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African-specific improvement of a polygenic hazard score for age at diagnosis of prostate cancer

Roshan A. Karunamuni,[1*] Minh-Phuong Huynh-Le,[1] Chun C. Fan,[2] Wesley Thompson,[3] Rosalind A. Eeles,[4,5] Zsofia Kote-Jarai,[4] Kenneth Muir,[6,7] UKGPCS collaborators,[8] Artitaya Lophatananon,[9] Catherine M. Tangen,[10] Phyllis J. Goodman,[10] Ian M. Thompson Jr.,[11] William J. Blot,[12,13] Wei Zheng,[14] Adam S. Kibel,[15] Bettina F. Drake,[16] Olivier Cussenot,[17,18] Géraldine Cancel-Tassin,[18,17] Florence Menegaux,[19] Thérèse Truong,[19] Jong Y. Park,[20] Hui-Yi Lin,[21] Jeannette T. Bensen,[22,23] Elizabeth T.H. Fontham,[24] James L. Mohler,[25,23] Jack A. Taylor,[26,27] Luc Multigner,[28] Pascal Blanchet,[29] Laurent Brureau,[29] Marc Romana,[30] Robin J. Leach,[31] Esther M. John,[32] Jay Fowke,[33,34] William S. Bush,[35] Melinda Aldrich,[36] Dana C. Crawford,[37] Shiv Srivastava,[38,39] Jennifer C. Cullen,[38,39] Gyorgy Petrovics,[38,39] Marie-Élise Parent,[40,41] Jennifer J. Hu,[42] Maureen Sanderson,[43] Ian G. Mills,[44] Ole A. Andreassen,[45] Anders M. Dale,[46] Tyler M. Seibert,[1] The PRACTICAL Consortium[47]

[1]Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA, USA
[2]Healthlytix, 4747 Executive Dr. Suite 820, San Diego, CA, USA
[3]Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA, USA
[4]The Institute of Cancer Research, London, SM2 5NG, UK
[5]Royal Marsden NHS Foundation Trust, London, SW3 6JJ, UK
[6]Division of Population Health, Health Services Research and Primary Care, University

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of Manchester, Oxford Road, Manchester, M13 9PL, UK
[7]Warwick Medical School, University of Warwick, Coventry, UK
[8]http://www.icr.ac.uk/our-research/research-divisions/division-of-genetics-and-epidemiology/oncogenetics/research-projects/ukgpcs/ukgpcs-collaborators
[9]Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK , M139PT
[10]SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[11]CHRISTUS Santa Rosa Hospital – Medical Center, San Antonio, TX, USA
[12]Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, 2525 West End Avenue, Suite 600, Nashville, TN 37232 USA.
[13]International Epidemiology Institute, Rockville, MD 20850, USA
[14]Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, 2525 West End Avenue, Suite 800, Nashville, TN 37232 USA.
[15]Division of Urologic Surgery, Brigham and Womens Hospital, 75 Francis Street, Boston, MA 02115, USA
[16]Washington University School of Medicine, 660 S. Euclid Avenue, Campus Box 8242, St. Louis, MO 63110 , USA
[17]Sorbonne Universite, GRC n°5 , AP-HP, Tenon Hospital, 4 rue de la Chine, F-75020 Paris, France
[18]CeRePP, Tenon Hospital, Paris, France.
[19]Université Paris-Saclay, UVSQ, Inserm, CESP, Villejuif, France.
[20]Department of Cancer Epidemiology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA
[21]School of Public Health, Louisiana State University Health Sciences Center, New Orleans, LA 70112, USA
[22]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[23]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill,

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Chapel Hill, NC, USA
[24]School of Public Health, Louisiana State University Health Sciences Center, New Orleans, LA, USA
[25]Department of Urology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA
[26]Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA
[27]Epigenetic and Stem Cell Biology Laboratory, National Institute of Environmental Health Sciences, Research Triangle Park, NC
[28]Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, Rennes, France
[29]CHU de Pointe-à-Pitre, Univ Antilles, Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, Pointe-à-Pitre, France
[30]UMR Inserm 1134 Biologie Intégrée du Globule Rouge, INSERM/Université Paris Diderot - Université Sorbonne Paris Cité/INTS/Université des Antilles, Paris, France
[31]Department of Cell System and Anatomy and Mays Cancer Center, University of Texas Health San Antonio, San Antonio Texas
[32]Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, 780 Welch Road, CJ250C, CA 94304-5769
[33]Department of Medicine and Urologic Surgery, Vanderbilt University Medical Center, 1211 Medical Center Drive, Nashville, TN 37232, USA
[34]Division of Epidemiology, Department of Preventive Medicine, The University of Tennessee Health Science Center, TN, USA
[35]Case Western Reserve University, Department of Population and Quantitative Health Sciences, Cleveland Institute for Computational Biology, 2103 Cornell Road, Wolstein Research Building, Suite 2530, Cleveland, OH, 44106 USA
[36]Vanderbilt University Medical Center, Department of Thoracic Surgery, 609 Oxford House, 1313 21st Avenue South, Nashville, TN 37232-4682 USA
[37]Case Western Reserve University, Department of Population and Quantitative Health Sciences, Cleveland Institute for Computational Biology, 2103 Cornell Road, Wolstein

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Research Building, Suite 2527, Cleveland, OH, 44106 USA
[38]Uniformed Services University, 4301 Jones Bridge Rd, Bethesda, MD 20814, USA
[39]Center for Prostate Disease Research, 6720A Rockledge Drive, Suite 300, Bethesda, MD 20817, USA
[40]Epidemiology and Biostatistics Unit, Centre Armand-Frappier Santé Biotechnologie, Institut national de la recherche scientifique, 531 Boul. des Prairies, Laval, QC, Canada H7V 1B7
[41]Department of Social and Preventive Medicine, School of Public Health, University of Montreal, Montreal, QC, Canada
[42]The University of Miami School of Medicine, Sylvester Comprehensive Cancer Center, 1120 NW 14th Street, CRB 1511, Miami, Florida 33136, USA
[43]Department of Family and Community Medicine, Meharry Medical College, 1005 Dr. DB Todd Jr. Blvd., Nashville, TN 37208 USA
[44]Center for Cancer Research and Cell Biology, Queen's University of Belfast, Belfast, UK
[45]NORMENT, KG Jebsen Centre, Oslo University Hospital and University of Oslo, Oslo, Norway
[46]Department of Radiology, University of California San Diego, La Jolla, CA, USA
[47]Institute of Cancer Research, Sutton, SW7 3RPm UK

* Additional members from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome consortium (PRACTICAL,http://practical.icr.ac.uk/) and associated funding are provided in the Appendix 1 and 2.

Corresponding Author:

Roshan Karunamuni, PhD
University of California, San Diego
Department of Radiation Medicine and Applied Sciences
3960 Health Sciences Dr, Mail Code 0865

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La Jolla, CA 92093
rakarunamuni@health.ucsd.edu

Tyler M. Seibert, MD, PhD
University of California, San Diego
Department of Radiation Medicine and Applied Sciences
3960 Health Sciences Dr, Mail Code 0865
La Jolla, CA 92093
tseibert@health.ucsd.edu

Short title

African polygenic hazard score for prostate cancer

Keywords

Prostate cancer; health disparities; genome wide association study; polygenic risk; genomics; genotypic ancestry; African

Abbreviations

HR	Hazard ratio
PHS	Polygenic hazard score
PHS46	Previously published polygenic hazard score model using 46 SNPs
PHS46+African	Updated polygenic hazard score model for men with African genetic ancestry
PRACTICAL	Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome consortium

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SNP	Single nucleotide polymorphism

Article Category

Cancer Epidemiology

Novelty and Impact

We identified three SNPs (rs76229939, rs74421890, and rs5013678), using cross-validation, that significantly improved performance of a previously published polygenic hazard model (PHS46) in men of African genetic ancestry. The performance of the novel PHS46+African score improved by as much as 79% after incorporation of rs76229939, rs74421890, and rs5013678. PHS46+African significantly improved association between polygenic risk with age at diagnosis of prostate cancer in Africans, a population generally under-served in genome-wide studies, to levels comparable with Europeans.

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Abstract

Polygenic hazard score (PHS) models are associated with age at diagnosis of prostate cancer. Our model developed in Europeans (PHS46), showed reduced performance in men with African genetic ancestry. We used a cross-validated search to identify SNPs that might improve performance in this population. Anonymized genotypic data were obtained from the PRACTICAL consortium for 6,253 men with African genetic ancestry. Ten iterations of a ten-fold cross-validation search were conducted, to select SNPs that would be included in the final PHS46+African model. The coefficients of PHS46+African were estimated in a Cox proportional hazards framework using age at diagnosis as the dependent variable and PHS46, and selected SNPs as predictors. The performance of PHS46 and PHS46+African were compared using the same cross-validated approach. Three SNPs (rs76229939, rs74421890, and rs5013678) were selected for inclusion in PHS46+African. All three SNPs are located on chromosome 8q24. PHS46+African showed substantial improvements in all performance metrics measured, including a 75% increase in the relative hazard of those in the upper 20% compared to the bottom 20% (2.47 to 4.34) and a 20% reduction in the relative hazard of those in the bottom 20% compared to the middle 40% (0.65 to 0.53). In conclusion, we identified three SNPs that substantially improved the association of PHS46 with age at diagnosis of prostate cancer in men with African genetic ancestry to levels comparable to Europeans.

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Introduction

Polygenic models can provide personalized estimates of the risk of developing prostate cancer. In the context of survival analysis, these models can provide insight into age at diagnosis of prostate cancer, and thus could be used to guide decisions on whether and when to offer screening[1]. Studies of polygenic models have often included only individuals of European genetic ancestry, owing to greater availability of data from that population[2,3]. As a consequence, these models have been tailored to identify and estimate coefficients of genetic common variants for that particular population, while potentially missing variants that may hold value in other populations[2]. There is concern that using these European-focused models could actually exacerbate health disparities[2–4].

As an example, our group recently published on the performance of a polygenic hazard score (PHS) originally developed using a European dataset, in a multi-ethnic dataset consisting of individuals of European, African, and Asian genetic ancestry[5]. The model (called here PHS46, referred to in the referenced manuscript as PHS_2), includes 46 single nucleotide polymorphisms (SNPs) in its calculation and was strongly associated with age at diagnosis in all three genetic populations ($p<10^{-16}$). However, the hazard ratio for prostate cancer between individuals in the upper 20th percentile to those in the lower 20th percentile of PHS46 was approximately half as large for those with African genetic ancestry (2.6) as it was for those with European (5.6) or Asian (4.6)

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ancestry. A similar pattern was observed for clinically significant prostate cancer and for death from prostate cancer.

In the current study, we attempt to bridge the apparent gap in model performance of PHS46 for individuals with African genetic ancestry. To this end, we used a machine learning approach to systematically search for SNPs that add statistical value to a base model of PHS46 among African men (PHS46+African). By including PHS46 as a covariate in our SNP search, we sought to identify those SNPs that may hold particular value for individuals with African genetic ancestry.

Material and Methods

Study dataset

We obtained genotype and phenotype data from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL)[6] consortium for this study. Genotyping was performed using the OncoArray platform[6,7] and had undergone quality assurance steps, as described previously[8]. The study dataset contains no overlap with that used to estimate model coefficients of PHS46. It is a subset of another dataset wherein the performance discrepancy of PHS46 between different genotypic ancestries was first observed[5]. All 46 SNPs of PHS46 were directly genotyped on the OncoArray platform.

The genotypic ancestry of each individual was also determined previously[6,9]. In total, the African dataset consisted of data from 6,253 men with African genotypic ancestry. Missing SNP calls were replaced with the mean of the genotyped data for that

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SNP in the African dataset. The percentage of individuals with missing SNP calls ranged from 0 to 5.9% across the SNPs, while the percentage of SNPs with missing calls ranged from 0.5% to 5.1% across the individuals. Individuals without prostate cancer were censored at age at last follow-up in the Cox proportional hazards models. A description of the PRACTICAL study groups that contributed data towards this analysis are described in Supplementary Table 1. PHS46 risk score for each individual in the African dataset was estimated as the sum of SNP allele counts (X) multiplied by their respective coefficients (β)[5]:

$$PHS46 = \sum_{i=1}^{46} X_i \beta_i$$

SNP-scan

A multi-step approach was used to select SNPs, from those directly genotyped on the OncoArray platform, that would improve the performance of PHS46 in the African dataset. Training and testing sets were generated using 10 iterations of a 10-fold cross-validation structure resulting in 100 total permutations. For each permutation, a multivariable logistic regression model using case/control status as the dependent variable was estimated using each genotyped SNP in turn, adjusting for PHS46 and four principal components based on genetic ancestry, determined previously[9]. SNPs with p-values less than $1x10^{-6}$ were considered for further analysis. In order of increasing p-value, each SNP was tested in a multiple Cox proportional hazards model, after adjusting for PHS46, four ancestral principal components, and previously selected

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SNPs. The Cox model in the SNP-scan used age at diagnosis of prostate cancer as the dependent variable. If the p-value of the coefficient of the tested SNP was less than $1x10^{-6}$, it was considered for the final model in that permutation. SNPs that reached this p-value threshold in more than 50% of the permutations were selected to construct the PHS46+African model, consisting of PHS46 and the newly identified SNPs.

Comparing performance between PHS46 and PHS46+African – Hazard Ratio

For each permutation of the previously described cross-validation structure, an PHS46+African Cox proportional hazards model was estimated in the training set using PHS46 and the selected SNPs as independent predictors. The PHS46+African risk score for each individual is then estimated using the corresponding PHS46 score, selected SNP allele counts (Y) and their respective coefficients (α):

$$PHS46 + African = PHS46 + \sum_{j=1}^{SNPs} Y_j \, \alpha_j$$

The performance of the PHS46+African and PHS46 models was then determined in the cross-validation testing set, and the resulting hazard ratios (HR) were obtained, as previously described[1]. For each model, the PHS risk scores within the cross-validation testing set are assigned to quantile groups identified using the corresponding training set control values. The hazard ratio between two quantile groups, such as those in the top 20% to those in the bottom 20%, is estimated as the exponential of the difference in mean PHS values for each group. In this calculation, the PHS values are linearly scaled by a sample-weight correction factor, to account for case-control sampling[1,5,10]. Three

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HR were calculated: HR80/20 (top 20% to bottom 20%), HR98/50 (top 2% to middle 40%) and HR20/50 (bottom 20% to middle 40%). The average HR across permutations for both PHS46+African and PHS46 are reported.

To allow for comparisons with previously published results, the performance metrics for PHS46 and PHS46+African were also estimated for age at diagnosis of clinically significant prostate cancer. When estimating performance for clinically significant prostate cancer, controls and non-clinically significant cancers were censored at age of last follow-up and age of diagnosis, respectively. The previously used criteria for clinically significant cancer were any of: Gleason score >=7, stage T3-T4, PSA concentration >= 10ng/mL, pelvic lymph nodal metastasis, or distant metastasis[1]. Paired t-tests were used to test for statistically significant differences ($\alpha = 0.05$) in HR between PHS46+African and PHS46.

Additionally, in each permutation, the performance of a Cox model consisting of PHS46 and SNPs that were considered in that permutation was also estimated. These results are provided within the Supplementary Table 2 and provide performance estimates that are not prone to information leakage from training to testing set.

Comparing performance between PHS46 and PHS46+African – C-index

In addition to the hazard ratio, the performances of PHS46 and PHS46+African were compared using Harrell's c-index[11]. For each permutation of the aforementioned cross-validation structure, the c-index of PHS46 and PHS46+African scores were estimated in the testing fold using the "coxph" function in the R "survival" package.

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Paired t-tests were used to test for statistically significant differences ($\alpha = 0.05$) between the two models.

Characterization of PHS46+African

Coefficients of the PHS46+African model, consisting of PHS46 and the SNPs selected in the SNP-scan, were estimated using 1000 bootstrapped samples of the African dataset.

Clinical utility of PHS46+African

As an example of the clinical utility of the PHS46+African risk score, the risk-equivalent age was estimated for those individuals in the upper 2 percentile of the distribution of PHS46+African risk scores. The risk-equivalent age, as defined previously[12], is when an individual from a given PHS percentile has prostate cancer risk equivalent to the average 60-year-old man. The age-specific general cumulative incidence curve was generated using data from SEER*Explorer incidence rates by age at diagnosis, 2003-2017 for Black Americans[13]. The corresponding risk-adjusted incidence curve was estimated by multiplying the general cumulative incidence curve by the mean value of HR98/50 for PHS46+African obtained from the analysis of the age-of-diagnosis of prostate cancer. The risk-equivalent age was then calculated as the age at which the risk-adjusted cumulative incidence curve had the same value as the general cumulative incidence curve at age 60.

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Results

Individual and OncoArray characteristics

In total, there were 3,013 men with (cases) and 3,240 men without (controls) prostate cancer in the African dataset. The mean [95% CI] ages of cases and controls were 62.4 [62.1, 62.7] and 61.8 [61.4, 62.1] years respectively. The OncoArray genotypic data, after the quality assurance process, included 444,323 SNPs.

Single Nucleotide Polymorphism (SNP)-scan

Across the 100 permutations of the cross-validation iterations, a total of twelve SNPs were considered for final selection (Supplementary Table 3). Three SNPs were selected in more than 50% of the permutations and included in the final PHS46+African model. By cross-referencing the chromosomal positions against dbSNP[14], these variants were identified as rs76229939[15], rs74421890[16], and rs5013678[17]. All three SNPs (Table 1) are located on chromosome 8q24, a region of the chromosome previously identified as containing common variants associated with prostate cancer[18,19]. An examination of the R^2 (Supplementary Table 4) showed little association, ranging from 0.0027 to 0.0057, among genotype data from the three SNPs in the African dataset.

Reference threshold (Supplementary Table 5) and mean (Supplementary Table 6) values for PHS46+African in the African dataset are presented in the Supplemental Data.

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HR performance of PHS46+African

Figure 1 demonstrates the difference in HRs between PHS46+African and PHS46 within the African dataset using age at diagnosis of any prostate cancer (Supplementary Table 7). Overall, we observed an improvement in all the metrics calculated: a 75% increase in HR98/50 from 2.10 to 3.67; a 79% increase in HR80/20 from 2.47 to 4.42; and a 23% decrease in HR20/50 from 0.65 to 0.51. We also observed improvements in all performance metrics when using age at diagnosis of clinically significant prostate cancer: 103% increase in HR98/50 from 1.91 to 3.88, 113% improvement in HR80/20 from 2.21 to 4.71, and 29% improvement in HR20/50 from 0.70 to 0.50. All observed changes in HR were statistically significant ($p < 1x10^{-16}$).

C-index of PHS46+African

The mean c-indices of PHS46 and PHS46+African across the cross-validation folds were estimated as 0.55 and 0.58 ($p < 1x10^{-16}$), respectively.

Risk-equivalent age for PHS46+African

The risk-equivalent age for those individuals in the top 2 percentiles of the distribution of PHS46+African scores was estimated as 50 years old, suggesting that a man with a PHS46+African score in the top 2 percentile reached a prostate cancer detection risk equivalent to that of a standard 60-year-old roughly 10 years earlier, at an age of 50 years. The corresponding risk-equivalent age when using PHS46 scores was 54 years.

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Discussion

Using a cross-validated search of a dataset made up entirely of men with African genetic ancestry, we were able to identify three SNPs that substantially improved the performance of PHS46 in this population to levels that are comparable to those observed in Europeans and Asians. Performance improvements were observed in hazard ratios tracking risk between PHS groups, concordance-indices tracking the overall utility of PHS as a continuous variable, and risk-equivalent age tracking the potential clinical utility of PHS. The three SNPs, rs76229939, rs74421890, and rs5013678, are all located on chromosome 8q24 – a region of the genome where variants have been associated with prostate cancer in both the general population and specifically in men with African genetic ancestry[19,20]. Despite the relative proximity of the three SNPs on chromosome 8, their genetic data was not strongly associated in our dataset, suggesting that each SNP provides non-redundant information for an individual's genetic score.

Each of the three SNPs have been previously identified in the literature to be associated with prostate cancer: rs76229939 is an intron variant of the prostate-cancer-associated transcript 2 (*PCAT2*) gene, while rs74421890 and rs5013678 are both non-coding transcript variants of the prostate-cancer-associated non-coding RNA 1 (*PRNCR1*) gene. The minor allele frequencies of rs76229939 and rs74421890 in Europeans, as reported by dbSNP[14], are approximately zero to three decimal places, which may explain why they were not selected in the original formulation of PHS46.

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This study is not meant to be an exhaustive search for all possible SNPs that are associated with the age of diagnosis of prostate cancer in individuals with African genetic ancestry. Our study is also limited by the small number of available observations relative to those often found in many genome-wide association studies, which can have tens or hundreds of thousands of individuals. However, we were able to extract information that is likely robust by employing a cross-validated search for those SNPs that specifically add value to the performance of PHS46, and not simply independently associated with prostate cancer. Future analysis will include a more detailed analysis of the 8q24 region, including SNPs that are imputed using TOPMed reference panels. We also note that no SNP score, including PHS46 and PHS46+African, has been shown to discriminate men at risk of aggressive prostate cancer from those at risk of indolent prostate cancer. Finally, the performance metrics reported in this study may be biased by the leakage of information across cross-validated folds of the data when identifying those SNPs to include in the final African-PHS model. This bias is expected to be similar for all SNPs and should not have influenced selection of the three SNPs included in the final model over those not selected.

In conclusion, we identified three SNPs (rs76229939, rs74421890, and rs5013678) on 8q24 that substantially improved the performance of PHS46 in a dataset of men with African genetic ancestry. The addition of these SNPs to the polygenic risk score substantially improved its association with age at diagnosis of prostate cancer in Africans, to levels comparable with those found in Europeans.

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Ethics Statement

All contributing studies were approved by the relevant ethics committees; written informed consent was obtained from the study participants[21]. The present analyses used de-identified data from the PRACTICAL consortium and have been approved by the review board at the corresponding authors' institution.

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Conflict of Interest:

All authors declare no personal or financial conflicts of interest for the submitted work except as follows. CCF is a scientific consultant for CorTechs Labs, Inc. RE reports honorarium as a speaker for GU-ASCO meeting in San Francisco Jan 2016, support from Janssen, and honorarium as speaker for RMH-FR meeting Nov 2017. She reports honorarium as a speaker at the University of Chicago invited talk May 2018, and an educational honorarium by Bayer & Ipsen to attend GU Connect "Treatment sequencing for mCRPC patients within the changing landscape of mHSPC" at ESMO Barcelona, Sep 2019. She reports member of external Expert Committee on the Prostate Dx Advisory Panel. OAA received speaker's honorarium from Lundbeck, and is a consultant for Healthlytix. AMD reports that he was a founder and holds equity in CorTechs Labs Inc., and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc., and the Mohn Medical Imaging and Visualization Centre. He received funding through research grants from GE Healthcare to UCSD. The terms of these arrangements have been reviewed by and approved by UCSD in accordance with its conflict of interest policies. TMS reports honoraria, outside of the present work, from: University of Rochester, Varian Medical Systems, Multimodal Imaging Servcies Corporation; and WebMD. He reports research funding from NIH/NBIB, U.S. Department of Defense, Radiological Society of North America, American Society for Radiation Oncology, and Varian Medical Systems.

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Data Availability Statement

The data used in this work were obtained from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) consortium. Readers who are interested in accessing the data must first submit a proposal to the Data Access Committee. If the reader is not a member of the consortium, their concept form must be sponsored by a principal investigator (PI) of one of the PRACTICAL consortium member studies. If approved by the Data Access Committee, PIs within the consortium, each of whom retains ownership of their data submitted to the consortium, can then choose to participate in the specific proposal. In addition, portions of the data are available for request from dbGaP (database of Genotypes and Phenotypes) which is maintained by the National Center for Biotechnology Information (NCBI): https://www.ncbi.nlm.nih.gov/gap/?term=Icogs+prostatehttps://www.ncbi.nlm.nih.gov/gap/?term=Icogs+prostate.

Anyone can apply to join the consortium. The eligibility requirements are listed here: http://practical.icr.ac.uk/blog/?page_id=9. Joining the consortium would not guarantee access, as a proposal for access would still be submitted to the Data Access Committee, but there would be no need for a separate member sponsor. Readers may find information about application by using the contact information below:

Rosalind Eeles
Principal Investigator for PRACTICAL
Professor of Oncogenetics
Institute of Cancer Research (ICR)
Sutton, UK
Email: PRACTICAL@icr.ac.uk
URL: http://practical.icr.ac.uk
Tel: ++44 (0)20 8722 4094

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Table Legends

Table 1. Characteristics of PHS46+African SNPs. RS-ID, chromosome and base-pair position (based on version 37), effect and reference alleles, bootstrap-estimated beta, and effect allele frequencies in aggregated Africans from 1000 Genomes (referenced from dbSNP) of the three SNPs selected for addition to PHS46

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Figure Legends

Figure 1 Comparison between PHS46 and PHS46+African. Mean hazard ratio metrics plotted for PHS46 and PHS46+African models in the African dataset. Improvements were observed in all performance metrics investigated. Error bars represent 95% confidence interval

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Appendix 1. Members of the PRACTICAL Consortium

Christopher A. Haiman[1], Fredrick R. Schumacher[2,3], Sara Benlloch[4,5], Ali Amin Al Olama[6,7], Sonja I. Berndt[8], David V. Conti[1], Fredrik Wiklund[9], Stephen Chanock[8], Susan M. Gapstur[10], Victoria L. Stevens[10], Jyotsna Batra[11,12], Judith Clements[11,12], APCB BioResource[13,14], Henrik Grönberg[15], Nora Pashayan[16,17], Johanna Schleutker[18,19], Demetrius Albanes[8], Stephanie Weinstein[8], Alicja Wolk[20,21], Catharine West[22], Lorelei Mucci[23], Stella Koutros[8], Karina Dalsgaard Sørensen[24,25], Eli Marie Grindedal[26], David E. Neal[27,28,29], Freddie C. Hamdy[30,31], Jenny L. Donovan[32], Ruth C. Travis[33], Robert J. Hamilton[34,35], Sue Ann Ingles[36], Barry S. Rosenstein[37,38], Yong-Jie Lu[39], Graham G. Giles[40,41,42], Ana Vega[43,44,45], Manolis Kogevinas[46,47,48,49], Kathryn L. Penney[50], Janet L. Stanford[51,52], Cezary Cybulski[53], Børge G. Nordestgaard[54,55], Hermann Brenner[56,57,58], Christiane Maier[59], Jeri Kim[60], Manuel R. Teixeira[61,62], Susan L. Neuhausen[63], Kim De Ruyck[64], Azad Razack[65], Lisa F. Newcomb[51,66], Davor Lessel[67], Radka Kaneva[68], Nawaid Usmani[69,70], Frank Claessens[71], Paul A. Townsend[72], Manuela Gago-Dominguez[73,74], Monique J. Roobol[75], Kay-Tee Khaw[76], Lisa Cannon-Albright[77,78], Hardev Pandha[79], Stephen N. Thibodeau[80], Peter Kraft[81], Elio Riboli[82]

[1]Center for Genetic Epidemiology, Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA 90015, USA

[2]Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH 44106-7219, USA

[3]Seidman Cancer Center, University Hospitals, Cleveland, OH 44106, USA.

[4]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge CB1 8RN, UK

[5]The Institute of Cancer Research, London, SM2 5NG, UK

[6]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge, UK

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[7]University of Cambridge, Department of Clinical Neurosciences, Stroke Research Group, R3, Box 83, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK
[8]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland, 20892, USA
[9]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, SE-171 77 Stockholm, Sweden
[10]Behavioral and Epidemiology Research Group, Research Program, American Cancer Society, 250 Williams Street, Atlanta, GA 30303, USA
[11]Australian Prostate Cancer Research Centre-Qld, Institute of Health and Biomedical Innovation and School of Biomedical Sciences, Queensland University of Technology, Brisbane QLD 4059, Australia
[12]Translational Research Institute, Brisbane, Queensland 4102, Australia
[13]Australian Prostate Cancer Research Centre-Qld, Queensland University of Technology, Brisbane; Prostate Cancer Research Program, Monash University, Melbourne; Dame Roma Mitchell Cancer Centre, University of Adelaide, Adelaide; Chris O'Brien Lifehouse and
[14]Translational Research Institute, Brisbane, Queensland, Australia
[15]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
[16]Department of Applied Health Research, University College London, London, WC1E 7HB, UK
[17]Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Strangeways Laboratory, Worts Causeway, Cambridge, CB1 8RN, UK
[18]Institute of Biomedicine, Kiinamyllynkatu 10, FI-20014 University of Turku, Finland
[19]Department of Medical Genetics, Genomics, Laboratory Division, Turku University Hospital, PO Box 52, 20521 Turku, Finland
[20]Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, SE-171 77 Stockholm, Sweden
[21]Department of Surgical Sciences, Uppsala University, 75185 Uppsala, Sweden
[22]Division of Cancer Sciences, University of Manchester, Manchester Academic Health

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Science Centre, Radiotherapy Related Research, The Christie Hospital NHS Foundation Trust, Manchester, M13 9PL UK

[23]Department of Epidemiology,Harvard T. H. Chan School of Public Health, Boston, MA 02115, USA

[24]Department of Molecular Medicine, Aarhus University Hospital, Palle Juul-Jensen Boulevard 99, 8200 Aarhus N, Denmark

[25]Department of Clinical Medicine, Aarhus University, DK-8200 Aarhus N

[26]Department of Medical Genetics, Oslo University Hospital, 0424 Oslo, Norway

[27]Nuffield Department of Surgical Sciences, University of Oxford, Room 6603, Level 6, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU, UK

[28]University of Cambridge, Department of Oncology, Box 279, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK

[29]Cancer Research UK, Cambridge Research Institute, Li Ka Shing Centre, Cambridge UK

[30]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, OX1 2JD, UK

[31]Faculty of Medical Science, University of Oxford, John Radcliffe Hospital, Oxford, UK

[32]Population Health Sciences, Bristol Medical School, University of Bristol, BS8 2PS, UK

[33]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, OX3 7LF, UK

[34]Dept. of Surgical Oncology, Princess Margaret Cancer Centre, Toronto ON M5G 2M9, Canada

[35]Dept. of Surgery (Urology), University of Toronto, Canada

[36]Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA 90015, USA

[37]Department of Radiation Oncology and Department of Genetics and Genomic Sciences, Box 1236, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA

[38]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029-5674 , USA.

[39]Centre for Molecular Oncology, Barts Cancer Institute, Queen Mary University of

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London, John Vane Science Centre, Charterhouse Square, London, EC1M 6BQ, UK
[40]Cancer Epidemiology Division, Cancer Council Victoria, 615 St Kilda Road, Melbourne, VIC 3004, Australia
[41]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Grattan Street, Parkville, VIC 3010, Australia
[42]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria 3168, Australia
[43]Fundación Pública Galega Medicina Xenómica, Santiago De Compostela, 15706, Spain.
[44]Instituto de Investigación Sanitaria de Santiago de Compostela, Santiago De Compostela, 15706, Spain.
[45]Centro de Investigación en Red de Enfermedades Raras (CIBERER), Spain
[46]ISGlobal, Barcelona, Spain
[47]IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
[48]Universitat Pompeu Fabra (UPF), Barcelona, Spain
[49]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[50]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA 02184, USA
[51]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, 98109-1024, USA
[52]Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington 98195, USA
[53]International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
[54]Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark
[55]Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, 2200 Copenhagen, Denmark
[56]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), D-69120, Heidelberg, Germany

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[57]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), D-69120 Heidelberg, Germany
[58]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Im Neuenheimer Feld 460 69120 Heidelberg, Germany
[59]Humangenetik Tuebingen, Paul-Ehrlich-Str 23, D-72076 Tuebingen, Germany
[60]The University of Texas M. D. Anderson Cancer Center, Department of Genitourinary Medical Oncology, 1515 Holcombe Blvd., Houston, TX 77030, USA
[61]Department of Genetics, Portuguese Oncology Institute of Porto (IPO-Porto), Porto, Portugal
[62]Biomedical Sciences Institute (ICBAS), University of Porto, Porto, Portugal
[63]Department of Population Sciences, Beckman Research Institute of the City of Hope, 1500 East Duarte Road, Duarte, CA 91010, 626-256-HOPE (4673)
[64]Ghent University, Faculty of Medicine and Health Sciences, Basic Medical Sciences, Proeftuinstraat 86, B-9000 Gent
[65]Department of Surgery, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
[66]Department of Urology, University of Washington, 1959 NE Pacific Street, Box 356510, Seattle, WA 98195, USA
[67]Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, D-20246 Hamburg, Germany
[68]Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Medical University of Sofia, Sofia, 2 Zdrave Str., 1431 Sofia, Bulgaria
[69]Department of Oncology, Cross Cancer Institute, University of Alberta, 11560 University Avenue, Edmonton, Alberta, Canada T6G 1Z2
[70]Division of Radiation Oncology, Cross Cancer Institute, 11560 University Avenue, Edmonton, Alberta, Canada T6G 1Z2
[71]Molecular Endocrinology Laboratory, Department of Cellular and Molecular Medicine, KU Leuven, BE-3000, Belgium
[72]Division of Cancer Sciences, Manchester Cancer Research Centre, Faculty of Biology,

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Medicine and Health, Manchester Academic Health Science Centre, NIHR Manchester Biomedical Research Centre, Health Innovation Manchester, Univeristy of Manchester, M13 9WL

[73]Genomic Medicine Group, Galician Foundation of Genomic Medicine, Instituto de Investigacion Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, Servicio Galego de Saúde, SERGAS, 15706, Santiago de Compostela, Spai

[74]University of California San Diego, Moores Cancer Center, La Jolla, CA 92037, USA

[75]Department of Urology, Erasmus University Medical Center, 3015 CE Rotterdam, The Netherlands

[76]Clinical Gerontology Unit, University of Cambridge, Cambridge, CB2 2QQ, UK

[77]Division of Epidemiology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA

[78]George E. Wahlen Department of Veterans Affairs Medical Center, Salt Lake City, Utah 84148, USA

[79]The University of Surrey, Guildford, Surrey, GU2 7XH

[80]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, USA

[81]Program in Genetic Epidemiology and Statistical Genetics, Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

[82]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, SW7 2AZ, UK

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Appendix 2. Funding sources for the PRACTICAL consortium

CRUK and PRACTICAL consortium

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Information of the PRACTICAL consortium can be found at http://practical.icr.ac.uk/

BioVU

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MOFFITT

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SCCS

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Table 1. Characteristics of PHS46+African SNPs. RS-ID, chromosome and base-pair position (based on version 37), effect and reference alleles, bootstrap-estimated beta, and effect allele frequencies in aggregated Africans from 1000Genomes (referenced from dbSNP) of the three SNPs selected for addition to PHS46.

RS number	Chromosome	Position	Effect	Ref	beta	Frequency (%)
rs76229939	8	128085394	G	A	0.441	4.8
rs74421890	8	128096183	A	G	0.415	4.1
rs5013678	8	128103979	G	A	-0.260	8.1

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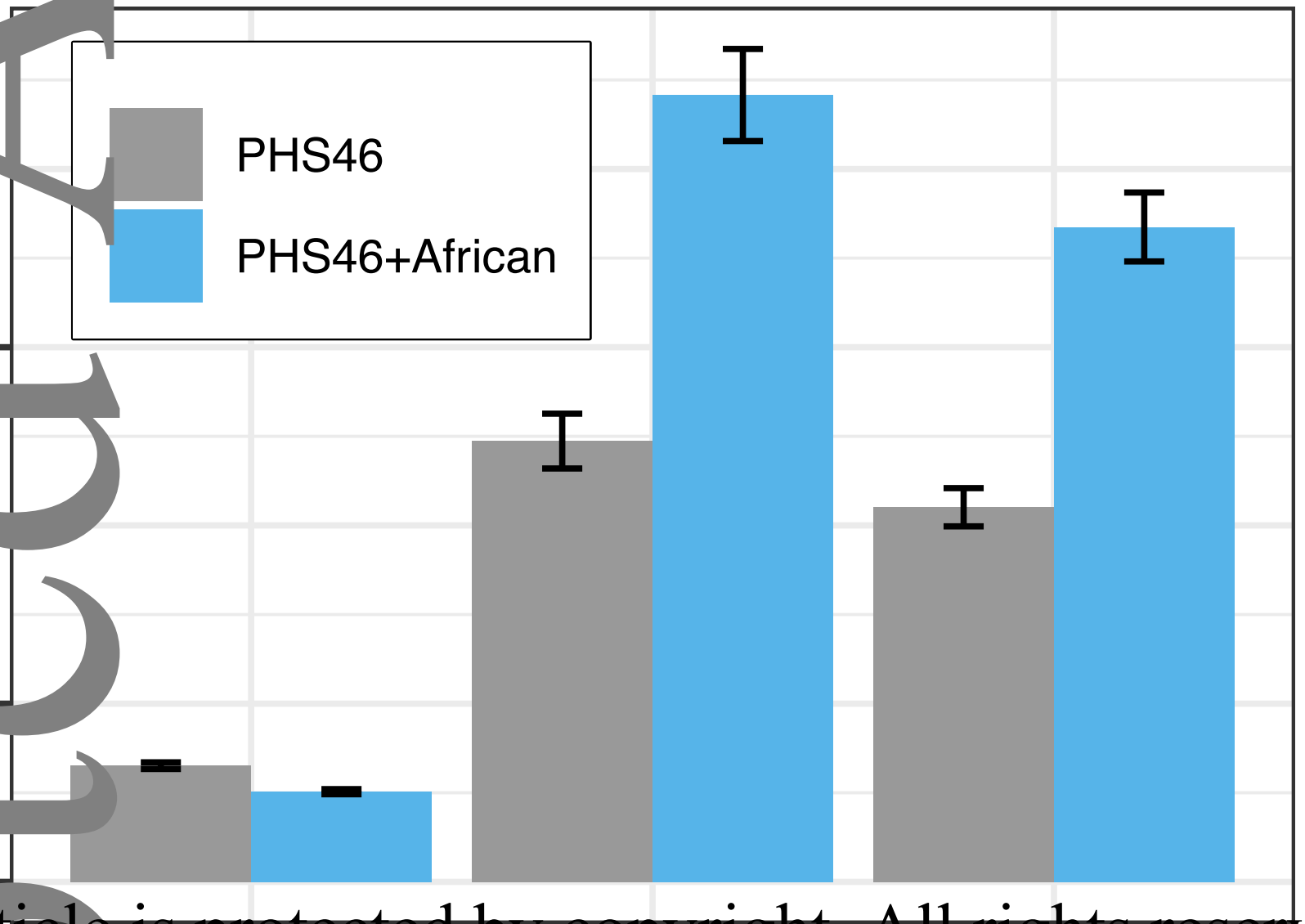

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