Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: GERMLINE GENETIC TESTING FOR GENE VARIANTS ASSOCIATED WITH BREAST CANCER IN INDIVIDUALS AT MODERATE AND HIGH BREAST CANCER RISK (E.G., CHEK2, ATM, BARD1, ETC.)

Description/Background

Breast Cancer and Genetics

Globally, breast cancer is the most frequently diagnosed non-skin cancer and the leading cause of cancer death in women. In the United States, breast cancer is the most commonly diagnosed non-skin cancer and the second most common cause of cancer death in women.[1] Breast cancers can be classified as sporadic, familial, or hereditary.[1]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,[2] while small proportions are attributed to pathogenic variants in other moderate to highly penetrant genes (*ATM, PALB2*,*TP53, CDH1, PTEN, STK11, BARD1, CHEK2, NFI, RAD51C, RAD51D,*).

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).[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.[6] 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.[7] Still, distinctions between a variant of uncertain significance and a pathogenic one from different laboratories may not always be identical.[8]

Genes Associated With a Moderate-to-High Penetrance of Breast Cancer

***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 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.

***CDH1* Gene**

The E-cadherin (E-cad) gene (CDH1) [OMIM + 192090] is a calcium-dependent cell-to-cell adhesion molecule and tumor suppressor protein that is the only germline molecular defect associated with hereditary diffuse gastric and lobular breast cancers. Deletion or deregulation of E-cad is also correlated with the infiltrative and metastatic ability of the tumor because of disruption of the cadherin-catenin complex, with consequent loss of cell adhesion and concomitant increase in cell motility[3]

***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.[4]

NF1 Gene

NF1 is a tumor suppressor gene that encodes for neurofibromin protein, which acts as a repressor of RAS-GTP activation, with loss of *NF1* resulting in RAS activation and downstream to the MAPK pathway activation. *NF1* germline mutations are associated with neurofibromatosis type 1 (NF1), Germline *NF1* mutation increases the risk of breast cancer especially in women under 50 years old that could lead to an increased risk of cancer-related death. Somatic mutations in *NF1* are rare in primary cancer, but are associated with poor prognosis and an increased risk of recurrence. Loss of *NF1* expression results in tamoxifen resistance in preclinical models.[5]

PTEN Gene

PTEN was the first phosphatase to be identified as a tumor suppressor with diverse functions, including regulation of cell cycle, apoptosis and metastasis. Mutations or a reduced expression of the *PTEN* gene are associated with a wide variety of human tumors. Germline mutations in *PTEN* are known to cause Cowden syndrome (CS), which is characterized by a high risk of breast cancer. In families with CS, ~80% have PTEN germline mutations and female CS patients have a 25–50% lifetime risk of developing breast cancer.[6]

RAD51C/RAD51DGene

RAD51C/RAD51D is an important DNA repair gene and is involved in the homologous recombination pathway. *Rad51d*-deficient cells exhibit extensive genomic instabilities, such as aneuploidy, chromosome fragments, deletions, rearrangements and a spontaneous increase in random mutagenesis. *RAD51D* deleterious mutations were found in breast cancer patients in the breast and/or ovarian cancer families suggesting that *RAD51D* germline mutations might be associated with breast cancer risk.[7]

RAD51C and RAD51D are included on widely available cancer panels because of the reported associations of pathogenic variants in these genes with tubo-ovarian carcinoma (TOC). The reported TOC risks for *RAD51C* pathogenic variant carriers vary widely with odds ratio (OR) estimates ranging from 3.4 to 15.8 based on case-control studies and a relative risk (RR) of 5.9 using family-based segregation analysis. Similarly, the reported TOC odds ratios and relative risks for RAD51D pathogenic variant carriers ranged from 6.3 to 12.0.[8]

STK11 Gene

The tumor suppressor *STK11* is another gene with a gene product important for cell cycle regulation and mediation of apoptosis. Germline pathogenic alterations in *STK11* are associated with Peutz–Jeghers syndrome. This is an autosomal dominant disorder characterized by hamartomatous gastrointestinal polyps, mucocutaneous pigmentation, and an increased risk of colorectal, gastric, pancreatic, gallbladder, small bowel, gynecologic (uterus, cervix, and ovary), breast, testicular, and lung cancers.[9] Carriers of *STK11* mutations have a cumulative lifetime risk of any cancer of up to 85%.[10]

TP53 Gene

The TP53 protein regulates the cell cycle, interacts in DNA repair, apoptosis, cellular senescence and metabolism. Inherited TP53 mutations are associated with the rare autosomal dominant disorder. Breast cancer is the most common tumor with a 49% risk of being affected before 60 years, but most women are diagnosed before age 40. The increased risk of breast cancer for disease-associated variants has been reported to be >100-fold (age-adjusted relative risk)[10]

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.[11] A family history of breast cancer confers between a 2- and 4-fold increased risk varying by several factors: the number and closeness of affected relatives, age at which cancers developed, whether breast cancers were bilateral and if other cancers occurred (e.g., ovarian).[12] 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),[13] screening tools (e.g., BRCAPRO,[14] Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen[15,16]), or by referring to guidelines that define specific family history criteria. For women with breast cancer, family history also affects the likelihood of carrying a pathogenic variant.[14]

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. *PALB2, CHEK2,* and *ATM* testing are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories offering to test and voluntarily listing is available through the National Center for Biotechnology Genetic Testing Registry. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

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

Medical Policy Statement

Testing for *ATM, CDH1, BARD1, CHEK2, NFI, PTEN, RAD51C, RAD51D, STK11 and TP53* variants for breast cancer risk assessment in adults is considered established. It may be considered a useful diagnostic option when criteria are met.

Inclusionary and Exclusionary Guidelines

For BRCA1/2 and PALB2 testing please refer to policy "Germline Genetic Testing for BRCA1, BRCA2 and PALB2 for Hereditary Breast Ovarian Cancer Syndrome and Other High-Risk Cancers".

It is highly recommended that genetic testing should be performed in a setting that has suitably trained healthcare providers who can give appropriate pre- and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments (CLIA)-licensed laboratory that offers comprehensive variant analysis.

Inclusions:
Testing is clinically indicated in the following scenarios:

- Individuals with any close blood relative with a known *ATM, CDH1, BARD1, CHEK2, NFI, PTEN, RAD51C, RAD51D, STK11 or TP53* pathogenic/likely pathogenic variant.
- Individuals meeting the criteria below but with previous limited testing (*e.g.*, single gene and/or absent deletion duplication analysis) who are interested in multi-gene testing.
- A pathogenic or likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline.
- To aid in surgical decision-making
- Genetic testing for ATM, CDH1, BARD1, CHEK2, NFI, PTEN, RAD51C, RAD51D, STK11 or TP53 variants in cancer-affected individuals may be considered appropriate under any of the following circumstances:
    - Personal history of **breast cancer**, including invasive and ductal carcinoma in situ breast cancers, and ANY of the following:
        - Diagnosed age ≤50 years; **OR**
        - Diagnosed at any age with ANY of the following:
            - Pathology/histology:
                - Triple-negative breast cancer; **OR**
                - Multiple primary breast cancers (synchronous or metachronous); **OR**
                - Lobular breast cancer with personal or family history of diffuse gastric cancer.
            - Male breast cancer
            - Ancestry: Ashkenazi Jewish ancestry
            - Family history of ANY of the following:
                - ≥1 close blood relative with ANY:
                    - Breast cancer diagnosed ≤50 years; **OR**
                    - Male breast cancer any age; **OR**

        - Ovarian cancer any age; **OR**
        - Prostate cancer with metastatic, or high- or very high-risk group any age, **OR**
        - Pancreatic cancer any age.

    OR

    - ≥3 diagnoses of breast cancer and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer.

OR

- Family history of breast cancer with either of the below :
    - Individuals affected with breast cancer not meeting the criteria above **or** unaffected individuals **with** breast cancer in a 1st - or 2nd -degree blood relative meeting any of the criteria listed above .

    OR

    - Individuals affected with breast cancer not meeting the criteria above **or** unaffected individuals **with** a probability >5% of a BRCA1/2 pathogenic/likely pathogenetic variant based on prior probability testing models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk).

In addition to the above gene variant testing for individuals with breast cancer, the following specific gene variants are established with the below criteria.

- Genetic testing for ATM, RAD51C and RAD51D variants in individuals may be considered appropriate under **any** of the following circumstances:
    - Personal history of **epithelial ovarian cancer** (including fallopian tube cancer or peritoneal cancer) at any age
    - Family history of epithelial ovarian cancer with either of the below:
        - An individual unaffected with ovarian cancer with a first- or second-degree blood relative with epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age.

    OR

        - An individual unaffected with ovarian cancer who otherwise does not meet the criteria above but has a probability >5% of a BRCA1/2 P/LP variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk).
- Genetic testing for ATM, STK11 and TP53 variants in the following individuals:
    - All individuals diagnosed with **exocrine pancreatic cancer**; **OR**
    - First-degree relatives of individuals diagnosed with exocrine pancreatic cancer.
- Genetic testing for ATM, CHEK2 and TP53 variants in individuals may be considered appropriate under any of the following circumstances:
    1. Personal history of **prostate cancer** and **ANY** of the following:
        - Metastatic (Stage IVB) or node positive (Stage IVA) prostate cancer;
        - High- or very-high-risk prostate cancer group;
        - Ashkenazi Jewish ancestry.
        - Family history of:
            - ≥1 close blood relative with **ANY**: Breast cancer at age ≤50 years; **OR**
            - Triple-negative breast cancer at any age; **OR**
            - Male breast cancer at any age; **OR**

- Ovarian cancer at any age; **OR**
- Pancreatic cancer at any age; **OR**
- Metastatic, node positive high-, or very-high-risk prostate cancer group at any age.

OR

- ≥3 close blood relatives with prostate cancer (any grade) and/or breast cancer on the same side of the family including the patient with prostate cancer;

OR

2. Family history of prostate cancer with the following:
   - An individual affected with prostate cancer not meeting testing criteria listed above **or** unaffected individual **with** a first-degree blood relative meeting any of the criteria listed.

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, https://www.nccn.org/professionals/physician_gls/default.aspx.

Note:

- For the purpose of this policy close blood relatives include 1st-, 2nd-, and 3rd-degree relatives that are blood relatives on the same side of the family (maternal or paternal), such as:
  - 1st-degree relatives, which are parents, siblings, and children.
  - 2nd-degree relatives, which are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
  - 3rd-degree relatives, which are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.
- For the purpose of this policy high-risk and very-high-risk prostate cancer groups are defined as follows:
  - High-risk group: no very-high-risk features and are T3a (American Joint Committee on Cancer staging T3a = tumor has extended outside of the prostate but has not spread to the seminal vesicles); OR Grade Group 4 or 5; OR prostate specific antigen of 20 ng/ml or greater.
  - Very-high-risk group: T3b-T4 (tumor invades seminal vesicle(s); or tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall); OR Primary Gleason Pattern 5; OR 2 or 3 high-risk features; OR greater than 4 cores with Grade Group 4 or 5.

Exclusions

- Patients not meeting any of the above criteria
- Genetic testing for *ATM, CDH1, BARD1, CHEK2, NFI, PTEN, RAD51C, RAD51D, STK11 or TP53* variants in minors

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81408* 81432 81479**

*81408 when used to represent ATM or NF1
**81479 when used to represent CHEK2, CDH1, BARD1, RAD51C, RAD51D, or TP53

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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

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

***ATM, CDH1, BARD1, CHEK2, NFI, PTEN, RAD51C, RAD51D, STK11* and *TP53* and Breast Cancer Risk Assessment**

The purpose of testing for *ATM*, *CDH1, BARD1, CHEK2, NFI, PTEN, RAD51C, RAD51D, STK11* and *TP53* variants in individuals at moderate and high-risk of breast cancer is to evaluate whether abnormal variants are present and, if so, to determine whether the variants convey a sufficiently moderate or high-risk that changes in surveillance and/or treatment likely to decrease the risk of mortality from breast cancer are warranted.

The question addressed in this evidence review is: Does genetic testing for *ATM, CDH1, BARD1, CHEK2, NFI, PTEN, RAD51C, RAD51D, STK11* and *TP53* variants improve the net health outcome in women at moderate and high-risk of breast cancer?

The following **PICOs** were used to select literature to inform this review.

Populations
Women at increased risk of developing hereditary breast cancer based on their family history or in women with breast cancer whose family history or cancer characteristics (e.g., triple-negative disease, young age) increase the likelihood that the breast cancer is hereditary. Testing may also be considered for women from families with known variants.

Interventions
The intervention of interest is *ATM, CDH1, BARD1, CHEK2, NFI, PTEN, RAD51C, RAD51D, STK11 and TP53* variant testing.

Comparators
The alternative would be to manage women at moderate and high-risk of breast cancer with no *ATM, CDH1, BARD1, CHEK2, NFI, PTEN, RAD51C, RAD51D, STK11 and TP53* genetic testing.

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

Note: literature review was taken from NCCN clinical practice guidelines: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3.2023.

***ATM* Gene Testing Review of Literature**
Pathogenic/likely pathogenic (P/LP) variants in the *ATM* (ataxia-telangiectasia mutated) gene may increase risk for breast cancer. A meta-analysis including 19 studies showed that the cumulative lifetime risk for breast cancer in individuals with an *ATM* P/LP variant is 6% by age 50 years and 33% by age 80 years.[17] A meta-analysis of three cohort studies of relatives with ataxiatelangiectasia showed an estimated RR of 2.8 (90% CI, 2.2–3.7; $P < .001$).322 Other analyses of patients with breast cancer showed that about 1% had an *ATM* P/LP variant.85,115,118,119,323-326 The association between specific types of *ATM* genetic variants and breast cancer susceptibility is less clear, 49-52 with some evidence showing that certain missense P/LP variants may act in a dominant-negative fashion to increase cancer risk, relative to truncating P/LP variants.[18,19] A meta-analysis including five studies showed that carriers of an *ATM* P/LP variant have a 38% lifetime risk of developing breast cancer, with carriers of the c.7271T>G missense P/LP variant having a 69% risk of developing breast cancer by 70 years of age.[20] An analysis from a case-control study (42,671 breast cancer cases and 42,164 controls) showed a significant association between the c.7271T>G variant and breast cancer risk (OR, 11.60; 95% CI, 1.50–89.90; $P = .001$).[21] An analysis of 27 families in which P/LP *ATM* variants were identified showed an association between the c.7271T>G variant and increased risk for breast cancer (HR, 8.0; 95% CI, 2.3–27.4; $P < .001$).[22]

***BARD1* Gene Testing Review of Literature**
A modest association between breast cancer and P/LP variants in the *BRCA1*-associated RING domain 1 (*BARD1*) gene has been found in case-control studies with a prevalence rate of 0.1% to 0.51% in patients with breast cancer.[23,24,2,25-27] Studies show that *BARD1* is prevalent in 0.41% to 0.90% of patients with triple-negative breast cancer.85,117-119 The Breast Cancer Association Consortium and the CARRIERS case-control studies also found associations between a *BARD1* P/LP variant and increased risk of triple-negative breast cancer (0.42%; OR, 9.29; 95% CI, 4.58–18.85 and 0.41%; OR, 3.18; 95% CI, 1.16–7.42, respectively).[23,28]

CDH1 Gene Testing Review of Literature

Germline P/LP variants in *CDH1* are associated with hereditary diffuse gastric cancer and lobular breast cancer, and studies have reported a cumulative lifetime risk for breast cancer of 39% to 52%.[29-32]

CHEK2 Gene Testing Review of Literature

Another breast cancer susceptibility gene that has been identified is *CHEK2* (cell cycle checkpoint kinase 2). Panel testing of germline DNA in large samples of patients with breast cancer has shown that the prevalence rate of a *CHEK2* P/LP variant is about 1% to 2%.[2,24,33-35] Deleterious *CHEK2* P/LP variants have been reported to occur with a higher frequency in Northern and Eastern European countries compared with North America.[36-39] The cumulative lifetime risk for breast cancer in women with *CHEK2* P/LP variants and familial breast cancer has been estimated to range from approximately 28% to 37%, and is higher in women with stronger family histories of breast cancer than in those without.[40-41] The estimated RR for breast cancer, based on data from two large case-control studies, was 3.0 (90% CI, 2.6–3.5).[42] The Breast Cancer Association Consortium and the CARRIERS case-control studies showed associations between a *CHEK2* P/LP variant and increased risk of ER-positive breast cancer (1.58%; OR, 2.67; 95% CI, 2.30–3.11 and 1.11%; OR, 2.60; 95% CI, 2.05–3.31, respectively).[23,28]

Studies investigating the association between breast cancer risk and specific *CHEK2* variants have primarily been based on the truncating variant 1100delC. An analysis from the Copenhagen General Population Study (N = 86,975) showed that *CHEK2* 1100delC heterozygotes had an increased risk for breast cancer when analyses were stratified by age and sex (HR, 2.08; 95% CI, 1.51–2.85).[43] A case-control study (10,860 cases and 9,065 controls) carried out by the CHEK2 Breast Cancer Case-Control Consortium of Europe and Australia showed that the 1100delC variant is associated with increased risk for breast cancer, even in women unselected for family history (OR, 2.34; 95% CI, 1.72–3.20; $P < .001$).[44]

Another case-control study (44,777 cases and 42,997 controls) showed that heterozygous 1100delC carriers have a significantly increased risk of developing ER-positive breast cancer (OR, 2.55; 95% CI, 2.10–3.10; $P <.001$), but not ER-negative breast cancer (OR, 1.32; 95% CI, 0.93–1.88; $P= 0.12$).350 Results from a meta-analysis including 18 case-control studies (26,336 cases and 44,219 controls) showed that the missense variant I157T is associated with a modestly increased risk for breast cancer (OR,1.58; 95% CI, 1.42–1.75; $P < .001$).[45]

NFI Gene Testing Review of Literature

A population-based study in Finland of 1404 patients with *NF1* showed an estimated lifetime cancer risk of 59.6%.[46] This study showed a significant association between *NF1* and increased risk for breast cancer (SIR, 3.04; 95% CI, 2.06–4.31; $P < .001$). Among patients with breast cancer, *NF1* was associated with poorer survival, with 5-year survival rates for patients with *NF1* being 67.9%, compared to 87.8% in patients without *NF1*. Excess incidence was highest in women younger than 40 years of age (SIR, 11.10; 95% CI, 5.56–19.50; $P < .001$). A population-based study in England of 848 patients with *NF1* also showed an increased risk for breast cancer (SIR, 3.5; 95% CI, 1.9–5.9), especially among women younger than 50 years (SIR, 4.9; 95% CI, 2.4–8.8).[47]

A prospective study of patients with NF1 from the United Kingdom (N= 448) showed that breast cancer risk in carriers of these P/LP variants is not significantly increased at 50 years of

age and beyond.[48] Case-control analyses of women with NF1 from England showed that RR estimates for women aged 30 to 39 years was 6.5 (95% CI, 2.6–13.5) and 4.4 for women aged 40 to 49 years (95% CI, 2.5–7.0).386 RR estimates then drop for women aged 50 to 59 years (RR, 2.6; 95% CI, 1.5–4.2) and continue to drop as age increases (RR, 1.9; 95% CI, 1.0–3.3 for women aged 60–69 years and RR, 0.8; 95% CI, 0.2–2.2 for women aged 70–79 years). These studies show that, beginning at age 50, breast cancer risk in women with *NF1* may not significantly differ from that of women in the general population.[49]

PTEN Gene Testing Review of Literature

The spectrum of disorders resulting from germline P/LP variants in *PTEN* are referred to as PHTS. The spectrum of PHTS includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), adult Lhermitte-Duclos disease (LDD), Proteus-like syndrome, and autism spectrum disorders with mcrocephaly.[49] The lifetime risk for breast cancer for women diagnosed with Cowden syndrome/PHTS has been estimated at 40% to 60%, with an average age of 38 to 50 years at diagnosis.[50,51] Some studies have reported a higher cumulative lifetime risk for breast cancer (77%–85%) in individuals with Cowden syndrome/PHTS or *PTEN* P/LP variants.[52-54] There have been only two cases of breast cancer reported in men with Cowden syndrome/PHTS. Although many women with Cowden syndrome/PHTS experience benign breast disease, there is no evidence that the rate is higher than in the general population.[51]

RAD51C/RAD51D Gene Testing Review of Literature

Studies have shown prevalence rates of 0.23% to 0.45% for *RAD51C* and 0.29% to 0.38% for *RAD51D* in patients with triple-negative breast cancer.[24,55,56] Case-control analyses from a large study including 56,480 breast tumors showed that both *RAD51C* and *RAD51D* P/LP variants (n = 68 and n = 29, respectively) were significantly associated with triple-negative disease (OR, 4.5; 95% CI, 2.61–7.50 for *RAD51C* and OR, 4.14; 95% CI, 1.80–7.04 for *RAD51D*).[23] The Breast Cancer Association Consortium study and the CARRIERS study showed associations between increased risk of ER-negative breast cancer and both *RAD51C* P/LP variant (OR, 3.99; 95% CI, 2.20–7.26 and OR, 2.19; 95% CI, 0.97–4.49, respectively) and *RAD51D* P/LP variant (OR, 2.92; 95% CI, 1.47–5.78 and OR, 3.93; 95% CI, 1.40–10.29, respectively), with prevalence rates of 0.26% and 0.24% for *RAD51C*, respectively, and 0.17% and 0.18% for *RAD51D*, respectively.[23,28]

STK11 Gene Testing Review of Literature

A study analyzed the incidence of cancer in 419 individuals with Peutz-Jeghers Syndrome (PJS), and 297 had documented *STK11* mutations. In women with PJS, the risk of breast cancer was substantially increased, being 8% and 31% at ages 40 and 60 years, respectively. Kaplan-Meier analysis showed that cancer risks were similar in PJS patients with identified *STK11* mutations and those with no detectable mutation (log-rank test of difference m2 = 0.62; 1 df; P = 0.43).[57]

TP53 Gene Testing Review of Literature

Li-Fraumeni Syndrome (LFS) is a rare hereditary cancer syndrome associated with germline *TP53* P/LP variants.[58] It has been estimated to be involved in only about 1% of hereditary breast cancer cases,[59] although results from other studies suggest that germline *TP53* P/LP variants may be more common than previously believed, with estimates of 1 in 5000 to 1 in 20,000.[60,61]

LFS is a highly penetrant cancer syndrome associated with a high lifetime risk for cancer. An analysis from the NCI Li-Fraumeni Syndrome Study (N= 286) showed a cumulative lifetime cancer incidence of nearly 100%.[62] LFS is characterized by a wide spectrum of neoplasms occurring at a young age. It is associated with soft tissue sarcomas, osteosarcomas (although Ewing sarcoma is less likely to be associated with LFS), premenopausal breast cancer, colon cancer, gastric cancer, adrenocortical carcinoma, bronchoalveolar carcinoma, and brain tumors.[58,60,63-68]

Case-control analyses from a large study including 56,480 breast tumors showed that *TP53* P/LP variants (*n* = 82) were significantly associated with HER2-positive disease, regardless of whether disease was ER-positive (OR, 11.95; 95% CI, 5.84–23.0) or negative (OR, 22.71; 95% CI, 10.45–45.49).85 These results are supported by two earlier retrospective studies that reported a very high frequency of HER2-positive breast tumors (67%–83% of evaluated breast tumors) among patients with germline *TP53* P/LP variants.[69-70] A cohort study including 45 patients diagnosed with breast cancer and harboring a germline *TP53* P/LP variant showed that 36.1% had triple-positive (HER2+/ER+/PR+) breast cancer.[71] Taken together, results suggest that amplification of HER2 may arise in conjunction with germline *TP53* P/LP variants.

Patients with early-onset breast cancer (age of diagnosis ≤30 years) who were assigned female at birth, with or without family history of core tumor types, are another group for whom *TP53* gene P/LP variant testing may be considered.[72] Several studies have investigated the likelihood of a germline *TP53* P/LP variant in this population.[60-61,72-75] Among women younger than 30 years of age with breast cancer and without a family history, the incidence of *TP53* P/LP variants has been reported at 3% to 8%.[60,61,75,76] Other studies have found an even lower incidence of germline *TP53* P/LP variants in this population. For example, Bougeard et al reported that only 0.7% of unselected women with breast cancer before 33 years of age were carriers of a germline *TP53* P/LP variant[72] Furthermore, Ginsburg and colleagues found no germline *TP53* P/LP variants in 95 unselected women with early-onset breast cancer who previously tested negative for *BRCA1/2* P/LP variants[73] When taking into account family history of LFS-associated tumors, the *TP53* germline P/LP variant prevalence increases. In a study including 83 patients with *BRCA1/2* P/LP variant-negative early-onset breast cancer (age of diagnosis ≤35 years), deleterious *TP53* P/LP variants were identified in 3 of 4 patients (75%) with a family history of at least 2 LFS associated tumors (breast cancer, bone or soft tissue sarcoma, brain tumors, or adrenocortical carcinoma) and in 1 of 17 patients (6%) with a family history of breast cancer only[74] In another study, all women younger than 30 years of age with breast cancer who had a first- or second-degree relative with at least one of the core cancer types (n = 5) had germline *TP53* P/LP variants.[60]

SUMMARY OF EVIDENCE

For individuals with moderate and high risk of breast cancer who receive genetic testing for *ATM, CDH1, BARD1, CHEK2, NFI, PTEN, RAD51C, RAD51D, STK11 and TP53* variants the evidence includes studies of variant prevalence and studies of breast cancer risk. There is strong evidence that genes beyond BRCA1/2 confer markedly increased risk of breast cancers. These genes include *ATM, BARD1, CDH1, CHEK2, NF1, RAD51C, RAD51D, STK11 and TP53*. The evidence is sufficient 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

American College of Radiology

The American College of Radiology (ACR) has established Appropriateness Criteria® for breast cancer screening.[4] 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 13. ACR 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
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 *PALB2*, *CHEK2*, or *ATM* 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.[4] Guidelines state that genetic testing should be made available to all patients 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, patients who had previous genetic testing may benefit from updated testing. Finally, genetic testing should be made available to patients 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 patients with mutations in *ATM* and *CHEK2*, enhanced screening may be recommended, however, the data are not sufficient to support risk-reducing mastectomy in the absence of other factors such as strong family history.

American Society of Clinical Oncology and Society of Surgical Oncology

In 2024, the American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology published recommendations on germline genetic testing in individuals with breast cancer.[80] The recommendations included the following relevant statements:

"Recommendation 4.2. Testing for moderate penetrance breast cancer genes currently offers no benefits for treatment of the index breast cancer but may inform risks of second primary cancer or family risk assessment, and thus may be offered to appropriate patients who are undergoing *BRCA1/2* testing (Type: Formal Consensus; Agreement: 87.50%)."

"Recommendation 4.3. If a multi-gene panel is ordered, the specific panel chosen should take into account the patient's personal and family history. Consultation with a provider experienced in clinical cancer genetics can be helpful in selecting a specific multi-gene panel or interpreting its results and should be made available to patients when possible (Type: Formal Consensus; Agreement: 91.43%)."

The document further states, "Other breast cancer susceptibility genes are often considered for testing. The particular genes included on breast cancer susceptibility gene panels varies between testing laboratories. Almost all include *ATM*, *CHEK2*, and *PALB2*. These genes do not currently have direct relevance for treatment of patients newly diagnosed with breast cancer as PARP inhibitors are not approved for treatment of individuals with germline PVs in any of these genes, and contralateral risks are modest at best. Affected women with PVs in these genes may be at sufficient risk to benefit from breast magnetic resonance imaging (MRI) screening and *PALB2* is linked to an increased risk of ovarian cancer that may warrant post-menopausal salpingoophorectomy. The major benefit of testing for these genes, however, is to inform risk assessment of family members."[80]

Also in 2024, ASCO published a consensus guideline on the selection of germline genetic testing panels in individuals with cancer.[81] The document included a list of genes recommended for testing and inclusion in multigene panels. For breast cancer, the more strongly recommended genes (higher relative risk of cancer or highly actionable) were *BRCA1*, *BRCA2*, *PALB2*, *CDH1*,*PTEN*, *STK11*, and *TP53*. Less strongly recommended genes (moderate risk of cancer or potential impact for therapy/change in medical management) were *ATM, BARD1, CHEK2, RAD51C, RAD51D*, and *NF1*.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (v.6.2024) The NCCN genetic testing criteria for moderate and high-penetrance breast, ovarian, pancreatic, and prostate cancer are organized into three sections: 1) testing is clinically indicated; 2) testing may be considered; and 3) there is a low probability of testing results having documented clinical utility (i.e., finding of high-penetrance genes). The testing criteria listed are for cancer susceptibility genes with strong or moderate evidence of actionability for breast, ovarian, pancreatic, and prostate cancer (e.g., BRCA1/2, CDH1 PALB2, PTEN, and TP53 for breast cancer); additionally, testing criteria for LFS and Cowden syndrome continue to be contained in their own dedicated sections. Included genes may change with emerging clinical data. Further, the personal and/or family history criteria included may suggest the possibility of additional syndromes and would necessitate additional unlisted genes to be evaluated. The NCCN Panel recommends that individuals from a family with a known P/LP variant in a breast, ovarian, pancreatic, and/or prostate cancer susceptibility gene be tested for the known variant.

The National Comprehensive Cancer Network guidelines on breast cancer screening and diagnosis (v.2.2024) and on genetic/familial high-risk assessment for breast and ovarian cancer (v.3.2024) 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 mastectomy based on family history.

The guidelines also state there is insufficient evidence to draw conclusions on risk-reducing mastectomy in individuals with *CHEK2*, *ATM*, BARD1 and NF1and that patients should be managed based on family history. For patients with *PALB2, CDH1,STK11, TP53* and *PTEN* the option of a risk-reducing mastectomy should be discussed.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02620852	Enabling a paradigm shift: a preference-tolerating RCT of personalized vs. annual screening for breast cancer (Wisdom Study)	100,00	Mar 2025
Unpublished			
NCT03989258	Implementation of a Model for Personalized Risk-Based Breast Cancer Prevention and Screening	28,389	Dec 2020

NCT: national clinical trial.

Government Regulations

National:

There is no national coverage determination.

Local:

There is no local coverage determination.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Germline Genetic Testing for BRACA1, BRACA2 and PALB2 for Hereditary Breast Ovarian Cancer Syndrome and Other High-Risk Cancers
- Genetic Cancer Susceptibility Panel Using Next-Generation Sequencing

- Genetic Testing SNV to Predict Risk of Nonfamilial Breast Cancer
- Genetic Testing-Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies
- Genetic Testing and Counseling

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/20	10/15/19		Joint policy established
5/1/20	2/18/20		Added codes 81307 and 81308 as established, effective 1/1/20.
5/1/21	2/16/21		Routine policy maintenance, added references # 28, 51-52 and 54-55. Title change, removed "and the individual has undergone testing for sequence variants in BRCA1 and BRCA2 with negative results" from MPS. No change in policy status.
5/1/22	2/15/22		Updated rationale, added references # 27 and 41. No change in policy status.
5/1/23	3/29/23		Rationale completely re-written according to NCCN 2022 recommendations. Added "Moderate" to title. (ds) 10/2/23: correction to coding section – code 81497 is corrected to 81479
5/1/24	3/7/24		• Deleted code 81445 as it does not fit this policy, added codes 81432 and 81433 as established • Inclusion/exclusion section rearranged and updated with NCCN guidelines Vendor managed: N/A (ds)
5/1/25	2/18/25		Code 81432 nomenclature change. Code 81433 deleted. MPS verbiage adjusted, inclusion section updated with NCCN guidelines, rationale updated, 2 references added. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 1st Qtr. 2026

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENE VARIANTS ASSOCIATED WITH BREAST CANCER IN INDIVIDUALS AT MODERATE AND HIGH BREAST CANCER RISK

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.