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. Some commercially available assays test for several SNPs and combine results 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 individuals 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 more of the genetic risk.

In contrast, several common SNPs 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, 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 to achieve an individualized risk prediction either alone or in combination with traditional predictors in order to personalize screening programs in which starting age and intensity would vary by risk. In particular, the American Cancer Society has recommended that women at high risk (greater than a 20% lifetime risk) should get breast magnetic resonance imaging (MRI) and a mammogram every year, while 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.

**SNP Panel Tests**

Several companies, such as those listed in Table 1, offer testing for breast cancer risk profiles using SNPs. Non U.S. companies offer testing direct-to-consumers (DTCs).

**Table 1. Tests for Breast Cancer Susceptibility Using SNP Based Risk Panels**

<table>
<thead>
<tr>
<th>Company</th>
<th>Location</th>
<th>Test Offered Direct to Consumer</th>
<th>Number of SNPs Used in Risk Panel</th>
</tr>
</thead>
</table>

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Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer

<table>
<thead>
<tr>
<th>City of Hope</th>
<th>Duarte, CA</th>
<th>No</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>easyDNA**</td>
<td>Elk Grove, CA</td>
<td>Yes</td>
<td>ND</td>
</tr>
<tr>
<td>GenePlanet</td>
<td>Dublin, Ireland</td>
<td>Yes</td>
<td>15</td>
</tr>
</tbody>
</table>

ND – not described

*This is not an exhaustive list

**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 directive it can only provide genetic health testing to U.S. residents if their physician has agreed to the test.”

Clinical-Genetic Tests

Two companies currently offer risk assessment based on SNP panel testing and clinical information. Neither is provided as a direct-to-consumer test. Only BREVAGen is currently 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 titled “Genetic Testing for Hereditary Breast and/or Ovarian Cancer”). 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.

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.

BREVAGenplus ®

BREVAGenplus ® (Phenogen Sciences, Charlotte, NC) evaluates breast cancer-associated SNPs identified in genome-wide association studies (GWAS). The first generation test, BREVAGen, included 7 SNPs. Per the company website, BREVAGenplus incorporates an “expanded panel” of SNPs. Risk is calculated by combining individual SNP 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. Like OncoVue®, BREVAGenplus does not detect known high-risk mutations, eg, in BRCA. According to the BREVAGenplus website, the test is best suited for women with a Gail lifetime risk of 15% or greater; or with one or more clinical risk factors for sporadic breast cancer; or concerned about their breast cancer risk. BREVAGenplus is not suitable for women with previous diagnoses of lobular carcinoma in situ, ductal carcinoma in situ, or breast cancer, since 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.
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Phenogen Sciences maintains on its website a list of physicians who have been trained to use BREVAGenplus. As of March 2015, BREVAGenplus is available in all states except New York.

FDA Status

No SNP-based test to predict breast cancer risk has been approved or cleared by the U.S. Food and Drug Administration (FDA). These tests are offered as laboratory-developed tests under the Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing.

FDA has not yet developed specific rules for DTC genetic testing. On November 22, 2013, FDA issued a warning letter to 23andMe ordering the site to “immediately discontinue marketing the Saliva Collection Kit and Personal Genome Service until such time as it receives FDA marketing authorization for the device.” In February 2015, FDA granted marketing authorization to 23andMe for its Bloom syndrome DTC carrier test. 23andMe also provides “ancestry related genetic reports and uninterpreted raw genetic data only.”

Under the current regulatory program, CLIA requires that laboratories demonstrate the analytical validity of the tests they offer. However, there is no requirement for a test to demonstrate either clinical validity or clinical utility. Some states (e.g., New York) have chosen to regulate DTC laboratories. Because these reviews are not public, it is not possible to determine what scientific standard is being applied to them.

Related Policies:
Genetic Testing for Hereditary Breast and/or Ovarian Cancer
Non-BRCA Breast Cancer Risk Assessment (OncoVue)

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Testing for one or more single nucleotide polymorphisms (SNPs) to predict an individual’s risk of breast cancer is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Non-BRCA Breast Risk Assessment with OncoVue® and BREVAGenplus® breast cancer risk tests are considered investigational for all applications. BCBSNC does not cover investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit
Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer

design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer is covered

Not applicable.

When Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer is not covered

Common genetic variants by testing for one or more single nucleotide polymorphisms (SNPs) to predict an individual’s risk of breast cancer is considered investigational.

The OncoVue® and BREVAGenplus® breast cancer risk tests are considered investigational as a method of estimating individual patient risk for developing breast cancer. BCBSNC does not cover investigational services.

Policy Guidelines

Clinical utility of single nucleotide polymorphisms (SNP) panel tests and clinical genetic tests (OncoVue®, BREVAGenplus®, 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81599, G0452

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer

Medical Director – 3/2011


23andMe. Changes to our health-related product. www.23andme.com/health/


Medical Director review 8/2015


Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer

Policy Implementation/Update Information

3/29/11 New policy implemented. Use of common genetic variants by testing for one or more single nucleotide polymorphisms (SNPs) to predict an individual’s risk of breast cancer is considered investigational. Notice given 4/12/2011. Policy effective 7/19/2011. (btw)


12/28/12 Removed the following statement from the Billing/Coding section; “Providers may use the following CPT codes for this service: 83894, 83898, 83900, 83909, and/or 83912.” Added the following codes to the Billing/Coding section; 81599 and G0452. (btw)


5/27/14 Policy combined with “Non-BRCA Breast Cancer Risk Assessment”. Added the following to Policy Statement section; “Non-BRCA Breast Risk Assessment with OncoVue® and BREVAGen™ breast cancer risk tests are considered investigational for all applications. BCBSNC does not cover investigational services or procedures.” Added the following statement to the “When not Covered” section: “The OncoVue® and BREVAGen™ breast cancer risk tests are considered investigational as a method of estimating individual patient risk for developing breast cancer. BCBSNC does not cover investigational services.” Description section and Policy Guideline section revised to incorporate information regarding non-BRCA breast cancer risk tests. References updated. Medical Director review 5/2014. (mco)

9/9/14 Specialty matched consultant advisory panel review 8/26/2014. No change to policy statement. (lpr)

10/1/15 Specialty Matched Consultant Advisory Panel review 8/26/2015. Description section updated as well as Table 1. Regulatory/FDA status and Policy Guidelines updated. Reference added. Removed “Use Of” from the title of the policy. Medical director review 8/2015. No change to policy statement. (lpr)

9/30/16 Specialty Matched Consultant Advisory Panel review 8/31/2016. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.