MEDICAL POLICY

POLICY TITLE	**GERMLINE GENETIC TESTING FOR GENE VARIANTS ASSOCIATED WITH BREAST CANCER IN INDIVIDUALS AT HIGH BREAST CANCER RISK (CHEK2, ATM, AND BARD1)**
POLICY NUMBER	**MP 2.279**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**RETIRED 7/1/2026**

POLICY

Testing for *CHEK2*, *ATM,* and *BARD1* variants in the assessment of breast cancer risk is considered **investigational** as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

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 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 **MP 2.211 - 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.

Cross-References:

MP 2.211 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
MP 2.255 Genetic testing for PTEN Hamartoma Tumor Syndrome
MP 2.274 Genetic testing for Li-Fraumeni Syndrome

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POLICY NUMBER	MP 2.279

MP 2.325 Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
MP 2.377 Molecular Testing for Germline Variants associated with Ovarian Cancer (BRIP1, RAD51C, RAD51D, NBN)
MP 2.393 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1, NTRK)
MP 2.394 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, NTRK Gene Fusion)
MP 2.395 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, NTRK)
MP 5.013 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

DESCRIPTION/BACKGROUND

BREAST CANCER AND GENETICS

The National Cancer Institute estimated there would be 297,790 new cases of female breast cancer (FBC) and 2,800 cases of male breast cancer (MBC) diagnosed in 2023, with an expected 43,170 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 cancer can be classified as sporadic, familial, or hereditary. Most breast cancers 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. Most inherited autosomal dominant breast cancer can be attributed to the *BRCA1* and *BRCA2* variants. For women who inherit a pathogenic *BRCA1* and *BRCA2* variants, 45% to 72% will develop breast cancer by 70-80 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 (e.g., *TP53, CDH1, PTEN, STK11*) contribute to a smaller number of cancer cases. *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* are addressed in **MP 2.211**.

Testing for mismatch repair genes linked to Lynch syndrome are addressed in **MP 5.013**.

Testing for genes linked to Cowden/PTEN Hamartoma Tumor syndrome are addressed in **MP 2.255**.

Testing for genes linked to Li-Fraumeni syndrome are addressed in **MP 2.274**.

Testing for genes linked to ovarian cancer (*BRIP1, RAD51C, RAD51D, NBN*) are addressed in **MP 2.377**.

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 (greater than 50%), moderate (20% to 50%), and low (less than 20%) (Corresponding relative risks of approximately greater than or equal to 5, 1.5 to 5, and less than1.5). 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 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 (e.g., founder sequence mutations) is generally straightforward because associations are repeatedly observed. For uncommonly identified variants, such as those found in a few individuals or families, defining pathogenicity can be more difficult. For example, predicting the pathogenicity of previously unidentified variants typically requires in silico (computational) analysis predicting protein structure/function, evolutionary conservation, and splice site prediction. The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines. Still, distinctions between a variant of uncertain significance and a pathogenic one from different laboratories may not always be identical.

Genes Associated with a Moderate Penetrance of Breast Cancer

CHEK2 Gene

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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. 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 variants 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. 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 according to 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). 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). For a woman without breast cancer, the probability of detecting a pathogenic variant can be estimated from a detailed multigenerational pedigree (e.g., Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), screening tools (e.g., BRCAPRO, Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen), or by referring to guidelines that define specific family history criteria (e.g., The American College of Radiology). 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.

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 testing 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

SUMMARY OF EVIDENCE

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For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a *CHEK2* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. 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 and confer a risk of breast cancer two to four times that of the general population. Direct evidence for the clinical utility of genetic testing for *CHEK2* variants in individuals with risk of hereditary breast/ovarian cancer was not identified. It is unclear whether the relative risk associated with the moderate penetrance variants other than *PALB2* would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to 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 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; 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 relative risk 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 an *ATM* variant. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

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DEFINITIONS

NA

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes								
0102U	0129U	0136U	81408	81479				

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POLICY HISTORY

MP 2.279	**01/14/2019 Consensus Review.** No change to the policy statements. Background and references updated. Policy guidelines and rationale revised. Appendix removed.
	10/01/2019 Administrative Update. New code 0137U added to policy.
	01/01/2020 Administrative Update. New codes added 81307 and 81308.
	02/17/2020 Consensus Review. No change to policy statement. Coding reviewed.
	10/12/2021 Consensus Review. Title changed to "Gene Variants (PALB2, CHEK2, and ATM) Associated With Breast Cancer in Individuals at High Breast Cancer Risk". Policy statements unchanged. Addition of NCCN statement, FEP statement revised, Description/Background section updated. Added unspecified diagnosis codes.

MEDICAL POLICY

POLICY TITLE	GERMLINE GENETIC TESTING FOR GENE VARIANTS ASSOCIATED WITH BREAST CANCER IN INDIVIDUALS AT HIGH BREAST CANCER RISK (CHEK2, ATM, AND BARD1)
POLICY NUMBER	MP 2.279

07/29/2022 Administrative Update. Added 2 new ICD-10 codes (Q85.81-Q85.82). Effective date 10/01/2022
10/27/2022 Minor Review. Removed PALB2 from this policy as it will now be housed in MP 2.211. Added BARD1 testing as INV per BCBSA. Changed title. Updated background, rationale, references. Added codes 0102U, 0129U, 0131U and 0136U as INV, and removed codes related to PALB2.
09/12/2023 Administrative Update. Revised code Q85.81, eff. 10/01/2023
10/04/2023 Consensus Review. No changes to policy statement. Updated background, references. Coding reviewed, no changes.
02/06/2024 Ad hoc Retirement Review. Genes in policy have been combined into MP 2.211.
06/07/2024 Administrative Update. Added 0474U as part of New Code. Eff 07/01/2024
01/13/2025 Minor Review. Brought out of retirement. Updated background, cross-references, references, and coding.
06/24/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
12/04/2025 Administrative Update. Removed procedure code 0131U as its been deleted effective 01/01/2026
03/09/2026 Retirement Review. EviCore Delegation.