Regence

Medical Policy Manual

**Topic:** Use of Common Genetic Variants to Predict Risk of Nonfamilial Breast Cancer  
**Date of Origin:** January 27, 2011

**Section:** Genetic Testing  
**Last Reviewed Date:** June 2013

**Policy No:** 23  
**Effective Date:** August 1, 2013

**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), 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. Some commercially available assays test for several SNPs and combine results to predict an individual’s risk of breast cancer relative to the general population in order to identify those at increased risk who might benefit from more intensive surveillance.

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.

**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 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.

At least 10 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), although Navigenics (Forest City, CA) and City of Hope (Duarte, CA) appear to offer testing only through physicians. The company does provide interested consumers with access to a network of physicians who are reported to be familiar with the company’s test profile and who utilize the test.

The algorithms or risk models used for all the tests identified, except for those offered by deCODE (Reykjavik, Iceland), are proprietary and not described on company websites. In the 5 tests providing some information on the SNPs used for testing, these range from panels as small as 6 SNPs (Matrix Genomics, Santa Fe, NM) to as large as 16 SNPs (deCODE). The Intergenetics Oncovue SNP-based test is profiled in a separate Policy (2.04.57 Non-BRCA Breast Cancer Risk Assessment (OncoVue)).

There appear to be two separate methods by which deCODE reports out risk for breast cancer. One is the deCODE BreastCancer™, test which includes a 16 SNP panel from which a risk assessment is derived for women of European ancestry. The second is the deCODEme Complete Scan for risk assessment of a broad assortment of diseases including breast cancer. A table in promotional material for this test suggests the risk levels differ based on ancestry with 17 SNPs of interest for patients of European descent, 6 for patients of Asian descent, and 1 for patients of African descent. It is not clear how or if deCODE uses this information in its Complete Scan report.

<table>
<thead>
<tr>
<th>Company</th>
<th>Location</th>
<th>Test Offered Direct-to-Consumer</th>
<th>Number of SNPs Used in Risk Panel</th>
</tr>
</thead>
</table>

*Tests for Breast Cancer Susceptibility Using SNP-Based Risk Panels*
## Tests for Breast Cancer Susceptibility Using SNP-Based Risk Panels

<table>
<thead>
<tr>
<th>Company</th>
<th>Location</th>
<th>Test Offered Direct-to-Consumer</th>
<th>Number of SNPs Used in Risk Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>23andme</td>
<td>Mt. View, CA</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>City of Hope</td>
<td>Duarte, CA</td>
<td>No</td>
<td>7</td>
</tr>
<tr>
<td>deCODE</td>
<td>Reykjavik, Iceland</td>
<td>Yes</td>
<td>deCode BreastCancer – 16; deCODE Complete Scan – 16</td>
</tr>
<tr>
<td>easyDNA</td>
<td>Elk Grove, CA</td>
<td>Yes</td>
<td>ND</td>
</tr>
<tr>
<td>GenePlanet</td>
<td>Dublin, Ireland</td>
<td>Yes</td>
<td>15</td>
</tr>
<tr>
<td>Matrix Genomics</td>
<td>Santa Fe, NM</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>MediChecks</td>
<td>Nottingham, UK</td>
<td>Yes</td>
<td>ND</td>
</tr>
<tr>
<td>Navigenics</td>
<td>Forest City, CA</td>
<td>No*</td>
<td>ND</td>
</tr>
<tr>
<td>Pathway Genomics</td>
<td>San Diego, CA</td>
<td>Yes</td>
<td>ND</td>
</tr>
<tr>
<td>The Genetic Testing Laboratories</td>
<td>Las Cruces, NM</td>
<td>Yes</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND – not described

*Consumers are referred to a network of providers for testing

### 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.
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

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

SCIENTIFIC BACKGROUND

Introduction

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.\(^{[1-9]}\) 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.\(^{[10-32]}\) Further, studies investigating SNP association in Hispanic women have also been conducted.\(^ {33,34}\)

SNP-based Risk Assessment

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. There is growing literature on these associations although public information on the actual models being offered commercially is sparse. 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. In July 2008, deCODE, 23andme, and Navigenics agreed to work with the Personalized Medicine Coalition (PMC) on a set of standards regarding the scientific validity of their genotyping panels; in the process test individuals were genotyped for 3 disease associations, but the PMC provides actual information on only one (breast cancer) with very little detail. (Report available online at: http://cancercontrol.cancer.gov/od/phg/docs/pmcsvalid.pdf.)

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.
In 2008, Pharoah et al.\cite{35} 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.

In a 2013 study, Michailidou and others genotyped 45,290 cases and 41,880 controls from European ancestry identified through 9 GWAS.\cite{36} Authors identified SNPs at 41 new breast cancer susceptibility loci at genome-wide significance. Authors conclude that further analyses suggest that more than 1,000 additional loci are involved in breast cancer susceptibility.

In order to identify additional genetic variants for estrogen receptor (ER)-negative breast cancer, in a 2013 study, authors conducted the largest meta-analysis of ER-negative disease to date, comprising 4,754 ER-negative cases and 31,663 controls from 3.\cite{37} Authors also confirmed three known loci associated with ER-negative (19p13) and both ER-negative and ER-positive breast cancer (6q25 and 12p11).

Hein and others evaluated the 6q25.1 locus, first identified via a GWAS study in Chinese women and marked by single nucleotide polymorphism (SNP)\cite{38} rs2046210. Authors examined the associations of both SNPs in 61,689 cases and 58,822 controls from forty-four studies collaborating in the Breast Cancer Association Consortium, of which four studies were of Asian and 39 of European descent. Authors concluded these results suggested the presence of two variants at 6q25.1 each independently associated with breast cancer risk in Asians and in Europeans. Of these two, the one tagged by rs2046210 was associated with a greater risk of ER-tumors.

Lambrechts and others in a 2012 study genotyped the variants rs2380205, rs1011970, rs704010, rs614367, and rs10995190 in 39 studies from the Breast Cancer Association Consortium (BCAC), involving 49,608 cases and 48,772 controls of predominantly European ancestry.\cite{39} Authors suggested the association for rs614367 was specific to ER-positive disease and strongest for ER plus progesterone receptor (PR)-positive breast cancer, whereas the associations for the other three loci did not differ by tumor subtype.

Wacholder et al\cite{40} evaluated the performance of a panel of 10 SNPs with established associations 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). The panel contained 5 SNPs included in the deCODE BreastCancer™ test. The SNP panel was examined as a risk predictor alone and in addition to readily available components of the Gail model (minus mammographic density and diagnosis of atypical hyperplasia). The authors found that adding the SNP panel to the Gail model resulted in slightly better stratification of a women’s risk than either the SNP panel or the Gail model alone but that this stratification was not adequate to inform clinical practice. For example, only 34% of the women who actually had breast cancer were assigned to the top 20% risk group. The area under the curve (AUC) for the combined SNP and Gail model was 61.8% (50% is random, 100%
• Reeves et al.[41] 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).

• Mealiffe et al.[42] evaluated a 7-SNP panel in a nested case-control cohort of 1,664 case patients and 1,636 controls. Again a multiplicative model was used and, as in the study by Wacholder et al., the genetic risk score was reviewed as a potential replacement for or add-on test to the Gail clinical risk model. These authors employed the net reclassification improvement, or NRI, to evaluate performance. While they concluded that statistically significant improvements could be observed by addition of the genomic risk assessment to the Gail clinical risk assessment, they were unable to posit or demonstrate that the observed changes would lead to improved clinical outcomes. They suggested further studies were needed and that benefit might be observed by careful selection of patients (e.g. those who on Gail score analysis exhibited intermediate risk) who might comprise a priori of candidates who would benefit from enhanced or improved risk assessment.

• Darabi et al.[43] investigated the performance of 18 breast cancer risk single-nucleotide polymorphisms (SNPs), together with mammographic percentage density (PD), body mass index (BMI), and clinical risk factors in predicting absolute risk of breast cancer in a population of Swedish women. The study estimated that using an individualized screening strategy based on risk models incorporating clinical risk factors, mammographic density, and SNPs, would capture 10% more cases. The outcomes of such a change remain unknown.

• Fasching and others in a 2012 study identified 11 SNPs associated with breast cancer (BC) risk. Authors investigated these and 62 other SNPs for their prognostic relevance.[44] Breast tumor expression of these genes was not associated with prognosis. Authors suggest with the exception of rs3803662, there was no evidence that any of the SNPs associated with BC susceptibility were associated with the BC survival.

It is assumed that many more genetic risk markers remain to be discovered as the majority of the genetic risk of breast cancer has not been explained by known gene variants and SNPs. One reason more genetic associations have not been found is that even large GWAS are underpowered to detect uncommon genetic variants.[45]

Multi-factor SNP analysis

Recently, Bloss et al.[46] reported on the psychological, behavioral, and clinical effects of risk scanning in 3,639 subjects followed for a short-term period. Investigators evaluated anxiety, intake of dietary fat, and exercise based on information from genomic testing. Authors concluded there were no significant changes before and after testing. They also noted no increase in the number of screening tests obtained in enrolled patients. While more than half of patients participating in the study indicated intent to have screening tests performed in the future, during the course of the study itself, no actual increase was observed.
Clinical Practice Guidelines

There are no evidence-based clinical practice guidelines that recommend utilization of SNP panels to determine breast cancer risk.

Summary

Common, single nucleotide polymorphisms (SNPs) have been shown to be significantly associated with breast cancer and to individually convey slightly elevated risk of breast cancer compared to the general population risk. These SNP panel tests can be physician-ordered only (e.g., deCODE BreastCancer™ test) or obtained direct to consumer (e.g., part of deCODEme’s deCODEme Cancer Scan, 23andme’s Health Edition test, or of Navigenic’s comprehensive genetic testing panel). However, the companies that manufacture the SNP panels do not provide sufficient information to the consumer on the SNPs included in the panel, and thus determining clinical utility of the panels is not feasible. 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.\[35,40-42,45,47,48\] 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.

REFERENCES


27. Palmer, JR, Ruiz-Narvaez, EA, Rotimi, CN, et al. Genetic susceptibility loci for subtypes of


46. Blond, CS, Schork, NJ, Topol, EJ. Effect of direct-to-consumer genomewide profiling to assess


**CROSS REFERENCES**

Non-BRCA Breast Cancer Risk Assessment (OncoVue®), Genetic Testing, Policy No. 03

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

<table>
<thead>
<tr>
<th>CODES</th>
<th>NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>