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ORIGINAL ARTICLE

The impact of a panel of 18 SNPs on breast cancer risk in women attending a UK familial screening clinic: a case–control study

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ABSTRACT

Background Breast cancer familial risk clinics offer screening and preventive strategies. While *BRCA1/BRCA2* genetic testing provides important risk information for some women, panels of more common breast cancer risk genetic variants may have relevance to greater numbers of women with familial risk.

Methods Three polygenic risk scores (PRS) based on 18 SNPs were investigated in a case–control study of women attending a familial risk clinic. PRS were derived from published general European population allele ORs and frequencies (18-SNPs (SNP18)). In women with *BRCA1/BRCA2* mutations, 3 SNPs/13 SNPs, respectively, generated the PRS estimates. In total, 364 incident breast cancer cases (112 with *BRCA1/2* mutations) were matched with 1605 controls (691 *BRCA1/2*) by age last mammogram and *BRCA1/2* genetic test result. 87 women with cancer before attendance were also considered. Logistic regression was used to measure PRS performance through ORs per IQR and calibration of the observed to expected (O/E) logarithm relative risk when unadjusted and adjusted for phenotypic risk factors assessed by the Tyrer-Cuzick (TC) model.

Results SNP18 was predictive for non-carriers of *BRCA1/2* mutations (IQR OR 1.55, 95% CI 1.29 to 1.87, O/E 96%). Findings were unaffected by adjustment from TC (IQR OR 1.56, 95% CI 1.29 to 1.89) or when prior cancers were included (IQR OR 1.55, 95% CI 1.30 to 1.87). There was some evidence to support polygenic scores with weights for individuals with *BRCA1/2* mutations (*BRCA1* IQR OR 1.44, 95% CI 1.17 to 1.76; *BRCA2* IQ OR 1.44, 95% CI 0.90 to 2.31).

Conclusions PRS may be used to refine risk assessment for women at increased familial risk who test negative/have low likelihood of *BRCA1/2* mutations. They may alter the recommended prevention strategy for many women attending family history clinics.

INTRODUCTION

Breast cancer is the most common malignancy among women.[1] It is approximately twice as common in first-degree relatives of affected women compared with the general population,[2 3] indicating that breast cancer risk has a substantial inherited component.[2–4] Mutations in *BRCA1* and *BRCA2* have been identified as a cause of hereditary breast cancer, but they account for only around 15–20% of the familial component.[5 6] Pathogenic mutations in these tumour suppressor genes lead to substantially increased inherited predisposition to breast cancer with lifetime risks of up to 60–90%.[7–9] Further high-risk genes include *TP53*, *CDH1*, *PTEN* and *STK11* and *PALB2*, but mutations in these are extremely rare and make up only a small proportion (~1–2%) of cases of inherited breast cancer.[6] Although some moderate-risk genes have also been identified conferring a twofold to threefold relative risk of breast cancer (eg, *CHEK2*, *ATM*), they account for ~5% of the familial component and their utility for risk prediction is largely untested.[6]

Large-scale genome-wide association studies (GWAS) have focused on identifying a large number of breast cancer-susceptibility alleles with much lower effect sizes.[10–13] Altogether approximately 100 SNPs have now been associated with breast cancer risk,[6] but the SNPs at 18 loci (SNP18) identified in 2010 account for about two-third of the familial component attributed by the identified associated variants.[6 12] There is evidence to suggest that some of these genetic variants also alter the risk of breast cancer for women with *BRCA1* or *BRCA2* mutations.[13–16] Antoniou *et al*[14 15] determined that nine of the common breast cancer-susceptibility SNPs (at the *TOX3*, *FGFR2*, *MAP3K*, *LSP1*, 2q35, *SLC4A7*, 1p11.2, 5p12, 6q25.1 loci) were associated with altered penetrance in *BRCA2* mutation carriers. More recent work from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) consortium has confirmed a contribution of SNPs to breast cancer risk in *BRCA1* carriers.[16] We previously assessed 18 variants (SNP18)[12] in *BRCA1* and *BRCA2* mutation carriers showing that using the risk weightings applied in the original report appear to predict risk in women with *BRCA2*, but not *BRCA1* mutations.[17]

The objective of this study was to assess the utility of polygenic risk scores (PRS) in a familial screening clinic, with subdivision of women into those with and without *BRCA1* or *BRCA2* mutations. We tested the hypothesis that the individual's SNP risk scores, generated from data from previous overview studies, combine independently for women at an elevated risk of breast cancer due to their family history.

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MATERIALS AND METHODS

Participants

A case–control study was designed to assess the predictive value of a combined SNP panel in women at increased risk of breast cancer due to their family history. Women with a family history of the disease attending the Genesis Prevention Centre in South Manchester for risk assessment and breast screening between 1987 and 2014 were recruited to a family history clinic. All breast cancers that occurred after entry to this clinic between 1987 and March 2014 were identified (first in June 1990), in addition to those previously diagnosed with breast cancer before they entered the clinic. Women with breast cancer and cancer-free controls were contacted between November 2010 and October 2013 to obtain informed consent and to provide a blood sample for DNA extraction if not already available. Of the 75 deceased cases, DNA was stored from 49 and consent was not required.

Assay methods

Blood samples were taken from all women from which DNA was extracted, or pre-existing DNA samples (also previously extracted from blood) were used. *BRCA1/2* mutation testing was carried out when clinically indicated (the prior probability of identifying a mutation must have met the threshold of *BRCA1/2* likelihood probability ≥10% in accordance with UK clinical guidance,[18] using the Manchester score[19]) using DNA Sanger sequencing and multiple ligation-dependent probe amplification analysis of all exons and intron–exon boundaries.[20] Relatives of those identified with *BRCA1/2* mutations were offered cascade screening for the family-specific genetic mutation. All women were genotyped for 18 SNPs that have been shown to be associated with breast cancer risk in general European populations (*FGFR2, CASP8, TOX3, MAP3K*, 2q, *CDKN2A*, 10q22, *COX11*, *NOTCH*, 11q13, 10q21, *SLC4A7*, 6q25.1, 8q24, *RAD51L1, LSP1*, 5p12, 10q) as previously described.[17] In brief, multiplex genotyping was performed using Sequenom iPlex Gold (Sequenom, San Diego, California, USA) and TaqMan assay (Life Technologies). Intra-plate duplicates and negative controls were included in all genotyping. Genotypes were verified by Scientific Data Systems (SDS) and MassARRAY TyperAnalyzer software.

Study design

The primary end point was diagnosis of invasive breast cancer or ductal carcinoma in situ. Diagnosis of breast cancer was confirmed by hospital records or the North West Cancer Intelligence Service. Case–control matching was by age at last mammogram (±1 year) and *BRCA1/2* genetic test result. Controls were ineligible if they did not attend the clinic during the period of recruitment. Individuals without breast cancer, but with a *BRCA1/2* mutation (*BRCA1/2* controls) were matched as available, and 3–5 controls for individuals without *BRCA1/2* mutations (table 2). The reason for matching cases and controls on age at mammogram was to ensure that an age when disease-free and at risk of breast cancer was balanced between cases and controls. Dates of last follow-up were either date of breast cancer diagnosis or date the woman was last in contact with the risk clinic or other National Health Service (NHS) service, the date of risk-reducing mastectomy or of death.

A polygenic score was used to provide an overall relative risk estimate. We calculated the OR for each of the three SNP genotypes (no risk alleles, one risk allele and two risk alleles) from published per-allele ORs, assuming independence and normalising by an assumed risk allele frequency.[12] Assay failures were ignored in the SNP score by imputing a relative risk of 1.0 when they occurred. An overall SNP risk score for each woman was formed by multiplying the genotype ORs for together (table 1). Phenotypic risk was assessed using predicted 10-year risks, and over the total follow-up period, from the Tyrer-Cuzick (TC) model (V.7.02). The following information from a risk questionnaire was incorporated: age at baseline; second-degree relatives (age affected by breast and ovarian cancer or current age or age at death); age at first child, menarche and menopause; height and weight; and history of prior benign breast disease.

Analysis methods

Quality control of the assay was tested by assessing Hardy-Weinberg equilibrium (HWE) for each SNP by comparing the observed number of homozygotes against expected assuming independence and by concordance between duplicate samples. Phenotypic risk factors at entry in the non-*BRCA1/2* mutation cases and controls and the complete cohort to 2014 were tabulated. A Wilcoxon rank-sum test was used for differences in age at entry for cases and controls. Analysis was stratified by *BRCA1/2* testing groups (positive or not). The main test statistic was a univariate likelihood ratio (LR) χ^2 (df=1) for the risk associated with the log PRS. ORs were estimated by logistic regression and CIs by profile likelihood. In non-*BRCA1/2* carriers and

Table 1 SNPs used with ORs per allele and weightings derived from iCOGS data set[13]

SNP	Chromosome	Position	Ref	EAF	EOR
rs614367	11	69328764	C	0.15	1.21
rs704010	10	80841148	T	0.62	0.92
rs713588	10	5886962	G	0.44	0.99
rs889312	5	56031884	C	0.72	0.89
rs909116	11	1941946	T	0.49	0.93
rs1011970	9	22062134	G	0.17	1.05
rs1156287	17	53076799	G	0.71	1.07
rs1562430	8	128387852	T	0.43	0.90
rs2981579	10	123337335	A	0.60	0.79
rs3757318	6	151914113	G	0.07	1.16
rs3803662	16	52586341	A	0.74	0.81
rs4973768	3	27416013	C	0.47	1.09
rs8009944	14	69039588	C	0.74	0.96
rs9790879	5	44899885	C	0.60	0.92
rs10995190	10	64278682	G	0.16	0.86
rs11249433	1	121280613	A	0.40	1.09
rs13387042	2	217905832	A	0.49	0.88
rs10931936	2	202143928	T	0.72	0.96

EAF, predicted risk allele frequency (COGS); EOR, expected per-allele OR (COGS).

Table 2 *BRCA1/2* testing groups

Family	Testing	Controls	Cases	Controls (%)	Cases (%)
No *BRCA1/2*	Low risk, not tested	656	126	40.9	27.9
No *BRCA1/2*	Family tested negative	258	158	16.1	35.0
BRCA1	Proband positive	201	79	12.5	17.5
BRCA1	Proband negative	141	2	8.8	0.4
BRCA2	Proband positive	204	78	12.7	17.3
BRCA2	Proband negative	145	8	9.0	1.8

prospective cases, the model also included the logarithm absolute risk from the TC model over the follow-up period for each woman. The Spearman correlation was calculated between TC 10-year risk and SNP18 in controls. Unadjusted area under the receiver operating curve (AUC) was used as a secondary measure of discrimination with DeLong CIs.[21] CIs for observed divided by expected proportions used Wilson's method for the binomial parameter. The change in lifetime risk categories calculated by lifetables (Manchester method[19 22 23]) was assessed. They were chosen to be relevant to UK National Institute for Health and Care Excellence (NICE) guidelines[18] of average 8–16%, moderately high 17–29%, high 30–39% and very high 40%+, and US MRI guidelines (above and below upper limit of 25%[24]). Analysis was carried out in GNU R V.3.1.1 (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/).

RESULTS

In total, 9222 women were seen at the family history clinic between 1987 and 2012 to assess breast cancer risk and initiate screening if appropriate. Also, 489 individuals were diagnosed with breast cancer after entry to the clinic, and of these 364 (112 with *BRCA1/2* mutation) were recruited to this study and provided a blood sample from which DNA was extracted. A total of 87 women with breast cancer prior to initial clinic attendance were also recruited. In total, there were 1605 controls (691 with *BRCA1/2* mutations). A summary of the composition of the sample separated by *BRCA1/2* testing status (individual and family) is shown in table 2. In the case–control study, there were 16 832 years of follow-up (median 7.9 years) from recruitment to the clinic to the last follow-up or breast cancer. The median year of entry to the clinic for the prospective cases was 1996 (IQR 1993–2002), it was 2004 (IQR 1998–2009) for controls.

A comparison of the distribution of phenotypic risk factors and 10-year risk at baseline in individuals without *BRCA1/2* mutations shows that the non-*BRCA1/2* controls were at a slightly higher risk of breast cancer than the overall cohort, being older and with a more substantial family history of the disease (table 3). The non-*BRCA1/2* controls were also younger at entry than non-*BRCA1/2* cases ($p<0.001$). The *BRCA1/2* cases and controls had a similar age at entry (controls: median 39, IQR 32–46; cases: 37, 33–45; $p=0.3$).

Quality control of the genotyping was satisfactory: the call rate for each SNP was >98%, and HWE was verified separately by *BRCA1/2* mutation group (see online supplementary material).

SNP18 in the group without *BRCA1/2* mutations was a significant predictive risk factor (LR χ^2 22.7, $p<0.001$, table 4), with an IQR OR of 1.55 (95% CI 1.30 to 1.87) and AUC 0.59 (0.55 to 0.63). Findings were similar when non-prospective cases were excluded. SNP18 was not correlated with TC 10-year risks (Spearman correlation 0.01 in controls, $p=0.7$) and was predictive when adjusted for TC risk over the period from entry to last follow-up (IQR OR 1.56, 95% CI 1.29 to 1.89). SNP scores in the *BRCA1/2* mutation-positive groups suggested that they might refine risk, but analysis was limited by sample size and the strength of the predictor.

Figure 1A plots histograms of SNP18 in cases and controls without *BRCA1/2* mutations. Analysis of SNP18 by quintiles is shown in table 5. There was more than a twofold higher risk between the bottom and top quintiles of SNP18 in women without *BRCA1/2* mutations. The observed risk was also close to expected, being 96% (95% CI 56% to 136%) of expected in the complete data. This excellent calibration is further illustrated in figure 1B, C. The predicted risk was 100% (95% CI 57% to 142%) of expected after adjustment for risk from classical factors.

A substantial proportion of the unaffected women without *BRCA1/2* mutations moved between clinically relevant lifetime risk categories if an unadjusted PRS was used. Of the 914 controls who did not test positive for *BRCA1/2* mutation, 475 (52%) moved category with 432 (25%) moving up a category and 443 (27%) moving down. Using a 25% lifetime risk threshold, 32/174 (18%) moved up into this category, whereas 149/740 (20%) moved down from this category.

DISCUSSION

SNP18 was predictive of breast cancer risk for women who did not test positive for *BRCA1/2* mutations as observed risks were

Table 3 Phenotypic risk characteristics at entry in the complete cohort and *BRCA1/2* negative or untested samples from study

Factor	Description	Complete cohort	Control (no *BRCA1/2*)	Prospective case (no *BRCA1/2*)
Questionnaire	Available	10 088*	1176	260
	Unavailable		24 (2%)	1 (<1%)
Age entry (year)	Median (IQR)	39 (33–46)	40 (35–46)	43 (37–48)
Menopause	Pre (%)	6103 (60%)	728 (62%)	169 (65%)
	Peri (%)	709 (7%)	58 (5%)	20 (8%)
	Post (%)	1051 (10%)	148 (13%)	44 (17%)
	Unknown (%)	2225 (22%)	242 (21%)	27 (10%)
Body mass index (kg/m^2)	Median (IQR)	24.0 (21.8–27.3)	24.4 (22.1–28.0)	23.8 (21.7–26.2)
	Unknown (%)	3715 (37%)	381 (32%)	56 (22%)
Parity	Unknown	1086 (11%)	179 (15%)	32 (12%)
	Nulliparous	4511 (45%)	661 (56%)	138 (53%)
	Parous	4491 (45%)	336 (29%)	90 (35%)
Age first child (parous)	Median (IQR)	25 (21–29)	25 (21–29)	25 (22–30)
First-degree	1	6727 (67%)	728 (62%)	168 (65%)
relatives (n (%))	≥2	1246 (12%)	207 (18%)	61 (23%)
Tyrer-Cuzick 10-year %	Median (IQR)	3.17% (1.73–5.09%)	3.86% (2.31–6.03%)	4.40% (2.98–6.14%)

*Number seen up to 2014.

Table 4 Results with use of polygenic risk scores as continuous risk factor

	IQR (controls)	IQR OR	95% CI	LR χ^2	AUC	95% CI
Prospective cases						
SNP18 (not *BRCA1/2*)	0.81–1.27	1.55	1.29–1.87	21.3	0.59	0.55–0.63
Adjusted for TC risk		1.56	1.29–1.89	21.7		
SNP3 (*BRCA1*)	0.94–0.99	1.44	1.17–1.76	12.6	0.64	0.55–0.72
SNP13 (*BRCA2*)	0.79–1.15	1.44	0.90–2.31	2.3	0.57	0.47–0.66
All cases						
SNP18 (not *BRCA1/2*)	0.81–1.27	1.55	1.30–1.87	22.7	0.59	0.55–0.63
SNP3 (*BRCA1*)	0.94–0.99	1.38	1.16–1.67	12.7	0.62	0.55–0.70
SNP13 (*BRCA2*)	0.79–1.14	1.32	0.91–1.93	2.1	0.55	0.48–0.62
SNP18 (*BRCA1*)	0.81–1.17	0.96	0.71–1.30	0.1	0.52	0.44–0.59
SNP18 (*BRCA2*)	0.74–1.20	1.19	0.80–1.77	0.7	0.53	0.45–0.60

AUC, area under the receiver operating characteristic; LR χ^2, likelihood ratio test statistic; PRS, polygenic risk score; TC, Tyrer-Cuzick absolute risk over follow-up period.

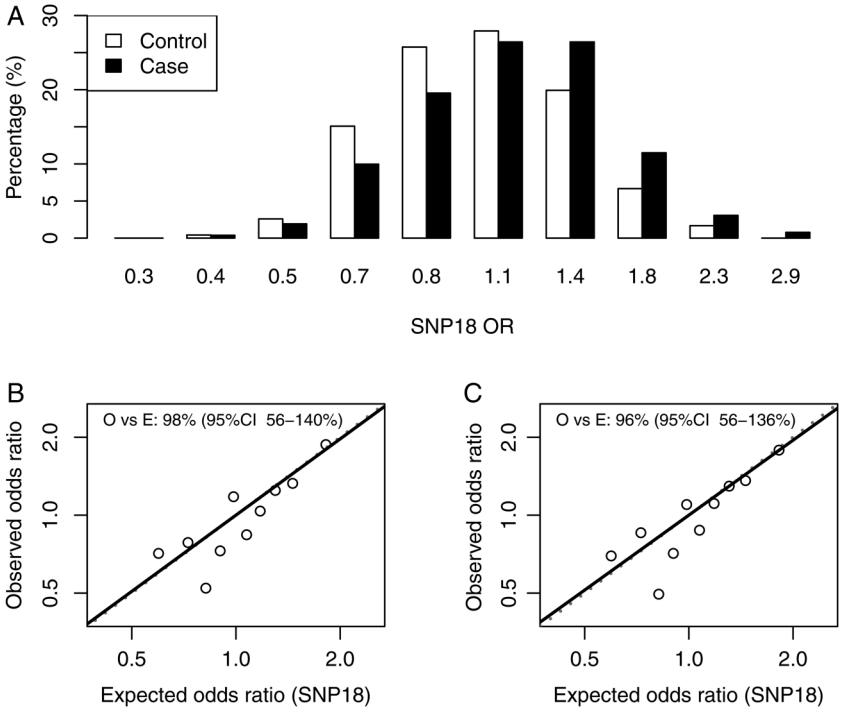

Figure 1 Results for non-*BRCA1/2* group. (A) A histogram of SNP18 in controls and prospective cases; then the observed versus expected OR is plotted in (B) for prospective cases and (C) all cases. In (B) and (C), the points (o) are observed and expected in each decile, the solid line (—) is from a logistic regression fit to the individual-level data, the dashed line is the 45° diagonal. E, expected number of cases; O, number of cases.

very close to expected. Findings were unaffected by adjustment from the TC model based on classical phenotypic risk factors or when prior cancers were included. Polygenic scores for women with *BRCA1/2* mutations were also informative, although analysis was limited by sample size and strength of these predictors. Our data suggest that PRS may be used to refine risk assessment for women already at increased familial risk without *BRCA1/2* mutations. PRS are likely to have a substantial impact on prevention strategies recommended for a woman based on her lifetime risk estimate.

Our study has several limitations. First, those who consented to join the study as controls were at a higher risk than the overall cohort. This meant that we were unable to assess how much the SNP score added in comparison with the TC model. However, there was no association between the PRS and risk from the TC model, and findings were unchanged after adjustment for phenotypic risk. Second, not all of the groups defined as without *BRCA1/2* mutations had been tested for *BRCA1/2* and therefore will include a number of individuals with mutations. This number will be small as all were below the NHS testing threshold of 10% a priori risk of mutation detection in England and Wales.[18] Among the 124 untested prospective breast cancers, we estimate no more than 5% would harbour a *BRCA1/2* mutation based on Manchester score; approximately six women. Among the untested unaffected women, we would assess an even smaller proportion may harbour *BRCA1/2* mutations. As such, this should have a very small effect on our results. Finally, we note that many of the *BRCA1* cohort were part of the EMBRACE project and were therefore used (with many other samples) to estimate the ORs for *BRCA1* carriers through CIMBA. Analysis excluding these is very limited, and there are only eight *BRCA1* controls. However, the results (see online supplementary material) at least show that ORs are in the correct direction for those who were not part of EMBRACE.

The predicted risk of SNP18 matched the observed risk and also held true after adjustment for risk from classical factors. This has important implications for provision of breast cancer risk information in clinics similar to the one in this study because it suggests that SNP scores can be used to refine risks in

Table 5 SNP18 results by quintile in non-*BRCA1/2* carriers

Quintile	SNP18 PRS cut point	O	E	n	O/E OR (95% CI)
Prospective cases					
1		42	37.6	300	1.14 (0.86–1.49)
2	0.78	34	44.9	286	0.72 (0.53–0.98)
3	0.94	54	55.0	301	0.98 (0.76–1.24)
4	1.11	57	60.7	286	0.92 (0.73–1.16)
5	1.37	74	75.1	288	0.98 (0.80–1.18)
All cases					
1		49	42.6	307	1.18 (0.91–1.51)
2	0.78	38	51.5	296	0.70 (0.52–0.93)
3	0.94	58	60.2	299	0.95 (0.75–1.19)
4	1.11	67	68.9	296	0.96 (0.78–1.18)
5	1.37	82	84.2	296	0.96 (0.80–1.15)

E, expected number of cases; n, total number of women (cases and controls) in quintile; O, number of cases; O/E OR, observed divided by expected OR; PRS, polygenic risk score; SNP18 cut point, lower limit of quantile.

women already at increased risk from their family history. If women without breast cancer are undergoing genetic testing for *BRCA1* and *BRCA2* mutations either as stand-alone tests or as part of a panel, use of multiple SNP testing could be considered at the same time. The great majority of women tested for *BRCA1/2* receive a negative 'uninformative' results, which in most instances will only slightly reduce their predicted risk of breast cancer. For these women, an SNP PRS would provide a more meaningful result once *BRCA1* and *BRCA2* mutations have been excluded. Use of SNP18 PRS resulted in over half of women changing a NICE-defined risk category. A substantial proportion of (18–20%) of women in our familial risk clinic also crossed the upper 25% lifetime risk boundary used in North America[24] to determine eligibility for MRI screening.

It is likely that use of a PRS may have more added value than extended gene mutation panel tests of moderate and highly penetrant genes. In a study of 198 women referred for *BRCA1/2* testing, 57 (29%) harboured pathogenic mutations in *BRCA1/2*.[25] A further 16 had what were classified as pathogenic mutations in the extended panel of 42 genes. However, the concept of what were 'actionable' (identifies pathogenic mutations in genes that substantially affect risk) mutations is debatable, especially when restricted to breast cancer. Only three women (2%) without a *BRCA1/2* mutation had a really useful result from the extended panel test. In contrast, an SNP PRS would provide an adjusted overall risk for all women testing negative for *BRCA1/2* mutations.

There is supporting evidence that our results may generalise to other settings. Importantly, our analysis used predefined SNP ORs from large case–control studies of the general population:[13 26] SNP risks were not calibrated to this case–control study. A further study from the Australian Family registry also showed that using an SNP PRS derived from these estimates added significantly to the prediction from risk algorithms including Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), BRCAPRO and TC,[27] although the observed risk appeared to be less than expected. In terms of *BRCA1/2* carriers, many of the SNPs have not been shown to add value for risk assessment. For women with *BRCA1* mutations, only three SNPs add value,[14 15] which is not surprising because the majority of cancers in this patient group are oestrogen receptor negative (whereas most of the SNP18 variants are associated with oestrogen receptor-positive breast cancer). Our data support the previous GWAS studies that suggest for an accurate risk for *BRCA1/2* a different weighting is required for each SNP than that applied to the general population. The prediction in table 4 shows that SNP18 with iCOGS weightings for *BRCA1* has a non-significant prediction that improved by using just the three SNPs validated with CIMBA weightings. Similarly, although there was partial prediction in *BRCA2* carriers from SNP18, this improved by using CIMBA *BRCA*2 weightings. We have previously used *BRCA1* weightings in three SNPs validated for a *BRCA1* (mutation-positive group[14 15]). A data set of 462 *BRCA1* carriers with 269 cancers showed no validity for the three SNPs.[17] The results for SNP3 in *BRCA1* carriers in the present data set were driven by rs3757318 in *ESR1*. The individual effect for this SNP was larger than expected (see online supplementary material). In summary, the current study provides evidence for utility of using a selected panel of risk-associated SNPs in the familial risk clinic in non-BRCA1/2 mutation carriers to refine risk estimations.[26 28] We advise using the iCOGS weightings in women at high risk of a *BRCA1/2* mutation only if *BRCA1/2* testing has already been undertaken and has proven negative or is undertaken at the same time. If women test positive for a *BRCA1* or *BRCA2* mutation, then different algorithms are needed if an SNP risk prediction element is to be used to refine their risk estimate.

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REFERENCES

1 Cancer Research UK. http://www.cancerresearchuk.org/cancer-info/cancerstats/incidence/commoncancers/ (accessed Feb 2016).
2 Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am J Hum Genet* 1991;48:232–42.
3 Newman B, Austin MA, Lee M, King M. Inheritance of human breast cancer: evidence for autosomal dominant transmission in high-risk families. *Proc Natl Acad Sci USA* 1988;85:3044–8.
4 Peto J, Mack TM. High constant incidence in twins and other relatives of women with breast cancer. *Nat Genet* 2000;26:411–14.
5 Mavaddat N, Antoniou AC, Easton DF, Garcia-Closas M. Genetic susceptibility to breast cancer. *Mol Oncol* 2010;4:174–91.
6 Eccles SA, Aboagye EO, Ali S, Anderson AS, Armes J, Berditchevski F, Blaydes JP, Brennan K, Brown NJ, Bryant HE, Bundred NJ, Burchell JM, Campbell AM, Carroll JS, Clarke RB, Coles CE, Cook GJ, Cox A, Curtin NJ, Dekker LV, Silva Idos S, Duffy SW, Easton DF, Eccles DM, Edwards DR, Edwards J, Evans D, Fenlon DF, Flanagan JM, Foster C, Gallagher WM, Garcia-Closas M, Gee JM, Gescher AJ, Goh V, Groves AM, Harvey AJ, Harvie M, Hennessy BT, Hiscox S, Holen I, Howell SJ, Howell A, Hubbard G, Hulbert-Williams N, Hunter MS, Jasani B, Jones LJ, Key TJ, Kirwan CC, Kong A, Kunkler IH, Langdon SP, Leach MO, Mann DJ, Marshall JF, Martin L, Martin SG, Macdougall JE, Miles DW, Miller WR, Morris JR, Moss SM, Mullan P, Natrajan R, O'Connor JP, O'Connor R, Palmieri C, Pharoah PD, Rakha EA, Reed E,

Robinson SP, Sahai E, Saxton JM, Schmid P, Smalley MJ, Speirs V, Stein R, Stingl J, Streuli CH, Tutt AN, Velikova G, Walker RA, Watson CJ, Williams KJ, Young LS, Thompson AM. Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer. *Breast Cancer Res* 2013;15:R92.

7 Evans DG, Shenton A, Woodward E, Lalloo F, Howell A, Maher ER. Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. *BMC Cancer* 2008;8:155.

8 Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, Evans DG, Izatt L, Eeles RA, Adlard J, Davidson R, Eccles D, Cole T, Cook J, Brewer C, Tischkowitz M, Douglas F, Hodgson S, Walker L, Porteous ME, Morrison PJ, Side LE, Kennedy MJ, Houghton C, Donaldson A, Rogers MT, Dorkins H, Miedzybrodzka Z, Gregory H, Eason J, Barwell J, McCann E, Murray A, Antoniou AC, Easton DF, EMBRACE. Cancer Risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst* 2013;105:812–22.

9 Evans DG, Harkness E, Lalloo F, Howell A. Long-term prospective clinical follow-up after BRCA1/2 presymptomatic testing: BRCA2 risks higher than in adjusted retrospective studies. 2014;51:573–80.

10 Easton DF, Pooley KA, Dunning AM, Pharoah PDP, Thompson D, Ballinger DG, Struewing JP, Morrison J, Field H, Luben R, Wareham N, Ahmed S, Healey CS, Bowman R, Meyer KB, Haiman CA, Kolonel LK, Henderson BE, Le Marchand L, Brennan P, Sangrajrang S, Gaborieau V, Odefrey F, Shen CY, Wu PE, Wang HC, Eccles D, Evans DG, Peto J, Fletcher O, Johnson N, Seal S, Stratton MR, Rahman N, Chenevix-Trench G, Bojesen SE, Nordestgaard BG, Axelsson CK, Garcia-Closas M, Brinton L, Chanock S, Lissowska J, Peplonska B, Nevanlinna H, Fagerholm R, Eerola H, Kang D, Yoo KY, Noh DY, Ahn SH, Hunter DJ, Hankinson SE, Cox DG, Hall P, Wedren S, Liu J, Low YL, Bogdanova N, Schurmann P, Dork T, Tollenaar RAEM, Jacobi CE, Devilee P, Klijn JGM, Sigurdson AJ, Doody MM, Alexander BH, Zhang J, Cox A, Brock IW, MacPherson G, Reed MWR, Couch FJ, Goode EL, Olson JE, Meijers-Heijboer H, van den Ouweland A, Uitterlinden A, Rivadeneira F, Milne RL, Ribas G, Gonzalez-Neira A, Benitez J, Hopper JL, McCredie M, Southey M, Giles GG, Schroen C, Justenhoven C, Brauch H, Hamann U, Ko YD, Spurdle AB, Beesley J, Chen X, Mannermaa A, Kosma VM, Kataja V, Hartikainen J, Day NE, Cox DR, Ponder BAJ. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature* 2007;447:1087–93.

11 Stacey SN, Manolescu A, Sulem P, Rafnar T, Gudmundsson J, Gudjonsson SA, Masson G, Jakobsdottir M, Thorlacius S, Helgason A, Aben KK, Strobbe LJ, Albers-Akkers MT, Swinkels DW, Henderson BE, Kolonel LN, Le Marchand L, Millastre E, Andres R, Godino J, Dolores M, Polo E, Tres A, Mouy M, Saemundsdottir J, Backman VM, Gudmundsson L, Kristjansson K, Bergthorsson JT, Kostic J, Frigge ML, Geller F, Gudbjartsson D, Sigurdsson H, Jonsdottir T, Hrafnkelsson J, Johannsson J, Sveinsson T, Myrdal G, Niels H, Jonsson T, von Holst S, Werelius B, Margolin S, Lindblom A, Mayordomo JI, Haiman CA, Kiemeney LA, Th O, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. *Nat Genet* 2007;39:865–86.

12 Turnbull C, Ahmed S, Morrison J, Pernet D, Renwick A, Maranian M, Seal S, Ghoussaini M, Hines S, Healey CS, Hughes D, Warren-Perry M, Tapper W, Eccles D, Evans DG, Hooning M, Schutte M, van den Ouweland A, Houlston R, Ross G, Langford C, Pharoah PDP, Stratton MR, Dunning AM, Rahman N, Easton DF. Genome-wide association study identifies five new breast cancer susceptibility loci. *Nat Genet* 2010;42:504–7.

13 Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, Schmidt MK, Chang-Claude J, Bojesen SE, Bolla MK, Wang Q, Dicks E, Lee A, Turnbull C, Rahman N, Fletcher O, Peto J, Gibson L, dos Santos Silva I, Nevanlinna H, Muranen TA, Aittomaki K, Blomqvist C, Czene K, Irwanto A, Liu J, Waisfisz Q, Meijers-Heijboer H, Adank M, van der Luijt RB, Hein R, Dahmen N, Beckman L, Meindl A, Schmutzler RK, Muller-Myhsok B, Lichtner P, Hopper JL, Southey MC, Makalic E, Schmidt DF, Uitterlinden AG, Hofman A, Hunter DJ, Chanock SJ, Vincent D, Bacot F, Tessier DC, Canisius S, Wessels LFA, Haiman CA, Shah M, Luben R, Brown J, Luccarini C, Schoof N, Humphreys K, Li J, Nordestgaard BG, Nielsen SF, Flyger H, Couch FJ, Wang X, Vachon C, Stevens KN, Lambrechts D, Moisse M, Paridaens R, Christiaens MR, Rudolph A, Nickels S, Flesch-Janys D, Johnson N, Aitken Z, Aaltonen K, Heikkinen T, Broeks A, Veer LJ, van der Schoot CE, Guenel P, Truong T, Laurent-Puig P, Menegaux F, Marme F, Schneeweiss A, Sohn C, Burwinkel B, Zamora MP, Perez JI, Pita G, Alonso MR, Cox A, Brock IW, Cross SS, Reed MWR, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Henderson BE, Schumacher F, Le Marchand L, Andrulis IL, Knight JA, Glendon G, Mulligan AM, Lindblom A, Margolin S, Hooning MJ, Hollestelle A, van den Ouweland AMW, Jager A, Bui QM, Stone J, Dite GS, Apicella C, Tsimiklis H, Giles GG, Severi G, Baglietto L, Fasching PA, Haeberle L, Ekici AB, Beckmann MW, Brenner H, Muller H, Arndt V, Stegmaier C, Swerdlow A, Ashworth A, Orr N, Jones M, Figueroa J, Lissowska J, Brinton L, Goldberg MS, Labreche F, Dumont M, Winqvist R, Pylkas K, Jukkola-Vuorinen A, Grip M, Brauch H, Hamann U, Bruning T, Radice P, Peterlongo P, Manoukian S, Bonanni B, Devilee P, Tollenaar RAEM, Seynaeve C, van Asperen CJ, Jakubowska A, Lubinski J, Jaworska K, Durda K, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Bogdanova NV, Antonenkova NN, Dork T, Kristensen VN, Anton-Culver H, Slager S, Toland AE, Edge S, Fostira F, Kang D, Yoo KY, Noh DY, Matsuo K, Ito H, Iwata H, Sueta A, Wu AH, Tseng CC, Van Den Berg D, Stram DO, Shu XO, Lu W, Gao YT, Cai H, Teo SH, Yip CH, Phuah SY, Cornes BK, Hartman M, Miao H, Lim WY, Sng JH, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Shen CY, Hsiung CN, Wu PE, Ding SL, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Blot WJ, Signorello LB, Cai Q, Zheng W, Deming-Halverson S, Shrubsole M, Long J, Simard J, Garcia-Closas M, Pharoah PDP, Chenevix-Trench G, Dunning AM, Benitez J, Easton DF. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet* 2013;45:353–61.

14 Antoniou AC, Beesley J, McGuffog L, Sinilnikova OM, Healey S, Neuhausen SL, Ding YC, Rebbeck TR, Weitzel JN, Lynch HT, Isaacs C, Ganz PA, Tomlinson G, Olopade OI, Couch FJ, Wang X, Lindor NM, Pankratz VS, Radice P, Manoukian S, Peissel B, Zaffaroni D, Barile M, Viel A, Allavena A, Dall'Olio V, Peterlongo P, Szabo CI, Zikan M, Claes K, Poppe B, Foretova L, Mai PL, Greene MH, Rennert G, Lejbkowicz F, Glendon G, Ozcelik H, Andrulis IL, Thomassen M, Gerdes AM, Sunde L, Cruger D, Jensen UB, Caligo M, Friedman E, Kaufman B, Laitman Y, Milgrom R, Dubrovsky M, Cohen S, Borg A, Jernström H, Lindblom A, Rantala J, Stenmark-Askmalm M, Melin B, Nathanson K, Domchek S, Jakubowska A, Lubinski J, Huzarski T, Osorio A, Lasa A, Durán M, Tejada MI, Godino J, Benitez J, Hamann U, Kriege M, Hoogerbrugge N, van der Luijt RB, van Asperen CJ, Devilee P, Meijers-Heijboer EJ, Blok MJ, Aalfs CM, Hogervorst F, Rookus M, Cook M, Oliver C, Frost D, Conroy D, Evans DG, Lalloo F, Pichert G, Davidson R, Cole T, Cook J, Paterson J, Hodgson S, Morrison PJ, Porteous ME, Walker L, Kennedy MJ, Dorkins H, Peock S, Godwin AK, Stoppa-Lyonnet D, de Pauw A, Mazoyer S, Bonadona V, Lasset C, Dreyfus H, Leroux D, Hardouin A, Berthet P, Faivre L, Loustalot C, Noguchi T, Sobol H, Rouleau E, Nogues C, Frénay M, Vénat-Bouvet L, Hopper JL, Daly MB, Terry MB, John EM, Buys SS, Yassin Y, Miron A, Goldgar D, Singer CF, Dressler AC, Gschwantler-Kaulich D, Pfeiler G, Hansen TVO, Jønson L, Agnarsson BA, Kirchhoff T, Offit K, Devlin V, Dutra-Clarke A, Piedmonte M, Rodriguez GC, Wakeley K, Boggess JF, Basil J, Schwartz PE, Blank SV, Toland AE, Montagna M, Casella C, Imyanitov E, Tihomirova L, Blanco I, Lazaro C, Ramus SJ, Sucheston L, Karlan BY, Gross J, Schmutzler R, Wappenschmidt B, Engel C, Meindl A, Lochmann M, Arnold N, Heidemann S, Varon-Mateeva R, Niederacher D, Sutter C, Deissler H, Gadzicki D, Preisler-Adams S, Kast K, Schönbuchner I, Caldes T, de la Hoya M, Aittomäki K, Nevanlinna H, Simard J, Spurdle AB, Holland H, Chen X, Platte R, Chenevix-Trench G, Easton DF. Common breast cancer susceptibility alleles and the risk of breast cancer for *BRCA1* and *BRCA2* mutation carriers: implications for risk prediction. *Cancer Res* 2010;70:9742–54.

15 Antoniou AC, Kartsonaki C, Sinilnikova OM, Soucy P, McGuffog L, Healey S, Lee A, Peterlongo P, Manoukian S, Peissel B, Zaffaroni D, Cattaneo E, Barile M, Pensotti V, Pasini B, Dolcetti R, Giannini G, Putignano ALL, Varesco L, Radice P, Mai PL, Greene MH, Andrulis IL, Glendon G, Ozcelik H, Thomassen M, Gerdes AMM, Kruse TA, Birk Jensen U, Crüger DG, Caligo MA, Laitman Y, Milgrom R, Kaufman B, Paluch-Shimon S, Friedman E, Loman N, Harbst K, Lindblom A, Arver B, Ehrencrona H, Melin B, SWE-BRCA Nathanson KL, Domchek SM, Rebbeck T, Jakubowska A, Lubinski J, Gronwald J, Huzarski T, Byrski T, Cybulski C, Gorski B, Osorio A, Ramón y Cajal T, Fostira F, Andrés R, Benitez J, Hamann U, Hogervorst FB, Rookus MA, Hooning MJ, Nelen MR, van der Luijt RB, van Os TA, van Asperen CJ, Devilee P, Meijers-Heijboer HE, Gómez Garcia EB, HEBON Peock S, Cook M, Frost D, Platte R, Leyland J, Evans DG, Lalloo F, Eeles R, Izatt L, Adlard J, Davidson R, Eccles D, Ong KrR, Cook J, Douglas F, Paterson J, Kennedy MJ, Miedzybrodzka Z, EMBRACE, Godwin A, Stoppa-Lyonnet D, Buecher B, Belotti M, Tirapo C, Mazoyer S, Barjhoux L, Lasset C, Leroux D, Faivre L, Bronner M, Prieur F, Nogues C, Rouleau E, Pujol P, Coupier I, Frénay M, CEMO Study Collaborators, Hopper JL, Daly MB, Terry MB, John EM, Buys SS, Yassin Y, Miron A, Goldgar D, Breast Cancer Family Registry, Singer CF, Tea MKK, Pfeiler G, Dressler ACC, Hansen Tv, Jønson L, Ejlertsen B, Barkardottir RBB, Kirchhoff T, Offit K, Piedmonte M, Rodriguez G, Small L, Boggess J, Blank S, Basil J, Azodi M, Toland AEE, Montagna M, Tognazzo S, Agata S, Imyanitov E, Janavicius R, Lazaro C, Blanco I, Pharoah PD, Sucheston L, Karlan BY, Walsh CS, Olah E, Bozsik A, Teo SHH, Seldon JL, Beattie MS, van Rensburg EJ, Sluiter MD, Diez O, Schmutzler RK, Wappenschmidt B, Engel C, Meindl A, Ruehl I, Varon-Mateeva R, Kast K, Deissler H, Niederacher D, Arnold N, Gadzicki D, Schönbuchner I, Caldes T, de la Hoya M, Nevanlinna H, Aittomäki K, Dumont M, Chiquette J, Tischkowitz M, Chen X, Beesley J, Spurdle AB, kConFab investigators, Neuhausen SL, Chun Ding Y, Fredericksen Z, Wang X, Pankratz VS, Couch F, Simard J, Easton DF, Chenevix-Trench G, CIMBA. Common alleles at 6q25.1 and 1p11.2 are associated with breast cancer risk for BRCA1 and BRCA2 mutation carriers. *Hum Mol Genet* 2011;20:3304–21.

16 Couch FJ, Wang X, McGuffog L, Lee A, Olswold C, Kuchenbaecker KB, Soucy P, Fredericksen Z, Barrowdale D, Dennis J, Gaudet MM, Dicks E, Kosel M, Healey S, Sinilnikova OM, Lee A, Bacot F, Vincent D, Hogervorst FB, Peock S, Stoppa-Lyonnet D, Jakubowska A, kConFab Investigators, Radice P, Katharina R, SWE-BRCA Domchek SM, Piedmonte M, Singer CF, Friedman E, Thomassen M, Ontario Cancer Genetics Network, Hansen TV, Neuhausen SL, Szabo CI, Blanco I, Greene MH, Karlan BY, Garber J, Phelan CM, Weitzel JN, Montagna M, Olah E, Andrulis IL, Godwin AK, Yannoukakos D, Goldgar DE, Caldes T, Nevanlinna H, Osorio A, Beth M, Daly MB, van Rensburg EJ, Hamann U, Ramus SJ, Ewart A, Caligo MA, Olopade OI, Tung N, Claes K, Beattie MS, Southey MC, Imyanitov EN, Tischkowitz M, Janavicius R, John EM, Kwong A, Diez O, Balmaña J, Barkardottir RB, Arun BK,

Rennert G, Teo SHH, Ganz PA, Campbell I, van der Hout AH, van Deurzen CH, Seynaeve C, Gómez Garcia EB, van Leeuwen FE, Meijers-Heijboer HE, Gille JJ, Ausems MG, Blok MJ, Ligtenberg MJ, Rookus MA, Devilee P, Verhoef S, van Os TA, Wijnen JT, HEBON EMBRACE, Frost D, Ellis S, Fineberg E, Platte R, Evans GG, Izatt L, Eeles RA, Adlard J, Eccles DM, Cook J, Brewer C, Douglas F, Hodgson S, Morrison PJ, Side LE, Donaldson A, Houghton C, Rogers MT, Dorkins H, Eason J, Gregory H, McCann E, Murray A, Calender A, Hardouin A, Berthet P, Delnatte C, Nogues C, Lasset C, Houdayer C, Leroux D, Rouleau E, Prieur F, Damiola F, Sobol H, Coupier I, Venat-Bouvet L, Castera L, Gauthier-Villars M, Léoné M, Pujol P, Mazoyer S, Bignon YJJ, GEMO Study Collaborators, Złowocka-Perłowska E, Gronwald J, Lubinski J, Durda K, Jaworska K, Huzarski T, Spurdle AB, Viel A, Peissel B, Bonanni B, Melloni G, Ottini L, Papi L, Varesco L, Grazia M, Peterlongo P, Volorio S, Manoukian S, Pensotti V, Arnold N, Engel C, Deissler H, Gadzicki D, Gehrig A, Kast K, Rhiem K, Meindl A, Niederacher D, Ditsch N, Plendl H, Preisler-Adams S, Engert S, Sutter C, Varon-Mateeva R, Wappenschmidt B, Weber BH, Arver B, Stenmark-Askmalm M, Loman N, Rosenquist R, Einbeigi Z, Nathanson KL, Rebbeck TR, Blank SV, Cohn DE, Rodriguez GC, Small L, Friedlander M, Bae-Jump VL, Fink-Retter A, Rappaport C, Gschwantler-Kaulich D, Pfeiler G, Tea MKK, Lindor NM, Kaufman B, Paluch SS, Laitman Y, Skytte ABB, Gerdes AMM, Sokilde I, Traasdahl S, Kruse TA, Birk U, Vijai J, Sarrel K, Robson M, Kauff N, Marie A, Glendon G, Ozcelik H, Ejlertsen B, Nielsen FC, Jønson L, Andersen MK, Chun Y, Steele L, Foretova L, Teulé A, Lazaro C, Brunet J, Angel M, Mai PL, Loud JT, Walsh C, Lester J, Orsulic S, Narod SA, Herzog J, Sand SR, Tognazzo S, Agata S, Vaszko T, Weaver J, Stavropoulou AV, Buys SS, Romero A, de la Hoya M, Aittomäki K, Muranen TA, Duran M, Chung WK, Lasa A, Dorfling CM, Miron A, BCFR Benitez J, Senter L, Huo D, Chan SB, Sokolenko AP, Chiquette J, Tihomirova L, Friebel TM, Agnarsson BA, Lu KH, Lejbkowicz F, James PA, Hall P, Dunning AM, Tessier D, Cunningham J, Slager SL, Wang C, Hart S, Stevens K, Simard J, Pastinen T, Pankratz VS, Offit K, Easton DF, Chenevix-Trench G, Antoniou AC, CIMBA. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. *PLoS Genet* 2013;9:e1003212.

17 Ingham SL, Warwick J, Byers H, Lalloo F, Newman WG, Evans DG. Is multiple SNP testing in BRCA2 and BRCA1 female carriers ready for use in clinical practice? Results from a large Genetic Centre in the UK. *Clin Genet* 2013;84:37–42.

18 Easton D, Emery J, Gray J, Halpin J, Hopwood P, McKay J, Sheppard C, Sibbering M, Watson W, Wailoo A, Hutchinson A, McIntosh A, Shaw C, Evans G, Turnbull N, Bahar N, Barclay M, *et al*. *Clinical guidelines and evidence review for the classification and care of women at risk of familial breast cancer*. London: National Collaborating Centre for Primary Care/University of Sheffield. NICE guideline, 2004 (updated 2006, 2013). http://www.nice.org.uk/guidance/cg164

19 Evans DG, Lalloo F, Cramer A, Jones EA, Knox F, Amir E, Howell A. Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for BRCA1 and BRCA2 testing. *J Med Genet* 2009;46:811–17.

20 Byers H, Wallis Y, van Veen EM, Lalloo F, Reay K, Smith P, Wallace AJ, Bowers N, Newman WG, Evans DG. Sensitivity of BRCA1/2 testing in high-risk breast/ovarian/male breast cancer families: little contribution of comprehensive RNA/NGS panel testing. *Eur J Hum Genet* 2016;24:1591–97.

21 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45.

22 Evans DGR, Lalloo F. Risk assessment and management of high risk familial breast cancer. *J Med Genet* 2002;39:865–71.

23 Evans DGR, Ingham S, Dawe S, Roberts L, Lalloo F, Brentnall AR, Stavrinos P, Howell A. Breast cancer risk assessment in 8,824 women attending a family history evaluation and screening programme. *Fam Cancer* 2014;13:189–96.

24 http://www.cancer.org/cancer/breastcancer/moreinformation/breastcancerearlydetection/breast-cancer-early-detection-acs-recs (accessed 23 Jun 2016).

25 Kurian AW, Hare EE, Mills MA, Kingham KE, McPherson L, Whittemore AS, McGuire V, Ladabaum U, Kobayashi Y, Lincoln SE, Cargill M, Ford JM. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol* 2014;32:2001–9.

26 Mavaddat N, Pharoah PDP, Michailidou K, Tyrer J, Brook MN, Bolla MK, Wang Q, Dennis J, Dunning AM, Shah M, Luben R, Brown J, Bojesen SE, Nordestgaard BG, Nielsen SF, Flyger H, Czene K, Darabi H, Eriksson M, Peto J, dos Santos-Silva I, Dudbridge F, Johnson N, Schmidt MK, Broeks A, Verhoef S, Rutgers EJ, Swerdlow A, Ashworth A, Orr N, Schoemaker MJ, Figueroa J, Chanock SJ, Brinton L, Lissowska J, Couch FJ, Olson JE, Vachon C, Pankratz VS, Lambrechts D, Wildiers H, Van Ongeval C, van Limbergen E, Kristensen V, Grenaker Alnæs G, Nord S, Borresen-Dale AL, Nevanlinna H, Muranen TA, Aittomäki K, Blomqvist C, Chang-Claude J, Rudolph A, Seibold P, Flesch-Janys D, Fasching PA, Haeberle L, Ekici AB, Beckmann MW, Burwinkel B, Marme F, Schneeweiss A, Sohn C, Trentham-Dietz A, Newcomb P, Titus L, Egan KM, Hunter DJ, Lindstrom S, Tamimi RM, Kraft P, Rahman N, Turnbull C, Renwick A, Seal S, Li J, Liu J, Humphreys K, Benitez J, Pilar Zamora M, Arias Perez JI, Menéndez P, Jakubowska A, Lubinski J, Jaworska-Bieniek K, Durda K, Bogdanova NV, Antonenkova NN, Dörk T, Anton-Culver H, Neuhausen SL, Ziogas A, Bernstein L, Devilee P, Tollenaar RAEM, Seynaeve C, van Asperen CJ, Cox A, Cross SS, Reed MWR, Khusnutdinova E, Bermisheva M, Prokofyeva D, Takhirova Z, Meindl A, Schmutzler RK, Sutter C, Yang R, Schürmann P, Bremer M, Christiansen H, Park-Simon TW, Hillemanns P, Guénel P, Truong T, Menegaux F, Sanchez M, Radice P, Peterlongo P, Manoukian S, Pensotti V, Hopper JL, Tsimiklis H, Apicella C, Southey MC, Brauch H, Brüning T, Ko YD, Sigurdson AJ, Doody MM, Hamann U, Torres D, Ulmer HU, Försti A, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Andrulis IL, Knight JA, Glendon G, Marie Mulligan A, Chenevix-Trench G, Balleine R, Giles GG, Milne RL, McLean C, Lindblom A, Margolin S, Haiman CA, Henderson BE, Schumacher F, Le Marchand L, Eilber U, Wang-Gohrke S, Hooning MJ, Hollestelle A, van den Ouweland AMW, Koppert LB, Carpenter J, Clarke C, Scott R, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Brenner H, Arndt V, Stegmaier C, Karina Dieffenbach A, Winqvist R, Pylkäs K, Jukkola-Vuorinen A, Grip M, Offit K, Vijai J, Robson M, Rau-Murthy R, Dwek M, Swann R, Annie Perkins K, Goldberg MS, Labrèche F, Dumont M, Eccles DM, Tapper WJ, Rafiq S, John EM, Whittemore AS, Slager S, Yannoukakos D, Toland AE, Yao S, Zheng W, Halverson SL, González-Neira A, Pita G, Rosario Alonso M, Álvarez N, Herrero D, Tessier DC, Vincent D, Bacot F, Luccarini C, Baynes C, Ahmed S, Maranian M, Healey CS, Simard J, Hall P, Easton DF, Garcia-Closas M. Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst* 2015;107:djv036.

27 Dite GS, MacInnis RJ, Bickerstaffe A, Dowty JG, Allman R, Apicella C, Milne RL, Tsimiklis H, Phillips KA, Giles GG, Terry MB, Southey MC, Hopper JL. Breast cancer risk prediction using clinical models and 77 independent risk-associated SNPs for women aged under 50 years: Australian Breast Cancer Family Registry. *Cancer Epidemiol Biomarkers Prev* 2016;25:359–65.

28 Brentnall AR, Evans DG, Cuzick J. Distribution of breast cancer risk from SNPs and classical risk factors in women of routine screening age in the UK. *Br J Cancer* 2014;110:827–8.

The impact of a panel of 18 SNPs on breast cancer risk in women attending a UK familial screening clinic: a case–control study

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