Medical Policy Manual

Genetic Testing, Policy No. 23

**Single-nucleotide Polymorphisms (SNPs) to Predict Risk of Nonfamilial Breast Cancer**

**Effective:** July 1, 2017

**Next Review:** May 2018
**Last Review:** May 2017

**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**DESCRIPTION**

Commercially available assays tests (OncoVue®, BREVAGenplus®, and others) for single-nucleotide polymorphisms (SNPs) combine results to predict an individual’s risk of breast cancer.

**MEDICAL POLICY CRITERIA**

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

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

**NOTE:** A summary of the supporting rationale for the policy criteria is at the end of the policy.

**CROSS REFERENCES**

1. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
BACKGROUND

Many single-nucleotide polymorphisms (SNPs) occur normally throughout a person’s DNA. They occur once in every 300 nucleotides on average, which means there are roughly 10 million SNPs in the human genome. Most commonly, these variations are found in the DNA between genes. They can act as biological markers, helping scientists locate genes that are associated with disease. When SNPs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by affecting the gene’s function.

SNPs are not absolute indicators of disease development. Most SNPs have no effect on health or development. SNPs do not cause disease, but they can help determine the likelihood that someone will develop a particular illness. Some of these genetic differences, however, have proven to be very important in the study of human health. Researchers have found SNPs that may help predict an individual’s response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing specific diseases. SNPs can also be used to track the inheritance of disease genes within families. Future studies will work to identify SNPs associated with complex diseases such as heart disease, diabetes, and cancer.

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, and combine results 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 these tests is to identify individuals at increased risk for breast cancer 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 more 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 to achieve an individualized risk prediction, either alone or in combination with traditional predictors, in order to personalize screening programs in which starting age and intensity would vary by risk. In particular, the American Cancer Society has recommended that women at high risk (greater than a 20% lifetime risk) should undergo breast magnetic resonance imaging (MRI) and a mammogram every year, while stating that there is not enough evidence regarding yearly MRI screening in women at moderately increased risk (15% to 20% lifetime risk) to make a recommendation.[1]

SNP PANEL TESTS

Several companies currently offer internet-based testing for breast cancer risk profiles using SNPs. Additionally, non-U.S. companies offer testing direct-to-consumers (DTCs). The algorithms or risk models for these tests are proprietary. When reported on company websites, panels range in number from six to 15 SNPs.

CLINICAL GENETIC TESTS
Two companies currently offer risk assessment based on SNP panel testing and clinical information. Neither is provided as a direct-to-consumer (DTC) test. Only BREVAGen is currently listed in the Genetic Testing Registry of the National Center for Biotechnology Information.

**OncoVue®**

The OncoVue® Breast Cancer Risk Test (InterGenetics™, Inc., Oklahoma City, OK) is a proprietary test that evaluates multiple, low-risk SNPs associated with breast cancer. Results are combined with personal history measures to determine breast cancer risk at different times during adulthood. The test does not detect known high-risk genetic factors such as BRCA. 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.

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 decide whether more frequent exams and/or more sophisticated surveillance techniques are indicated.

**BREVAGenplus®**

BREVAGenplus® (Phenogen Sciences, Charlotte, NC) evaluates breast cancer-associated SNPs identified in genome-wide association studies (GWAS). The first-generation test, BREVAGen, included seven SNPs. Per the company website, BREVAGenplus® incorporates “an expanded panel” of SNPs. Risk is calculated by combining individual SNP risks with the Gail model risk. BREVAGenplus® has been evaluated for use in African-American, white, and Hispanic patient samples, age 35 years and older. Like OncoVue®, BREVAGenplus® does not detect known high-risk mutations (e.g., in BRCA). According to the company website, the test is “not applicable to women who have a personal or extensive family history of breast and/or ovarian cancer.”[2] BREVAGenplus® is not suitable for women with previous diagnoses of lobular carcinoma in situ, ductal carcinoma in situ, or breast cancer, since the Gail model cannot calculate breast cancer risk accurately for such women, or for women with an extensive family history of breast and ovarian cancer. Phenogen Sciences maintains on its website a list of physicians who have been trained to use BREVAGenplus®.

**REGULATORY STATUS**

No test combining the results of SNPs 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.

The FDA has not yet developed specific rules for direct-to-consumer (DTC) genetic testing. On November 22, the FDA issued a warning letter to 23andMe ordering it to “immediately discontinue marketing the Saliva Collection Kit and Personal Genome Service (PGS) until such time as it receives FDA marketing authorization for the device.” FDA marketing authorization was granted to 23andMe in February 2015 for its Bloom syndrome DTC carrier test, and in
April 2017 this authorization was extended to tests for 10 more conditions, including celiac disease, Parkinson’s disease, and hereditary thrombophilia. The 23andMe test also provides “ancestry-related genetic reports and uninterpreted raw genetic data only.”

Under the current regulatory program, CLIA requires that laboratories demonstrate the analytical validity of the tests they offer. However, there is no requirement for a test to demonstrate either clinical validity or clinical utility. Some states (e.g., New York) have chosen to regulate DTC laboratories. Because these reviews are not public, it is not possible to determine what scientific standard is being applied to them.

### EVIDENCE SUMMARY

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Genome-wide association studies (GWAS) examine the entire genome of each of thousands of individuals for single nucleotide polymorphisms (SNPs), single base-pair variations in the DNA sequence at semi-regular intervals, and attempt to associate variant SNP alleles with particular diseases. Several case-control GWASs have been carried out, primarily in women of European descent, to investigate common risk markers of breast cancer. In recent years, a number of SNPs associated with breast cancer have been reported at a high level of statistical significance and validated in two or more large, independent studies.[3-11] SNPs associated with breast cancer risk in Asian, African women, and Hispanic women have been the subject of many articles, although these appear exploratory.[12-39]

### SNP PANEL TESTS

As noted in the background, estimates of breast cancer risk based on SNPs derived from large GWASs 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 these commercially available breast cancer risk estimators have been compared to each other to determine if they report similar results on the same individuals, specifically for breast cancer.

### ANALYTICAL VALIDITY

In 2012, Silva et al. reported on the use of DNA pooling methods to aid in detection of genetic polymorphisms.[40] They combined DNA from many individuals (up to 200 patients or controls) into a single sample in an effort to pre-select 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.

**CLINICAL VALIDITY**

Cuzick (2017) tested the impact of an 88-SNP panel on breast cancer risk in high-risk women.\(^{[41]}\) This nested case-control study included 359 women who developed cancer and 636 matched controls that participated in the International Breast Intervention Study or the Royal Marsden study. The performance of the SNP array, alone or in combination with clinical risk factors, was compared to the Tyrer-Cuzick (TC) model. The median age of participants was 50 years, and 41% were randomly assigned to tamoxifen treatment and 59% to placebo, as part of the parent studies. All were at increased risk for breast cancer due to family history and/or previous diagnosis of benign tissue proliferation. Of the SNPs in the array, three were significantly associated with breast cancer development. The 88-SNP panel was associated with all breast cancers and with ER-positive disease (interquartile odds ratio [IQ-OR], 1.37; 95% CI, 1.14 to 1.66 and IQ-OR, 1.44; 95% CI, 1.16 to 1.79, respectively), but not ER-negative cancer. The SNP score was not significantly correlated with the TC model, and did improve predictive power when added to this model. However, the authors noted that the score likely needed to be recalibrated for use in high-risk patients.

Reeves (2010) evaluated the performance of a panel of seven SNPs with established associations with breast cancer in a study of 10,306 women with breast cancer and 10,383 without cancer in the U.K.\(^{[42]}\) The risk panel also contained five SNPs included in the deCODE BreastCancer™ test and used a similar multiplicative approach. Sensitivity studies were performed using only four SNPs and using 10 SNPs, both demonstrating no significant change in performance. While there were 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%) according to risk score, these changes were not viewed as clinically useful when compared to patients with an estimated overall background risk of 6.3%. Of note, simple information on patient histories, such as the presence of one or two first-degree relatives with breast cancer, provided equivalent or superior risk discrimination (9.1% and 15.4%, respectively).

Blanco (2015) published results from a retrospective study that genotyped 41 SNPs in 15,252 BRCA1 and 8,211 BRCA2 mutation carriers to assess the association between breast cancer and SNP mutations.\(^{[43]}\) The authors reported an association of HMMR rs299290 with breast cancer risk in BRCA1 mutation carriers (per-allele hazard ratio (HR) = 1.10, 95% confidence interval (CI) 1.04-1.15, \(p = 1.9 \times 10^{-4}\) (false discovery rate (FDR)-adjusted \(p = 0.043\))). Additionally, variation in CSTF1, located next to AURKA, was also found to be associated with breast cancer risk in BRCA2 mutation carriers (rs2426618 per-allele HR = 1.10, 95% CI 1.03-1.16, \(p = 0.005\) (FDR-adjusted \(p = 0.045\))). Further assessment of pairwise interactions suggested that deviations from the multiplicative model for rs299290 and CSTF1 rs6064391, and rs299290 and TUBG1 rs11649877 were associated in both BRCA1 and BRCA2 mutation carriers.

A study by Campa (2015) evaluated the association of breast cancer (BC) susceptibility loci with breast cancer in situ (BCIS) risk.\(^{[44]}\) Thirty-nine SNPs were genotyped with known associated risk of invasive breast cancer in 1,317 BCIS cases, 10,645 invasive BC cases, and 14,006 healthy controls from the National Cancer Institute’s Breast and Prostate Cancer Cohort Consortium (BPC3). The authors found that five SNPS (CDKN2BAS-rs1011970, FGFR2-rs3750817, FGFR2-rs2981582, TNRC9-rs3803662, 5p12-rs10941679) were
significantly associated with BCIS risk (P value adjusted for multiple comparisons <0.0016). When comparing invasive BC and BCIS, the largest difference was for CDKN2BAS-rs1011970 SNP, which showed a positive association with BCIS (OR = 1.24, 95 % CI: 1.11-1.38, P = 1.27 x 10^{-4}) and no association with invasive BC (OR = 1.03, 95 % CI: 0.99-1.07, P =0.06), with a P value for case-case comparison of 0.006.

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.[45] The authors assessed two-way interactions among 3277 breast cancer-associated SNPs. Of 2.5 billion possible two 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.

Also in 2014, the Breast and Prostate Cancer Cohort Consortium published a systematic review with meta-analysis of eight prospective cohort studies conducted in the United States, Europe, and Australia to examine two-way interactions between genetic and established clinical risk factors.[46] Based on published GWAS, three SNPs were selected for analysis in 10,146 cases of invasive breast cancer and 12,760 controls. After correction for multiple comparisons, a statistically significant excess in relative risk was attributed to the interaction between rs10483813 mutations in RAD51L1 and body mass index (BMI).

Zhou (2013) found that a specific polymorphism in the vitamin D receptor gene increased breast cancer risk in African but not Caucasian women.[47] Breast cancer risk associated with SNPs in microRNAs is commonly modified by ethnicity,[48-51] and several studies have evaluated the risk associated with specific SNPs in Chinese populations.[52,53] Meta-analyses of GWAS have identified SNPs at new breast cancer susceptibility loci.[54-56] All of these markers are considered to be in an investigational phase of development.

Aston (2005) evaluated more than 14,000 oligogenotypes, defined by two or more SNPs in 10 breast cancer-associated genes.[57] 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.

CLINICAL UTILITY

Research by McCarthy (2015) at the University of Pennsylvania examined the impact of BMI, Gail model risk, and a 12-SNP version of the deCODE BreastCancer™ test on breast cancer risk prediction and biopsy decisions among women with Breast Imaging-Reporting and Data System (BI-RADS) four mammograms who had been referred for biopsy (N=464).[58] The original deCODE BreastCancer™ panel included seven SNPs; neither panel is currently commercially available. 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 SNP panel risk as a continuous variable, a statistically significant association between SNP panel risk and breast cancer diagnosis was observed (odds ratio, 2.30; 95% confidence interval), 1.06 to 4.99; Hosmer-Lemeshow goodness-of-fit test, p=0.035). However, categorized SNP panel risks (e.g., relative increase or decrease in risk compared with the general population), which
resembled 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, SNP 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 SNP panel, reclassified nine women (3.4%) below a 2% risk threshold for biopsy, none of whom were diagnosed with cancer. Numerous other studies have also revealed the interaction between environment (e.g., obesity; age at menarche)\(^{[59,60]}\) or ethnicity\(^{[61-67]}\) and breast cancer risk conferred by certain SNPs.

Bloss (2011) 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).\(^{[68]}\) 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, no increase was observed during the course of the study.

Pharoah (2008) considered a combination of seven well-validated SNPs associated with breast cancer, five of which are included in the deCODE BreastCancer™ test.\(^{[69]}\) A model that simply multiplies the individual risks of the seven common SNPs was assumed, and would explain approximately 5% of the total genetic risk of non-familial breast cancer. Applying the model to the population of women in the U.K., the authors concluded that the risk profile provided by the seven SNPs would 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 did consider the effect on a population screening program that could be personalized with the results of SNP panel testing. They concluded that no women would be included in the high-risk category (currently defined as 20% risk within the next 10 years at age 40–49 years, according to the National Institute for Health and Clinical Excellence), and therefore none would warrant the addition of MRI screening or the consideration of more aggressive intervention on the basis of the SNP panel results.

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.\(^{[42,69-74]}\) Many more genetic risk markers remain to be discovered because substantial unexplained heritability remains.\(^{[75]}\) Researchers from the Collaborative Oncological Gene-Environment Study (COGS) group, a mega-consortium established to follow-up previous GWAS and candidate gene association studies, estimate that “more than 1,000 additional loci are involved in breast cancer susceptibility.”\(^{[54]}\) One reason more genetic associations have not been found is that even large GWAS are underpowered to detect uncommon genetic variants.\(^{[70]}\)

**SECTION SUMMARY**

Single-nucleotide polymorphisms (SNPs) panel tests are commercially available, with results synthesized into breast cancer risk estimates. These studies show common SNPs are significantly associated with breast cancer risk, and some SNPs convey slightly elevated risk of compared with the general population risk. However, these tests have not been analytically or clinically validated. Furthermore, clinical utility, that is how the results will be used to change patient management and improve health outcomes, has not been demonstrated. The use of
such risk panels for individual patient care or for population screening programs is premature, as performance of these panels in the intended-use populations is uncertain and most genetic breast cancer risk has yet to be explained by gene variants and SNPs. Therefore, 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 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.[76] 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.[77]

Using the same case-control validation data, OncoVue® was also compared to risk estimation determined by seven SNPs reported in other GWAS,[78] 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.[42]

The majority of reports that address conceptual aspects of the OncoVue® test do not report data using the final OncoVue® test configuration. These reports are limited to abstracts presented at scientific meetings and have not yet been published in peer-reviewed journals.[79,80] One fully published study characterizes SNPs that exhibit breast cancer risk associations that vary with age.[81] This study stratified breast cancer cases and normal controls into three age groups, then determined breast cancer risk for SNP homozygotes and heterozygotes for each of 18 candidate SNPs within each age group. Of these, five SNP variants had statistically significant odds ratios for at least one age group. In a separate validation sample, only one had a statistically significant odds ratio, but not in a pattern like that of the discovery set. The other four SNPs, although not significant, were judged to have patterns of results similar to that of the discovery set. These were investigated further by a sliding 10-year window strategy, and the authors suggested that the results this clarified age-specific breast cancer risk associations. The authors noted the need for additional validation in other populations and nonwhite ethnicities.

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.[82] 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.

A pilot study using buccal samples from women in a retrospective case-control study described above aimed to examine the genotypes of individuals 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).[83,84] 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 AND BREVAGENPLUS®**

Dite (2013) published a similar case-control study of the same seven SNPs assuming the same multiplicative model (based on independent risks of each SNP).[85] Predictive ability of the Gail model with and without the seven SNP panel was compared in 962 case patients and 463 controls, all 35 years of age or older (mean age, approximately 45 years). AUC of the Gail model was 0.58 (95% CI, 0.54 to 0.61); in combination with the seven 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 seven-SNP panel was added to the Gail model. Risk classes were defined by five-year risk of developing breast cancer: <1.5%, ≥1.5% to <2.0%, and≥2.0%. Although addition of the seven-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.

Mealiffe (2010) performed a clinical validation study of the BREVAGen test.[74] 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, or NRI, 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, e.g. those classified as intermediate risk by the Gail model.

Information about analytic validity of the BREVAGen test was provided in the published study, but was 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 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 controls. The authors acknowledged that the two assays performed “relatively poorly,” but asserted that consensus calls were nonetheless accurate.

Section Summary

There is a lack of published evidence regarding OncoVue® and BREVAGenplus® test validation, supportive data, and management implications. Available data suggest that OncoVue® and BREVAGenplus® 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 BREVAGenplus® in asymptomatic individuals changes management decisions and improves patient outcomes.

GENETIC TESTS AND CLINICAL PREDICTORS

Other large studies have evaluated 8 to 18 common, candidate SNPs in breast cancer cases and normal controls to determine whether breast cancer assessments based on clinical predictors (e.g. mammogram, biopsy, etc.) plus various SNP combinations were more accurate than risk assessments based on clinical predictors alone.

In 2013, 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.[86] Currently, one year probability of breast cancer among women with Breast Imaging–Reporting and Data System (BI-RADS) category three mammograms is 2%; these women undergo six-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 one 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.

Darabi (2012) 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.[87] Performance of a risk prediction model based on an initial set of seven breast cancer risk SNPs was improved by including 11 more recently established breast cancer risk SNPs (p=4.69 × 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 five year low-, intermediate-, and high-risk categories (p=8.93 × 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. Impacts on net health outcomes from such a change are unknown.
In 2011, 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.[88]

In 2010, Zheng et al. found that eight 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.[89] Also in 2010, 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 three 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).[71] 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).

Section Summary

Studies have demonstrated that adding testing of clinical predictors, such as mammography and biopsy, to single-nucleotide polymorphism (SNP) testing can improve the discriminatory accuracy of testing. However, these studies do not provide direct evidence of clinical validity. Furthermore, these studies do not demonstrate clinical utility. More high-quality prospective studies are needed to determine the net health outcomes.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

In 2017, the National Comprehensive Cancer Network (NCCN) updated their guidelines on breast and/or ovarian cancer. They recognize the limitations of genetic testing by and state that the unknown significance of some variants provides uncertain level of risk associated with most variants; therefore, this provides unclear guidance on risk management for carriers of some variants.[90]

SUMMARY

There is not enough research to show how testing for single nucleotide polymorphisms (SNPs) can be used to guide treatment decisions and improve health outcomes for patients. Also, practice guidelines based on research do not recommend testing for SNPs for the management of breast cancer. Therefore, the use of SNP panel tests and clinical-genetic tests to predict breast cancer risk, including but not limited to OncoVue® and BREVAGenplus®, is considered investigational.

REFERENCES

1. American Cancer Society screening recommendations for women at higher than


45. Milne, RL, Herranz, J, Michailidou, K, et al. A large-scale assessment of two-way SNP interactions in breast cancer susceptibility using 46,450 cases and 42,461 controls from


<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>0008M</td>
<td>Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score</td>
</tr>
<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>Codes</td>
<td>Number</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

*Date of Origin: January 2011*