Medical Policy

Use of Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer

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- Policy: Commercial
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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
- Non-BRCA Breast Cancer Risk Assessment – e.g., OncoVue #188

Policy

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

Testing for one or more single nucleotide polymorphisms (SNPs) to predict an individual’s risk of breast cancer is INVESTIGATIONAL.

The OncoVue® and BREVAGen™ breast cancer risk tests are 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
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 for outpatient services.
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>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</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 CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<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 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, 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
Several single nucleotide polymorphisms (SNPs), 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 several SNPs 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 both types of test is to identify subjects at increased risk who may benefit from more intensive surveillance.

Background
Rare, single gene variants conferring a high risk of breast cancer have been linked to hereditary breast cancer syndromes. Examples are mutations 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 SNPs associated with breast cancer have been identified primarily through genome-wide association studies (GWAS) of very large case-control populations. These alleles occur with high frequency in the general population, although the increased breast cancer risk associated with each is very small relative to the general population risk. Some have suggested that these common-risk SNPs could be combined for individualized risk prediction either alone or in combination with traditional
predictors; personalized 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 (MRI) and a mammogram every year, and those at moderately increased risk (15% to 20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram.\(^1\)

**SNP Panel Tests**
Several companies, such as those listed in Table 1, offer testing for breast cancer risk profiles using SNPs. Most companies offer testing direct-to-consumers (DTCs). Algorithms or risk models for these tests are proprietary. When reported on company websites, panels range in number from 6 to 15 SNPs.

<table>
<thead>
<tr>
<th>Company</th>
<th>Location</th>
<th>Test Offered DTC</th>
<th>Number of SNPs Used in Risk Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>23andme</td>
<td>Mountain View, CA</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>City of Hope Breast Cancer</td>
<td>Duarte, CA</td>
<td>No</td>
<td>7</td>
</tr>
<tr>
<td>Susceptibility Assay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>deCODE BreastCancer™</td>
<td>Reykjavik, Iceland</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>easyDNA</td>
<td>Elk Grove, CA</td>
<td>No(^b)</td>
<td>ND</td>
</tr>
<tr>
<td>GenePlanet</td>
<td>Dublin, Ireland</td>
<td>Yes</td>
<td>15</td>
</tr>
<tr>
<td>Matrix Genomics</td>
<td>Santa Fe, NM</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>The Genetic Testing Laboratories</td>
<td>Las Cruces, NM</td>
<td>Yes</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND, not described.

\(^a\) This is not an exhaustive list.

\(^b\) The easyDNA website includes a “note for U.S. residents” that states, “easyDNA would like to inform all its clients that as per the U.S. Food and Drug Administration’s [FDA] directive, it can only provide genetic health testing to U.S. residents if their physician has agreed to the test.”\(^2\)

**Clinical Genetic Tests**
Two companies currently offer risk assessment based on SNP panel testing and clinical information. Neither is provided as a DTC test. Both are listed in the Genetic Testing Registry of the National Center for Biotechnology Information.

**OncoVue®**
The OncoVue® Breast Cancer Risk Test (InterGenetics™ Inc., Oklahoma City, OK) is a proprietary test that evaluates multiple, low-risk SNPs associated with breast cancer. Results are combined with personal history measures to determine breast cancer risk at different times during adulthood. The test does not detect known high-risk genetic factors such as BRCA mutations (associated with hereditary breast and ovarian cancer, see Policy #245. OncoVue® synthesizes various genetic and medical history risk measures into a personalized single-risk estimate for premenopause, perimenopause, and postmenopause for each patient, with comparison to the average population risk at each of these life stages. The test is stated to be “an aid in the qualitative assessment of breast cancer risk…not intended as a stand-alone test for the determination of breast cancer risk in women.”\(^3\)

For women without a strong family history of breast cancer and at average risk before testing, OncoVue® purports to estimate a woman’s individual risk and place her in standard-, moderate-, or high-risk groups. The results are intended to help a woman and her physician decide if more frequent exams and/or more
sophisticated surveillance techniques are indicated. For women already known to be at high risk based on a family history consistent with hereditary breast cancer, the test is represented as having added value by indicating greater or lesser risk at different life stages.

OncoVue® is available only through the Breast Cancer Risk Testing Network (BCRTN), described as a network of Breast Care Centers engaged in frontline genetic identification of breast cancer risk levels in their patients. BCRTN member centers will provide genetic breast cancer risk testing for their patients using OncoVue® as part of a comprehensive education program to help OncoVue® “at-risk” women understand their risk level and intervention strategies. BCRTN members will be selected for the network based on a number of criteria, including quality standards of care, level of breast cancer surveillance technology, and the capacity to provide patient education on genetic testing and future risk management protocols. As of March 2014, 32 participating centers (36 locations), located in 20 states, were listed on the company website.

**BREVAGen™**

BREVAGen™ (Phenogen Sciences, Charlotte, NC) evaluates 7 breast cancer-associated SNPs identified in GWAS. Risk is calculated by multiplying the product of the individual SNP risks by the Gail model risk. BREVAGen has been evaluated for use in Caucasian women of European descent age 35 years and older. Like OncoVue®, BREVAGen does not detect known high-risk mutations, eg, in BRCA. According to the BREVAGen website, “suitable candidates” for testing include women with a Gail lifetime risk of 15% or greater; with high lifetime estrogen exposure (eg, early menarche and late menopause); or with relatives diagnosed with breast cancer. BREVAGen is not suitable for women with previous diagnoses of lobular carcinoma in situ, ductal carcinoma in situ, or breast cancer, because the Gail model cannot calculate breast cancer risk accurately for such women, or for women with an extensive family history of breast and ovarian cancer.

Phenogen Sciences maintains on its website a list of physicians who have been trained to use BREVAGen. As of March 2014, more than 100 participating centers in 19 states were listed on the company website.

**Summary**

Clinical utility of single nucleotide polymorphisms (SNP) panel tests and clinical genetic tests (OncoVue®, BREVAGen™, and others) is unknown. Information about analytic performance (reproducibility) of marketed tests is lacking. Most tests are in an investigational phase of development, having demonstrated associations between the SNPs tested and breast cancer risk. Clinical genetic tests may improve predictive accuracy of currently used clinical risk predictors. However, the magnitude of improvement is small and clinical significance is uncertain. Whether potential harms of these tests due to false negative and false positive results are outweighed by potential benefit associated with improved risk assessment is unknown. Use of these tests is therefore considered investigational.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<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>
</tr>
<tr>
<td>6/2014</td>
<td>Investigational policy statement for OncoVue® and BREVAGen™ clarified to indicate investigational for all indications.</td>
</tr>
<tr>
<td>6/2013</td>
<td>New references from BCBSA National medical policy.</td>
</tr>
<tr>
<td>7/2011</td>
<td>Reviewed - Medical Policy Group – Hematology and Oncology</td>
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</table>
No changes to policy statements.


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


Jupe ER, Ralph DA, Manjeshwar S. The OncoVue model for predicting breast cancer risk. 2007 San Antonio Breast Cancer Symposium; Abstract 4038.


Jupe ER, Pugh TW, Knowlton NS. Breast cancer risk estimation using the OncoVue model compared to combined GWAS single nucleotie polymorphisms. 2009 San Antonio Breast Cancer Symposium; Abstract 3177.


Dalessandri KM, Miike R, Wrensch MR. Breast cancer risk assessment in the high risk Marin County population using OncoVue compared to SNPs from genome wide association studies. 2009 San Antonio Breast Cancer Symposium; Abstract 3057.


