



Universiteit  
Leiden  
The Netherlands

## **Clinical applicability of the Polygenic Risk Score for breast cancer risk prediction in familial cases**

Lakeman, I.M.M.; Rodriguez Girondo, M.D.M.; Lee, A.; Celosse, N.; Braspenning, M.E.; Engelen, K. van; ... ; Devilee, P.

### **Citation**

Lakeman, I. M. M., Rodriguez Girondo, M. D. M., Lee, A., Celosse, N., Braspenning, M. E., Engelen, K. van, ... Devilee, P. (2022). Clinical applicability of the Polygenic Risk Score for breast cancer risk prediction in familial cases. *Journal Of Medical Genetics*.  
doi:10.1136/jmg-2022-108502

Version: Publisher's Version

License: [Creative Commons CC BY-NC 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3563452>

**Note:** To cite this publication please use the final published version (if applicable).



OPEN ACCESS

Original research

# Clinical applicability of the Polygenic Risk Score for breast cancer risk prediction in familial cases

Inge M M Lakeman <sup>1,2</sup>, Mar D M Rodríguez-Girondo,<sup>3</sup> Andrew Lee <sup>4</sup>, Nandi Celosse,<sup>1</sup> Merel E Braspenning,<sup>1</sup> Klaartje van Engelen,<sup>5</sup> Irma van de Beek,<sup>5</sup> Annemiek H van der Hout,<sup>6</sup> Encarna B Gómez García,<sup>7</sup> Arjen R Mensenkamp <sup>8</sup>, Margreet G E M Ausems,<sup>9</sup> Maartje J Hooning,<sup>10</sup> Muriel A Adank,<sup>11</sup> Antoinette Hollestelle,<sup>10</sup> Marjanka K Schmidt,<sup>2,12</sup> Christi J van Asperen,<sup>2</sup> Peter Devilee <sup>1,13</sup>

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jmg-2022-108502>).

For numbered affiliations see end of article.

## Correspondence to

Dr Peter Devilee, Department of Human Genetics, Leiden University Medical Center, Leiden, Zuid-Holland 2333, The Netherlands; [p.devilee@lumc.nl](mailto:p.devilee@lumc.nl)

Received 10 February 2022  
Accepted 19 July 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Lakeman IMM, Rodríguez-Girondo MDM, Lee A, et al. *J Med Genet* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jmedgenet-2022-108502

## ABSTRACT

**Background** Common low-risk variants are presently not used to guide clinical management of familial breast cancer (BC). We explored the additive impact of a 313-variant-based Polygenic Risk Score (PRS<sub>313</sub>) relative to standard gene testing in non-*BRCA1/2* Dutch BC families.

**Methods** We included 3918 BC cases from 3492 Dutch non-*BRCA1/2* BC families and 3474 Dutch population controls. The association of the standardised PRS<sub>313</sub> with BC was estimated using a logistic regression model, adjusted for pedigree-based family history. Family history of the controls was imputed for this analysis. SEs were corrected to account for relatedness of individuals. Using the BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) V.5 model, lifetime risks were retrospectively calculated with and without individual PRS<sub>313</sub>. For 2586 cases and 2584 controls, the carrier status of pathogenic variants (PVs) in *ATM*, *CHEK2* and *PALB2* was known.

**Results** The family history-adjusted PRS<sub>313</sub> was significantly associated with BC (per SD OR=1.97, 95% CI 1.84 to 2.11). Including the PRS<sub>313</sub> in BOADICEA family-based risk prediction would have changed screening recommendations in up to 27%, 36% and 34% of cases according to BC screening guidelines from the USA, UK and the Netherlands (National Comprehensive Cancer Network, National Institute for Health and Care Excellence, and Netherlands Comprehensive Cancer Organisation), respectively. For the population controls, without information on family history, this was up to 39%, 44% and 58%, respectively. Among carriers of PVs in known moderate BC susceptibility genes, the PRS<sub>313</sub> had the largest impact for *CHEK2* and *ATM*.

**Conclusions** Our results support the application of the PRS<sub>313</sub> in risk prediction for genetically uninformative BC families and families with a PV in moderate BC risk genes.

## INTRODUCTION

Breast cancer (BC) is the most common cancer among women.<sup>1</sup> Current screening strategies to

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Polygenic Risk Score (PRS) is useful in stratifying women into different risk categories but is presently not used to guide clinical management of familial breast cancer (BC).

## WHAT THIS STUDY ADDS

⇒ Including the PRS<sub>313</sub> in addition to family history-based risk prediction may change screening recommendations in up to 34% of individuals from BC families with no pathogenic variant in any of the five BC genes modelled in BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) and up to 18% and 26% for *ATM* and *CHEK2* pathogenic variant carriers, respectively.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports the implementation of a comprehensive risk prediction and shows the impact on clinical management recommendations for women from BC families as seen in the context of clinical genetic services.

reduce the burden of the disease have several disadvantages, including overdiagnosis.<sup>2</sup> By taking into account all relevant risk factors, personalised estimation of risk of BC could help to target preventive measures to those who would benefit the most and to reduce screening for women in the lowest risk categories.

One of the main risk factors for BC is having a positive family history of the disease.<sup>3</sup> The familial relative risk of ~2 is partly explained by germline pathogenic variants (PVs) in the BC susceptibility genes *BRCA1/2*, *PALB2*, *ATM* and *CHEK2*. Furthermore, another important part is explained by common low-risk variants,<sup>4,5</sup> which if summarised in the Polygenic Risk Score (PRS) are useful in stratifying the population into different risk categories.<sup>5,6</sup>

A similar stratification of risk of BC by the PRS is observed in the familial setting,<sup>7–10</sup> providing an opportunity to personalise risk and clinical management of women from BC families who are seen at clinical genetic services. Furthermore, the PRS can be useful in refining the risk of women carrying a PV in *BRCA1/2*, *PALB2*, *CHEK2* or *ATM*.<sup>11–14</sup> However, using the PRS for risk prediction is not yet implemented in the practice of genetic counselling for familial BC in the Netherlands.

Currently, risk prediction for women from non-*BRCA1/2* BC families is mainly based on family history, which can be calculated by various well-validated risk prediction algorithms,<sup>15–16</sup> such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA).<sup>17</sup> Several studies have shown improved discriminative power between BC cases and controls by combining the PRS with other risk factors in a BC risk prediction tool.<sup>18–21</sup> Previously, we showed that in a selected group of high-risk non-*BRCA1/2* BC families, a 161-variant PRS alone would have led 20% of women to receive different screening recommendations based on the Dutch screening guideline (Netherlands Comprehensive Cancer Organisation (IKNL) guideline).<sup>22</sup> Currently, an established PRS based on 313 variants (PRS<sub>313</sub>)<sup>5</sup> is one of the several PRS incorporated in the validated, comprehensive risk prediction model BOADICEA,<sup>17</sup> which was recently made easily accessible to clinicians through the CanRisk webtool.<sup>23</sup>

Here, we explore the clinical applicability of the PRS<sub>313</sub> for risk prediction in a new cohort of 3918 familial Dutch BC cases who tested negative in a diagnostic setting for PVs in *BRCA1/2* and of whom the majority were evaluated for PVs in *PALB2*, *CHEK2* and *ATM* in a research setting. The clinical impact of the PRS<sub>313</sub> on BC risk prediction based on family history and PV carrier status was investigated by determining the potential change in clinical management, as stipulated by three currently used guidelines (National Comprehensive Cancer Network (NCCN),<sup>24</sup> National Institute for Health and Care Excellence (NICE),<sup>25</sup> and IKNL guidelines).<sup>22</sup>

## MATERIALS AND METHODS

We used the Strengthening the Reporting of Observational Studies in Epidemiology case–control checklist when writing our report.<sup>26</sup>

### Study cohorts

Dutch familial BC cases, henceforth ‘cases’, were derived from three different cohorts: the Hereditary Breast and Ovarian cancer study in the Netherlands (HEBON),<sup>27</sup> the Amsterdam Breast Cancer Study-Familial (ABCS-F),<sup>28</sup> and the Rotterdam Breast Cancer Study (RBCS)<sup>29</sup> (online supplemental methods). All three studies included participants who visited a clinical genetic centre in the Netherlands for familial BC counselling. During this counselling, a DNA test was performed according to the clinical guidelines applicable at the time. Women with BC who met the following criteria were eligible for this study: (1) negative DNA test result for *BRCA1/2* PVs; (2) family without *BRCA1/2* PVs; (3) available DNA sample or genotyping data; (4) European ancestry based on genotyping data; and (5) available pedigree. In total, 3918 cases were included (online supplemental figure S1). All cancers were verified by linkage to the Dutch Cancer Registry and the Pathological Anatomical National Automated Archive (HEBON cases) or by clinical confirmation from medical records in the hospital (ABCS-F and RBCS cases).

In total, 3474 Dutch population controls of age 18 years or older were included. These controls were healthy female blood

donors (ABCS, Oorsprong van borstkanker integraal onderzocht (ORIGO)) or healthy women who were included after DNA diagnostic testing for cystic fibrosis carrier status (RBCS)<sup>4–29</sup> for which age of last follow-up was known. For the ABCS and ORIGO control cohorts, BC status was known to be negative at age of last follow-up. For the RBCS control cohort, BC status was unknown. In total, 2584 controls were known to be negative for *BRCA1/2* PVs. For the remaining 890 controls, *BRCA1/2* status was unknown.

Informed consent was obtained from all included cases. All controls were anonymised.

### Gene panel

As part of the BRIDGES project (Breast cancer RiSk after Diagnostic GEne Sequencing), 2586 cases and 2584 controls were sequenced for a panel of 34 genes, as described elsewhere.<sup>30</sup> For all controls and 2037 cases, we received variant call files of all 34 genes, including their last exons. Truncating and missense variants were reported as described previously.<sup>30</sup> In summary, pathogenic truncating variants were defined as frameshift insertions/deletions, stop/gain or canonical splice variants as classified by the Ensembl Variant Effect Predictor,<sup>31</sup> with the exception of variants in the last exon of each gene. In our study, we included truncating variants in the last exon of *PALB2* as this exon encodes an important functional domain and variants in this exon were shown to destabilise the resulting *PALB2* protein.<sup>32</sup> Missense variants were included if their frequency in the gnomAD database or among the BRIDGES project control data set<sup>30</sup> was below 0.001. For genes with evidence of an association with BC,<sup>30</sup> pathogenicity was reported for missense variants based on the ClinVar archive.<sup>33</sup> Variants that were classified as (likely) pathogenic by at least one submitter were manually curated by two experts according to the ACMG/ACP (American College of Medical Genetics and Genomics/American College of Physicians) variant classification guidelines. For the remaining 549 cases, however, only pseudo-anonymised results of truncating variants in the three additional BC genes, *ATM*, *CHEK2* and *PALB2*, were received, excluding truncating variants in the last exon.

### Genotyping and imputation

The DNA samples of all included individuals were genotyped for common variants with either the iCOGS,<sup>34</sup> OncoArray<sup>4</sup> or Global Screening Array (GSA), containing 211 155, 499 170 and 642 824 SNPs, respectively. Genotyping and quality control of the samples genotyped with iCOGS and OncoArray were performed as part of association studies conducted by the Breast Cancer Association Consortium (BCAC).<sup>4–34</sup> Genotyping and quality control of the samples genotyped with the GSA are described in the online supplemental methods.

The variants that were not directly genotyped were imputed using the Michigan Imputation Server,<sup>35</sup> using the Haplotype Reference Consortium (HRC) V.1.1 reference panel,<sup>36</sup> including both the reference panels 1000 Genomes Phase 3 and Genome of the Netherlands.<sup>37–38</sup> In total, 72 of the 313 variants could not be imputed with the HRC V.1.1 reference panel and were imputed with the 1000 Genomes Phase 3 reference panel only<sup>38</sup> (online supplemental table S1).

### Polygenic Risk Score

The PRS was calculated as described previously.<sup>5</sup> The three PRS (for overall BC, estrogen receptor (ER)-positive BC and ER-negative BC) were calculated for all included individuals.

**Table 1** Characteristics of the participants

	Population controls	Family-based cases	Family-based cases: subset*
n	3474	3918	1968
Families		3492	1602
Relatives per family included			
1	3474	3099	1263
2	0	364	309
3	0	25	25
4	0	4	3
Study			
ABCS	1563	904	82
HEBON	0	2248	1671
ORIGO	987	0	0
RBCS	924	766	215
Array			
GSA		1781	1781
iCOGS	2388	1680	163
OncoArray	1086	457	24
Age			
Mean	45.6	45.1	46.8
Range	18–93	21–91	21–91
First breast cancer			
Invasive	NA	3575	1630
In situ	NA	312	308
Unknown	NA	31	30
ER status			
Positive	NA	1755	927
Negative	NA	488	213
Unknown	NA	1675	828
Second breast tumour (n)	NA	719	327
Age			
Mean	NA	52.6	52.9
Range	NA	26–80	26–79
Unknown	NA	130	29
Invasiveness			
Invasive	NA	460	220
In situ	NA	116	77
Unknown	NA	144	30
ER status			
Positive	NA	290	153
Negative	NA	49	21
Unknown	NA	380	153
Gene panel results			
All	2584	2586	1586
No PV	2537	2369	1463
CHEK2 PV	31	167	98
ATM PV	9	39	18
CHEK2+ATM PV	0	2	1
PALB2 PV†	7	10	6
Standardised PRS <sub>313</sub> (SD)			
Overall BC	0 (1.03)	0.71 (0.96)	0.64 (0.88)
ER+ BC	0 (1.03)	0.72 (0.97)	0.65 (0.88)
ER– BC	0 (1.01)	0.45 (0.94)	0.29 (0.85)
BOADICEA <sub>FH</sub>			
Mean (SD)	0 (0.99)	0.55 (0.39)	0.69 (0.35)
Affected FDR			
0	NA	1125	
1	NA	1454	

Continued

**Table 1** Continued

	Population controls	Family-based cases	Family-based cases: subset*
2	NA	555	
>2	NA	176	
Affected SDR			
0	NA	1360	
1	NA	1086	
2	NA	583	
>2	NA	281	
Unknown	NA	615	

\*Cases included in the association analyses which were not part of the development data set for the PRS<sub>313</sub> as described in Mavaddat *et al.*<sup>5</sup>

†Excluding variants in the last exon of *PALB2* to make it uniform for all 2586 cases. ABCS, Amsterdam Breast Cancer Study; BC, breast cancer; BOADICEA<sub>FH</sub>, polygenic load calculated in the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; ER, Estrogen Receptor; FDR, first-degree relatives; GSA, Global Screening Array; HEBON, Hereditary Breast and Ovarian cancer study in the Netherlands; n, number of individuals; NA, Not Applicable; ORIGO, Oorsprong van borstkanker integraal onderzocht; PRS, Polygenic Risk Score; PV, pathogenic variant; RBCS, Rotterdam Breast Cancer Study; SDR, second-degree relatives.

The variants and their corresponding weights used in the PRS as published previously<sup>5</sup> and the imputation quality are listed in online supplemental table S1. The PRS for each individual was standardised to the mean of all population controls in this study and to the SD in the BCAC population controls that were included in the validation data set.<sup>5</sup> These SDs were 0.6093, 0.6520 and 0.5920 for the overall BC PRS, ER-positive BC PRS and ER-negative BC PRS, respectively. Using these SDs, the OR estimates for the associations of the standardised PRS<sub>313</sub> in our study are directly comparable with the OR estimates reported in the BCAC population-based study.<sup>5</sup>

#### Pedigree collection

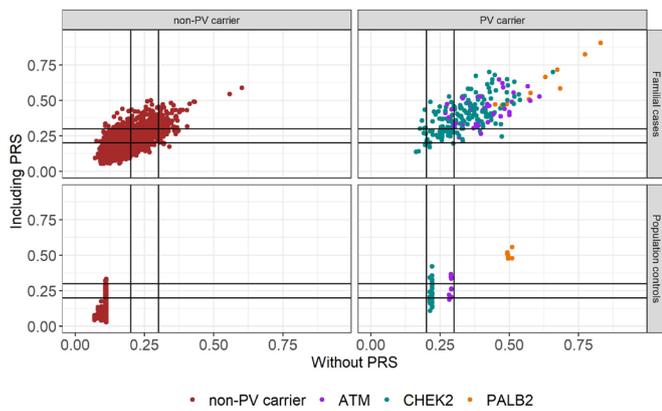
Pedigrees were collected for all families and were drawn previously in the clinical genetic centres during counselling and DNA diagnostic testing of *BRCA1/2* PVs. The pedigrees were used as they were drawn in the clinic, including at least all known first-degree and second-degree relatives of the genotyped individuals. Imputation of missing data is described in the online supplemental methods.

#### Family history score

A model-based family history score for BC, also called the ‘polygenic load’, was derived from the BOADICEA V.3 model based on the available pedigree, as described previously.<sup>7</sup> The polygenic load in BOADICEA is a latent polygenetic component representing the combined effect of a large number of variants, each of small effect to capture the residual familial aggregation of BC and is therefore a measure of the BC family history,<sup>7 10</sup> henceforth referred to as BOADICEA<sub>FH</sub>. No pedigree or family history data were available for the controls. Therefore, BOADICEA<sub>FH</sub> was imputed based on the distribution of BOADICEA<sub>FH</sub> (normally distributed with mean=0 and SD=1).

#### BC lifetime risk

As all cases had developed BC, the lifetime risks of developing a first breast tumour were calculated for all included individuals with the BOADICEA V.5 model,<sup>17</sup> simulating an individual to be aged 1 year and unaffected. Initial lifetime risks (BOADICEA<sub>ILR</sub>) were calculated based on *BRCA* status (all negative), pedigree



**Figure 1** Change in individual breast cancer lifetime risk after including the PRS<sub>313</sub>. Scatter plot of the change in breast cancer lifetime risk. For every individual, BOADICEA<sub>ILR</sub> was plotted against BOADICEA<sub>PRS313</sub>. Non-carriers do not have a pathogenic variant in *ATM*, *CHEK2* or *PALB2* in addition to *BRCA1/2*. The solid lines represent the 20% and 30% breast cancer lifetime risk cut-off levels based on the Dutch IKNL breast cancer screening guideline.<sup>22</sup> BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; BOADICEA<sub>ILR</sub>, initial breast cancer lifetime risk at age 80 based on *BRCA* status (all negative), *CHEK2*, *ATM* and *PALB2* status (if applicable), pedigree information (for cases), and birth year. BOADICEA<sub>PRS313</sub>, breast cancer lifetime risk at age 80 including the PRS<sub>313</sub> in addition to initial breast cancer lifetime risk; IKNL, Netherlands Comprehensive Cancer Organisation; PRS, Polygenic Risk Score; PV, pathogenic variant.

information (for cases) as described above and birth year. The *BRCA1* and *BRCA2* mutation detection sensitivity in BOADICEA was set at 0.9. For individuals in whom information regarding PVs in the BC genes *CHEK2*, *PALB2* and *ATM* was available, initial risks included the PV carrier status of these genes as well. To make it uniform for all included cases, PVs in the last exon of *PALB2* were ignored. The initial lifetime risks were compared with the lifetime risks calculated with the above information and the PRS<sub>313</sub> (BOADICEA<sub>PRS313</sub>).

#### Statistical analysis

The BC lifetime risks for cases and controls with (BOADICEA<sub>PRS313</sub>) and without (BOADICEA<sub>ILR</sub>) inclusion of the PRS<sub>313</sub> were compared to define the change in risk category and thus advice for BC surveillance according to three different guidelines: NICE,<sup>25</sup> NCCN<sup>24</sup> and IKNL.<sup>22</sup>

To define how much of the variance in the PRS<sub>313</sub> is explained by family history in this study, the degree of correlation between the standardised PRS<sub>313</sub> and the BOADICEA<sub>FH</sub> for cases was determined by the Pearson correlation coefficient. This coefficient was calculated as well to estimate the linear correlation between the PRS<sub>313</sub> of the proband (ie, youngest BC diagnosis) and the PRS<sub>313</sub> of other affected family members. If more than two family members were included, the average PRS<sub>313</sub> of the family members was used. The association between overall BC (first breast tumour, invasive or in situ) and the PRS<sub>313</sub> was determined with logistic regression using generalised estimating equations, adjusting for age and family history (BOADICEA<sub>FH</sub>). SEs were corrected to account for relatedness of individuals using a robust estimator of the variance. To reduce overfitting, association analyses included only cases that were not part of the development data set for the PRS<sub>313</sub>, as described in Mavaddat *et al.*<sup>5</sup>

In a secondary analysis, we determined the association of the PRS<sub>313</sub> with invasive and in situ BC risk separately. Cases that

developed an invasive BC after the development of an in situ BC were only included in the invasive BC analysis with the age of diagnosis of the invasive breast tumour. Two of these cases were excluded because the age of diagnosis of invasive breast tumour was unknown.

In addition, the association between risk of BC and the prevalence of a truncating variant in each of the 34 genes included in the BRIDGES gene panel<sup>30</sup> was determined with a two-sided Fisher's exact test.

Statistical significance was established at 5%. Analysis was performed using R V4.0.3.<sup>39</sup>

## RESULTS

The analyses included 3918 cases from 3492 families and 3474 female population controls. In the association analyses, a subset of cases were included, that is, those not included previously in the development data set of the PRS<sub>313</sub>.<sup>5</sup> These comprised 1968 cases from 1602 families (online supplemental figure S1 and table 1).

The characteristics of the included cases and controls are shown in table 1. The mean age at last follow-up for controls and age at diagnosis for cases was similar, 45 years, with an age range between 18 and 93 years. Most of the included cases had an invasive breast tumour (91%), 8% an in situ breast tumour and 1% a tumour of unknown invasiveness. Of all included cases, 18% developed a second breast tumour. The standardised PRS<sub>313</sub> was higher for cases compared with controls, with a mean of 0.71 (SD=0.96) compared with 0 for controls (SD=1.03). The distribution curves and descriptives of the standardised PRS<sub>313</sub>, ER-positive PRS<sub>313</sub> and ER-negative PRS<sub>313</sub> are shown in online supplemental figures S2 and S3 and online supplemental tables S2 and S3. In total, 218 (8.4%) cases and 47 (1.8%) controls were carriers of a truncating PV in either *ATM*, *CHEK2* or *PALB2*, excluding PVs in the last exon.

#### Gene panel results

The BRIDGES study<sup>30</sup> completed sequencing for 2037 cases with clinical data and 2584 controls. Truncating (likely) PVs were found in 22 of 34 genes for 227 (11.1%) cases and 105 (4.1%) controls (online supplemental table S4). The majority (6.4% of cases, 1.2% of controls) had a truncating variant in *CHEK2*, which, in all except one, was the founder PV c.1100delC. In addition, truncating variants were relatively frequently found in *ATM*, *FANCM* and *PALB2* (1.8%, 0.7% and 0.6% of cases and 0.3%, 0.6% and 0.3% of controls, respectively). The number of (pathogenic) missense variants is listed in online supplemental table S5.

#### PRS-based individualised risk score

Adding the PRS<sub>313</sub> into the BOADICEA model (BOADICEA<sub>PRS313</sub>) changed the absolute lifetime risk of almost all women (figure 1) to a maximum of 34.5% for cases and to a maximum of 22.1% for controls (online supplemental figure S4 and online supplemental table S6). Clinically relevant shifts, that is, from one to another screening category, based on the IKNL,<sup>22</sup> NICE<sup>25</sup> or NCCN<sup>24</sup> guidelines, were 32.4%, 36.0% and 25.7%, respectively, for 1331 cases without a gene test result (ie, only tested negative for a *BRCA1/2* PV in diagnostic setting) (table 2 and online supplemental tables S7 and S8). Similar results were seen for 2369 cases that were known non-carriers of a PV in *PALB2*, *CHEK2* and *ATM*. In both groups and all age categories, a higher percentage of cases shifted to the moderate-risk and high-risk category compared with the lowest risk category

**Table 2** Breast cancer lifetime risk category change based on the IKNL guideline

Group	BOADICEA lifetime risk		No gene test result		Non-PV carriers		CHEK2 PV carriers*		ATM PV carriers*		PALB2 PV carriers	
	Without PRS <sub>313</sub> (%)	Including PRS <sub>313</sub> (%)	n	% change	n	% change	n	% change	n	% change	n	% change
Cases	<20	<20	697	30.4	1126	30.1	3	70.0	NA	NA	NA	NA
		>20	305		486		7					
	20–30	20–30	161	42.5	376	43.5	27	52.6	0	100.0	NA	NA
		<20	37		149		4		0			
		>30	82		141		26		5			
	>30	>30	42	14.3	65	28.6	93	7.0	32	5.9	10	0.0
		<30	7		26		7		2		0	
Overall change			32.4		33.9		26.3		17.9		0.0	
Upward change			29.1		26.4		19.8		12.8		0.0	
Controls	<20	<20	851	4.4	2429	4.7	NA	NA	NA	NA	NA	NA
		>20	39		118							
	20–30	20–30	NA		NA		13	58.1	4	55.6	NA	NA
		<20					12		1			
		>30					6		4			
	>30	>30	NA		NA		NA	NA	NA	NA	7	0.0
		<30									0	
Overall change			4.4		4.7		58.1		55.6		0.0	
Upward change			4.4		4.7		19.4		44.4		0.0	

In total, 1331 cases and 890 controls were included without a gene test result; 2369 cases and 2537 controls in the non-PV carrier group; 167 cases and 31 controls in the CHEK2 PV carrier group; 39 cases and 9 controls in the ATM PV carrier group; and 10 cases and 7 controls in the PALB2 PV carrier group.

\*Two individuals with both a pathogenic variant in CHEK2 and ATM were excluded.

BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; IKNL, Netherlands Comprehensive Cancer Organisation; NA, Not Applicable; PRS, Polygenic Risk Score; PV, pathogenic variant.

(online supplemental table S9). Change towards higher risk categories was less frequent in controls than in cases (online supplemental tables S7 and S8). For cases carrying a PV in ATM or CHEK2, the proportions changing risk category were 26.3% and 17.9%, respectively, for IKNL, and 23.4% and 17.9% for NICE guidelines, but substantially lower based on the NCCN guideline (6.7% and 0.0%); this was due to the single cut-off point of 20% in the NCCN guideline. The 10 PALB2 PV carriers in the study did not change risk category based on any of the three guidelines.

Of the 890 controls without a gene test result for ATM, CHEK2 or PALB2 status, 4.4%, 12.0% and 4.4% changed to another risk category based on the IKNL, NICE and NCCN guidelines, respectively. Similar results were seen for the group where no PV was found. For CHEK2 PV carriers, and to a lesser extent ATM PV carriers, these percentages were higher. Similar to cases, no change in risk category was seen for the seven controls with a PALB2 PV carrier with either of the three guidelines.

The distributions of the absolute lifetime risk after including the PRS<sub>313</sub> for all groups (BOADICEA<sub>PRS313</sub>) are shown in online supplemental figure S5.

### Correlation analysis

For cases, there was a very weak correlation between the PRS<sub>313</sub> and the BOADICEA<sub>FH</sub> ( $r=0.053$ ,  $p=8.23 \times 10^{-4}$ ); only 0.3% of the variance in the PRS<sub>313</sub> is explained by family history. This poor correlation is visualised in online supplemental figures S6 and S7, where respectively the continuous and categorical BOADICEA<sub>FH</sub> are shown versus the PRS<sub>313</sub>.

In contrast, there was a significant correlation between the PRS<sub>313</sub> of the 393 probands and that of their affected family members ( $r=0.333$ ,  $p=1.00 \times 10^{-11}$ ; figure 2).

### Association analyses of PRS and BC

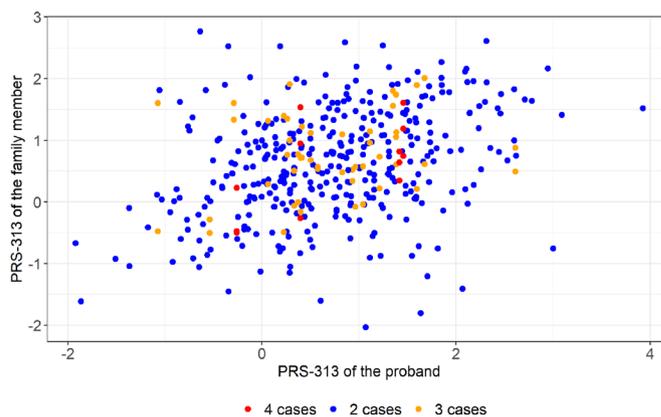
The PRS<sub>313</sub> was significantly associated with overall BC (OR per SD=1.97, 95% CI 1.84 to 2.11,  $p \leq 2.00 \times 10^{-16}$ ) (table 3 and

online supplemental figure S8). The analyses per decile followed the trend for the continuous PRS<sub>313</sub>, despite the CIs of the two lowest and highest categories not overlapping with the continuous line (table 3 and online supplemental figure S9).

Secondary analyses for invasive BC showed similar results. In situ BC was also significantly associated with the PRS<sub>313</sub> (OR=1.69, 95% CI 1.50 to 1.89,  $p \leq 2.00 \times 10^{-16}$ ) (table 3 and online supplemental figure S8).

### DISCUSSION

In this study, we have shown that including a well-validated PRS for BC based on 313 variants<sup>3</sup> leads to substantially different patient stratification from current clinical practice, in which only family history is included in risk prediction. This supports the implementation of the PRS<sub>313</sub> in standard care for individuals



**Figure 2** Correlation between the PRS<sub>313</sub> of the proband and their family members. Scatter plot of the PRS<sub>313</sub> of the proband (youngest breast cancer diagnosis) and their family members. Families with two individuals included are shown as blue dots, three individuals included with orange dots and four individuals included with red dots. PRS, Polygenic Risk Score.

**Table 3** Results of the association analyses between breast cancer and the PRS<sub>313</sub>

	Cases (n)	OR	95% CI	P value
Main analysis				
Overall breast cancer	1968	1.97	1.84 to 2.11	<2.00×10 <sup>-16</sup>
Secondary analyses*				
Invasive breast cancer	1701	2.00	1.86 to 2.15	<2.00×10 <sup>-16</sup>
In situ breast cancer	262	1.69	1.50 to 1.89	<2.00×10 <sup>-16</sup>
Categorical PRS <sub>313</sub> †				
0–10	21	0.10	0.06 to 0.17	<2.00×10 <sup>-16</sup>
10–20	58	0.30	0.21 to 0.42	2.30×10 <sup>-11</sup>
20–40	222	0.66	0.52 to 0.82	2.20×10 <sup>-04</sup>
40–60 (reference)	354	1.00	NA	NA
60–80	491	1.37	1.13 to 1.66	1.10×10 <sup>-3</sup>
80–90	396	2.27	1.84 to 2.79	1.10×10 <sup>-14</sup>
90–100	426	2.29	1.86 to 2.83	8.90×10 <sup>-15</sup>

\*Individuals with unknown invasiveness (n=3) and individuals with unknown age of diagnosis of the (second) invasive breast tumour (n=2) were excluded.  
†Category boundaries of the PRS<sub>313</sub> were -3.93, -1.27, -0.88, -0.26, 0.23, 0.84, 1.34 and 3.41.  
PRS, Polygenic Risk Score.

from these families in clinical genetic services. Using a validated, comprehensive risk prediction model, BOADICEA,<sup>17,40</sup> pedigree-based family history can be easily combined with the individual PRS<sub>313</sub>, as well as with gene panel results, to calculate personal BC lifetime risk. We have shown that this procedure leads to a different risk category and corresponding clinical advice for substantial numbers of both non-carriers and carriers of a PV in a moderate BC risk gene. Furthermore, our results confirm the association between risk of BC and the PRS<sub>313</sub> in familial BC cases in the Dutch population.<sup>5,41</sup>

For *ATM* and *CHEK2* PV carriers, previous studies showed that including the PRS is of additive value for risk prediction and risk management.<sup>13,14,42</sup> A population-based study using a PRS of 105 variants<sup>13</sup> and a case-control study using a PRS of 86 variants<sup>14</sup> found similar results for *CHEK2* PV carriers and showed that there is no need for intensified breast screening for about 30% of the women. Dissimilar percentages were found for *ATM* carriers; about 50% based on the PRS<sub>105</sub> but a substantially lower percentage using the PRS<sub>86</sub> would not need intensified screening after including the PRS.<sup>13,14</sup> These results were based on the NCCN guideline, with a single cut-off of 20% guiding clinical management. Compared with these results and using the same guideline, we found a slightly higher percentage of *CHEK2* carriers in the unaffected population would have received different screening advice (39%), but a much lower percentage (7%) for cases with a positive family history. Although we did not see a shift in screening category for *PALB2* carriers, there was an absolute risk difference, with a maximum of 9.8% for cases and 4.8% for population controls, corresponding to a lifetime risk range of 47%–91% for cases and 48%–56% for controls. A previous study found a similar effect for cases by including the PRS.<sup>43</sup> Such differences in risk could inform choices regarding preventive surgeries. It is to be expected that we will have a more extensive PRS for BC in the future, knowing that the PRS<sub>313</sub> explains about half of the estimated part of the familial relative risk that could be explained by common low-risk variants<sup>4,5</sup> and that recent studies already discovered 38 novel BC susceptibility loci at genome-wide significance level.<sup>44,45</sup> Using a more extensive PRS in the future possibly gives an even better

risk stratification and may lead to a higher percentage of women shifting to another risk category.

Our study did not have enough power to perform an association analysis between the PRS and BC for PV carriers in *PALB2*, *CHEK2* or *ATM*. However, previous studies showed that the per-SD effect size of a PRS with BC in PV carriers of moderate BC genes, such as *CHEK2*, is similar as in non-carriers or untested individuals,<sup>13,46</sup> but lower in carriers of PV in *BRCA1/2*.<sup>12</sup> Few studies have been performed on *ATM* or *PALB2* carriers, but a recent study showed that the effect sizes of the associations were in between those for *BRCA1/2* and *CHEK2*.<sup>14</sup> However, BOADICEA assumes that the effect of the PRS is similar for non-PV carriers and carriers of a PV in the genes *PALB2*, *ATM* and *CHEK2*, that is, PVs and the PRS contribute to risk independently. This may need some adjustment once the exact per-SD effect sizes and interactions are known for these specific genes.

We found a higher effect size for the association between BC and the PRS<sub>313</sub> (OR=1.97, 95% CI 1.84 to 2.11) than found in the population-based cohorts of BCAC (OR=1.61, 95% CI 1.57 to 1.65)<sup>5</sup> or the Dutch population (HR=1.56, 95% CI 1.40 to 1.73).<sup>41</sup> This can possibly be explained by a higher genetic predisposition in families that visit the clinical genetic centre for counselling. Although we adjusted for family history, the weak correlation between the PRS and family history showed that adjustment for family history does not suffice to correct for the higher genetic predisposition based on the common low-risk variants. Furthermore, family history (BOADICEA<sub>FH</sub>) of the controls was imputed based on the assumption that the family history in controls was normally distributed with mean=0. This might have introduced bias since the real family history of each control is unknown.

The virtually absent correlation between family history and the PRS<sub>313</sub> was found in previous studies as well,<sup>7,10,19</sup> underscoring the additive value of including the PRS in family-based risk prediction. However, to avoid double-counting this requires careful joint consideration of family history and an explicitly measured PRS as provided by the BOADICEA algorithm. Altogether, risk stratification using the PRS in addition to family-based risk prediction in non-carriers and PV carriers highlights the need for using a comprehensive model including the PRS to calculate individual BC lifetime risks to guide screening and prevention advice. Of note, there is also no evidence that the per-SD PRS<sub>313</sub> OR differs across strata defined by lifestyle and hormonal risk factors.<sup>47</sup>

The strengths of this study include the detailed family history that was available for the cases. As we used only cases who visited clinical genetic centres for counselling, this cohort is a good representation of the families that are seen in a clinical genetic context. Furthermore, our results are based on a well-validated, comprehensive risk prediction model, BOADICEA, which has been shown to have accurate risk predictions for the general population and in familial setting.<sup>40,41</sup>

A limitation of this study is that we had only data for women of European ancestry, even though some studies have shown that (a subset of) the PRS<sub>313</sub> is associated with BC in other ancestries as well.<sup>48,49</sup> For Asian<sup>48</sup> and Latina<sup>49</sup> populations, the PRS showed similar performance as in the European population, but for the African population<sup>50</sup> there was an attenuated effect size. Therefore, caution is needed for comprehensive risk prediction including the PRS for women of African ancestry.

In summary, including the PRS<sub>313</sub> in family history-based risk prediction may change screening recommendations in up to 34% of individuals from families with no PVs in any of the

five BC genes modelled in BOADICEA. Adding the PRS<sub>313</sub> also had a large impact on screening recommendations for *ATM* and *CHEK2* PV carriers. Because BOADICEA has been prospectively validated and calibrated,<sup>40 41</sup> clinical implementation of comprehensive risk prediction should be considered, although this will be a logistic challenge for clinical genetic centres and would require clinical geneticists to become aware of its limitations.

#### Author affiliations

- <sup>1</sup>Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands  
<sup>2</sup>Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands  
<sup>3</sup>Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands  
<sup>4</sup>Public Health and Primary Care, University of Cambridge Centre for Cancer Genetic Epidemiology, Cambridge, UK  
<sup>5</sup>Department of Human Genetics, Amsterdam UMC Locatie VUmc, Amsterdam, The Netherlands  
<sup>6</sup>Department of Clinical Genetics, University Medical Centre Groningen, Groningen, The Netherlands  
<sup>7</sup>Department of Clinical Genetics, Maastricht University Medical Centre+, Maastricht, The Netherlands  
<sup>8</sup>Department of Human Genetics, University Medical Center Nijmegen, Nijmegen, The Netherlands  
<sup>9</sup>Department of Medical Genetics, University Medical Centre Utrecht, Utrecht, The Netherlands  
<sup>10</sup>Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus Medical Center, Rotterdam, The Netherlands  
<sup>11</sup>Family Cancer Clinic, Antoni van Leeuwenhoek Netherlands Cancer Institute, Amsterdam, The Netherlands  
<sup>12</sup>Division of Psychosocial Research and Epidemiology, Antoni van Leeuwenhoek Netherlands Cancer Institute, Amsterdam, The Netherlands  
<sup>13</sup>Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

**Acknowledgements** We would like to thank Mary Velthuisen (University Medical Center Utrecht), J Margriet Collée (Erasmus Medical Center Rotterdam), Wendy Prager-van den Smissen (Erasmus Medical Center Rotterdam), Daoud Ait Moha (The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital), Jan C Oosterwijk (University Medical Center Groningen), Janet R Vos (Radboud University Medical Center), Jeroen FJ Laros (Leiden University Medical Center) and Adri JM Krol (Leiden University Medical Center) for collecting and converting the pedigree files of the included families.

**Contributors** Conceptualisation: PD, CJvA, IMML, MR-G. Collected the data: IMML, MEB, NC. Formal analysis: IMML, MR-G, AL. Resources: all authors. Supervision: PD, CJvA, MKS, MR-G. Writing—original draft: IMML, PD, CJvA, MKS, MR-G. Writing—review and editing: all authors. Guarantors: PD, CJvA.

**Funding** This work was supported by the Dutch Cancer Society (KWF) (grant UL2014-7473).

**Competing interests** AL is listed as an inventor of BOADICEA V.5, which is commercialised through Cambridge Enterprise, part of Cambridge University.

**Patient consent for publication** Not required.

**Ethics approval** This study involves human participants and was approved by NKI-AVL: pTC11.1799; LUMC, P06.021; EMC, MEC-2011-471; UMCG, 011/303; UMCN, 2015-2207; UMCU, 11/339; UMCB, 11-4-089; VUmc: 2011-253. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. The gene sequencing and SNP array genotyping results, and digitalised family histories of this study are part of the BCAC database. Access to the BCAC data is governed by a data access coordinating committee. If you are interested in gaining access to the BCAC data, please contact the BCAC coordinator by email (BCAC@medschl.cam.ac.uk). Summary results from the iCOGS and OncoArray projects are now publicly available and can be accessed via the links on the BCAC website (<https://bcac.ccg.medschl.cam.ac.uk/bcacdata/>).

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability

of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

Inge M M Lakeman <http://orcid.org/0000-0002-2990-7154>  
 Andrew Lee <http://orcid.org/0000-0003-0677-0252>  
 Arjen R Mensenkamp <http://orcid.org/0000-0003-3805-877X>  
 Peter Devilee <http://orcid.org/0000-0002-8023-2009>

#### REFERENCES

- 1 Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, Gavin A, Visser O, Bray F. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018;103:356–87.
- 2 Ripping TM, Verbeek ALM, Fracheboud J, de Koning HJ, van Ravesteyn NT, Broeders MJM. Overdiagnosis by mammographic screening for breast cancer studied in birth cohorts in the Netherlands. *Int J Cancer* 2015;137:921–9.
- 3 Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet* 2001;358:1389–99.
- 4 Michailidou K, Lindström S, Dennis J, Beesley J, Hui S, Kar S, Lemaçon A, Soucy P, Glubb D, Rostamianfar A, Bolla MK, Wang Q, Tyrer J, Dicks E, Lee A, Wang Z, Allen J, Keeman R, Eilber U, French JD, Qing Chen X, Fachel L, McCue K, McCart Reed AE, Ghoussaini M, Carroll JS, Jiang X, Finucane H, Adams M, Adank MA, Ahsan H, Aittomäki K, Anton-Culver H, Antonenkova NN, Arndt V, Aronson KJ, Arun B, Auer PL, Bacot F, Barrdahl M, Baynes C, Beckmann MW, Behrens S, Benitez J, Bermisheva M, Bernstein L, Blomqvist C, Bogdanova NV, Bojesen SE, Bonanni B, Børresen-Dale A-L, Brand JS, Brauch H, Brennan P, Brenner H, Brinton L, Broberg P, Brock IW, Broeks A, Brooks-Wilson A, Brucker SY, Brüning T, Burwinkel B, Butterbach K, Cai Q, Cai H, Caldés T, Canzian F, Carracedo A, Carter BD, Castela JE, Chan TL, David Cheng T-Y, Seng Chia K, Choi J-Y, Christiansen H, Clarke CL, Collée M, Conroy DM, Cordina-Duverger E, Cornelissen S, Cox DG, Cox A, Cross SS, Cunningham JM, Czene K, Daly MB, Devilee P, Doherty KF, Dörk T, Dos-Santos-Silva I, Dumont M, Durcan L, Dwek M, Eccles DM, Ekici AB, Eliassen AH, Ellberg C, Elvira M, Engel C, Eriksson M, Fasching PA, Figueroa J, Flesch-Janys D, Fletcher O, Flyger H, Fritschi L, Gaborieau V, Gabrielson M, Gago-Dominguez M, Gao Y-T, Gapstur SM, García-Sánchez JA, Gaudet MM, Georgoulas V, Giles GG, Glendon G, Goldberg MS, Goldgar DE, González-Neira A, Grenaker Alnæs GI, Grip M, Gronwald J, Grundy A, Guénel P, Haeberle L, Hahnen E, Haiman CA, Håkansson N, Hamann U, Hamel N, Hankinson S, Harrington P, Hart SN, Hartikainen JM, Hartman M, Hein A, Heyworth J, Hicks B, Hilleman P, Ho DN, Hollestelle A, Hooning MJ, Hoover RN, Hopper JL, Hou M-F, Hsiung C-N, Huang G, Humphreys K, Ishiguro J, Ito H, Iwasaki M, Iwata H, Jakubowska A, Janni W, John EM, Johnson N, Jones K, Jones M, Jukkola-Vuorinen A, Kaaks R, Kabisch M, Kaczmarek K, Kang D, Kasuga Y, Kerin MJ, Khan S, Khusnutdinova E, Kiiski JI, Kim S-W, Knight JA, Kosma V-M, Kristensen VN, Krüger U, Kwong A, Lambrechts D, Le Marchand L, Lee E, Lee MH, Lee JW, Neng Lee C, Lejbkowitz F, Li J, Lilyquist J, Lindblom A, Lissowska J, Lo W-Y, Loibl S, Long J, Lophatananon A, Lubinski J, Luccarini C, Lux MP, Ma ESK, MacInnis RJ, Maishman T, Makalic E, Malone KE, Kostovska IM, Mannermaa A, Manoukian S, Manson JE, Margolin S, Mariapun S, Martinez ME, Matsuo K, Mavroudis D, McKay J, McLean C, Meijers-Heijboer H, Meindl A, Menéndez P, Menon U, Meyer J, Miao H, Miller N, Taib NAM, Muir K, Mulligan AM, Mulot C, Neuhausen SL, Nevanlinna H, Neven P, Nielsen SF, Noh D-Y, Nordestgaard BG, Norman A, Olopade OI, Olson JE, Olsson H, Olszow D, Orr N, Pankratz VS, Park SK, Park-Simon T-W, Lloyd R, Perez JIA, Peterlongo P, Peto J, Phillips K-A, Pinchev M, Plaseska-Karanfilska D, Prentice R, Presneau N, Prokofyeva D, Pugh E, Pylkäs K, Rack B, Radice P, Rahman N, Rennert G, Rennert HS, Rhenius V, Romero A, Romm J, Ruddy KJ, Rüdiger T, Rudolph A, Ruebner M, Rutgers EJT, Saloustros E, Sandler DP, Sangrajrang S, Sawyer EJ, Schmidt DF, Schmutzler RK, Schneeweiss A, Schoemaker MJ, Schumacher F, Schürmann P, Scott RJ, Scott C, Seal S, Seynaeve C, Shah M, Sharma P, Shen C-Y, Sheng G, Sherman ME, Shrubsole MJ, Shu X-O, Smeets A, Sohn C, Southey MC, Spinelli JJ, Stegmaier C, Stewart-Brown S, Stone J, Stram DO, Surowy H, Swerdlow A, Tamimi R, Taylor JA, Tengström M, Teo SH, Beth Terry M, Tessier DC, Thanasiithichai S, Thöne K, Tollenaar RAEM, Tomlinson I, Tong L, Torres D, Truong T, Tseng C-C, Tsugane S, Ulmer H-U, Ursini G, Untch M, Vachon C, van Asperen CJ, Van Den Berg D, van den Ouweland AMW, van der Kolk L, van der Luijt RB, Vincent D, Vollenweider J, Waisfisz Q, Wang-Gohrke S, Weinberg CR, Wendt C, Whittemore AS, Wildiers H, Willett W, Winqvist R, Wolk A, Wu AH, Xia L, Yamaji T, Yang XR, Har Yip C, Yoo K-Y, Yu J-C, Zheng W, Zheng Y, Zhu B, Ziogas A, Ziv E, Lakhani SR, Antoniou AC, Droit A, Andrulis IL, Amos CI, Couch FJ, Pharoah PDP, Chang-Claude J, Hall P, Hunter DJ, Milne RL, Garcia-Closas M, Schmidt MK, Chanock SJ, Dunning AM, Edwards SL, Bader GD, Chenevix-Trench G,

- Simard J, Kraft P, Easton DF, NBCS Collaborators, ABCTB Investigators, ConFab/AOCS Investigators. Association analysis identifies 65 new breast cancer risk loci. *Nature* 2017;551:92-94.
- 5 Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, Lee A, Tyrer JP, Chen T-H, Wang Q, Bolla MK, Yang X, Adank MA, Ahearn T, Aittomäki K, Allen J, Andrulis IL, Anton-Culver H, Antonenkova NN, Arndt V, Aronson KJ, Auer PL, Auvinen P, Barrdahl M, Beane Freeman LE, Beckmann MW, Behrens S, Benitez J, Bermisheva M, Bernstein L, Blomqvist C, Bogdanova NV, Bojesen SE, Bonanni B, Børresen-Dale A-L, Brauch H, Bremer M, Brenner H, Brentnall A, Brock IW, Brooks-Wilson A, Brucker SY, Brüning T, Burwinkel B, Campa D, Carter BD, Castela JE, Chanock SJ, Chlebowski R, Christiansen H, Clarke CL, Collé JM, Cordina-Duverger E, Cornelissen S, Couch FJ, Cox A, Cross SS, Czene K, Daly MB, Devilee P, Dörk T, Dos-Santos-Silva I, Dumont M, Durcan L, Dwek M, Eccles DM, Ekici AB, Eliassen AH, Ellberg C, Engel C, Eriksson M, Evans DG, Fasching PA, Figueroa J, Fletcher O, Flyger H, Försti A, Fritschi L, Gabrielson M, Gago-Dominguez M, Gapstur SM, García-Sánchez JA, Gaudet MM, Georgoulas V, Giles GG, Gilyazova IR, Glendon G, Goldberg MS, Goldgar DE, González-Neira A, Grenaker Alnæs GI, Grip M, Gronwald J, Grundy A, Guénel P, Haerle L, Hahnen E, Haiman CA, Håkansson N, Hamann U, Hankinson SE, Harkness EF, Hart SN, He W, Hein A, Heyworth J, Hillemanns P, Hollestelle A, Hoening MJ, Hoover RN, Hopper JL, Howell A, Huang G, Humphreys K, Hunter DJ, Jakimovska M, Jakubowska A, Janni W, John EM, Johnson N, Jones ME, Jukkola-Vuorinen A, Jung A, Kaaks R, Kaczmarek K, Kataja V, Keeman R, Kerin MJ, Khusnutdinova E, Kiiski JI, Knight JA, Ko Y-D, Kosma V-M, Koutros S, Kristensen VN, Krüger U, Kühn T, Lambrechts D, Le Marchand L, Lee E, Lejbkowitz F, Lilyquist J, Lindblom A, Lindström S, Lissowska J, Lo W-Y, Loibl S, Long J, Lubiński J, Lux MP, Maclinnis RJ, Maishman T, Makalic E, Maleva Kostovska I, Mannermaa A, Manoukian S, Margolin S, Martens JWM, Martinez ME, Mavroudis D, McLean C, Meindl A, Menon U, Middha P, Miller N, Moreno F, Mulligan AM, Mulot C, Muñoz-Garzon VM, Neuhausen SL, Nevanlinna H, Neven P, Newman WG, Nielsen SF, Nordestgaard BG, Norman A, Offit K, Olson JE, Olsson H, Orr N, Pankratz VS, Park-Simon T-W, Perez JIA, Pérez-Barrios C, Peterlongo P, Peto J, Pinchev M, Plaseska-Karanfilska D, Polley EC, Prentice R, Presneau N, Prokofyeva D, Purrington K, Pykäs K, Rack B, Radice P, Rau-Murthy R, Rennert G, Rennert HS, Rhenius V, Robson M, Romero A, Ruddy KJ, Ruebner M, Saloustros E, Sandler DP, Sawyer EJ, Schmidt DF, Schmutzler RK, Schneeweiss A, Schoemaker MJ, Schumacher F, Schürmann P, Schwentner L, Scott C, Scott RJ, Seynaeve C, Shah M, Sherman ME, Shrubsole MJ, Shu X-O, Slager S, Smeets A, Sohn C, Soucy P, Southey MC, Spinelli JJ, Stegmaier C, Stone J, Swerdlow AJ, Tamimi RM, Tapper WJ, Taylor JA, Terry MB, Thöne K, Tollenaar RAEM, Tomlinson I, Truong T, Tzardi M, Ulmer H-U, Untch M, Vachon CM, van Veen EM, Vijai J, Weinberg CR, Wendt C, Whittemore AS, Wildiers H, Willett W, Winqvist R, Wolk A, Yang XR, Yannoukakis D, Zhang Y, Zheng W, Ziogas A, Dunning AM, Thompson DJ, Chenevix-Trench G, Chang-Claude J, Schmidt MK, Hall P, Milne RL, Pharoah PDP, Antoniou AC, Chatterjee N, Kraft P, García-Closas M, Simard J, Easton DF, ABCTB Investigators, kConFab/AOCS Investigators, NBCS Collaborators. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. *Am J Hum Genet* 2019;104:21-34.
- 6 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 Ongevel C, van Limbergen E, Kristensen V, Grenaker Alnæs G, Nord S, Børresen-Dale A-L, Nevanlinna H, Muranen TA, Aittomäki K, Blomqvist C, Chang-Claude J, Rudolph A, Seibold P, Flesch-Janys D, Fasching PA, Haerle 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, Durka 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, Takhira Z, Meindl A, Schmutzler RK, Sutter C, Yang R, Schürmann P, Bremer M, Christiansen H, Park-Simon T-W, 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 Y-D, Sigurdson AJ, Doody MM, Hamann U, Torres D, Ulmer H-U, 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, Hoening MJ, Hollestelle A, van den Ouweland AMW, Koppert LB, Carpenter J, Clarke C, Scott R, Mannermaa A, Kataja V, Kosma V-M, Hartikainen JM, Brenner H, Arndt V, Stegmaier C, Karina Dieffenbach A, Winqvist R, Pykäs 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, Yannoukakis 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 A, Ahmed S, Maranian M, Healey CS, Simard J, Hall P, Easton DF, García-Closas M. Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst* 2015;107. doi:10.1093/jnci/djv036. [Epub ahead of print: 08 04 2015].
- 7 Lakeman IMM, Hilbers FS, Rodríguez-Gironde M, Lee A, Vreeswijk MPG, Hollestelle A, Seynaeve C, Meijers-Heijboer H, Oosterwijk JC, Hoogerbrugge N, Olah E, Vasen HFA, van Asperen CJ, Devilee P. Addition of a 161-SNP polygenic risk score to family history-based risk prediction: impact on clinical management in non-*BRCA1/2* breast cancer families. *J Med Genet* 2019;56:581-9.
- 8 Sawyer S, Mitchell G, McKinley J, Chenevix-Trench G, Beesley J, Chen XQ, Bowtell D, Trainer AH, Harris M, Lindeman GJ, James PA. A role for common genomic variants in the assessment of familial breast cancer. *JCO* 2012;30:4330-6.
- 9 Li H, Feng B, Miron A, Chen X, Beesley J, Bimeh E, Barrowdale D, John EM, Daly MB, Andrulis IL, Buys SS, Kraft P, Thorne H, Chenevix-Trench G, Southey MC, Antoniou AC, James PA, Terry MB, Phillips K-A, Hopper JL, Mitchell G, Goldgar DE, kConFab investigators. Breast cancer risk prediction using a polygenic risk score in the familial setting: a prospective study from the breast cancer family registry and kConFab. *Genet Med* 2017;19:30-5.
- 10 Muranen TA, Mavaddat N, Khan S, Fagerholm R, Peltari L, Lee A, Aittomäki K, Blomqvist C, Easton DF, Nevanlinna H. Polygenic risk score is associated with increased disease risk in 52 Finnish breast cancer families. *Breast Cancer Res Treat* 2016;158:463-9.
- 11 Kuchenbaecker KB, McGuffog L, Barrowdale D, Lee A, Soucy P, Dennis J, Domchek SM, Robson M, Spurdle AB, Ramus SJ, Mavaddat N, Terry MB, Neuhausen SL, Schmutzler RK, Simard J, Pharoah PDP, Offit K, Couch FJ, Chenevix-Trench G, Easton DF, Antoniou AC. Evaluation of polygenic risk scores for breast and ovarian cancer risk prediction in *BRCA1* and *BRCA2* mutation carriers. *J Natl Cancer Inst* 2017;109. doi:10.1093/jnci/djw302. [Epub ahead of print: 01 07 2017].
- 12 Barnes DR, Rookus MA, McGuffog L, Leslie G, Mooij TM, Dennis J, Mavaddat N, Adlari J, Ahmed M, Aittomäki K, Andrieu N, Andrulis IL, Arnold N, Arun BK, Azzollini J, Balmaña J, Barkardottir RB, Barrowdale D, Benitez J, Berthet P, Bialkowska K, Blanco AM, Blok MJ, Bonanni B, Boonen SE, Borg Åke, Boszik A, Bradbury AR, Brennan P, Brewer C, Brunet J, Buys SS, Caldés T, Caligo MA, Campbell I, Christensen LL, Chung WK, Claes KBM, Colas C, Collonge-Rame M-A, Cook J, Daly MB, Davidson R, de la Hoya M, de Putter R, Delnatte C, Devilee P, Diez O, Ding YC, Domchek SM, Dorfling CM, Dumont M, Eeles R, Ejertsen B, Engel C, Evans DG, Faivre L, Foretova L, Fostira F, Friedlander M, Friedman E, Frost D, Ganz PA, Garber J, Gehrig A, Gerdes A-M, Gesta P, Giraud S, Glendon G, Godwin AK, Goldgar DE, González-Neira A, Greene MH, Gschwanter-Kaulich D, Hahnen E, Hamann U, Hanson H, Hentschel J, Hogervorst FBL, Hoening MJ, Horvath J, Hu C, Hulick PJ, Imyanitov EN, Isaacs C, Izatt L, Izquierdo A, Jakubowska A, James PA, Janavicius R, John EM, Joseph V, Karlan BY, Kast K, Koudijs M, Kruse TA, Kwong A, Laitman Y, Lasset C, Lazaro C, Lester J, Lesueur F, Liljegren A, Loud JT, Lubiński J, Mai PL, Manoukian S, Mari V, Mebirouk N, Meijers-Heijboer HEJ, Meindl A, Mensenkamp AR, Miller A, Montagna M, Mouret-Fourme E, Mukherjee S, Mulligan AM, Nathanson KL, Neuhausen SL, Nevanlinna H, Niederacher D, Nielsen FC, Nikitina-Zake L, Nogués C, Olah E, Olopade OI, Ong K-R, O'Shaughnessy-Kirwan A, Osorio A, Ott C-E, Papi L, Park SK, Parsons MT, Pedersen IS, Peissel B, Peixoto A, Peterlongo P, Pfeiler G, Phillips K-A, Prajzandanc K, Pujana MA, Radice P, Ramser J, Ramus SJ, Rantalaja J, Rennert G, Risch HA, Robson M, Ronlund K, Salani R, Schuster H, Senter L, Shah PD, Sharma P, Side LE, Singer CF, Slavin TP, Soucy P, Southey MC, Spurdle AB, Steinemann D, Steinsnyder Z, Stoppa-Lyonnet D, Sutter C, Tan YY, Teixeira MR, Teo SH, Thull DL, Tischkowitz M, Tognazzo S, Toland AE, Trainer AH, Tung N, van Engelen K, van Rensburg EJ, Vega A, Vierstraete J, Wagner G, Walker L, Wang-Gohrke S, Wappenschmidt B, Weitzel JN, Yadav S, Yang X, Yannoukakis D, Zimbalatti D, Offit K, Thomassen M, Couch FJ, Schmutzler RK, Simard J, Easton DF, Chenevix-Trench G, Antoniou AC, GEMO Study Collaborators, EMBRACE Collaborators, kConFab Investigators, HEBON Investigators, GENEPSO Investigators, Consortium of Investigators of Modifiers of *BRCA* and *BRCA2*. Polygenic risk scores and breast and epithelial ovarian cancer risks for carriers of *BRCA1* and *BRCA2* pathogenic variants. *Genet Med* 2020;22.
- 13 Gao C, Polley EC, Hart SN, Huang H, Hu C, Gnanaolivu R, Lilyquist J, Boddicker NJ, Na J, Ambrosio CB, Auer PL, Bernstein L, Burnside ES, Eliassen AH, Gaudet MM, Haiman C, Hunter DJ, Jacobs EJ, John EM, Lindström S, Ma H, Neuhausen SL, Newcomb PA, O'Brien KM, Olson JE, Ong IM, Patel AV, Palmer JR, Sandler DP, Tamimi R, Taylor JA, Teras LR, Trentham-Dietz A, Vachon CM, Weinberg CR, Yao S, Weitzel JN, Goldgar DE, Domchek SM, Nathanson KL, Couch FJ, Kraft P. Risk of breast cancer among carriers of pathogenic variants in breast cancer predisposition genes varies by polygenic risk score. *J Clin Oncol* 2021;39:2564-73.
- 14 Gallagher S, Hughes E, Wagner S, Tshiaba P, Rosenthal E, Roa BB, Kurian AW, Domchek SM, Garber J, Lancaster J, Weitzel JN, Gutin A, Lanchbury JS, Robson M. Association of a polygenic risk score with breast cancer among women carriers of high- and moderate-risk breast cancer genes. *JAMA Netw Open* 2020;3:e208501-e01.
- 15 Cintolo-Gonzalez JA, Braun D, Blackford AL, Mazzola E, Acar A, Plichta JK, Griffin M, Hughes KS. Breast cancer risk models: a comprehensive overview of existing models, validation, and clinical applications. *Breast Cancer Res Treat* 2017;164:263-84.
- 16 Kim G, Bahl M. Assessing risk of breast cancer: a review of risk prediction models. *J Breast Imaging* 2021;3:144-55.
- 17 Lee A, Mavaddat N, Wilcox AN, Cunningham AP, Carver T, Hartley S, Babb de Villiers C, Izquierdo A, Simard J, Schmidt MK, Walter FM, Chatterjee N, García-Closas M, Tischkowitz M, Pharoah P, Easton DF, Antoniou AC. Boadicea: a comprehensive breast

- cancer risk prediction model incorporating genetic and nongenetic risk factors. *Genet Med* 2019;21:1708–18.
- 18 Cuzick J, Brentnall AR, Segal C, Byers H, Reuter C, Detre S, Lopez-Knowles E, Sestak I, Howell A, Powles TJ, Newman WG, Dowsett M. Impact of a panel of 88 single nucleotide polymorphisms on the risk of breast cancer in high-risk women: results from two randomized tamoxifen prevention trials. *J Clin Oncol* 2017;35:743–50.
  - 19 Dite GS, MacInnis RJ, Bickerstaffe A, Dowty JG, Allman R, Apicella C, Milne RL, Tsimiklis H, Phillips K-A, 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.
  - 20 Shieh Y, Hu D, Ma L, Huntsman S, Gard CC, Leung JWT, Tice JA, Vachon CM, Cummings SR, Kerlikowske K, Ziv E. Breast cancer risk prediction using a clinical risk model and polygenic risk score. *Breast Cancer Res Treat* 2016;159:513–25.
  - 21 van Veen EM, Brentnall AR, Byers H, Harkness EF, Astley SM, Sampson S, Howell A, Newman WG, Cuzick J, Evans DGR. Use of single-nucleotide polymorphisms and mammographic density plus classic risk factors for breast cancer risk prediction. *JAMA Oncol* 2018;4:476–82.
  - 22 IKNL. Richtlijn Borstkanker - Screening buiten het bevolkingsonderzoek, 2017. Available: [https://richtlijndatabase.nl/richtlijn/borstkanker/screening/screening\\_buiten\\_het\\_bob/screening\\_buiten\\_het\\_bevolkingsonderzoek.html](https://richtlijndatabase.nl/richtlijn/borstkanker/screening/screening_buiten_het_bob/screening_buiten_het_bevolkingsonderzoek.html) [Accessed 03 Dec 2021].
  - 23 Carver T, Hartley S, Lee A, Cunningham AP, Archer S, Babb de Villiers C, Roberts J, Ruston R, Walter FM, Tischkowitz M, Easton DF, Antoniou AC. CanRisk tool-a web interface for the prediction of breast and ovarian cancer risk and the likelihood of carrying genetic pathogenic variants. *Cancer Epidemiol Biomarkers Prev* 2021;30:469–73.
  - 24 NCCN. Clinical practice guidelines in oncology; breast cancer screening and diagnosis, 2017. Available: [https://www.nccn.org/professionals/physician\\_gls/pdf/breast-screening.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf) [Accessed Apr 2018].
  - 25 NICE. National Institute for health and care excellence: familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer, 2013. Available: [www.nice.org.uk/guidance/cg164](http://www.nice.org.uk/guidance/cg164) [Accessed Apr 2018].
  - 26 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806–8.
  - 27 van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, Hoogerbrugge N, Verhoef S, Vasen HFA, Ausems MGEM, Menko FH, Gomez Garcia EB, Klijn JGM, Hogervorst FBL, van Houtwelingen JC, van't Veer LJ, Rookus MA, van Leeuwen FE, Netherlands Collaborative Group on Hereditary Breast Cancer (HEBON). Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. *J Med Genet* 2005;42:711–9.
  - 28 Schmidt MK, Hogervorst F, van Hien R, Cornelissen S, Broeks A, Adank MA, Meijers H, Waisfisz Q, Hollestelle A, Schutte M, van den Ouweland A, Hoening M, Andrusil IL, Anton-Culver H, Antonenkova NN, Antoniou AC, Arndt V, Bermisheva M, Bogdanova NV, Bolla MK, Brauch H, Brenner H, Brüning T, Burwinkel B, Chang-Claude J, Chenevix-Trench G, Couch FJ, Cox A, Cross SS, Czene K, Dunning AM, Fasching PA, Figueroa J, Fletcher O, Flyger H, Galle E, Garcia-Closas M, Giles GG, Haeberle L, Hall P, Hillemanns P, Hopper JL, Jakubowska A, John EM, Jones M, Khusnutdinova E, Knight JA, Kosma V-M, Kristensen V, Lee A, Lindblom A, Lubinski J, Mannermaa A, Margolin S, Meindl A, Milne RL, Muranen TA, Newcomb PA, Offit K, Park-Simon T-W, Peto J, Pharoah PDP, Robson M, Rudolph A, Sawyer EJ, Schmutzler RK, Seynaeve C, Soens J, Southey MC, Spurdle AB, Surowy H, Swerdlow A, Tollenaar RAEM, Tomlinson I, Tretham-Dietz A, Vachon C, Wang Q, Whittemore AS, Ziogas A, van der Kolk L, Nevanlinna H, Dörk T, Bojesen S, Easton DF, Age- Age- and tumor subtype-specific breast cancer risk estimates for CHEK2\*1100delC carriers. *J Clin Oncol* 2016;34:2750–60.
  - 29 Liu J, Prager-van der Smissen WJC, Schmidt MK, Collé JM, Cornelissen S, Lamping R, Nieuwlaar A, Foekens JA, Hoening MJ, Verhoef S, van den Ouweland AMW, Hogervorst FBL, Martens JWM, Hollestelle A. Recurrent HOXB13 mutations in the dutch population do not associate with increased breast cancer risk. *Sci Rep* 2016;6:30026.
  - 30 Dorling L, Carvalho S, Allen J, González-Neira A, Luccarini C, Wahlström C, Pooley KA, Parsons MT, Fortuno C, Wang Q, Bolla MK, Dennis J, Keeman R, Alonso MR, Álvarez N, Herraiz B, Fernandez V, Núñez-Torres R, Osorio A, Valcich J, Li M, Törngren T, Harrington PA, Baynes C, Conroy DM, Decker B, Fachtal L, Mavaddat N, Ahearn T, Aittomäki K, Antonenkova NN, Arnold N, Arveux P, Ausems MGEM, Auvinen P, Becher H, Beckmann MW, Behrens S, Bermisheva M, Bialkowska K, Blomqvist C, Bogdanova NV, Bogdanova-Markov N, Bojesen S, Bonanni B, Børresen-Dale A-L, Brauch H, Bremer M, Briceno I, Brüning T, Burwinkel B, Cameron DA, Camp NJ, Campbell A, Carracedo A, Castela JE, Cessna MH, Chanock SJ, Christiansen H, Collé JM, Cordina-Duverger E, Cornelissen S, Czene K, Dörk T, Ekici AB, Engel C, Eriksson M, Fasching PA, Figueroa J, Flyger H, Försti A, Gabrielson M, Gago-Dominguez M, Georgoulas V, Gil F, Giles GG, Glendon G, Garcia EBG, Alnæs GIG, Guénel P, Hadjisavvas A, Haeberle L, Hahnen E, Hall P, Hamann U, Harkness EF, Hartikainen JM, Hartman M, He W, Heemskerk-Gerritsen BAM, Hillemanns P, Hogervorst FBL, Hollestelle A, Ho WK, Hoening MJ, Howell A, Humphreys K, Idris F, Jakubowska A, Jung A, Kapoor PM, Kerin MJ, Khusnutdinova E, Kim S-W, Ko Y-D, Kosma V-M, Kristensen VN, Kyriacou K, Lakeman IMM, Lee JW, Lee MH, Li J, Lindblom A, Lo W-Y, Loizidou MA, Lophatananon A, Lubinski J, MacInnis RJ, Madsen MJ, Mannermaa A, Manoochehri M, Manoukian S, Margolin S, Martinez ME, Maurer T, Mavroudis D, McLean C, Meindl A, Mensenkamp AR, Michailidou K, Miller N, Mohd Taib NA, Muir K, Mulligan AM, Nevanlinna H, Newman WG, Nordstgaard BG, Ng P-S, Oosterwijk JC, Park SK, Park-Simon T-W, Perez JIA, Peterlongo P, Porteous DJ, Prajezandac K, Prokofyeva D, Radice P, Rashid MU, Rhenius V, Rookus MA, Rüdiger T, Saloustros E, Sawyer EJ, Schmutzler RK, Schneeweiss A, Schürmann P, Shah M, Sohn C, Southey MC, Surowy H, Suvanto M, Thanasitthichai S, Tomlinson I, Torres D, Truong T, Tzardi M, Valova Y, van Asperen CJ, Van Dam RM, van den Ouweland AMW, van der Kolk LE, van Veen EM, Wendt C, Williams JA, Yang XR, Yoon S-Y, Zamora MP, Evans DG, de la Hoya M, Simard J, Antoniou AC, Borg Åke, Andrusil IL, Chang-Claude J, Garcia-Closas M, Chenevix-Trench G, Milne RL, Pharoah PDP, Schmidt MK, Spurdle AB, Vreeswijk MPG, Benitez J, Dunning AM, Kvist A, Teo SH, Devilee P, Easton DF, Breast Cancer Association Consortium. Breast cancer risk genes - association analysis in more than 113,000 Women. *N Engl J Med* 2021;384:428-439.
  - 31 McLaren W, Gil L, Hunt SE, Riat HS, Ritchie GR, Thormann A, Flicek P, Cunningham F. The Ensembl variant effect predictor. *Genome Biol* 2016;17:122.
  - 32 Boonen RACM, Rodrigue A, Stoepker C, Wiegant WW, Vroling B, Sharma M, Rother MB, Celosse N, Vreeswijk MPG, Couch F, Simard J, Devilee P, Masson J-Y, van Attikum H. Functional analysis of genetic variants in the high-risk breast cancer susceptibility gene PALB2. *Nat Commun* 2019;10:5296.
  - 33 Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, Gu B, Hart J, Hoffman D, Jang W, Karapetyan K, Katz K, Liu C, Maddipati Z, Malheiro A, McDaniel K, Ovetsky M, Riley G, Zhou G, Holmes JB, Kattman BL, Maglott DR. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res* 2018;46:D1062–7.
  - 34 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, Aittomäki 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, Müller-Miyshok 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, Christiansen M-R, Rudolph A, Nickels S, Flesch-Janys D, Johnson N, Aitken Z, Aaltonen K, Heikkinen T, Broeks A, Veer Laura J Van't, van der Schoot CE, Guénel P, Truong T, Laurent-Puig P, Menegaux F, Marme F, Schneeweiss A, Sohn C, Burwinkel B, Zamora MP, Perez JIA, 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, Andrusil IL, Knight JA, Glendon G, Mulligan AM, Lindblom A, Margolin S, Hoening 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, Müller H, Arndt V, Stegmaier C, Swerdlow A, Ashworth A, Orr N, Jones M, Figueroa J, Lissowska J, Brinton L, Goldberg MS, Labrèche F, Dumont M, Winqvist R, Pylkäs K, Jukkola-Vuorinen A, Grip M, Brauch H, Hamann U, Brüning T, Radice P, Peterlongo P, Manoukian S, Bonanni B, Devilee P, Tollenaar RAEM, Seynaeve C, van Asperen CJ, Jakubowska A, Lubinski J, Jaworska K, Dürda K, Mannermaa A, Kataja V, Kosma V-M, Hartikainen JM, Bogdanova NV, Antonenkova NN, Dörk T, Kristensen VN, Anton-Culver H, Slager S, Toland AE, Edge S, Fostira F, Kang D, Yoo K-Y, Noh D-Y, Matsuo K, Ito H, Iwata H, Sueti A, Wu AH, Tseng C-C, Van Den Berg D, Stram DO, Xu X-O, Lu W, Gao Y-T, Cai H, Teo SH, Yip CH, Phuah SY, Cornes BK, Hartman M, Miao H, Lim WY, Sng J-H, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsana P, Shen C-Y, Hsiung C-N, Wu P-E, Ding S-L, 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, Breast and Ovarian Cancer Susceptibility Collaboration, Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON), kConFab Investigators, Australian Ovarian Cancer Study Group, GENICA (Gene Environment Interaction and Breast Cancer in Germany) Network . Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet* 2013;45:353–2.
  - 35 Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, Vrieze SJ, Chew EY, Levy S, McGue M, Schlessinger D, Stambolian D, Loh P-R, Iacono WG, Swarow A, Scott LJ, Cucca F, Kronenberg F, Boehnke M, Abecasis GR, Fuchsberger C. Next-generation genotype imputation service and methods. *Nat Genet* 2016;48:1284–7.
  - 36 McCarthy S, Das S, Kretzschmar W, Delaneau O, Wood AR, Teumer A, Kang HM, Fuchsberger C, Danecek P, Sharp K, Luo Y, Sidore C, Kwong A, Timpson N, Koskinen S, Vrieze S, Scott LJ, Zhang H, Mahajan A, Veldink J, Peters U, Pato C, van Duijn CM, Gillies CE, Gandin I, Mezzavilla M, Gilly A, Cocca M, Traglia M, Angius A, Barrett JC, Boomsma D, Branham K, Breen G, Brummert CM, Busonero F, Campbell H, Chan A, Chen S, Chew E, Collins FS, Corbin LJ, Smith GD, Dedoussis G, Dorr M, Farmaki A-E, Ferrucci L, Forer L, Fraser RM, Gabriel S, Levy S, Groop L, Harrison T, Hattersley A, Holmen OL, Hveem K, Kretzler M, Lee JC, McGue M, Meitinger T, Melzer D, Min JL, Mohlke KL, Vincent JB, Nauck M, Nickerson D, Palotie A, Pato M, Pirastu N, McInnis M, Richards JB, Sala C, Salomaa V, Schlessinger D, Schoenherr S, Slagboom PE, Small

- K, Spector T, Stambolian D, Tuke M, Tuomilehto J, Van den Berg LH, Van Rheenen W, Volker U, Wijmenga C, Toniolo D, Zeggini E, Gasparini P, Sampson MG, Wilson JF, Frayling T, de Bakker PIW, Swertz MA, McCarroll S, Kooperberg C, Dekker A, Altschuler D, Willer C, Iacono W, Ripatti S, Soranzo N, Walter K, Swaroop A, Cucca F, Anderson CA, Myers RM, Boehnke M, McCarthy MI, Durbin R, Haplotype Reference Consortium. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet* 2016;48:1279–83.
- 37 Deelen P, Menelaou A, van Leeuwen EM, Kanterakis A, van Dijk F, Medina-Gomez C, Francioli LC, Hottenga JJ, Karssen LC, Estrada K, Kreiner-Møller E, Rivadeneira F, van Setten J, Gutierrez-Achury J, Westra H-J, Franke L, van Enckevort D, Dijkstra M, Byelas H, van Duijn CM, de Bakker PIW, Wijmenga C, Swertz MA, Genome of Netherlands Consortium. Improved imputation quality of low-frequency and rare variants in European samples using the 'Genome of The Netherlands'. *Eur J Hum Genet* 2014;22:1321–6.
- 38 1000 Genomes Project Consortium, Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurler ME, McVean GA. A map of human genome variation from population-scale sequencing. *Nature* 2010;467:1061–73.
- R\_core\_team. R: A language and environment for statistical computing. vienna, austria r foundation for statistical computing; 2017. <https://www.r-project.org/>
- 40 Pal Choudhury P, Brook MN, Hurson AN, Lee A, Mulder CV, Coulson P, Schoemaker MJ, Jones ME, Swerdlow AJ, Chatterjee N, Antoniou AC, Garcia-Closas M. Comparative validation of the boadicea and tyrer-cuzick breast cancer risk models incorporating classical risk factors and polygenic risk in a population-based prospective cohort of women of European ancestry. *Breast Cancer Res* 2021;23.
- 41 Lakeman IMM, Rodríguez-Girondo M, Lee A, Ruiter R, Stricker BH, Wijntan SRA, Kavousi M, Antoniou AC, Schmidt MK, Uitterlinden AG, van Rooij J, Devilee P. Validation of the boadicea model and a 313-variant polygenic risk score for breast cancer risk prediction in a dutch prospective cohort. *Genet Med* 2020;22:1803–11.
- 42 Borde J, Ernst C, Wappenschmidt B, Niederacher D, Weber-Lassalle K, Schmidt G, Hauke J, Quante AS, Weber-Lassalle N, Horváth J, Pohl-Rescigno E, Arnold N, Rump A, Gehrig A, Hentschel J, Faust U, Dutranoy V, Meindl A, Kuzjakova M, Wang-Gohrke S, Weber BHF, Sutter C, Volk AE, Giannakopoulou O, Lee A, Engel C, Schmidt MK, Antoniou AC, Schmutzler RK, Kuchenbaecker K, Hahnen E. Performance of breast cancer polygenic risk scores in 760 Female *CHEK2* germline mutation carriers. *J Natl Cancer Inst* 2021;113:893–9.
- 43 Mars N, Widén E, Kerminen S, Meretoja T, Pirinen M, Della Briotta Parolo P, Palta P, Palotie A, Kaprio J, Joensuu H, Daly M, Ripatti S, FinnGen. The role of polygenic risk and susceptibility genes in breast cancer over the course of life. *Nat Commun* 2020;11:6383.
- 44 Zhang H, Ahearn TU, Lecarpentier J, Barnes D, Beesley J, Qi G, Jiang X, O'Mara TA, Zhao N, Bolla MK, Dunning AM, Dennis J, Wang Q, Ful ZA, Aittomäki K, Andrulis IL, Anton-Culver H, Arndt V, Aronson KJ, Arun BK, Auer PL, Azzollini J, Barrowdale D, Becher H, Beckmann MW, Behrens S, Benitez J, Bermisheva M, Bialkowska K, Blanco A, Blomqvist C, Bogdanova NV, Bojesen SE, Bonanni B, Bondavalli D, Borg A, Brauch H, Brenner H, Briceño I, Broeks A, Brucker SY, Brüning T, Burwinkel B, Buys SS, Byers H, Caldés T, Caligo MA, Calvella M, Campa D, Castela JE, Chang-Claude J, Chanock SJ, Christiansen M, Christiansen H, Chung WK, Claes KBM, Clarke CL, Cornelissen S, Couch FJ, Cox A, Cross SS, Czene K, Daly MB, Devilee P, Diez O, Domchek SM, Dörk T, Dwek M, Eccles DM, Ekici AB, Evans DG, Fasching PA, Figueroa J, Foretova L, Fostira F, Friedman E, Frost D, Gago-Dominguez M, Gapstur SM, Garber J, Garcia-Sáenz JA, Gaudet MM, Gayther SA, Giles GG, Godwin AK, Goldberg MS, Goldgar DE, González-Neira A, Greene MH, Gronwald J, Guénel P, Häberle L, Hahnen E, Haiman CA, Hake KR, Hall P, Hamann U, Harkness EF, Heemskerk-Gerritsen BAM, Hillemanns P, Hogervorst FBL, Holleczek B, Hollestelle A, Hoening MJ, Hoover RN, Hopper JL, Howell A, Huebner H, Hulick PJ, Ilyanov EN, Isaacs C, Izatt L, Jager A, Jakimovska M, Jakubowska A, James P, Janavicius R, Janni W, John EM, Jones ME, Jung A, Kaaks R, Kapoor PM, Karlan BY, Keeman R, Khan S, Khusnutdinova E, Kitahara CM, Ko Y-D, Konstantopoulou I, Koppert LB, Koutros S, Kristensen VN, Laenkholm A-V, Lambrechts D, Larsson SC, Laurent-Puig P, Lazaro C, Lazarova E, Lejbkowitz F, Leslie G, Lesueur F, Lindblom A, Lissowska J, Lo W-Y, Loud JT, Lubinski J, Lukomska A, MacInnis RJ, Mannermaa A, Manoochehri M, Manoukian S, Margolin S, Martinez ME, Matricardi L, McGuffog L, McLean C, Mebirouk N, Meindl A, Menon U, Miller A, Mingazheva E, Montagna M, Mulligan AM, Mulot C, Muranen TA, Nathanson KL, Neuhausen SL, Nevanlinna H, Neven P, Newman WG, Nielsen FC, Nikitina-Zake L, Nodora J, Offit K, Olah E, Olopade OI, Olsson H, Orr N, Papi L, Papp J, Park-Simon T-W, Parsons MT, Peissel B, Peixoto A, Peshkin B, Peterlongo P, Peto J, Phillips K-A, Piedmonte M, Plaseska-Karanfilska D, Prajezdanc K, Prentice R, Prokofyeva D, Rack B, Radice P, Ramus SJ, Rantala J, Rashid MU, Rennert G, Rennert HS, Risch HA, Romero A, Rookus MA, Rübner M, Rüdiger T, Saloustros E, Sampson S, Sandler DP, Sawyer EJ, Scheuermann MT, Scherkl RK, Schneeweiss A, Schoemaker MJ, Schöttker B, Schürmann P, Senter L, Sharma P, Sherman ME, Shu X-O, Singer CF, Smichkoska S, Soucy P, Southey MC, Spinelli JJ, Stone J, Stoppa-Lyonnet D, Swerdlow AJ, Szabo CI, Tamimi RM, Tapper WJ, Taylor JA, Teixeira MR, Terry M, Thomassen M, Thull DL, Tischkowitz M, Toland AE, Tollenaar RAEM, Tomlinson I, Torres D, Troester MA, Truong T, Tung N, Untch M, Vachon CM, van den Ouweland AMW, van der Kolk LE, van Veen EM, vanRensburg EJ, Vega A, Wappenschmidt B, Weinberg CR, Weitzel JN, Wildiers H, Winqvist R, Wolk A, Yang XR, Yannoukakos D, Zheng W, Zorn KK, Milne RL, Kraft P, Simard J, Pharoah PDP, Michailidou K, Antoniou AC, Schmidt MK, Chenevix-Trench G, Easton DF, Chatterjee N, García-Closas M, kConFab Investigators, ABCTB Investigators, EMBRACE Study, GEMO Study Collaborators. Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses. *Nat Genet* 2020;52:572–81.
- 45 Adedokun B, Du Z, Gao G, Ahearn TU, Lunetta KL, Zirpoli G, Figueroa J, John EM, Bernstein L, Zheng W, Hu JJ, Ziegler RG, Nyante S, Bandera EV, Ingles SA, Press MF, Deming-Halverson SL, Rodriguez-Gil JL, Yao S, Ogundiran TO, Ojengbode O, Blot W, Troester MA, Nathanson KL, Hennis A, Nemesure B, Ambis S, Fiorica PN, Sucheston-Campbell LE, Bensen JT, Kushi LH, Torres-Mejia G, Hu D, Fejerman L, Bolla MK, Dennis J, Dunning AM, Easton DF, Michailidou K, Pharoah PDP, Wang Q, Sandler DP, Taylor JA, O'Brien KM, Kitahara CM, Falusi AG, Babalola C, Yarney J, Awuah B, Addai-Wiafe B, Chanock SJ, Olshan AF, Ambrosone CB, Conti DV, Ziv E, Olopade OI, Garcia-Closas M, Palmer JR, Haiman CA, Huo D, GBHS Study Team. Cross-ancestry GWAS meta-analysis identifies six breast cancer loci in African and European ancestry women. *Nat Commun* 2021;12:4198.
- 46 Muranen TA, Greco D, Blomqvist C, Aittomäki K, Khan S, Hogervorst F, Verhoef S, Pharoah PDP, Dunning AM, Shah M, Luben R, Bojesen SE, Nordestgaard BG, Schoemaker M, Swerdlow A, Garcia-Closas M, Figueroa J, Dörk T, Bogdanova NV, Hall P, Li J, Khusnutdinova E, Bermisheva M, Kristensen V, Borresen-Dale A-L, Peto J, Dos Santos Silva I, Couch FJ, Olson JE, Hilleman P, Park-Simon T-W, Brauch H, Hamann U, Burwinkel B, Marme F, Meindl A, Schmutzler RK, Cox A, Cross SS, Sawyer EJ, Tomlinson I, Lambrechts D, Moisse M, Lindblom A, Margolin S, Hollestelle A, Martens JWM, Fasching PA, Beckmann MW, Andrulis IL, Knight JA, Anton-Culver H, Ziogas A, Giles GG, Milne RL, Brenner H, Arndt V, Mannermaa A, Kosma V-M, Chang-Claude J, Rudolph A, Devilee P, Seynaeve C, Hopper JL, Southey MC, John EM, Whittemore AS, Bolla MK, Wang Q, Michailidou K, Dennis J, Easton DF, Schmidt MK, Nevanlinna H, NBCS Investigators, kConFab/AOCS Investigators. Genetic modifiers of *CHEK2*\*1100delC-associated breast cancer risk. *Genet Med* 2017;19.
- 47 Kapoor PM, Mavaddat N, Choudhury PP, Wilcox AN, Lindström S, Behrens S, Michailidou K, Dennis J, Bolla MK, Wang Q, Jung A, Abu-Ful Z, Ahearn T, Andrulis IL, Anton-Culver H, Arndt V, Aronson KJ, Auer PL, Freeman LEB, Becher H, Beckmann MW, Beeghly-Fadiel A, Benitez J, Bernstein L, Bojesen SE, Brauch H, Brenner H, Brüning T, Cai Q, Campa D, Canzian F, Carracedo A, Carter BD, Castella JE, Chanock SJ, Chatterjee N, Chenevix-Trench G, Clarke CL, Couch FJ, Cox A, Cross SS, Czene K, Dai JY, Earp HS, Ekici AB, Eliassen AH, Eriksson M, Evans DG, Fasching PA, Figueroa J, Fritschi L, Gabrielson M, Gago-Dominguez M, Gao C, Gapstur SM, Gaudet MM, Giles GG, González-Neira A, Guénel P, Haeberle L, Haiman CA, Håkansson N, Hall P, Hamann U, Hatse S, Heyworth J, Holleczek B, Hoover RN, Hopper JL, Howell A, Hunter DJ, John EM, Jones ME, Kaaks R, Keeman R, Kitahara CM, Ko Y-D, Koutros S, Kurian AW, Lambrechts D, Le Marchand L, Lee E, Lejbkowitz F, Linet M, Lissowska J, Llaneza A, MacInnis RJ, Martinez ME, Maurer T, McLean C, Neuhausen SL, Newman WG, Norman A, O'Brien KM, Olshan AF, Olson JE, Olsson H, Orr N, Perou CM, Pita G, Polley EC, Prentice RL, Rennert G, Rennert HS, Ruddy KJ, Sandler DP, Saunders C, Schoemaker MJ, Schöttker B, Schumacher F, Scott C, Scott RJ, Shu X-O, Smeets A, Southey MC, Spinelli JJ, Stone J, Swerdlow AJ, Tamimi RM, Taylor JA, Troester MA, Vachon CM, van Veen EM, Wang X, Weinberg CR, Weltens C, Willett W, Winham SJ, Wolk A, Yang XR, Zheng W, Ziogas A, Dunning AM, Pharoah PDP, Schmidt MK, Kraft P, Easton DF, Milne RL, Garcia-Closas M, Chang-Claude J, ABCTB Investigators, kConFab/AOCS Investigators. Combined associations of a polygenic risk score and classical risk factors with breast cancer risk. *J Natl Cancer Inst* 2021;113:329–37.
- 48 Ho W-K, Tan M-M, Mavaddat N, Tai M-C, Mariapun S, Li J, Ho P-J, Dennis J, Tyrer JP, Bolla MK, Michailidou K, Wang Q, Kang D, Choi J-Y, Jamaris S, Shu X-O, Yoon S-Y, Park SK, Kim S-W, Shen C-Y, Yu J-C, Tan EY, Chan PMY, Muir K, Lophatananon A, Wu AH, Stram DO, Matsuo K, Ito H, Chan CW, Ngeow J, Yong WS, Lim SH, Lim GH, Kwong A, Chan TL, Tan SM, Seah J, John EM, Kurian AW, Koh W-P, Khor CC, Iwasaki M, Yamaji T, Tan KMV, Tan KTB, Spinelli JJ, Aronson KJ, Hasan SN, Rahmat K, Vijayanathan A, Sim X, Pharoah PDP, Zheng W, Dunning AM, Simard J, van Dam RM, Yip C-H, Taib NAM, Hartman M, Easton DF, Teo S-H, Antoniou AC. European polygenic risk score for prediction of breast cancer shows similar performance in Asian women. *Nat Commun* 2020;11:3833.
- 49 Shieh Y, Fejerman L, Lott PC, Marker K, Sawyer SD, Hu D, Huntsman S, Torres J, Echeverry M, Bohorquez ME, Martinez-Chequer JC, Polanco-Echeverry G, Estrada-Florez AP, Haiman CA, John EM, Kushi LH, Torres-Mejia G, Vidaurer T, Weitzel JN, Zambrano SC, Carvajal-Carmona LG, Ziv E, Neuhausen SL. A polygenic risk score for breast cancer in U. S. Latinas and Latin-American women. *J Natl Cancer Inst* 2019.
- 50 Du Z, Gao G, Adedokun B, Ahearn T, Lunetta KL, Zirpoli G, Troester MA, Ruiz-Narváez EA, Haddad SA, PalChoudhury P, Figueroa J, John EM, Bernstein L, Zheng W, Hu JJ, Ziegler RG, Nyante S, Bandera EV, Ingles SA, Mancuso N, Press MF, Deming SL, Rodriguez-Gil JL, Yao S, Ogundiran TO, Ojengbode O, Bolla MK, Dennis J, Dunning AM, Easton DF, Michailidou K, Pharoah PDP, Sandler DP, Taylor JA, Wang Q, Weinberg CR, Kitahara CM, Blot W, Nathanson KL, Hennis A, Nemesure B, Ambis S, Sucheston-Campbell LE, Bensen JT, Chanock SJ, Olshan AF, Ambrosone CB, Olopade OI, Yarney J, Awuah B, Wiafe-Addai B, Conti DV, Palmer JR, Garcia-Closas M, Huo D, Haiman CA, GBHS Study Team. Evaluating polygenic risk scores for breast cancer in women of African ancestry. *J Natl Cancer Inst* 2021;113:1168–76.