Medical Policy
Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer

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Policy Number: 252
BCBSA Reference Number: 2.04.63
NCD/LCD:
- Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)
- Local Coverage Determination (LCD): MolDX: BRCA1 and BRCA2 Genetic Testing (L36082)

Related Policies
Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome (BRCA1/BRCA2) #245

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

Testing for one or more single nucleotide variants to predict an individual’s risk of breast cancer is considered INVESTIGATIONAL.

The BREVAGenplus breast cancer risk test is considered INVESTIGATIONAL for all indications, including but not limited to use as a method of estimating individual patient risk for developing breast cancer.

Medicare HMO Blue™ and Medicare PPO Blue™ Members

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

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

Local Coverage Determination (LCD): MolDX: BRCA1 and BRCA2 Genetic Testing (L36082)

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.

<table>
<thead>
<tr>
<th>Product</th>
<th>Prior Authorization Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare HMO Blue℠</td>
<td>Prior authorization is not required.</td>
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<tr>
<td>Medicare PPO Blue℠</td>
<td>Prior authorization is not required.</td>
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</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 CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81432</td>
<td>Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53</td>
</tr>
<tr>
<td>81433</td>
<td>Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11</td>
</tr>
</tbody>
</table>

Description
GENE VARIANTS AND BREAST CANCER RISK
Rare, single-gene variants conferring a high risk of breast cancer have been linked to hereditary breast cancer syndromes. Examples are variants in BRCA1 and BRCA2. These, and a few others, account for less than 25% of inherited breast cancer. Moderate risk alleles, such as variants in the CHEK2 gene, are also relatively rare and apparently explain very little of the genetic risk.

In contrast, several common single nucleotide variants (SNVs) associated with breast cancer have been identified primarily through genome-wide association studies of very large case-control populations. These alleles occur with high frequency in the general population, and the increased breast cancer risk associated with each is very small relative to the general population risk. Some have suggested that these common-risk SNVs could be combined for individualized risk prediction either alone or in combination with traditional predictors; personalized breast cancer screening programs could then vary by starting age and intensity according to risk. Along these lines, the American Cancer Society recommends that women at high risk (>20% lifetime risk) should undergo breast magnetic resonance imaging and a mammogram every year, and those at moderately increased risk (15%-20% lifetime risk) should talk with their doctors about the benefits and limitations of adding magnetic resonance imaging screening to their yearly mammogram.¹
Clinical Genetic Tests

**BREVAGenplus**

*BREVAGenplus* evaluates breast cancer-associated SNVs identified in genome-wide association studies. The first-generation test, BREVAGen, included 7 SNVs. In a 2015 report, the test included over 70 susceptibility SNVs. Risk is calculated by combining individual SNV risks with the Gail model risk. *BREVAGenplus* has been evaluated for use in African-American, white, and Hispanic patient samples age 35 years and older. *BREVAGenplus* does not detect known high-risk variants (eg, in *BRCA*).

According to the *BREVAGenplus* website, the test is “not applicable to women who are already at high risk of breast cancer including those that have a personal or extensive family history of breast and/or ovarian cancer, LCIS [lobular carcinoma in situ], DCIS [ductal carcinoma in situ], AH [atypical hyperplasia] or have thoracic RT [radiotherapy] under 30y. Any women with these risk factors are already at increased risk of breast cancer and should be screened and followed as such.”

**Summary**

A number of single nucleotide variants (SNVs), which are single base-pair variations in the DNA sequence of the genome, have been found to be associated with breast cancer and are common in the population but confer only small increases in risk. Commercially available assays test for a number of SNVs to predict an individual’s risk of breast cancer relative to the general population. Some of these incorporate clinical information into risk prediction algorithms. The intent of this type of test is to identify subjects at increased risk who may benefit from more intensive surveillance.

For individuals who are asymptomatic and at average risk of breast cancer by clinical criteria who receive testing for common SNVs variants associated with a small increase in the risk of breast cancer, the evidence includes observational studies. Relevant outcomes are test accuracy and validity, morbid events, and quality of life. Information about analytic performance (reproducibility) of currently marketed tests is lacking. Clinical genetic tests may improve the predictive accuracy of currently used clinical risk predictors. However, the magnitude of improvement is small, and clinical significance is uncertain. Whether the potential harms of these tests due to false-negative and false-positive results are outweighed by the potential benefit associated with improved risk assessment is unknown. Evaluation of this technology is further complicated by the rapidly increasing numbers of SNVs associated with a small risk of breast cancer. Long-term prospective studies with large sample sizes are needed to determine the clinical validity and utility of SNV-based models for use in predicting breast cancer risk. The discrimination offered by the genetic factors currently known is insufficient to inform clinical practice. 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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<tbody>
<tr>
<td>1/2018</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>12/2017</td>
<td>BCBSA National medical policy review. Policy clarified, polymorphisms changed to “variants.” OncoVue removed from the policy; it is no longer commercially available. 12/1/2017</td>
</tr>
<tr>
<td>1/2016</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>6/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>6/2014</td>
<td>Investigational policy statement for OncoVue® and BREVAGen™ clarified to indicate investigational for all indications.</td>
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<tr>
<td>6/2013</td>
<td>New references from BCBSA National medical policy.</td>
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<tr>
<td>7/2011</td>
<td>Reviewed - Medical Policy Group – Hematology and Oncology</td>
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</table>
No changes to policy statements.


