**MEDICAL POLICY – 12.04.126**

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

**BCBSA Ref. Policy:** 2.04.126*

**Effective Date:** March 1, 2018

**Last Revised:** Feb. 27, 2018

**Replaces:** 2.04.126

**RELATED MEDICAL POLICIES:**
- 12.04.93 Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
- 12.04.504 Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1/BRCA2)

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- POLICY CRITERIA | CODING | RELATED INFORMATION
- EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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**Introduction**

Some types of breast cancer may be inherited. These cancers may be caused by variants (mutations) in certain genes such as the BRCA1 and BRCA2 genes. Other genes have also been found to be related to breast cancer. In certain cases, doing genetic testing to look for these other variants may be medically necessary if a person has already been tested for BRCA1 and BRCA2, and these tests were negative. This policy describes when genetic testing to look for variants in other breast cancer-related genes is medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

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**Policy Coverage Criteria**
Testing for PALB2 variants may be considered medically necessary for breast cancer risk assessment in adults when all of the following criteria are met:

- The patient meets criteria for genetic risk evaluation (see Genetic Risk Evaluation section below)

AND

- The patient has undergone testing for sequence variants in BRCA1 and BRCA2 with negative results

Testing for PALB2 sequence variants is considered investigational when criteria are not met.

Testing for the CHEK2 mutation may be considered medically necessary in patients with or without breast cancer if they have a personal or family history that meets the criteria listed for BRCA gene testing (See Tables 1 and 2) AND one of the following criteria is met:

- BRCA1/BRCA2 gene mutation testing was done and the result is negative

OR

- A first or second degree family member* had a positive CHEK2 gene test.

Testing for the CHEK2 mutation is considered investigational when criteria are not met.

*See Definition of Terms below

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

Genetic Risk Evaluation

Tables 1 and 2 provide breast cancer risk criteria.
### Table 1. Criteria for Genetic Risk Evaluation of an Individual Without a History of Breast Cancer

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

Adapted from NCCN, Version 1.2018, page 7
GI: gastrointestinal; NCCN: National Comprehensive Cancer Network

### Table 2. Criteria for Genetic Risk Evaluation of an Individual With Breast Cancer

<table>
<thead>
<tr>
<th>Individual With Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>A known sequence variant in a cancer susceptibility gene within the family:</td>
</tr>
<tr>
<td>Breast cancer onset ≤50 years</td>
</tr>
<tr>
<td>Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 years</td>
</tr>
<tr>
<td>Two breast cancer primaries in a single individual</td>
</tr>
<tr>
<td>Breast cancer at any age, and</td>
</tr>
<tr>
<td>- ≥1 close blood relative with breast cancer ≤50 years, or</td>
</tr>
<tr>
<td>- ≥1 close blood relative with invasive ovarian cancer at any age, or</td>
</tr>
<tr>
<td>- ≥2 close blood relatives with breast cancer, prostate cancer (Gleason score ≥7 or metastatic) and/or pancreatic cancer at any age, or</td>
</tr>
<tr>
<td>- From a population at increased risk</td>
</tr>
<tr>
<td>Male breast cancer</td>
</tr>
</tbody>
</table>
Individual With Breast Cancer

<table>
<thead>
<tr>
<th>Metastatic prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age</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>
</tr>
<tr>
<td>An individual with an ovarian cancer</td>
</tr>
</tbody>
</table>

Adapted from NCCN, Version 1.2018, page 7

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

A Recommended Testing Strategy

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

- In patients with a known familial BRCA sequence variant, targeted testing for the specific sequence variant is recommended.
- In patients with an unknown familial BRCA sequence variant:
  - Non-Ashkenazi Jewish descent
    - To identify clinically significant variants, NCCN advises testing a relative who has breast or ovarian cancer, especially with early-onset disease, bilateral disease, multiple primaries, or ovarian cancer, because that individual has the highest likelihood for a positive test result.
    - If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious BRCA1 or BRCA2 sequence variants (eg, prostate cancer, pancreatic cancer, melanoma).
    - If no familial sequence variant can be identified, 2 possible testing strategies are:
      - Full sequencing followed by testing for common large genomic rearrangements (deletions/duplications) only if sequencing detects no sequence variant (negative result).
More than 90% of BRCA sequence variants will be detected by full sequencing.

- Alternatively, simultaneous full sequencing and testing for common large genomic rearrangements (also known as comprehensive BRCA testing; see the Comprehensive Variant Analysis section below) may be performed as is recommended by NCCN.

- Comprehensive testing can detect 92.5% of BRCA1 and BRCA2 sequence variants.

- If comprehensive BRCA testing is negative, testing for uncommon large genomic rearrangements (eg, BART™) may be done.

- Testing for uncommon large rearrangements should not be done unless both sequencing and testing for common large rearrangements have been performed and are negative.

- Among patients with negative comprehensive testing, BART™ identified a deleterious sequence variant (positive result) in less than 1%.

- Ashkenazi Jewish descent

  - In patients of known Ashkenazi Jewish descent, NCCN recommends testing for the 3 known founder sequence variants (185delAG and 5182insC in BRCA1; 6174delT in BRCA2) first.

  - If testing is negative for founder sequence variants, comprehensive genetic testing may be considered (see the Comprehensive Variant Analysis section below).

Comprehensive Variant Analysis

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

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

Testing Unaffected Individuals

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

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
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</tbody>
</table>
| 81406 | Molecular pathology procedure Level 7  
Includes: PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer), full gene sequence |
| 81408 | Molecular pathology procedure level 9  
Includes: ATM (ataxia telangiectasia mutated) (eg, ataxia telangiectasia), full gene sequence. |
| 81479 | Unlisted molecular pathology procedure  
Note: Might be used to report CHEK2 variant testing |
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<tr>
<td>G0452</td>
<td>Molecular pathology procedure: physician interpretation and report</td>
</tr>
</tbody>
</table>

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**Related Information**

**Definition of Terms**

**Blood relatives - degrees of relationship:** Blood relatives may be maternal (mother) or paternal (father). The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

<table>
<thead>
<tr>
<th>Degree</th>
<th>Family Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Degree</td>
<td>Parents, siblings (brother/sister), and children</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Degree</td>
<td>Grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings (brother/sister)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Degree</td>
<td>Great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins</td>
</tr>
</tbody>
</table>

**BRCA Gene Test:** A blood based DNA test used to identify an inherited gene mutation (alteration) in BRCA1 and BRCA2. A mutation increases a person’s risk for developing breast and ovarian cancer. The test is offered to people with a personal history or strong family history of breast cancer.

**Founder mutation or founder variant:** A gene mutation (alteration) found in greater numbers in groups of people that are or were from geographically or culturally isolated regions and one or more of the ancestors was a carrier of the mutant gene. This phenomenon is often called a founder effect (http://www.cancer.gov/publications/dictionaries/genetics-dictionary?cdrid=570712)

**Genetic Counseling**

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an
inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Consideration of Age

The ages described in the policy statements are based on current guidelines from the National Comprehensive Cancer Network.

Evidence Review

Description

It is estimated that 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. PALB2, CHEK2, and ATM variants are considered to be of moderate penetrance. Carriers of PALB2 have an approximately 2- to 13-fold increased risk of developing breast cancer compared with the general population, and the risk for CHEK2 and ATM carriers is increased approximately 2- to 4-fold. Risk estimates may be higher in patients with a family history of breast cancer or a family history of for a specific variant.

Background

Breast Cancer and Genetics

In 2016, researchers anticipated 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 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 to be 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 are considered highly penetrant. These genes include BRCA1 and BRCA2 [hereditary breast/ovarian cancer syndrome], TP53 [Li-Fraumeni syndrome], PTEN [Cowden syndrome], CDH1 [hereditary diffuse gastric cancer], and STK11 [Peutz-Jeghers syndrome]. 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 variants) is generally straightforward because associations are repeatedly observed. For uncommonly identified variants, such as those found in a few individuals or families, defining pathogenicity can be more difficult. For example, predicting the pathogenicity of previously unidentified variants typically requires in silico (computational) analysis predicting protein structure/function, evolutionary conservation, and splice site prediction. The approach to defining pathogenicity is clearly outlined in standards and reporting guidelines. Still, distinctions between a 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 and has 13 exons. The PALB2 protein assists BRCA2 in DNA repair and tumor suppression. Heterozygous pathogenic PALB2 variants increase the risk of developing breast and pancreatic cancers; homozygous variants are found in Fanconi anemia. Most pathogenic PALB2 variants are truncating frameshift or stop codons, and are found throughout the gene. Pathogenic PALB2 variants are uncommon in unselected populations and prevalence varies by ethnicity and family history. For example, Antoniou et al (2014) assumed a prevalence of 8 per 10,000 in the general population when modeling breast cancer risks.

Variants are more prevalent in ethnic populations where founder variants have persisted (e.g., Finns, French Canadians, Poles), while infrequently found in others (e.g., 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 variants causes 0.5% to 1% of all breast cancers.

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

**Note:**

a. Short (p) arm of chromosome 16 at position 12.2

b. Fanconi anemia is a rare disorder, primarily affecting children, that causes bone marrow failure. Affected individuals also carry a risk of cancers including leukemia.

**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, particularly leukemia and lymphoma. Heterozygote female ATM 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. 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 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.
**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 (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. 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:

- That a test accurately identifies variants and pathogenicity can be determined
- 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
- Management changes informed by testing can lead to improved health outcomes

**Summary of Evidence**

For individuals with a risk of hereditary breast/ovarian cancer who receive genetic testing for a PALB2 variant, the evidence includes studies of analytic and 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 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. These interventions include screening with magnetic resonance imaging, chemoprevention, and risk reduction mastectomy. 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 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 a risk of hereditary breast/ovarian cancer who receive genetic testing for a CHEK2 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 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 a risk of hereditary breast/ovarian cancer was not identified.

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 a CHEK2 variant. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a risk of hereditary breast/ovarian cancer who receive genetic testing for 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 ATM variants are of moderate penetrance, with lower relative risks for breast cancer than PALB2; however, 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 a risk of hereditary breast/ovarian cancer was not identified. 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. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in October 2017 did not identify any ongoing or unpublished trials that would likely influence this policy review.
Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, 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, in 2014 input on this policy was received from 5 specialty societies and 2 academic medical centers, for a total of 7 reviewers. The review was limited to input about whether PALB2 testing to estimate 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 Society of Clinical Oncology

In a 2015 policy statement update on genetic and genomic testing for cancer susceptibility, the American Society of Clinical Oncology (ASCO) stated that testing for highly penetrant variants in appropriate populations has clinical utility in that variants inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes. The update noted: “Clinical utility remains the fundamental issue with respect to testing for variants in moderate penetrance genes. It is not yet clear whether the management of an individual patient or his or her family should change based on the presence or absence of a variant. There is insufficient evidence at the present time to conclusively demonstrate the clinical utility of testing for moderate-penetrance variants, and no guidelines exist to assist oncology providers.”

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2018) review single-gene tests for PALB2, CHEK2, or ATM. The guidelines state that a number of genes, including but not limited to PALB2, CHEK2, and ATM “could potentially” be included in a multigene test. They note that there are limited data on the degree of cancer risk associated with some genes in multigene panels.
The National Comprehensive Cancer Network guidelines on breast cancer screening and diagnosis (v.1.2017)\textsuperscript{53} and on genetic/familial high-risk assessment for breast and ovarian cancer (v.1.2018)\textsuperscript{5} recommend the following:

- Annual mammogram
- Annual breast magnetic resonance imaging if patient has >20% risk of breast cancer based on gene and/or risk level, including ATM, CDH1, CHEK2, PALB2, PTEN, and TP53
- Consideration of a risk reducing mastectomy based on family history.

The guidelines state that there is insufficient evidence to draw conclusions on risk-reducing mastectomy in individuals with PALB2, CHEK2, or ATM and that patients should be managed based on family history.

**U.S. Preventive Services Task Force Recommendations**

No U.S. Preventive Services Task Force recommendations for PALB2, CHEK2, or ATM variant testing have been identified.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). PALB2, CHEK2, and ATM testing are available under the auspices of CLIA. Laboratories offering testing and voluntarily listing is available through the National Center for Biotechnology Genetic Testing Registry. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.
Customized next-generation sequencing panels provide simultaneous analysis of multiple cancer predisposition genes, and typically include both moderate-penetrant and high-penetrant genes.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/12/16</td>
<td>Annual Review. Policy updated with literature review through October 27, 2015; references 5, 11-17, and 19-26 added; references 27-28 updated. Policy statement unchanged.</td>
</tr>
<tr>
<td>03/01/17</td>
<td>Annual Review, approved February 14, 2017. Content from 12.04.516 Genetic Testing for CHEK2 Mutations combined with this policy. Title changed to &quot;Moderate Penetrance Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk.&quot; Related Policies updated 12.04.504 added, 12.04.516 removed. PALB2 testing changed from investigational to may be considered medically necessary when criteria are met. CHEK2 testing may also be considered medically necessary when criteria are met. Policy statement added that ATM variant testing is considered investigational. Policy updated with literature review and the reference list was revised. Removed Appendix Table 8. *The policy statements vary from BCBSA.</td>
</tr>
<tr>
<td>10/01/17</td>
<td>Policy moved to new format. No changes to policy statement.</td>
</tr>
<tr>
<td>11/01/17</td>
<td>Updated Related Policies, removed 7.01.561 as it was archived.</td>
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Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5952. TTY 800-842-5537
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at:
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at:

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5537).

Oromo (Cushite):
Lakkoofisa biibila 800-722-1471 (TTY: 800-842-5537) ti biibila.

Français (French):
Appelez le 800-722-1471 (TTY: 800-842-5537).

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladan. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kék aksyon avan sèten dat limit pou ka tenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewa enfòmasyon sa a ak asistans nan lang ou paile a, san ou pa gen pou peye ou pou sa. Rate nan 800-722-1471 (TTY: 800-842-5537).

Deutsche (German):

Hmoob (Hmong):

Ilokano (Illocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impomarsion. Daytoy a pakdaar mabalini nga adda ket naglaon iti napateg nga impomarsion maipanggepp iiti aplikasyonno weno coverage babaen iiti Premera Blue Cross. Daytoy ket mabalini dagiti importante a pelta iti daytoy a pakdaar. Mabalini nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partiklar k a naituding nga alaid napo tapn napologtaliyed nga tigcoverage ti salun-atyo weno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impomarsion ken tulong iti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti nuerno nga 800-722-1471 (TTY: 800-842-5537).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente.
Chiama 800-722-1471 (TTY: 800-842-5537).
Premera Blue Cross.

Este aviso contiene información importante. Es posible que esté contenido en su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas claras en este aviso. Es posible que deba volver a alguna fecha antes de determinadas fechas para mantener su cobertura médica de ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

Tiếng Việt (Vietnamese):