

Corporate Medical Policy

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

File Name: moderate_penetrance_variants_associated_with_breast_cancer_in_individuals_at_high_risk

Origination: 2/2016

Last CAP Review: 3/2018

Next CAP Review: 3/2019

Last Review: 3/2018

Description of Procedure or Service

Breast Cancer and Genetics

In 2016, researchers anticipate breast cancer will be diagnosed in 252,710 women and 40,610 will die from the disease; a woman's lifetime risk is 12.4% (seer.cancer.gov/statfacts/html/breast.html). Breast cancers can be classified as sporadic, familial, or hereditary. Most are sporadic (70% to 75%), occurring in women without a family history of disease. Familial cancers (15% to 25%) aggregate within families but lack clearly discernable patterns of inheritance and are likely polygenic. Hereditary cancers have discernable inheritance patterns, often occur at younger ages, may be bilateral, and comprise between 5% and 10% of breast cancers. Pathogenic *BRCA1* and *BRCA2* variants appear responsible for 20% to 25% of hereditary breast cancers, a while small proportions are attributed to pathogenic variants in other highly penetrant genes (eg, *TP53*, *CDH1*, *PTEN*, *STK11*).

Penetrance of Pathogenic Variants

Penetrance is the risk conferred by a pathogenic variant, or the proportion of individuals with the variant expected to develop cancer. Variant penetrance is considered high, moderate, or low according to lifetime risk: high (>50%), moderate (20% to 50%), and low (<20%) (corresponding relative risks of approximately ≥ 5 , 1.5 to 5, and <1.53). Variants in only a few breast cancer susceptibility genes (*BRCA1* and *BRCA2* [hereditary breast/ovarian cancer syndrome], *TP53* [Li-Fraumeni syndrome], *PTEN* [Cowden syndrome], *CDH1* [hereditary diffuse gastric cancer], *STK11* [Peutz-Jeghers syndrome]) are considered highly penetrant. For example, a woman with a *BRCA1* or *BRCA2* variant has roughly a 75% lifetime risk of developing breast cancer and a relative risk of 11 to 12 compared with the general population.

Penetrance can be modified by environmental factors and by family history, which is a particularly important modifier for low- and moderate-penetrance genes. In addition, specific pathogenic variants within a gene may confer somewhat different risks.

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

Determining Variant Pathogenicity

Determining the pathogenicity of variants in a cancer-susceptibility gene most commonly detected (eg, founder sequence variants) is generally straightforward because associations are repeatedly observed. For uncommonly identified variants, such as those found in a few individuals or families, defining pathogenicity can be more difficult. For example, predicting the pathogenicity of previously unidentified variants typically requires in silico (computational) analysis predicting protein structure/function, evolutionary conservation, and splice site prediction. The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines. Still, distinctions between a

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

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 16p12.2a and has 13 exons (www.omim.org/entry/610355). The *PALB2* protein assists *BRCA2* in DNA repair and tumor suppression. Heterozygous pathogenic *PALB2* variants increase the risk of developing breast and pancreatic cancers; homozygous variants are found in Fanconi anemia. Most pathogenic *PALB2* variants are truncating frameshift or stop codons, and are found throughout the gene. Pathogenic *PALB2* variants are uncommon in unselected populations and prevalence varies by ethnicity and family history. For example, Antoniou et al (2014) assumed a prevalence of 8 per 10,000 in the general population when modeling breast cancer risks. Variants are more prevalent in ethnic populations where founder variants have persisted (eg, Finns, French Canadians, Poles), while infrequently found in others (eg, in Ashkenazi Jews). In women with a family history of breast cancer, the prevalence of pathogenic *PALB2* variants ranges between 0.9% and 3.9%, 8 or substantially higher than in an unselected general population. Depending on population prevalence, *PALB2* may be responsible for as much as 2.4% of hereditary breast cancers; and in populations with founder variants cause 0.5% to 1% of all breast cancers.

Protein-truncating *PALB2* variants appear responsible for some cases of familial pancreatic cancers, but the proportion is unclear. Whether screening asymptomatic high-risk patients for pancreatic cancer can improve health outcomes is uncertain.

CHEK2 Gene

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

In 2002, a single recurrent truncating mutation in the *CHEK2* gene (c.1100delC) was first reported as a cause of breast cancer, and studies have since confirmed this. The incidence of *CHEK2* variants varies widely among populations. It is most prevalent in Eastern and Northern Europe, where the population frequency of the c.1100delC allele ranges from 0.5% to 1.4%; the allele is less frequent in North America and virtually absent in Spain and India.

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

ATM Gene

ATM (ataxia-telangiectasia [AT] mutated), located on chromosome 11q22.3, is associated with the autosomal recessive condition AT. This condition is characterized by progressive cerebellar ataxia with onset between the ages of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition. Female *ATM* heterozygotes carriers have a risk of breast cancer about twice as high as that of the general population, 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 non-genetic factors. Risk is increased in women experiencing an earlier age at menarche, nulliparity, late age of first pregnancy, fewer births, late menopause, proliferative breast disease, menopausal hormone therapy, alcohol, obesity, inactivity, and radiation. A family history of breast cancer confers between a 2- and a 4-fold increased risk varying

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

according to the number and closeness of affected relatives, age at which cancers developed, whether breast cancers were bilateral, and if other cancers occurred (eg, ovarian). 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.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Commercially-available genetic tests for epilepsy are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

PALB2, *CHEK2*, and *ATM* testing are available under the auspices of CLIA (a list of laboratories offering testing is available at NCBI's Genetic Testing Registry (GTR) [<https://www.ncbi.nlm.nih.gov/htr/>]). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

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

Related Policies:

General Cancer Susceptibility Panels Using Next Generation Sequencing

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for moderate penetrance variants associated with breast cancer in individuals at high risk when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Risk is covered

Testing for *PALB2* variants for breast cancer risk assessment in adults who meet the following criteria may be considered medically necessary:

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

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

When Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Risk is not covered

Testing for *PALB2* sequence variants in individuals who do not meet the criteria outlined above is considered investigational.

Testing for *CHEK2* and *ATM* variants in the assessment of breast cancer risk is considered investigational.

Policy Guidelines

About 3% to 5% of women presenting for assessment for hereditary breast/ovarian cancer risk have a variant in a gene that moderately increases the risk of cancer, rather than having one of the well-described familial breast/ovarian cancer syndromes (eg, *BRCA1*, *BRCA2*). *PALB2*, *CHEK2*, and *ATM* variants are considered to be of moderate penetrance and carriers have an approximately 2- to 4-fold increased risk of developing breast cancer compared with the general population. Risk estimates may be higher in patients with a family history of breast cancer or for a specific variant.

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a *PALB2* variant, the evidence include studies of analytic validity, variant prevalence, and multiple studies of breast cancer risk, including 1 meta-analysis. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The reported evidence supporting analytic validity is not substantial, but given current next-generation sequencing techniques with variant confirmation by conventional methods, high analytic sensitivity such as reported by Judkins et al (2015) is expected in a laboratory certified by the Clinical Laboratory Improvement Amendments meeting standards for high-complexity molecular diagnostics. Evidence supporting clinical validity was obtained from 9 studies reporting relative risks or odds ratios (2 studies estimated penetrance). Study designs included family segregation, kin-cohort, family-based case-control, and population-based case-control. The number of pathogenic variants identified in studies varied from 1 (founder variants) to 48. Relative risks for breast cancer associated with a *PALB2* variant ranged from 2.3 to 13.4, with the 2 family-based studies reporting the lowest values. Evidence on preventive interventions in women with *PALB2* variants is indirect, relying on studies of high-risk women and *BRCA* carriers. Compared with other screening modalities, magnetic resonance imaging (MRI) has a higher sensitivity, but increased false positives when high-risk women are screened. Screening recommendations for high-risk asymptomatic women include beginning at an earlier age and addition of MRI to mammography. However, there is no direct evidence and limited observational data suggesting improved outcomes. There is limited observational evidence that chemoprevention can decrease the risk of invasive cancers in high-risk women; the U.S. Preventive Services Task Force (USPSTF) report and National Comprehensive Cancer Network (NCCN) support a chemoprevention option. In high-risk women, prophylactic mastectomy (bilateral or contralateral) reduces the risk of breast cancer and breast cancer mortality and decision analytic models project increased life-expectancy. Prophylactic mastectomy can be accompanied by a significant risk of adverse effects and studies have found a minority of asymptomatic *BRCA* carriers choose to undergo a bilateral prophylactic mastectomy. Given the penetrance of *PALB2* variants, the outcomes following bilateral and contralateral prophylactic mastectomy examined in women with a family history consistent with hereditary breast cancer (including *BRCA1* and *BRCA2* carriers) can be applied to women with *PALB2* variants—with the benefit to risk balance affected by penetrance. In women at high risk of hereditary breast cancer who would consider preventive interventions, identifying a *PALB2* variant provides a more precise estimated risk of developing breast cancer compared with family history alone and can offer women a more accurate understanding of tradeoffs involved for any intervention. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing of for a *CHEK2* variant or an *ATM* variant, the evidence includes studies of analytic validity, variant

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

prevalence, and studies of breast cancer risk. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The available studies on clinical validity have demonstrated that both *CHEK2* and *ATM2* variants are of moderate penetrants, with lower relative risks for breast cancer than *PALB2*, and confer a risk of breast cancer 2 to 4 times that of the general population. Direct evidence for the clinical utility of genetic testing for *CHEK2* or *ATM* variants in individuals with risk of hereditary breast/ovarian cancer was not identified. For women with high-risk hereditary cancer syndromes, interventions to decrease breast cancer risk in high-risk women include screening (eg, starting at an early age, addition of MRI to mammography, and annually), chemoprevention, prophylactic mastectomy, and prophylactic oophorectomy. Following the logic applied in the case of *PALB2*, there is limited evidence that chemoprevention can decrease the risk of invasive cancers in high-risk women; the USPSTF report and NCCN support a chemoprevention option. In contrast to the case of *PALB2*, where the penetrance approaches that of a *BRCA* variant, there is unlikely to be a similar benefit-to-risk calculus for women with a *CHEK2* variant making a decision about a prophylactic mastectomy. It is unclear that the relative risk associated with the moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. The evidence is insufficient to determine the effects of the technology on health outcomes.

Criteria from National Comprehensive Cancer Network (NCCN) guidelines for genetic risk evaluation of women without and with breast cancer are listed in Tables PG1 and PG2.

Table PG1. 2016 NCCN Criteria for Genetic Risk Evaluation of an Individual Without a History of Breast Cancer

<i>“A close relative with any of the following:</i>
<i>A known sequence variant in a cancer susceptibility gene within the family</i>
<i>≥2 breast cancer primaries in a single individual</i>
<i>≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 years</i>
<i>Ovarian Cancer</i>
<i>Male Breast Cancer</i>
<i>First or second-degree relative with breast cancer ≤45 years</i>
<i>Family history of three or more of the following (especially if early onset and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, and/or macrocephaly, hamartomatous polyps of GI tract.”</i>
<i>GI: gastrointestinal; NCCN: National Comprehensive Cancer Network.</i>

Table PG2. 2016 NCCN Criteria for Genetic Risk Evaluation of an Individual With Breast Cancer

<i>“A known sequence variant in a cancer susceptibility gene within the family:</i>
<i>Early-age onset breast cancer</i>
<i>Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 years</i>
<i>Two breast cancer primaries in a single individual</i>
<i>Breast cancer at any age, and</i>

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

<i>≥1 close blood relative with breast cancer ≤50 years, or</i>
<i>≥1 close blood relative with invasive ovarian cancer at any age, or</i>
<i>≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or</i>
<i>From a population at increased risk</i>
<i>Male breast cancer</i>
<i>An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age</i>
<i>An individual with a personal and/or family history of three or more of the following (especially if early onset and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract.”</i>
<i>An individual with an ovarian cancer</i>
<i>ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; NCCN: National Comprehensive Cancer Network; PR: progesterone receptor.</i>

A Recommended Testing Strategy

Patients who meet criteria for genetic testing as outlined in the policy statements above should be tested for sequence variants in *BRCA1* and *BRCA2*.

- In patients with a known familial *BRCA* sequence variant, targeted testing for the specific sequence variant is recommended.
- In patients with unknown familial *BRCA* sequence variant:
 - Non-Ashkenazi Jewish descent
 - To identify clinically significant variants, NCCN advises testing a relative who has breast or ovarian cancer, especially with early-onset disease, bilateral disease, multiple primaries, or ovarian cancer, because that individual has the highest likelihood for a positive test result.
 - If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1* or *BRCA2* sequence variants (eg, prostate cancer, pancreatic cancer, melanoma).
 - If no familial sequence variant can be identified, 2 possible testing strategies are:
 - Full sequencing followed by testing for *common* large genomic rearrangements (deletions/duplications) only if sequencing detects no sequence variant (negative result).
 - More than 90% of *BRCA* sequence variants will be detected by full sequencing.
 - Alternatively, simultaneous full sequencing and testing for *common* large genomic rearrangements (also known as comprehensive *BRCA* testing; see the Comprehensive Variant Analysis section below) may be performed as is recommended by NCCN.
 - Comprehensive testing can detect 92.5% of *BRCA1* and *BRCA2* sequence variants.
 - If comprehensive *BRCA* testing is negative, testing for *uncommon* large genomic rearrangements (eg, BART™) may be done.
 - Testing for *uncommon* large rearrangements should not be done unless both sequencing and testing for *common* large rearrangements have been performed and are negative.

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

- Among patients with negative comprehensive testing, BART™ identified a deleterious sequence variant (positive result) in less than 1%.
- Ashkenazi Jewish descent
 - In patients of known Ashkenazi Jewish descent, NCCN recommends testing for the 3 known founder sequence mutations (185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*) first.
 - If testing is negative for founder sequence variants, comprehensive genetic testing may be considered (see the Comprehensive Variant Analysis section below).

Comprehensive Variant Analysis

Comprehensive variant analysis currently includes sequencing the coding regions and intron and exon splice sites, as well as tests to detect common large deletions and rearrangements that can be missed with sequence analysis alone. In addition, before August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative *BRCA* testing before this time may consider repeat testing for the rearrangements (see Policy Statements section for criteria).

High-Risk Ethnic Groups

Testing in eligible individuals who belong to ethnic populations in which there are well-characterized founder sequence mutations should begin with tests specifically for these variants. For example, founder mutations account for approximately three-quarters of the *BRCA* sequence variants found in Ashkenazi Jewish populations (see Rationale section). When testing for founder sequence variants is negative, comprehensive variant analysis should then be performed.

Testing Unaffected Individuals

In unaffected family members of potential *BRCA* sequence variant families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an affected family member be tested first whenever possible to adequately interpret the test. Should a *BRCA* variant be found in an affected family member(s), DNA from an unaffected family member can be tested specifically for the same variant of the affected family member without having to sequence the entire gene. Interpreting test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated variant but leads to difficulties in interpreting negative test results (uninformative negative) or variants of uncertain significance because the possibility of a causative *BRCA* variant is not ruled out.

Prostate Cancer

Patients with *BRCA* sequence variants have an increased risk of prostate cancer, and patients with known *BRCA* sequence variants may therefore consider more aggressive screening approaches for prostate cancer. However, the presence of prostate cancer in an individual, or in a family, is not itself considered sufficient justification for *BRCA* testing.

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

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

may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: No specific code

There is no specific CPT code for PALB2 testing, but it is included in the CPT Tier 2 molecular pathology code 81406.

PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer), full gene sequence.

Testing for ATM variants is included in CPT Tier 2 molecular pathology code 81408;

ATM (ataxia telangiectasia mutated) (eg, 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.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.126, 1/14/16

Senior Medical Director Review 1/2016

Specialty Matched Consultant Advisory Panel 3/2016

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis. Version 1.2016.
https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf. Accessed December 1, 2016.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 2.2016.
https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed December 1, 2016.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.126, 12/8/16

Medical Director Review 12/2016

Specialty Matched Consultant Advisory Panel 3/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.126, 12/14/17

Specialty Matched Consultant Advisory Panel 3/2018

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

Policy Implementation/Update Information

For Policy Titled: Genetic Testing for PALB2 Mutations

- 2/29/16 New medical policy issued. Genetic testing for *PALB2* mutations in patients with breast or pancreatic cancer or for cancer risk assessment in patients with or without a family history of breast or pancreatic cancer is considered **investigational**. Senior medical director review 1/2016. Reference added. Notification given 2/29/16 for effective date 4/29/16. (lpr)
- 4/29/16 Specialty Matched Consultant Advisory Panel review 3/30/16. No change to policy intent. (lpr)

For Policy Titled: Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Risk

- 2/24/17 Policy title revised. Extensive revisions to Description and Policy Guidelines sections. Under When Covered section: added medically necessary indication for PALB2 testing: Testing for *PALB2* variants for breast cancer risk assessment in adults who meet the following criteria may be considered medically necessary: 1. The individual meets criteria for genetic risk evaluation (see Policy Guidelines section) AND 2. The individual has undergone testing for sequence variants in *BRCA1* and *BRCA2* (see Policy Guidelines section) with negative results. Under When Not Covered section, added the following statements: Testing for *PALB2* sequence variants in individuals who do not meet the criteria outlined above is considered investigational and testing for *CHEK2* and *ATM* variants in the assessment of breast cancer risk is considered investigational. Medical director review 12/2016. References added. (lpr)
- 4/28/17 Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (lpr)
- 1/12/18 Reference added. No change to policy statement. (lpr)
- 4/27/18 Specialty Matched Consultant Advisory Panel review 3/28/2018. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.