.34), and Hispanic (OR 0.36; 95% CI, 0.18 to 0.62) individuals.[13,]

Although most data for truncating *CHEK2* variants are limited to the c.1100delC allele, 3 other founder mutations of *CHEK2* (IVS2+1G>A, del5395, I157T) have been associated with breast cancer in Eastern Europe. Both IVS2+1G>A and del5395 are protein-truncating variants, and I157T is a missense variant. The truncating variants are associated with breast cancer in the Slavic populations of Poland, Belarus, Russia, and the Czech Republic. The I157T variant has a wider geographic distribution and has been reported to be associated with breast cancer in Poland, Finland, Germany, and Belarus.[14,]

ATM Gene

ATM (ataxia-telangiectasia mutated), located on chromosome 11q22.3, is associated with the autosomal recessive condition ataxia-telangiectasia syndrome. This condition is characterized by progressive cerebellar ataxia with onset between the ages of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition. Female *ATM* 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.

BARD1 Gene

The *BARD1* (BRCA1-associated RING [Really Interesting New Gene] domain) gene is located on chromosome 2 (sequence 2q34-q35). *BARD1* encodes a protein which interacts with the N-terminal region of *BRCA1*, and *BARD1* and *BRCA1* can form a heterodimer by their N-terminal RING finger domains which form a stable complex.[6,] *BARD1* variants have been associated with an increased risk of estrogen-receptor (ER) negative breast cancer, triple-negative breast cancer, and with breast cancer at a younger age (under age 50 years) in some studies, but do not appear to increase risk of ovarian cancer.[5,15,]

Identifying Individuals at Risk of an Inherited Susceptibility to Breast Cancer

Breast cancer risk can be affected by genetic and nongenetic factors. The risk is increased in women experiencing an earlier age at menarche, nulliparity, late age of first pregnancy, fewer births, late menopause, proliferative breast disease, menopausal hormone therapy, alcohol, obesity, inactivity, and radiation.[16,] A family history of breast cancer confers between a 2- and 4-fold increased risk varying by several factors: the number and closeness of affected relatives, age at which cancers developed, whether breast cancers were bilateral and if other cancers occurred (e.g., ovarian).[17,] In men, family history is associated with increased risk of breast cancer, along with being older than 65 years, health conditions that result in elevated estrogen levels, and lifestyle factors (e.g., obesity).[4,] 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),[18,] screening tools (e.g., BRCAPRO,[19,] Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen[20,21,]), or by referring to guidelines that define specific family history criteria (see Supplemental Information section on Practice Guidelines and Position Statements). For women with breast cancer, family history also affects the likelihood of carrying a pathogenic variant.[18,]

Variant Interpretation

Valid variant classification is required to assess penetrance and is of particular concern for low prevalence variants. While there are guidelines for variant classification, the consistency of interpretation among laboratories is of interest. Balmaña et al (2016) examined the agreement in variant classification by different laboratories from tests for inherited cancer susceptibility from individuals undergoing panel testing.[22,] The Prospective Registry of Multiplex Testing is a volunteer sample of patients invited to participate when test results were provided to patients from participating laboratories. From 518 participants, 603 variants were interpreted by multiple laboratories and/or found in ClinVar. Discrepancies were most common with *CHEK2* and *ATM*. Given the nature of the sample, there was a significant potential for biased selection of women with either reported variants of uncertain significance or other uncertainty in interpretation. In addition, discrepancies were confined to missense variants. It is therefore difficult to draw conclusions concerning the frequency of discrepant conclusions among all tested women.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

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

CHEK2 and Breast Cancer Risk Assessment

Clinical Context and Test Purpose

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

Potential benefit derives from interventions (screening, chemoprevention, risk-reducing surgery) that can prevent first breast cancer, contralateral breast cancer, or cancer in a different organ caused by the same variant. Whether benefit outweighs harms depends on the risk of developing breast cancer (first cancer or a contralateral one) and the effectiveness and the harms of interventions.

Assessing the net health outcome requires:

- That a test accurately identifies variants and pathogenicity can be determined;
- 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
- Management changes informed by testing can lead to improved health outcomes.

The question addressed in this evidence review is: Does genetic testing for *CHEK2* variants improve the net health outcome in women at high-risk of HBOC?

The following PICO was used to select literature to inform this review.

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.

The relevant population of interest in this review is patients who are undergoing assessment for HBOC syndrome.

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

Comparators
The alternative would be to manage women at high-risk of HBOC with no CHEK2 genetic testing.

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

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Included a suitable reference standard
- Patient/sample clinical characteristics were described with women at high breast cancer risk
- Patient/sample selection criteria were described.

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).

Review of Evidence
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.[10,] Most studies assessing the risk of breast cancer associated with *CHEK2* are population- and family-based case-control studies.

Systematic Reviews
Systematic reviews of *CHEK2* and breast cancer risk have been reported. A systematic review conducted by Suszynska et al (2019) included association estimates for *CHEK2* variants.[23,] Characteristics are shown in Table 1 and the results are shown in Table 2. The systematic review included studies published through July 2017 reporting on genetic test results of breast and ovarian cancer patients who were referred for evaluation by a multi-gene panel. Given that the Suszynska et al (2019) report included only studies reporting on test results from a panel, it does not substantially overlap with the studies described in the following section. The studies of panel results were used to calculate mutation frequencies by the gene. As a control, population mutation frequencies were extracted from the Genome Aggregation Database. In the 43 breast cancer studies included in the review, 94,845 patients contributed to the meta-analysis of *CHEK2* in breast cancer patients. The OR of breast cancer for *CHEK2* variants including variants c.470T>C and c.1283C>T was OR 0.96 (95% CI, 0.90 to 1.03); after excluding variants c.470T>C and c.1283C>T, the association between the remaining *CHEK2* variants and breast cancer was OR 1.73 (95% CI, 1.58 to 1.89). Given that the Suszynska et al (2019) report included only studies reporting on test results from a panel, it does not substantially overlap with the studies described in the following section including other *CHEK2* association studies.
An article by Schmidt et al (2016) evaluated data on *CHEK2* variant status and breast cancer risk from the BCAC.[24,25,] 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).

A meta-analysis by Yang et al (2012) examined the risk of breast cancer in whites with the *CHEK2* c.1100delC variant.[24,] Twenty-five case-control studies conducted in Europe and North and South America published in 16 articles were analyzed, with a total of 29,154 breast cancer cases and 37,064 controls. Of the cases, 13,875 patients had unselected breast cancer, 7945 had familial breast cancer, and 5802 had early-onset breast cancer. In total, 391 (1.3%) of the cases had a *CHEK2* c.1100delC variant and 164 (0.4%) of the controls. The association between the *CHEK2* c.1100delC variant and breast cancer risk was statistically significant (OR 2.75; 95% CI, 2.25 to 3.36). By subgroup, odds were 2.33 (95% CI, 1.79 to 3.05) for unselected, 3.72 (95% CI, 2.61 to 5.31) for familial, and 2.78 (95% CI, 2.28 to 3.39) for early-onset breast cancer.

Weischer et al (2008) performed a meta-analysis of studies on *CHEK2* c.1100delC heterozygosity and the risk of breast cancer among patients with unselected (including the general population), early-onset (<51 years of age), and familial breast cancer.[26,] 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 noncarriers, the aggregated ORs for breast cancer were 2.7 (95% CI, 2.1 to 3.4) and 2.4 (95% CI, 1.8 to 3.2) in studies of unselected breast cancer, 2.6 (95% CI, 1.3 to 5.5) and 2.7 (95% CI, 1.3 to 5.6) in studies of early-onset breast cancer, and 4.8 (95% CI, 3.3 to 7.2) and 4.6 (95% CI, 3.1 to 6.8) in studies of familial breast cancer, respectively.

Table 1. 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
Suszynska et al (2019)[23,]	To Jul 2017	Cases: Patients with breast and/or ovarian cancer referred for evaluation by a multi-gene panel Controls: Patients from the Genome Aggregation Database	Studies reporting prevalence of genetic variants	48 (overall) 43 (breast cancer)	94,845 included in CHEK2 analysis Unclear how many controls were included from the Genome Aggregation Database	37 *CHEK2* variants
Schmidt et al (2016)[24,25,24,]	NR	European women in the Breast Cancer Association Consortium	Case-control	33	87,754	c.1100delC
Yang et al (2012)[24,]	To May 2012	Mixed	Case-control	16	66,218	c.1100delC
Weischer et al (2008)[26,]	To Mar 2007	Unilateral breast cancer, Northern or Eastern European descent, *BRCA1*- or *BRCA2*-negative or -unknown, and breast cancer-free controls	Prospective cohort and case-control	16	26,488	c.1100delC

NR: not reported.

Table 2. Results of Systematic Reviews of *CHEK2* and Risk of Breast Cancer

Study	Relative Risk/Odds Ratio (95% CI)	Penetrance at Age 70 (95% CI), %
Suszynska et al (2019)[23,]	1.73 (95% CI, 1.58 to 1.89)[a]	NR
Schmidt et al (2016)[25,]		
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
Yang et al (2012)[24,]		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)	
Weischer et al (2008)[26,]		
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)

CI: confidence interval; NR: not reported.
[a]Excluding variants c.470T>C and c.1283C>T.

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 3 and 4. The number of included patients ranged from 4000 to over 95,000. 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 a family history of breast cancer and in biallelic carriers of *CHEK2* pathogenic variants.

Table 3. Characteristics of Studies of *CHEK2* and Risk of Breast Cancer

Study	Dates	Population	No. of Participants	Pathogenic Variants Identified
Hu et al (2021)[15,] CARRIERS Consortium	NR	Female patients with breast cancer and unaffected controls from studies within population-based studies from the Cancer Risk Estimates Related to Susceptibility (CARRIERS) consortium	32,247 cases 32,544 controls	Unclear; p.Ile157Thr and p.Ser428Phe excluded from analyses
Southey et al (2021)[27,]	NR	Female patients included in either the Australian Breast Cancer Family Study (ABCFS) or the ASPirin in Reducing Events in the Elderly (ASPREE) study	1464 cases and 7411 controls	c.1100delC and unclear others
Li et al (2021)[28,](BEACON)	NR	Female patients with breast and/or ovarian cancer from non-*BRCA1* and *BRCA2* hereditary breast and ovarian cancer families. The control population was older women without cancer at the time of the study.	1990 cases 1902 population-matched controls	85% were c.1100delC

Study	Dates	Population	No. of Participants	Pathogenic Variants Identified
Nguyen-Dumont (2021)[29],	NR	Segregation analysis of cases and controls in 26 families	1476 cases 861 controls	c.1100delC plus 8 rare variants
Rainville et al (2020)[30],	2013-2019	Monoallelic and biallelic female carriers of *CHEK2* pathogenic variants identified through clinical pan-hereditary cancer panel testing	6515	c.1100delC and unclear
Lu et al (2019) [31],	2014 - 2015	Cases with breast and/or ovarian cancer referred for genetic testing and controls referred for genetic testing for noncancer conditions	15,404	'Known breast or ovarian cancer gene'
Kurian et al (2017)[32],	2013 - 2015	Cases and controls referred for testing for hereditary cancer; Controls were those without cancer at the time of testing	95,561	Unclear
Fan et al (2018)[33],	2003-2015	Breast cancer patients at Chinese university cancer hospital who received gene panel sequencing	8085	c.1100delC
Hauke et al (2018)[34],	NR	Met inclusion criteria of the German Consortium for Hereditary Breast and Ovarian Cancer for germ-line testing	5589	Unclear
Decker et al (2017)[35],	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)[36],	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)[37],	2003-2010	Copenhagen General Population Study: White participants and those of Danish descent from certain areas of Copenhagen	86,975	c.1100delC
Cybulski et al (2011)[14],	1996-2006	Poland; *BRCA1*-negative breast cancer patients unselected for family history and controls from 4 sources	11,840	del5395, IVS21GA, I157T, 1100delC

BEACCON: Hereditary BrEAst Case CONtrol study; NR: not reported.

Table 4. 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), %
Hu et al (2021)[15], CARRIERS Consortium			
Overall			
Total N		64,791	
Estimate (95% CI)	1.08% in breast cancer patients 0.42% in population-based controls	2.47 (2.02 to 3.05)	~25 (CI NR)
With family history of breast cancer			
Total N		6361	
Estimate (95% CI)	1.52% in breast cancer patients	3.59 (2.75 to 4.68)	NR
Without family history of breast cancer			
Total N		24,873	
Estimate (95% CI)	0.95% in breast cancer patients	2.25 (1.81 to 2.79)	NR
≤50 years			
Total N		11,338	
Estimate (95% CI)	1.40% in breast cancer patients 0.43% in population-based controls	3.06 (2.32 to 4.08)	NR
>50 years			
Total N			
Estimate (95% CI)	1.03% in breast cancer patients 0.42% in population-based controls	2.53 (1.88 to 2.97)	NR

Study	Prevalence of *CHEK2* Variants	OR (95% CI)	Penetrance at Age 70 (95% CI), %
Southey et al (2021)[27,]	1.35% in breast cancer patients 0.50% in population-based controls	1.30 (0.53 to 3.00)	NR
Li et al (2021)[28,](BEACON)			
Total N		3892	
Loss of Function	78 (1.35%) familial breast cancer patients 29 (0.51%) population-matched controls	2.70 (1.74 to 4.30)	NR
Missense	122/1900 (2.11%) familial breast cancer patients 71/1902 (1.24%) population-matched controls	1.73 (1.27 to 2.35)	NR
Nguyen-Dumont (2021)[29,]	20 (1.4%) case probands 7 (0.8%) control probands		26 (16 to 40)
	For all variants	4.9 (2.5 to 9.5)	
	c.1100delC	3.5 (1.02 to 11.6)	
Rainville et al (2020)[30,]			
Monoallelic	6473/6515 (99.4%) monoallelic carriers of *CHEK2* variants 2668/6473 (41.2%) in breast cancer patients 3234 (50.0%) in no personal cancer history	Ductal invasive: 2.02 (1.90 to 2.15) DCIS: 1.82 (1.66 to 2.00)	NR
Biallelic	42/6515 (0.6%) biallelic carriers of *CHEK2* variants (16/42 homozygous for c.1100delC) 25/31 (80.6%) in breast cancer patients 3 (9.7%) in no personal cancer history	Ductal invasive: 8.69 (3.69 to 20.47) DCIS: 4.98 (2.00 to 12.35)	NR
Lu et al (2019) [31,]	0.8% in breast or ovarian cancer cases 0.3% in controls	2.19 (1.40 to 3.56)	NR
Kurian et al (2017)[32,]	1.2% in breast cancer patients 1% in patients without breast or ovarian cancer	1.99 (1.70 to 2.33)	NR
Fan et al (2018)[33,]			
Overall			
Total N	7657		NR
Estimate (95% CI)	0.34% in breast cancer patients	NR	
Hauke et al (2018)[34,]			
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
Decker et al (2017)[35,]			
Overall			
Total N		18,575	
Estimate (95% CI)	1.6% in breast cancer patients 0.5% in controls	3.1 (2.2 to 4.7)	NR
Couch et al (2017)[36,]			
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)[37,]			
Overall			
Total N		86,975	
Estimate (95% CI)	0% homozygotes 0.8% heterozygotes	2.1 (1.5 to 2.9)	»17
Cybulski et al (2011)[14,]			
Overall			
Total N		11,842	

Study	Prevalence of *CHEK2* Variants	OR (95% CI)	Penetrance at Age 70 (95% CI), %
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)	

BEACCON: Hereditary BrEAst Case CONtrol study; CI: confidence interval; DCIS: ductal carcinoma in situ; NR: not reported; OR: odds ratio.

Study design and conduct limitations are shown in Tables 5 and 6. Only 1 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 5. Study Relevance Limitations of Individuals Studies of *CHEK2* and Risk of Breast Cancer

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Hu et al (2021)[15,] CARRIERS Consortium	4. Case-control population included primarily non-Hispanic, white women (77%)	1. Not clear which variants were included			
Southey et al (2021)[27,]	4. Case-control population of breast cancer patients (and controls) conducted in Australia, race/ethnicity not reported	1. Not clear which variants other than c.1100delC were included			
Li et al (2021)[28,](BEACON)	4. Case-control population of breast cancer patients (and controls), included primarily participants of European ancestry				
Nguyen-Dumont (2021)[29,]	4. Included primarily participants of European ancestry				
Rainville (2020)[30,]	4. No control population, likely overestimated risk	1. Not clear which variants were included			1. Unclear if follow-up duration is sufficient due to retrospective review

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of FU[e]
Lu et al (2019)[31],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk	1. Not clear which variants were included			
Kurian et al (2017)[32],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk	1. Not clear which variants were included			1. Control chosen from patients being tested for hereditary cancer; unclear how many developed cancer
Fan et al (2018)[33],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk; only included Chinese patients				
Hauke et al (2018)[34],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk; only included participants of European ancestry				
Decker et al (2017)[35],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk				
Couch et al (2017)[36],	4. Case-control population of breast cancer patients referred to genetic testing (and controls), likely overestimated risk				
Naslund-Koch et al (2016)[37],	4. Includes only White participants and those of Danish descent				
Cybulski et al (2011)[14],	4. Case-control population of breast cancer patients (and controls), likely overestimated risk				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
BEACCON: Hereditary BrEAst Case CONtrol study; 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 6. Study Design and Conduct Limitations of Individuals Studies of *CHEK2* and Risk of Breast Cancer

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Hu et al (2021)[15,] CARRIERS Consortium	1. Incomplete description of how controls selected for some CARRIERS studies			1. Registration not reported		
Southey et al (2021)[27,]	1. Incomplete description of how ABCFS controls were selected			1. Registration not reported		
Li et al (2021)[28,](BEACON)				1. Registration not reported	1. No description of disposition of eligible patients/samples	
Nguyen-Dumont (2021)[29,]				1. Registration not reported		
Rainville (2020)[30,]				1. Registration not reported	1. Only exclusion criteria are provided	
Lu et al (2019)[31,]	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Kurian et al (2017)[32,]				1. Registration not reported	1. No description of disposition of eligible patients/samples	
Fan et al (2018)[33,]	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Hauke et al (2018)[34,]	1. Incomplete description of how controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Decker et al (2017)[35,]	1. No description of how cases or controls selected			1. Registration not reported	1. No description of disposition of eligible patients/samples	
Couch et al (2017)[36,]	1. Incomplete description of how controls selected			1. Registration not reported		
Naslund-Koch et al (2016)[37,]				1. Registration not reported		

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Cybulski et al (2011)[14,]				1. Registration not reported	1. No description of disposition of eligible patients/samples	

BEACCON: Hereditary BrEAst Case CONtrol study; CARRIERS: Cancer Risk Estimates Related to Susceptibility consortium
The study limitations 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 with 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 a worse prognosis than noncarriers.

Fan et al (2018) investigated the clinical relevance of *CHEK2* variants in breast cancer patients.[33,] In this observational study, the genomes of 7657 Chinese *BRCA1*- and *BRCA2*-negative breast cancer patients were analyzed. Researchers reported a *CHEK2* germline variant rate of 0.34%, and those with the variants were significantly more likely (p=.022) to have family histories of cancer and to develop lymph node-positive and progesterone receptor-positive cancers. Limitations include sample homogeneity and retrospective design.

A study by Huzarski et al (2014) estimated the 10-year survival rate for patients with early-onset breast cancer, with and without *CHEK2* variants.[38,] Patients were consecutively identified women with invasive breast cancer diagnosed at or below the age of 50, between 1996 and 2007, in 17 hospitals throughout Poland. Patients were tested for 4 founder mutations in the *CHEK2* gene after diagnosis, and their medical records were used to retrieve tumor characteristics and treatments received. Dates of death were retrieved from a national registry. A total of 3592 women were eligible for the study, of whom 487 (13.6%) carried a *CHEK2* variant (140 with truncating variants, 347 with missense variants). Mean follow-up was 8.9 years. Ten-year survival for *CHEK2*-variant carriers (78.8%; 95% CI, 74.6% to 83.2%) was similar to noncarriers (80.1%; 95% CI, 78.5% to 81.8%). After adjusting for other prognostic features, the HR comparing carriers of the missense variant with noncarriers was similar, as was the HR for carriers of a truncating variant and noncarriers.

A study by Kriege et al (2014) compared breast cancer outcomes in patients with and without *CHEK2* variants.[39,] Different study cohorts were combined to compare 193 carriers with 4529 noncarriers. Distant disease-free survival and breast cancer-specific survival were similar in the first 6 years after diagnosis. After 6 years, both distant disease-free survival (multivariate HR 2.65; 95% CI 1.79 to 3.93) and breast cancer-specific survival (multivariate HR 2.05; 95% CI, 1.41 to 2.99) were worse in *CHEK2* carriers. No interaction between *CHEK2* status and adjuvant chemotherapy was observed.

Weischer et al (2012) reported on breast cancer associated with early death, breast cancer-specific death, and the increased risk of a second breast cancer (defined as a contralateral tumor) in *CHEK2*-variant carriers and noncarriers in 25,571 white women of Northern and Eastern European descent who had invasive breast cancer, using data from 22 studies participating in the BCAC conducted in 12

countries.[40,] 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 second breast cancer in 25,094. Of the 25,571 women, 459 (1.8%) were *CHEK2* c.1100delC heterozygous and 25,112 (98.2%) were noncarriers. Median follow-up was 6.6 years, over which time the following was observed: 124 (27%) early deaths occurred, 100 (22%) breast cancer-specific deaths occurred, and 40 (9%) second breast cancers among *CHEK2* c.1100delC variant carriers were observed. Corresponding numbers among noncarriers were 4864 (19%), 2732 (11%), and 607 (2%), respectively. At the time of diagnosis, *CHEK2*-variant carriers versus noncarriers were on average 4 years younger (p<.001); additionally, *CHEK2*-variant carriers were more likely to have a family history of cancer (p<.001). Multifactorially adjusted HRs for *CHEK2* versus noncarriers were 1.43 (95% CI, 1.12 to 1.82; p=.004) for early death and 1.63 (95% CI, 1.24 to 2.15; p<.001) for breast cancer-specific death.

Section Summary: Clinically Valid

Studies have shown that a *CHEK2* variant is of moderate penetrance and confers a risk of breast cancer 2 to 4 times that of the general population. This risk appears to be higher in patients who also have a strong family history of breast cancer. Although the *CHEK2* variant appears to account for approximately one-third of variants identified in *BRCA1*- and *BRCA2*-negative patients, it is relatively rare with estimates ranging from 1.5% to 4.7% of breast cancer patients in the included studies, and risk estimates, which have been studied in population- and family-based case-controls, are subject to bias and overestimation. One systemic review and 2 studies published since the review estimated the risk of breast cancer by age 70 years in women with *CHEK2* variants was close to 20%. However, another review estimated that it may be as high as 37% (95% CI, 26% to 56%) in women with familial breast cancer. Several studies have suggested that *CHEK2* carriers with breast cancer may have worse breast cancer-specific survival and distant-recurrence free survival, with about twice the risk of early death.

Clinically Useful

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

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.

Weidner et al (2020) conducted a retrospective, consecutive study on 69 *CHEK2* carriers enrolled in the Inherited CAncer REgistry (ICARE) at Vanderbilt University and their relatives.[41,] Eligibility for annual breast magnetic resonance imaging surveillance was based on ≥20% lifetime risk of breast cancer based on family cancer history alone as calculated by the BOADICEA predictive model, or family cancer history and proband CHEK2 variant status, utilizing an updated version of the BOADICEA model (BWA v4). Among the *CHEK2* carriers and family history alone, 21 first-degree relatives (FDRs) (14.9%) and 14 second-degree relatives (SDRs) (13.9%) had a lifetime cancer risk ≥20%. Inclusion of the proband's variant status significantly increased identification of FDRs to 78 (55.3%; p<.0001) and SDRs to 22 (21.8%; p=.008), respectively. While the study revealed that family history alone may be insufficient to appropriately identify at-risk FDRs and SDRs of CHEK2 carriers, the study authors note that the expanded BOADICEA predictive model (BWA v4) is not intended for

clinical use.[42,] Additionally, this version has not been licensed for commercial use. Additional study limitations include the retrospective study design, lack of clarity regarding to what extent study participants met society criteria for genetic testing for breast cancer risk, and no reporting of outcomes associated with enhanced screening for *CHEK2* variant carriers.

For women with high-risk hereditary cancer syndromes, interventions to decrease breast cancer risk in high-risk women include screening (e.g., starting at an early age, the addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention, prophylactic mastectomy, and prophylactic oophorectomy. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a *CHEK2* variant. Surveys assessing adherence to guideline-based recommendations have explored this relationship but are limited in sample size and generally have not reported variant-stratified long-term outcomes of prophylactic or preventative interventions in controlled studies to support standard actionable thresholds for *CHEK2*.[43,8,] Findings from other studies point to potential overtreatment through risk-reducing bilateral mastectomy among those with *ATM/CHEK2* variants, with over half of all carriers reporting use of prophylactic surgery independent of family history or personal breast cancer history.[44,]

Section Summary: *CHEK2* and Breast Cancer Risk Assessment

Despite some studies showing potentially poorer outcomes for breast cancer patients who have *CHEK2* variants, it is unclear how such knowledge would be used to alter the treatment of such a patient. Furthermore, updated predictive models utilizing information on *CHEK2* status have not been approved for widespread clinical use. No evidence is available to support the clinical utility of genetic testing for *CHEK2* variants in breast cancer patients to guide patient management. There is no strong chain of evidence supporting *CHEK2* testing in breast cancer patients.

ATM and Breast Cancer Risk Assessment

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Does genetic testing for *ATM* variants improve the net health outcome in women at high-risk of HBOC?

The following PICO was used to select literature to inform this review.

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.

The relevant population of interest in this review is patients who are undergoing assessment for HBOC syndrome.

Interventions

The intervention of interest is *ATM* variant testing.

Comparators

The alternative would be to manage women at high-risk of HBOC with no ATM genetic testing.

Outcomes

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

Study Selection Criteria

For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Included a suitable reference standard
- Patient/sample clinical characteristics were described with women at high breast cancer risk
- Patient/sample selection criteria were described.

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).

Review of Evidence

Systematic Reviews

A systematic review conducted by Moslemi et al (2021) included 24 cross-sectional studies reporting on the prevalence of *ATM* variants in individuals with breast cancer.[45,] The review found a pooled prevalence of 7% (95% CI, 6% to 9%) based on 21 studies included in the meta-analysis with high heterogeneity (I^2=93%). In individuals with an *ATM* and *BRCA1* or *BRCA2* mutation, prevalence was 11% (95% CI, 7% to 11%; I^2=99%), in those with an *ATM* mutation but without a *BRCA1/2* mutation, the prevalence was 3% (95% CI, 2% to 4%; I^2=85%). Meta-regression found age did not have a significant effect on prevalence of ATM in individuals with breast cancer, and Egger's test did not reveal evidence of publication bias (p=.98).

The Suszynska et al (2019) systematic review described previously also included association estimates for *ATM* variants.[23,] In the 43 breast cancer studies included in the review, 94,787 patients contributed to the meta-analysis of *ATM* in breast cancer patients. The OR of breast cancer for *ATM* variants was 2.42 (95% CI, 2.16 to 2.71). Given that the Suszynska et al (2019) report included only studies reporting on test results from a panel, it does not substantially overlap with the studies described in the following section including other *ATM* association studies.

Marabelli et al (2016) reported on a meta-analysis of the penetrance of *ATM* variants in breast cancer, which used a model allowing the integration of different types of cancer risk estimates to generate a single estimate associated with heterozygous *ATM* gene variants.[46,] The meta-analysis included 19 studies, which were heterogeneous in terms of population, study designs, and baseline breast cancer risk. The estimated cumulative absolute risk of breast cancer in heterozygous *ATM* variant carriers was 6.02% by age 50 (95% credible interval, 4.58% to 7.42%) and 32.83% by age 80 (95% credible interval, 24.55% to 40.43%).

Association Studies

Individual studies published after the meta-analyses have also reported on the association between breast cancer development and pathogenic *ATM* variants. The study characteristics and limitations of Hu et al (2021), Southey et al (2021), Li et al (2021), Lu et al (2019), Hauke et al (2018), Kurian et al (2017), Decker et al (2017), and Couch et al (2017), were included in the previous section on *CHEK2* (Tables 3, 5, and 6). Study results are shown in Table 7.

Table 7. Risk of Breast Cancer Associated with Pathogenic *ATM* Variants

Study	Prevalence of *ATM* Variants	RR/OR (95% CI)
Hu et al (2021)[15,]CARRIERS Consortium		

Study	Prevalence of *ATM* Variants	RR/OR (95% CI)
Overall	0.78% in breast cancer patients 0.41% in population-based controls	1.82 (1.46 to 2.27)
With family history of breast cancer	0.96% in breast cancer patients	2.15 (1.56 to 2.93)
Without family history of breast cancer	0.74% in breast cancer patients	1.72 (1.37 to 2.16)
≤50 years	1.27% in breast cancer patients 0.46% in population-based controls	2.30 (1.46 to 3.71)
>50 years	0.69% in breast cancer patients 0.40% in population-based cohorts	1.68 (1.31 to 2.17)
Southey et al (2021)[27,]	1.2% in breast cancer patients 0.3% in population-based controls	3.40 (1.40 to 8.40)
Li et al (2021)[28,](BEACON)		
Loss of Function	0.90% familial breast cancer patients 0.26% population-matched controls	2.88 (1.60 to 5.45)
Missense	5.53% familial breast cancer patients 3.81% population-matched controls	1.48 (1.23 to 1.77)
Lu et al (2019)[31,]	0.7% in breast and ovarian cancer cases 0.2% in controls	2.97 (1.67 to 5.68)
Hauke et al (2018)[34,]	1.3% in breast cancer cases 0.4% and 0.2% in control samples	3.63 (2.67 to 4.94)
Decker et al (2017)[35,]	0.6% in breast cancer patients 0.2% in controls	3.26 (1.82 to 6.46)
Couch et al (2017)[36,]	0.9% in breast cancer patients referred for testing 0.3% in controls	2.78 (2.22 to 3.62)
Kurian et al (2017)[32,]	0.92% in breast cancer patients referred for testing 1% in patients referred for testing without breast or ovarian cancer	1.74 (1.46 to 2.07)

BEACCON: Hereditary BrEAst Case CONtrol study; CI: confidence interval; OR: odds ratio; RR: relative risk.

Section Summary: Clinically Valid

ATM heterozygotes appear to have an RR of breast cancer about 2 to 3 times that of the general population, with an estimated absolute risk of 6% by age 50 and 33% by age 80. Estimates come from the population- and family-based case-controls, and are applicable to individuals at high risk of breast and/or ovarian cancer.

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, more effective therapy, or avoid unnecessary therapy or 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 RCTs.

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

Weidner et al (2020) conducted a retrospective, consecutive study on 56 *ATM* carriers enrolled in the Inherited CAncer REgistry (ICARE) at Vanderbilt University and their relatives.[41,] Eligibility for annual breast magnetic resonance imaging surveillance was based on ≥20% lifetime risk of breast cancer based on family cancer history alone as calculated by the BOADICEA predictive model, or family cancer history and proband CHEK2 variant status, utilizing an updated version of the BOADICEA model (BWA v4). Among the *ATM* carriers and family history alone, 24 FDRs (22.6%) and 15 SDRs

(13.6%) had a lifetime cancer risk ≥20%. Inclusion of the proband's variant status significantly increased identification of FDRs to 60 (56.6%; p<.0001) and SDRs to 31 (28.1%; p<.0001), respectively. While the study revealed that family history alone may be insufficient to appropriately identify at-risk FDRs and SDRs of *ATM* carriers, the study authors note that the expanded BOADICEA predictive model (BWA v4) is not intended for clinical use.[42,] Additionally, this version has not been licensed for commercial use. Additional study limitations include the retrospective study design, lack of clarity regarding to what extent study participants met society criteria for genetic testing for breast cancer risk, and no report of outcomes associated with enhanced screening for *ATM* variant carriers.

For women with high-risk hereditary cancer syndromes, interventions to decrease breast cancer risk in high-risk women include screening (e.g., starting at an early age, the addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention, prophylactic mastectomy, and prophylactic oophorectomy. In contrast to high penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with an *ATM* variant. Surveys assessing adherence to guideline-based recommendations have explored this relationship but are limited in sample size and generally have not reported variant-stratified long-term outcomes of prophylactic or preventative interventions in controlled studies to support standard actionable thresholds for *ATM*.[43,8,] Findings from a study by Cragun et al (2020) point to potential overtreatment through risk-reducing bilateral mastectomy among those with *ATM/CHEK2* variants, with over half of all carriers reporting use of prophylactic surgery independent of family history or personal breast cancer history.[44,]

Section Summary: *ATM* and Breast Cancer Risk Assessment

Updated predictive models utilizing information on *ATM* status for enhanced screening have not been approved for widespread clinical use. 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.

BARD1 and Breast Cancer Risk Assessment

Clinical Context and Test Purpose

The purpose of testing for *BARD1* variants in individuals at high-risk of HBOC is to evaluate whether an abnormal variant is present and, if so, to determine whether the variant conveys a sufficiently high-risk that changes in surveillance and/or treatment likely to decrease the risk of mortality from breast and/or ovarian cancer are warranted.

The question addressed in this evidence review is: Does genetic testing for *BARD1* variants improve the net health outcome in women at high-risk of HBOC?

The following PICO was used to select literature to inform this review.

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.

The relevant population of interest in this review is patients who are undergoing assessment for HBOC syndrome.

Interventions

The intervention of interest is *BARD1* variant testing.

Comparators

The alternative would be to manage women at high-risk of HBOC with no *BARD1* genetic testing.

Outcomes

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

Study Selection Criteria

For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Included a suitable reference standard
- Patient/sample clinical characteristics were described with women at high breast cancer risk
- Patient/sample selection criteria were described.

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).

Review of Evidence

Systematic Reviews

Two systematic reviews conducted by Suszynska et al in 2019[23,] and 2020[47,] reported estimates on the association of *BARD1* variants with risk of breast cancer; study characteristics are summarized in Table 8. Prevalence of BARD1 mutations was 0.22% to 0.25% in individuals with breast cancer; prevalence in cases was about 0.09%. Study results appear in Table 9. The reviews found presence of a *BARD1* mutation associated with approximately a 2 to 3-fold increased risk of breast cancer. The 2020 review identified 60 distinct pathogenic variants (PVs) among individuals with breast cancer, 21 of which were present in controls. In individuals with a recurrent PV (defined as occurring in 3 or more cases), risk was elevated among those with the c.334C>T (R112*), c.1652C>G (S551*), c.1690C>T (Q564*) PVs, but prevalence was very low (≤0.03% among cases and ≤0.004% among controls) and these estimates were imprecise.

Table 8. Characteristics of Systematic Reviews of *BARD1* and Risk of Breast Cancer

Study	Dates	Population	Designs Included	No. of Studies	No. of Participants	Pathogenic Variants Identified
Suszynska et al (2020)[47,]	Through Apr 2020	Cases: Patients with breast and/or ovarian cancer referred for evaluation by a multi-gene panel Controls: Patients from the Genome Aggregation Database	Study designs not reported; studies reporting prevalence of BARD1 variants were included	105		144 *BARD1* variants • 60 were distinct PVs • 10 were recurrent PVs (present in 3 or more cases)
Suszynska et al (2019)[23,]	Through Jul 2017	Cases: Patients with breast and/or ovarian cancer referred for evaluation by a multi-gene panel Controls: Patients from the Genome Aggregation Database	Studies reporting prevalence of genetic variants	48 (overall) 43 (breast cancer)	93,160 included in *BARD1* analysis Unclear how many controls were included from the Genome Aggregation Database	23 *BARD1* variants

NR: not reported; PV: pathogenic variant

Table 9. Results of Systematic Reviews of *BARD1* and Risk of Breast Cancer

Study	Relative Risk/Odds Ratio (95% CI)	Penetrance at Age 70 (95% CI), %
Suszynska et al (2020)[47,]		
Total study population	2.90 (2.25 to 3.75)	NR
Familial breast cancer population	3.67 (2.52 to 5.34)	NR
European population	2.73 (1.94 to 3.86)	NR
Asian population	2.50 (1.43 to 4.35)	NR
c.334C>T (R112*) PV	7.28 (1.47 to 35.08)	NR
c.1652C>G (S551*) PV	5.67 (1.47 to 21.93)	NR
c.1690C>T (Q564*) PV	8.81 (3.23 to 24.05)	NR
Suszynska et al (2019)[23,]	2.37 (1.86 to 3.01)	NR

OR: odds ratio; PV: pathogenic variant; RR: relative risk

Association Studies

Individual studies not included in either of the meta-analyses have also reported on the association between breast cancer development and pathogenic *BARD1* variants. The study characteristics and limitations of Hu et al (2021), Southey et al (2021), Li et al (2021), Couch et al (2017), and Kurian et al (2017) were described in the previous section on *CHEK2* (Tables 3, 5, and 6). Study results are shown in Table 10. Although these studies found *BARD1* associated with an elevated risk of breast cancer, the risk estimates were not statistically significant, potentially due to the low prevalence among controls.

Table 10. Risk of Breast Cancer Associated with Pathogenic *BARD1* Variants

Study	Prevalence of *BARD1* Variants	RR/OR (95% CI)
Hu et al (2021)[15,] CARRIERS Consortium		
Overall	0.15% in breast cancer patients 0.11% in population-based controls	1.37 (0.87 to 2.16)
With family history of breast cancer	0.14% in breast cancer patients	1.36 (0.61 to 2.74)
Without family history of breast cancer	0.14% in breast cancer patients	1.38 (0.86 to 2.21)
≤50 years	0.17% in breast cancer patients 0.13% in population-based controls	0.94 (0.34 to 2.61)
>50 years	0.15% in breast cancer patients 0.10% in population-based cohorts	1.44 (0.87 to 2.42)
Southey et al (2021)[27,]	0.20% in breast cancer patients 0.04% in population-based controls	8.20 (0.73 to 83)
Li et al (2021)[28,](BEACON)		
Loss of Function	0.12% familial breast cancer patients 0.05% population-matched controls	2.32 (0.53 to 13.93)
Missense	1.33% familial breast cancer patients 0.96% population-matched controls	1.40 (0.97 to 2.02)
Couch et al (2017)[36,]	0.18% in breast cancer patients referred for testing 0.08% in controls	2.16 (1.31 to 3.63)
Kurian et al (2017)[32,]	0.25% in breast cancer patients referred for testing 0% in patients referred for testing without breast or ovarian cancer	1.92 (1.36 to 2.72)

BEACCON: Hereditary BrEAst Case CONtrol study; CI: confidence interval; OR: odds ratio; RR: relative risk.

Section Summary: Clinically Valid

BARD1 heterozygotes appear to have an increased risk of breast cancer about 2 to 3 times that of the general population based on evidence from 2 systematic reviews that included a mix of population- and family-based controls. Presence of certain rare *BARD1* PVs was associated with higher risk based

on imprecise estimates. Evidence from individual studies not included in one of the reviews was generally consistent with that from the systematic reviews.

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, more effective therapy, or avoid unnecessary therapy or 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 RCTs.

Direct evidence of clinical utility for genetic testing in individuals with *BARD1* variants was not identified.

For women with high-risk hereditary cancer syndromes, interventions to decrease breast cancer risk in high-risk women include screening (e.g., starting at an early age, the addition of magnetic resonance imaging to mammography, and screening annually), chemoprevention, prophylactic mastectomy, and prophylactic oophorectomy. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a moderate penetrance *BARD1* variant.

Section Summary: *BARD1* and Breast Cancer Risk Assessment

No evidence is available to support the clinical utility of genetic testing for *BARD1* variants in breast cancer patients to guide patient management, and there is no chain of evidence supporting *BARD1* testing in breast cancer patients.

Summary of Evidence

For individuals with risk of HBOC who receive genetic testing for a *CHEK2* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are OS, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *CHEK2* variants are of moderate penetrance, and confer a risk of breast cancer 2 to 4 times that of the general population. Direct evidence for the clinical utility of genetic testing for *CHEK2* variants in individuals with risk of HBOC was not identified. It is unclear the RR associated with the moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for risk-reducing mastectomy in women with a moderate penetrance variant such as *CHEK2*. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with risk of HBOC who receive genetic testing for an *ATM* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are OS, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *ATM* variants are of moderate penetrance ; moreover, *ATM* variants confer a risk of breast cancer 2 to 4 times that of the general population. Direct evidence for the clinical utility of genetic testing for *ATM* variants in individuals with risk of HBOC was not identified. It is unclear that the RR associated with the moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a moderate penetrance variant such as *ATM*. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with risk of HBOC who receive genetic testing for a *BARD1* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are OS, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *BARD1* variants are of low to moderate penetrance; *BARD1* variants confer a risk of breast cancer about 2 to 3 times that of the general population. Direct evidence for the clinical utility of genetic testing for *BARD1* variants in individuals with risk of HBOC was not identified. It is unclear that the RR associated with the low to moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a low to moderate penetrance variant such as *BARD1*. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 5 specialty societies and 2 academic medical centers (total of 7 reviewers) while this policy was under review in 2014. The input was limited on whether *PALB2* testing to estimate the risk of developing breast cancer should be medically necessary, and whether testing results alter patient management. Reviewer input on both questions was mixed.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Radiology

The American College of Radiology (ACR) has established Appropriateness Criteria® for breast cancer screening (Table 11).[48,] This includes high-risk women with a BRCA gene mutation and their untested first-degree relatives, women with a history of chest irradiation between 10 to 30 years of age, and women with 20% or greater lifetime risk of breast cancer as follows:

Table 11. American College of Radiology Appropriateness Criteria for Breast Cancer Screening in High-Risk Women

Screening Procedure	Appropriateness Category
Mammography	Usually appropriate
DBT	Usually appropriate
Breast MRI without and with IV contrast	May be appropriate
Breast US	May be appropriate
FDG-PEM	Usually not appropriate
Sestamibi MBI	Usually not appropriate
Breast MRI without IV contrast	Usually not appropriate

DBT: digital breast tomosynthesis; FDG-PEM: flurodeoxyglucose positron emission mammography; IV: intravenous; MBI: molecular breast imaging; MRI: magnetic resonance imaging; US: ultrasound.

Specific recommendations for *CHEK2, ATM* and *BARD1* variant carriers are not available.

American Society of Breast Surgeons

A consensus guideline on genetic testing for hereditary breast cancer was updated in February 2019.[49,] Guidelines state that genetic testing should be made available to all individuals with a personal history of breast cancer and that such testing should include *BRCA1/BRCA2* and *PALB2*, with other genes as appropriate for the clinical scenario and patient family history. Furthermore, individuals who had previous genetic testing may benefit from updated testing. Finally, genetic testing should be made available to individuals without a personal history of breast cancer when they meet National Comprehensive Cancer Network (NCCN) guideline criteria. The guidelines also note that variants of uncertain significance are not clinically actionable.

For individuals with mutations in *ATM* and *CHEK2*, enhanced screening is recommended, however, the data are not sufficient to support risk-reducing mastectomy in the absence of other factors such as strong family history. For individuals with *BARD1* mutations, evidence is insufficient to support change in breast cancer risk management based on the presence of a mutation alone.

National Comprehensive Cancer Network

The NCCN (v.2.2022) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer review single-gene tests for *CHEK2, ATM,* and *BARD1*.[50,] The guidelines state that for those that meet hereditary cancer testing criteria, testing for a specific familial pathogenic/likely pathogenic variant may be recommended for appropriate genes. For individuals who meet criteria with no known familial variants, comprehensive testing of a multigene panel may be considered. This testing may consider a number of genes, including but not limited to *CHEK2, ATM,* and *BARD1.* However, the inclusion of certain genes in the guideline does not imply the endorsement "for or against multigene testing for moderate-penetrance genes" and there are limited data on the degree of cancer risk associated with some genes in multigene panels. Testing an affected family member first has the highest likelihood of a positive result. The guidelines state that the panel recommends an annual mammogram for women with *CHEK2*, *ATM,* or *BARD1* mutations beginning at age 40, with consideration of annual breast magnetic resonance imaging. The guidelines also state there is insufficient evidence to draw conclusions on risk-reducing mastectomy in individuals with *CHEK2*, *ATM,* or *BARD1* mutations and that patients should be managed based on family history.

The NCCN guidelines on breast cancer screening and diagnosis (v.1. 2022)[51,] recommend the following:

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

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for *CHEK2, ATM* and *BARD1* variant testing have been identified.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12.

Table 12. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02620852	Enabling a Paradigm Shift: A Preference-Tolerant RCT of Personalized vs. Annual Screening for Breast Cancer (Wisdom Study)	100,000	Mar 2025
Unknown			
NCT03989258	Implementation of a Model for Personalised Risk-Based Breast Cancer Prevention and Screening	28,389	Dec 2020 (last updated June 2019)

NCT: national clinical trial.

References

1. National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Common Cancer Sites. https://seer.cancer.gov/statfacts/html/common.html. Accessed June 14, 2022.
2. National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Female Breast Cancer. n.d.; https://seer.cancer.gov/statfacts/html/breast.html. Accessed June 13, 2022.
3. National Cancer Institute. BRCA Mutations: Cancer Risk and Genetic Testing. November 19, 2020; https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet. Accessed June 15, 2022.
4. American Society of Clinical Oncology. Breast Cancer in Men: Risk Factors. https://www.cancer.net/cancer-types/breast-cancer-men/risk-factors. Accessed June 14, 2022.
5. Sniadecki M, Brzezinski M, Darecka K, et al. BARD1 and Breast Cancer: The Possibility of Creating Screening Tests and New Preventive and Therapeutic Pathways for Predisposed Women. Genes (Basel). Oct 24 2020; 11(11). PMID 33114377
6. Alenezi WM, Fierheller CT, Recio N, et al. Literature Review of BARD1 as a Cancer Predisposing Gene with a Focus on Breast and Ovarian Cancers. Genes (Basel). Jul 27 2020; 11(8). PMID 32726901
7. Suszynska M, Kluzniak W, Wokolorczyk D, et al. BARD1 is A Low/Moderate Breast Cancer Risk Gene: Evidence Based on An Association Study of the Central European p.Q564X Recurrent Mutation. Cancers (Basel). May 28 2019; 11(6). PMID 31142030
8. Vysotskaia V, Kaseniit KE, Bucheit L, et al. Clinical utility of hereditary cancer panel testing: Impact of PALB2, ATM, CHEK2, NBN, BRIP1, RAD51C, and RAD51D results on patient management and adherence to provider recommendations. Cancer. Feb 01 2020; 126(3): 549-558. PMID 31682005
9. Apostolou P, Fostira F. Hereditary breast cancer: the era of new susceptibility genes. Biomed Res Int. 2013; 2013: 747318. PMID 23586058
10. Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med. Jun 04 2015; 372(23): 2243-57. PMID 26014596
11. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. May 2015; 17(5): 405-24. PMID 25741868
12. Kurian AW, Antoniou AC, Domchek SM. Refining Breast Cancer Risk Stratification: Additional Genes, Additional Information. Am Soc Clin Oncol Educ Book. 2016; 35: 44-56. PMID 27249685
13. Yadav S, LaDuca H, Polley EC, et al. Racial and Ethnic Differences in Multigene Hereditary Cancer Panel Test Results for Women With Breast Cancer. J Natl Cancer Inst. Oct 01 2021; 113(10): 1429-1433. PMID 33146377

14. Cybulski C, Wokolorczyk D, Jakubowska A, et al. Risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer. J Clin Oncol. Oct 01 2011; 29(28): 3747-52. PMID 21876083
15. Hu C, Hart SN, Gnanaolivu R, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. N Engl J Med. Feb 04 2021; 384(5): 440-451. PMID 33471974
16. Schottenfeld D, Fraumeni JF. Cancer epidemiology and prevention. 3rd ed. New York: Oxford University Press; 2006.
17. Singletary SE. Rating the risk factors for breast cancer. Ann Surg. Apr 2003; 237(4): 474-82. PMID 12677142
18. Antoniou AC, Pharoah PP, Smith P, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer. Oct 18 2004; 91(8): 1580-90. PMID 15381934
19. Berry DA, Iversen ES, Gudbjartsson DF, et al. BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. J Clin Oncol. Jun 01 2002; 20(11): 2701-12. PMID 12039933
20. Nelson HD, Fu R, Goddard K, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA- Related Cancer (AHRQ Publication No. 12-05164-EF-1). Rockville, MD: Agency for Healthcare Research and Quality; 2013.
21. Nelson HD, Pappas M, Zakher B, et al. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med. Feb 18 2014; 160(4): 255-66. PMID 24366442
22. Balmana J, Digiovanni L, Gaddam P, et al. Conflicting Interpretation of Genetic Variants and Cancer Risk by Commercial Laboratories as Assessed by the Prospective Registry of Multiplex Testing. J Clin Oncol. Dec 2016; 34(34): 4071-4078. PMID 27621404
23. Suszynska M, Klonowska K, Jasinska AJ, et al. Large-scale meta-analysis of mutations identified in panels of breast/ovarian cancer-related genes - Providing evidence of cancer predisposition genes. Gynecol Oncol. May 2019; 153(2): 452-462. PMID 30733081
24. Yang Y, Zhang F, Wang Y, et al. CHEK2 1100delC variant and breast cancer risk in Caucasians: a meta-analysis based on 25 studies with 29,154 cases and 37,064 controls. Asian Pac J Cancer Prev. 2012; 13(7): 3501-5. PMID 22994785
25. Schmidt MK, Hogervorst F, van Hien R, et al. Age- and Tumor Subtype-Specific Breast Cancer Risk Estimates for CHEK2*1100delC Carriers. J Clin Oncol. Aug 10 2016; 34(23): 2750-60. PMID 27269948
26. Weischer M, Bojesen SE, Ellervik C, et al. CHEK2*1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. J Clin Oncol. Feb 01 2008; 26(4): 542-8. PMID 18172190
27. Southey MC, Dowty JG, Riaz M, et al. Population-based estimates of breast cancer risk for carriers of pathogenic variants identified by gene-panel testing. NPJ Breast Cancer. Dec 09 2021; 7(1): 153. PMID 34887416
28. Li N, Lim BWX, Thompson ER, et al. Investigation of monogenic causes of familial breast cancer: data from the BEACCON case-control study. NPJ Breast Cancer. Jun 11 2021; 7(1): 76. PMID 34117267
29. Nguyen-Dumont T, Dowty JG, Steen JA, et al. Population-Based Estimates of the Age-Specific Cumulative Risk of Breast Cancer for Pathogenic Variants in CHEK2 : Findings from the Australian Breast Cancer Family Registry. Cancers (Basel). Mar 18 2021; 13(6). PMID 33803639
30. Rainville I, Hatcher S, Rosenthal E, et al. High risk of breast cancer in women with biallelic pathogenic variants in CHEK2. Breast Cancer Res Treat. Apr 2020; 180(2): 503-509. PMID 31993860
31. Lu HM, Li S, Black MH, et al. Association of Breast and Ovarian Cancers With Predisposition Genes Identified by Large-Scale Sequencing. JAMA Oncol. Jan 01 2019; 5(1): 51-57. PMID 30128536

32. Kurian AW, Hughes E, Handorf EA, et al. Breast and Ovarian Cancer Penetrance Estimates Derived From Germline Multiple-Gene Sequencing Results in Women. JCO Precis Oncol. Nov 2017; 1: 1-12. PMID 35172496
33. Fan Z, Ouyang T, Li J, et al. Identification and analysis of CHEK2 germline mutations in Chinese BRCA1/2-negative breast cancer patients. Breast Cancer Res Treat. May 2018; 169(1): 59-67. PMID 29356917
34. Hauke J, Horvath J, Gross E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. Cancer Med. Apr 2018; 7(4): 1349-1358. PMID 29522266
35. Decker B, Allen J, Luccarini C, et al. Rare, protein-truncating variants in ATM , CHEK2 and PALB2 , but not XRCC2 , are associated with increased breast cancer risks. J Med Genet. Nov 2017; 54(11): 732-741. PMID 28779002
36. Couch FJ, Shimelis H, Hu C, et al. Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. JAMA Oncol. Sep 01 2017; 3(9): 1190-1196. PMID 28418444
37. Naslund-Koch C, Nordestgaard BG, Bojesen SE. Increased Risk for Other Cancers in Addition to Breast Cancer for CHEK2*1100delC Heterozygotes Estimated From the Copenhagen General Population Study. J Clin Oncol. Apr 10 2016; 34(11): 1208-16. PMID 26884562
38. Huzarski T, Cybulski C, Wokolorczyk D, et al. Survival from breast cancer in patients with CHEK2 mutations. Breast Cancer Res Treat. Apr 2014; 144(2): 397-403. PMID 24557336
39. Kriege M, Hollestelle A, Jager A, et al. Survival and contralateral breast cancer in CHEK2 1100delC breast cancer patients: impact of adjuvant chemotherapy. Br J Cancer. Aug 26 2014; 111(5): 1004-13. PMID 24918820
40. Weischer M, Nordestgaard BG, Pharoah P, et al. CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. J Clin Oncol. Dec 10 2012; 30(35): 4308-16. PMID 23109706
41. Weidner AE, Liggin ME, Zuniga BI, et al. Breast cancer screening implications of risk modeling among female relatives of ATM and CHEK2 carriers. Cancer. Apr 15 2020; 126(8): 1651-1655. PMID 31967672
42. Lee A, Mavaddat N, Wilcox AN, et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. Genet Med. Aug 2019; 21(8): 1708-1718. PMID 30643217
43. Hall ET, Parikh D, Caswell-Jin JL, et al. Pathogenic variants in less familiar cancer susceptibility genes: what happens after genetic testing? JCO Precision Oncology. 2018; 2: 1-10. DOI: 10.1200/PO.18.00167
44. Cragun D, Weidner A, Tezak A, et al. Cancer risk management among female BRCA1/2, PALB2, CHEK2, and ATM carriers. Breast Cancer Res Treat. Jul 2020; 182(2): 421-428. PMID 32445176
45. Moslemi M, Vafaei M, Khani P, et al. The prevalence of ataxia telangiectasia mutated (ATM) variants in patients with breast cancer patients: a systematic review and meta-analysis. Cancer Cell Int. Sep 08 2021; 21(1): 474. PMID 34493284
46. Marabelli M, Cheng SC, Parmigiani G. Penetrance of ATM Gene Mutations in Breast Cancer: A Meta-Analysis of Different Measures of Risk. Genet Epidemiol. Jul 2016; 40(5): 425-31. PMID 27112364
47. Suszynska M, Kozlowski P. Summary of BARD1 Mutations and Precise Estimation of Breast and Ovarian Cancer Risks Associated with the Mutations. Genes (Basel). Jul 15 2020; 11(7). PMID 32679805
48. American College of Radiology (ACR). ACR Appropriateness Criteria: Breast Cancer Screening. 2017. https://acsearch.acr.org/docs/70910/Narrative/. Accessed June 15, 2022.
49. The American Society of Breast Surgeons. Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer. 2019. https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf. Accessed June 16, 2022.

50. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed June 17, 2022.
51. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/breast- screening.pdf. Accessed June 13, 2022.

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Ethnicity/Ancestry
  - Personal and/or family history of cancer (if applicable) including:
    - Family relationship(s): (maternal or paternal), (family member [e.g., sibling, aunt, grandparent]), (living or deceased) ((if applicable)
    - Site(s) of cancer
    - Age at diagnosis (including family members)
    - If breast cancer, indicate if bilateral, premenopausal, or triple negative cancer
    - Personal or family BRCA1/BRCA2, PALB2 or related mutation history, multiple primaries, or ovarian cancer, because that individual has the highest likelihood for a positive test result (if applicable)
- Genetic counseling/professional results (if applicable)
- Laboratory or Pathology reports (e.g., BRCA results for BART testing requests, or hormone receptor assay) (if applicable)
- Name of the test being requested or the Concert Genetics GTU identifier
  The Concert Genetics GTU can be found at https://app.concertgenetics.com

Post Service (in addition to the above, please include the following):

- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0102U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])
	0129U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer),

Type	Code	Description
		genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
	0131U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure)
	81307	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence
	81308	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; known familial variant
	81406	Molecular pathology procedure level 7
	81408	Molecular pathology procedure level 9
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

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

Effective Date	Action
05/29/2015	BCBSA Medical Policy adoption
04/01/2016	Policy revision without position change
03/01/2017	Policy title change from Genetic Testing for PALB2 Mutations Policy revision with position change
02/01/2018	Policy revision without position change
09/01/2018	Policy revision without position change
03/01/2019	Policy revision without position change
05/01/2019	Policy revision without position change/Coding update
11/01/2019	Coding update
01/01/2020	Annual review. No change to policy statement. Literature review updated.
03/01/2020	Coding update
05/01/2020	Admin update
11/01/2020	Annual review. Policy title changed from Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk to current one. Policy statement, and literature review updated.
01/01/2021	Coding update
10/01/2021	Annual review. Policy statement and literature review updated. Policy title changed from Gene Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk to current one.
05/01/2022	Administrative update.
10/01/2022	Annual review. Policy statement, guidelines and literature review updated. Policy title changed from Gene Variants (PALB2, CHEK2 and ATM) Associated with Breast Cancer in Individuals at High Breast Cancer Risk to current one. Coding update.
12/01/2022	Administrative update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to

treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1) 2.04.126 **Policy Statement:** I. Individual or large panel testing for *CHEK2, ATM, and BARD1* variants when not included as part of an approved small panel in the assessment of breast cancer risk is considered **investigational.** **NOTE**: Germline genetic testing for BRCA1, BRCA2 and PALB2 is addressed separately in Blue Shield of California Medical Policy: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)	**Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1) 2.04.126** **Policy Statement:** I. Individual or large panel testing for *CHEK2, ATM, and BARD1* variants when not included as part of an approved small panel in the assessment of breast cancer risk is considered **investigational.** **NOTE**: Germline genetic testing for BRCA1, BRCA2 and PALB2 is addressed separately in Blue Shield of California Medical Policy: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)