BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.126 Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)

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Related Policies:

2.04.02 - Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
2.04.08 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
2.04.101 - Genetic Testing for Li-Fraumeni Syndrome
2.04.149 - Molecular Testing for Germline Variants Associated with Ovarian Cancer (BRIP1, RAD51C, RAD51D, NBN)
2.04.88 - Genetic Testing for PTEN Hamartoma Tumor Syndrome
2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
6.01.29 - Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer

Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)

Description

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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. *CHEK2, ATM,* and *BARD1* variants are considered to be of moderate penetrance. Female carriers of *CHEK2, ATM,* and *BARD1* 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 a family history of a specific variant.

OBJECTIVE

The objective of this review is to determine whether testing for *CHEK2, ATM, and BARD1* variants in individuals with a risk of hereditary breast/ovarian cancer improves the net health outcome.

POLICY STATEMENT

Testing for *CHEK2, ATM, and BARD1* variants in the assessment of breast cancer risk is considered **investigational.**

POLICY GUIDELINES

Criteria for Genetic Risk Evaluation

The National Comprehensive Cancer Network (NCCN) provides criteria for genetic risk evaluation for individuals with no history of breast cancer and for those with breast cancer. Updated versions of the criteria are available on the NCCN website.

The recommended testing strategy for *BRCA1, BRCA2,* and *PALB2* is described in review 2.04.02 (genetic testing for hereditary breast/ovarian cancer syndrome).

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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. *CHEK2, ATM,* and *BARD1* testing are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories offering 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.

RATIONALE

Summary of Evidence

For individuals with risk of hereditary breast cancer/ovarian cancer (HBOC) who receive genetic testing for a checkpoint kinase 2 (*CHEK2)* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are overall survival (OS), disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *CHEK2* variants are of moderate penetrance, and confer a risk of breast cancer 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 HBOC was not identified. It is unclear whether the relative risk (RR) associated with the moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for risk-reducing mastectomy in women with a moderate penetrance variant such as *CHEK2*. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with risk of HBOC who receive genetic testing for an ataxia-telangiectasia mutated (*ATM)* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are OS, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *ATM* variants are of moderate penetrance; 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 HBOC was not identified. It is unclear whether the RR associated with the moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a moderate penetrance variant such as *ATM*. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with risk of HBOC who receive genetic testing for a BRCA1-associated RING [Really Interesting New Gene] domain (*BARD1)* variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. Relevant outcomes are OS, disease-specific survival, and test validity. The available studies on clinical validity have demonstrated that *BARD1* variants are of low to moderate penetrance; *BARD1* variants confer a risk of breast cancer about 2 to 3 times that of the general population. Direct evidence for the clinical utility of genetic testing for *BARD1* variants in individuals with a risk of HBOC was not identified. It is unclear whether the RR associated with the low to moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a low to moderate penetrance variant such as *BARD1*. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Radiology

The American College of Radiology (ACR) has established Appropriateness Criteria for breast cancer screening (Table 1).[48,] 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 1. American College of Radiology 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
FDG-PEM	Usually not 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 *CHEK2, ATM,* and *BARD1* 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.[49,] Guidelines state that genetic testing should be made available to all individuals 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, individuals who had previous genetic testing may benefit from updated testing. Finally, genetic testing should be made available to individuals 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 individuals with mutations in *ATM* and *CHEK2*, enhanced screening is recommended, however, the data are not sufficient to support risk-reducing mastectomy in the absence of other factors such as strong family history. For individuals with *BARD1* mutations, evidence is insufficient to support change in breast cancer risk management based on the presence of a mutation alone.

National Comprehensive Cancer Network

The NCCN (v.3.2023) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer review single-gene tests for *CHEK2, ATM,* and *BARD1*.[50,] The guidelines state that for those that meet hereditary cancer testing criteria, testing for a specific familial pathogenic/likely pathogenic variant may be recommended for appropriate genes. For individuals who meet criteria with no known familial variants, comprehensive testing of a multigene panel may be considered. This testing may consider a number of genes, including but not limited to *CHEK2, ATM,* and *BARD1.* However, the inclusion of certain genes in the guideline does not imply the endorsement "for or against multigene testing for moderate-penetrance genes" and there are limited data on the degree of cancer risk associated with some genes in multigene panels. Testing an affected family member first has the highest likelihood of a positive result. The guidelines state that the panel recommends an annual mammogram for women with *CHEK2*, *ATM,* or *BARD1* mutations beginning at age 40, with consideration of annual breast magnetic resonance imaging. The guidelines also state there is insufficient evidence to draw conclusions on risk-reducing mastectomy in individuals with *CHEK2*, *ATM,* or *BARD1* mutations and that patients should be managed based on family history.

The NCCN guidelines on breast cancer screening and diagnosis (v.1.2023)[51,] 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 strategies based on family history.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for *CHEK2, ATM,* and *BARD1* variant testing have been identified.

Medicare National Coverage

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

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy-FEP	Policy updated with literature review through July 17, 2023; no references added. Removed outdated clinical input. Policy statement unchanged. New FEP Policy.