The BARCODE1 Pilot : a feasibility study of a screening programme utilising germline SNPs to target men with increased genetic risk of prostate cancer

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Abstract

Objectives:
To assess the feasibility and uptake of a community based prostate cancer (PrCa) screening programme selecting men according to their genetic risk of PrCa.
To assess the uptake of PrCa screening investigations by men invited for screening.
The uptake of the pilot study would guide the opening of the larger BARCODE1 study recruiting 5000 men.

Subjects and Methods: Healthy males aged 55-69 years were invited to participate via their General Practitioners (GPs). Saliva samples were collected via mailed collection kits. After DNA extraction, genotyping was conducted using a study specific assay. Genetic risk was based on genotyping 130 germline PrCa risk single nucleotide polymorphisms (SNPs). A polygenic risk score (PRS) was calculated for each participant using the sum of weighted alleles for 130 SNPs. Study participants with a PRS lying above the 90th centile value were invited for PrCa screening by prostate MRI and biopsy.

Results: Invitation letters were sent to 1434 men. Overall study uptake was 26% (375/1436). 87% of responders were eligible for study entry. DNA genotyping data were available for 297. Twenty-five participants were invited for screening. After exclusions due to medical comorbidity/ invitations declined, 18 of 25 men (72%) underwent MRI and biopsy of the prostate. There were 7 diagnoses of PrCa (38.9%). All cancers were low-risk and were managed with Active Surveillance.

Conclusion: The BARCODE1 pilot has shown this community study in the UK to be feasible, with an overall uptake of 26%. The main BARCODE1 study is now open and will recruit 5,000 men. The results of BARCODE1 will be important in defining the role of genetic profiling in targeted PrCa population screening.

Keywords: prostate cancer, SNPs, screening**,** precision medicine, GWAS.

Introduction

In common with other complex diseases, the genetic heritability of prostate cancer (PrCa) is composed of both rare, high to moderately penetrant variants conferring a high risk of disease (e.g. *BRCA2* mutations), and commonly occurring single nucleotide variants (SNVs) that confer risks of lower magnitude. With the advent of the genome wide association study (GWAS) and the increasing numbers of cases and controls included in such studies, PrCa GWAS and meta-analyses have identified more than 200 loci associated with PrCa development (1-3). Most of these SNVs are commonly occurring single nucleotide polymorphisms (SNPs; i.e. minor allele frequency (MAF) ≥5%) and although each locus is associated with a low to moderate per allele odds ratio, the genetic risk increases with increasing number of risk alleles in a person's germline DNA. (4) The currently known PrCa susceptibility loci explain an estimated 34-43% of the familial relative risk of PrCa (2, 3, 5, 6).

There are very few population PrCa screening programmes due to the lack of a test with adequate sensitivity and specificity required for large scale population screening. The use of the prostate specific antigen (PSA) blood test was investigated in two large randomised screening studies: the Prostate, Lung, Colorectal and Ovary (PLCO) study and the European Randomised Study of Screening for Prostate Cancer (ERSPC) (7, 8). Although long term follow-up in the ERSPC studies has shown a survival benefit (absolute reduction of 13 PrCa deaths per 10,000 men), the complications of prostate biopsies, high rate of false positive results (10 % in PLCO and 18% in ERSPC) as well as over-diagnosis of indolent PrCa has led to caution around the use of PSA testing.

Guidelines from national screening programmes such as the USPSTF (US Preventive Services Task Force) have fluctuated from advising against PSA screening (2012) to recommending that men make an individualised decision regarding PSA testing in conjunction with their clinician (for those aged 55-69 years)(9, 10). In the UK, the National Screening Committee (NSC) recommends against universal PSA screening.

To our knowledge, no prospective studies utilising genetic profiling to stratify men in the population according to their PrCa risk have been performed. The use of a genetic test utilising the known PrCa risk SNPs could allow PrCa screening to be targeted to men at high risk of PrCa development. Germline DNA for genotyping requires a one-off collection, usually in the form of a blood draw or saliva sample. Using the genotyping data, a polygenic risk score (PRS) can be calculated for an individual to estimate their risk of PrCa development relative to the average population risk. When used at scale, a genotyping test is relatively cheap and can be carried out ahead of likely disease onset to identify men with a high PRS who may benefit from screening starting at a pre-determined timepoint. In parallel, men with a low PRS may avoid the potential complications of invasive tests.

Utilising the known PrCa risk loci, the relative risk (RR) of PrCa for European ancestry men in the top 1% of the PRS distribution is 5.7 compared with the average risk of men in the general population; this level of risk is in the range of that associated with *BRCA2* mutations. (11) For men in the top 10% of PRS distribution the RR is 2.7 (2).

The use of PRS stratification within a PrCa screening programme has been shown through modelling studies to reduce the level of over-diagnosis of indolent disease through screening. (12) In the breast cancer setting, using genetics to take a risk-stratified approach to refine screening also reduces the rate of over-diagnosis and improves cost-effectiveness of screening. (13)

The BARCODE1 study (NCT03857477) is enrolling men of European ancestry from the community via their General Practitioners (GP) to undergo a germline genetic profile test utilising 130 PrCa risk SNPs. Men in the top 10% of the study population's genetic risk distribution are offered screening with MRI of the prostate followed by systematic and targeted biopsy. As the PRS used in BARCODE1 is based on SNPs discovered in European populations, there is a portability problem across different populations. Although multi-ethnic

GWAS have demonstrated that many PrCa risk SNPs are shared between populations, the risk associated with a variant may vary according to ethnicity.(3) Additionally, some PrCa risk SNPs will be population specific. Studies are underway to investigate the use of genetic profiling in PrCa screening in other ethnic groups. (14)

This is the first prospective study to assess the utility of genetic profiling in a community setting to guide PrCa screening and aims to recruit a total of 5000 men. Here, we report the results of the BARCODE1 pilot, which was set up as a feasibility study to examine the acceptability of the study to men in the UK community prior to opening the main BARCODE1 study.

Methods

Trial Design

The BARCODE1 pilot was a feasibility study aiming to recruit 300 participants prior to the launch of a larger trial with 5000 participants. The study was coordinated and managed by the Oncogenetics Team at The Institute of Cancer Research, UK. Recruitment was carried out via 7 GP centres in London, and participants were invited into the study by letter.

Eligible responders were sent a consent form to sign and return to the study team. They were also sent a saliva collection kit to provide a saliva sample for DNA extraction and genotyping (Figure 1). Participants found to lie in the top 10% of the PRS distribution were offered a MRI of the prostate followed by prostate biopsy. Participants with negative biopsies were followed up with annual PSA measurement and repeat biopsies were performed if there was a significant PSA rise (study protocol in supplementary material).

Trial Registration

This study was reviewed by the London-Chelsea Research Ethics Committee (REC) under reference number: 15/LO/1992 and was approved to be conducted in NHS England by the Health Research Authority under reference number: 147536.

Participants

GP sites acted as recruiting centres. Practice records were reviewed to identify men aged 55-69 years meeting study eligibility criteria. A Participant Information Sheet (PIS) and health questionnaire was sent to all suitable men and responses screened to ensure eligibility. Participants were required to have no history of PrCa, no prostate biopsy within 12 months, no contra-indications to MRI or prostate biopsy, and to be of European ethnicity. Responders meeting the criteria were requested to complete a postal saliva (DNA) sample.

Sample Size

For the main BARCODE1 study, a sample size of 5000 men will be required to identify 500 men within the top 10% of the PRS distribution, who will undergo screening. The pilot study was planned with the aim of recruiting 300 men, with approximately 30 in the top 10% of PRS distribution. This sample size was chosen pragmatically assuming recruitment of 100 men from each of the (initial) 3 GP centres. A further 4 centres were added during the course of the pilot study to complete recruitment due to a lower than anticipated recruitment rate. All initial study procedures including invitations to participate, informed consent and saliva collection were carried using the postal system.

DNA Extraction and Genotyping

DNA extraction from saliva was carried out externally by Tepnel Pharma Services, Livingston, UK. Extracted DNA was sent to Affymetrix® (part of Thermo Fisher Scientific, Massachusetts, USA) for genotyping using a custom high throughput “genotyping by sequencing” assay (Eureka myDesign Genotyping Panel; https://tools.thermofisher.com/content/sfs/brochures/Eureka_Genotyping_Solution_datasheet.pdf).(15) At the time of BARCODE1 study setup, 147 index PrCa susceptibility SNPs had been reported in European ancestry populations (2). Our assay design aimed to capture all of these known variants, however 17 index SNPs could not be successfully designed or failed quality control (QC) using this technology, whilst a further 3 index variants needed to be substituted for a suitable proxy variant to achieve inclusion. Our final genotyping panel therefore consisted of 130 European ancestry PrCa risk SNPs (Supplementary Table). Additional QC was performed on the raw computer assigned genotype calls, through manual examination of cluster plots using Eureka™ Analysis Suite (https://www.thermofisher.com/uk/en/home/life-science/microarray-analysis/microarray-analysis-instruments-software-services/microarray-analysis-software/eureka-analysis-suite.html).

Statistical Methods

We calculated a PRS for each participant based on the sum of risk alleles for the 130 PrCa risk loci, weighted by their per-allele log odds ratio (formula in supplementary material). In instances where a variant failed genotype QC within a specific individual, to reflect the probability of their carrying the risk allele for that variant, missing genotype(s) were assigned a risk allele count corresponding to the population risk allele frequency for the variant, doubled for autosomal variants.

The PRS mean and standard deviation for the BARCODE1 pilot cohort were used to calculate the PRS threshold at the 90th centile based on a normal distribution (Supplementary material). Using this method to calculate the 90th centile accounts for the potential large rise in PRS value at the extremes of the distribution in the small sample size. BARCODE1 pilot study participants with a PRS above the 90th centile were identified for PrCa screening.

Screening Procedures

Participants received a letter informing them of the outcome of genotyping and whether their PRS fell in the top 10% of the study PRS distribution. Those found to have a PRS above the the 90th centile were invited to undergo PrCa screening at The Royal Marsden Hospital (RMH). Screening involved a multi-parametric MRI scan of the prostate and a prostate biopsy. Baseline PSA level was measured but did not alter management. The MRI included T2-weighted, diffusion-weighted and dynamic contrast (gadolinium) enhanced images. Scans were performed either at 3T with endorectal coil or at 1.5T with an external phased array coil and reported by a specialist uro-radiologist. Prostate lesions identified were scored 1-5 according to PIRADS (Prostate Imaging Reporting and Data System) as developed by the European Society of Urogenital Radiology (16). A score of 1 indicated clinically significant disease is highly unlikely to be present while a score of 5 indicated clinically significant cancer is highly likely to be present.

MRI was followed by prostate biopsy. A systematic 12-core transrectal ultrasound biopsy was carried out by the study urologist. If a lesion/ lesions were identified on DW-MRI, additional targeted sampling was undertaken (Koeils Urostation™). Prostate biopsy samples were examined by a specialist uro-pathologist at RMH, and reported as per the 2014 International Society of Urological Pathologists guidelines.

Outcomes

Response rates across all recruiting centres were examined, as well as uptake of screening tests (MRI and biopsy) in men who were invited for screening based on their PRS. Outcomes from screening include the number of cancers diagnosed (clinically significant and insignificant), MRI lesions detected and biopsy-related complications.

An additional sub-study is ongoing to examine the psychosocial impact of screening in this group of high-risk individuals, the results of which will be reported separately.

Results

Study Recruitment

Recruitment to the BARCODE1 pilot commenced in April 2016 and completed in April 2018. Initially, 3 GP centres were involved. Four more sites were added to the study in April 2017 to increase recruitment rate and complete the pilot study.

GPs screened the medical records of 1,802 men registered at their practices; 1,436 potentially eligible men (80% of those screened) were sent a study invitation letter, which included the study PIS and a health questionnaire. The health questionnaire was used to exclude men who did not meet study eligibility criteria, as well as those with any co-morbidities that would make the risk of prostate biopsy unacceptable.

Of 1,436 men invited to the study, 375 men responded to the invitation letter giving a study uptake rate of 26% (range: 13-47%, Table 1) of whom 329 (88%) were eligible for study entry (Figure 2). Reasons for exclusion from study entry included medical co-morbidities and non-European ethnicities.

Saliva collection kits were posted to 328 eligible participants with a study consent form. 307 saliva samples were returned, giving a return rate of 94%; 21 participants withdrew from the study after providing a saliva sample and 1 participant withdrew prior to providing a saliva sample, giving an overall withdrawal rate of 6.7% of eligible responders.

Participant Characteristics and Genotyping

Mean age of study participants at the time of consent was 61 years (range 55-69). DNA was extracted for 303 participants whose saliva sample was returned before the cut-off date (15th April 2018) for the pilot study. Of 303 saliva samples that underwent DNA extraction, one sample had a low DNA yield and could not be genotyped (further saliva was collected later from this participant). Genotyping was therefore carried out for 302 samples. 17 samples (5.6%) failed QC processes due to a SNP call rate of <90%; for 12 of these, a repeat saliva sample was subsequently returned by the participant and passed genotyping QC. Therefore, 297 samples underwent successful genotyping. Mean genotype call rate across the 130 SNPs for all study participants was 99.6% and median 100% (in total 162 of 38,610 genotypes across all 297 samples failed genotyping QC).

PRS Results

The PRS for 297 men in the BARCODE1 pilot ranged from 8.42-12.21 (median 10.34). The mean (10.33) and standard deviation (0.64) were used to calculate the 90th centile value, which was 11.15 (Figure 3). Using this threshold value, 26 participants were eligible for screening based on their PRS. The 271 men whose PRS fell in the bottom 90% were not eligible for screening and received standard care through their GP.

To ensure that participants in the BARCODE1 pilot were representative of the general population, we compared the PRS distribution to one calculated in another UK genotyping dataset taken from the Prostate Testing for Cancer Treatment (ProtecT) trial. (17) There was no significant difference in the PRS distribution (Supplementary Figure 1; P=0.92).

Uptake of Screening by Men in the Top 10% of PRS Distribution

Of 26 participants identified to be in the top 10% of the PRS distribution, 7 men did not proceed with PrCa screening: one patient died of a non prostate-related cause after entering the study, 2 were lost to follow-up and 4 men withdrew when offered PrCa screening. An 8th participant underwent MRI but did not proceed to biopsy due to persistent sterile pyuria. Therefore, the overall uptake of PrCa screening was 72% (18 of 25 living eligible participants).

Outcomes of Prostate Cancer Screening

MRI of the prostate (18 with endorectal coil at 3T, 1 with phased array coil at 1.5T) followed by systematic (±targeted sampling) biopsies was carried out for 18 participants. PSA was measured prior to MRI. The mean PSA for 19 men undergoing MRI was 1.60 ng/ml (range 0.3-5.8 ng/ml).

Assigned PIRADS scores were 1-2 in 10 participants (53%), PIRADS 3 in 5 participants (26%) and PIRADS 4 in 4 participants (21%). There were no PIRADS 5 lesions detected (Table 2).

Biopsy results were available for 18 men. One man did not proceed to biopsy due to persistent sterile pyuria for which he was referred for urological investigations. Table 3 displays biopsy outcomes. All initial screening biopsies were performed via the transrectal route except for one (Participant 2 in Table 3), which was carried out via the transperineal route to allow adequate sampling of small bilateral lesions detected on MRI.

PrCa was diagnosed in 6 of 18 participants (33%) who underwent an initial screening biopsy; 4 of these had a target lesion identified on MRI (3 PIRADS 4 lesions and 1 PIRADS 3 lesion) while 4 participants with identified target lesions (3 PIRADS 3 and 1 PIRADS 4) were negative on biopsy. The mean maximum cancer core length (MCCL) in the 4 MRI identified lesions was 1.2mm with a mean pre-biopsy PSA of 1.6 ng/ml, and in the 2 cancers not identified on MRI, the mean MCCL was 1mm with a mean pre-biopsy PSA of 1.1 ng/ml.

In the remaining 12 participants, two were diagnosed with atypical small acinar proliferation (ASAP) and high-grade prostatic intra-epithelial neoplasia (HGPIN); a repeat MRI and biopsy was carried out for both at 6 months as per trial protocol. The participant with ASAP was diagnosed with Gleason 3+4 PrCa (MCCL 1.5mm, 1%) and the participant with HGPIN had benign findings. All cancers were discussed in the RMH uro-oncology multidisciplinary team meeting and management by active surveillance (AS) was recommended for all 7 cases (Table 4).

Incidental Findings and Post Biopsy Complications

There was one case of an incidental finding reported on MRI of the prostate that required further investigation, resulting in a diagnosis of low-grade B cell non-Hodgkin's lymphoma. An uncomplicated lower urinary tract infection was diagnosed in 2 out of 18 men (11%) who underwent a prostate biopsy. Both cases were managed successfully with oral antibiotics. There were no other post-biopsy complications.

Post Biopsy Follow-Up

Men diagnosed with PrCa in this pilot study (n=7; 6 initially, 1 at follow-up) are currently undergoing follow-up in the RMH uro-oncology clinic. For the 11 participants who had a benign biopsy result, study follow up will continue with annual PSA measurement for at least 5 years with repeat MRI and biopsy if the PSA rises above the protocol set threshold for repeat biopsy.

Cancer registries will be reviewed and data will be collected for all men enrolled in the study for a minimum of 10 years to determine cancer incidence and mortality.

Discussion

The BARCODE1 pilot study was successful in demonstrating the acceptability and feasibility of community based PrCa screening guided by germline genetics in the UK. There was good uptake by men invited by their GPs, and a high level of interest from primary care centres wishing to participate after the pilot transitioned to the larger main study. Uptake of PrCa screening by men offered it was 72% which is comparable to the uptake of national screening programmes such as the bowel and breast cancer screening programmes in England (59-72%) (18, 19).

The BARCODE1 main study has now commenced recruitment with the aim of genotyping 5000 men in the community and in turn, offer screening to those lying in the top 10% of the PRS distribution. The PRS threshold for screening within BARCODE1 was chosen pragmatically so as to lead to a feasible number of men that could be offered screening procedures within the study. It was also guided by the latest scientific estimates that men of European ancestry with a PRS between the 90th and 99th centiles have a 2.7-fold higher risk of developing PrCa compared with the population average. This is similar to the PrCa risk of a man with a first degree family history and for whom guidance advises PrCa screening is considered. (20)

A 26% study uptake rate by invitees was comparable to the PROFILE pilot screening study reported by our team in 2016 (21), which had an uptake of 12.8% in men with a family history of PrCa. The uptake in the BARCODE1 pilot study is lower than that reported in the ProtecT (17) study that invited participants via their GPs for PSA based screening and had an uptake of 36%. This may partly be explained by one of the GP sites in our study having a large proportion of patients of non-European ethnicities (in keeping with the local population demographic) who were not eligible for study entry; unfortunately patient ethnicity is not recorded routinely at some practices therefore some study invitations would have been sent to men who were not eligible and therefore would not have responded to the study invitation.

To offset the lower than expected uptake, an additional 4 GP sites opened recruitment, and for the main study a large network of over 70 GP sites will be recruiting. By expanding the main study to a large number of GPs and with modifications in response to participants' feedback, such as reducing the size of the information pack sent out with study invitations, we may find that uptake increases in the main BARCODE1 study.

In this pilot, 39% (7/18) of men screened were diagnosed with low Gleason grade (Gleason 3+3 or 3+4), low stage (no nodal involvement on imaging) PrCa amenable to management by AS. The rate of progression to disease that requires treatment could not be evaluated because of the short follow-up in the pilot phase of the study (mean 4.5 months; range 1-11 months). Management with AS (regular PSA tests, interval MRI scans and repeat biopsies), although resource intensive, potentially offers early curative treatment options in this high-risk relatively young population.

The PRS used in BARCODE1 includes 130 PrCa risk SNPs that associate with both aggressive and non-aggressive PrCa. There have been no risk loci identified thus far that are specific to aggressive PrCa. Despite the lack of predictive biomarkers for aggressive disease, a recent pan-ancestry meta-analysis of PrCa GWAS data found that approximately a third of aggressive PrCa cases occurred in men whose genetic risk lay in the top 10% of the risk distribution. (3) Therefore, using a PRS based approach to target screening could identify a subset of men in the population in which a substantial proportion of aggressive PrCa cases will develop. The results of the larger BARCODE1 study and long term follow-up will examine this further.

Apart from identifying men at risk of PrCa, some of whom will develop aggressive disease, utilising a PRS for PrCa screening may reduce the level of over-diagnosis of indolent disease which has prevented the adoption of PSA based population screening (22). Over-diagnosis is defined as the 'detection by screening of tumours that would not have presented clinically in

a person's lifetime in the absence of screening' (12). In the context of PSA based PrCa screening, the proportion of over-diagnosed cases has been shown to be inversely proportional to PRS (12). In a retrospective analysis of a PrCa PRS in 17,000 men in the UK, there was a 56% reduction in over-diagnosis between the lowest and highest PRS quartiles when using PSA for screening. Therefore, utilising a PRS as part of a program to target screening to men in the top quartile or upper decile of the genetic risk distribution has the potential to reduce over-diagnosis compared with unselected PSA screening. This in turn would spare men at low genetic risk from undergoing screening procedures (12, 23, 24).

Although over-diagnosis is unavoidable in most screening programmes, attempts to minimise this by utilising a targeted approach based on genetic risk while still balancing the identification of high-risk cancers will be investigated in the BARCODE1 study. With the increased acceptability and safety of using AS, study participants whose low grade PrCa doesn't progress can avoid the complications of radical treatment while those who experience disease progression can be treated promptly.

As the BARCODE1 study PRS is based on SNPs identified in European populations, study recruitment was restricted to men of European ethnicity. Dedicated studies in populations of other ethnicities are in progress to establish population-specific genotyping panels and thresholds for PrCa screening. In a recent multi-ancestry PrCa GWAS meta-analysis reported by Conti and colleagues(3), case-control data was analysed from European, African and East Asian ancestry men. This analysis confirmed that many PrCa loci are shared across populations though the risk associated with PRS varied between populations. The absolute risk of PrCa in men lying in the top decile of the genetic risk distribution was highest in men of European and African ancestry at 38%, while the top decile in East Asian ancestry men had the lowest risk of 26%. Identifying this ancestry related variation in genetic risk will be useful in the development of tailored approaches to PrCa risk assessment in different populations.(3) In this vein, one of the screening arms in the ongoing PROFILE screening study

(NCT02543905) is recruiting men of African and Afro-Caribbean ancestry to investigate the relationship between a genetic profile and outcome at prostate biopsy during screening. Several international efforts are also trying to identify ethnic-specific risk SNPs and assess generally the utility of the polygenic risk scores currently in use (3, 25). These will help guide the development of a cross-ethnic PrCa screening programme in diverse populations. (26-28).

BARCODE1 is the first prospective study to utilise a germline SNP profile to target PrCa screening in a community based setting. The STOCKHOLM3 study, (29) reported in 2015, was the first large prospective and population based PrCa screening study that assessed a targeted approach to screening. The study utilised a screening model combining plasma protein biomarkers (including PSA), 232 risk SNPs and a set of defined clinical variables (e.g. age, family history) and compared this with PSA measurement alone (≥3ng/ml) (29). Although the sensitivity for the detection of high risk PrCa was significantly improved with the STHLM3 model (AUC 0.74 vs 0.56), the value of the SNP profile within the larger model was difficult to ascertain. Since this study was reported, the STHLM3 model has been combined with MRI targeted biopsies in a prospective study comparing it with PSA screening and reported a 69% reduction in over-diagnosis while maintaining the sensitivity for the detection of significant PrCa.(30) By examining the role of targeting screening using only a germline SNP profile in BARCODE1, the contribution of a PRS in such multi-factor models can be evaluated and guide the future design of screening programmes that may use a SNP profile alongside other biomarkers and/ or imaging. By carrying out a biopsy for all men who undergo a MRI of the prostate (as well as PSA test), the utility of MRI as a screening tool for men at increased genetic risk of PrCa will be investigated in BARCODE1. Thus far, the usefulness of pre-biopsy MRI has been reported in men with an elevated PSA in studies such as PROMIS and PRECISION (31, 32). By correlating the results of MRI and biopsy in the ~500 men in BARCODE1 we aim to define the role of MRI in guiding the decision to undergo a prostate biopsy in men with an increased genetic risk of PrCa.

Additional studies are required to establish the role of MRI outside and within the context of genetic risk. The ReIMAGINE Prostate Cancer Screening study (NCT04063566) is currently inviting PSA naive men aged 50-75 via their GP to undergo MRI of the prostate. Those with lesions assigned a PIRADS score of 3-5 (or with a suspicious PSA density >0.12ng/ml) will be referred for prostate biopsy. In the sister study, ReIMAGINE Prostate Cancer Risk (NCT04060589), participants accepting a biopsy based on their study MRI will be invited to donate samples including germline DNA, which will be genotyped to retrospectively assess polygenic risk. The BARCODE1 study and complimentary studies such as ReIMAGINE will allow a robust assessment of different screening modalities and provide valuable information to guide the application of less invasive screening methods, and potentially plan for precision PrCa screening in the population.

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References

1. Benafif S, Kote-Jarai Z, Eeles RA. A review of prostate cancer genome wide association studies (GWAS). Cancer Epidemiol Biomarkers Prev. 2018.
2. Schumacher FR, Al Olama AA, Berndt SI, Benlloch S, Ahmed M, Saunders EJ, et al. Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. Nat Genet. 2018;50:928-36.
3. Conti DV, Darst BF, Moss LC, Saunders EJ, Sheng X, Chou A, et al. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. Nat Genet. 2021;53(1):65-75.
4. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. 2018;50(9):1219-24.
5. Matejcic M, Saunders EJ, Dadaev T, Brook MN, Wang K, Sheng X, et al. Germline variation at 8q24 and prostate cancer risk in men of European ancestry. Nat Commun. 2018;9(1):4616.
6. Dadaev T, Saunders EJ, Newcombe PJ, Anokian E, Leongamornlert DA, Brook MN, et al. Fine-mapping of prostate cancer susceptibility loci in a large meta-analysis identifies candidate causal variants. Nat Commun. 2018;9(1):2256.
7. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009;360(13):1320-8.
8. Pinsky PF, Prorok PC, Yu K, Kramer BS, Black A, Gohagan JK, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer. 2017;123(4):592-9.
9. Moyer VA, Force USPST. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157(2):120-34.
10. Carroll PR. USPTF Prostate Cancer Screening Recommendations-A Step in the Right Direction. JAMA Surg. 2018;153(8):701-2.
11. Nyberg T, Frost D, Barrowdale D, Evans DG, Bancroft E, Adlard J, et al. Prostate Cancer Risks for Male BRCA1 and BRCA2 Mutation Carriers: A Prospective Cohort Study. Eur Urol. 2020;77(1):24-35.
12. Pashayan N, Duffy SW, Neal DE, Hamdy FC, Donovan JL, Martin RM, et al. Implications of polygenic risk-stratified screening for prostate cancer on overdiagnosis. Genet Med. 2015;17(10):789-95.
13. Pashayan N, Morris S, Gilbert FJ, Pharoah PDP. Cost-effectiveness and Benefit-to-Harm Ratio of Risk-Stratified Screening for Breast Cancer: A Life-Table Model. JAMA Oncol. 2018;4(11):1504-10.
14. Darst BF, Wan P, Sheng X, Bensen JT, Ingles SA, Rybicki BA, et al. A Germline Variant at 8q24 Contributes to Familial Clustering of Prostate Cancer in Men of African Ancestry. Eur Urol. 2020;78(3):316-20.
15. ThermoFisher. http://assets.thermofisher.com/TFS-Assets/GSD/posters/high-quality-genotypes-using-eureka-genotyping-poster.pdf.
16. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. European Radiology. 2012;22(4):746-57.
17. Lane JA, Donovan JL, Davis M, Walsh E, Dedman D, Down L, et al. Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. Lancet Oncol. 2014;15(10):1109-18.
18. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/661677/NHS_Screening_Programmes_in_England_2016_to_2017_web_version_final.pdf.
19. https://fingertips.phe.org.uk/profile/cancerservices.

20. NCCN. https://www.nccn.org/professionals/physician_gls/PDF/prostate_detection.pdf. 2021.
21. Castro E, Mikropoulos C, Bancroft EK, Dadaev T, Goh C, Taylor N, et al. The PROFILE Feasibility Study: Targeted Screening of Men With a Family History of Prostate Cancer. Oncologist. 2016;21(6):716-22.
22. Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RAM, Schröder FH, et al. Lead Times and Overdetection Due to Prostate-Specific Antigen Screening: Estimates From the European Randomized Study of Screening for Prostate Cancer. JNCI: Journal of the National Cancer Institute. 2003;95(12):868-78.
23. Callender T, Emberton M, Morris S, Eeles R, Kote-Jarai Z, Pharoah P, et al. Polygenic risk-tailored screening for prostate cancer: A cost-effectiveness analysis. Cancer Res 2019;79(13 Suppl).
24. Liss MA, Xu J, Chen H, Kader AK. Prostate genetic score (PGS-33) is independently associated with risk of prostate cancer in the PLCO trial. Prostate. 2015;75(12):1322-8.
25. Han Y, Rand KA, Hazelett DJ, Ingles SA, Kittles RA, Strom SS, et al. Prostate Cancer Susceptibility in Men of African Ancestry at 8q24. J Natl Cancer Inst. 2016;108(7).
26. Darst BF, Wan P, Sheng X, Bensen JT, Ingles SA, Rybicki BA, et al. A Germline Variant at 8q24 Contributes to Familial Clustering of Prostate Cancer in Men of African Ancestry. Eur Urol. 2020.
27. Conti DV, Wang K, Sheng X, Bensen JT, Hazelett DJ, Cook MB, et al. Two Novel Susceptibility Loci for Prostate Cancer in Men of African Ancestry. JNCI: Journal of the National Cancer Institute. 2017;109(8).
28. Harlemon M, Ajayi O, Kachambwa P, Kim MS, Simonti CN, Quiver MH, et al. A custom genotyping array reveals population-level heterogeneity for the genetic risks of prostate cancer and other cancers in Africa. Cancer research. 2020:canres.2165.019.
29. Gronberg H. Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. Lancet Oncol. 2015.
30. Nordstrom T, Discacciati, A., Bergman, M., Clements, M., Aly, M., Annerstedt, M., Glaessgen, A., Carlsson, S., Jäderling, F., Eklund, M. and Grönberg, H. Prostate cancer screening using a combination of risk-prediction, magnetic resonance imaging and targeted prostate biopsies: A randomised trial. Available at SSRN: https://ssrncom/abstract=3788918 or http://dxdoiorg/102139/ssrn3788918. 2021.
31. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017;389(10071):815-22.
32. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018;378(19):1767-77.

Figure 1: BARCODE1 Study Outline

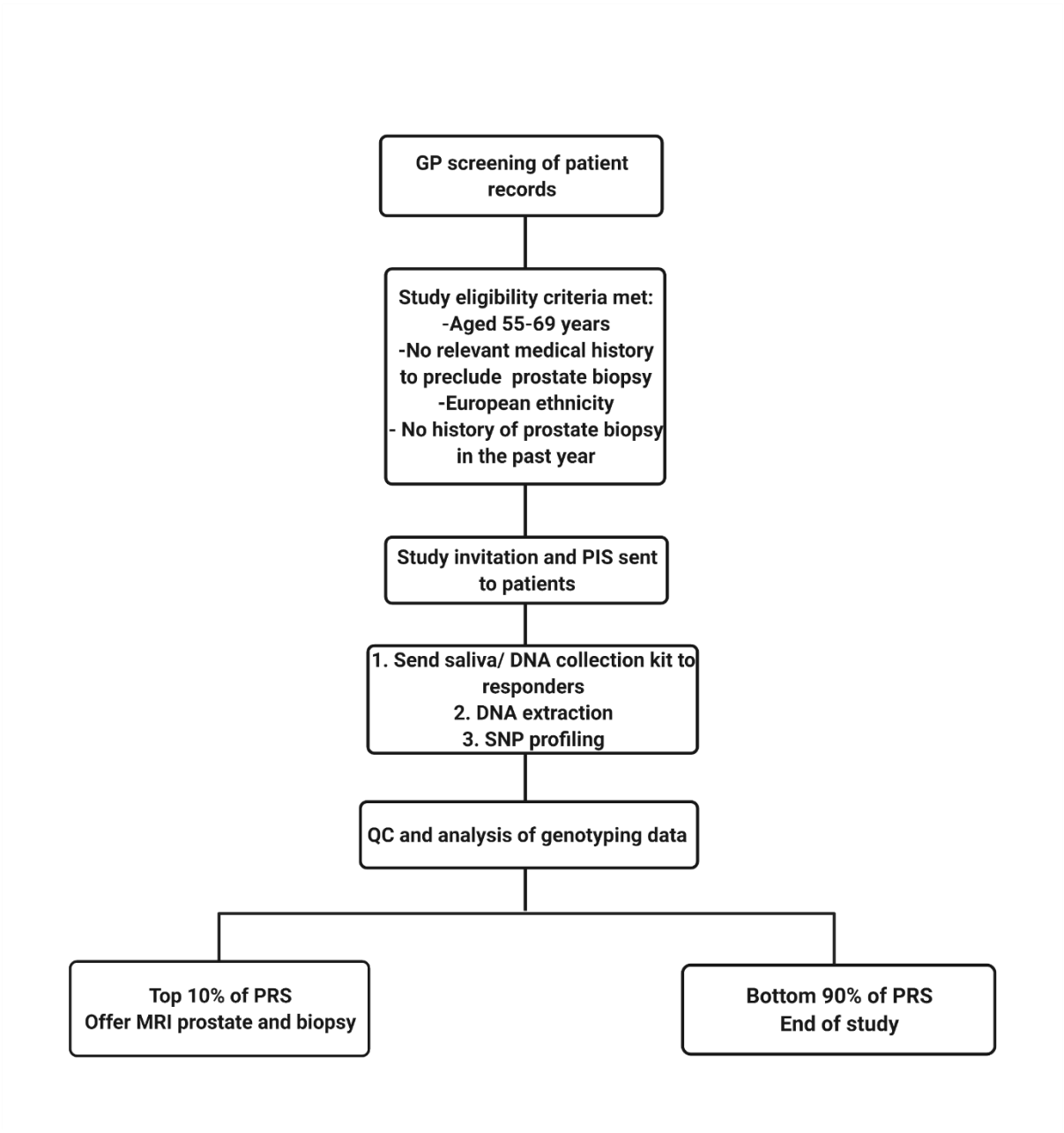
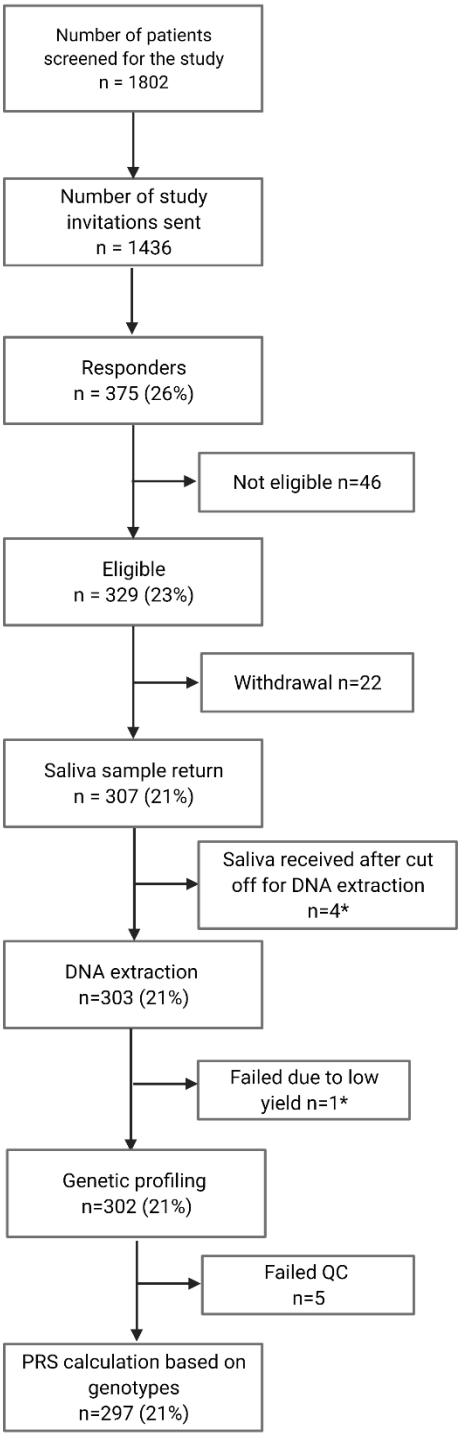
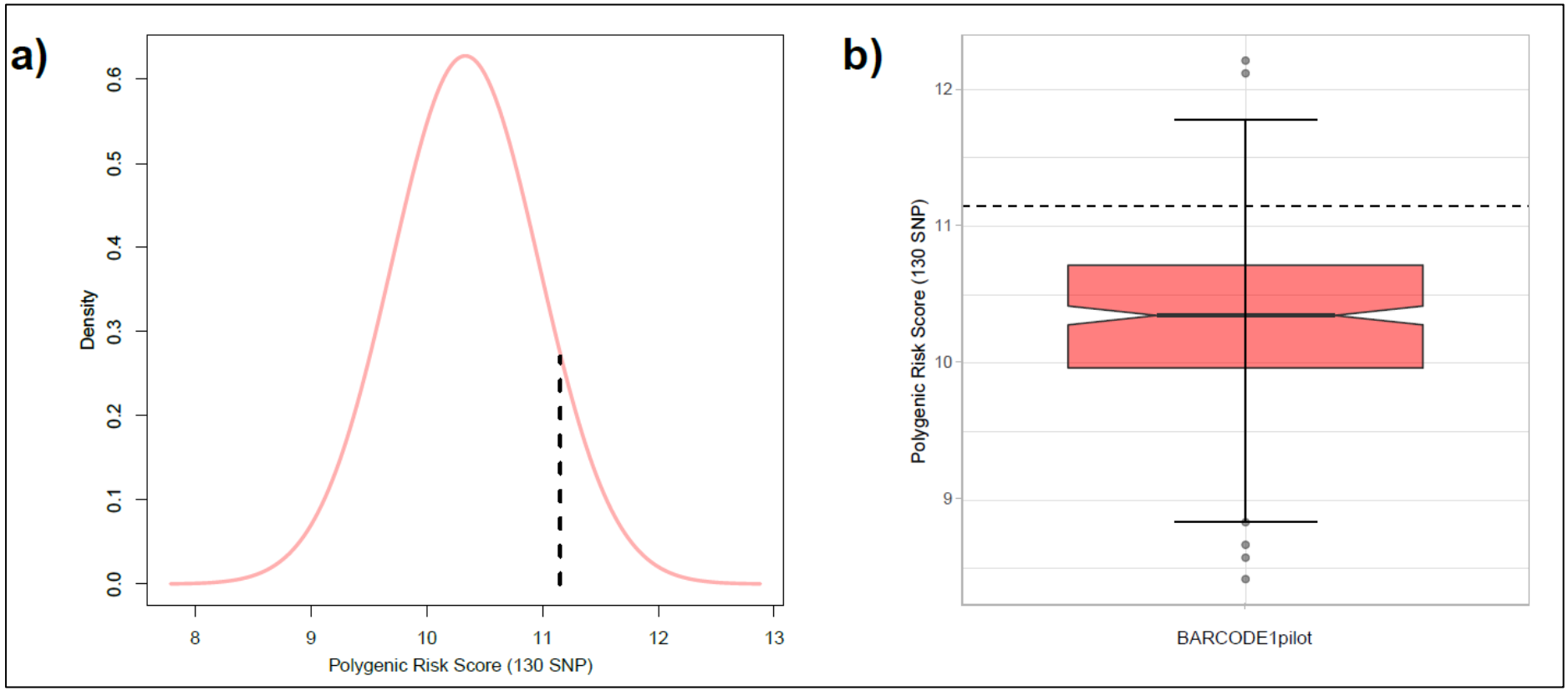


Figure 2: BARCODE1 pilot study recruitment
Percentages relate to the proportion of invitations to the study



*Saliva samples from 4 participants were received after April 15th 2018 which was the cut-off date for DNA extraction in the pilot study. These participants will have DNA extracted and analysed in the main BARCODE1 study.1 saliva sample did not yield sufficient DNA at extraction and a new saliva sample was requested. This participant will also be added to the main BARCODE1 study.
QC= Quality control
PRS= Polygenic risk score

Figure 3: PRS Distribution in BARCODE1 Pilot



A. The dashed line denotes the 90th centile PRS value (11.15).
B. Boxplot of the PRS distribution in BARCODE1 pilot displaying minimum and maximum values of PRS in whole study cohort as well as outliers. The dashed line denotes the 90th centile PRS value (11.15)

Table 1: BARCODE1 Pilot Study Screening, Response Rates and Saliva Returns

Site	Screened	Mail-outs	Total Responders (%)	Eligible	Returned saliva samples (% of eligible responders)
GP 1	148	148	45 (30)	45	42 (93%)
GP 2	350	326	78 (24)	66	62 (94%)
GP 3	277	175	23 (13)	12	12 (100%)
GP 4	267	232	46 (20)	44	41 (93%)
GP 5	223	211	51 (24)	49	44 (90%)
GP 6	390	200	93 (47)	77	74 (96%)
GP 7	145	142	37 (26)	34	30 (88%)
RMH*	2	2	2	2	2
Total	1802	1436	375 (26)	329	307 (93%)

*2 participants recruited via Oncogenetics Research clinic in RMH.
GP= General Practice site
RMH= Royal Marsden Hospital

Table 2: Distribution of PIRADS score in 19 men who underwent MRI prostate in BARCODE1 Pilot

Two scans repeated due to initial findings of ASAP and HGPIN on first biopsy. PIRADS score was unchanged as both had a score of 2 on first and second scans.

PIRADS Score	MRI N(%)	Number of repeat MRI
1	2 (11)	0
2	8 (42)	2
3	5 (26)	0
4	4 (21)	0
5	0	0
Total	19	2

Table 3: Outcomes of screening for 19 men in the BARCODE1 pilot study

Age	Pre-Biopsy PSA	PIRADS pre-biopsy MRI	Histology (Gleason score, n+n)	Management	Repeat MRI PIRADS	Repeat Biopsy Histology	Management	PRS
62	0.78	4	3+3	AS				12.12
66	5.8	4	3+3	AS				11.19
66	2.3	3	3+3	AS				11.32
55	2.4	1	3+4	AS	2	3+3	AS	11.17
56	1	2	3+3	AS				11.53
64	3.6	4	3+3	AS				11.31
64	0.64	2	ASAP	Repeat MRI and Bx at 6 months	2	3+4	AS	11.42
55	0.35	2	HGPIN	Repeat MRI and Bx at 6 months	2	Benign	Trial f/u	11.32

56	2.6	2	Benign	Trial f/u	11.49
59	0.89	4	Benign	Trial f/u	11.38
60	0.46	3	Benign	Trial f/u	11.17
56	0.89	2	Benign	Trial f/u	11.69
56	0.3	2	Benign	Trial f/u	11.32
59	1.5	1	Benign	Trial f/u	11.53
60	0.93	3	Benign	Trial f/u	11.73
55	0.41	2	Benign	Trial f/u	12.21
66	1.7	2	Benign	Trial f/u	11.49
59	1.8	3	Benign	Trial f/u	11.44

* Participant 4 underwent an MRI prostate and transperineal template biopsy as part of the local AS protocol and Gleason score was downgraded on the second biopsy to 3+3. Patients 7 and 8 underwent a repeat MRI and biopsy as part of the pilot study, 6 months after initial biopsy due to findings of ASAP and HGPIN respectively.

AS= Active surveillance

ASAP= atypical small acinar proliferation

HG PIN= High grade prostatic intra-epithelial neoplasia

f/u= follow up

Bx= Biopsy

Table 4: Features of prostate cancers diagnosed in pilot study

	Number of biopsies carried out	Gleason score on final biopsy	MCCL (mm)	TCCL (mm)
Participant 1	1	3+3	1	2
Participant 2	1	3+3	2	2
Participant 3	1	3+3	1	1
Participant 4	2	3+3	1	1
Participant 5	1	3+3	1	1
Participant 6	1	3+3	0.5	0.5
Participant 7	2	3+4	1.5	2

MCCL= Maximum cancer core length, TCCL= Total cancer core length

Supplementary material

Polygenic Risk Score (PRS) Calculation:

A polygenic risk score (PRS) was calculated for each study participant based on their genotyping data:

$$Score_j = \sum_{i=1}^{N} \beta_i g_{ij}$$

Where:

N = Number of SNPs included in the assay

g_{ij} = genotype at SNP locus *i* (0, 1, 2) for individual *j*. 0= homozygous for non-risk allele, 1=heterozygous for risk allele, 2=homozygous for risk allele. For any SNP that failed genotype QC at locus *i* in individual *j*, the population risk allele frequency (a non-integer value between 0 and 1) was substituted in place of genotype to reflect the probability of individual *j* carrying the risk allele at locus *i*, with this population risk allele frequency value doubled for autosomal variants.

β_i = Per-allele log-odds ratio of SNP *i*

PRS 90th centile calculation:

$$X = \mu + Z\sigma$$

Where:

X: the PRS at the 90th centile

μ: mean PRS in the study population

Z: the Z score corresponding to the 90th centile taken from a standard normal distribution table; here Z=1.282

σ: the standard deviation in the study population

Supplementary Table: 130 SNPs included in BARCODE1 Pilot Genetic Profile:

rsID	Chr	hg19 position	Risk Allele	Protective Allele	RAF	Risk Allele Beta	OR
rs56391074	1	88210715	AT	A	0.37	0.0466	1.05
rs17599629	1	150658287	G	A	0.21	0.0654	1.07
rs1043608*	1	153909069	C	G	0.31	0.061	1.06
rs1218582	1	154834183	G	A	0.44	0.0457	1.05
rs4245739	1	204518842	A	C	0.73	0.0924	1.10
rs62106670	2	8597123	T	C	0.38	0.0524	1.05
rs9287719	2	10710730	C	T	0.46	0.0663	1.07
rs13385191	2	20888265	G	A	0.24	0.0528	1.05
rs1465618	2	43553949	T	C	0.21	0.0829	1.09
rs721048	2	63131731	A	G	0.18	0.0971	1.10
rs74702681	2	66652885	T	C	0.02	0.1586	1.17
rs10187424	2	85794297	T	C	0.57	0.0744	1.08
rs11691517	2	111893096	T	G	0.74	0.0635	1.07
rs12621278	2	173311553	A	G	0.94	0.2423	1.27
rs34925593	2	174234547	C	T	0.48	0.0466	1.05
rs59308963	2	202123479	T	TATTCTGTC	0.72	0.0505	1.05
rs7584330	2	238387228	G	A	0.22	0.0547	1.06
rs3771570	2	242382864	T	C	0.15	0.0841	1.09
rs2660753	3	87110674	T	C	0.10	0.1198	1.13
rs1283104	3	106962521	G	C	0.38	0.047	1.05
rs7611694	3	113275624	A	C	0.57	0.0831	1.09
rs10934853	3	128038373	A	C	0.27	0.0989	1.10
rs6763931	3	141102833	A	G	0.44	0.0428	1.04
rs142436749	3	169093100	G	A	0.01	0.2212	1.25
rs10936632	3	170130102	A	C	0.51	0.0972	1.10
rs10009409	4	73855253	T	C	0.31	0.0555	1.06
rs1894292	4	74349158	G	A	0.52	0.062	1.06
rs17021918	4	95562877	C	T	0.65	0.0852	1.09
rs7679673	4	106061534	C	A	0.59	0.1201	1.13
rs2242652	5	1280028	G	A	0.79	0.1598	1.17
rs12653946	5	1895829	T	C	0.43	0.0786	1.08
rs2121875	5	44365545	C	A	0.33	0.0481	1.05
rs76551843	5	169172133	A	G	0.99	0.2705	1.31
rs4976790	5	177968915	T	G	0.11	0.0737	1.08
rs4713266	6	11219030	C	T	0.52	0.0514	1.05
rs7767188	6	30073776	A	G	0.21	0.0544	1.06
rs12665339	6	30601232	G	A	0.16	0.0615	1.06
rs3096702	6	32192331	A	G	0.38	0.0559	1.06
rs3129859	6	32400939	G	C	0.67	0.0602	1.06
rs9296068	6	32988695	T	G	0.65	0.0477	1.05
rs1983891	6	41536427	T	C	0.28	0.0816	1.09

rs2273669	6	109285189	G	A	0.15	0.0694	1.07
rs339331	6	117210052	T	C	0.70	0.0837	1.09
rs1933488	6	153441079	A	G	0.58	0.076	1.08
rs9364554	6	160833664	T	C	0.28	0.1037	1.11
rs11452686	7	20414110	T	TA	0.56	0.0497	1.05
rs12155172	7	20994491	A	G	0.22	0.0925	1.10
rs10486567	7	27976563	G	A	0.76	0.1335	1.14
rs17621345	7	40875192	A	C	0.74	0.0715	1.07
rs56232506	7	47437244	A	G	0.45	0.054	1.06
rs6465657	7	97816327	C	T	0.46	0.1005	1.11
rs2928679	8	23438975	A	G	0.44	0.0534	1.05
rs11135910	8	25892142	T	C	0.15	0.0782	1.08
rs12543663	8	127924659	C	A	0.30	0.1114	1.12
rs10086908	8	128011937	T	C	0.70	0.1255	1.13
rs183373024	8	128104117	G	A	0.007	1.068	2.91
rs16901979	8	128124916	A	C	0.03	0.445	1.56
rs620861	8	128335673	G	A	0.63	0.1386	1.15
rs6983267	8	128413305	G	T	0.51	0.2004	1.22
rs1447295	8	128485038	A	C	0.11	0.345	1.41
rs1048169	9	19055965	C	T	0.38	0.0609	1.06
rs17694493	9	22041998	G	C	0.14	0.0726	1.08
rs1182	9	132576060	A	C	0.22	0.0581	1.06
rs61830900*	10	871481	G	C	0.16	0.0773	1.08
rs76934034	10	46082985	T	C	0.92	0.1151	1.12
rs10993994	10	51549496	T	C	0.38	0.2075	1.23
rs1935581	10	90195149	C	T	0.62	0.0477	1.05
rs3850699	10	104414221	A	G	0.70	0.0704	1.07
rs4962416	10	126696872	C	T	0.27	0.0593	1.06
rs1881502	11	1507512	T	C	0.19	0.0581	1.06
rs7127900	11	2233574	A	G	0.20	0.1704	1.19
rs61890184	11	7547587	A	G	0.12	0.0706	1.07
rs2277283	11	61908440	C	T	0.31	0.0558	1.06
rs7931342	11	68994497	G	T	0.50	0.1565	1.17
rs11290954	11	76260543	AC	A	0.68	0.0609	1.06
rs11568818	11	102401661	T	C	0.55	0.0742	1.08
rs1800057	11	108143456	G	C	0.025	0.15	1.16
rs11214775	11	113807181	G	A	0.71	0.071	1.07
rs138466039	11	125054793	T	C	0.01	0.2806	1.32
rs878987	11	134266372	G	A	0.15	0.0639	1.07
rs2066827	12	12871099	T	G	0.76	0.0564	1.06
rs10845938	12	14416918	G	A	0.55	0.0572	1.06
rs80130819	12	48419618	A	C	0.91	0.0957	1.10
rs10875943	12	49676010	C	T	0.29	0.0688	1.07
rs902774	12	53273904	A	G	0.15	0.1258	1.13
rs7968403	12	65012824	T	C	0.64	0.0589	1.06
rs5799921	12	90160530	GA	G	0.70	0.0608	1.06

rs1270884	12	114685571	A	G	0.48	0.0697	1.07
rs7295014	12	133067989	G	A	0.34	0.0516	1.05
rs1004030	14	23305649	T	C	0.59	0.0462	1.05
rs11629412	14	37138294	C	G	0.58	0.0573	1.06
rs8008270	14	53372330	C	T	0.81	0.0832	1.09
rs7141529	14	69126744	C	T	0.50	0.0505	1.05
rs8014671	14	71092256	G	A	0.58	0.0466	1.05
rs4924487	15	40922915	C	G	0.84	0.0622	1.06
rs33984059	15	56385868	A	G	0.98	0.1761	1.19
rs201158093	16	82178893	TAA	TA	0.44	0.0487	1.05
rs684232	17	618965	C	T	0.35	0.0832	1.09
rs28441558	17	7803118	C	T	0.06	0.1507	1.16
rs11649743	17	36074979	G	A	0.81	0.1216	1.13
rs4430796	17	36098040	A	G	0.53	0.1973	1.22
rs138213197	17	46805705	T	C	0.002	1.3475	3.85
rs11650494	17	47345186	A	G	0.08	0.0992	1.10
rs2680708	17	56456120	G	A	0.61	0.0462	1.05
rs1859962	17	69108753	G	T	0.48	0.1606	1.17
rs8093601	18	51772473	C	G	0.44	0.0451	1.05
rs28607662	18	53230859	C	T	0.096	0.0746	1.08
rs12956892	18	56746315	T	G	0.30	0.0498	1.05
rs10460109	18	73036165	T	C	0.42	0.0441	1.05
rs7241993	18	76773973	C	T	0.70	0.0761	1.08
rs11666569	19	17214073	C	T	0.71	0.0516	1.05
rs118005503	19	32167803	G	C	0.91	0.0902	1.09
rs8102476	19	38735613	C	T	0.54	0.0902	1.09
rs11672691	19	41985587	G	A	0.74	0.0916	1.10
rs61088131	19	42700947	T	C	0.84	0.0624	1.06
rs2735839	19	51364623	G	A	0.85	0.1666	1.18
rs11480453	20	31347512	C	CA	0.60	0.0463	1.05
rs12480328	20	49527922	T	C	0.93	0.1071	1.11
rs6126982*	20	52456445	T	G	0.47	0.0669	1.07
rs2427345	20	61015611	C	T	0.62	0.0452	1.05
rs6062509	20	62362563	T	G	0.70	0.0775	1.08
rs1041449	21	42901421	G	A	0.43	0.0509	1.05
rs9625483	22	28888939	A	G	0.03	0.1338	1.14
rs9623117	22	40452119	C	T	0.22	0.064	1.07
rs5759167	22	43500212	G	T	0.50	0.1423	1.15
rs2405942	X	9814135	A	G	0.78	0.0486	1.05
rs17321482	X	11482634	C	T	0.87	0.0671	1.07
rs5945619	X	51241672	C	T	0.36	0.1043	1.11
rs2807031	X	52896949	C	T	0.18	0.0581	1.06
rs5919432	X	67021550	T	C	0.80	0.0429	1.04

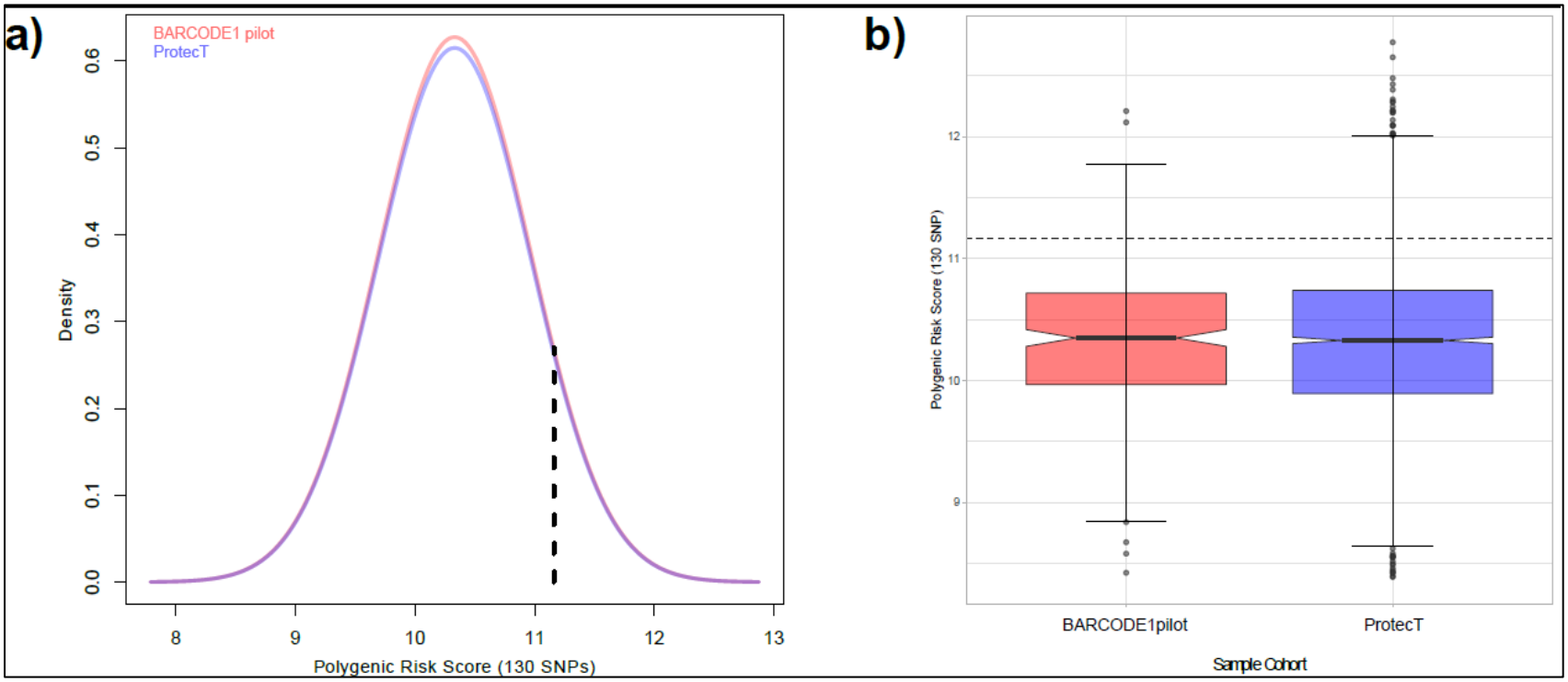
rsID: reference SNP cluster ID
Chr: chromosome
hg19: Genome Reference Consortium Human Build 37 (GRCh37)
RAF: Risk allele frequency

OR: odds ratio
Risk Allele and Protective Allele are reported relative to the forward strand.
*Proxy replacement for undesignable target SNP from Schumacher et al. (rs1043608-rs34579442, r2 = 0.80; rs61830900-rs141536087, r2 = 0.91; rs6126982-rs6091758, r2 = 0.93)

Supplementary Figure 1. PRS Distribution in BARCODE1 Pilot and ProtecT

ProtecT was a UK PSA screening study recruiting participants via their GPs (1). The genotyping data for 2,571 men aged 55-69 years who were not diagnosed with cancer in ProtecT were used to calculate the PRS (using the 130 SNPs in the BARCODE1 genetic profile). These men were genotyped using the OncoArray platform (2). The two populations were compared using an independent t-test.

Supplementary Figure 1: PRS Distribution in BARCODE1 Pilot and ProtecT



A. The dashed line denotes the 90th centile PRS value (11.15). There was no significant difference in PRS distribution between the two cohorts (t-test P=0.92)
B. Boxplot of the PRS distribution in BARCODE1 pilot and in ProtecT. The dashed line denotes the 90th centile PRS value (11.15)

References

1. Lane JA, Donovan JL, Davis M, Walsh E, Dedman D, Down L, et al. Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. Lancet Oncol. 2014;15(10):1109-18.
2. Schumacher FR, Al Olama AA, Berndt SI, Benlloch S, Ahmed M, Saunders EJ, et al. Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. Nat Genet. 2018;50:928-36.