Regence

Medical Policy Manual Genetic Testing, Policy No. 23

Single-nucleotide Variants (SNVs) to Predict Risk of Nonfamilial Breast Cancer

Effective: September 1, 2024

Next Review: May 2025
Last Review: July 2024

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 variants (SNVs, also known as single-nucleotide polymorphisms, or SNPs) combine results to predict an individual's risk of breast cancer.

MEDICAL POLICY CRITERIA

I. Testing for one or more single-nucleotide variants (SNVs) to predict an individual's risk of breast cancer is considered **investigational.**

II. The OncoVue®, GeneType®, BREVAGen®, and BREVAGen*plus*® 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 variants (SNVs) occur normally throughout a person's DNA. They occur once in every 300 nucleotides on average, which means there are roughly 10 million SNVs 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 SNVs 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.

SNVs are not absolute indicators of disease development. Most SNVs have no effect on health or development. SNVs 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 SNVs that may help predict an individual's response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing specific diseases. SNVs can also be used to track the inheritance of disease genes within families. Future studies will work to identify SNVs associated with complex diseases such as heart disease, diabetes, and cancer.

SNVs, 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 SNVs and combine results to predict an individual's risk of breast cancer relative to the general population. Some of these assays 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 SNVs 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 SNVs 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 (ACS) has recommended that women at high risk (greater than a 20% lifetime risk according to risk assessment tools based mainly on family history) should undergo breast magnetic resonance imaging (MRI) and a mammogram every year. The ACS states that there is not enough evidence of benefit from yearly MRI screening in women at moderately increased risk (15% to 20% lifetime risk), or with increased risk due to a personal history of any of the following factors:[1]

- Breast cancer
- Ductal carcinoma in situ
- Lobular carcinoma in situ
- Atypical ductal or atypical lobular hyperplasia
- Dense breasts

SNV PANEL TESTS

Several companies currently offer internet-based testing for breast cancer risk profiles using SNVs. Additionally, non-U.S. companies offer testing direct-to-consumers (DTCs). The algorithms or risk models for these tests are proprietary.

CLINICAL GENETIC TESTS

GeneType for Breast Cancer (and the previous versions of the test, BREVAGen*plus*® and BREVAGen®) evaluates breast cancer-associated single nucleotide variants (SNVs) identified in genome-wide association studies. The first-generation test, BREVAGen, included 7 SNVs. Currently, GeneType calculates breast cancer risk by combining individual SNV risks with other risk factors. GeneType has been evaluated for use in African-American, Caucasian, and Hispanic patient samples, age 35 years and older, who do not have a history of *in situ* or invasive breast cancer and are not carriers of a known pathogenic variant or rearrangement in a breast cancer susceptibility gene.[2] BREVAGen is currently listed in the Genetic Testing Registry of the National Center for Biotechnology Information.

GeneType (formerly BREVAGen*plus*®)

Several SNV-based tests have been marketed by Phenogen Sciences (Charlotte, NC), including the GeneType test and the BREVAGen*plus*®.

The GeneType for Breast Cancer test includes over 70 SNVs and generates a risk score based on these in combination with clinical and other variables, including breast density and family history. The first-generation test, BREVAGen, included seven SNVs. BREVAGen*plus*® incorporated a larger panel of SNVs. Risk calculation for this test combined individual SNV risks with the Gail model risk. Like OncoVue®, GeneType or BREVAGen*plus*® does not detect known high-risk variants (e.g., in *BRCA*). and they are not suitable for women with previous diagnoses of lobular carcinoma in situ, ductal carcinoma in situ, or breast cancer.

REGULATORY STATUS

No test combining the results of SNVs 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. 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

Human Genome Variation Society (HGVS) nomenclature[3] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term

"variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

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 variant that is present or in excluding a variant 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.

The evidence review is focused on the clinical validity and utility of testing.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Genome-wide association studies (GWAS) examine the entire genome of each of thousands of individuals for SNVs (single base-pair variations in the DNA sequence at semi-regular intervals) and attempt to associate variant SNV 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 SNVs associated with breast cancer have been reported at a high level of statistical significance and validated in two or more large, independent studies.[4-12] SNVs associated with breast cancer risk in Asian, African women, and Hispanic women have been the subject of many articles, although these appear exploratory.[13-40]

SNV PANEL TESTS

As noted in the background, estimates of breast cancer risk based on SNVs derived from large GWASs and/or from SNVs 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 SNV-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

Silva (2012) reported on the use of DNA pooling methods to aid in detection of genetic variants.[41] They combined DNA from many individuals (up to 200 patients or controls) into a single sample in an effort to pre-select SNVs 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

A study published by Curtit (2017) evaluated the use of a 93-SNV panel in 8,703 patients from the PHARE and SIGNAL prospective cohort studies.[42] The SNVs were selected for analysis based on previous publications associating them with breast cancer risk, and were measured as part of a GWAS. A risk score generated from these SNVs was tested for associations with clinical and pathologic breast cancer characteristics in the study participants. The results indicated that the 94-SNV risk score was not associated with traditional prognostic factors, such as age, tumor size, nodal status, ER/PR/HER2 status, or breast cancer subtype, and was also not associated with survival endpoints.

Cuzick (2017) tested the impact of an 88-SNV panel on breast cancer risk in high-risk women.[43] 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 SNV 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 SNVs in the array, three were significantly associated with breast cancer development. The 88-SNV panel was associated with all breast cancers and with ER-positive disease (interquartile odds ratio [IQ-OR] 1.37, 95% confidence interval [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 SNV 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. The SNV score did not predict which women would benefit from tamoxifen.

Mavaddat (2015) 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.[44] 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 three-fold increased risk of developing breast cancer compared with women in the middle quintile (OR 3.36, 95% CI 2.95 to 3.83). Lifetime risk of breast cancer was 16.6% 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).

Reeves (2010) evaluated the performance of a panel of seven SNVs 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.[45] The risk panel also contained five SNVs included in the deCODE BreastCancer™ test and used a similar multiplicative approach. Sensitivity studies were performed using only four SNVs and using 10 SNVs, 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 SNVs in 15,252 *BRCA1* and 8,211 *BRCA2* variant carriers to assess the association between breast cancer and SNVs.[46] The authors reported an association of HMMR rs299290 with breast cancer risk in BRCA1 variant carriers (per-allele hazard ratio [HR] 1.10, 95% CI 1.04 to 1.15, $p=1.9x10^{-4}$, 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* variant carriers (rs2426618 per-allele HR 1.10, 95% CI 1.03 to 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* variant carriers.

A study by Campa (2015) evaluated the association of breast cancer susceptibility loci with breast cancer in situ (BCIS) risk.[47] Thirty-nine SNVs were genotyped with known associated risk of invasive breast cancer in 1,317 BCIS cases, 10,645 invasive breast cancer cases, and 14,006 healthy controls from the National Cancer Institute's Breast and Prostate Cancer Cohort Consortium (BPC3). The authors found that five SNVs (*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 breast cancer and BCIS, the largest difference was for *CDKN2BAS*-rs1011970 SNV, which showed a positive association with BCIS (OR 1.24, 95 % CI 1.11 to 1.38, $p=1.27x10^{-4}$) and no association with invasive breast cancer (OR 1.03, 95 % CI 0.99 to 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.[48] The authors assessed two-way interactions among 3,277 breast cancer-associated SNVs. Of 2.5 billion possible two SNV 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.[49] Based on published GWAS, three SNVs 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 variants in *RAD51L1* and body mass index (BMI).

Aston (2005) evaluated more than 14,000 oligogenotypes, defined by two or more SNVs in 10 breast cancer-associated genes.[50] The association with breast cancer was considered statistically significant for 37 oligogenotypes. The authors observed that oligogenic combinations of 2 to 10 SNVs 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 SNVs, these combinations

stratified risk over a broader range.

Many smaller studies have explored associations between SNVs and breast cancer, particularly in specific ethnic and racial populations.[51, 52] Breast cancer risk associated with SNVs in microRNAs is commonly modified by ethnicity,[53-57] and several studies have evaluated the risk associated with specific SNVs in Chinese populations.[58, 59] Meta-analyses of GWAS have identified SNVs at new breast cancer susceptibility loci.[60-62] All of these markers are considered to be in an investigational phase of development and are not reviewed in detail.

CLINICAL UTILITY

Boltz (2024) performed a retrospective case-control analysis of 25,591 female study (Healthy Nevada Project) participants to determine whether genetic information can identify women at low risk for breast cancer who may be able to safely delay initiation of screening mammography.[63] Low risk for breast cancer was defined as the absence of any gene variants in *BRCA1*, *BRCA2*, *PALB2*, and *CHEK2*, and having a polygenic risk score (PRS) in the bottom 10% of PRS distribution using a 313-single nucleotide variant model. The low-risk group included 2338 (9.1%) of participants, and 22843 (89.3%) women were classified as average risk. 1.6% of participants were classified as high risk based on the presence of germline single-gene variants. By age 45 years, 0.40% of women with a low-risk classification were diagnosed with breast cancer, compared to 0.69% at average risk (Hazard Ratio [HR] 0.53). By age 70 years 3.65% of the low risk group had been diagnosed with breast cancer compared to 9.9% of the average risk group (HR 0.40). The authors concluded that similar screening performance would be seen if the low risk group defers screening mammogram by 5-10 years after the initiation of average risk screening mammography. Limitations of the study include the possibility the PRS score alone may not be sufficient to determine breast cancer risk, especially in non-white populations.

Using data from a large study population (n=246,142) and four breast cancer risk prediction tools, Ho (2023) assessed the proportion of women identified as high risk for breast cancer based on the individual tools, and studied the overlap patterns among the tools.[64] The risk prediction tools used were the polygenic risk score that used 313 SNPs (PRS), the presence of loss of function (LoF) variants identified in nine breast cancer risk genes (*ATM, BRCA1, BRCA2, CHEK2, PALB2, BARD1, RAD51C, RAD51D, TP53*), the Gail model, and breast cancer family history in first-degree relative(s) (FH, binary). Thirty percent (n=73,775) of women were identified as high risk using PRS. Of the 1209 women who were diagnosed with breast cancer within two years, 52% (n=632) were considered high risk using PRS. Of the women diagnosed with breast cancer, the most common overlap was women identified as high risk with PRS and the Gail model (28%). The authors concluded that the combination of PRS, FH, and LoF was associated with the highest gain in number of breast cancer cases identified as high risk when compared to a random sample (63% vs. 48%). Regarding PRS, the authors state that while PRS identifies some women who would be missed by other tools, it identifies a larger number of women who may not develop breast cancer, and risk-based screening may require the use of multiple risk tools.

Reseach by McCarthy (2015) at the University of Pennsylvania 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 Breast Imaging-Reporting and Data System (BI-RADS) four mammograms who had been referred for biopsy (n=464).[65] The

original deCODE BreastCancer™ panel included seven SNVs; 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 SNV panel risk as a continuous variable, a statistically significant association between SNV panel risk and breast cancer diagnosis was observed (OR 2.30, 95% CI 1.06 to 4.99, Hosmer-Lemeshow goodness-of-fit test p=0.035). However, categorized SNV 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, 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 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)[66, 67] or ethnicity[68-74] and breast cancer risk conferred by certain SNVs.

A study by Allman (2015) included 7,539 African-American and 3,363 Hispanic women from the Women's Health Initiative.[75] 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 IBIS (Tyrer-Cuzick model) risk prediction for African Americans and Hispanics, respectively.

Bloss (2011) reported on the psychological, behavioral, and clinical effects of risk scanning in 3,639 patients followed for a short time (mean [SD], 5.6 [2.4] months).[76] 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 SNVs associated with breast cancer, five of which are included in the deCODE BreastCancer™ test.[77] A model that simply multiplies the individual risks of the seven common SNVs 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 SNVs 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 SNV 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 to 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 SNV panel results.

Although there are no guidelines regarding the clinical use of SNV 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.[45, 77-82] Many more genetic risk markers remain to be discovered because substantial unexplained heritability remains.[83] 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.”[60] One reason more genetic associations have not been found is that even large GWAS are underpowered to detect uncommon genetic variants.[78]

SECTION SUMMARY

SNV panel tests are commercially available, with results synthesized into breast cancer risk estimates. These studies show common SNVs are significantly associated with breast cancer risk, and some SNVs 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 SNVs. Therefore, 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 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 variants, mostly SNVs, in candidate genes likely to influence breast carcinogenesis. A model using weighted combinations of 22 SNVs 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.[84] 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.[85]

Using the same case-control validation data, OncoVue® was also compared to risk estimation determined by seven SNVs reported in other GWAS,[86] 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, SNVs derived from GWAS are known to result in only low-level estimates of risk at best; in one example, a 14-SNV 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.[45]

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.[87, 88] One fully published study characterizes SNVs that exhibit breast cancer risk associations that vary with age.[89] This study stratified breast cancer cases and normal controls into three age groups, then determined breast cancer risk for SNV homozygotes and heterozygotes for each of 18 candidate SNVs within each age group. Of these, five SNV 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 SNVs, 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.[90] 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 SNVs 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).[91, 92] Clinical trials demonstrating improved health outcomes in patients identified as high risk due to OncoVue® detection of the rs7975232 SNV who were subsequently treated with vitamin D supplementation have not been reported.

BREVAGEN AND BREVAGEN*PLUS*®

Dite (2013) published a similar case-control study of the same seven SNVs assuming the same multiplicative model (based on independent risks of each SNV).[93] Predictive ability of the Gail model with and without the seven SNV panel was compared in 962 case patients and 463 controls, all 35 years of age or older (mean age, approximately 45 years). The area under the curve (AUC) of the Gail model was 0.58 (95% CI 0.54 to 0.61); in combination with the seven 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 seven-SNV 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-SNV 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.[82] The authors evaluated a seven-SNV panel in a nested case-control cohort of 1,664 case patients and 1636 controls. A model that multiplied the individual risks of the seven 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, or NRI, was used to evaluate performance. Combining seven validated SNVs 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 SNV 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 eight to 18 common, candidate SNVs in breast cancer cases and normal controls to determine whether breast cancer assessments based on clinical predictors (e.g., mammogram, biopsy, etc.) plus various SNV combinations were more accurate than risk assessments based on clinical predictors alone.

Armstrong (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.[94] 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 SNVs 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 SNVs, 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.[95] Performance of a risk prediction model based on an initial set of seven breast cancer risk SNVs was improved by including 11 more recently established breast cancer risk SNVs ($p=4.69\times10^{-4}$). Adding mammographic PD, 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 five-year low-, intermediate-, and high-risk categories ($p=8.93 \times 10^{-9}$). It was estimated that using an individualized screening strategy based on risk models incorporating clinical risk factors, mammographic density, and SNVs, would capture 10% more cases. Impacts on net health outcomes from such a change are unknown.

Campa (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.[96]

Zheng (2010) found that eight SNVs, combined with other clinical predictors, were significantly associated with breast cancer risk; the full model gave an area under the curve of 0.63.[97]

Wacholder (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 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).[79] The SNV 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 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 actually 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).

Section Summary

Studies have demonstrated that adding testing of clinical predictors, such as mammography and biopsy, to SNV testing can improve the discriminatory accuracy of testing. However, these studies to 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

The National Comprehensive Cancer Network (NCCN) guidelines for breast cancer screening and diagnosis (v.2.2024) state:[98]

> "Ongoing validation studies using the polygenic risk score (PRS) are underway, including those with diverse populations. At the present time, PRS would best be utilized in the setting of a clinical trial."

The National Comprehensive Cancer Network (NCCN) guidelines on genetic risk assessment for breast, ovarian, and pancreatic cancer (v.3.2024) do not recommend SNV or SNP testing

and include the following statement:[99]

> Polygenic risk scores (PRS) are now sometimes included in some genetic test reports. PRS are groups of SNPs associated with a specific disorder or disease, such as cancer. Studies evaluating the validity of PRS to refine risks in those with hereditary cancer have been conducted primarily with breast and prostate cancers. […] Studies of PRS have largely been done with those of European ancestry. Studies with larger samples from more diverse populations are needed. Given that the clinical value of PRS has not yet been established, these should not be used to inform clinical management at this time.

SUMMARY

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

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CODES

Codes	Number	Description
CPT	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Date of Origin: *January 2011*