Short report

Integrating a Polygenic Risk Score into a clinical setting would impact risk predictions in familial breast cancer

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ABSTRACT

Background Low-impact genetic variants identified in population-based genetic studies are not routinely measured as part of clinical genetic testing in familial breast cancer (BC). We studied the consequences of integrating an established Polygenic Risk Score (PRS) into clinical sequencing of women with familial BC in Sweden.

Methods We developed an add-on sequencing panel to capture 313 risk variants in addition to the clinical screening of hereditary BC genes. Index patients with no pathogenic variant from 87 families, and 1000 population controls, were included in comparative PRS calculations. Including detailed family history, sequencing results and tumour pathology information, we used BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) V6 to estimate contralateral and lifetime risks without and with PRS313.

Results Women with BC but no pathogenic variants in hereditary BC genes have a higher PRS313 compared with population controls (mean+0.78 SD, p=3.9). Implementing PRS313 in the clinical risk before their BC diagnosis would have changed the recommended follow-up in 24%–45% of women.

Conclusions Our results show the potential impact of incorporating PRS313 directly in the clinical genomic investigation of women with familial BC.

INTRODUCTION

Breast cancer (BC) is the most common type of cancer in women and affect approximately one in eight.1,2 Screening programmes using mammography enable early detection of BC for which effective treatment is available and reduce the BC-related mortality.3 Since screening also leads to harmful overdiagnosis, the aim is to target the women with the highest risk.4–6 Personalised risk estimates could help to identify women most likely to benefit from preventive measures, ideally without increasing the risk of overdiagnosis in women with low risk. Results from genome-wide association studies (GWAS) have enabled the construction of Polygenic Risk Scores (PRSs) useful for population risk stratification and individual risk assessments.7 A PRS with 313 common low-impact variants (PRS313) has been validated to predict future BC in prospective cohorts and has been implemented together with other risk factors in the BOADICEA model V6, and made available through the CanRisk tool.8–10

Families with suspected BC predisposition are offered a genetic screening to identify pathogenic variants in established hereditary BC genes.11,12 Pathogenic variants have large effect on lifetime risk of BC and their identification enables personalised surveillance or even risk-reducing therapy for high-risk individuals.13 However, less than 10% of all BC cases are attributable to the monogenic causes sought in clinical practice.14 Women with familial BC for whom sequencing studies do not detect a pathogenic variant are usually offered a risk assessment based on their detailed family history and demographic risk factors, for instance, using the CanRisk tool.15 Although a PRS may have the potential to change an individual’s screening recommendations,16 common low-impact variants are not used in clinical risk estimations in Sweden.

In this study, we investigate the consequences of incorporating the PRS313 in the risk prediction of 87 Swedish women with familial BC, all of whom tested negative for pathogenic variants in BRCA1, BRCA2, PALB2, CHEK2, ATM, RAD51C, RAD51D, BARD1 and TP53 according to the national health programme. To this end, we developed an in-house sequencing panel to capture the 313 low-impact variants used to calculate the PRS. We make a comparative study of personal screening recommendations issued without and with the addition of PRS313, in accordance with guidelines from the USA and the UK (National Comprehensive Cancer Network (NCCN) and The National Institute for Health and Care Excellence (NICE), respectively).11,12

RESULTS

PRS313 in women with familial BC and in the Swedish population

We first studied the distribution of PRS313 in 1000 Swedish population controls (SweGen)12 and found that they had similar population parameters as those implemented in CanRisk, our tool of choice for risk calculations (online supplemental results).

We then applied our targeted sequencing panel to capture the PRS313 in addition to the established BC susceptibility genes. We analysed 87 consecutive women diagnosed with BC and evaluated for familial BC, but for whom no pathogenic variant could be identified (online supplemental figure S1 and table S1). The average age of first BC was 48...
years (range 25–76) and 15% of women had a contralateral BC at time of genetic counselling. Age at the contralateral BC was, on average, 53 years (range 40–80). Of all tumours, 16% were negative for hormone receptors and HER2 (triple negative BC).

Compared with SweGen, patients with familial BC had elevated PRS313, reflecting their increased burden of common risk variants (mean+0.78 SD, p<3e-9) (figure 1A,B). Three out of four women with familial BC had a PRS above the population average (74%), and one out of five had a PRS313 more than 2 SD above average. To investigate whether PRS calculation could have an impact on clinical decision-making, we re-evaluated the women using detailed family history and tumour pathology, without and with PRS313 at hand.

**Lifetime risk of BC**

By disregarding the BC diagnosis of index cases, we estimated their hypothetical lifetime risk of BC (n=87). Adding PRS313 changed the estimated lifetime risk by 5 percentage points or more in 41% of women (figure 1C,D). The individual patient with the largest percentage point difference had her lifetime risk re-evaluated from 13% to 34%. In terms of risk classification according to NCCN and NICE guidelines, including PRS313 in BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) estimations changed recommended follow-up for 21 (24%), 39 (45%) women, respectively; 19 (22%), 35 (40%) women shifted to a higher risk class, whereas 2 (2%), 4 (5%) shifted to a lower risk class (figure 2A). According to the NICE guidelines and the patients’ age, the reclassification would imply additional yearly mammograms for 27 women, and a recommendation to consider risk-reducing surgery for 6 women (figure 2B).

**Contralateral risk of BC**

Because all women in the study were diagnosed with BC, we could estimate their risk of contralateral cancer, without and with PRS313 (n=87). Adding PRS made a significant difference on the estimated contralateral risk in 14 (16%) women, defined as a difference of at least 5 percentage points. For 9 (10%) of them, the risk increased, and for 5 (6%), the risk decreased.

The risk of contralateral BC decreases with age. To test the impact of PRS while taking age into account, we compared the predicted contralateral risk to an approximated risk in women who have previously been diagnosed with BC (figure 2C). By including PRS313, 24 (27%) women had their risk estimates...
Figure 2  Panel A: Risk classification of women without and with PRS, according to the National Comprehensive Cancer Network (NCCN) and The National Institute for Health and Care Excellence (NICE) guidelines. Every row displays the results for one woman (n=87). Women are recommended preventive surveillance corresponding to their risk class. Panel B: Recommended follow-up according to NICE and NCCN guidelines, without and with Polygenic Risk Score (PRS) (n=87). Of the 87 women, 32 were younger than 40 or older than 59 years and would be offered surveillance as part of the population screening programme, even if assigned a moderate risk (top bars, shaded). Panel C: Estimates of contralateral risk of breast cancer (BC) for individual women made without (points, n=87) and with (triangles) the use of PRS. Vertical dashed lines connect results without and with PRS. The line coloured magenta marks an approximate risk of contralateral BC in a population of women who have had BC. Only differences of 2 percentage points or more are depicted with triangles. Panel D: Risk of contralateral BC by the age of 80 years, calculated without and with PRS, respectively (n=87). The women were subdivided according to risk estimates at 17% and 20%.
increased above average and 7 (8%) decreased. Taken together, the proportion of women above average risk increased (OR 2.3 (1.2–4.6), p=0.01). Looking at individual risk predictions rather than average differences, women with an increased risk using PRS313 were likely to be reclassified as above population average risk, whereas women with a decreased risk were reclassified as below average (OR 28 (8.0–120), p=9e-11).

The single largest change in contralateral risk was an increase from 11% to 20% and exceeded the average for the patient’s age group, which was 15%. Notably, she developed contralateral BC 10 years later. Although underpowered for statistical testing, we noticed that none of the women later diagnosed with bilateral BC had their contralateral risk decreased from above to below population average risk by addition of PRS313. In contrast, five women with bilateral BC had their estimates increased to above average (increase ranged 2.1%–8.7%).

DISCUSSION
With potentially large effect on personal risk estimates, PRSs hold promise to improve outcomes of BC screening programmes via precision medicine. The results of this study demonstrate the substantial impact of adding PRS313 in the evaluation of familial BC cases in Sweden. The proportion of women with changed screening recommendations are in line with results from a previous study by Lakeman and colleagues, 27%–36% depending on guidelines.16 The predictive validity of the risks estimated with this method has been shown in prospective cohorts.8–10

By integrating PRS in the clinical sequencing workflow, valuable information could be gained efficiently. The presented approach enables us to avoid using both panel sequencing for pathogenic variants and SNP arrays for PRS calculation. Sequencing hereditary BC genes and PRS SNPs in parallel is a cost-effective and feasible way for clinical genetic laboratories to incorporate PRS predictions in clinical practice.

Yet, important challenges remain on the way to implementation, and as of now, the NCCN do not recommend the use of PRS in routine risk assessment.11 Whereas pathogenic variants in BC susceptibility genes cause an increased risk by themselves, the risk captured by a PRS draws on results from GWASs where the causal mechanisms typically remain unknown. Therefore, and in contrast to a pathogenic variant, the implications of a BC PRS vary by ancestry and has been proven more accurate in patients with European ancestry than ancestries under-represented in GWASs.18–21 This inequality must be overcome by greater diversity in genetic studies.22 Initiatives to implement a PRS in routine risk assessment, motivated by the potential to personalise recommended care, should consider its limitations and potential pitfalls. We lack sufficient evidence that personalised breast screening programmes reduce mortality and await the results from ongoing international studies investigating the role of PRS in this context.

This study benefits from pathology information and the detailed family history collected and curated by clinical geneticists for all families in pretest counselling sessions. Included families represent a real-world sample of women referred for genetic evaluation of familial BC. The risk predictions are limited by the lack of data on established risk factors such as breastfeeding and mantle radiation. The scope of the study is limited to women affected by BC.

Taken together, we demonstrate the effect of adding PRS313 in the evaluation of women with familial BC. Furthermore, we show that extension of a clinical sequencing panel to include variants of an established PRS could yield results that impact risk management.

MATERIALS AND METHODS

Study participants
The Department of Clinical Genetics, Uppsala University Hospital, evaluates women referred for familial BC. Women with a personal history of BC (1) at age 40 or younger; (2) at age 50 or younger with a first-degree or second-degree relative diagnosed with BC*; or (3) at age 60 or younger with two first-degree or second-degree relatives diagnosed with BC*, were consecutively included March through December 2022. *The criterion was also considered met by ovarian cancer or prostate cancer before age 65. BC in this study refers to both invasive BC as well as ductal carcinoma in situ. Bilateral BC was considered two events. Women with triple negative BC were included regardless of age.

Population controls
The SweGen dataset represents a cross section of the Swedish population, including 1000 Swedes without disease information.17 The median age of sampling was 65 years, so SweGen may not reflect the genetic background of the most recent migrants among our patients. The SweGen dataset was generated by Science for Life Laboratory and its whole genome sequencing data has been made available to the research community.

Development of a targeted sequencing panel
A Next Generation Sequencing-based panel was designed to capture the 313 targets described in online supplemental table S7 in Mavaddat et al18 (custom design TE-99246333, Twist Bioscience, San Francisco, California, USA). Most were directly targeted, but 6 targets were captured indirectly with shadow coverage, and 13 by linkage disequilibrium proxies.

Score calculation
Using the weights and methods described previously,5 the PRS for overall BC was computed for all individuals and normalised to a Z score using CanRisk parameters for BCAC 313 (µ=−0.424, sigma=0.611). Scores for missing genotype calls were replaced (imputed) with the expected scores based on (1) the weight of the risk allele and (2) the population allele frequency.

Risk calculations
Contralateral and lifetime risks were calculated in BOADICEA V615 and based on detailed family history and tumour pathology without and with PRS313 (please see supplementary methods). To simulate lifetime risk estimates, the age of the proband was set to 20 years and the BC diagnosis erased. For contralateral risk predictions, the age of the proband was set to age of first BC, and the age of any contralateral BC was erased. The average population risk for women who have had a BC was approximated by a linear model of about 0.5% risk reduction per year (39−0.5 × age of first BC).21

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REFERENCES