| BLUE CROSS OF NORTHEASTERN PA<br>"BCNEPA"<br>MEDICAL POLICY BULLETIN | **MANUAL:** MEDICAL POLICY |
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| | **REFERENCE NO.:** MPO-083-0025 |
| **EFFECTIVE DATE**<br>July 1, 2014 | **SUBJECT:** Use of Common Genetic Variants (SNPs) to Predict Risk of Nonfamilial Breast Cancer |

**Blue Cross of Northeastern Pennsylvania ("BCNEPA") Medical Policy**

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical policy and claims payment policy are applied. Policies are provided for informational purposes only and are developed to assist in administering plan benefits and do not constitute medical advice.

Treating providers are solely responsible for medical advice and treatment. Policies are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease.

Medical practices and information are constantly changing and BCNEPA may review and revise its medical policies periodically. Also, due to the rapid pace of changing technology and the advent of new medical procedures, BCNEPA may not have a policy to address every procedure.

In those cases, BCNEPA may review other sources of information including, but not limited to, current medical literature and other medical resources, such as Technology Evaluation Center Assessments (TEC) published by the Blue Cross Blue Shield Association. BCNEPA may also consult with health care providers possessing particular expertise in the services at issue.

## 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 individuals at increased risk who may benefit from more intensive surveillance.

## BENEFIT POLICY STATEMENT:

BCNEPA makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on product line, group or contract, therefore, Member benefits must be verified. In the event of a conflict between the Member's benefit plan document and topics addressed in Medical Policy Bulletins (i.e., specific contract exclusions), the Member's benefit plan document always supersedes the information in the Medical Policy Bulletins. BCNEPA determines medical necessity only if the benefit exists and no contract exclusions are applicable.

Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

**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 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 (greater than 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.

**Table1. Tests for Breast Cancer Susceptibility Using SNP-Based Risk Panels[a]**

| Company | Location | Test Offered Direct-to-Consumer | Number of SNPs Used in Risk Panel |
|---|---|---|---|
| 23andme | Mt. View, CA | Yes | 7 |
| City of Hope Breast Cancer Susceptibility Assay | Duarte, CA | No | 7 |
| deCODE Breast Cancer™ | Reykjavik, Iceland | Yes | 7 |
| easyDNA | Elk Grove, CA | No[b] | ND |
| GenePlanet | Dublin, Ireland | Yes | 15 |
| Matrix Genomics | Santa Fe, NM | Yes | 6 |
| The Genetic Testing Laboratories | Las Cruces, NM | Yes | ND |

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 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 direct-to-consumer 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 2.04.02). 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. (4) 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 genome-wide association studies (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. (5) BREVAGen 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.

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.

**MEDICAL POLICY STATEMENT:**

BCNEPA will not provide coverage for the following:

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

The OncoVue® and BREVAGen™ breast cancer risk tests are considered investigational for all indications, including but not limited to use as a method of estimating individual patient risk for developing breast cancer.

**GUIDELINES:**

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 direct-to-consumer (DTC) genetic testing. On November 22, 2013, FDA issued a warning letter to 23andMe ordering it to "immediately discontinue marketing the Saliva Collection Kit and Personal Genome Service (PGS) until such time as it receives FDA marketing authorization for the device." (6) Currently, the test is available on the company website with the alert, "At this time we do not offer health-related genetic reports." (7) Current and new customers receive "ancestry-related information and raw genetic data without 23andMe's interpretation."

Under current regulations, 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 (eg, New York) have chosen to regulate DTC laboratories. Because these reviews are not public, the scientific standards applied are unknown.

Neither OncoVue® nor BREVAGen™ is offered over the Internet or directly to consumers. Patients may self-refer by finding the location of a participating member of the Breast Cancer Risk Testing Network, available on the InterGenetics website (for OncoVue®) or by using the BREVAGen Doctor Locator, available on the Phenogen Sciences website (for BREVAGen™), and making an appointment.

BRCA genetic testing should be used in those from high-risk families.

**RATIONALE:**

Clinical utility of 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. Clincal-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.

**Practice Guidelines and Position Statements**

National Comprehensive Cancer Network
Current guidelines from the National Comprehensive Cancer Network (NCCN) identify the following limitations of multigene cancer panels: unknown significance of some variants, uncertain level of risk associated with most variants, and unclear guidance on risk management for carriers of some variants. (101) For breast cancer risk assessment, the Gail model (102) or risk models for women with elevated risk based on family history (eg, Claus et al (103) or Tyrer-Cuzick et al (104)) are recommended. (101, 105)

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**DEFINITIONS:**

N/A

**CODING:**



- **The identification of a code in this section does not denote coverage or separate reimbursement.**
- Covered procedure codes are dependent upon meeting criteria of the policy and appropriate diagnosis code.
- The following list of codes may not be all-inclusive, and are subject to change at any time.
- Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

**PROCEDURE CODES**

81479 81599

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**APPROVALS:**

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