



Louisiana

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

Policy # 00504

Original Effective Date: 07/20/2016

Current Effective Date: 01/11/2021

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: 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.

When Services May Be Eligible for Coverage

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

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

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

Patient Selection Criteria

Coverage eligibility will be met in individuals with the following:

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

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Services Are Considered Investigational

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

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

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

Policy Guidelines

Criteria 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* and *BRCA2* is described in policy 00047 (*Genetic Testing for Hereditary Breast and or Ovarian Cancer*).

Background/Overview

Breast Cancer and Genetics

In 2016, researchers estimated breast cancer would be diagnosed in 252710 women and 40610 would die from the disease; a woman's lifetime risk is 12.4%. Breast cancers can be classified as sporadic, familial, or hereditary. Most breast cancers, however, are sporadic (70% to 75%), occurring in women 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. Pathogenic *BRCA1* and *BRCA2* variants appear responsible for 20% to 25% of hereditary breast cancers, while small proportions are attributed to pathogenic variants in other highly penetrant genes (eg, *TP53*, *CDH1*, *PTEN*, *STK11*).

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Penetrance of Pathogenic Variants

Penetrance is the risk conferred by a pathogenic variant or the proportion of individuals with the variant expected to develop cancer. Variant penetrance is considered high, moderate, or low according to lifetime risk: high (>50%), moderate (20% to 50%), and low (<20%) (corresponding relative risks of approximately ≥ 5 , 1.5 to 5, and <1.5). Variants in only a few breast cancer susceptibility genes (BRCA1 and BRCA2 [hereditary breast/ovarian cancer syndrome], TP53 [Li-Fraumeni syndrome], PTEN [Cowden syndrome], CDH1 [hereditary diffuse gastric cancer], STK11 [Peutz-Jeghers syndrome]) are considered highly penetrant. For example, a woman with a BRCA1 or BRCA2 variant has roughly a 75% lifetime risk of developing breast cancer and a relative risk of 11 to 12 compared with the general population.

Penetrance can be modified by environmental factors and by family history, which is a particularly important modifier for low and moderate penetrance genes. 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

PALB2 Gene

The *PALB2* gene (partner and localizer of *BRCA2*) encodes for a protein first described in 2006. The gene is located at 16p12.2[a] and has 13 exons. PALB2 protein assists *BRCA2* in DNA repair and tumor suppression. Heterozygous pathogenic *PALB2* variants increase the risk of developing breast and pancreatic cancers; homozygous variants are found in Fanconi anemia.[b] Most

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pathogenic *PALB2* variants are truncating frameshift or stop codons, and are found throughout the gene. Pathogenic *PALB2* variants are uncommon in unselected populations and prevalence varies by ethnicity and family history. For example, Antoniou et al (2014) assumed a prevalence of 8 per 10000 in the general population when modeling breast cancer risks. Variants are more prevalent in ethnic populations where founder mutations have persisted (eg, Finns, French Canadians, Poles), while infrequently found in others (eg, in Ashkenazi Jews). In women with a family history of breast cancer, the prevalence of pathogenic *PALB2* variants ranges between 0.9% and 3.9%, or substantially higher than in an unselected general population. Depending on population prevalence, *PALB2* may be responsible for as much as 2.4% of hereditary breast cancers; and in populations with founder mutations cause 0.5% to 1% of all breast cancers.

CHEK2 Gene

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

In 2002, a single recurrent truncating 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.

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 one and four years, telangiectasias of

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the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition. Female *ATM* heterozygotes carriers have a risk of breast cancer about twice as high as that of the general population; however, they do not appear to have an elevated ovarian cancer risk.

Identifying Women at Risk of an Inherited Susceptibility to Breast Cancer

Breast cancer risk can be affected by genetic and nongenetic factors. 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). 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). *PALB2*, *CHEK2*, and *ATM* testing are available under the auspices of CLIA (a list of laboratories offering testing is available at NCBI's Genetic Testing Registry (GTR [<https://www.ncbi.nlm.nih.gov/htr/>]). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

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

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Rationale/Source

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

For individuals with a risk of hereditary breast/ovarian cancer who receive genetic testing for a *PALB2* variant, the evidence includes studies of clinical validity and studies of breast cancer risk, including a meta-analysis. The relevant outcomes are overall survival, disease-specific survival, and test validity. Evidence supporting clinical validity was obtained from numerous studies reporting relative risks (RR) or odds ratios (two studies estimated penetrance). Study designs included family segregation, kin-cohort, family-based case-control, and population-based case-control. The number of pathogenic variants identified in studies varied from 1 (founder mutations) to 48. The RR for breast cancer associated with a *PALB2* variant ranged from 2.3 to 13.4, with the two family-based studies reporting the lowest values. Evidence of preventive interventions in women with *PALB2* variants is indirect, relying on studies of high-risk women and *BRCA* carriers. These interventions include screening with magnetic resonance imaging, chemoprevention, and risk-reducing mastectomy. Given the penetrance of *PALB2* variants, the outcomes following bilateral and contralateral risk-reducing mastectomy examined in women with a family history consistent with hereditary breast cancer (including *BRCA1* and *BRCA2* carriers) can be applied to women with *PALB2* variants-with the benefit-to-risk balance affected by penetrance. In women at high-risk of hereditary breast cancer who would consider risk-reducing interventions, identifying a *PALB2* variant provides a more precise estimated risk of developing breast cancer compared with family history alone and can offer women a more accurate understanding of benefits and potential harms of any intervention. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a *CHEK2* variant, the evidence includes studies of variant prevalence and studies of breast cancer

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risk. The relevant outcomes are overall survival, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *CHEK2* variants are of moderate penetrance, with lower RR for breast cancer than *PALB2*, and confer a risk of breast cancer two to three times that of the general population. Direct evidence for the clinical utility of genetic testing for *CHEK2* variants in individuals with risk of hereditary breast/ovarian cancer was not identified. It is unclear the RR associated with the moderate penetrance variants other than *PALB2* would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to the case of *PALB2*, where the penetrance approaches that of a *BRCA* variant, there is unlikely to be a similar benefit-to-risk calculus for risk-reducing mastectomy in women with a *CHEK2* variant. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for an *ATM* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. The relevant outcomes are overall survival, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *ATM* variants are of moderate penetrance, with lower RR for breast cancer than *PALB2*; moreover, *ATM* variants confer a risk of breast cancer two to four times that of the general population. Direct evidence for the clinical utility of genetic testing for *ATM* variants in individuals with risk of hereditary breast/ovarian cancer was not identified. It is unclear that the RR associated with the moderate penetrance variants-other than *PALB2* would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to the case of *PALB2*, where the penetrance approaches that of a *BRCA* variant, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with an *ATM* variant. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

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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

American Society of Clinical Oncology

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

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (v.3.2019) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer review single-gene tests for *PALB2*, *CHEK2*, or *ATM*. The guidelines state that a number of genes, including but not limited to *PALB2*, *CHEK2*, and *ATM*, "could potentially" be included in a multigene test and that there are limited data on the degree of cancer risk associated with some genes in multigene panels. The guidelines state that the panel recommends an annual mammogram for women with mutated *PALB2* gene beginning at age 30 and with mutated *ATM* or *CHEK2* gene beginning at age 40 with consideration of annual breast MRI.

The National Comprehensive Cancer Network guidelines on breast cancer screening and diagnosis (v.1.2019) and on genetic/familial high-risk assessment for breast and ovarian cancer (v.3.2019) 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.

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- Consideration of a risk-reducing mastectomy based on family history.

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

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for *PALB2*, *CHEK2*, or *ATM* 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 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT02620852	Enabling a Paradigm Shift: A Preference-Tolerant RCT of Personalized vs. Annual Screening for Breast Cancer (Wisdom Study)	100,000	Dec 2020

NCT: national clinical trial.



Louisiana

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Louisiana

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

Policy # 00504

Original Effective Date: 07/20/2016

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Policy History

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|------------|---|
| 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. |

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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.
Coding update
12/03/2020 Medical Policy Committee review
12/09/2020 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 12/2021

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	0129U, 0136U, 0137U, 81307, 81308, 81406, 81408, 81479
HCPCS	No codes
ICD-10 Diagnosis	C25.0-C25.9, C50.01-C50.929, Z15.01, Z80.0, Z80.3

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

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the 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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;

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

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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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.

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