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Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Nonfamilial Breast Cancer

Policy # 00268
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers testing for 1 or more single nucleotide polymorphisms (SNPs) to predict an individual's risk of breast cancer to be **investigational.***

Based on review of available data, the Company considers the OncoVue®‡ and BREVAGen™‡ breast cancer risk tests for all indications, including but not limited to use as a method of estimating individual patient risk for developing breast cancer to be **investigational.***

Background/Overview

Several 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.

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.

Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Nonfamilial Breast Cancer

Policy # 00268
Original Effective Date: 09/15/2010
Current Effective Date: 09/17/2014

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

Company	Location	Test Offered DTC	Number of SNPs Used in Risk Panel
23andme	Mountain View, CA	Yes	7
City of Hope Breast Cancer Susceptibility Assay	Duarte, CA	No	7
deCODE BreastCancer™‡	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 [FDA] 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 DTC test. Both are listed in the Genetic Testing Registry of the National Center for Biotechnology Information.

Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Nonfamilial Breast Cancer

Policy # 00268
Original Effective Date: 09/15/2010
Current Effective Date: 09/17/2014

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. 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."

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.

Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Nonfamilial Breast Cancer

Policy # 00268
Original Effective Date: 09/15/2010
Current Effective Date: 09/17/2014

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
No SNP-based test to predict breast cancer risk has been approved or cleared by 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 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." Currently, the test is available on the company website with the alert, "At this time we do not offer health-related genetic reports." 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 (e.g., New York) have chosen to regulate DTC laboratories. Because these reviews are not public, the scientific standards applied are unknown.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Genome-wide association studies examine the entire genome of thousands of subjects for SNPs, single base-pair variations in the DNA sequence at semiregular intervals, and attempt to associate variant SNP alleles with particular diseases. Several case-control GWAS, primarily in white women, have investigated common risk markers of breast cancer. In recent years, several SNPs associated with breast cancer have been reported at a high level of statistical significance and have been validated in 2 or more large, independent studies. Recently, SNPs associated with breast cancer risk in Asian and African women have been the subject of more than a dozen articles, although these appear exploratory. GWAS also have identified SNPs in specific genes associated with the onset or severity of chemotherapy-induced toxicity.

SNP Panel Tests
As noted in the Background section, estimates of breast cancer risk, based on SNPs derived from large GWAS and/or from SNPs in other genes known to be associated with breast cancer, are available as laboratory-developed test services from different companies. The literature on these associations is growing, although information about the risk models is proprietary. Independent determination of clinical validity in an intended-use population to demonstrate clinical validity has not been performed. There are also no studies to suggest that use of SNP-based risk assessment has any impact on health care outcomes. No peer-reviewed reports have been published in which commercially available breast cancer

risk estimators have been compared with each other to determine if they report similar results on the same individuals, specifically for breast cancer.

Meta-Analyses
Several meta-analyses have investigated the association between breast cancer and various SNPs. Meta-analyses of case control studies have indicated that specific SNPs are associated with increased or decreased breast cancer risk (see Table 2). Other meta-analyses have revealed the interaction between environment (e.g., obesity, age at menarche) or ethnicity and breast cancer risk conferred by certain SNPs. Zhou et al (2013) found that a specific polymorphism in the vitamin D receptor gene increased breast cancer risk in African but not Caucasian women. Breast cancer risk associated with SNPs in microRNAs is commonly modified by ethnicity. Meta-analyses of GWAS have identified SNPs at new breast cancer susceptibility loci. All of these markers are considered to be in an investigational phase of development.

In 2014, the Breast Cancer Association Consortium published a mega-analysis of 46,450 case patients and 42,461 controls from 38 international meta-analytic studies. The authors assessed 2-way interactions among 3277 breast cancer-associated SNPs. Of 2.5 billion possible 2-SNP combinations, none were statistically significantly associated with breast cancer risk. The study suggests that risk models may be simplified by eliminating interaction terms. Nonetheless, the authors cautioned that despite the large sample size, the study may have been underpowered to detect very small interaction effects, which tend to be smaller than main effects.

Table 2. Results of Meta-Analyses of SNPs and Associations with Breast Cancer

SNP(s)	Association			Study
	Positive	None	Protective	
2q35 [rs13387042]	●			Gu 2013
8q24 [G-allele of rs13281615]	●			Gong 2013
8q24 [homozygous A-alleles of rs13281615]			●	
ATR-CHEK1 checkpoint pathway genes[a]		●		Lin 2013
Chemotactic cytokines[b]		●		Bodelon 2013
COMT [V158M]			●	He 2012
COX11 [rs6504950]			●	Tang 2012
CYP1A1 [T3801C]	●			He 2013
CYP1A2 1F [A-allele of rs762551]	●			Tian 2013
CYP19 [rs10046]		●		Pineda 2013

Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Nonfamilial Breast Cancer

Policy # 00268
Original Effective Date: 09/15/2010
Current Effective Date: 09/17/2014

Fibroblast growth factor receptor genes[c]		●		kConFab Investigators 2014
IL-10 [rs1800871]		●		Yu 2013
IRS1 [rs1801278]	●			Zhang 2013
MAP3K1 [C-allele of rs889312 and G-allele of rs16886165	●			Zheng 2014
MDR1 [C3435T]	●			Wang 2013
MTR [A2756G]	●	●		Zhong 2013
PON1 [L55M],	●			Saadat 2012
STK15 [F31I]	●			Qin 2013
STK15 [V571I]		●		
XRCC2 [R188H]		●		He 2014
XRCC3 [A17893G]			●	He 2012
XRCC3 [T241M]	●			
TCF7L2 [rs7903146]	●			Chen 201
VDR [rs731236]	●			Perna 2013

[a] 40 *ATR* and 50 *CHEK1* SNPs genotyped.

[b] 34 SNPs and groups of SNPs genotyped in 8 chemokine candidate genes: *CCL3*, *CCL4*, *CCL5*, *CCL20*, *CCR5*, *CCR6*, *CXCL12*, and *CXCR4*.

[c] 384 SNPs genotyped in *FGFR1*, *FGFR3*, *FGFR4*, and *FGFRL1*.

Primary Studies
Because there are no published studies of commercial SNP-based breast cancer risk predictors, published studies of the clinical usefulness of other similar SNP combinations as risk predictors will be considered here.

Aston et al (2005) evaluated more than 14,000 oligogenotypes, defined by 2 or more SNPs in 10 breast cancer-associated genes. The association with breast cancer was considered statistically significant for 37 oligogenotypes. The authors observed that oligogenic combinations of 2 to 10 SNPs were strongly associated with wide variation in breast cancer risk; that for many combinations, genes affected breast cancer risk in a manner not predictable from single gene effects; and that compared with individual SNPs, these combinations stratified risk over a broader range.

Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Nonfamilial Breast Cancer

Policy # 00268
Original Effective Date: 09/15/2010
Current Effective Date: 09/17/2014

In 2008, Pharoah et al considered a combination of 7 well-validated SNPs associated with breast cancer, 5 of which are included in the deCODE BreastCancer™‡ test. A model that simply multiplies the individual risks of the 7 common SNPs was assumed, and would explain approximately 5% of the total genetic risk of nonfamilial breast cancer. Applying the model to the population of women in the U.K., the risk profile provided by the 7 SNPs did not provide sufficient discrimination between those who would and would not experience future breast cancer to enable individualized preventive treatment such as tamoxifen. However, the authors suggested that a population screening program could be personalized with results of SNP panel testing. They concluded that no women would be included in the high-risk category (defined as 20% risk within the next 10 years at age 40 to 49 years, according to the National Institute for Health and Care Excellence), and therefore none would warrant the addition of MRI screening or consideration of more aggressive intervention.

Reeves et al (2010) evaluated the performance of a panel of 7 SNPs associated with breast cancer in 10,306 women with breast cancer and 10,383 without cancer in the U.K. The risk panel also contained 5 SNPs included in the deCODE BreastCancer test and used a similar multiplicative approach. Sensitivity studies were performed using only 4 SNPs and using 10 SNPs, both demonstrating no significant change in performance. Although the risk score showed marked differences in risk between the upper quintile of patients (8.8% cumulative risk to age 70 years) and the lower quintile of patients (4.4%), these changes were not viewed as clinically useful when compared with patients with an estimated overall background risk of 6.3%. Of note, simple information on patient histories; for example, presence of 1 or 2 first-degree relatives with breast cancer, provided equivalent or superior risk discrimination (9.1% and 15.4%, respectively).

It is assumed that many more genetic risk markers remain to be discovered because substantial unexplained heritability remains. Researchers from the Collaborative Oncological Gene-Environment Study group, a mega-consortium established to follow-up previous GWAS and candidate gene association studies, estimate that “more than 1000 additional loci are involved in breast cancer susceptibility.” One reason more genetic associations have not been found is that even large GWAS are underpowered to detect uncommon genetic variants.

Two approaches have recently been described to help address this problem. Braun and Buetow (2011) described a technique for multi-SNP analysis of GWAS data based on the study of patient cases selected using their association with known pathways related to disease risk. The authors coined the term Pathways of Distinction Analysis to describe this methodology and demonstrated that using this approach facilitated the identification of disease-related SNPs by creating clusters of similar variants within disease groups that stood out when compared with control groups.

In 2012, Silva et al reported on the use of DNA pooling methods to aid in detection of genetic polymorphisms. They combined DNA from many individuals (up to 200 patients or controls) into a single sample in an effort to preselect SNPs of interest in different populations. They concluded that test accuracy was sufficiently robust to allow use of pooling to estimate allelic distributions in populations of interest.

Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Nonfamilial Breast Cancer

Policy # 00268
Original Effective Date: 09/15/2010
Current Effective Date: 09/17/2014

Although there are no guidelines regarding the clinical use of SNP panels for estimating breast cancer risk, the published literature is in general agreement that their use in clinical or screening settings is premature due to a lack of a more complete set of explanatory gene variants and to insufficient discriminatory power at this time. Whether or not additional SNP studies are likely to be informative is under debate, as the study size to detect more and more rare variants becomes prohibitively large. As the cost of whole genome sequencing continues to decrease, some predict that this will become the preferred avenue for researching risk variants. Challenges to sorting through the growing literature on this diagnostic approach include nonstandardization and nontransparency of studies. Janssens et al (2011) published a methods paper providing a road map for optimal reporting and an accompanying detailed article describing good reporting practices.

In 2011, Bloss et al reported on the psychological, behavioral, and clinical effects of risk scanning in 3639 patients followed for a short time (mean [SD], 5.6 [2.4] months). These investigators evaluated anxiety, intake of dietary fat, and exercise based on information from genomic testing. There were no significant changes before and after testing and no increase in the number of screening tests obtained in enrolled patients. Although more than half of patients participating in the study indicated an intent to undergo screening in the future, during the course of the study itself, no actual increase was observed.

Section Summary
Common SNPs have been shown in primary studies and meta-analyses to be significantly associated with breast cancer risk; some SNPs convey slightly elevated risk of compared with the general population risk. Panels of SNPs are commercially available, with results synthesized into breast cancer risk estimates. These have not been clinically validated and clinical utility has not been demonstrated. Most of these tests are commercially available as direct-to-consumer (DTC) tests. Use of such risk panels for individual patient care or for population screening programs is premature because (1) performance of these panels in the intended-use populations is uncertain, and (2) most genetic breast cancer risk has yet to be explained by undiscovered gene variants and SNPs. Long-term prospective studies with large sample sizes are needed to determine the clinical validity and utility of SNP-based models for use in predicting breast cancer risk. The discrimination offered by the limited genetic factors currently known is insufficient to inform clinical practice.

Clinical Genetic Tests
OncoVue
The OncoVue test was developed by evaluating samples from a large case-control study for 117 common, functional polymorphisms, mostly SNPs, in candidate genes likely to influence breast carcinogenesis. A model using weighted combinations of 22 SNPs in 19 genes together with several Gail model (personal and family history characteristics) risk factors was subsequently identified by multiple linear regression analysis. OncoVue improved individual sample risk estimation, compared with the Gail model alone ($p<0.001$), by correctly placing more cases and fewer controls at elevated risk. In the same study, the model was validated on an independent sample set with similarly significant results. To date, this study has only been published in a meeting abstract; no details of the study or its results are available. Note that the Gail model

has been shown to accurately estimate the proportion of women (without a strong family history) who will develop cancer in large groups but is a poor discriminator of risk among individuals.

Using the same case control validation data, OncoVue was also compared with risk estimation determined by 7 SNPs reported in other GWAS; the GWAS risk scores were unable to stratify subjects by risk for breast cancer, whereas OncoVue significantly stratified patients by risk. This study has not been published. Independently, SNPs derived from GWAS are known to result in only low-level estimates of risk at best; in 1 example, a 14-SNP polygenic risk score yielded an odds ratio of only 1.3 for estrogen receptor (ER)-positive breast cancer and 1.05 for ER-negative breast cancer.

An additional analysis of the same case-control data was reported at the 2010 San Antonio Breast Cancer Symposium. The OncoVue risk score was calculated in the same discovery set (4768 Caucasian women, 1592 cases, 3176 controls) and 2 independent validation sets (1137 Caucasian women, 376 cases, 761 controls; 494 African American women, 149 cases, 345 controls). For both OncoVue and Gail model risk scores, positive likelihood ratios (proportion of patients with breast cancer with an elevated risk estimate [≥20%] divided by the proportion of disease-free subjects with an elevated risk estimate) were calculated. OncoVue exhibited a 1.6- to 1.8-fold improvement compared with the Gail model in more accurately assigning elevated risk estimates to breast cancer cases rather than controls. At higher risk thresholds, the fold improvement increased and exceeded 2.5 in some sample sets.

Does OncoVue testing improve the accuracy of breast cancer risk prediction beyond standard risk prediction measures?

The performance of OncoVue was studied in women from the Marin County, CA, Breast Cancer Adolescent Risk Factor study. A retrospective case control study was developed within the cohort, and samples were evaluated with OncoVue testing. OncoVue assigned high-risk status (defined as ≥12% lifetime risk of developing breast cancer) to 19 more women who had had breast cancer (of 169 cases) than did the Gail model, which represented an approximately 50% improvement. OncoVue was also more effective at stratifying risk in the high-risk Marin County population than 7 SNPs reported in other GWAS. These studies have not yet been published in a peer-reviewed journal.

Several supportive studies are listed on the InterGenetics, Inc. website; most are meeting abstracts. These address conceptual aspects of the OncoVue test but do not appear to report data using the final OncoVue test configuration. One fully published study characterizes SNPs that exhibit breast cancer risk associations that vary with age. This study stratified breast cancer cases and normal controls into 3 age groups, then determined breast cancer risk for SNP homozygotes and heterozygotes for each of 18 candidate SNPs within each age group. Of these, 5 SNP variants had statistically significant odds ratios for at least 1 age group. In a separate validation sample, only 1 had a statistically significant odds ratio but not in a pattern similar to that of the discovery set. The other 4 SNPs, although not significant, were judged to have patterns of results similar to that of the discovery set and were investigated further by a sliding 10-year window strategy, the results of which the authors suggest clarify age-specific breast cancer risk associations. The authors note the need for additional validation in other populations and nonwhite ethnicities.

Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Nonfamilial Breast Cancer

Policy # 00268
Original Effective Date: 09/15/2010
Current Effective Date: 09/17/2014

Do results of OncoVue testing lead to changes in management that result in health outcome improvements?

The medical management implications of this test are unclear. The Gail model was originally designed for use in clinical trials, not for individual patient care and management. Thus using the Gail model as a baseline for comparison may not be sufficiently informative. In addition, no evidence of improved outcomes as a result of management changes in OncoVue-identified high-risk patients has been presented or published. The OncoVue sample report makes no recommendations regarding patient management. The InterGenetics Inc. website makes this statement regarding test results: "A Moderate to High Risk result gives a woman several options: More comprehensive surveillance for breast cancer with mammograms, ultrasound and now Magnetic Resonance Imaging-MRI. Earlier detection means better long-term survival. Breast cancer prevention drugs like Tamoxifen can actually reduce breast cancer in high risk women."

A pilot study using buccal samples from women in the Marin County, CA retrospective case control study previously described aimed to examine the genotypes of subjects determined to be high risk (≥12%) by OncoVue. Of 22 SNPs assessed by the OncoVue assay, one (rs7975232 in the vitamin D receptor gene) occurred significantly more often in high-risk cases than in the overall (all cases plus controls) sample (64% vs 34%; $p<0.001$); however, the incidence among all cases (29%) was less than that among controls (39%). The authors postulate a potential prevention strategy using vitamin D supplementation in women with this genotype. Although recent retrospective studies support an association between sunlight exposure, elevated serum levels of vitamin D (25[OH]D)/vitamin D supplementation, and reduced risk of breast cancer, prospective uncontrolled studies gave mixed results (positive or no association).(94,95) Clinical trials demonstrating improved health outcomes in patients identified as high risk due to OncoVue detection of the rs7975232 SNP who were subsequently treated with vitamin D supplementation have not been reported.

BREVAGen
In 2010, Mealiffe et al published a clinical validation study of the BREVAGen test. The authors evaluated a 7-SNP panel in a nested case control cohort of 1664 case patients and 1636 controls. A model that multiplied the individual risks of the 7 SNPs was assumed, and the resulting genetic risk score was assessed as a potential replacement for or add-on test to the Gail clinical risk model. The net reclassification improvement was used to evaluate performance. Combining 7 validated SNPs with the Gail model resulted in a modest improvement in classification of breast cancer risks, but area under the curve (AUC) only increased from 0.557 to 0.594 (0.50 represents no discrimination, 1.0 perfect discrimination). The impact of reclassification on net health outcome was not evaluated. The authors suggested that best use of the test might be in patients who would benefit from enhanced or improved risk assessment, eg those classified as intermediate risk by the Gail model.

Information about analytic validity of the BREVAGen test is provided in the published study, but is indeterminate. Genomic DNA samples were analyzed on custom oligonucleotide arrays (Affymetrix Inc., Santa Clara, CA). Mean concordance across duplicate samples included for quality control was 99.8%; breast cancer loci had call rates (a measure of SNP detection) above 99%. For approximately 70% of

samples with sufficient DNA available, whole genome amplification also was carried out using the Sequenom (San Diego, CA) MassARRAY platform. Across samples that had not been excluded for lack of DNA or poor quality data (proportion not reported), concordance between the 2 assays was 97%, and the resulting call rate was 96.8%. Genotype data for 121 samples that had 1 or more inconsistencies between the Sequenom analysis, and the corresponding custom array genotype were excluded. Conflicting calls were not differentially distributed across case patients and controls. The authors acknowledged that the 2 assays performed "relatively poorly," but asserted that consensus calls were nonetheless accurate.

In 2013, Dite et al published a similar case control study of the same 7 SNPs assuming the same multiplicative model (based on independent risks of each SNP). Predictive ability of the Gail model with and without the 7 SNP panel was compared in 962 case patients and 463 controls, all 35 years of age or older (mean age, »45 years). AUC of the Gail model was 0.58 (95% confidence interval [CI], 0.54 to 0.61); in combination with the 7-SNP panel, AUC increased to 0.61 (95% CI, 0.58 to 0.64; bootstrap resampling, p<0.001). In reclassification analysis, 12% of cases and controls were correctly reclassified and 9% of cases and controls were incorrectly reclassified when the 7-SNP panel was added to the Gail model. Risk classes were defined by 5-year risk of developing breast cancer (<1.5%, ≥1.5% to <2.0%, and ≥2.0%). Although addition of the 7-SNP panel to the Gail model improved predictive accuracy, the magnitude of improvement is small, the overall accuracy is moderate, and the impact on health outcomes is uncertain.

Other Clinical Genetic Tests

Other large studies have evaluated 8 to 18 common, candidate SNPs breast cancer cases and normal controls to determine whether breast cancer assessments based on clinical factors plus various SNP combinations were more accurate than risk assessments based on clinical factors alone.

- Zheng et al found that 8 SNPs, combined with other clinical predictors, were significantly associated with breast cancer risk; the full model gave an AUC of 0.63.
- Campa et al evaluated 17 SNP breast cancer susceptibility loci for any interaction with established risk factors for breast cancer but found no evidence that the SNPs modified the associations between established risk factors and breast cancer. The results of these studies support the concept of OncoVue but do not represent direct evidence of its clinical validity or utility.
- Wacholder et al evaluated the performance of a panel of 10 SNPs associated with breast cancer that had, at the time of the study, been validated in at least 3 published GWAS. Cases (n=5590) and controls (n=5998) from the National Cancer Institute's Cancer Genetic Markers of Susceptibility GWAS of breast cancer were included in the study (women of primarily European ancestry). The SNP panel was examined as a risk predictor alone and in addition to readily available components of the Gail model (e.g., diagnosis of atypical hyperplasia was not included). Mammographic density also was not included. The authors found that adding the SNP panel to the Gail model resulted in slightly better stratification of a woman's risk than either the SNP panel or the Gail model alone but that this stratification was not adequate to inform clinical practice. For example, only 34% of the women who actually had breast cancer were assigned to the top 20% risk group. AUC for the combined SNP and Gail model was 62% (50% is random, 100% is perfect).
- Darabi et al investigated the performance of 18 breast cancer risk SNPs, together with mammographic percentage density (PD), body mass index (BMI), and clinical risk factors in

predicting absolute risk of breast cancer, empirically, in a well-characterized case-control study of postmenopausal Swedish women. Performance of a risk prediction model based on an initial set of 7 breast cancer risk SNPs was improved by including 11 more recently established breast cancer risk SNPs ($p=4.69\times10^{-4}$). Adding mammographic PD, BMI and all 18 SNPs to a modified Gail model improved the discriminatory accuracy (the AUC statistic) from 55% to 62%. The net reclassification improvement was used to assess improvement in classification of women into 5-year low-, intermediate-, and high-risk categories ($p=8.93\times10^{-9}$). It was estimated that using an individualized screening strategy based on risk models incorporating clinical risk factors, mammographic density, and SNPs, would capture 10% more cases. Impacts on net health outcomes from such a change are unknown.

- Armstrong et al examined the impact of pretest breast cancer risk prediction on the classification of women with an abnormal mammogram above or below the risk threshold for biopsy. Currently, 1-year probability of breast cancer among women with Breast Imaging–Reporting and Data System (BI-RADS) category 3 mammograms is 2%; these women undergo 6-month follow-up rather than biopsy. In contrast, women with BI-RADS4 mammograms have a 6% (BI-RADS 4A) or greater (BI-RADS 4B and 4C) probability of developing breast cancer in 1 year; these women are referred for biopsy. Using the Gail model plus 12 SNPs for risk prediction and a 2% biopsy risk threshold, 8% of women with a BI-RADS3 mammogram were reclassified above the threshold for biopsy and 7% of women with BI-RADS4A mammograms were reclassified below the threshold. The greatest impact on reclassification was attributed to standard breast cancer risk factors. Net health outcomes were not compared between women who were reclassified and those who were not.

Although results of these studies support the concept of clinical genetic tests, they do not represent direct evidence of their clinical validity or utility.

Section Summary
There is a lack of published detail regarding OncoVue and BREVAGen test validation, supportive data, and management implications. Available data suggest that OncoVue and BREVAGen may add predictive accuracy to the Gail model. However, the degree of improved risk prediction may be modest, and clinical implications are unclear. There is insufficient evidence to determine whether using breast cancer risk estimates from OncoVue or BREVAGen in asymptomatic individuals changes management decisions and improves patient outcomes.

Ongoing Clinical Trials
An online search of ClinicalTrials.gov identified the following active studies:

- A U.S. prospective cohort study on SNP panels and risk assessment in women undergoing mammography (NCT01124019): The primary objective of this study is to compare predicted lifetime risk by SNP analysis with predicted lifetime risk by commonly used prediction models. Estimated completion date was February 2013; however, this study is currently listed as recruiting participants, with an estimated enrollment of 1600 women.
- A prospective cohort trial by the University of Kansas in collaboration with InterGenetics (NCT00329017): The purpose of the trial is to examine potential associations between SNPs and

cytomorphology in breast tissue specimens from postmenopausal women. Estimated completion date is May 2014.

- A Canadian cohort study (NCT00122239) is examining gene polymorphisms associated with normal tissue radiation injury in patients treated for breast, prostate, brain, lung, and head and neck cancers. Data collection was completed in 2014.
- An Italian pharmacogenetic study (NCT01935102) aims to identify SNPs in vascular endothelial growth factor-A (VEGF-A) associated with bevacizumab response. Estimated completion date is December 2014.

Summary
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. 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.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81599

Use of Common Genetic Variants (single nucleotide polymorphisms) to Predict Risk of Nonfamilial Breast Cancer

Policy # 00268
Original Effective Date: 09/15/2010
Current Effective Date: 09/17/2014

HCPCS	No codes
ICD-9 Diagnosis	174.0 thru 174.9, 175.0, 175.9, 233.0, V16.3
ICD-9 Procedure	No codes

Policy History

Original Effective Date: 09/15/2010
Current Effective Date: 09/17/2014

09/09/2010	Medical Policy Committee review
09/15/2010	Medical Policy Implementation Committee approval. New policy.
09/01/2011	Medical Policy Committee review
09/14/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2012	Medical Policy Committee review
09/19/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/19/2013	Coding updated
09/05/2013	Medical Policy Committee review
09/18/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. Title changed to "Use of Common Genetic Variants (SNPs) to Predict Risk of Nonfamilial Breast Cancer." Investigational policy statement for OncoVue and BREVAGen modified to indicate investigational for all indications. Combined with Non-BRCA-Breast Cancer Risk Assessment (e.g., OncoVue).

Next Scheduled Review Date: 09/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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