Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer

Description of Procedure or Service

Rare, single-gene variants conferring a high risk of breast cancer have been linked to hereditary breast cancer syndromes. Examples are variants in \textit{BRCA1} and \textit{BRCA2}. These, and a few others, account for less than 25% of inherited breast cancer. Moderate risk alleles, such as variants in the \textit{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.

Clinical-Genetic Tests

\textit{BREVAGenplus}

\textit{BREVAGenplus} evaluates breast cancer-associated SNVs identified in genome-wide association studies. The first-generation test, \textit{BREVAGen}, included seven 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. \textit{BREVAGenplus} has been evaluated for use in African-American, white, and Hispanic patient samples age 35 years and older. \textit{BREVAGenplus} does not detect known high-risk variants (eg, in \textit{BRCA1}). According to the \textit{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.”

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.
Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer

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 Breast and Ovarian Cancer

***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 variants 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 BREVAGenplus® breast cancer risk test is 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 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

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 as a method of estimating individual patient risk for developing breast cancer. BCBSNC does not cover investigational services.
Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer

Policy Guidelines

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.

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


Medical Director – 3/2011


Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer


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


Medical Director review 8/2015


Specialty Matched Consultant Advisory Panel- 8/2018

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)
Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer


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)

9/29/17 Specialty Matched Consultant Advisory Panel review 8/30/2017. No change to policy statement. (lpr)

11/28/17 Updated Description and Policy Guidelines sections. “Polymorphism” changed to “variants” throughout the policy. OncoVue removed as it is no longer commercially available. No change to policy statement. Reference added. (lpr)

9/28/18 Specialty Matched Consultant Advisory Panel review 8/2018. 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.