Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)

Policy # 00504
Original Effective Date: 07/20/2016
Current Effective Date: 11/13/2023

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

Note: Germline Genetic Testing for Hereditary Breast and or Ovarian Cancer is addressed separately in medical policy 00047.

Note: Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer is addressed separately in medical policy 00084.

Note: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing is addressed separately in medical policy 00382.

Note Genetic Testing for Lynch Syndrome and Other Inherited Colon is addressed separately in medical policy 00190.

Note Genetic Testing for Li-Fraumeni Syndrome is addressed separately in medical policy 00424.

Note Genetic Testing for PTEN Hamartoma Tumor Syndrome is addressed separately in medical policy 00417.

Services Are Considered Investigational

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

Based on review of available data, the Company considers testing for *CHEK2, ATM, and BARD1* variants in the assessment of breast cancer risk to be **investigational.***

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Policy Guidelines

Criteria for Genetic Risk Evaluation

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

The recommended testing strategy for BRCA1, BRCA2, and PALB2 is described in policy 00047 (*Germline Genetic Testing for Hereditary Breast and or Ovarian Cancer*).

Genetic Counseling

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

Background/Overview

Breast Cancer and Genetics

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. 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. 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). Pathogenic variants in other highly penetrant genes (eg, *TP53*, *CDH1*, *PTEN*, *STK11*) contribute to a smaller number of cancers. *CHEK2 and ATM* are believed to be moderately penetrant and *BARD1* has alternatively been described as moderate, low/moderate, and low penetrance.

Testing for *BRCA1, BRCA2, and PALB2* is addressed in medical policy 00047.

Testing for mismatch repair genes linked to Lynch syndrome is addressed in medical policy 00190.

Testing for genes linked to Cowden/PTEN Hamartoma Tumor syndrome is addressed in medical policy 00417.

Testing for genes linked to Li-Fraumeni syndrome is addressed in medical policy 00424.

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. 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 (eg, founder sequence mutations) is generally straightforward because associations are repeatedly observed. For uncommonly identified variants, such as those found in a few individuals or families,

defining pathogenicity can be more difficult. For example, predicting the pathogenicity of previously unidentified variants typically requires in silico (computational) analysis predicting protein structure/function, evolutionary conservation, and splice site prediction. The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines. Still, distinctions between a variant of uncertain significance and a pathogenic one from different laboratories may not always be identical.

Genes Associated With a Moderate Penetrance of Breast Cancer

***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.

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.

***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.*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.

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. 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 (eg, ovarian).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 (eg, obesity). For a woman without breast cancer, the probability of detecting a pathogenic variant can be estimated from a detailed multigenerational pedigree (eg, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), screening tools (eg, BRCAPRO, Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen), 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.

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. 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests 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 FDA has chosen not to require any regulatory review of this test.

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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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 in medical policy 00047.

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

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 1). 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 1. 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. 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*. 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) 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 2.

Table 2. 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 Personalized Risk-Based Breast Cancer Prevention and Screening	28,389	Dec 2020 (last updated June 2019)

NCT: national clinical trial.

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Policy History

Original Effective Date: 07/20/2016
Current Effective Date: 11/13/2023

06/30/2016	Medical Policy Committee review
07/20/2016	Medical Policy Implementation Committee approval. New Policy.
01/01/2017	Coding update: Removing ICD-9 Diagnosis codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. Added coverage statement with criteria for PALB2 variants, added CHEK2 and ATM to the policy. Added policy guidelines section and updated rationale and references. Title change.
06/08/2017	Removed colons from NCCN guideline sections.
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. No change to coverage.
02/07/2019	Medical Policy Committee review
02/20/2019	Medical Policy Implementation Committee approval. No change to coverage.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. No change to coverage.

Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)

Policy # 00504
Original Effective Date: 07/20/2016
Current Effective Date: 11/13/2023

	Coding update
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. No change to coverage.
12/02/2021	Medical Policy Committee review
12/08/2021	Medical Policy Implementation Committee approval. No change to coverage. Title changed.
03/25/2022	Coding update
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. Policy statement and corresponding evidence review for BARD1 added to policy. Title changed to "Germline Genetic Testing for Gene Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM and BARD1)." Policy statement and corresponding evidence review on PALB2 moved to another policy.
10/05/2023	Medical Policy Committee review
10/11/2023	Medical Policy Implementation Committee approval. No change to coverage. Body of policy updated.

Next Scheduled Review Date: 10/2024

Coding

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

Code Type	Code
CPT	0136U, 81408, 81479 Delete codes effective 01/01/2023: 0129U, 81307, 81308, 81406
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

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NOTICE: 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 eligibility for coverage.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.