GeneType for Breast Cancer

Advanced Breast Cancer Risk Prediction
November 2019

Highlights

GeneType for Breast Cancer combines the key risk factors for breast cancer — family history, mammographic breast density and single nucleotide polymorphisms — in a proprietary algorithm to provide integrated 5-year and lifetime risk scores for the patient. The test is designed to assess the risk of sporadic breast cancer using genomic and clinical markers common to the general population.

GeneType for Breast Cancer has been cross-validated in the world-renowned Nurses' Health Study dataset and provides key clinical advantages for the physician.

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Background

Breast cancer accounts for 30% of new cancer cases in US women making it the most common form of cancer affecting women.[1] It is estimated that in the United States approximately one in eight women will develop the disease in their lifetime; in 2019 over 268,000 women will have been diagnosed with invasive breast cancer and approximately 41,000 will have died as a result[2]. Early detection and treatment options for breast cancer patients have improved over the years, and have thus extended patient survival rates and modestly lowered mortality rates. However, incidence rates remain largely the same. There is a need to predict which women will develop the disease, and to apply measures to prevent it. Additionally, early detection (while substantially improved since the onset of routine mammography over 30 years ago) could be further improved upon if women were appropriately screened. Approximately a third of women are not up-to-date with the recommended screening.[2] There is a need to better predict which women will develop breast cancer, and to apply appropriate screening measures for that increased risk population.

The past 20 years has witnessed substantial improvement in the understanding of hereditary breast cancer where deleterious genetic alterations are passed down through generations, parent to child. There has been much interest, education, and professional guidance regarding testing for germline genetic mutations in *BRCA1* and *BRCA2* allowing for the identification of individuals at significantly increased risk of hereditary breast and ovarian cancers (HBOC). However, such mutations are relatively rare in the general population, accounting for 1 in every 400 women.[3,4] Of women diagnosed with breast cancer, the frequency of *BRCA1/BRCA2* mutations are higher and account for ~6% of all breast cancer cases in the United States.[5] A further group of breast cancer cases (~5%) are associated with moderate penetrance genes such as *PALB2, ATM, CHEK2*, etc[5]. However, the reality remains that ~85% of breast cancers are sporadic for which no causative mutation is known. Most women will not have a strong family history or other risk factors that would justify genetic counselling and/or subsequent *BRCA1/2* and/or multi-gene mutation testing indicated for suspected hereditary/familial breast cancer. Furthermore, those women that have tested negative for *BRCA1/2* and/or multi-gene mutation testing, are often inappropriately placed back at population level risk. The risk of developing breast cancer in these two groups of women—***the majority of women—***has to be defined by other genomic/clinical markers common to the population at large.

Accurate Risk Stratification for Healthy, Asymptomatic Women

Current clinical guidelines outlining qualifying criteria for women to be screened for BRCA testing, or other hereditary cancer syndromes are lengthy, and largely revolve around cancer family history.[6,7] For those women who subsequently return a negative BRCA (or multi-gene panel) test result, their screening recommendations often reflex back to the general population guidelines despite the fact that these women may actually be at higher risk of breast cancer compared to the average woman. Similarly, those women who may have some family history of breast cancer, but who do not meet the criteria for germline genetic testing often remain, inappropriately, in a general population screening category. And finally, there are also women with no breast cancer family history who may in fact be at increased risk of the disease, but have not yet presented with any of the common clinical “red flags” that suggest they may be at increased risk. Together, the three aforementioned scenarios represent ~99% of healthy, asymptomatic women.

GeneType for Breast Cancer is designed to assess the risk of sporadic breast cancer using genomic and clinical markers common to the general population. Risk stratification can help identify at-risk women who may be currently hidden within the general patient population by incorporating unique risk factors into the prediction model.

Importance of accurate risk stratification in women:

- with negative BRCA (or multi-gene panel) test result
- who do not meet criteria for germline genetic testing
- with no breast cancer family history

Mammographic Breast Density: A Notifiable Risk Factor

Mammographic density (also called 'breast density') is a term used to measure and compare the different types of breast tissue visible on a mammogram. Research shows that breast density can itself be a risk factor for developing breast cancer and federal law in the US requires all imaging facilities to include breast density information on mammography reports sent to patients and physicians. However, the majority of such legislation falls short of providing any guidance on what to do with that information.

GeneType for Breast Cancer incorporates breast density into its risk model allowing the translation of breast density information into a clinical risk prediction result for the patient.

Genomic Markers: The Next Generation in Risk Prediction

There is no single mutation associated with sporadic breast cancer, nor a repository of information about genomic contribution to complex disease such as Breast Cancer. Breast Cancer is a heterogeneous and multifactorial disease, and as such, many different risk factors can influence and contribute to the type and presentation of the disease. At present the measurable genomic markers associated with complex disease are identified using genome wide association studies. These 77 SNPs were identified from over 500,000 SNPs in multiple genome-wide association studies (GWAS) involving over 50,000 women.[8,9] The SNPs are assessed by Phenogen Sciences Laboratory using TaqMan Multiplexed Array technology.

GeneType for Breast Cancer: Product Design Features

The test is designed to facilitate better informed decisions about screening and prevention plans. It is applicable to women aged 35 years or older who have not been diagnosed with breast cancer or LCIS/DCIS. The test considers the following:

Clinical Risk Factors

- Age
- Number of affected female first-degree relatives
- Age of youngest affected first-degree relative
- Number of affected second-degree relatives
- BIRADS/Percent mammographic breast density
- BMI (Height & Weight)
- Menopausal Status
- Ethnicity

Genomic Risk Factors

- 77 SNP Polygenic Risk Score*

**test includes a painless, quick cheek swab collection.*

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The integrated risk score combines clinical risk factors and genomic markers to estimate the risk of developing breast cancer over two time periods. The report generates objective, actionable results to support the creation of a personalized breast health plan. Any patient identified as at increased risk based on her 5-year or lifetime risk score can be referred to a specialist* for follow-up.

5-Year Risk Score	Utilized to establish eligibility for risk reducing medication/ chemoprevention and modified clinical surveillance.[10-12]
Lifetime Risk Score	Utilized to establish eligibility for modified clinical surveillance and modified screening surveillance.[13-15]

** a specialist may be one of several clinicians who specializes in the area of breast cancer screening and prevention, with an emphasis on both sporadic and hereditary/familial breast cancers*

GeneType for Breast Cancer: The Science Behind the Test

GeneType for Breast Cancer incorporates the three key risk factors for breast cancer: extended family history, mammographic breast density, and a polygenic risk score comprised of the key low-penetrance genetic susceptibility loci.

Family History

Having a family history of breast cancer is a well-established risk factor for breast cancer. However, most women who develop breast cancer do not have an extensive family history of the disease. Because breast cancer is a common condition, it is not unusual for more than one family member to develop cancer (including breast cancer) during their lifetime. Only about 5% of breast cancer can be explained by an inherited gene mutation such as *BRCA1* or *BRCA2*.[5] However, a family history on either the mother's side or the father's side increases a woman's risk of breast cancer.

The magnitude of risk associated with a family history of breast cancer increases with the number of family members affected and the younger their ages at diagnosis. Women with one first-degree relative (parent, sibling or child) who has had breast cancer have about double the risk of breast cancer compared to women with no family history. Women with one or more second-degree relatives who have had breast cancer have about 1.5 times the risk of breast cancer as women with no family history. A second-degree relative is an aunt, uncle, grandparent, grandchild, niece, nephew or half-sibling.

Because cancer is a common condition, it is not unusual for more than one family member to develop cancer (including breast cancer) during their lifetime. Cancer can occur in more than one family member simply by chance or because of genomic, lifestyle or environmental factors. Family members have genetic factors in common and often have similar environments and lifestyles as each other. These shared backgrounds may contribute to the increased breast cancer risk in women with a family history of breast cancer.

Mammographic Breast Density

Breasts are made up of several different components that include fat, glandular tissues (the milk ducts and lobules) and connective tissues. High breast density means there is a greater amount of glandular and connective tissue compared to fat. Low breast density means there is a greater amount of fat compared to glandular and connective tissue.

Glandular and connective tissue shows up white on a mammogram whereas fat shows up dark on a mammogram. White areas that are present on a mammogram are usually quantified as “percent dense area” or categorized using the BI-RADS (Breast Imaging-Reporting and Data System) tool developed by the American College of Radiology, that provides a widely accepted reporting method for imaging of the breast. Whilst there are several automated methods for defining “percent dense area” or the BI-RADS category, the majority of mammograms are subjectively classified into the BI-RADS categories by interpreting radiologists. Approximately 43% of women aged 40–74 in the U.S. have heterogeneously or extremely dense breasts by mammography (Categories 3 and 4).[16]

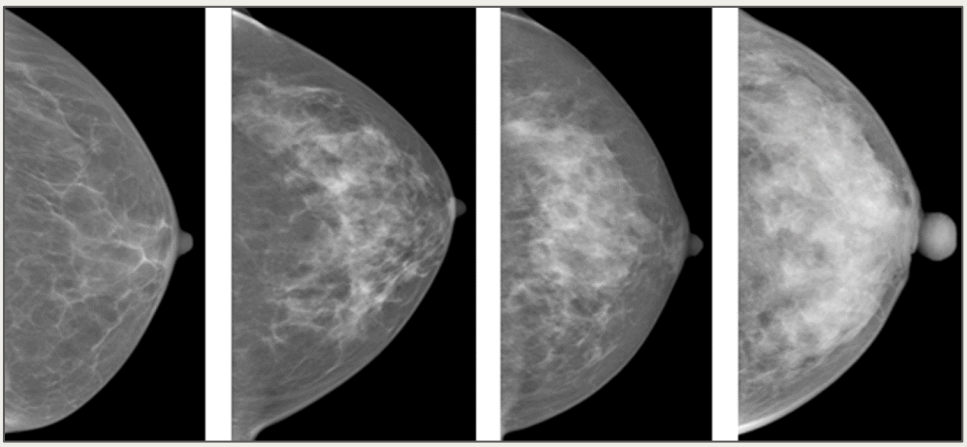

Figure 1. Craniocaudal views of the left breast in four different patients representing (from left to right): Category 1; almost entirely fatty breasts, Category 2; scattered fibroglandular tissue, Category 3; heterogeneously dense breasts, and Category 4; extremely dense breasts.

Polygenic Risk

Approximately half of all breast cancers in women with a family history of the disease are explained by a known genomic component.[17,18] In addition to pathogenic variants in high or moderate penetrant genes such as *BRCA1/BRCA2*, single-nucleotide polymorphisms (SNPs) explain a large proportion of the risk in women with a strong family history. Furthermore, SNPs also contribute to the development of non-familial breast cancer in women, accounting for at least 16% of genomic risk.[17] On a population basis, the polygenic risk conferred by these susceptibility SNPs is greater than the risk from single pathogenic variants in a single high- or moderate-risk gene,[18] especially for women without any family history of breast cancer.[19,20] Dependent on genotyping of susceptibility SNPs (*i.e.*, 0 risk alleles, 1 risk allele, or 2 risk alleles), a risk estimate can be derived. In isolation, each of these SNPs may only augment risk by a small amount, but in combination, they confer clinically significant risk. Most importantly, these SNP appear independent of other risk factors and therefore can be added to other known risk factors and assessment tools. Thus, the combination of risk estimates for each SNP into a polygenic risk score (PRS) can improve breast cancer risk prediction.

Scientific Validation

GeneType for Breast Cancer is a risk assessment test, not a diagnostic test. Diagnostic tests can be evaluated on the basis of sensitivity/specificity and the positive- and negative-predictive values. However, the accuracy of risk assessment tests can be assessed in several ways, the most common being discrimination. Discrimination is a measure of how well the model can separate those who do and do not have the disease of interest. The AUC (area under the ROC curve) or c-statistic, is a measure of test discrimination, that is, the probability that a predicted risk is higher for a case than for a non-case. Results range from a value of 0.5 up to 1.0 for a test with perfect discrimination.

We have determined and validated the accuracy and clinical validity of the risk scores using approximately 800 cases and 2,000 controls from the Australian Breast Cancer Family Registry and the Australian Twins and Sisters Study.[21-24] However, the gold standard in assessing the performance of a new model is a cross-validation in a study population that is independent from that used to build the risk model. To that end, we have cross-validated the model using 1,272 cases and 1,820 controls from the Nurses' Health Study.[25]

Log-Transformed Risk Score	**AUC**	**(95% CI)**
Caucasian (n = 2,601 from the Nurses' Health Study)		
Breast Cancer SNP-based	0.61	(0.59,0.63)
IBIS	0.58	(0.56,0.60)
IBIS plus SNPs	0.64	(0.62,0.66)
GeneType for Breast Cancer	0.65	(0.63,0.67)

Table 1: AUC and 95% confidence intervals (CI) in a benchmark comparison with the IBIS breast cancer risk model. Importantly, these results confirm that our approach to risk model development is valid and that we can simplify complex family history algorithms to incorporate the most important risk factors (family history, mammographic density, and PRS) without detracting from model performance. Moreover, we have shown improved test performance over standard assessments with a model that is easier for physicians and patients to use.

The GeneType for Breast Cancer Model has been fully validated for use in Caucasian patients. The risk model incorporates ethnicity-specific polygenic risk scores as previously reported [22-24]. The model also incorporates population incidence data for patients of African American and Hispanic American descent derived from the Surveillance, Epidemiology, and End Results Program (SEER),[22] however, the full model has not been validated in these populations yet. The discriminatory performance of GeneType for Breast Cancer compared very favorably with the Industry Standard breast cancer risk assessment model IBIS (Tyrer-Cuzick Model) when measured in a direct benchmark comparison. It represents an approximate 25% improvement in test performance over our earlier BREVAGen*plus* test.

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Clinical Utility

The current retrospective data supporting clinical utility of PRS is strong across some diseases. Although not yet included in practice guidelines for any major medical organization, there is a significant amount of data supporting the risk variants used to calculate PRS in Caucasian women for breast cancer risk assessment.[23,26,27,28] Similarly, the PRS for both African American and Hispanic women have been validated in ethnic-specific cohorts.[22] As the research community continues to expand multiethnic cohorts, PRS will continue to improve in its capacity to stratify at-risk individuals.[29]

Prospective cohort studies consistently provide evidence that PRS for breast cancer provides more accurate risk prediction than family history alone and that PRS can aid in risk-stratified screening and prevention.

Li *et al*. analyzed 4,365 women from the Australian Breast Cancer Family Registry and the KConFab familial breast cancer cohorts, with 2,599 prospectively analyzed over 7.4 years.[30] During this follow-up period, 205 breast cancers occurred. The hazard ratios for continuous PRS per standard deviation was 1.38 (95% CI: 1.22–1.56), and the upper vs. lower quintile hazard ratio was and 3.18 (95% CI: 1.84–5.23). Based on a threshold of 20% lifetime risk, the authors concluded that the clinical management of 23% of women could be altered by incorporating PRS into their risk assessment. This conclusion provided support for the use of breast cancer-associated SNPs in risk assessment within family breast cancer cohorts by showing more accurate risk prediction than family history alone. More importantly, this can influence recommendations for cancer screening and prevention modalities for high-risk women.

In a large prospective study, Naslund-Koch *et al*.; approximately 35,000 women from the Danish general population were followed in Danish health registries for up to 21 years after blood sampling.[31] Patients were genotyped for 72 breast cancer associated SNPs. These alleles were not associated with incidence of other cancers but each breast cancer risk allele was associated with a 4% increase of breast cancer incidence, and with 5% increased breast cancer mortality. After including the breast cancer allele sum in risk assessment, 25% of women currently being offered screening mammography had an absolute 5-year risk below the cut-off of average risk for a 50-year-old woman. The study provides strong evidence that a polygenic risk score can aid in risk-stratified breast cancer screening.

Van Veen *et al*. analyzed 9,363 women in a prospective cohort between 2009-2017 in the UK. Of these, 466 were found to have breast cancer (271 prevalent; 195 incident).[32] A combined risk assessment stratified the cohort such that those at 5% or greater 10-year risk were 5-fold more likely to develop a high stage cancer than those at less than 2% 10-year risk. Furthermore, 54% of the cases were stratified to a risk category above average consisting of 62% interval-detected cancers and 64% stage 2+ cancers. In contrast, 33% of the control cohort had 10-year risk scores below average at less than 2% compared to 18% of breast cancer cases (17% interval-detected and 14% stage 2+) with low 10-year risk scores. The conclusion supporting the view that PRS-combined risk is likely to aid risk-stratified screening and prevention strategies.

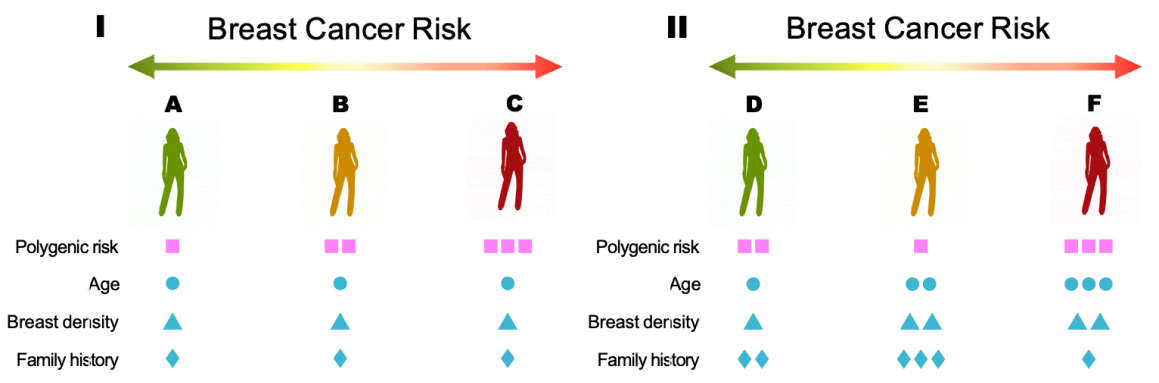

Figure 2: Polygenic risk score incorporation improves breast cancer risk prediction models through reclassification. It can (I) "boost" a patient's absolute risk score. As illustrated in patients A, B and C, the women have identical clinical risk factors but their absolute breast cancer risk scores vary due to the influence of PRS. Alternatively, polygenic risk scores can (II) "counteract" traditional risk factors by lowering a patient's absolute risk score as illustrated by patients D, E and F who all have varying clinical risk factors suggestive of breast cancer risk. In these scenarios, the polygenic risk may in fact lower a patient's absolute risk score compared to her risk score using an alternative risk assessment model.

GeneType for Breast Cancer

GeneType for Breast Cancer brings together – for the first time – research on all the important risk factors for breast cancer [23, 26, 33-36] to provide women with a simple risk prediction score.

To provide each woman with an estimate of her five-year absolute risk of breast cancer and her remaining lifetime risk of breast cancer, GeneType for Breast Cancer uses the woman's age, a polygenic risk score based on 77 SNPs, mammographic density, a simple measure of family history of breast cancer, menopausal status, and body mass index. The risks are expressed as percentages for ease of comprehension.

GeneType for Breast Cancer data collection is simple. Clinicians collect a non-invasive, buccal specimen and subsequently complete a simple questionnaire about their patient's family history of breast cancer, menopausal status, body mass index, and breast density (% density or BIRADS as reported by the patient's mammography screening service). Genotyping and analysis is performed by Genetic Technologies Limited in their CLIA certified and NATA approved laboratory.

GeneType for Breast Cancer simply asks for the number of affected first-degree and second-degree relatives and the earliest age at diagnosis for each. We have eliminated the need for elaborate cancer pedigree analysis and have thus greatly reduced the burden of data collection on the women and their clinicians.

Other models (BOADICEA, BRCAPRO, IBIS, BCRAT) have only taken some risk factors into account, and until recently none of these have incorporated mammographic density. Some require extensive pedigree information to be entered and all include many other factors of nominal value in risk

discrimination. This is a problem for their applicability to the general population, such as women undergoing mammography or for use at the primary care level. Other risk prediction models (e.g. BCRAT) are simple to use but do not incorporate important risk factors such as the polygenic risk score and mammographic density.

Conclusions

GeneType for Breast Cancer predicts a woman's absolute risk of developing breast cancer over the next five years as well as over her remaining lifetime. Risk assessment is important in determining a personalized breast health plan, including options for screening and risk-reducing medications. GeneType for Breast Cancer integrates cutting-edge genomics with traditional risk assessment modeling to provide the clinician and patient access to the forefront of personalized risk prediction.

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