Medical Policy

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

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 722
BCBSA Reference Number: 2.04.126
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing, #574
- Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome (BRCA1/BRCA2), #245
- Magnetic Resonance Imaging of the Breast, #774

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

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 AND
2. The individual has undergone testing for sequence variants in BRCA1 and BRCA2 with negative results. (See policy #245 Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome (BRCA1/BRCA2))

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.

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

<table>
<thead>
<tr>
<th>Individual Without a History of Breast</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>“A close relative with any of the following:”</td>
<td></td>
</tr>
<tr>
<td>A known sequence variant in a cancer susceptibility gene within the family</td>
<td></td>
</tr>
<tr>
<td>≥2 breast cancer primaries in a single individual</td>
<td></td>
</tr>
<tr>
<td>≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 years</td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td></td>
</tr>
<tr>
<td>Male breast cancer</td>
<td></td>
</tr>
<tr>
<td>First- or second-degree relative with breast cancer ≤45 years</td>
<td></td>
</tr>
<tr>
<td>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”</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Individual With Breast Cancer</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>“A known sequence variant in a cancer susceptibility gene within the family:”</td>
<td></td>
</tr>
<tr>
<td>Early-age-onset breast cancer</td>
<td></td>
</tr>
<tr>
<td>Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 years</td>
<td></td>
</tr>
<tr>
<td>Two breast cancer primaries in a single individual</td>
<td></td>
</tr>
<tr>
<td>Breast cancer at any age, and</td>
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<tr>
<td>≥1 close blood relative with breast cancer ≤50 years, or</td>
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<tr>
<td>≥1 close blood relative with invasive ovarian cancer at any age, or</td>
<td></td>
</tr>
<tr>
<td>≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or</td>
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<tr>
<td>From a population at increased risk</td>
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<tr>
<td>Male breast cancer</td>
<td></td>
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<tr>
<td>An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age</td>
<td></td>
</tr>
<tr>
<td>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.”</td>
<td></td>
</tr>
<tr>
<td>An individual with an ovarian cancer</td>
<td></td>
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</tbody>
</table>

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; NCCN: National Comprehensive Cancer Network; PR: progesterone receptor.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.
**Prior Authorization Information**
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th></th>
<th>Outpatient</th>
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</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>No</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>No</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>No</td>
</tr>
</tbody>
</table>

**CPT Codes / HCPCS Codes / ICD Codes**
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81406</td>
<td>MOLECULAR PATHOLOGY PROCEDURE LEVEL 7</td>
</tr>
</tbody>
</table>

According to the policy statement above, the following CPT code is considered investigational for the conditions listed for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
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<tr>
<td>81408</td>
<td>MOLECULAR PATHOLOGY PROCEDURE LEVEL 9</td>
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</table>

**Description**
**BREAST CANCER AND GENETICS**
In 2016, researchers anticipate breast cancer will be diagnosed in 246,660 women and 40,450 will die from the disease; a woman’s lifetime risk is 12.3% (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, 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.4

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.5 The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines.5 Still, distinctions between a variant of uncertain significance and a pathogenic one from different laboratories may not always be identical.6

**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 2006.7 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.b 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.8 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 9,10). 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.11

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, but do not appear to have an elevated ovarian cancer risk.

IDENTIFYING WOMEN AT RISK OF AN INHERITED SUSCEPTIBILITY TO BREAST CANCER
Breast cancer risk can be affected by genetic and nongenetic factors. 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 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 (see Table 1). For women with breast cancer, family history also affects the likelihood of carrying a pathogenic variant, although somewhat different criteria are applied (see Table 2) as is risk assessment from a pedigree.

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

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GI: gastrointestinal; NCCN: National Comprehensive Cancer Network

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- ≥1 close blood relative with breast cancer ≤50 years, or
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- ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or

From a population at increased risk

**Male breast cancer**

An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age

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 polypos of gastrointestinal (GI) tract."

An individual with an ovarian cancer

**PATIENT POPULATIONS**

Genetic testing can be considered for 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 (eg, 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. Potential benefit derives from interventions (screening, chemoprevention, risk reducing surgery) that can prevent a first breast cancer, a contralateral breast cancer, or cancer in a different organ caused by the same variant. Whether benefit outweighs harms depends on the risk of developing breast cancer (a first cancer or a contralateral one), the effectiveness and the harms of interventions. Assessing the net health outcome requires:

1. that a test accurately identifies variants and pathogenicity can be determined;
2. that a variant alters (increasing or decreasing) a woman’s risk of developing breast cancer (including contralateral disease in women already diagnosed) sufficient to change decision making, and of a magnitude that
3. management changes informed by testing can lead to improved health outcomes.

Additionally, if a familial pathogenic variant is identified, asymptomatic at-risk family members may benefit from cascade testing for the known variant. If that variant is identified in an at-risk relative, then risk-reducing management options could be offered; if the familial variant is not identified, then the relative may be considered near population risk and could avoid increased surveillance for breast cancer and risk reducing options would not be considered.

**Summary**

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 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.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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</table>
Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References

35. Seil E, Jack B. Breast magnetic resonance imaging (MRI) for screening of high-risk women. MSAC application no 1098.1. Assessment report. 2014.


