The importance of ethnicity: Are breast cancer polygenic risk scores ready for women who are not of White European origin?

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Abstract
Polygenic risk scores (PRS) for disease risk stratification show great promise for application in general populations, but most are based on data from individuals of White European origin. We assessed two well validated PRS (SNP18, SNP143) in the Predicting-Risk-of-Cancer-At-Screening (PROCAS) study in North-West England for breast cancer prediction based on ethnicity. Overall, 9475 women without breast cancer at study entry, including 645 who subsequently developed invasive breast cancer or ductal carcinoma in situ provided DNA. All were genotyped for SNP18 and a subset of 1868 controls were genotyped for SNP143. For White Europeans both PRS discriminated well between individuals with and without cancer. For n = 395 Black (n = 112), Asian (n = 119), mixed (n = 44) or Jewish (n = 120) women without cancer both PRS overestimated breast cancer risk, being most marked for women of Black and Jewish origin (P < .001). SNP143 resulted in a potential mean 40% breast cancer risk overestimation in the combined group of non-White/non-European origin. SNP-PRS that has been normalized based on White European ethnicity for breast cancer should not be used to predict risk in women of other ethnicities. There is an urgent need to develop PRS specific for other ethnicities, in order to widen access of this technology.

Keywords
breast cancer, ethnicity, risk

What’s new?
Associations between genetic variants and breast cancer risk have enabled the development of polygenic risk scores for disease risk stratification. These scores, however, generally are derived from White European women and may not apply for breast cancer risk prediction in women of other ethnicities.

Abbreviations: BAME, Black, Asian, and Minority Ethnic; DRS, density risk score; OR, odds ratio; PROCAS, Predicting-Risk-of-Cancer-At-Screening; PRS, polygenic risk score; SNP, single nucleotide polymorphism.

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INTRODUCTION

Since the first major successful breast cancer genome wide association study in 2007,1 multiple further single nucleotide polymorphisms (SNPs) have been identified to be associated with breast cancer risk.2 These SNPs have been predominantly identified through case control studies of women of White European origin through the Breast Cancer Association Consortium (BCAC).2 More recently, an assessment of a panel of 287 SNPs previously identified in White European women showed a similar strength of association to invasive breast cancer for women of Asian origin.3 However, even if the odds ratios (ORs) associated with each SNP are constant between ethnic groups, there is a need to standardize polygenic risk score (PRS) for different populations because allele frequencies are known to differ between ethnic groups. For instance, the title of this article could potentially be misleading “European polygenic risk score for prediction of breast cancer shows similar performance in Asian women” because 26 SNPs were excluded from the analysis because they had imputation accuracy scores of <0.9 in the Malaysian Breast Cancer Genetic Study and Singapore Breast Cancer Cohort. Also, by using the SNP polygenic risk score (PRS) developed for Europeans showed that “the mean of the 287-SNP PRS was markedly higher in Asian women compared to European women for overall breast cancer.”3 Thus, naively (agnostically) using a PRS designed for White European women SNP allele frequencies and ORs would overestimate breast cancer risk in Asian women.

We, and others, have shown that combining a PRS with standard risk factors and measures of mammographic density may provide more accurate risk predictions that substantially increase the proportion of women at high and moderate risk of breast cancer (>5% 10-year risk aged ≥46 years) as well as those at low-risk (≤2% 10-year risk).4,5 Such PRS are now available through commercial companies, including information on standard risk factors, to assess breast cancer risk. For example, one company in the United States offers a 94 SNP PRS https://myriadmyrisk.com/riskscore/#eligibility (accessed February 25, 2021), and eligibility clearly states that these are only suitable for women of White European origin, but including those of Ashkenazi Jewish ancestry. However, the order form does not exclude acceptance of a sample based on ethnicity. In the United Kingdom, another test does not appear to have any exclusion based on ethnicity for their 77-SNP PRS https://www.check4cancer.com/private-cancer-tests/mybreastrisk (accessed February 25, 2021). Although, the issues with ethnicity and PRS are well known in the research community, they are unlikely to be similarly understood in those clinicians involved in clinical assessments outside a research environment. Also development of PRS in the commercial and service sector will be standardized and unlikely to allow for “individualized” variation in the applications of a PRS.

In this article, we assess two PRS based on 18 and 143 SNPs in women not of White European origin, including those of Ashkenazi Jewish ancestry.

METHODS

A total of 57,902 women (904 with a previous breast cancer) were recruited to the Predicting-Risk-of-Cancer-At-Screening (PROCAS) study between October 01, 2009 and June 31, 2015. Saliva samples

Saliva DNA samples from PROCAS recruits n = 10,021

No breast cancer at entry n = 9,475

Prior breast cancer at entry n = 546

Breast cancer in follow up n = 645

SNP18 all samples

SNP18 n = 546

Oncoarray n = 1794

Oncoarray n = 621

Oncoarray n = 185

Non-White European n = 395

Non-White European = 24

Non-White European ethnicity n = 13

FIGURE 1 Consort diagram showing numbers of recruited women from each ethnic group providing DNA and whose sample were tested by oncoarray [Color figure can be viewed at wileyonlinelibrary.com]
|                         | Asian | Black | Mixed | Jewish | BAME combined | Unknown | White other | White British | Presumed White European |
|-------------------------|-------|-------|-------|--------|---------------|---------|-------------|--------------|-------------------------|
| **Total number**        | 123   | 117   | 48    | 131    | 419           | 274     | 159         | 8623         | 9056                    |
| **Number without breast cancer** | 119   | 112   | 44    | 120    | 395           | 255     | 141         | 8039         | 8435                    |
| **Number with breast cancer** | 4     | 5     | 4     | 11     | 24            | 19      | 18          | 584          | 621                     |
| **%BC**                 | 3.31% | 4.35% | 8.33% | 8.40%  | 5.78%         | 6.93%   | 11.32%      | 6.77%         | 6.86%                   |
| **Prospective breast cancer** | 2     | 1     | 1     | 8      | 12            | 10      | 10          | 256          | 276                     |
| **% prospective BC**    | 1.68% | 0.90% | 2.22% | 6.25%  | 2.98%         | 3.77%   | 6.62%       | 3.08%         | 3.16%                   |
| **Mean 10-year TCDR**²  | 3.11% | 3.17% | 3.25% | 4.46%  | 3.61%         | 3.13%   | 4.07%       | 3.56%         | 3.69%                   |
| **IQR**                 | 1.79 - 3.45 | 1.82 - 4.11 | 1.83 - 3.90 | 2.55 - 5.44 | 1.89 - 4.21 | 2.00 - 3.79 | 2.28 - 4.89 | 2.15 - 4.41 | 2.12 - 4.39 |
| **Expected cancers**⁴   | 3.23  | 3.04  | 1.28  | 4.85   | 12.40         | 7.18    | 5.18        | 265.99        | 278.34                  |

**Demographic features in those without breast cancer at sampling**

|                         | Median age at entry | IQR                | BMI                | IQR                | Missing (n) | Median age FFTP | IQR                | Nulliparous (n) | % nulliparous | Mean age at menarche | IQR                | Postmenopausal (n) | % postmenopausal | Mean age at menopause | IQR | FDR breast cancer (n) | % FDR                |
|-------------------------|---------------------|--------------------|--------------------|--------------------|-------------|----------------|--------------------|----------------|--------------|----------------------|--------------------|-------------------|-------------------|---------------------|------|----------------------|---------------------|
|                         | 57.1                | 51.86-62.07        | 26.04              | 22.69-28.12        | 7 (6.0%)    | 26.0            | 23.8-28.8         | 15             | 12.82%       | 13.1                 | 12-14              | 81                | 69.23%            | 48.1                | 46-50 | 17                  | 14.29%              |
|                         | 57.1                | 51.56-60.92        | 28.60              | 24.39-31.26        | 21 (19.1%)  | 24.2            | 20-27             | 13             | 11.82%       | 13.3                 | 12-14              | 64                | 58.18%            | 47.8                | 45-51 | 10                  | 9.01%                |
|                         | 56.8                | 51.49-62.06        | 28.71              | 24.45-30.67        | 2 (4.5%)    | 23.7            | 19-26             | 13             | 29.55%       | 13.3                 | 12-14              | 27               | 61.36%            | 47.8                | 46-50 | 4                  | 8.89%                |
|                         | 61.0                | 55.24-65.78        | 25.83              | 22.29-28.59        | 2 (1.8%)    | 26.6            | 19-26             | 13             | 15.83%       | 12.7                 | 12-14              | 92               | 76.67%            | 49.0                | 46-50 | 4                  | 13.28%               |
|                         | 58.4                | 52.29-64.08        | 26.77              | 22.99-28.91        | 32 (8.2%)   | 25.4            | 23-29             | 19             | 15.35%       | 13.1                 | 12-14              | 264              | 67.52%            | 48.3                | 46-51 | 17                  | 11.91%               |
|                         | 62.8                | 57.89-68.30        | 27.05              | 23.57-29.70        | 21 (8.2%)   | 24.7            | 21-26             | 19             | 10.20%       | 13.0                 | 12-14              | 264              | 81.18%            | 47.7                | 45-51 | 28                  | 10.57%               |
|                         | 57.8                | 51.83-63.05        | 26.64              | 21.96-30.03        | 16 (11.3%)  | 27.0            | 21-26             | 26             | 21.28%       | 12.6                 | 12-14              | 88               | 62.41%            | 49.8                | 48-52 | 28                  | 11.92%               |
|                         | 59.7                | 53.91-65.17        | 27.13              | 23.36-29.82        | 16 (11.3%)  | 25.3            | 21-26             | 30             | 14.75%       | 12.8                 | 12-14              | 264              | 74.18%            | 48.4                | 46-52 | 1145               | 13.80%               |
|                         | 59.8                | 53.92-65.27        | 27.12              | 23.32-29.82        | 379 (4.7%)  | 25.3            | 21-26             | 1186           | 14.72%       | 12.8                 | 12-14              | 264              | 74.19%            | 48.4                | 46-52 | 1191               | 13.67%               |

Abbreviations: BC, breast cancer; BMI, body mass index; FDR, first degree relative; FFTP, first full-term pregnancy; IQR, interquartile range; TCDR, Tyrer Cuzick density residual.

²Only includes prospective cancers not women sampled after breast cancer.
were obtained on drop-in days from 10 017 women largely based on proximity to the drop-in sites although those with breast cancer were prioritized (Figure 1). DNA was extracted from the saliva samples in women who were unaffected with breast cancer and aged 46–73 years at recruitment as previously described \(^{5,6}\). Of the 9475, 346/645 (53.6%) who developed breast cancer since recruitment provided their sample after diagnosis. Testing for SNP18 was available for all women using a custom-designed Sequenom MassARRAY iPLEX assay\(^5\) and in a subgroup of all incident breast cancers and three controls per woman with breast cancer for SNP143 using the Illumina OncoArray, as previously described.\(^6\) Both PRS were developed using published per allele ORs and allele frequencies were not “fit” to the population. Ethnicity was self-reported by questionnaire as (Asian/Asian British, Black/Black British, Mixed, White British, Jewish or other). Nearly all of the submitted OncoArray samples from Black and Asian samples were excluded for SNP313 imputation based on their ethnicity by genotype.\(^2\) As the remaining 170 SNPs (after SNP143) require imputation based on White European studies it was not possible to derive a White European SNP313. In Manchester most people of Black origin are Afro-Caribbean (~90%) and those of Asian origin from the Indian subcontinent in South Asia. Here we assessed non-White/non-European as mixed, Black, Asian and Jewish, which were considered to fit the definition of Black, Asian, and Minority Ethnic (BAME) in the United Kingdom. A subgroup of 542 women with breast cancer before entry to PROCAS were available for SNP18 also (total with DNA \(= 10\ 021\)). Per-allele risks for each SNP were derived based on White European women using a combined meta-analysis estimate (the GWAS, iCOGS and

| Table 2 | Results of SNP18 in all ethnicities and SNP143 in women excluded from the White European group compared to White European in prospective PROCAS without breast cancer and breast cancers in White British |
|----------------|---------------------------------------------------------------|
| **Group SNP18** | **Total number** | **Mean PRS no cancer except White British** | **Mean log PRS (95% CI)** | **P value** \(^c\) |
| White British no cancer | 8039 | 1.00 | \(-0.053 \ (-0.060, -0.046)\) | Ref. |
| White British cancer | 584 | 1.10 | \(0.049 \ (0.024, 0.075)\) | <.001 |
| Asian \(^b\) | 119 | 1.06 | \(0.012 \ (-0.044, 0.067)\) | .29 |
| Black \(^b\) | 112 | 1.22 | \(0.150 \ (0.090, 0.211)\) | <.001 |
| Unknown \(^b\) | 274 | 1.03 | \(-0.031 \ (-0.073, 0.011)\) | .28 |
| Jewish \(^b\) | 120 | 1.14 | \(0.078 \ (0.018, 0.139)\) | <.001 |
| Mixed \(^b\) | 44 | 1.16 | \(0.084 \ (-0.030, 0.199)\) | .005 |
| White other \(^b\) | 159 | 1.05 | \(-0.010 \ (-0.065, 0.045)\) | .117 |
| **Combined groups SNP18** | | | | |
| Presumed White European no cancer | 8436 | 1.00 | \(-0.051 \ (-0.058, -0.044)\) | Ref. |
| Presumed White European cancer | 621\(^a\) | 1.11\(^a\) | \(0.056 \ (0.031, 0.081)\) | <.001 |
| **BAME group: Jewish, Black, Asian, mixed** | | | | |
| No cancer | 395 | 1.14 | \(0.079 \ (0.046, 0.112)\) | <.001 (ref. White no cancer) |
| BAME group cancer | 37 | 1.15 | \(0.086 \ (-0.022, 0.195)\) | .902 (ref. BAME no cancer) |
| Jewish | 120 | 1.14 | \(0.078 \ (0.018, 0.139)\) | <.001 (ref. White no cancer) |
| Jewish cancer | 15 | 1.06 | \(-0.011 \ (-0.227, 0.204)\) | - |
| **Group SNP143** | | | | |
| Presumed White European no cancer | 1784 | 0.98 | \(-0.150 \ (-0.174, -0.127)\) | Ref. |
| Presumed White European cancer | 621 | 1.27 | \(0.116 \ (0.077, 0.155)\) | <.001 |
| BAME group no cancer | 84 | 1.40 | \(0.201 \ (0.087, 0.315)\) | <.001 (ref. White no cancer) |
| BAME group cancer | 30 | 1.31 | \(0.134 \ (-0.055, 0.323)\) | .551 (ref. BAME no cancer) |
| Jewish no cancer | 31 | 1.26 | \(0.092 \ (-0.107,0.291)\) | <.001 |
| Jewish cancer | 12 | 1.30 | \(0.049 \ (-0.356,0.453)\) | - |
| Black no cancer | 18 | 1.91 | \(0.504 \ (0.234, 0.774)\) | <.001 |
| Asian no cancer | 26 | 1.29 | \(0.167 \ (-0.018, 0.351)\) | .002 |
| Mixed no cancer | 8 | 1.15 | \(0.065 \ (-0.281, 0.412)\) | .202 |

\(^a\)Mean SNP18 PRS for 525 White European women diagnosed with breast cancer before entry was identical at 1.11 to the 621 diagnosed after entry.

\(^b\)Number of cancers too small to provide separately and not included in numbers.

\(^c\)P value given for comparison with reference category.
OncoArray study estimate), and each SNP OR was normalized to be 1.0 for the White European group based on White European allele frequencies; the PRS was derived by multiplying the resultant normalized ORs. None of the women in the present study were used in the discovery set for the 143 SNPs assessed. The distribution of PRS across ethnic groups (independent variable) was compared using a linear regression on the log PRS (dependent variable) and P-values reported in relation to the reference group. Differences in allele frequencies were evaluated by a chi-square test. Ten-year risks were assessed by Tyrer-Cuzick v8 and a normalized assessment of mammographic density (density risk score [DRS]), as previously described. PROCAS was approved in 2009 by the Central Manchester Research Ethics Committee (reference: 09/H1008/81). All women gave informed consent for genetic analysis on DNA extracted from saliva samples and for breast cancer risks to be derived from other information.

3 | RESULTS

The demographic characteristics and breast cancer risk factors for 8830 women without breast cancer and numbers in each ethnic group with breast cancer are shown in Table 1. Results for 8830 women without breast cancer at their last assessment for the SNP18 panel and a subgroup of 584 from a total of 645 (90.5%) women with breast cancer who self-reported as White British are shown in Table 2. As reported previously, the mean SNP18 PRS was well aligned with the expected value (~1.0), and with a higher PRS in the 584 White British women with breast cancer (1.10). All other groups had a mean PRS above 1.0, with this being most marked in the Black subgroup (P < .001) and to a lesser extent in the Jewish group (P < .001). Taking the Asian, Black, mixed and Jewish groups as a combined BAME group; and the data not known and “other” (predominantly these were non-British White European) as presumed White European, we next assessed the combined groups for both 10-year risk from Tyrer-Cuzick and DRS as well as SNP18 and SNP143 (Tables 1 and 2). There was little difference in the risk evaluation from classical factors with breast density (Tyrer-Cuzick/DRS 10-year risk) in the BAME group (estimated 10-year risk mean = 3.61%) and the White European group (mean = 3.69%) Table 1. There was also a similar length of follow up of 8.28 and 8.26 years, respectively. There were 12 prospective breast cancers in the women who provided saliva samples in the BAME group (12 provided DNA after diagnosis), giving a 10-year rate of 3.6% (expected breast cancers = 12.40 by Tyrer-Cuzick/DRS) and 276 in the White European group (345 provided after diagnosis) giving a 10-year rate of 3.7% (expected breast cancers = 278.34 by Tyrer-Cuzick/DRS). The White European group had a PRS close to 1.0, whereas the BAME group controls had a mean SNP143 PRS of ~1.4 (P < .001). Again, the Black group were the most discordant with a mean of 1.91 (also included the individual with the highest PRS = 5.32), but all BAME subgroups were well above 1.0. There was good discrimination between the ORs comparing individuals with cancer and controls for White European women (P < .001), as we have shown previously, however there was insufficient power to evaluate this in the BAME group. We did nonetheless assess discrimination using Tyrer-Cuzick/DRS incorporating SNP143 to show the

| TABLE 3 | Assessment of SNP rs3803662 (TOX3) and rs2981579 (FGFR2) in different ethnicities in women without breast cancer |
|---------|---------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|         | White | Black | Jewish | Mixed | Asian | White | Black | Jewish | Mixed | Asian |
| rs3803662 no cancer |       |       |       |       |       |       |       |       |       |       |
| Total tested | 7929 | 105  | 116  | 44   | 114  | 8404 | 110  | 120  | 44   | 113  |
| Mean OR | 0.999 | 1.111 | 1.048 | 1.063 | 1.031 | 0.996 | 1.090 | 1.016 | 1.047 | 1.003 |
| Heterozygous CT | 2947 | 50   | 49   | 25   | 52   | 4055 | 53   | 61   | 23   | 60   |
| Homozygous TT | 538  | 27   | 17   | 5    | 11   | 1367 | 39   | 23   | 11   | 18   |
| Allele Freq T | 6.8% | 25.4% | 35.8% | 39.8% | 32.5% | 40.39% | 59.55% | 44.58% | 51.14% | 42.48% |
| %Homozygous TT | T | 4023 | 104  | 83   | 35   | 74   |       |       |       |       |
| C | 11835 | 106  | 149  | 53   | 154  |       |       |       |       |       |
| Significance | Ref. | P < .0001 | P = .0012 | P = .005 | P = .037 | Ref. | P < .0001 | P = .21 | P = .05 | P = .57 |
| rs2981579* no cancer |       |       |       |       |       |       |       |       |       |       |
| Total tested | 8404 | 110  | 120  | 44   | 113  |       |       |       |       |       |
| Mean OR | 0.996 | 1.090 | 1.016 | 1.047 | 1.003 |       |       |       |       |       |
| Heterozygous CT | 4055 | 53   | 61   | 23   | 60   |       |       |       |       |       |
| Homozygous TT | 1367 | 39   | 23   | 11   | 18   |       |       |       |       |       |
| Allele Freq T | 40.39% | 59.55% | 44.58% | 51.14% | 42.48% |       |       |       |       |       |
| %Homozygous TT | T | 6789 | 131  | 107  | 45   | 96   |       |       |       |       |
| C | 10019 | 89   | 133  | 43   | 130  |       |       |       |       |       |
| Significance | Ref. | P < .0001 | P = .21 | P = .05 | P = .57 |       |       |       |       |       |
distribution of risk groups in cases and controls in the BAME group (Supplementary Table S1). The numbers of cancers are too small to make firm conclusions but with 55% of controls and only slightly higher cases at 58% being above average risk this suggests that SNP143 is not adding useful information to the BAME group. This compares to 34% of controls and 59% of cases in the White European group. Thirteen of 37 cancers assessed in the ethnic minority group were in women from the group of 542 who were diagnosed with breast cancer before study entry.

We finally assessed the most divergent SNP between White and BAME groups (rs3803662) in SNP18 to assess the potential for error on an individual SNP basis (Table 3). All ethnicities other than the presumed White European group had a significantly higher frequency of the risk allele “T”. This was most marked in those of Black origin. The potential error from this SNP alone for people of Black origin using an agnostic approach would be an 11% increase in their estimated risk of breast cancer (OR 1.11). We next assessed the SNP with the largest effect size in the PRS (rs2981579, located in FGFR2). Although there was little apparent difference in allele frequencies or ORs for women of Asian (OR 1.01) or Jewish origin, there was again a larger difference in Black women. These data suggest that using White European allele frequencies to normalize the ORs for these two SNPs in Black women would generate an OR of 1.21 in those without breast cancer compared to the White European group.

4 DISCUSSION

We have previously shown that both SNP18 and SNP143 PRS are likely to be well calibrated, and discriminate well between women with and without breast cancer, both in the general population5,6 and in a high-risk population with a family history of breast cancer,7 where the great majority of the population are of White European origin. However, our previous study included some controls (395/8830, 4.5%) and cases (24/645, 3.7%) who were not of White European origin. We have shown here that a direct application of a White European PRS is inaccurate in Black, Asian, mixed race and Jewish women. The SNPs in a PRS differ across populations, both in terms of allele frequencies and the ORs for disease association and a direct application of a PRS developed in a specific population in estimating disease risk in other populations would be misleading. This should not be recommended as any bias in the risk estimate, depending on its direction could either create reassurance or anxiety for women for whom the PRS-based risk estimation is applied. We have shown that for both SNP18 and SNP143 the main bias is an exaggeration of the risk. While a direct application of a PRS derived from White European women to those of Asian origin is known a priori to artificially increase risk,3 this has not yet been reported directly for women of Black or mixed-race ethnicities, where the agnostic application of the PRS may be even more misleading, due to the even higher mean PRS reported here and in previous studies.8 The substantially increased PRS in the minority ethnicities are actually associated with lower numbers of breast cancers.

While some companies indicate that their PRS is only valid for White European and Ashkenazi Jewish women, others do not make this clear. There are also large population research programs using SNP PRS as part of personalized methods for early detection of breast cancer in both the United States (target = 100 000)9 and Europe (target = 85 000).10 Companies and population-based research programs using PRS for personalized prevention and early detection strategies should highlight this important limitation and advocate an ethnicity specific PRS development/adjustment. It is not clear how this will be done from the protocols from a number of the population-based research programs. The WISDOM trial9 is apparently making adjustments in those not of White European origin, but this has not yet been published (Personal communication, Laura van’t Veer). Certainly, there is currently no published adjustment for Black women and the version for Asian women has only just been published.3

The difference in underlying allele frequencies between ethnic groups in our data also casts doubt on whether a White European PRS is appropriate for women of Jewish origin. Although the Myriad SNP94 has been validated in a population that included 4632 Ashkenazi women without breast cancer they made up only 3% of the study population and no separate analysis of Jewish women was included in the original report.4 Our data on a Jewish population that is likely to be >90% Ashkenazi (based on Greater Manchester statistics) suggest that there could be a systematic overestimation of risk using the White European PRS, especially when using more SNPs. Our SNP143 panel contains all the SNPs in the commercial tests. It is important that a much larger validation is carried out on the Ashkenazi Jewish population before further widespread adoption of an ethnicity agnostic PRS in breast cancer risk assessment. Equally all future applications of PRS need to be based on ethnicity adjustment at a minimum based on allele frequencies. Large initiatives have now developed PRS in both the Asian and Hispanic/Latina populations.3,11 However, the issue of risk ORs is also still underevaluated for women of Black origin.3,12 A very recent large case control study in women of “African” descent showed an attenuated performance compared to that reported in European, Asian and Latina populations,12 with a number of SNPs requiring replacements. Although they did not find that recalibrating the PRS made any improvement to the risk prediction.12

For allele frequency normalization, it is likely that PRS may also need to differentiate between the British Black, predominantly Afro-Caribbean, population and those from different parts of Africa. However, a simple adjustment of the PRS in controls to match the White European control PRS may not be sufficient as each SNP’s effect size may be different in different ethnicities and adjustments will almost certainly be necessary on a SNP by SNP basis, with some being excluded.3 Therefore, care should be taken in assigning PRS that may not be relevant to certain populations as they can falsely reassure or create anxiety and inappropriate requirements for excessive breast cancer screening or preventative treatment. While our study was not powered to assess the predictive effects of PRS for cancers in BAME groups the agnostic application of White European PRS particularly for high numbers and in the Black subgroup substantially overestimates risk in unaffected women. Although other larger studies have
addressed the predictive effect of a modified White European PRS and indicated that use of this without adjustments will overpredict risk, they have not shown the extent of this.²,³,⁸,⁹,¹² Given the availability of commercial PRS it is important to know the scale of any overestimate if White European PRSs are misapplied. Our analysis is sufficiently powered with the three ethnicities to show this would lead to substantial overestimation particularly in those of Black origin, but that there are likely to be overestimations even in Jewish women for which the PRS is currently used. Therefore, current evidence would suggest that an agnostic application of a White European breast cancer PRS to those outside this population is likely to erroneously exaggerate the risks. This effect may not be trivial, with our BAME population having a mean 40% increase in predicted breast cancer risk using SNP143 (>90% in Black women) with no evidence that this identifies a higher risk in that population. While, developing these separate ethnicity specific PRS will take time and necessary sampling in different populations this is of some urgency if we are not to further increase health disparities in minority populations in Europe, Australasia and North America.¹³,¹⁴

ACKNOWLEDGMENTS
D. Gareth Evans, Elaine F. Harkness, William G. Newman, Sacha J. Howell and Anthony Howell are supported by the National Institute for Health Research (NIHR) BRC Manchester (Grant Reference Number 1215-200074). This work was also supported by Prevent Breast Cancer (GA19-002).

CONFLICT OF INTEREST
Jack Cuzick provides consultancy to Myriad Genetics. Adam Brentnall and Jack Cuzick received royalty payments through Cancer Research UK for use of the Tyrer-Cuzick breast cancer risk assessment algorithm. There are no other conflicts.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
PROCAS was approved in 2009 by the Central Manchester Research Ethics Committee (reference: 09/H1008/81). All women gave informed consent for genetic analysis on DNA extracted from saliva samples and for breast cancer risks to be derived from other information.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Evans DG, van Veen EM, Byers H, et al. The importance of ethnicity: Are breast cancer polygenic risk scores ready for women who are not of White European origin? Int. J. Cancer. 2022;150(1):73-79. doi: 10.1002/ijc.33782