MASSACHUSETTS

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Medical Policy

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

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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

Individual Without a History of Breast
"A close relative with any of the following:

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

GI: gastrointestinal; NCCN: National Comprehensive Cancer Network

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

Individual With Breast Cancer
"A known sequence variant in a cancer susceptibility gene within the family:
Early-age-onset breast cancer
Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 years
Two breast cancer primaries in a single individual
Breast cancer at any age, and
≥1 close blood relative with breast cancer ≤50 years, or
≥1 close blood relative with invasive ovarian cancer at any age, or
≥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 polyps of gastrointestinal (GI) tract."
An individual with an ovarian cancer

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

Medicare HMO Blue[SM] and Medicare PPO Blue[SM] 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

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **not required**.
Commercial PPO and Indemnity	Prior authorization is **not required**.
Medicare HMO Blue℠	Prior authorization is **not required**.
Medicare PPO Blue℠	Prior authorization is **not required**.

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:

CPT Codes

CPT codes:	Code Description
81406	MOLECULAR PATHOLOGY PROCEDURE LEVEL 7

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:

CPT Codes

CPT codes:	Code Description
81408	MOLECULAR PATHOLOGY PROCEDURE LEVEL 9

Description

BREAST CANCER AND GENETICS

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

Penetrance of Pathogenic Variants

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

penetrant. For example, a woman with a *BRCA1* or *BRCA2* variant has roughly a 75% lifetime risk of developing breast cancer and a relative risk of 11 to 12 compared with the general population. Penetrance can be modified by environmental factors and by family history, which is a particularly important modifier for low and moderate penetrance genes. Moreover, specific pathogenic variants within a gene may confer somewhat different risks.

Determining Variant Pathogenicity

Determining the pathogenicity of variants in a more commonly detected cancer susceptibility gene (eg, founder sequence mutations) is generally straightforward because associations are repeatedly observed. For uncommonly identified variants, such as those found in a few individuals or families, defining pathogenicity can be more difficult. For example, predicting the pathogenicity of previously unidentified variants typically requires in silico (computational) analysis predicting protein structure/function, evolutionary conservation, and splice site prediction. The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines. Still, distinctions between a variant of uncertain significance and a pathogenic one from different laboratories may not always be identical.

Genes Associated With a Moderate Penetrance of Breast Cancer

PALB2 Gene

The *PALB2* gene (partner and localizer of *BRCA2*) encodes for a protein first described in 2006. The gene is located at 16p12.2[a] and has 13 exons. PALB2 protein assists *BRCA2* in DNA repair and tumor suppression. Heterozygous pathogenic *PALB2* variants increase the risk of developing breast and pancreatic cancers; homozygous variants are found in Fanconi anemia.[b] Most pathogenic *PALB2* variants are truncating frameshift or stop codons, and are found throughout the gene. Pathogenic *PALB2* variants are uncommon in unselected populations and prevalence varies by ethnicity and family history. For example, Antoniou et al (2014) assumed a prevalence of 8 per 10,000 in the general population when modeling breast cancer risks. Variants are more prevalent in ethnic populations where founder mutations have persisted (eg, Finns, French Canadians, Poles), while infrequently found in others (eg, in Ashkenazi Jews). In women with a family history of breast cancer, the prevalence of pathogenic *PALB2* variants ranges between 0.9% and 3.9%,or substantially higher than in an unselected general population. Depending on population prevalence, *PALB2* may be responsible for as much as 2.4% of hereditary breast cancers; and in populations with founder mutations cause 0.5% to 1% of all breast cancers.

CHEK2 Gene

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

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

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

ATM Gene

ATM (ataxia-telangiectasia mutated), located on chromosome 11q22.3, is associated with the autosomal recessive condition ataxia-telangiectasia syndrome. This condition is characterized by progressive cerebellar ataxia with onset between the ages of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition. Female *ATM*

heterozygotes carriers have a risk of breast cancer about twice as high as that of the general population; however, they do not appear to have an elevated ovarian cancer risk.

IDENTIFYING WOMEN AT RISK OF AN INHERITED SUSCEPTIBILITY TO BREAST CANCER

Breast cancer risk can be affected by genetic and nongenetic factors. The risk is increased in women experiencing an earlier age at menarche, nulliparity, late age of first pregnancy, fewer births, late menopause, proliferative breast disease, menopausal hormone therapy, alcohol, obesity, inactivity, and radiation. A family history of breast cancer confers between a 2- and 4-fold increased risk varying by several factors: the number and closeness of affected relatives, age at which cancers developed, whether breast cancers were bilateral and if other cancers occurred (eg, ovarian). For a woman without breast cancer, the probability of detecting a pathogenic variant can be estimated from a detailed multigenerational pedigree (eg, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), screening tools (eg, BRCAPRO, Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, Family History Screen), or by referring to guidelines that define specific family history criteria (see Supplemental Information section on Practice Guidelines and Position Statements). For women with breast cancer, family history also affects the likelihood of carrying a pathogenic variant.

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 (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.

Summary

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a *PALB2* variant, the evidence includes studies of clinical validity and studies of breast cancer risk, including a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Evidence supporting clinical validity was obtained from numerous 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 mutations) 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. These interventions include screening with magnetic resonance imaging, chemoprevention, and risk-reducing mastectomy. Given the penetrance of *PALB2* variants, the outcomes following bilateral and contralateral risk-reducing mastectomy examined in women with a family history consistent with hereditary breast cancer (including *BRCA1* and *BRCA2* carriers) can be applied to women with *PALB2* variants—with the benefit-to-risk balance affected by penetrance. In women at high risk of hereditary breast cancer who would consider risk-reducing interventions, identifying a *PALB2* variant provides a more precise estimated risk of developing breast cancer compared with family history alone and can offer women a more accurate understanding of benefits and potential harms of any intervention. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for a *CHEK2* variant, the evidence includes studies of variant prevalence, and studies of breast cancer risk. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The available studies on clinical validity have demonstrated that *CHEK2* variants are of moderate penetrance, 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* variants in individuals with risk of hereditary breast/ovarian cancer was not identified. It is unclear 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 the case of *PALB2,* where the penetrance approaches that of a *BRCA* variant, there is unlikely to be a similar benefit-to-risk calculus for risk-reducing mastectomy in women with a *CHEK2* variant. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with risk of hereditary breast/ovarian cancer who receive genetic testing for an *ATM* variant, the evidence includes studies of variant prevalence, and studies of breast cancer risk. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. The available studies on clinical validity have demonstrated that *ATM* variants are of moderate penetrance, with lower relative risks for breast cancer than *PALB2*; moreover, *ATM* variants 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 *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—other than *PALB2*—would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to the case of *PALB2,* where the penetrance approaches that of a *BRCA* variant, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with an *ATM* variant. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

Date	Action
9/2018	BCBSA National medical policy review. No changes to policy statements. New references added. Background and summary clarified.
3/2018	New references added from BCBSA National medical policy.
5/2017	BCBSA National medical policy review. New medically necessary and investigational indications described. Title changed. New references added. Clarified coding information. Effective 5/1/2017.
3/2016	New references added from BCBSA National medical policy.
6/2015	New medical policy describing investigational indications. Effective 6/1/2015.

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

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