Use of Common Genetic Variants (Single NucleotideVariants) to Predict Risk of Nonfamilial Breast Cancer

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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 variants (SNVs) to predict an individual's risk of breast cancer to be **investigational.***

Based on review of available data, the Company considers the BREVAGen*plus*®‡ breast cancer risk test 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

GENE VARIANTS AND BREAST CANCER RISK

Rare, single-gene variants conferring a high risk of breast cancer have been linked to hereditary breast cancer syndromes. Examples are variants 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 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

BREVAGenplus

BREVAGen*plus* evaluates breast cancer-associated SNVs identified in genome-wide association studies. The first-generation test, BREVAGen, included 7 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. BREVAGen*plus* has been evaluated for use in African-American, white, and Hispanic patient samples age 35 years and older. BREVAGen*plus* does not detect known high-risk variants (eg, in *BRCA*). According to the 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 or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). BREVAGen*plus* (Phenogen Sciences, a subsidiary of Genetic Technologies, Melbourne, Australia) is available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

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 clinical validity or clinical utility. Some states (eg, New York) have chosen to regulate direct-to-consumer 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

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) analytic validity (including test-retest reliability); (2) clinical validity (sensitivity, specificity, positive and negative predictive values) in relevant populations of patients; and (3) clinical utility (ie, demonstration that the information can be used to improve patient outcomes).

SINGLE NUCLEOTIDE VARIANTS AND BREAST CANCER RISK

Clinical Context and Test Purpose

The purpose of genetic testing in asymptomatic individuals is to predict the risk of disease occurrence. The criteria under which prognostic testing may be considered clinically useful are as follows:

- An association of the marker with the disease has been established; and

- The clinical utility of identifying the variants has been established (eg, by demonstrating that testing will lead to changes in surveillance).

The question addressed in this evidence review is: Does testing of common genetic variants in breast cancer tumor improve the net health outcome?

The specific clinical context of each test is described briefly in the following section. The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals who have not been identified as being at high risk of breast cancer. This population would include individuals who do not have a family member who had breast cancer.

Interventions
The intervention of interest is the BREVAGen*plus* test.

Comparator
The comparator of interest is standard clinical risk prediction without testing for common SNVs associated with risk of breast cancer.

Outcomes
The outcomes of interest are reclassification of individuals from normal risk and evidence of a change in management (eg, preventative or screening strategies) that result in improved health outcomes.

Time
The time of interest is 5 to 10 years to evaluate the occurrence of breast cancer.

Setting
This test is offered commercially and requires a physician's prescription.

Analytic Validity
Information about the analytic validity of the BREVAGen*plus* 7 SNV test was provided in a published study by Mealiffe et al (2010), but is indeterminate. Genomic DNA samples were analyzed on custom oligonucleotide arrays (Affymetrix, Santa Clara, CA). The mean concordance across duplicate samples included for quality control was 99.8%; breast cancer loci had call rates (a measure of SNV detection) above 99%. For approximately 70% of samples with sufficient DNA available, whole genome amplification 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.

Section Summary: Analytic Validity
Evidence of the analytic validity of the BREVAGen*plus* 7 SNV test is limited. Discordance between BREVAGen*plus* and an orthogonal technology was noted in a published study. The analytic validity of BREVAGen*plus* is therefore uncertain.

Clinical Validity
SNVs and Breast Cancer
Genome-wide association studies (GWAS) examine the entire genome of thousands of subjects for SNVs at semiregular intervals, and attempt to associate variant SNV alleles with particular diseases. Several case-control GWAS, primarily in white women, have investigated common-risk markers of breast cancer. A number of SNVs associated with breast cancer have been reported at a high level of statistical significance and have been validated in two or more large, independent studies. SNVs associated with breast cancer risk in Asian and African women have been the subject of more than a dozen articles.

A number of meta-analyses have investigated the association between breast cancer and individual SNVs. Meta-analyses of case-control studies have indicated that specific SNVs are associated with increased or decreased breast cancer risk (see Table 1). Other meta-analyses have revealed the interaction between environment (eg, obesity, age at menarche) or ethnicity and breast cancer risk conferred by certain SNVs. Zhou et al (2013) found that a specific variant in the vitamin D receptor gene increased breast cancer risk in African-American but not white women. Breast cancer risk associated with SNVs in microRNAs is commonly modified by ethnicity. Meta-analyses of GWAS have identified SNVs 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. Reviewers assessed 2-way interactions among 3277 breast cancer-associated SNVs. Of 2.5 billion possible 2-SNV combinations, none were statistically significantly associated with breast cancer risk. The meta-analysis suggested that risk models may be simplified by eliminating interaction terms. Reviewers cautioned that despite the large sample size, the study might have been underpowered to detect very small interaction effects, which tend to be smaller than main effects.

In 2014, the Breast and Prostate Cancer Cohort Consortium published a meta-analysis of 8 prospective cohort studies conducted in the United States, Europe, and Australia to examine 2-way interactions between genetic and established clinical risk factors. Based on published GWAS, 23 SNVs were selected for analysis in 10,146 cases of invasive breast cancer and 12,760 controls. Patients were of European ancestry and matched on age and other factors specific to each study. After correction for multiple

comparisons, a statistically significant excess in relative risk was attributed to the interaction between rs10483813 variants in the *RAD51L1* gene and body mass index (BMI).

Table 1. Examples of Meta-Analyses of SNVs and Associations With Breast Cancer

SNVs	Association			Study (Year)
	Positive	None	Protective	
2q35 [rs13387042]	●			Gu et al (2013)
8q24 [G-allele of rs13281615]	●			Gong et al (2013)
8q24 [homozygous A-alleles of rs13281615]			●	Gong et al (2013)
AKAP9 [M463I]	●			Milne et al (2014)
ATR-CHEK1 checkpoint pathway genes[a]		●		Lin et al (2013)
ATXN7 [K264R]	●			Milne et al (2014)
Chemotactic cytokines[b]		●		Bodelon et al (2013)
COMT [V158M]			●	He et al (2012)
COX2 [rs20417]	●			Dai et al (2014)
COX2 [rs689466]			●	Dai et al (2014)
COX2 [rs5275]		●		Dai et al (2014)
COX11 [rs6504950]			●	Tang et al (2012)
CYP1A1 [T3801C]	●			He et al (2014)
CYP1A2 1F [A-allele of rs762551]	●			Tian et al (2013)
CYP19 [rs10046]		●		Pineda et al (2013)
Fibroblast growth factor receptor genes[c]		●		kConFab Investigators (2014)
IL-10 [rs1800871]		●		Yu et al (2013)
IRS1 [rs1801278]	●			Zhang et al (2013)
MAP3K1 [C-allele of rs889312 and G-allele of rs16886165]	●			Zheng et al (2014)
MDM2 [rs2279744]	●			Gao et al (2014)
MDR1 [C3435T]	●			Wang et al (2013)
MTR [A(2756G]	●	●		Zhong et al (2013)
PON1 [L55M]	●			Saadat et al (2012)
STK15 [F31I]	●			Qin et al (2013)
STK15 [V571I]		●		Qin et al (2013)
TCF7L2 [rs7903146]	●			Chen et al (2013)
VDR [rs731236]	●			Perna et al (2013)
VDR [rs2228570]	●			Zhang et al (2014)
VEGF [C936T]		●		Li et al (2015)
XRCC2 [R188H]		●		He et al (2014)
XRCC3 [A17893G]			●	He et al (2012)
XRCC3 [T241M]	●			He et al (2012)

SNV: single nucleotide variant.
[a] Forty *ATR* and 50 *CHEK1* SNVs genotyped.
[b] Thirty-four SNVs and groups of SNVs genotyped in 8 chemokine candidate genes: *CCL3*, *CCL4*, *CCL5*, *CCL20*, *CCR5*, *CCR6*, *CXCL12*, and *CXCR4*.
[c] Three hundred eighty-four SNVs genotyped in *FGFR1*, *FGFR3*, *FGFR4*, and *FGFRL1*.

Primary Studies

In 2008, Pharoah et al considered a combination of 7 well-validated SNVs 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 SNVs was assumed; such a model 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 SNVs 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 SNV 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 magnetic resonance imaging screening or consideration of more aggressive intervention.

Reeves et al (2010) evaluated the performance of a panel of 7 SNVs 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 SNVs included in the deCODE BreastCancer test and used a similar multiplicative approach. Sensitivity studies were performed using only 4 SNVs and using 10 SNVs, 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%. Simple information on patient histories was noted; eg, the presence of 1 or 2 first-degree relatives with breast cancer provided equivalent or superior risk discrimination (9.1% and 15.4%, respectively).

Many more genetic risk markers remain to be discovered because substantial unexplained heritability remains. In 2013, researchers from the Collaborative Oncological Gene-Environment Study group, a mega-consortium established to follow-up previous GWAS and candidate gene association studies, identified 41 additional SNVs that were associated with breast cancer and estimated 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. As the cost of whole genome sequencing continues to decrease, some predict that this will become the preferred avenue for researching risk variants.

BREVAGen and BREVAGenplus

In 2010, Mealiffe et al published a clinical validation study of the BREVAGen test. The authors evaluated a 7-SNV panel in a nested case-control cohort of 1664 case patients and 1636 controls. A model that multiplied the individual risks of the 7 SNVs 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 SNVs with the Gail model resulted in a modest improvement in classification of breast cancer risks, but the 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.

In 2013, Dite et al published a similar case-control study of the same 7 SNVs, assuming the same multiplicative model (based on independent risks of each SNV). The predictive ability of the Gail model with and without the 7 SNV 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-SNV 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-SNV 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-SNV panel to the Gail model improved predictive accuracy, the magnitude of improvement is small, overall accuracy is moderate, and impact on health outcomes is uncertain.

A 2015 study by Allman et al included 7539 African American and 3363 Hispanic women from the Women's Health Initiative. Adding a risk score based on over 70 susceptibility loci improved risk prediction by about 10% to 19% over the Gail model and 18% to 26% over the International Breast Cancer Intervention Study risk prediction for African Americans and Hispanics, respectively.

Other Clinical Genetic Tests

In 2015, Mavaddat et al reported a multicenter study that assessed risk stratification using 77 breast cancer–associated SNVs in 33,673 breast cancer cases and 33,381 control women of European descent. Polygenic risk scores were developed based on an additive model plus pairwise interactions between SNVs. Women in the highest 1% of the polygenic risk score had a 3-fold increased risk of developing breast cancer compared with women in the middle quintile (odds ratio, 3.36; 95% CI, 2.95 to 3.83). Lifetime risk of breast cancer was16.6% for women in the highest quintile of the risk score compared with 5.2% for women in the lowest quintile. The discriminative accuracy was 0.622 (95% CI, 0.619 to 0.627).

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

- Zheng et al (2010) found that 8 SNVs, combined with other clinical predictors, were significantly associated with breast cancer risk; the full model gave an AUC of 0.63.
- Campa et al (2011) evaluated 17 SNV breast cancer susceptibility loci for any interaction with established risk factors for breast cancer but found no evidence that the SNVs modified the associations between established risk factors and breast cancer.
- Wacholder et al (2010) evaluated the performance of a panel of 10 SNVs 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 SNV panel was examined as a risk predictor alone and in addition to readily available components of the Gail model (eg, diagnosis of atypical hyperplasia was not included). Mammographic density also was not included. The authors found that adding the SNV panel to the Gail model resulted in slightly better stratification of a woman's risk than either the SNV 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 had breast cancer were assigned to the top 20% risk group. AUC for the combined SNV and Gail model was 62% (50% is random, 100% is perfect).

- Darabi et al (2012) investigated the performance of 18 breast cancer risk SNVs, together with mammographic percentage density, 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 SNVs was improved by including 11 more recently established breast cancer risk SNVs ($p<0.001$). Adding mammographic percentage density, BMI and all 18 SNVs 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 ($p<0.001$). It was estimated that using an individualized screening strategy based on risk models incorporating clinical risk factors, mammographic density, and SNVs, would capture 10% more cases. Impacts on net health outcomes from such a change are unknown.
- Armstrong et al (2013) 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-RADS category 4 mammograms have a 6% (BI-RADS category 4A) or greater (BI-RADS categories 4B and 4C) probability of developing breast cancer in 1 year; these women are referred for biopsy. Using the Gail model *plus* 12 SNVs for risk prediction and a 2% biopsy risk threshold, 8% of women with a BI-RADS category 3 mammogram were reclassified above the threshold for biopsy, and 7% of women with BI-RADS category 4A 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: Clinical Validity

Common SNVs have been shown in primary studies and meta-analyses to be significantly associated with breast cancer risk; some SNVs convey slightly elevated risk compared with the general population risk. Estimates of breast cancer risk, based on SNVs derived from large GWAS and/or from SNVs in other genes

known to be associated with breast cancer, are available as a laboratory-developed test service. The literature on these associations is growing, although information about the risk models is proprietary. Available data suggest that BREVAGen*plus* may add predictive accuracy to the Gail model. However, the degree of improved risk prediction may be modest, and clinical implications are unclear. Independent determination of clinical validity in an intended-use population has not been performed. Use of such risk panels for individual patient care or 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 SNVs.

Clinical Utility
One potential use of SNV testing is to evaluate the risk of breast cancer for chemoprevention. In 2017, Cuzick et al assessed whether a panel of 88 SNVs could improve risk prediction over traditional risk stratification using data from 2 randomized tamoxifen prevention trials. The study included 359 cases and 636 controls, with the 88 SNVs assessed on an Illumina OncoArray that evaluated approximately half a million SNVs. The primary outcome was breast cancer or ductal carcinoma in situ. The 88 SNV score improved discriminability above the Tyrer-Cuzick risk evaluator; however, there was modest improvement in the percentage of women who were classified as high risk. The percentage of women with a 10-year risk of recurrence of 8% or more was estimated to be 18% for Tyrer-Cuzick and 21% when the 88 SNV score was added. The SNV score did not predict which women would benefit from tamoxifen.

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, 5.6 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 study itself, no actual increase was observed.

In 2015, McCarthy et al examined the impact of BMI, Gail model risk, and a 12-SNV version of the deCODE BreastCancer test on breast cancer risk prediction and biopsy decisions among women with BI-RADS category 4 mammograms who had been referred for biopsy (N=464). The original deCODE BreastCancer panel included 7 SNVs; neither panel is currently commercially available. The mean patient age was 49 years, 60% were white, and 31% were black. In multivariate regression models that included age, BMI, Gail risk factors, and SNV panel risk as a continuous variable, a statistically significant association between SNV panel risk and breast cancer diagnosis was observed (odds ratio, 2.30; 95% CI, 1.06 to 4.99; p=0.035). However, categorized SNV panel risks (eg, relative increase or decrease in risk compared with the general population), resembling how the test would be used in clinical practice, were not statistically associated with breast cancer diagnosis. In subgroups defined by black or white race, SNV panel risk also was not statistically associated with breast cancer diagnosis. Risk estimated by a model that included age, Gail risk factors, BMI, and the SNV panel, reclassified 9 (3.4%) women below a 2% risk threshold for biopsy, none of whom were diagnosed with cancer.

Section Summary: Clinical Utility
The number of common low-penetrance SNVs associated with breast cancer is rapidly increasing. No studies were identified that provide direct evidence that use of SNV-based risk assessment has any impact on health care outcomes. Indirect evidence from an improvement in risk prediction with an 88 SNV panel has been reported, although the improvement in risk prediction is modest.

For the specific loci evaluated by the most recent BREVAGen*plus* test, there is insufficient evidence to determine whether using breast cancer risk estimates in asymptomatic individuals changes management decisions and improves patient outcomes.

SUMMARY OF EVIDENCE
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.

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Policy History

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Current Effective Date: 11/21/2018

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).
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. BREVAGenplus replaces BREVAGen test in the policy.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. "Polymorphisms" changed to "variants" throughout policy. OncoVue removed from policy; it is no longer commercially available.

Next Scheduled Review Date: 11/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA).

Use of Common Genetic Variants (Single NucleotideVariants) to Predict Risk of Nonfamilial Breast Cancer

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CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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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			
HCPCS	No codes			
ICD-10 Diagnosis	C50.011-C50.029	C50.111-C50.129	C50.211-C50.229	C50.311-C50.329
	C50.411-C50.429	C50.511-C50.529	C50.611-C50.629	C50.811-C50.829
	C50.911-C50.929	D05.00-D05.02	D05.10-D05.12	D05.80-D05.82
	D05.90-D05.92	Z80.3		

*****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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