Kansas City

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# Non-BRCA Breast Cancer Risk Assessment (e.g., OncoVue)

**Policy Number:** 2.04.57
**Origination:** 12/2013
**Last Review:** 12/2013
**Next Review:** 12/2014

## Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for non-BRCA Breast Cancer Risk Assessment. This is considered investigational.

Note: This is a type of genetic testing that may be excluded in some contracts. Verify benefits prior to review for Medical Necessity.

## When Policy Topic is covered

Not Applicable

## When Policy Topic is not covered

The OncoVue® and BREVAGen™ breast cancer risk tests are considered **investigational** as a method of estimating individual patient risk for developing breast cancer.

## Description of Procedure or Service

Tests that incorporate both clinical and genetic information have been developed to provide predictive information about breast cancer risk in asymptomatic women. Current methods of assessing breast cancer risk are imperfect, and genetic testing may offer improvements on current ability to assess breast cancer risk.

### Background

*OncoVue*®

The OncoVue® Breast Cancer Risk Test (InterGenetics, Inc., Oklahoma City, OK) is a proprietary test that evaluates multiple, low-risk single nucleotide polymorphisms (SNPs) associated with breast cancer. The results are incorporated along 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 the 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 prior to 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.

The OncoVue® test 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 capability of providing patient education on genetic testing and future risk management protocols. As of July 2013, 32 participating centers (36 locations), located in 20 states, were listed on the company website. OncoVue® is not listed in the Genetic Testing Registry of the National Center for Biotechnology Information.

*BREVAGen™*
BREVAGen™ 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, e.g., 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 (e.g., 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, 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.

As of July 2013, approximately 40 participating centers in 17 states were listed on the company website. BREVAGen™ is listed in the Genetic Testing Registry of the National Center for Biotechnology Information.

### Regulatory Status

No test combining the results of SNP analysis with clinical factors to predict breast cancer risk has been approved or cleared by the U.S. Food and Drug Administration (FDA). These are offered as laboratory-developed tests; that is, tests developed and used at a single testing site. Laboratory developed tests, as a matter of enforcement discretion, have not been traditionally regulated by FDA in the past. They do require oversight under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), and the development and use of laboratory developed tests is restricted to laboratories certified as high complexity under CLIA.

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.

## Rationale

### Introduction
Validation of genotyping to improve treatment outcomes is a multistep process. In general, important steps in the validation process address the following:

- **Analytic validity**: measures technical performance, i.e., whether the test accurately and reproducibly detects the gene markers of interest.
- **Clinical validity**: measures the strength of the associations between the selected genetic markers and clinical status.
- **Clinical utility:** determines whether the use of genotyping for specific genetic markers to guide treatment decisions improves patient outcomes such as survival or adverse event rate compared to standard treatment without genotyping.

### Literature Review
An updated literature search was performed using the MEDLINE database for the period of June 1, 2012 through June 24, 2013.

*OncoVue®*

The OncoVue® test was developed by evaluating samples from a large case-control study for 117 common, functional polymorphisms, mostly single nucleotide polymorphisms (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 to the Gail Model alone ($p<0.0001$), by correctly placing more cases and fewer controls at elevated risk. (1) 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. (2)

Using the same case-control validation data, OncoVue was also compared to risk estimation determined by 7 SNPs reported in other GWAS (3); the GWAS risk scores were unable to stratify individuals 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 one 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. (4)

An additional analysis of the same case-control data was reported at the 2010 San Antonio Breast Cancer Symposium. (5) The OncoVue risk score was calculated in the same discovery set (4,768 Caucasian women, 1,592 cases and 3,176 controls) and 2 independent validation sets (1,137 Caucasian women, 376 cases and 761 controls; 494 African American women, 149 cases and 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 individuals with an elevated risk estimate) were calculated. OncoVue exhibited a 1.6- to 1.8-fold improvement compared to 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. (6) OncoVue was also more effective at stratifying risk in the high-risk Marin County population than 7 SNPs reported in other GWAS. (7) 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. (8) 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 non-white ethnicities.

*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. (9) 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 described above aimed to examine the genotypes of individuals determined to be high risk (≥12%) by OncoVue®. (10) 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). (11, 12) 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™*

One clinical validation study of the BREVAGen test has been published: Mealiffe et al. (13) evaluated a 7-SNP panel in a nested case-control cohort of 1,664 case patients and 1,636 controls. A model that multiplied the individual risks of the 7 SNPs was assumed. The genetic risk score was assessed as a potential replacement for or add-on test to the Gail clinical risk model. The authors concluded that combining 7 validated SNPs with the Gail model resulted in a modest improvement in classification of breast cancer risks, but area under the curve 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.

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 available DNA, 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 two assays was 97%, and the resulting call rate was 96.8%. Genotype data for 121 samples that had one 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 control subjects. The authors acknowledge that the two assays performed "relatively poorly," but assert that consensus calls are nonetheless accurate.

*Other Clinical-Genetic Tests*

Other published studies have evaluated 8-18 common, candidate SNPs in a large number of 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. (14) found that 8 SNPs, combined with other clinical predictors, were significantly associated with breast cancer risk; the full model gave an area under the curve of 0.63.
- Campa et al. (15) 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. (16) evaluated the performance of a panel of 10 SNPs with established associations with breast cancer validated in at least 3 published GWAS. Cases (n=5,590) and controls (n=5,998) 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. The area under the curve (AUC) for the combined SNP and Gail model was 61.8% (50% is random, 100% is perfect).
- Darabi et al. (17) 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. The 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 ($p=4.69 \times 10^{-4}$). 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 low, intermediate, and high categories of 5-year risk ($p=8.93 \times 10^{-9}$). 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. The net health outcomes of such a change remain unknown.
- Armstrong et al. (18) examined the impact of pre-test 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.

The results of these studies support the concept of clinical-genetic tests but do not represent direct evidence of their clinical validity or utility.

**Ongoing Clinical Trials**

A prospective cohort trial is underway by University of Kansas in collaboration with InterGenetics (NCT00329017, online at: http://www.clinicaltrials.gov/ct2/show/NCT00329017). The purpose of the trial is to examine the potential associations between SNPs and cytomorphology in breast tissue specimens from postmenopausal women. The trial ceased recruitment in 2010, and as of July 2013, the results of this study are pending.

## Summary

There is a lack of published detail regarding OncoVue® and BREVAGen™ test validation, supportive data, and management implications. The 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 the 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. Therefore, OncoVue and BREVAGen testing for breast cancer risk assessment are considered investigational.

## Practice Guidelines and Position Statements

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.(19) For breast cancer risk assessment, the Gail model (20) or risk models for women with elevated risk based on family history (e.g., Claus et al. (21) or Tyrer-Cuzick et al. (22)) are recommended.(23, 24)

## Medicare National Coverage

No national coverage determination.

References


1. Jupe ER, Ralph DA, Manjeshwar S. The OncoVue model for predicting breast cancer risk. 2007 San Antonio Breast Cancer Symposium; Abstract 4038.
2. Cummings SR, Tice JA, Bauer S et al. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. J Natl Cancer Inst 2009; 101(6):384-98.
3. Jupe ER, Pugh TW, Knowlton NS. Breast cancer risk estimation using the OncoVue model compared to combined GWAS single nucleotie polymorphisms. 2009 San Antonio Breast Cancer Symposium; Abstract 3177.
4. Reeves GK, Travis RC, Green J et al. Incidence of breast cancer and its subtypes in relation to individual and multiple low-penetrance genetic susceptibility loci. JAMA 2010; 304(4):426-34.
5. Jupe E, Pugh T, Knowlton N et al. Accurate Identification of Women at High Risk of Breast Cancer Using OncoVue. 2010 San Antonio Breast Cancer Symposium; Poster P6-09-04.
6. Dalessandri KM, Miike R, Wrensch MR. Validation of OncoVue, a new individualized breast cancer risk estimator in the Marin County, California adolescent risk study. 2008 San Antonio Breast Cancer Symposium; Abstract 502.
7. Dalessandri KM, Miike R, Wrensch MR. Breast cancer risk assessment in the high risk Marin County population using OncoVue compared to SNPs from genome wide association studies. 2009 San Antonio Breast Cancer Symposium; Abstract 3057.
8. Ralph DA, Zhao LP, Aston CE et al. Age-specific association of steroid hormone pathway gene polymorphisms with breast cancer risk. Cancer 2007; 109(10):1940-8.
9. Evans DG, Howell A. Breast cancer risk-assessment models. Breast Cancer Res 2007; 9(5):213.
10. Dalessandri KM, Miike R, Wiencke JK et al. Vitamin D Receptor Polymorphisms and Breast Cancer Risk in a High-Incidence Population: A Pilot Study. J Am Coll Surg 2012; 215(5):652-57.
11. van der Rhee H, Coebergh JW, de Vries E. Is prevention of cancer by sun exposure more than just the effect of vitamin D? A systematic review of epidemiological studies. Eur J Cancer 2013; 49(6):1422-36.
12. Bolland MJ, Grey A, Gamble GD et al. Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. Am J Clin Nutr 2011; 94(4):1144-49.
13. Mealiffe ME, Stokowski RP, Rhees BK et al. Assessment of clinical validity of a breast cancer risk model combining genetic and clinical information. J Natl Cancer Inst 2010; 102(21):1618-27.
14. Zheng W, Wen W, Gao YT et al. Genetic and clinical predictors for breast cancer risk assessment and stratification among Chinese women. J Natl Cancer Inst 2010; 102(13):972-81.
15. Campa D, Kaaks R, Le Marchand L et al. Interactions Between Genetic Variants and Breast Cancer Risk Factors in the Breast and Prostate Cancer Cohort Consortium. J Natl Cancer Inst 2011.

16. Wacholder S, Hartge P, Prentice R et al. Performance of common genetic variants in breast-cancer risk models. N Engl J Med 2010; 362(11):986-93.
17. Darabi H, Czene K, Zhao W et al. Breast cancer risk prediction and individualised screening based on common genetic variation and breast density measurement. Breast Cancer Res 2012; 14(1):R25.
18. Armstrong K, Handorf EA, Chen J et al. Breast cancer risk prediction and mammography biopsy decisions: a model-based study. Am J Prev Med 2013; 44(1):15-22.
19. NCCN Guidelines® Version 3.2013: Genetic/familial high-risk assessment: breast and ovarian (discussion update in progress). Available online at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
20. Breast cancer risk assessment tool. Available online at: http://www.cancer.gov/bcrisktool/
21. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 1994; 73(3):643-51.
22. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004; 23(7):1111-30.
23. NCCN Guidelines® Version 1.2013: Breast cancer risk reduction (discussion update in progress). Available online at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
24. Visvanathan K, Hurley P, Bantug E et al. Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2013 [Epub ahead of print].

## Billing Coding/Physician Documentation Information

There is no specific code for the OncoVue or BREVAGen test.

**81479** Unlisted molecular pathology procedure

**99090** Analysis of clinical data stored in computers

## Additional Policy Key Words

N/A

## Policy Implementation/Update Information

12/1/13 New Policy; considered investigational.

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