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Medical Policy Manual

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

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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

Several 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 particular 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.

Background

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 those at moderately increased risk (15% to 20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram.[1]

SNP Panel Tests

Several companies (see Table below) currently offer Internet-based testing for breast cancer risk profiles using SNPs. Most of these 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 6 to 15 SNPs.

Tests for Breast Cancer Susceptibility Using SNP-Based Risk Panels*			
Company	**Location**	**Test Offered Direct-to-Consumer**	**Number of SNPs Used in Risk Panel**
23andme	Mt. View, CA	Yes	7
City of Hope	Duarte, CA	No	7
deCODE	Reykjavik, Iceland	Yes	7
easyDNA**	Elk Grove, CA	No	ND
GenePlanet	Dublin, Ireland	Yes	15

Tests for Breast Cancer Susceptibility Using SNP-Based Risk Panels*			
Company	**Location**	**Test Offered Direct-to-Consumer**	**Number of SNPs Used in Risk Panel**
Matrix Genomics	Santa Fe, NM	Yes	6
The Genetic Testing Laboratories	Las Cruces, NM	Yes	ND

ND – not described
*This is not an exhaustive list.
**The easyDNA website includes a "note for U.S. residents" that states, "easyDNA would like to inform all its clients that as per the U.S. Food and Drug Administration's directive it can only provide genetic health testing to U.S. residents if their physician has agreed to the test."[2]

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 test. Both are 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. 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."[3]

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. For women already known to be at high risk based on a family history consistent with hereditary breast cancer, the test is represented as having added value by indicating greater or lesser risk at different life stages.

OncoVue® is available only through the Breast Cancer Risk Testing Network (BCRTN), described as a network of Breast Care Centers engaged in frontline genetic identification of breast cancer risk levels in their patients.[4] BCRTN member centers will provide genetic breast cancer risk testing for their patients using OncoVue® as part of a comprehensive education program to help OncoVue® "at-risk" women understand their risk level and intervention strategies. BCRTN members will be selected for the network based on a number of criteria, including quality standards of care, level of breast cancer surveillance technology, and the capacity to provide patient education on genetic testing and future risk management

protocols.

BREVAGen™

BREVAGen™ (Phenogen Sciences, Charlotte, NC) 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., in *BRCA*. According to the BREVAGen website, "suitable candidates" for testing include women with a Gail lifetime risk of 15% or greater; with high lifetime estrogen exposure (eg, early menarche and late menopause); or with relatives diagnosed with breast cancer.[5] 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.

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.

FDA has not yet developed specific rules for direct-to-consumer (DTC) genetic testing. On November 22, 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." Currently, the test is available on the company website with the alert, "At this time we do not offer health-related genetic reports." Current and new customers receive "ancestry-related information and raw genetic data without 23andMe's interpretation."

Under 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.

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® and BREVAGen™ 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.

SCIENTIFIC BACKGROUND

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 2 or more large, independent studies.[6-14] Recently SNPs associated with breast cancer risk in Asian and African women have been the subject of more than a dozen articles, although these appear exploratory.[15-37] Further, studies investigating SNP association in Hispanic women have also been conducted.[38,39]

SNP Panel Tests

As noted in the Description, 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.

Meta-analyses

Several meta-analyses have investigated the association between breast cancer and various SNPs. Meta-analyses of case control studies have indicated that specific SNPs are associated with increased or decreased breast cancer risk. Other meta-analyses have revealed the interaction between environment (eg, obesity, age at menarche)[40,41] or ethnicity[42-46] and breast cancer risk conferred by certain SNPs. Zhou et al. (2013) found that a specific polymorphism in the vitamin D receptor gene increased breast cancer risk in African but not Caucasian women.[47] Breast cancer risk associated with SNPs in microRNAs is commonly modified by ethnicity.[48-51] Meta-analyses of GWAS have identified SNPs at new breast cancer susceptibility loci.[52-54] All of these markers are considered to be in an investigational phase of development.

In 2014, the Breast Cancer Association Consortium published a mega-analysis of 46,450 case patients and 42,461 controls from 38 international meta-analytic studies.[55] The authors assessed 2-way interactions among 3277 breast cancer-associated SNPs. Of 2.5 billion possible 2-SNP combinations, none were statistically significantly associated with breast cancer risk. The study suggests that risk models may be simplified by eliminating interaction terms. Nonetheless, the authors cautioned that despite the large sample size, the study may have been underpowered to detect very small interaction effects, which tend to be smaller than main effects.

Nonrandomized Studies

Since there are no published studies of commercial SNP-based breast cancer risk predictors, other published studies of the clinical usefulness of other similar combinations of SNPs as risk predictors are considered here.

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

In 2008, Pharoah et al.[56] considered a combination of 7 well-validated SNPs associated with breast cancer, 5 of which are included in the deCODE BreastCancer™ test. A model that simply multiplies the individual risks of the 7 common SNPs was assumed, and would explain approximately 5% of the total genetic risk of 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 7 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 magnetic resonance imaging (MRI) screening or the consideration of more aggressive intervention on the basis of the SNP panel results.

Reeves et al.[57] evaluated the performance of a panel of 7 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. The risk panel also contained 5 SNPs included in the deCODE BreastCancer™ test and used a similar multiplicative approach. Sensitivity studies were performed using only 4 SNPs and using 10 SNPs, both demonstrating no significant change in performance. While use of the risk score was able to show marked differences in risk between the upper quintile of patients (8.8% cumulative risk to age 70 years) and the lower quintile of patients (4.4%), these changes were not viewed as clinically useful when compared to patients with an estimated overall background risk of 6.3%. Of note, simple information on patient histories, for example, presence of one or two first-degree relatives with breast cancer, provided equivalent or superior risk discrimination (9.1% and 15.4%, respectively).

It is assumed that many more genetic risk markers remain to be discovered because substantial unexplained heritability remains.[58] Researchers from the Collaborative Oncolgoical 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."[52] One reason more genetic associations have not been found is that even large GWAS are underpowered to detect uncommon genetic variants.[59]

Two approaches have recently been described to help address this problem. Braun and Buetow described a technique for multi-SNP analysis of GWAS data based on the study of patient cases selected using their association with known pathways related to disease risk.[60] The authors coined the term Pathways of Distinction Analysis (PoDA) to describe this methodology and demonstrated that using this approach facilitated the identification of disease-related SNPs by creating clusters of similar variants within disease groups that stood out when compared with control groups.

In 2012, Silva et al. reported on the use of DNA pooling methods to aid in detection of genetic polymorphisms.[61] 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.

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.[56,57,59,62-65] Whether or not additional SNP studies are likely to be informative is under debate, as the study size to detect more and more rare variants becomes prohibitively large. As the cost of whole genome sequencing continues to decrease, some predict that this will become the preferred avenue for researching risk variants. Challenges to sorting through the growing literature on this diagnostic approach include nonstandardization and nontransparency of studies.[66] Janssens et al. published a methods paper providing a road map for optimal reporting and an accompanying detailed article describing good reporting practices.[67]

In 2011, Bloss et al. reported on the psychological, behavioral, and clinical effects of risk scanning in 3639 patients followed for a short time (mean [SD], 5.6 [2.4] months).[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, during the course of the study itself, no actual increase was observed.

Conclusion

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

Clinical Genetic Tests

OncoVue®

The OncoVue® test was developed by evaluating samples from a large case-control study for 117 common, functional polymorphisms, mostly 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.[69] 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.[70]

Using the same case-control validation data, OncoVue was also compared to risk estimation determined by 7 SNPs reported in other GWAS,[71] 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.[57]

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

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.[72,73] One fully published study characterizes SNPs that exhibit breast cancer risk associations that vary with age.[74] This study stratified breast cancer cases and normal controls into 3 age groups, then determined breast cancer risk for SNP homozygotes and heterozygotes for each of 18 candidate SNPs within each age group. Of these, 5 SNP variants had statistically significant odds ratios for at least 1 age group. In a separate validation sample, only 1 had a statistically significant odds ratio but not in a pattern similar to that of the discovery set. The other 4 SNPs, although not significant, were judged to have patterns of results similar to that of the discovery set and were investigated further by a sliding 10-year window strategy, the results of which the authors suggest clarify age-specific breast cancer risk associations. The authors note the need for additional validation in other populations and nonwhite ethnicities.

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.[75] 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).[76,77] 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.

<u>BREVAGen™</u>

In 2010, Mealiffe et al.. published a clinical validation study of the BREVAGen™ test.[65] 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 2 assays performed "relatively poorly," but asserted that consensus calls were nonetheless accurate.

In 2013, Dite et al. published a similar case-control study of the same 7 SNPs assuming the same multiplicative model (based on independent risks of each SNP).[78] Predictive ability of the Gail model with and without the 7 SNP panel was compared in 962 case patients and 463 controls, all 35 years of age or older (mean age, approximately 45 years). AUC of the Gail model was 0.58 (95% CI, 0.54 to 0.61); in combination with the 7-SNP panel, AUC increased to 0.61 (95% CI, 0.58 to 0.64; bootstrap resampling, $p<0.001$). In reclassification analysis, 12% of cases and controls were correctly reclassified and 9% of cases and controls were incorrectly reclassified when the 7-SNP panel was added to the Gail model. Risk classes were defined by 5-year risk of developing breast cancer: <1.5%, ≥1.5% to <2.0%, and≥2.0%. Although addition of the 7-SNP panel to the Gail model improved predictive accuracy, the magnitude of improvement is small, the overall accuracy is moderate, and the impact on health outcomes is uncertain.

Other Clinical-Genetic Tests

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

- Zheng et al. found that 8 SNPs, combined with other clinical predictors, were significantly associated with breast cancer risk; the full model gave an area under the curve of 0.63.[79]

- 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.[80] The results of these studies support the concept of OncoVue but do not represent direct evidence of its clinical validity or utility.

- Wacholder et al. evaluated the performance of a panel of 10 SNPs associated with breast cancer that had, at the time of the study, been validated in at least 3 published GWAS. Cases (n=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).[62] The SNP panel was examined as a risk predictor alone and in addition to readily available components of the Gail model (eg, diagnosis of atypical hyperplasia was not included). Mammographic density also was not included. The authors found that adding the SNP panel to the Gail model resulted in slightly better stratification of a woman's risk than either the SNP panel or the Gail model alone but that this stratification was not adequate to inform clinical practice. For example, only 34% of the women who actually had breast cancer were assigned to the top 20% risk group. AUC for the combined SNP and Gail model was 62% (50% is random, 100% is perfect).

- Darabi et al. investigated the performance of 18 breast cancer risk SNPs, together with mammographic percentage density (PD), body mass index (BMI), and clinical risk factors in predicting absolute risk of breast cancer, empirically, in a well-characterized case-control study of postmenopausal Swedish women.[81] 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 × 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 5-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.

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

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

Conclusion

There is a lack of published detail regarding OncoVue® and BREVAGen™ test validation, supportive data, and management implications. Available data suggest that OncoVue® and BREVAGen™ may add predictive accuracy to the Gail Model. However, the degree of improved risk prediction may be modest, and clinical implications are unclear. There is insufficient evidence to determine whether using breast

cancer risk estimates from OncoVue® or BREVAGen™ in asymptomatic individuals changes management decisions and improves patient outcomes.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

Current NCCN guidelines 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.[83] For breast cancer risk assessment, the Gail model[84] or risk models for women with elevated risk based on family history (eg, Claus et al[85] or Tyrer-Cuzick et al)[86] are recommended.[83,87]

Summary

There is insufficient evidence in the published peer-reviewed scientific literature to determine how testing for single-nucleotide polymorphisms (SNPs) may predict the risk of nonfamilial breast cancer and guide decisions in the clinical setting related to breast cancer treatment, management, or prevention. Additionally, it is not known whether health outcomes are improved as a result of clinical decision-making based on these gene tests. Further, evidence-based guidelines do not recommend testing for SNPs for the management of breast cancer. Therefore, the use of SNP panel tests and clinical-genetic tests (OncoVue®, BREVAGen™, and others) to predict breast cancer risk is considered investigational.

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CROSS REFERENCES

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

CODES	NUMBER	DESCRIPTION
CPT	0008M	Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score
	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	