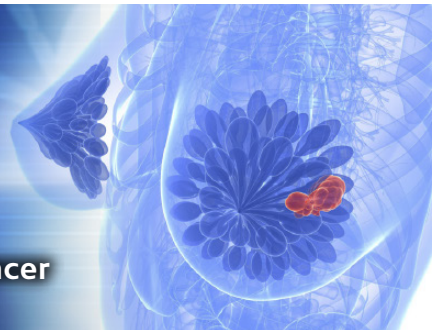
Research Review™
PRODUCT REVIEW

Comprehensive risk assessments with geneType™ for breast cancer



Making Education Easy 2023

Independent expert commentary by Dr Nicole Yap
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Dr. Nicole F.S Yap, is a highly specialized breast surgeon who practices oncoplastic surgery in Melbourne, Australia.

Dr. Yap possesses a unique skill set that allows her to remove and treat breast cancer while simultaneously focusing on preserving or enhancing the aesthetic and cosmetic aspects of the breast. Her exceptional proficiency is the result of her dual training, which eliminates the need for patients to engage with two separate surgeons. This innovative approach to breast cancer management not only simplifies the process but also empowers patients to confront the disease with a positive mindset, a crucial factor in achieving a better overall outcome.

One concerning trend is the rising incidence of breast cancer among younger women, those under the age of 50. In the United States, statistics reveal a 2% yearly increase in this demographic. Currently, a significant 23% of all breast cancer cases occur in women under 50 years old.

Despite the increasing prevalence of breast cancer, there has been a notable reduction in mortality rates, primarily due to heightened public awareness. However, younger women still tend to seek medical attention at later stages of the disease. This delay could be attributed to apprehension about the unknown or concerns about potential alterations to their sense of femininity.

To better serve patients in need, Dr. Yap offers consultations and surgical interventions at multiple locations across Melbourne. Her dedication to improving breast cancer care, particularly among younger women, reflects her commitment to advancing healthcare outcomes in the realm of breast surgery.

Abbreviations used in this review:

AUC = area under the curve
BI-RADS = breast imaging reporting and data system
BMI = body mass index
E/O = expected/observed
ER = oestrogen receptor
GWAS = genome-wide association studies
HR = hazard ratio
HRT = hormone replacement therapy
IQR = interquartile range
MRI = magnetic resonance imaging
NRI = net reclassification improvement
OR = odds ratio
PRS = polygenic risk score
SD = standard deviation
SNP = single-nucleotide polymorphism

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This publication focuses on the geneType™ for Breast Cancer risk prediction test. This proprietary tool combines family history, mammographic breast density and single nucleotide polymorphisms to provide patients with 5-year and remaining lifetime breast cancer risk scores. As most breast cancers occur in women who do not have a family history of the disease, the geneType™ test provides a more accurate assessment than traditional approaches, thereby allowing for personalised discussions about how patients wish to manage their risk. For some, this may involve changes in lifestyle, increased screening and/or preventative interventions, while other patients at lower risk levels may be reassured by their result.

Background

Breast cancer was estimated to be the most frequently diagnosed cancer in Australia in 2021.[1] It is also the most common cancer in women with one in eight to ten women developing breast cancer during their lifetime.[1,2] In terms of mortality, breast cancer is second only to lung cancer in Australia, accounting for 3,102 estimated deaths in 2021.[1]

Early detection of breast cancer is critical for patient outcomes as the disease is curable in its earliest stages, whereas the goals of care switch to prolonging survival and maintaining quality of life in those with metastatic disease.[2] In Europe and North America, breast cancer mortality has decreased largely due to early detection and the efficacy of systemic therapies.[2]

Breast cancer screening

Screening for breast cancer promotes early detection when less aggressive treatment options are more realistic and survival is more likely.[3] From the 73,440 breast cancers diagnosed in Australian women from 2002 to 2012, 55.3% of cancers detected via BreastScreen Australia were small (≤15 mm), compared to 27.6% of cases in women who had never screened through this service.[4] Furthermore, breast cancers detected through screening had a 54-63% lower risk of causing death* than women who had never screened.[4]

*Using lead times and correction factors appropriate for Australian women aged 50-69 years

Current guidelines

Breast screening for women in Australia is modified according to the degree of individual risk. Female gender is the strongest risk factor for developing breast cancer.[3] Age is the second most significant factor with women aged 50 years being 10 times more likely to have breast cancer than women aged 30 years.[3]

Currently, BreastScreen Australia recommends that asymptomatic women with a low risk of breast cancer should undergo mammographic screening every two years between the ages of 50 and 74 years, with more frequent monitoring for those at higher risk (**Table 1**).[5] Women who are asymptomatic and aged 40-49 years or ≥75 years can access free mammogram screening, however, they are not automatically invited to participate in the screening programme.

Table 1. Breast screening recommendations according to individual risk[5]

Risk category	Screening strategy
Average or slightly higher risk • >95% of the female population • Approximately 1.5 times the population average	Mammogram every two years from 50-74 years of age
Moderately increased risk • <4% of the female population • Approximately 1.5-3 times the population average	Mammogram at least every two years from 50-74 years; annual mammograms from age 40 years if a first-degree relative aged <50 years has been diagnosed with breast cancer. Consider consultation with a family cancer clinic for further assessment and management.
Potentially high-risk or carrying a mutation • <1% of the female population • >3 times the population average*	Advise referral to a cancer specialist or family cancer clinic for assessment, possible genetic testing and management. Surveillance may include regular clinical breast examination and annual imaging with mammography, MRI or ultrasound.

*Risk may be higher or lower if genetic test results are known

N.B. The geneType™ test increases the proportion of women who are classified as at increased-risk. Definitions for traditional risk categories based on family history are available here.

Overdiagnosis due to current Australian breast screening strategies is estimated at approximately 15%.[6] This means that for every 2,000 individuals invited to screening over 10 years, one will be prevented from dying from breast cancer and 5 women who would not have otherwise been diagnosed will be unnecessarily treated.[5] Despite the potential for overdiagnosis and false positive results, the majority of women who receive comprehensive information about overtreatment retain positive attitudes towards breast screening.[7]

Women who are categorised as having a high risk of breast cancer based on their family history may be offered chemoprevention with selective oestrogen-receptor modulators, e.g. tamoxifen or raloxifene, or aromatase inhibitors, e.g. exemestane or anastrozole.[5] Mastectomy or salpingo-oophorectomy are more invasive alternative prevention strategies that may be offered to patients carrying highly penetrant breast cancer risk genes, following a full medical history and careful individual risk and benefit assessments.[5]

Despite the success of breast cancer screening at detecting early malignancy and reducing mortality, the participation rate for BreastScreen Australia is 55% for women aged 50-74 years.[1]

Screening using family history

The current screening strategy in Australia relies on assessing the risk of developing hereditary forms of breast cancer by asking:[5]

- Have any of your close relatives had breast cancer before 50 years of age?
- Do you have more than one relative from the same side of the family who has had breast cancer at any age?

However, most women who develop breast cancer do not have a family history of the disease as approximately 85% of breast cancer cases are sporadic and hereditary forms only account for approximately 5% of all breast cancer cases.[8]

The heritability of breast cancer risk

Attempts have been made to numerically define the heritability of breast cancer risk. Approximately 16% of heritability can be attributed to high and moderately penetrant pathogenic variants, with 5% of cases being due to germline mutations in either the *BRCA* 1 and 2 early onset genes.[8,9] Additional high penetrance genes associated with hereditary breast cancers that have been identified include *CHEK2, PTEN, TP53, ATM, STK11/LKB1, CDH1, NBS1, RAD50, BRIP1* and *PALB2*.[9]

While heritability analysis suggests that most genetic contribution comes from the above high and moderate genes commonly assessed in clinical genetics, the remaining "missing" heritability is likely due to non-coding regions.[10] GWAS have identified low penetrance SNP that represent 18% of hereditary risk.[11] While twin studies have identified 31% of heritability associated with low penetrance risk loci.[12]

Additional risk factors

There are many other risk factors beyond gender, age, genetics and family history that contribute to the risk of breast cancer. These include clinical factors, e.g. breast density, onset of menopause, sleep, HRT and oral contraception use, breast feeding, and behavioural factors, e.g. diet, physical activity, alcohol consumption, and adherence to screening.[3]

Expert comment

In the targeted age group of 50-74 years, 55% of women participated in BreastScreen Australia. This is the latest statistic available and as noted, the incidence of breast cancer is continuing to creep up in this age bracket, but with decreased mortality.

In 2019, 12% of women who screened for the first time and 4% of women attending a subsequent screen, were recalled for further investigation. More than half of the cancers detected by BreastScreen Australia are small (<15mm), allowing for more breast conserving surgery, lower morbidity and improved survival.

The problem is 23% of all breast cancers are in younger women (aged <50 years), where there are no screening programs available. These younger people tend to develop more biologically aggressive breast cancers, which are subsequently picked up late in the disease progress, hence mortality rates are greater. Younger people also tend to have denser breasts and therefore require different imaging such as 3D tomosynthesis mammography, contrast mammography and/or MRI. These are not offered at BreastScreen, even if BreastScreen lowered the age bracket to 40 years.

The interval between BreastScreen visits is 2 years. About 20% to 30% of women with breast cancer have tumours that are missed by mammogram screening. And these interval breast cancers discovered between routine mammograms seem to be more lethal than those detected by screening. Patients with interval breast cancers have poorer outcomes in terms of 10-year disease-specific (DSS) and disease-free survival (DFS) in comparison to those with screen-detected breast cancers (DSS: 68.2% vs 98.1%, p=0.002; DFS: 78.6% vs 96.5%, p=0.011).[13]

geneType™ for breast cancer

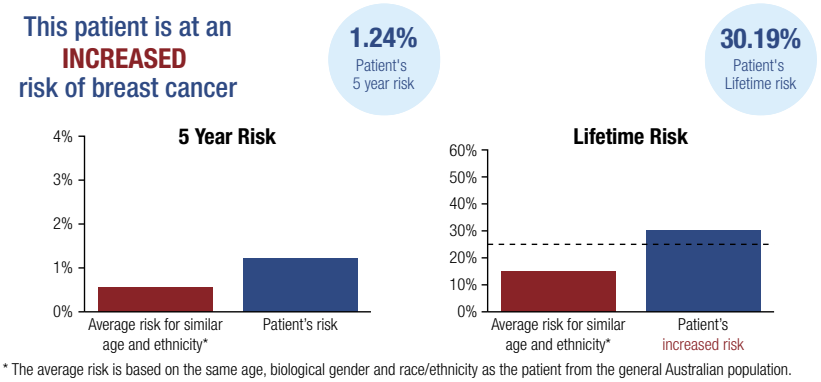
The incidence of breast cancer is highest in developed countries and despite improvements in detection and treatment, mortality rates remain relatively high.[14] Accurate stratification of breast cancer risk in the general population is the first step towards structured conversations about individual risk reduction.

In practice, this means providing women with elevated risk the option of accessing additional imaging modalities or to reduce their risk with medications. Women who are concerned about their breast cancer risk may also be reassured once they understand their risk of developing the disease and the steps that they can take to mitigate this risk. This process promotes awareness and facilitates shared decision-making that may result in additional screening and/or risk reduction strategies for women at average or elevated risk. In the future, women at very low risk may also choose to undergo less frequent screening to reduce the potential risk of overtreatment and its associated harms and costs.

The geneType™ risk prediction test is a relatively simple tool that minimises the amount of information the patient needs to provide. The goal of the test is to accurately predict breast cancer risk in unaffected women by combining multiple risk factors. The test combines the following clinical information with the results of saliva analysis into two risk prediction scores:[15]

- Age
- Number of female first-degree relatives affected
- Age of youngest first-degree relative affected
- Number of second-degree relatives affected
- Mammographic breast density (percentage or BI-RADS)
- BMI
- Menopausal status
- Polygenic risk score based on the presence or absence of 313 SNP

The 5-year risk prediction score (**Figure 1**) is useful for guiding short-term risk-reduction strategies and is of greatest benefit for older women, while the remaining lifetime risk score is potentially more helpful to younger women to guide surveillance strategies.



* The average risk is based on the same age, biological gender and race/ethnicity as the patient from the general Australian population.

Figure 1. Fictional example of the geneType™ for breast cancer risk assessment final report

Family history

Eight out of nine women who develop breast cancer do not have an affected mother, sister or daughter.[16] However, evidence from large meta-analyses, cohort and case-control studies clearly shows that a positive family history is associated with an increased risk of breast cancer.[3] The combined data from 52 epidemiological studies estimates the respective risk ratios for breast cancer for women with one, two, and three or more affected first-degree relatives as 1.80 (99% CI 1.69-1.91), 2.93 (2.36-3.64), and 3.90 (2.03-7.49), compared to women with no affected relatives ($p<0.0001$ for each).[16] The risk ratio for breast cancer for women with a second-degree affected relative is estimated to be 1.5 (95% CI 1.4-1.6).[17]

A woman may have a family history of breast cancer on her father or mother's side due to chance, genetic factors, common environmental exposures, or shared lifestyle or dietary factors.[3] The risk of breast cancer for women with an affected family member is likely to be higher for those aged under 50 years and for women with a relative who was diagnosed before age 50 years.[3,16,17]

Mammographic breast density

Breast density on mammography indicates the relative proportions of fat (viewed as dark) and the stromal and epithelial glandular tissue (viewed as white).[3,18] The density of a breast does not correlate with how it appears or feels and mammography is the only method for assessing breast density.[19] The most frequently used tool for assessing mammographic density is the BI-RADS which provides four different density categories (**Figure 2**):[18,20]

- **A.** Almost entirely fatty: calculated* as <25% glandular tissue
- **B.** Scattered fibroglandular densities: calculated as approximately 25-50% glandular tissue
- **C.** Heterogeneously dense: calculated as approximately 51-75% glandular tissue
- **D.** Extremely dense: calculated as >75% glandular tissue

* Approximate percentage for volumetric percent density calculated by imaging software

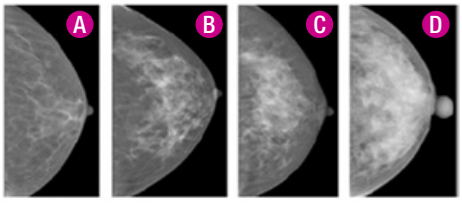


Figure 2. Craniocaudal views of the left breast from four patients with differing breast densities classified from left to right according to the BI-RADS system as: (A) almost entirely fatty, (B) scattered fibroglandular tissue, (C) heterogeneously dense, (D) extremely dense.[15]

There is consistent evidence across meta-analyses that higher mammographic breast density is associated with an increased risk of breast cancer.[3] In postmenopausal women, a large meta-analysis found that the age-adjusted OR for a one standard deviation increment in percentage dense area was 1.53 (95% CI 1.44-1.64).[21] There is currently no data on the prevalence of differing breast densities in Australia, although it is expected to be similarly distributed to the United States where 35.9% of women aged 40-74 years have "heterogeneously dense" breasts and 7.4% have "extremely dense" breasts.[19,22] Currently, it is the policy of BreastScreen Australia and the Royal Australian and New Zealand College of Radiologists not to inform women if they have dense breasts on mammography.[19] Although, Breast Screen Western Australia does notify women and their general practitioners when there is markedly increased breast density on mammogram.[23]

Polygenic risk

Many SNP have been identified via GWAS that are associated with an increased risk of developing breast cancer.[3] Individual SNP may confer little risk, however, additively they bestow a clinically significant risk of developing breast cancer.[24] Polygenic risk scores (PRS) can be created from panels of SNP to calculate cancer risk and combined with other independent epidemiological factors.[24,25]

Polygenic risk scores derived from SNP and mammographic breast density are both independent risk factors for breast cancer and therefore they can be easily combined to improve risk stratification.[26]

Expert comment

The Breast Cancer Risk Assessment Tool (the Gail model) is often used by health care providers to estimate risk. The tool calculates a woman's risk of developing breast cancer within the next 5 years and within her lifetime (up to age 90). It uses 7 key risk factors for breast cancer:

- Age
- Age at first period
- Age at the time of the birth of a first child (or has not given birth)
- Family history of breast cancer (mother, sister or daughter)
- Number of past breast biopsies
- Number of breast biopsies showing atypical hyperplasia
- Race/ethnicity

Women with a 5-year risk of 1.67% or higher are classified as "high-risk".

The major limitation of the Gail model is the inclusion of only first-degree relatives, which results in underestimating risk in the 50% of families with cancer in the paternal lineage, and it also takes no account of the age of onset of breast cancer.

GeneType uses PRS developed by GWAS. "The PRS is a *powerful and reliable predictor* of breast cancer risk that may improve breast cancer prevention programs."[27] PRS refine risk estimates currently based on clinical factors and monogenic germline testing.

Despite earlier concerns, the latest research has demonstrated that PRS is a strong predictor of breast cancer risk. Polygenic factors are estimated to account for an additional 18% of the familial relative risk of breast cancer, with those at the highest level of polygenic risk distribution having at least a twofold increased risk of the disease.

The clinical utility of polygenic risk

Studies have shown that by including polygenic risk into assessments, the number of women with an elevated risk of developing breast cancer who are identified is increased.

To examine the utility of including sets of SNP in familial but non-*BRCA*-associated breast cancer risk assessments, a PRS based on 24 SNP was created for 4,365 women from the Breast Cancer Family Registry and Kathleen Cunningham Consortium Foundation for Research into Familial Breast Cancer cohorts.[28] A group of 2,599 women who were unaffected at enrolment were prospectively followed for an average of 7.4 years, during which time 205 cases of breast cancer occurred with a mean age at diagnosis of 53.6 years. The hazard ratios for continuous PRS per standard deviation was 1.38 (95% CI 1.22-1.56) and 3.18 (1.84-5.23) for the upper vs lower quintile. The cumulative risk of breast cancer for the PRS quintiles of the combined cohort are shown in **Figure 3**. The risk of developing breast cancer at age 70 years was 51% (95% CI 42-60%) for women in the highest PRS quintile and 21% (14-31%) in the lowest quintile.

When the authors compared their PRS-based risk assessment against the recommendation that women with a lifetime breast cancer risk of 20-25% should be offered MRI screening, 23% of women in the study cohort would have undergone a change in management when the threshold of 20% was applied.

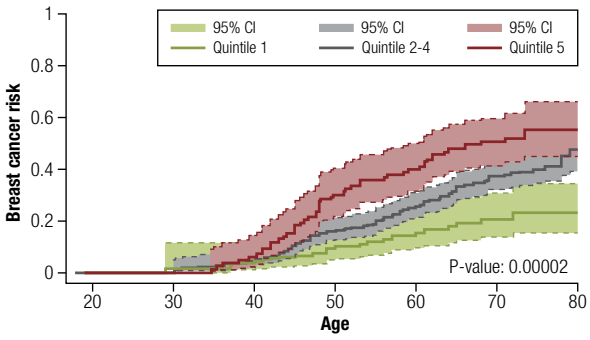


Figure 3. Kaplan-Meier plot of breast cancer risk in a prospective cohort for women in the lower, middle three, and upper polygenic risk score quintiles.
Adapted from Li *et al* (2016).[28]
P-value = log-rank test comparing the 3 curves

Another prospective study followed 35,441 women from the Danish general population for up to 21 years after they had provided blood samples.[29] Genotyping was performed for 72 loci previously identified by GWAS to be independently associated with breast cancer risk and a breast cancer allele sum was calculated for each individual. In 19,010 women, the incidence of breast cancer increased across allele sum quintiles, but the incidence of other cancers did not (p=0.41). The age- and study-adjusted HR for the fifth versus the first allele sum quintile was 1.82 (95% CI 1.53-2.18) and the HRs per allele for breast cancer incidence and mortality were 1.04 (1.03-1.05) and 1.05 (1.02-1.08) respectively.

Interestingly, it was discovered that after including the breast cancer allele sum in risk assessments, 25% of women aged 50-69 years (who are currently offered screening mammography) had a 5-year absolute risk below the 1.5% average risk for a 50-year-old woman.[29] This supports the hypothesis that PRS can be used to stratify breast cancer risk and help guide individual patients with screening and surveillance decisions.

Combining breast density and polygenic risk

To determine whether SNP could be incorporated into a risk prediction tool along with mammographic density and traditional risk factors, 9,363 women aged 46 to 73 years were enrolled from the Predicting Risk of Cancer at Screening (PROCAS) study.[30] Genotyping of 18 SNP, visual-assessment percentage mammographic density and class risk assessment from a self-completed questionnaire were conducted. A total of 466 women developed breast cancer (271 prevalent; 195 incident) with the SNP18 PRS being higher in case patients (median, 1.12; IQR 0.87-1.33) than controls (median, 1.01; IQR 0.77-1.19) and "almost perfectly calibrated" across the subgroups of predicted relative risk. When the SNP were combined with the traditional risk factors and the mammographic density, the number of cases in the ≥5% 10-year risk category (moderate/high-risk) increased by 11% and this group was 5-fold more likely to develop a high-stage cancer than the low-risk group (p<0.001).

Overall, the panel of 18 SNP was found to be similarly predictive of breast cancer risk whether adjusted or unadjusted for both mammographic density and traditional risk factors.[30] These results demonstrate that SNP panels can substantially improve risk prediction models to help identify women who may benefit from additional screening or preventative treatments.

Expert comment

As previously mentioned, PRS are a major component of accurate breast cancer risk prediction and have the potential to improve screening and prevention strategies. PRS combine the risk from SNPs associated with breast cancer in GWAS and explain over 30% of breast cancer heritability. When incorporated into risk models, the more personalised risk assessment derived from PRS help identify women at higher risk of breast cancer development and enables the implementation of stratified screening and prevention approaches.

Validating the geneType™ model

To validate the geneType™ test, the handicapped performance of the geneType model that utilises mammographic breast density, polygenic risk and traditional risk factors was compared against the Breast Cancer Risk Assessment Tool (BCRAT, also referred to as Gail) using data from the UK Biobank.[31] This is a population-based cohort of >500,000 adults aged 40-69 years that began accrual from 2006-2010.[32] The UK Biobank contains genomic information for all of its participants, however, information on mammographic breast density or extended family history are not included, as they are in the geneType model. These factors are often also unknown in clinical situations, therefore demonstrating the performance of the geneType model when the risk factors were only partially completed was an important step in validation.

BCRAT's original purpose was to estimate 5-year breast cancer risk in mammography screening trials and it has also been used to determine eligibility for risk-reducing treatments in breast cancer prevention trials.[31] BCRAT is currently considered a standard tool for estimating 5-year breast cancer risk in the general population.

Two versions of geneType (referred to as BRISK) were compared against BCRAT, with the only difference between the versions being the modification of the PRS from a 77-SNP PRS to the 313-SNP PRS.[25,27,31] The iteration of geneType moved from the 77-SNP PRS to the 313-SNP PRS in January 2023 following the results of this validation.

Results

The dataset contained 200,195 women who were genetically Caucasian and aged 40 to 69 years.[31] During five years of follow-up, 3,138 women were diagnosed with invasive breast cancer with a mean age of 60.8 years at diagnosis, leaving 197,057 women who were unaffected by breast cancer over this timeframe. Affected women had a mean 5-year breast cancer risk of 2.53% (SD=2.1%) for 313-SNP geneType, 2.35% (SD=1.71%) for 77-SNP geneType, and 1.62% (SD=0.07%) for BCRAT. For unaffected women, the 5-year breast cancer risk was 1.70% (SD=1.44%) for 313-SNP geneType, 1.75% (SD=1.20%) for 77-SNP geneType, and 1.46% (SD=0.62%) for BCRAT.

The HR per quintile of risk for 313-SNP geneType was 1.45 (95% CI 1.40-1.49; p<0.001) and 1.38 (1.34-1.42; p<0.001) for 77-SNP geneType, while the HR per quintile of risk for BCRAT was 1.12 (1.08-1.16; p<0.001).[31]

Comparing the predictive ability of the models with Harrell's C-index provided a value of 0.649 (95% CI 0.640-0.695) for 313-SNP geneType, 0.628 (95% CI 0.618-0.638) for 77-SNP geneType and 0.567 (95% CI 0.556-0.577) for BCRAT.[31] The 313-SNP geneType was found to provide statistically improved discrimination compared to both BCRAT and the 77-SNP geneType (p<0.001 for both).

Figure 4 shows the calibration of the models. The 313-SNP geneType showed an improved calibration over the 77-SNP geneType model, but still slightly overestimated risk for the top risk decile.[31] BCRAT also overestimated 5-year risk for the top decile, however, it also underestimated risk for the lowest deciles.

Reclassification analysis showed the ability of 313-SNP geneType to improve upon the classification of BCRAT by reclassifying more affected women into a higher 5-year risk category and more unaffected women into a lower category of risk than BCRAT.[31] For example, this reclassification resulted in nearly five times as many affected women being classified at increased risk (≥3%) by geneType compared to BCRAT (26.5% versus 5.5% respectively)

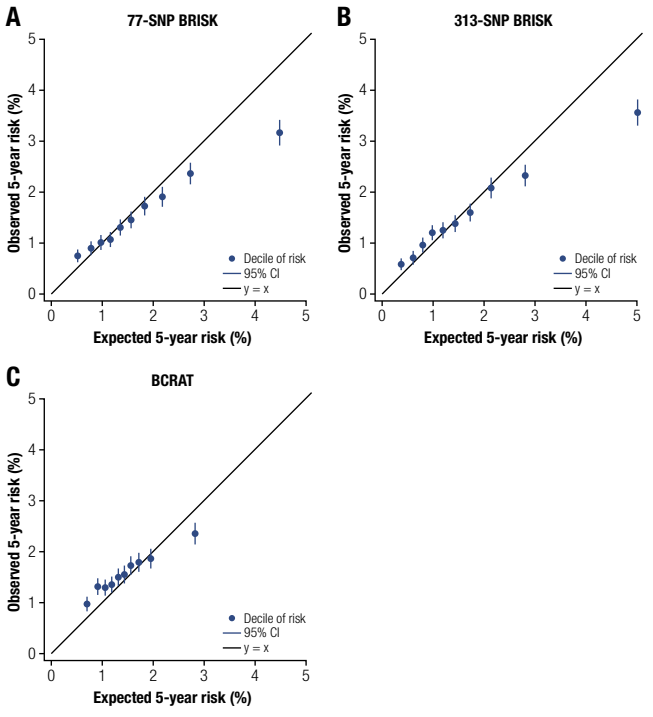


Figure 4. Calibration plots 5-year breast cancer risk for (A) 77-SNP geneType, (B) 313-SNP geneType and (C) BCRAT models. Adapted from Spaeth *et al* (2023)[31]

The authors concluded that the performance of the geneType risk assessment model was superior to the gold-standard BCRAT model, thereby demonstrating the ability of prediction models to improve risk stratification and refine the implementation of risk-reduction strategies.[31]

Validating geneType against additional models

To further validate the geneType™ test, the geneType model was compared against a similar model with more risk factors (simplified Rosner), BCRAT and another clinical model (Tyrer–Cuzick also referred to as IBIS).[33] Classification performance was compared between BCRAT and geneType for 5-year risk and between IBIS and geneType for remaining lifetime risk (to age 85 years). A nested case-control dataset was created of 1,131 cases and 1,700 controls for whom questionnaire data, mammographic density and genotyping were available from the Nurses' Health Study.[34] A subset of 881 cases and 1,327 controls had IBIS risk predictions available and an additional subset had ER status available (562 positive, 106 negative).[33]

The input variables for this version of the geneType model included age, number of affected first-degree relatives, age of youngest first-degree relative, number of affected second-degree relatives, percent mammographic density (or BI-RADs category), BMI, and menopausal status.[33] The estimated 5-year breast cancer risk was stratified into four categories, i.e. <1%, ≥1 to <1.67%, ≥1.67% to <3%, and ≥3%, and estimated remaining lifetime risk was categorised as <6%, ≥6% to <12%, ≥12% to <20%, ≥20% to < 25%, and ≥25%.[33]

Results

Discrimination for geneType 5-year risk was superior to BCRAT 5-year risk and for remaining lifetime risk compared to IBIS (p<0.001 for both).[33] There was no difference in AUC between the simplified Rosner 10-year risk and either of the geneType 5-year risk or the geneType remaining lifetime risk (p<0.06 and p<0.3, respectively).

GeneType was found to be well calibrated for both 5-year risk (E/O = 1.03; 95% CI 0.73, 1.46) and remaining lifetime risk (1.01; 0.86, 1.17).[33] Whereas the BCRAT 5-year risk (E/O = 0.85; 95% CI 0.58, 1.24) and IBIS remaining lifetime risk (0.73; 0.60, 0.87) significantly under-estimated risk. The distribution of cases (orange) and controls (blue) according to the 5-year or lifetime risk estimates provided by the relevant models are presented in **Figure 5**. This data shows that geneType tended to better assign controls to lower risk (the left) and cases to higher risk (the right), compared to the BCRAT and IBIS models.

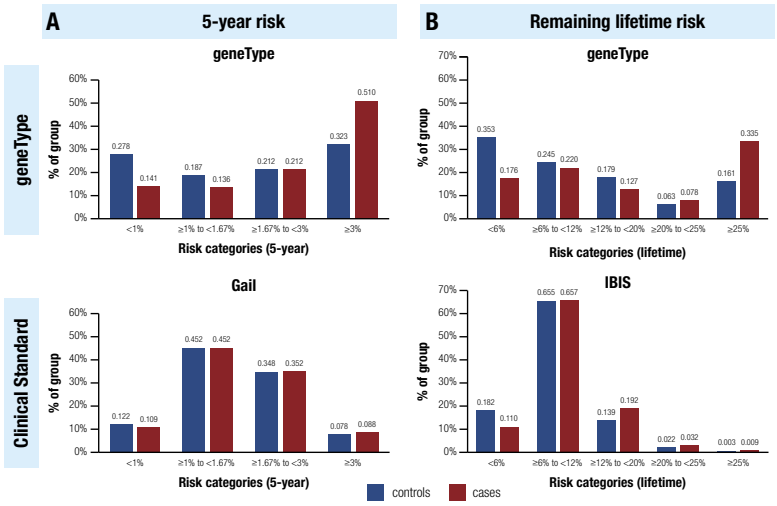


Figure 5. Distribution of risk scores at clinically relevant thresholds for cases and controls for (A) geneType and BCRAT 5-year risk, and (B) geneType and IBIS remaining lifetime risk. Adapted from Allman (2023)[33]

Reclassification tables were used to assess the assignment to 5-year risk categories for geneType and BCRAT.[33] GeneType improved classification of 5-year risk over BCRAT with an overall NRI of 0.31 for cases and controls. GeneType assigned 51% of cases above the 3% threshold, compared to BCRAT where 8.75% of cases were assigned to this increased risk category. Above this 3% 5-year risk threshold, the benefit of risk-reducing medication begins to outweigh the harms.[35] The classification performance of geneType was consistent for both ER positive and ER negative cases.

For remaining lifetime risk, reclassification tables were also used to assess the assignment of risk categories.[33] GeneType improved classification over IBIS for remaining lifetime risk with an overall NRI of 0.287 for cases and controls. GeneType assigned 41.3% of cases above the 20% National Comprehensive Cancer Network lifetime risk threshold for offering MRI screening, whereas the IBIS model assigned 4.1% of cases above this threshold. For the 25% remaining lifetime risk threshold, geneType assigned 33.5% of cases above this level, compared to 0.9% of cases for IBIS. Again, the improved classification performance was consistent for both ER positive and ER negative cases.

It was concluded that the geneType risk prediction model performed better than two widely used clinical risk models and its predictive performance was similar to a model containing more risk factors.[33] The enhancement of risk stratification was significant, thereby allowing for clinical improvements in the provision of screening and risk-reduction modalities.

Expert comment

The study by Allman *et al* (2023) compared a polygenic risk-integrated breast cancer risk prediction model, BRISK (the non-commercial name for geneType), against a similar model with more risk factors (simplified Rosner), as well as two commonly used clinical models (Gail and IBIS).[33] The conclusion was that implications for screening modifications based on the BRISK model at 20% or 25% actionable thresholds for at-risk women are substantial. In this study, BRISK was shown to identify both stage 1 as well as stage 2 and beyond breast cancers, suggesting that if the women with stage 2-4 breast cancers had been assessed with BRISK prior to diagnosis, they would have been identified at-risk and provided additional screening which may have allowed for diagnosis at an earlier stage with a better prognosis.

Take-home messages

- Breast cancer is the most common cancer in women, with one in eight to ten women developing the disease in their lifetime
- Early detection of breast cancer is associated with improved survival
- Current risk stratification tools for the general population use family history to estimate the likelihood of a woman developing breast cancer
- Most women who develop breast cancer do not have a family history of the disease
- The geneType™ test for breast cancer utilises family history, mammographic breast density and polygenic risk to calculate an absolute risk score that enables discussions about breast cancer risk that are appropriate to the individual patient
- Polygenic risk is an independent epidemiological factor that can be incorporated into a clinical model to improve risk stratification
- The geneType breast risk assessment model has been validated using two large population datasets with both validations showing that:
  - geneType increased the number of women classified as at increased-risk of breast cancer compared to traditional models; and
  - Once classified as being at increased-risk, these women showed an increased incidence of breast cancer compared to classification by traditional models

Expert's concluding comments

Breast cancer is one of the most common cancers in women, following skin cancers. Its incidence is increasing in the younger age groups (<50 years) where there are no screening programs readily available.

Up till now, the standard risk profile was based on family history and in recent times breast density. This only captures 15-20% of all breast cancers. It is important that we improve management of breast health in a more personalised manner. Polygenic risk score has changed this landscape via the addition of another risk profile measurement to this algorithm that has been proven to be more accurate in predicting the risk of an individual and thus improving personalised management of breast cancer.

The BRISK model (geneType), as with all models, can be improved upon. However, it has been shown to outperform standard clinical models and thus it should be considered in personalised management in order to improve breast cancer outcomes and survival rates especially in the younger age groups.

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