ORIGINAL ARTICLE

Assessment of a Polygenic Risk Score in Screening for Prostate Cancer

J.K. McHugh,[1,2] E.K. Bancroft,[1,2] E. Saunders,[1] M.N. Brook,[1] E. McGrowder,[1] S. Wakerell,[1] D. James,[1,2] R. Rageevakumar,[1] B. Benton,[1,2] N. Taylor,[1,2] K. Myhill,[1,2] M. Hogben,[1,2] N. Kinsella,[2,3] A.A. Sohaib,[2] D. Cahill,[2] S. Hazell,[2] S.J. Withey,[2] N. Mcaddy,[2] E.C. Page,[1,2] A. Osborne,[1,2] S. Benafif,[1,4] A.-B. Jones,[1,2] D. Patel,[5] D.Y. Huang,[5] K. Kaur,[2] B. Russell,[2] R. Nicholson,[2] F. Croft,[2] J. Sobczak,[2] C. McNally,[2] F. Mutch,[2] S. Bennett,[2] L. Kingston,[2] Q. Karlsson,[1] T. Dadaev,[1] S. Saya,[1,6] S. Merson,[1] A. Wood,[1] N. Dennis,[1,2] N. Hussain,[1] A. Thwaites,[1] S. Hussain,[1] I. Rafi,[7] M. Ferris,[8] P. Kumar,[2] N.D. James,[1,2] N. Pashayan,[9] Z. Kote-Jarai,[1] and R.A. Eeles,[1,2] for the BARCODE1 Steering Committee and Collaborators*

ABSTRACT

BACKGROUND

The incidence of prostate cancer is increasing. Screening with an assay of prostate-specific antigen (PSA) has a high rate for false positive results. Genomewide association studies have identified common germline variants in persons with prostate cancer, which can be used to calculate a polygenic risk score associated with risk of prostate cancer.

METHODS

We recruited persons 55 to 69 years of age from primary care centers in the United Kingdom. Using germline DNA extracted from saliva, we derived polygenic risk scores from 130 variants known to be associated with an increased risk of prostate cancer. Participants with a polygenic risk score in the 90th percentile or higher were invited to undergo prostate cancer screening with multiparametric magnetic resonance imaging (MRI) and transperineal biopsy, irrespective of PSA level.

RESULTS

Among 40,292 persons invited to participate, 8953 (22.2%) expressed interest in participating and 6393 had their polygenic risk score calculated; 745 (11.7%) had a polygenic risk score in the 90th percentile or higher and were invited to undergo screening. Of these 745 participants, 468 (62.8%) underwent MRI and prostate biopsy; prostate cancer was detected in 187 participants (40.0%). The median age at diagnosis was 64 years (range, 57 to 73). Of the 187 participants with cancer, 103 (55.1%) had prostate cancer classified as intermediate or higher risk according to the 2024 National Comprehensive Cancer Network (NCCN) criteria, so treatment was indicated; cancer would not have been detected in 74 (71.8%) of these participants according to the prostate cancer diagnostic pathway currently used in the United Kingdom (high PSA level and positive MRI results). In addition, 40 of the participants with cancer (21.4%) had disease classified as unfavorable intermediate risk or as high or very high risk according to NCCN criteria.

CONCLUSIONS

In a prostate cancer screening program involving participants in the top decile of risk as determined by a polygenic risk score, the percentage found to have clinically significant disease was higher than the percentage that would have been identified with the use of PSA or MRI. (Funded by the European Research Council Seventh Framework Program and others; BARCODE1 ClinicalTrials.gov number, NCT03857477.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Eeles can be contacted at ros.eeles@icr.ac.uk or at the Oncogenetics Team, Institute of Cancer Research, 123 Old Brompton Rd., London SW3 6JJ, United Kingdom.

*The BARCODE1 steering committee members and collaborators are listed in the Supplementary Appendix, available at NEJM.org.

Drs. McHugh and Bancroft contributed equally to this article.

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Prostate cancer is a considerable health burden worldwide; it is the most common cancer, after skin cancer, in persons assigned male sex at birth and caused 375,000 deaths in 2020.[1] There is no internationally accepted population-based screening program for the early detection of prostate cancer. The clinical usefulness of a prostate-specific antigen (PSA) assay for monitoring the progression of prostate cancer is indisputable, but its use as a screening tool is debated because the potential harms outweigh the benefits. The use of a PSA test for screening has been evaluated in two large, randomized trials: the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[2] and the European Randomized Study of Screening for Prostate Cancer (ERSPC).[3] Criticisms of PSA testing as a screening tool include a high rate of false positive results, overdiagnosis, complications associated with prostate biopsies, and overtreatment of low-grade disease; however, data from 22 years of follow-up in the ERSPC showed that PSA-based screening resulted in 30% lower mortality from prostate cancer in the group of men who were offered screening with PSA testing every 2 years than in the control group of men who underwent unorganized, opportunistic PSA testing.[3]

Among persons with prostate cancer diagnosed at stage I or II, the 5-year survival is almost 100%; among persons whose disease is diagnosed at stage IV, the 5-year survival is 50%.[4] Therefore, an effective screening tool to detect early-stage, clinically significant prostate cancer is urgently needed. Research is focused on magnetic resonance imaging (MRI)–based screening,[5-7] biomarkers,[8,9] and modeling multiple risk factors.[10,11]

Older age and family history of prostate cancer are established risk factors for prostate cancer. Prostate cancer is highly heritable, with 58% heritability observed in studies involving twins.[12] A small proportion of germline genetic risk is caused by rare pathogenic variants in DNA-repair genes (e.g., *BRCA1* and *BRCA2*), and a greater proportion is due to the combined effect of multiple low-risk variants, called single-nucleotide polymorphisms (SNPs), from which a person's polygenic risk score can be calculated.[13] After the completion of a pilot study,[14] the BARCODE1 study was designed to test prospectively the performance of a polygenic risk score with regard to stratification for targeted screening as part of a prostate cancer screening program in the general population.

We report the initial results from the BARCODE1 study. In addition, we report on the uptake and positive predictive value of MRI and biopsy, the percentage of participants whose cancer was detected with MRI and biopsy, and the percentage of participants with a polygenic risk score in the 90th percentile or higher for risk of prostate cancer who subsequently received a diagnosis of prostate cancer.

METHODS

STUDY DESIGN AND PARTICIPANTS

BARCODE1 is an ongoing, prospectively designed, single-group study that received approval from the London–Chelsea Research Ethics Committee and the Health Research Authority. The corresponding author and the first two authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol. The Institute of Cancer Research provides regulatory oversight of the BARCODE1 study. Recruitment was coordinated at 69 primary care centers across three clinical research networks (Kent, Surrey, and Sussex; South London; and the Thames Valley and South Midlands). Patient databases were screened, and eligible persons were invited by letter. Patients were eligible if they had been assigned male sex at birth, were 55 to 69 years of age, reported European ancestry, had no personal history of prostate cancer, were not currently undergoing testing for suspected prostate cancer, had not undergone prostate biopsy within the previous 12 months, and had no known contraindications to MRI or biopsy (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Interested persons completed a health-screening questionnaire, provided written informed consent, and mailed a saliva sample for genetic analysis.

DNA extraction was carried out at Yourgene Health. Extracted DNA was sent to Affymetrix (Thermo Fisher Scientific) for genotyping with the use of a custom-designed high-throughput assay (Eureka myDesign genotyping panel).[14] The panel consisted of 130 European-ancestry SNPs known to be associated with an increased risk of prostate cancer (Table S2) and has been validated for use only in persons of European ancestry.[15] The polygenic risk score for each participant was calculated with the use of the sum of weighted alleles for the 130 SNPs.

Study participants with a polygenic risk score in at least the 90th percentile (on the basis of a reference population from the ProtecT [Prostate Testing for Cancer and Treatment] study)[16] were referred to a cancer center for genetic-risk counseling. This counseling involved a discussion with experienced clinicians about the meaning of the polygenic risk score results. Participants were offered a PSA test, multiparametric MRI, and transperineal biopsy. The InHealth Group performed MRIs at seven diagnostic centers. One of two consultant radiologists, both considered to be expert according to European Society of Urogenital Radiology consensus guidance, reported the results of these MRIs in accordance with Prostate Imaging Reporting and Data System (PI-RADS), version 2.1.[17] All participants underwent a systematic prostate biopsy with the use of a transperineal approach while under local anesthesia; when lesions were identified on MRI, an MRI-guided targeted biopsy was performed to obtain additional biopsy cores from the lesion. Histopathological findings were reported by a urologic histopathologist.

Participants with a prostate cancer diagnosis were treated in accordance with National Institute for Health and Care Excellence guidelines.[18] Cancers were defined according to Gleason score (scores range from 6 to 10, with higher scores indicating a more aggressive form of prostate cancer, and are reported as the sum of the primary grade plus the secondary grade) and the 2024 National Comprehensive Cancer Network (NCCN) prostate cancer risk groups (very low, low, favorable intermediate, unfavorable intermediate, high, or very high).[19] Cancers were clinically significant if the Gleason score was at least 7 (i.e., 3 [primary grade]+4 [secondary grade]). Participants with negative biopsies were screened annually for 5 years (Fig. S1).

SAMPLE SIZE

We calculated that a sample of 5000 participants would be needed to identify approximately 500 persons with a polygenic risk score in the 90th percentile or higher. Assuming that the 130 SNPs interact log additively, we estimated the polygenic variance to be 0.52 by first calculating the variance explained by each SNP and then summing the contributions.[20] On the basis of this total polygenic variance, and using previously described methods,[21] we assumed that participants in the top 10% of the risk distribution would account for 29% of all cases of prostate cancer.

STATISTICAL ANALYSIS

Descriptive statistics were used to analyze uptake of the PSA test, MRI, and biopsy; the percentage of participants who agreed to undergo biopsy; the percentage of participants with detected cancer; age at diagnosis; the positive predictive value of prostate biopsy, of a PSA level greater than 3 μg per liter, and of MRI (the presence of a lesion with a PI-RADS score of ≥3 [on a scale from 1 to 5, with higher scores indicating a higher cancer risk]); and stratification of tumors according to Gleason score and 2024 NCCN risk classification. The statistical analysis was conducted by the first, second, fourth, and third-to-last authors. Annual study data are presented to an independent data and safety monitoring committee. A full copy of the protocol, which includes the statistical analysis, is available at NEJM.org.

Logistic regression was used to model the association of biopsy outcome with age, family history of prostate cancer (defined as any first- or second-degree relative with prostate cancer), PSA level, PI-RADS score, and PSA density higher than 0.12 ng per milliliter per cubic centimeter. PSA density is calculated as the PSA level in nanograms per milliliter divided by the volume of the prostate in milliliters and takes into account that a larger prostate gland may produce more PSA. Biopsy outcome was modeled for any prostate cancer and for clinically significant prostate cancer. Univariable models were evaluated for each variable of interest. Models were then developed to include older age and family history of prostate cancer (as established risk factors) along with exhaustive combinations of PSA level and PI-RADS score. The area under the curve (AUC) was calculated for each model. For each of the 6393 participants who had a polygenic risk score calculated, the 10-year absolute risk was calculated with the use of the R package iCARE[22] by incorporating age-specific incidence of prostate cancer,[4] competing risks of death,[23] relative risk on the basis of family history of prostate cancer,[24] and polygenic risk score.

We estimated the probability of overdiagnosis as the probability that screening-detected cancer would have taken longer than the remaining lifetime to progress to clinically detected cancer.[24]

We calculated the age-specific mean sojourn time (the time between when a condition can be detected by screening and when it would manifest clinically) as the weighted sum of the mean sojourn time for tumors with a Gleason score of less than 7 and that for tumors with a Gleason score of 7 or higher for each scenario (i.e., a PSA level of >3.0 μg per liter, a PI-RADS score of ≥3, or a polygenic risk score in the 90th percentile or higher).[25] We derived the expected remaining lifetime according to age from the U.K. national life table for the period from 2020 to 2022.[23] We calculated the probability of overdiagnosis as the probability that the mean sojourn time would be greater than the expected remaining lifetime.[25]

RESULTS

STUDY POPULATION

From March through July 2019, a total of 40,292 persons were invited, of whom 8953 (22.2%) expressed an interest in participating in the study (Fig. 1). A polygenic risk score was calculated for 6393 participants, of whom 745 (11.7%) had a score in the 90th percentile or higher. Of these 745 participants, 468 (62.8%) underwent MRI and biopsy. A total of 177 participants withdrew from the study because of personal choice; 95 withdrew on the basis of a decision by the study team, including 8 participants who had prostate cancer diagnosed before they received their polygenic risk score; and 5 died from unrelated causes before study completion (Table S3). The most common reason for participants choosing to withdraw, both before and after MRI, was reluctance to undergo biopsy (40.7% of participants). The study population comprised self-selected participants who were highly educated and largely from professional occupations. The mean age of the participants at enrollment was 61.2 years, and 20.9% of the participants reported a family history of prostate cancer (Table S4).

PROSTATE CANCER DETECTION AND CANCER CHARACTERISTICS

We detected prostate cancer in 187 of the 468 participants (40.0%) who underwent MRI and biopsy (Fig. 1). The median age at diagnosis was 64 years (range, 57 to 73 years) (Table 1). The mean number of cores taken at biopsy was 13 (range, 5 to 18). Of the 187 participants with cancer detected by biopsy, 103 (55.1%) had cancer with a Gleason score of at least 7 that was classified as intermediate risk or higher according to 2024 NCCN classification criteria; 40 participants (21.4%) had cancer classified as unfavorable intermediate, high, or very high risk and therefore warranted radical treatment. Among the 6393 participants who had their polygenic risk score calculated, stratification of risk according to polygenic risk score led to the detection of prostate cancer that was classified as intermediate risk or higher and therefore warranted clinical management in 103 participants, of whom 74 (71.8%) had disease that would have been missed with the standard diagnostic pathway used in the United Kingdom (high PSA level and positive MRI results) (Table 2).

CANCER DETECTION AND PSA LEVEL

The median PSA level at diagnosis was 2.1 μg per liter (range, 0.3 to 274). Among the 187 participants with cancer, 118 (63.1%) had a PSA level of 3.0 μg per liter or lower; 51 of these 118 participants (43.2%) had cancer with a Gleason score of 7 or higher. Among the 69 participants with cancer and a PSA level higher than 3.0 μg per liter, 52 (75.4%) had cancer with a Gleason score of 7 or higher. The percentage of participants with detected cancer with stratification according to PSA level is shown in Table S5.

CANCER DETECTION AND MRI CHARACTERISTICS

Overall, 97 participants had a lesion with a PI-RADS score of 3 or higher and underwent a targeted biopsy. Of the 43 participants who had a lesion with a PI-RADS score of 3, a total of 19 had cancer detected at biopsy (9 had a Gleason score ≥7). Of the 54 participants who had a lesion with a PI-RADS score of 4 or higher, 42 (77.8%) had cancer detected at biopsy (36 had a Gleason score ≥7, and 25 had disease classified as unfavorable intermediate, high, or very high risk). Of the 370 participants with negative MRI results (PI-RADS score ≤2), 125 had cancer detected on biopsy, of whom 57 had a Gleason score of at least 7.

Of the 187 participants who received a diagnosis of prostate cancer, 100 had either a high PSA level (>3.0 μg per liter) or a lesion with a PI-RADS score of 3 or higher; only 30 (16.0%) had both a high PSA level and a lesion with a PI-RADS score of 3 or higher and therefore met the standard criterion for progressing to prostate

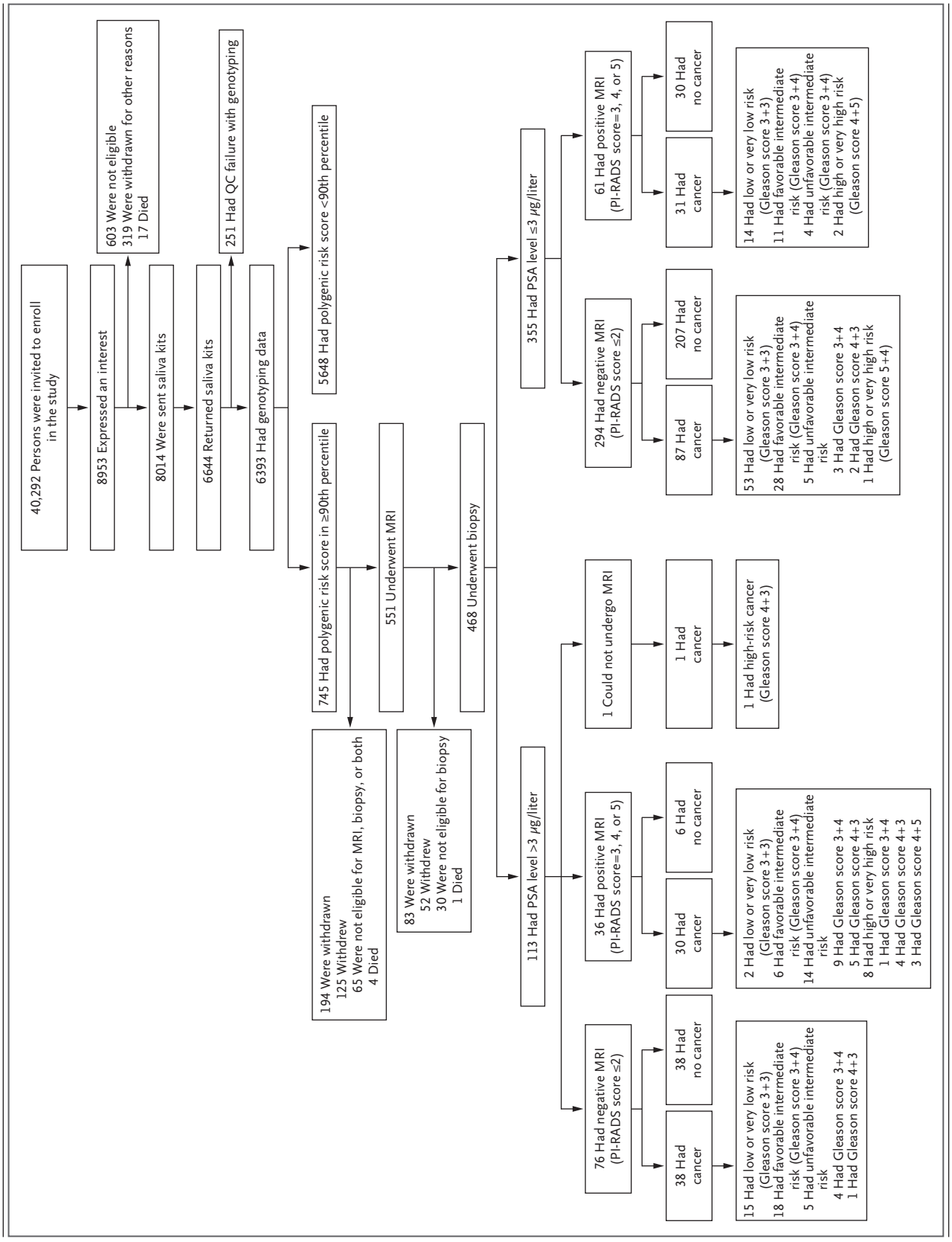

Figure 1 (facing page). Participant Pathway through the BARCODE1 Study.

Shown is the participant pathway through the study, from initial invitation to biopsy outcome. Cancers were classified in accordance with the National Comprehensive Cancer Network 2024 criteria for risk of metastasis (very low, low, favorable intermediate, unfavorable intermediate, high, or very high risk) and Gleason score (scores range from 6 to 10 [sum of the primary grade plus the secondary grade], with higher scores indicating a more aggressive form of prostate cancer). Prostate Imaging Reporting and Data System (PI-RADS) scores range from 1 to 5, with higher scores indicating a higher cancer risk. PSA denotes prostate-specific antigen, and QC quality control.

biopsy in accordance with the traditional management pathway in the United Kingdom (Fig. 2 and Table 2). Of the 40 participants with cancer classified as unfavorable intermediate, high, or very high risk, 17 (42.5%) had cancer that would have been missed with the use of the standard criterion. The addition of PSA density did not add discriminatory value; 48 of the 186 participants with prostate cancer had a PSA density higher than 0.12 ng per milliliter per cubic centimeter.[26]

POSITIVE PREDICTIVE VALUES

The positive predictive value of a PSA level greater than 3.0 μg per liter for the detection of prostate cancer on biopsy (among the 468 participants who underwent biopsy) was 61.1%, and the positive predictive value of MRI (among the participants with a PI-RADS score of ≥3) was 62.9%. These results are shown in Table S6.

LOGISTIC REGRESSION

Univariable models involving the participants in the top 10% of the polygenic risk score distribution showed that older age and family history of prostate cancer were not associated with any prostate cancer as a biopsy outcome and provided no discriminatory accuracy in predicting this outcome. However, these factors were strongly associated with and provided modest discriminatory accuracy in predicting clinically significant prostate cancer. The PSA level and PI-RADS score were strongly associated with both any prostate cancer and clinically significant prostate cancer as biopsy outcomes and provided strong discriminatory accuracy in predicting both outcomes. PSA density did not add any discriminatory value.

Table 1. Characteristics of the Participants According to Cancer Diagnosis.*

Characteristic	No Cancer (N=281)	Any Prostate Cancer (N=187)	Clinically Significant Prostate Cancer (N=103)
Median age at diagnosis (IQR) — yr	63 (60–67)	64 (60–68)	65 (60–69)
Median PSA (IQR) — μg/liter	1.4 (0.9–2.3)	2.1 (1.3–4.2)	3.1 (1.8–6.3)
Median polygenic risk score percentile (IQR)	95 (92–98)	95 (93–99)	96 (93–99)
PI-RADS score — no. (%)†			
1	7 (2.5)	1 (0.5)	1 (1.0)
2	238 (84.7)	124 (66.7)	56 (54.9)
3	24 (8.5)	19 (10.2)	9 (8.8)
4	10 (3.6)	22 (11.8)	17 (16.7)
5	2 (0.7)	20 (10.8)	19 (18.6)
Family history of prostate cancer — no. (%)‡			
No	232 (82.6)	147 (78.6)	74 (71.8)
Yes	49 (17.4)	40 (21.4)	29 (28.2)

* IQR denotes interquartile range, and PSA prostate-specific antigen.
† Prostate Imaging Reporting and Data System (PI-RADS) scores range from 1 to 5, with higher scores indicating a higher cancer risk. Data were available for 186 participants with any prostate cancer and for 102 participants with clinically significant prostate cancer because one participant was unable to undergo magnetic resonance imaging owing to claustrophobia.
‡ Family history of prostate cancer was defined as any first- or second-degree relative with prostate cancer.

Table 2. Characteristics of the Cancers Detected and Those That Would Have Been Missed, with Stratification According to Polygenic Risk Score, PSA Level, and MRI Results.*

NCCN Cancer Classification	Polygenic Risk Score ≥90th Percentile	PSA Level >3 μg/Liter		Positive MRI Results†		PSA Level >3 μg/Liter and Positive MRI Results†	
	Cancer Detected (N=187)	Cancer Detected (N=69)	Cancer Missed (N=118)	Cancer Detected (N=61)	Cancer Missed (N=125)	Cancer Detected (N=30)	Cancer Missed (N=156)
	number of participants (percent)						
Low or very low	84 (44.9)	17 (24.6)	67 (56.8)	16 (26.2)	68 (54.4)	2 (6.7)	82 (52.6)
Intermediate favorable	63 (33.7)	24 (34.8)	39 (33.1)	17 (27.9)	46 (36.8)	6 (20.0)	57 (36.5)
Intermediate unfavorable	28 (15.0)	19 (27.5)	9 (7.6)	18 (29.5)	10 (8.0)	14 (46.7)	14 (9.0)
High or very high	12 (6.4)	9 (13.0)	3 (2.5)	10 (16.4)	1 (0.8)	8 (26.7)	3 (1.9)

* NCCN denotes National Comprehensive Cancer Network.
† Data were available for 186 participants with prostate cancer because one participant was unable to undergo magnetic resonance imaging (MRI) owing to claustrophobia. Positive MRI results were defined by the presence of a lesion with a PI-RADS score of 3 or higher.

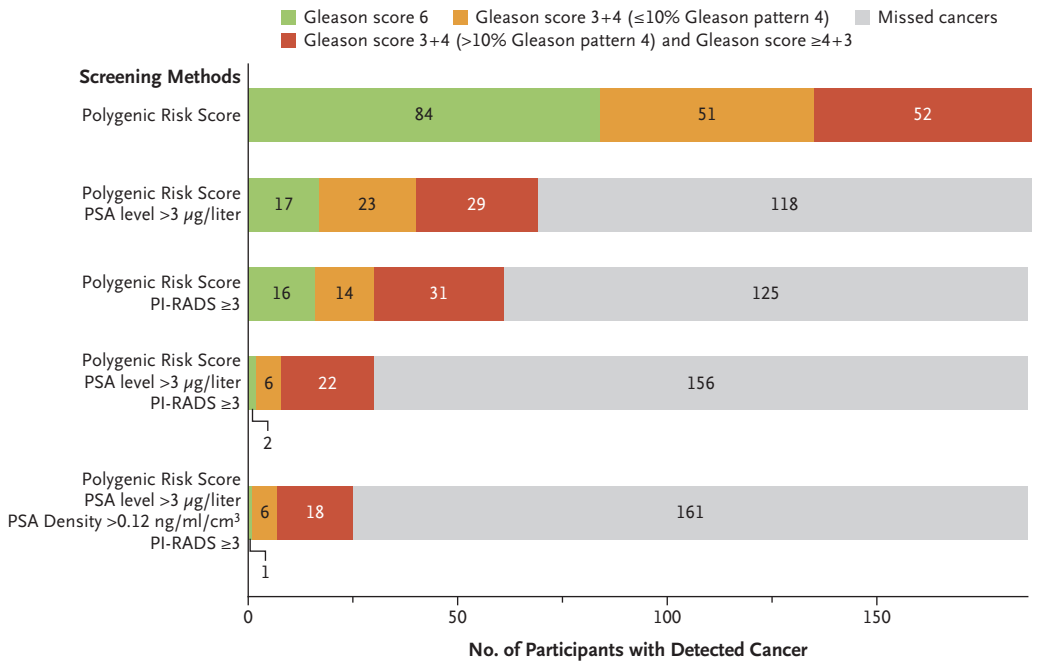

Figure 2. Participants with Detected Cancer, with Stratification According to Screening Method and Gleason Score.
Shown is the number of participants with prostate cancer detected with the use of polygenic risk score alone and polygenic risk score combined with prostate-specific antigen (PSA) level, with PI-RADS score on MRI, with both PSA level and PI-RADS score, and with PSA level, PSA density, and PI-RADS score. Participants with detected cancer are grouped according to Gleason score. Gleason pattern is the measure of how aggressive the cancer looks on microscopic examination; scores range from 1 to 5, with higher scores indicating a more aggressive appearance. For the groups that include PI-RADS score, the number of participants with cancer totals 186 of the overall 187 because one participant was unable to undergo MRI owing to claustrophobia.

The strongest-performing model included age, family history of prostate cancer, PSA level, and PI-RADS score. When combined with age and family history of prostate cancer, both the PSA level and PI-RADS score were strongly associated with biopsy outcome and provided good discrimination with respect to any prostate cancer (AUC, 0.69) and clinically significant prostate cancer (AUC, 0.78) (Table S7). Further stratification according to polygenic risk score (i.e., 90th vs. 99th percentile) was not associated with biopsy outcome and added little to any of the models described.

ABSOLUTE RISK

The 10-year absolute risk of prostate cancer in relation to polygenic risk score percentile, with stratification according to age and family history of prostate cancer, is shown in Figure 3. Among the 6393 participants who had a polygenic risk score calculated, almost all those with a polygenic risk score in the 90th percentile or higher had a 10-year absolute risk above 3.8%, a cutoff that was derived from a threshold range of 3.5 to 4% that was shown in a previous study to yield the greatest number of quality-adjusted life-years gained.[27] Other participants with a 10-year absolute risk above the cutoff but a polygenic risk score in a lower percentile had a family history of prostate cancer. These findings highlight the fact that polygenic risk score does not replace known risk factors but supplements them in risk stratification.

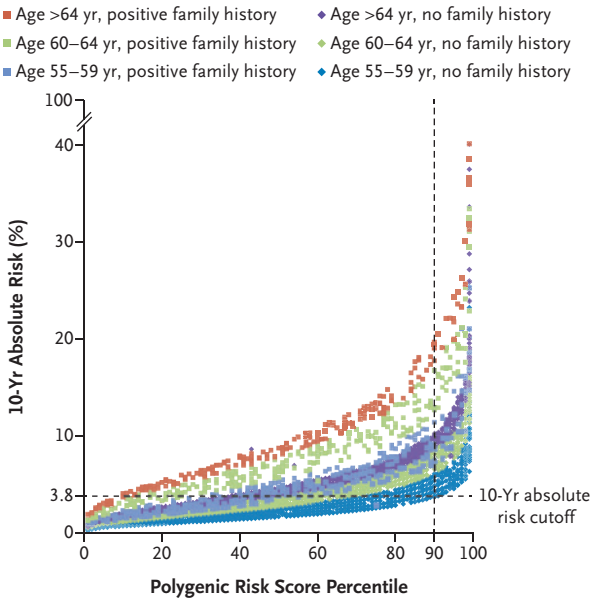

Figure 3. Absolute Risk of Prostate Cancer.

Shown is the 10-year absolute risk of prostate cancer (estimated from the iCARE22 algorithm) for all 6393 participants who agreed to screening and for whom we calculated a polygenic risk score, stratified according to participant age, family history of prostate cancer, and polygenic risk score. A threshold of 3.5 to 4% for the 10-year absolute risk of prostate cancer has been suggested as generating the greatest number of quality-adjusted life-years from risk-based screening and was used to calculate the 3.8% cutoff in this study.

OVERDIAGNOSIS

We estimated that 39 participants (20.8%; range, 9.7 to 33.9) 55 to 74 years of age (accounting for participants remaining in screening for up to 5 years) with a polygenic risk score in at least the 90th percentile and with screen-detected cancer would have overdiagnosed disease (i.e., their screen-detected prostate cancer would take longer than their remaining lifetime to progress to clinical cancer). Had only a PSA threshold of more than 3.0 μg per liter been used for screening, 12 of 69 participants (weighted average percentage, 17.2%; range, 4.0 to 25.0) would have had overdiagnosed cancer, and had only a lesion with a PI-RADS score of 3 or higher been used, 10 of 61 participants (weighted average percentage, 15.6%; range, 7.0 to 21.0) would have had overdiagnosed cancer (Tables S8, S9, and S10). Had the prostate cancer diagnostic pathway that is standard in the United Kingdom been used for the 187 participants in whom cancer was diagnosed, a cancer diagnosis would have been missed in 17 of the 40 participants (42.5%) with disease classified as intermediate unfavorable risk or higher and would have been avoided in 82 of the 84 participants (97.6%) with cancer classified as low or very low risk.

ADVERSE EVENTS

One participant (0.2%) had sepsis after biopsy and was hospitalized to receive intravenous antibiotics. Two participants (0.4%) had a urinary tract infection 7 days or less after biopsy that was treated with oral antibiotics. One participant (0.2%) underwent temporary catheterization immediately after biopsy (Table S12).

DISCUSSION

Our results show that offering targeted screening to participants in at least the 90th percentile of genetic risk distribution as determined by a polygenic risk score resulted in the detection of prostate cancer warranting clinical management in 55.1% of these participants and radical treatment in 21.4% of those with cancer classified as unfavorable intermediate risk or higher. The current diagnostic pathway for suspected prostate cancer in the United Kingdom involves either a high PSA level (>2.5 μg per liter in persons <50 years of age, >3.5 μg per liter in persons 50 to 59 years of age, or >4.5 μg per liter in persons 60 to 69 years of age) or an abnormal digital rectal examination[18] followed by a referral for MRI. If a lesion is present or there is other clinical concern, biopsy is indicated. If the participants of the BARCODE1 study had followed this pathway, prostate cancer would have been missed in 42.5% of those with clinically significant disease, and a prostate cancer diagnosis would have been avoided in 97.6% of those with clinically insignificant disease.

Of note, prostate cancer was detected at biopsy in 40.0% of the participants who underwent the procedure, and 55.1% of these participants had a Gleason score of 7 or higher. In the ERSPC, the decision to perform biopsy was based on PSA level, and 35.5% of the participants who underwent biopsy were found to have prostate cancer.[28] In the BARCODE1 study, when we only included in the analysis participants with a polygenic risk score in the 90th percentile or higher and a PSA level greater than 3.0 μg per liter, we found that 75.4% of the participants with detected cancer had a Gleason score of 7 or higher. In the ERSPC, the positive predictive value of a PSA level greater than 3.0 μg per liter with respect to having biopsy-confirmed prostate cancer was 24.1%.

The STHLM3 (Stockholm 3) screening study compared PSA level alone (with a threshold of ≥3 μg per liter) with a combination of plasma biomarkers, 232 risk SNPs, and clinical variables for detecting prostate cancer.[11] In that study, the AUC for PSA level alone was 0.56; the AUC for PSA level and the additional risk factors was 0.74. In the BARCODE1 study, the AUC was 0.78 when age, family history of prostate cancer, PI-RADS score, and PSA level were combined. In the STHLM3 study, assessment of the contribution of the SNP profile to the screening model was difficult[11]; in contrast, our study used polygenic risk score alone as a risk-stratification tool.

Studies have shown that combining multiparametric MRI with targeted biopsies of lesions improves detection of clinically significant prostate cancer (i.e., Gleason score ≥7).[6,7,29,30] However, real-world data indicate that up to 25% of men with no lesion detected on MRI may have clinically significant prostate cancer on biopsy.[31] We identified clinically significant prostate cancer in participants without MRI-detected lesions, which suggests that for those with a polygenic risk score in at least the 90th percentile, prostate biopsy warrants consideration regardless of MRI outcome. However, nearly half the cancers diagnosed on the basis of biopsy alone would be predicted to have a Gleason score of less than 7, so there is a trade-off between minimizing the odds of overdiagnosis and missing clinically significant prostate cancer. Adding PSA density to our models did not improve detection of clinically significant prostate cancer.[26] The biologic features of prostate cancer may differ between persons who have a genetic predisposition to prostate cancer and those who do not. Further research is needed to determine the link between specific SNPs and aggressiveness of prostate cancer.[32]

The IMPACT (Identification of Men with a Genetic Predisposition to Prostate Cancer: Targeted Screening in Men at Higher Genetic Risk and Controls) study targeted prostate cancer screening in persons with pathogenic variants in *BRCA1* and *BRCA2*. When a PSA level of more than 3.0 μg per liter was used to indicate biopsy, the positive predictive value of PSA screening was 36% overall and 48% among carriers of *BRCA2* in the IMPACT study, as compared with 61.1% in the BARCODE1 study.[33] A higher percentage of participants with clinically significant prostate cancer was reported in the IMPACT study (61%) than in our study (55.1%). The results of the IMPACT study led the European Association of Urology to recommend screening in carriers of *BRCA2* beginning at 40 years of age.[34]

A study in the United Kingdom showed that the use of a 10-year absolute risk of 3.5 to 4% as the threshold for the development of prostate cancer in risk-based screening yields the greatest

number of quality-adjusted life-years gained.[27] The BARCODE1 study showed that almost all the participants with a polygenic risk score in the 90th percentile or higher, those with a family history of disease, and those of older age and with a polygenic risk score not in the lower percentiles had an absolute risk above a threshold of 3.8% (Fig. 3). This finding supports the use of polygenic risk score together with established risk factors in screening for prostate cancer. Further study will be necessary to determine whether polygenic risk score could identify persons at low risk who may benefit from a less-intensive screening regimen and those in whom further evaluation is warranted if the PSA level is below commonly accepted thresholds and in whom a biopsy is indicated if MRI findings are nonsuspicious. A polygenic risk score can be determined once in a person's lifetime because it does not change with age. In our study, all the men were 55 years of age or older, and further evaluation of the timing of polygenic risk score and subsequent screening algorithms will be needed to assess the trade-off of benefits, harms, and cost-effectiveness.

Our estimate of overdiagnosis (15.6 to 20.8%) is similar to the overdiagnosis estimates in two PSA-based screening studies.[24,35] Further screening will be key in ascertaining the incidence of prostate cancer over time among currently unaffected persons at high risk. Follow-up of the whole cohort is continuing in order to evaluate the prostate cancer incidence and tumor characteristics among the participants with polygenic risk scores below the 90th percentile. Such data would allow an evaluation of the economic and clinical effect of using a polygenic risk score as a risk-stratification tool within a prostate cancer screening program.

Good evidence exists that active surveillance manages indolent prostate cancer at relatively low cost while detecting progression at a curable stage.[36] Approximately 30 to 40% of persons undergoing active surveillance have disease progression, with those at higher genetic risk more likely to be in this category.[37] All but one of the participants with prostate cancer with a Gleason score of 6 in our study (comprising 44.9% of the participants with detected prostate cancer) are under active surveillance. Although some overdiagnosis occurred, overtreatment of indolent disease did not occur.

This study has several limitations. First, 22.2% of the persons who were invited expressed an interest in participating. The information that was provided to potential participants emphasized the appropriateness of prostate biopsy in those identified as high-risk. Reluctance to undergo biopsy was the predominant reason for participants choosing to withdraw, both before and after MRI. Uptake of and adherence to the screening regimen were probably heavily affected by the coronavirus disease 2019 pandemic, which coincided with the rollout of the BARCODE1 study.

Second, this homogeneous population comprised self-selected participants; participants were highly educated and largely from professional occupations. All the participants were of European ancestry because of the limitations of the polygenic risk score at the time of study design and therefore were not representative of the general population in the United Kingdom (Table S11). Genomewide association studies have provided data on risk SNPs across diverse ancestral groups, and research focused on the use of genetic ancestry-specific polygenic risk score for risk-based screening is in progress. Our study provides a framework on which to build further research on the role of genetic risk in screening for cancer in persons of non-European ancestries. These persons include those at higher risk for prostate cancer such as persons of Black African and Caribbean ancestry, whose lifetime risk in the United Kingdom is quoted as 1 in 4 as compared with 1 in 8 among persons of European ancestry.[4] Future work will need to consider the role of both rare and common genetic variants in understanding genetic risk of prostate cancer in all ancestries.

A third limitation is the potential for selection bias among persons with a family history of prostate cancer; such persons may have been more likely to accept the invitation to join the study. However, only approximately 20% of the participants reported having a family history of prostate cancer, which indicates that this variable does not seem to have had a major effect on screening uptake in this study.

In a population-based prostate cancer screening program involving participants in the top decile of risk as determined by a polygenic risk score, the percentage found to have clinically significant prostate cancer (Gleason score ≥7)

warranting treatment in accordance with national guidelines was higher than the percentage that would have been identified with the use of PSA or MRI. To evaluate fully the implementation of polygenic risk score alongside established risk factors in a national screening program, further research is required, including research into the recommended age at which to obtain a polygenic risk score, tests of replication in persons of non-European ancestry, and an evaluation of economic effects.

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AUTHOR INFORMATION

Jana K. McHugh, F.F.R.C.S.I.,[1,2] Elizabeth K. Bancroft, Ph.D.,[1,2] Edward Saunders, M.Sc.,[1] Mark N. Brook, Ph.D.,[1] Eva McGrowder, Ph.D.,[1] Sarah Wakerell, M.Sc.,[1] Denzil James, M.Sc.,[1,2] Reshma Rageevakumar, M.Sc.,[1] Barbara Benton, R.N.,[1,2] Natalie Taylor, R.N.,[1,2] Kathryn Myhill, R.N.,[1,2] Matthew Hogben, R.N.,[1,2] Netty Kinsella, Ph.D.,[2,3] Aslam A. Sohaib, F.R.C.R.,[2] Declan Cahill, F.R.C.S.,[2] Stephen Hazell, F.R.C.Path.,[2] Samuel J. Withey, M.B., B.S.,[2] Naami Mcaddy, M.B., B.S.,[2] Elizabeth C. Page, M.Sc.,[1,2] Andrea Osborne,[1,2] Sarah Benafif, Ph.D.,[1,4] Ann-Britt Jones, M.R.C.P.,[1,2] Dhruv Patel, F.R.C.R.,[5] Dean Y. Huang, M.D.,[5] Kaljit Kaur, R.N.,[2] Bradley Russell, R.N.,[2] Ray Nicholson, R.N.,[2] Fionnuala Croft, R.N.,[2] Justyna Sobczak, R.N.,[2] Claire McNally, R.N.,[2] Fiona Mutch, R.N.,[2] Samantha Bennett,[2] Lenita Kingston,[2] Questa Karlsson, Ph.D.,[1] Tokhir Dadaev, M.Sc.,[1] Sibel Saya, Ph.D.,[1,6] Susan Merson, B.Sc.,[1] Angela Wood,[1] Nening Dennis, B.Sc.,[1,2] Nafisa Hussain, B.Sc.,[1] Alison Thwaites,[1] Syed Hussain, B.Sc.,[1] Imran Rafi, Ph.D.,[7] Michelle Ferris, M.D.,[8] Pardeep Kumar, F.R.C.S.,[2] Nicholas D. James, Ph.D.,[1,2] Nora Pashayan, Ph.D.,[9] Zsofia Kote-Jarai, Ph.D.,[1] and Rosalind A. Eeles, Ph.D.[1,2]

[1] Institute of Cancer Research, London; [2] Royal Marsden NHS Foundation Trust, London; [3] Translational Oncology and Urology Research Center for Cancer, Society, and Public Health, King's College London, London; [4] University College London Hospitals NHS Foundation Trust, London; [5] InHealth Limited, InHealth Group HQ, High Wycombe, United Kingdom; [6] University of Melbourne, Melbourne, VIC, Australia; [7] St. George's University of London, London; [8] Lane End Medical Group, London; [9] University of Cambridge, Cambridge, United Kingdom.

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