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TITLE: Creation and Validation of a Prebiopsy Nomogram for Predicting High-Risk Prostate Cancer in African American Men

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14. ABSTRACT: Background: Over 1 million prostate biopsies are performed annually and up to 70% of them are deemed unnecessary because many biopsies are negative or only have evidence for indolent prostate cancer (PCa). Risk calculators are one tool that can help men make decisions about whether to undergo their biopsy for an elevated prostate specific antigen (PSA) based on their reported probability of having clinically significant (csPCa), i.e. Gleason grade group 2-5 PCa. The Prostate Cancer Prevention Trial Risk Calculator version 2.0 (PCPT RC) is a popular risk calculator model. Since the grant was initially funded, 2 additional calculators have become popular including the Prostate Biopsy Collaborative Group (PBCG), which uses the same variables as the PCPT, and the Kaiser Permanente Prostate Cancer (KPPC) risk calculators. Our preliminary data on the PCPT RC performance in a multi-ethnic cohort showed that the PCPT RC seemed to have a lower accuracy in Black men. We hypothesized that since Black race or African ancestry is a term in the PCPT risk calculator model and simply adds a fixed probability adjustment across the entire risk distribution, that a risk calculator developed in a Black cohort would outperform these popular risk calculators. In Aim 1, we will assess the accuracy of a popular prostate biopsy risk calculator (Prostate Cancer Prevention Trial Risk Calculator 2.0) in Black men aged 40-79 with elevated prostate specific antigen (PSA) or abnormal digital rectal exam for the detection of Gleason grade group (GG) 2-5 prostate cancer (PCa). For Aim 2, we will develop and internally and validate a new risk Black-race tailored risk calculator in a retrospective (Biological and Environmental Mediators of Serum Vitamin D3 and Prostate Cancer Risk, NIMHD R01, PI Rick Kittles) and prospective cohort (Creation and Validation of a Prebiopsy Nomogram for Predicting High-Risk Prostate Cancer in African American Men) of Black men undergoing diagnostic prostate biopsy, age 40-79, with elevated PSA or abnormal digital rectal exam and PSA <50ng/ml. Lastly, in Aim 2B, we will add genetic West African ancestry into the best performing Aim 2A risk calculator (binary logistic regressions) models to determine if the inclusion of individual ancestry data improves GG2-5 PCa prediction accuracy. Lastly, we will externally validate the Aim 2 models in a prospectively recruited set of men undergoing prostate biopsy for elevated PSA or abnormal DRE in Aim 3.					
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1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Over 1 million prostate biopsies are performed annually and up to 70% of them are deemed unnecessary because many biopsies are negative or only have evidence for indolent prostate cancer (PCa). Risk calculators are one tool that can help men make decisions about whether to undergo their biopsy for an elevated prostate specific antigen (PSA) based on their reported probability of having clinically significant (csPCa), i.e. Gleason grade group 2-5 PCa. The Prostate Cancer Prevention Trial Risk Calculator version 2.0 (PCPT RC) is a popular risk calculator model. Since the grant was initially funded, 2 additional calculators have become popular including the Prostate Biopsy Collaborative Group (PBCG), which uses the same variables as the PCPT, and the Kaiser Permanente Prostate Cancer (KPPC) risk calculators. Our preliminary data on the PCPT RC performance in a multi-ethnic cohort showed that the PCPT RC seemed to have a lower accuracy in Black men. We hypothesized that since Black race or African ancestry is a term in the PCPT risk calculator model and simply adds a fixed probability adjustment across the entire risk distribution, that a risk calculator developed in a Black cohort would outperform these popular risk calculators.

In Aim 1, we will assess the accuracy of a popular prostate biopsy risk calculator (Prostate Cancer Prevention Trial Risk Calculator 2.0) in Black men aged 40-79 with elevated prostate specific antigen (PSA) or abnormal digital rectal exam for the detection of Gleason grade group (GG) 2-5 prostate cancer (PCa). For Aim 2, we will develop and internally and validate a new risk Black-race tailored risk calculator in a retrospective (*Biological and Environmental Mediators of Serum Vitamin D3 and Prostate Cancer Risk, NIMHD R01, PI Rick Kittles*) and prospective cohort (*Creation and Validation of a Prebiopsy Nomogram for Predicting High-Risk Prostate Cancer in African American Men*) of Black men undergoing diagnostic prostate biopsy, age 40-79, with elevated PSA or abnormal digital rectal exam and PSA <50ng/ml. Lastly, in Aim 2B, we will add genetic West African ancestry into the best performing Aim 2A risk calculator (binary logistic regressions) models to determine if the inclusion of individual ancestry data improves GG2-5 PCa prediction accuracy. Lastly, we will externally validate the Aim 2 models in a prospectively recruited set of men undergoing prostate biopsy for elevated PSA or abnormal DRE in Aim 3.

2. KEYWORDS:

Prostate cancer detection, Prostate cancer, prostate biopsy Risk Calculator, Nomogram, Prostate Biopsy

3. OVERALL PROJECT SUMMARY: *Summarize the progress during appropriate reporting period (single annual or comprehensive final). This section of the report shall be in direct alignment with respect to each task outlined in the approved SOW in a summary of Current Objectives, and a summary of Results, Progress and Accomplishments with Discussion. Key methodology used during the reporting period, including a description of any changes to originally proposed methods, shall be summarized. Data supporting research conclusions, in the form of figures and/or tables, shall be embedded in the text, appended, or referenced to appended manuscripts. Actual or anticipated problems or delays and actions or plans to resolve them shall be included. Additionally, any changes in approach and reasons for these changes shall be reported. Any change that is substantially different from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc.) requires review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.*

Northwestern University (Initiating PI site) / The University of Illinois at Chicago (Partnering PI site)

Broad Summary: We accomplished all of our specific aims and recruited 91% of our targeted enrollment (n = 364/400) for Aim 3. This was good considering our COVID delays and staffing issues. Because new risk calculators (i.e. PBCG and KPPC Risk Calculators) were published and popularized after the grant was written, we incorporated the PBCG risk calculator into our Aim 1 objectives and incorporated both the PBCG and the KPPC into analyses of Aim 2 and Aim 3. There were no patents. We had one issue during the study

with troubleshooting the problems with obtaining genetic ancestry estimates. We were using whole blood that was frozen before DNA extraction. The process created DNA that was contaminated by protein which interrupted the genotyping. This took 6 months to troubleshoot and resulted in samples that were not salvageable. We published 4 abstracts, the Aim 1 paper, and 3 other manuscripts unrelated to the proposal that leveraged the data from this study. The results of our Aim 1 hypothesis have been published in BMC Urology in 2019. Aim 2 is being prepared for the Journal of Urology currently. Aim 3 will likely be incorporated into the same Journal of Urology publication.

Direct:

1. Carbutaru S, Netter OS, Gogana P, Helenowski IB, Jovanovic B, Ruden M, Hollowell CMP, Sharifi R, Kittles RA, Schaeffer E, **Gann P, Murphy AB**. A comparative effectiveness analysis of the PBCG vs. PCPT risks calculators in a multi-ethnic cohort. BMC Urol. 2019 Nov 27;19(1):121. doi: 10.1186/s12894-019-0553-6. PMID: 31771578; PMCID: PMC6880480.

Indirect:

1. Press DJ, Shariff-Marco S, Lichtensztajn DY, Lauderdale D, **Murphy AB**, Inamdar PP, DeRouen MC, Hamilton AS, Yang J, Lin K, Hedeker D, Haiman CA, Cheng I, Gomez SL. Contributions of Social Factors to Disparities in Prostate Cancer Risk Profiles among Black Men and Non-Hispanic White Men with Prostate Cancer in California. Cancer Epidemiol Biomarkers Prev. 2021 Nov 30. doi: 10.1158/1055-9965.EPI-21-0697. Epub ahead of print. PMID: 34853020.
2. Babajide R, Carbutaru S, Netter OS, Watson KS, Holloway-Beth A, McDowell T, Ben Levi J, Murray M, Stinson J, Hollowell CMP, Dalton DP, Moore L, Kittles RA, **Gann PH**, Schaeffer EM, **Murphy AB**. Performance of Prostate Health Index in Biopsy Naïve Black Men. J Urol. 2021 Mar;205(3):718-724. doi: 10.1097/JU.0000000000001453. Epub 2020 Oct 26. PMID: 33103942; PMCID: PMC8320068.
3. **Murphy AB**, Carbutaru S, Netter OS, Gornbein C, Dixon MA, Macias V, Sharifi R, Kittles RA, Yang X, Kajdacsy-Balla A, **Gann P**. A 17-Gene Panel Genomic Prostate Score Has Similar Predictive Accuracy for Adverse Pathology at Radical Prostatectomy in African American and European American Men. Urology. 2020 Aug;142:166-173. doi: 10.1016/j.urology.2020.01.052. Epub 2020 Apr 8. PMID: 32277993; PMCID: PMC7387177.

Major Task 1: Prepare protocol and obtain IRB approval

Objectives:

To prepare an initial protocol and receive its approval from the IRB at all four sites plus the HRPO.
To gain IRB approvals for amendments as the need arises.

Results:

IRB approvals were continuously maintained throughout the project without interruption. Several amendments were submitted to the IRBs and approved, mainly for changes in study personnel. Since enrollment and data collection have been completed, no further changes in the protocol or applications for amendment to the IRBs are planned. Annual IRB approvals will be maintained as long as data analyses and publication work continue.

Accomplishments:

All study sites have maintained continuing review IRB approval except Dr. Kittles in Year 4. He essentially had a dramatic reduction in budget and became a collaborator.

Discussion:

We have and will continue to submit continuing reviews to the IRB as long as data analysis and manuscript preparation remains active. Dr. Kittles did not do a continuing review for 2021 since he only provided the genetic ancestry estimates as a consultant.

Major Task 2: Data Quality Check

Objectives: Complete data merger from R01 study and Washington DC study. Quality Control check and entry of missing data. Export data as CSV or Excel databases

Results: We were unable to merge the data from the Washington DC study because most participants were missing Gleason scores on their biopsy results. This meant that we were left only with the 393 eligible Black men (PSA <50ng/ml) of 463 Black men we recruited in Dr. Kittles' R01 study from 2008-2014.

Quality control checks were done by the PI and a senior coordinator at the close of the study in 2014. We repeated this step to address missing data and account for missing biopsy and PSA information. We did not uniformly collect residential address, BMI and prior biopsy status and therefore have just completed a new assessment of missing data and have attempted to complete all the relevant data. Our data is now >95% complete on our covariates across both the retrospective development and our prospectively recruited validation data sets.

We will be exporting this finalized data to an Excel spreadsheet for uploading to R and to SPSS for data. It will be locked on 1-31-2022 once the genetic ancestry estimates are reported by Dr. Kittles' laboratory, which are pending now for the last 75 participants.

Accomplishments: We completed the database updates for prior biopsy status and residential address. We completed the data quality assessment which was very high.

Discussion: We will complete the ancestry estimates data entry shortly after study final progress report due date. We should be completed with the database locking on 1-31-2022.

Major Task 3: Compute and Input the PCPT Risk Calculator

Objectives: To download the R code for the prediction of high-grade GG2-5 PCa using the code available at riskcalc.org/PCPTRC/ and <https://riskcalc.org/PBCG/>. To input the predicted probability of GG2-5 PCa, probability of negative biopsy and of GG1-5 PCa.

Results: We downloaded the R code for both the PCPT and PBCG risk calculators directly from study author Donna Ankerst. We then calculated and recorded the model calculated probability of GG2-5 PCa in all men using both PCPT and PBCG RCs. This was validated by manual entry of 10% of the patients into the online calculator at <https://riskcalc.org/PCPTRC/> and <https://riskcalc.org/PBCG/>.

Accomplishments: We input all of the participants' GG2-5 predicted probabilities from both RCs for Aim 1 and have added in the Kaiser Permanente Prostate Cancer RC for Aim 2 and 3 analyses. This was responsive the state of current clinical practice.

Discussion: We adequately cleaned the data for all the calculators' variables and outcomes. We assessed accuracy for 100% of important covariates. We used the R code for the 3 publicly available risk calculators (PCPT, PBCG and KPPC RCs). We validated a subset of the outputs from all 3 publicly available risk calculators with their websites' outputs. We calculated probabilities of GG2-5 PCa based on our own models for the internal and external validation databases for comparison of discrimination. The biopsy risk calculators predicted probabilities of GG2-5 PCa are included in the study database for our discrimination analysis.

Major Task 4: Perform Data Analysis (Aim 1)

Field Code Changed

Objectives: To compare the discrimination, calibration, and specificity (avoided unnecessary biopsies) of the PCPT RC in Black vs. White men.

Results: We completed this analysis using only the 463 Blacks, 395 Whites and 136 Other race men. We initially only intended to report on the PCPT risk calculator findings, but the PBCG RC was released by the same authors (Andrew Vickers & Donna Ankerst) in 2018, so we compared the PBGC and PCPT RCs in terms of the discrimination, calibration and avoided biopsies by racial group and included the "Other" racial group which was predominantly made up of Hispanic men.

Accomplishments: This analysis of Aim 1 was published as a manuscript in BMC Urology in November 2019 with Dr. Gann and Dr. Murphy as senior authors.

Citation (see Appendix 1): Carbutaru S, Netley OS, Gogana P, Helenowski IB, Jovanovic B, Ruden M, Hollowell CMP, Sharifi R, Kittles RA, Schaeffer E, **Gann P, Murphy AB.** A comparative effectiveness analysis of the PBCG vs. PCPT risks calculators in a multi-ethnic cohort. BMC Urol. 2019 Nov 27;19(1):121. PMID: 31771578; PMCID: PMC6880480.

Discussion: We had adequate power to compare the accuracy of the established risk calculators with our reduced population of Black men. We were powered to detect a 7% AUC difference between PCPT and PBCG in Blacks and Whites at alpha = 5% with greater than 99% power. For Other race men we achieved a 76% power. Dr. Murphy (Initiating PI) shared senior author with the Partnering PI (Dr. Peter Gann) on this manuscript.

The calibration curves and net benefit curves are being produced for the manuscript but are not included in this Final Report.

Aim 1 Paper Abstract

Background: Predictive models that take race into account like the Prostate Cancer Prevention Trial Risk Calculator 2.0 (PCPT RC) and the new Prostate Biopsy Collaborative Group (PBCG) RC have been developed to equitably mitigate the overdiagnosis of prostate specific antigen (PSA) screening. Few studies have compared the performance of both calculators across racial groups.

Methods: From 1485 prospectively recruited participants, 954 men were identified undergoing initial prostate biopsy for abnormal PSA or digital rectal examination in five Chicago hospitals between 2009 and 2014. Discrimination, calibration, and frequency of avoided biopsies were calculated to assess the performance of both risk calculators.

Results: Of 954 participants, 463 (48.5%) were Black, 355 (37.2%) were White, and 136 (14.2%) identified as Other (see Table 1). Biopsy results were as follows: 310 (32.5%) exhibited no cancer, 323 (33.9%) Gleason grade group 1 (GG1) prostate cancer, and 321 (33.6%) clinically significant prostate cancer (GG2-5 or csPCa).

Continuous Variables	Black (n = 463) Median [IQR]	White (n = 355) Median [IQR]	Other (n = 136) Median [IQR]	p Value ¹
Age, years	61.0 [57.0, 67.0]	62.0 [58.0, 67.0]	62.0 [57.0, 67.0]	0.47
BMI, kg/m ²	27.8 [24.5, 31.8]	27.5 [25.0, 30.6]	27.4 [24.2, 30.3]	0.56
PSA, ng/ml	7.8 [5.3, 15.5]	4.8 [3.6, 7.3]	7.2 [5.1, 12.4]	< 0.001
Prostate Volume, cm ³	39.5 [28.8, 55.4]	39.5 [29.7, 51.0]	48.7 [30.0, 69.4]	< 0.001
PSA density, ng/cm ³	0.23 [0.12, 0.43]	0.13 [0.09, 0.20]	0.18 [0.11, 0.32]	< 0.001
PCPT csPCa Risk, %	25.0 [17.0, 40.0]	7.0 [5.0, 12.0]	11.5 [7.0, 18.0]	< 0.001
PBCG csPCa Risk, %	45.0 [31.0, 65.0]	26.0 [18.0, 41.0]	37.5 [22.0, 54.2]	< 0.001
Categorical Variables	Black n (%)	White n (%)	Other n (%)	p Value ²
Clinical Risk Factors				
Family History of PCa	93 (20.1)	88 (24.8)	21 (15.4)	0.055
Abnormal DRE	140 (30.3)	112 (31.5)	43 (31.3)	0.92
BPH/LUTS	151 (32.6)	135 (38.0)	66 (48.5)	0.003
5-ARI Use (current)	43 (9.3)	19 (5.4)	26 (19.1)	< 0.001
Substance Use History				
Heavy Smoking (>1ppd)	29 (6.4)	19 (5.4)	1 (0.7)	0.034
Heavy Alcohol Use (> 10 drinks/week)	30 (6.6)	46 (13.0)	5 (3.7)	< 0.001
Demographic Factors				
Married	192 (42.1)	269 (76.2)	105 (77.2)	< 0.001
College Completion	165 (36.2)	248 (70.3)	46 (33.8)	< 0.001
Income < \$30,000	161 (43.9)	39 (12.0)	42 (55.2)	< 0.001
Biopsy Outcomes				< 0.001 ³
Indolent Cancer	167 (36.1)	118 (33.2)	38 (27.9)	0.20
Clinically Significant Cancer	175 (37.8)	120 (33.8)	26 (19.1)	< 0.001
No Cancer	121 (26.1)	117 (33.0)	72 (52.9)	< 0.001

Note Clinically significant prostate cancer (csPCa) = Gleason grade group 2-5 prostate cancer (GG2-5 PCa).

Statistically, there was no difference in the AUCs between PBCG and PCPT for overall PCa when all men are included. The AUC for GG2-5 PCa was 0.64 (95% CI: 0.61–0.68) for PCPT and 0.65 (95% CI: 0.62–0.68) for PBCG ($p = 0.27$). The AUCs slightly improved with PBCG in Whites (0.64 vs. 0.66; $p = 0.07$) and Blacks (0.67 vs. 0.68; $p = 0.25$), but not in Others (0.64 vs. 0.64; $p = 0.81$). Differences in area under the curve (AUC) for the detection of csPCa (GG2-5 PCa) between PCPT and PBCG were not statistically different across all racial groups.

PBCG did not improve calibration plots in Blacks and Others, as it showed higher levels of overprediction at most risk thresholds (see Figure 1).

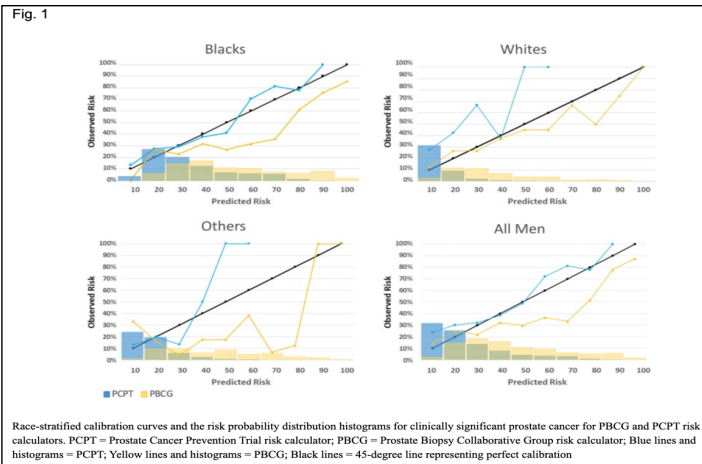
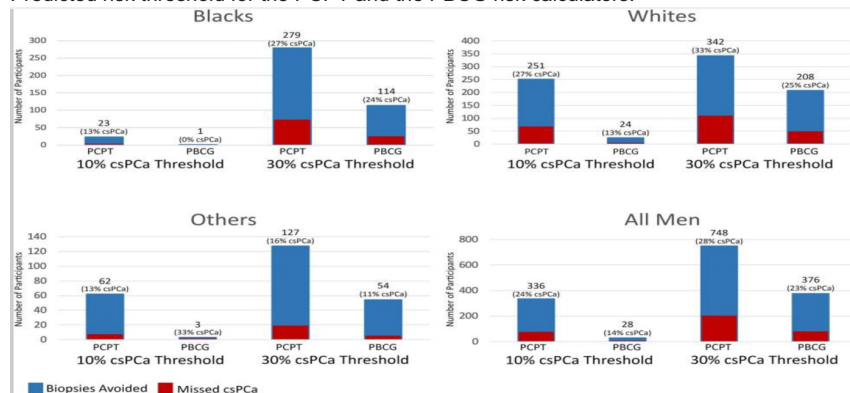


Figure 2 below shows that the PCPT led to an increased number of avoidable biopsies in minorities compared to PBCG at the 30% threshold (68% vs. 28% of all patients) with roughly similar rates of missed csPCa (23% vs. 20%).

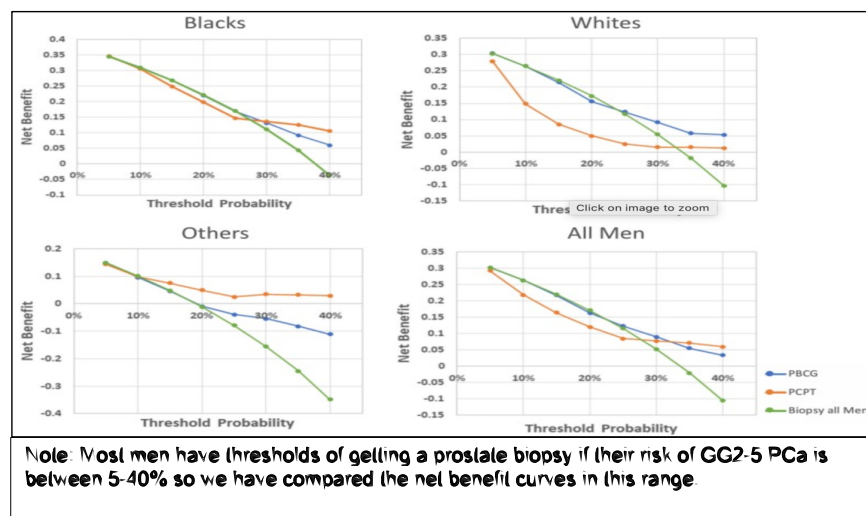
Figure 2: Comparison of the biopsies avoided and the GG2-5 PCa that were missed at the 10% Predicted risk threshold for the PCPT and the PBCG risk calculators.



Note: Theoretical number of avoided biopsies and missed clinically significant GG2-5 PCas at the 10% and 30% predictive thresholds by race. PCPT = Prostate Cancer Prevention Trial 2.0 risk calculator; PBCG = Prostate Biopsy Collaborative Group risk calculator; csPCa = clinically significant GG2-5 prostate cancer; Blue bar: Total number of biopsies avoided; Red bar: Missed clinically significant prostate cancer.

In terms of Net Benefit, the PCPT and PBCG perform very similarly to one another for Blacks (see Figure 3); for men in the Other race group, the PCPT is clearly better performing than the PBCG RC. In Whites, the PBCG clearly outperforms the original PCPT risk calculator throughout the 0-40% thresholds.

Figure 3: Net benefit curves for the PCPT and PBCG risk calculator versus the Biopsy all men with elevated PSA strategy



Conclusion: Significant improvements were noticed in PBCG's calibrations and net benefits in Whites compared to PCPT. Since PBCG's improvements in Blacks are disputable and potentially biases a greater number of low risk Black and Other men towards unnecessary biopsies, PCPT may lead to better biopsy decisions in racial minority groups. Further comparisons of commonly used risk calculators across racial groups are warranted to minimize excessive biopsies and overdiagnosis in ethnic minorities.

Major Task 5: Select Variables for inclusion for Aim 2 Models

Objectives: To search the published literature using PUBMED and Google Scholar to identify covariates from other prostate cancer (PCa) risk calculators that are previously established independent predictors of any PCa or GG2-5 PCa.

Results: We identified over 20 manuscripts that developed and internally and, in some cases, externally validated a risk calculator that predicted either any PCa or GG2-5 PCa on initial or repeat prostate biopsy. Within the ~20 manuscripts we found 31 covariates that we could potentially incorporate into a risk calculator. Some were not feasible because they are not collected routinely in US clinical practice like suspicious abnormality in the prostate on transrectal ultrasound.

Accomplishments: We are using these covariates but are assessing the potential of other predictors including genetic West African ancestry, neighborhood socioeconomic factors (concentrated disadvantage) and other social determinants of health like marital status, educational attainment, and substance use in future unplanned manuscripts.

Discussion: The variable selection process was accomplished in 2019. Newer models have been published by Presti et al at Kaiser Permanente that suggest we devise a second set of calculator models that include prostate volume based covariates including prostate volume and PSA density.

Presti J Jr., Alexeeff S, Horton B, Prausnitz S, Avins AL. Prospective development of a prostate cancer risk calculator in a racially diverse population: The Kaiser Permanente Prostate Cancer Risk Calculator. *Urol Oncol.* 2020 Nov;38(11):847.e1-847.e8.

Major Task 6: Perform Data Analysis for Aim 2

2A) Develop and validate a Black race-tailored pre-biopsy regression model for the prediction of potentially lethal GG2-5 PCa

2B) Determine if adding genetic WA ancestry to the best performing Black race-tailored model improves prediction performance

Objectives: Divide the Black participants into 2 groups as a Development (70%) and Internal Validation Cohort (30%). Derive a best-fit binary logistic regression model using the iterative variable selection process in the Development cohort and internally validate the models in 30% of the cohort using models' area under the curve.

Results: We identified 393 Black men among the 463 Black men for the Development cohort from the R01 Vitamin D study that were eligible for inclusion after excluding men with PSA >50ng/ml and men with missing PSA or prostate biopsy outcomes. We have worked with our new study statistician (Zequn Sun PhD) to develop these models. We decided to create 2 best-fit models in the Development cohort; one model will include prostate volume based measures (PSA density or prostate volume) given the growing use of prostate MRI before initial and repeat prostate biopsies.

Table 3 shows that we had missing genetic ancestry data for 76 participants (317/393 = 80.7%) in the Development Cohort. We also assessed for statistically significant differences in median levels of the continuous variables and significant differences in the proportions of the categorical variables with GG2-5 PCa versus GG1 PCa + negative biopsies.

Hosmer and Lemeshow propose a "purposeful model selection" approach, which can be adapted to logistic regression. Careful univariate analysis of each independent variable is carried out (see Table 3 above) using contingency table analysis for categorical variables (including Chi square test, Fisher's Exact test) and two-sample t-tests for continuous variables. Log₂(pre-biopsy PSA), prostate volume (cm³), history of prior biopsy (yes vs. no), and abnormal digital rectal exam (DRE, yes vs. no/not palpable/not performed) are kept for further analysis with p-value less than 0.25.

Table 3: Selected Characteristics of the variables of interest of the Retrospective Development data

	GS ≤- 6 (N=225)	GS ≥ 6 (N=92)	P-value
WA			
Mean (SD)	76.9 (14.3)	78.6 (11.8)	0.297
Median [Min, Max]	78.7 [8.38, 99.0]	80.5 [48.1, 97.4]	
NA			
Mean (SD)	5.68 (6.74)	5.13 (4.98)	0.423
Median [Min, Max]	3.55 [0.200, 77.2]	3.15 [0.470, 26.8]	
EUR			
Mean (SD)	0.174 (0.129)	0.163 (0.111)	0.453
Median [Min, Max]	0.147 [0.00400, 0.796]	0.151 [0.0140, 0.494]	
PSA_Log2			
Mean (SD)	2.86 (1.03)	3.33 (1.14)	<0.001
Median [Min, Max]	2.74 [-1.12, 5.63]	3.05 [1.60, 5.66]	
ProstateVolume			
Mean (SD)	50.1 (29.3)	37.6 (18.1)	<0.001
Median [Min, Max]	41.7 [12.2, 192]	33.0 [9.87, 106]	
PriorBiopsy			
0	187 (83.1%)	86 (93.5%)	0.0248
1	38 (16.9%)	6 (6.5%)	
Site_PubFund			
0	45 (20.0%)	27 (29.3%)	0.0979
1	180 (80.0%)	65 (70.7%)	
Abnmi_DRE			
0	177 (78.7%)	55 (59.8%)	<0.001
1	48 (21.3%)	37 (40.2%)	
FamHx1_Binary			
0	176 (78.2%)	74 (80.4%)	0.775
1	49 (21.8%)	18 (19.6%)	
Age			
Mean (SD)	60.6 (7.30)	61.3 (6.90)	0.448
Median [Min, Max]	61.0 [43.0, 79.0]	60.0 [45.0, 81.0]	
BMI			
Mean (SD)	28.8 (5.34)	28.5 (5.14)	0.617
Median [Min, Max]	28.2 [19.4, 48.9]	27.9 [18.0, 42.7]	
HS			
0	142 (63.1%)	56 (60.9%)	0.805
1	83 (36.9%)	36 (39.1%)	
ARI			
0	204 (90.7%)	87 (94.6%)	0.356
1	21 (9.3%)	5 (5.4%)	

Percentage of West African (WA) and of Native American (NA) ancestry is also included due to its clinical importance for Aim 2B. A 70%/30% split ratio is used for internal validation, and the prospectively recruited DOD database is used for external validation. Table 4 below presents the characteristics of the external validation data. At the time of the report we have genetic ancestry data on 212 of the 364 participants. 75 are still pending and only 73.4% (212/289) of the previously recruited participants whole blood derived DNA was suitable for genetic ancestry estimation.

Table 4: Selected Characteristics of the variables of interest of the external testing data

	GS ≤ 6 (N=138)	GS > 6 (N=74)	P-value
WA			
Mean (SD)	80.2 (11.7)	78.5 (11.8)	0.328
Median [Min, Max]	80.2 [2.00, 99.0]	81.2 [39.5, 97.0]	
NA			
Mean (SD)	5.17 (5.24)	4.95 (4.30)	0.75
Median [Min, Max]	3.69 [0.110, 32.6]	3.00 [0.600, 21.8]	
EA			
Mean (SD)	14.8 (12.8)	16.8 (11.8)	0.262
Median [Min, Max]	13.3 [0, 93.3]	15.5 [0.300, 58.1]	
PSA_Log2			
Mean (SD)	2.50 (0.835)	3.28 (0.913)	<0.001
Median [Min, Max]	2.56 [-0.515, 5.08]	3.18 [0.642, 5.22]	
ProstateVolume			
Mean (SD)	52.2 (28.1)	39.6 (24.0)	<0.001
Median [Min, Max]	44.9 [5.21, 206]	32.3 [9.30, 135]	
PriorBiopsy			
0	117 (84.8%)	65 (87.8%)	0.688
1	21 (15.2%)	9 (12.2%)	
Abnml_DRE			
0	119 (86.2%)	48 (64.9%)	<0.001
1	19 (13.8%)	26 (35.1%)	
Site_PubFund			
JHS-Stroger	63 (45.7%)	19 (25.7%)	0.00249
Northwestern	33 (23.9%)	32 (43.2%)	
Provident	9 (6.5%)	1 (1.4%)	
UIC	30 (21.7%)	22 (29.7%)	
UroPartners	3 (2.2%)	0 (0%)	

Note: WA: percentage of West African ancestry; NA: percentage of Native American ancestry; EA: percentage of European ancestry; PSA was log-2 transformed to normalize the distribution; prostate volume is calculated as the prolate ellipsoid formula and is measured in cm³; history of prior negative prostate biopsies was modeled as a binary yes/no variable; Abnormal digital rectal exam (DRE) was modeled as a yes vs. no/not palpable/not performed binary variable; Site_PubFund is showing the distribution of recruitment site by biopsy status.

The best fit regressions are included in the Table 5 and the p values are in Figure 4 below. For Aim 2A, the best fit regression model includes Log₂(PSA), prostate volume and abnormal DRE. The best fit regression model includes Log₂(PSA), prostate volume and abnormal DRE (AUC 72.31). The best fit regression model that excludes prostate volume data only includes Log₂(PSA) and abnormal DRE (AUC 65.41).

For Aim 2B, West African ancestry models with (AUC 72.69) and without prostate volume (AUC 67.20) are very similar in accuracy to models containing Native American ancestry estimates (AUC with prostate volume 72.42 vs. AUC without 66.37). Both ancestry containing models are statistically better than the PCPT and PBCG risk calculators. The model with PSA, Prostate volume and abnormal DRE without genetic ancestry terms has a borderline higher AUC than the PCPT, PBCG and Kaiser RCs. The best performing models with genetic ancestry have very similar AUCs to the models without ancestry variables but have slightly higher discrimination in comparison. The confidence intervals between the NA or WA ancestry containing models are

very overlapping with the models with only clinical variables and the differences in AUC fail to reach statistical significance (all $p > 0.10$).

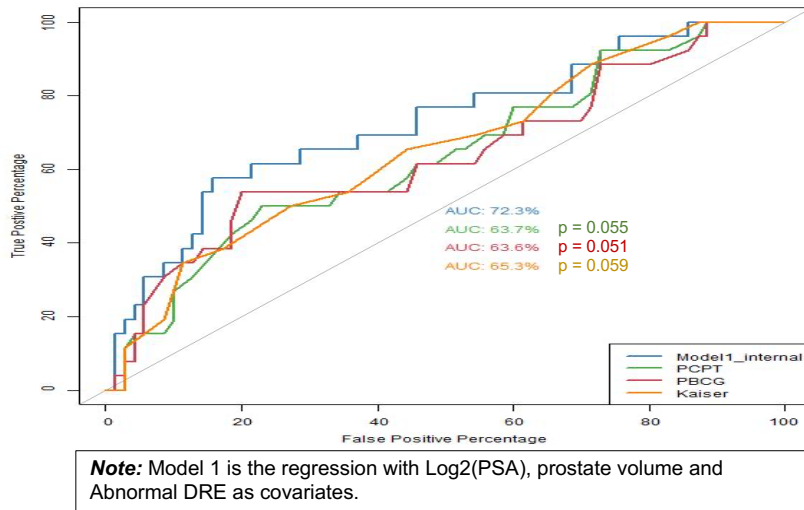
Table 5: Binary Logistic Regression models for GG2-5 PCa vs. GG1 PCa + Negative biopsy using clinical variables with or without prostate volume based covariates (PSA density, prostate volume), and with or without genetic ancestry based variables (WA, NA, or EA).

Binary Logistic Regression Models for GG2-5 PCa	AUC Development (Aim 2A and 2B)	95% CI
<u>Without Ancestry & With Volume</u>		
Log2PSA + Prostate Volume + Abnormal DRE	72.308	60.371, 84.245
Log2PSA + Prostate Volume + Prior Biopsy + Abnormal DRE	71.593	59.771, 83.416
Log2PSA + Prostate Volume	68.901	56.616, 81.187
Log2PSA + Prostate Volume + Prior Biopsy	67.692	55.608, 79.777
<u>Without Ancestry & Without Volume</u>		
Log2(PSA) + Abnormal DRE	65.412	52.414, 78.410
Log2(PSA) + Abnormal DRE + Prior Biopsy	64.038	50.611, 77.466
Log2(PSA) + Prior Biopsy	58.819	45.071, 72.567
Log2(PSA)	59.286	45.711, 72.860
<u>With Ancestry & With Volume (Aim 2B)</u>		
WA ancestry + NA ancestry + Log2(PSA) + Prostate Volume + Abnormal DRE	72.912	61.334, 84.490
WA ancestry + Log2(PSA) + Prostate Volume + Abnormal DRE	72.692	61.092, 84.292
NA ancestry + Log2(PSA) + Prostate Volume + Abnormal DRE	72.418	60.564, 84.271
WA ancestry + Log2(PSA) + Prostate Volume + Abnormal DRE + Prior Biopsy	72.088	60.412, 83.764
<u>With Ancestry & Without Volume (Aim 2B)</u>		
NA ancestry + Log2(PSA) + Abnormal DRE	66.374	53.440, 79.307
WA ancestry + NA ancestry + Log2(PSA) + Abnormal DRE	67.198	55.065, 79.330
WA ancestry + Log2(PSA) + Abnormal DRE	67.198	55.083, 79.312
WA ancestry + NA ancestry + Log2(PSA) + Abnormal DRE + Prior Biopsy	66.319	53.441, 79.197
Note: Models include clinical variables alone, with prostate volume or genetic ancestry variables or with both ancestry		

Table 4: Area under the curve for best models selected from internal and external validation compared to PCPT, PBCG, and Kaiser Risk Calculator (4A) and corresponding P-values (4B)

Figure 4A		Internal					External				
Model Selection	AUC	95% CI	PCPT	PBCG	Kaiser	AUC	95% CI	PCPT	PBCG	Kaiser	
Best Model: +PV, -WA, -NA	72.308*	60.371, 84.245	63.7	63.6	65.3	76.518	69.598, 83.438	65.7*	65.2	70.0	
Best Model: -PV, -WA, -NA	65.412	52.414, 78.410	63.7	63.6	65.3	73.370	66.071, 80.668	65.7*	65.2	70.0	
Best Model: +PV, +WA, -NA	72.692	61.092, 84.292	63.7	63.6	65.3	50.362	49.652, 51.072	65.7*	65.2	70.0	
Best Model: -PV, +WA, -NA	67.198	55.083, 79.312	63.7	63.6	65.3	50.362	49.652, 51.072	65.7	65.2	70.0	
Best Model: +PV, -WA, +NA	72.418	60.564, 84.271	63.7	63.6	65.3	52.017	43.885, 60.150	65.7*	65.2	70.0	
Best Model: -PV, -WA, +NA	66.374	53.440, 79.307	63.7	63.6	65.3	50.460	42.366, 58.555	65.7	65.2	70.0	
Figure 4B		Internal					External				
Model Selection	AUC	95% CI	PCPT	PBCG	Kaiser	AUC	95% CI	PCPT	PBCG	Kaiser	
Best Model: +PV, -WA, -NA	72.308	60.371, 84.245	0.055*	0.051*	0.059*	76.518	69.598, 83.438	0.076*	0.127	0.266	
Best Model: -PV, -WA, -NA	65.412	52.414, 78.410	0.333	0.321	0.478	73.370	66.071, 80.668	0.080*	0.233	0.644	
Best Model: +PV, +WA, -NA	72.692	61.092, 84.292	0.045	0.040	0.052*	50.362	49.652, 51.072	0.094*	0.154	0.317	
Best Model: -PV, +WA, -NA	67.198	55.083, 79.312	0.192	0.164	0.272	50.362	49.652, 51.072	0.262	0.501	0.888	
Best Model: +PV, -WA, +NA	72.418	60.564, 84.271	0.050	0.048	0.054	52.017	43.885, 60.150	0.081*	0.135	0.282	
Best Model: -PV, -WA, +NA	66.374	53.440, 79.307	0.257	0.248	0.342	50.460	42.366, 58.555	0.134	0.307	0.697	
Note: PV = prostate volume, WA = West African ancestry, NA = Native American ancestry; +/- refers to whether the covariate is included in the regression model. * denotes borderline statistical significance with $p < 0.10$.											

Figure 4: Area under the receiver operating characteristics curve (AUC) using the Development internal validation cohort



Conclusion for Aim 2B: Adding genetic ancestry does not significantly improve the AUC for the Black-tailored risk calculator models over the versions without genetic ancestry terms. However, the models with genetic ancestry have statistically higher AUCs relative to the clinically utilized models. The best model without volume has only serum PSA and abnormal digital rectal exam as covariates (AUC 65.41). The best model with a volume based covariate contains prostate volume as a continuous variable in addition to serum PSA and abnormal digital rectal exam (AUC 72.69).

3) Test the prediction accuracy of the PCPT RC and the Black-race-tailored model in a prospective cohort of Black men undergoing prostate biopsy

For Aim 3, we await the genetic ancestry results from the Kittles lab for the external validation cohort to complete these analyses. The effective sample size is only 212 participants when excluding those with missing ancestry data.

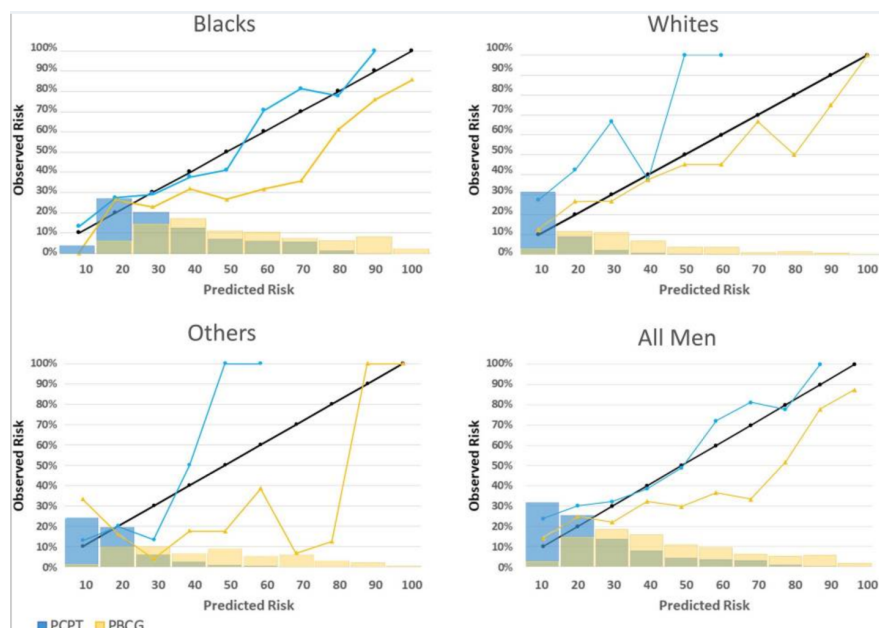
Table 4A and 4B lists the AUCs and the p values for the best performing models using both the Internal validation (30% of the Vitamin D & Prostate Cancer Risk cohort) and the prospectively recruited cohort funded by this DOD Award. We are missing ~1/3rd of the ancestry results on the prospective cohort and will wait until next month to complete and finalize these analyses.

Accomplishments:

We completed the analyses for Aim 2A and 2B. We randomly divided the 393 Black men in the Development cohort as (n=275) 70% for deriving the Black tailored models vs. (n=118) 30% for internally validating its accuracy metrics.

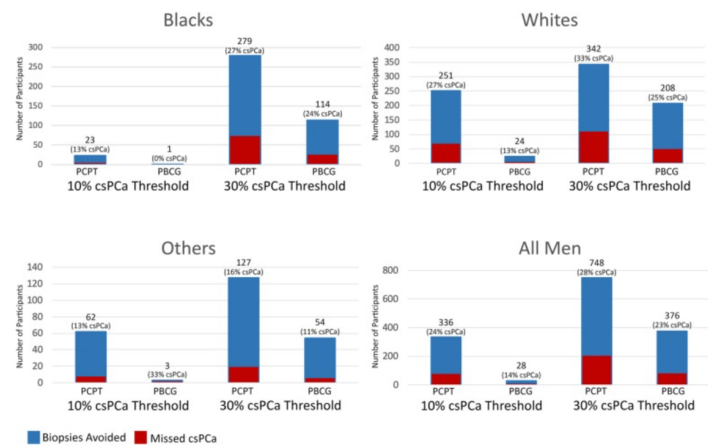
We evaluated the distributions of the variables of interest by dividing the cohort into a group with GG2-5 PCa and a group with GG1 PCa combined with those who had a negative prostate biopsy.

We completed the Aim 1 data analyses and presented it in the manuscript in BMC Urology in 2019. In short, the PBCG RC is not more accurate than the older PCPT version 2.0 in Black men and the PCPT RC actually helps more Black men avoid unnecessary biopsies.

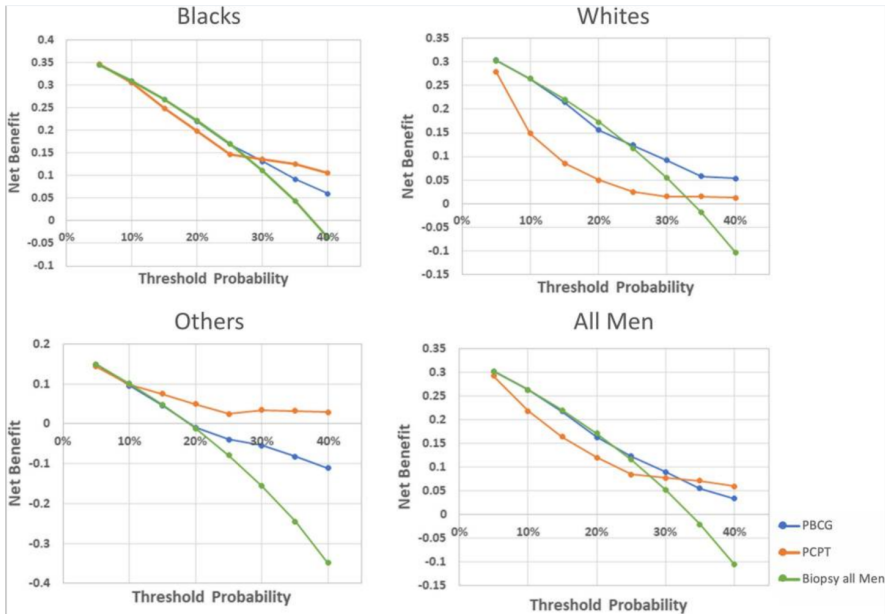


Race-stratified calibration curves and the risk probability distribution histograms for clinically significant prostate cancer for PBCG and PCPT risk calculators. PCPT = Prostate Cancer Prevention Trial risk calculator; PBCG = Prostate Biopsy Collaborative Group risk calculator; Blue lines and histograms = PCPT; Yellow lines and histograms = PBCG; Black lines = 45-degree line representing perfect calibration

Fig. 2



Theoretical number of avoided biopsies and missed clinically significant cancers at the 10 and 30% predictive thresholds by race. PCPT = Prostate Cancer Prevention Trial risk calculator; PBCG = Prostate Biopsy Collaborative Group risk calculator; csPca = clinically significant prostate cancer. Blue bar: Total number of biopsies avoided; Red bar: Missed clinically significant prostate cancer



We have completed a preliminary analysis of Aim 2 by creating several risk calculator models that are tailored for Black men and report it below. Briefly, our models which include prostate volume do perform better than the publicly available risk calculators (PCPT, PBCG and KPPC RCs). Models without volume based variables (PSA density and prostate volume) have higher area under the curve numerically but are not statistically more accurate.

The analysis of Aim 3, using the same models in Aim 2 but with various mathematical forms for West African, Native American and European ancestry have very similar area under the curve to models without the ancestry variables included. They are not statistically different than the versions without the ancestry variables added. We will re-assess this when Dr. Kittles sends the remainder of the genetic ancestry estimates.

Table: Best performing regression models when averaged over the Development (30% of cohort) and the Validation (100%).

Binary Logistic Regression Models for GG2-5 PCa	AUC Development (Aim 2A and 2B)		AUC Validation (Aim 3)		Mean AUC
<i>Without Ancestry & With Volume</i>		95% CI		95% CI	
Log2PSA + Prostate Volume + Abnormal DRE	72.308	60.371, 84.245	76.518	69.598, 83.438	74.413
Log2PSA + Prostate Volume + Prior Biopsy + Abnormal DRE	71.593	59.771, 83.416	74.334	67.137, 81.531	72.964
Log2PSA + Prostate Volume	68.901	56.616, 81.187	76.929	70.039, 83.819	72.915
Log2PSA + Prostate Volume + Prior Biopsy	67.692	55.608, 79.777	72.816	65.413, 80.220	70.254
<i>Without Ancestry & Without Volume</i>					
Log2(PSA) + Abnormal DRE	65.412	52.414, 78.410	73.370	66.071, 80.668	69.391
Log2(PSA) + Abnormal DRE + Prior Biopsy	64.038	50.611, 77.466	69.746	61.934, 77.559	66.892
Log2(PSA) + Prior Biopsy	58.819	45.071, 72.567	69.090	61.302, 76.879	63.955
Log2(PSA)	59.286	45.711, 72.860	73.634	66.434, 80.834	66.460
<i>With Ancestry & With Volume (Aim 2B)</i>					
WA ancestry + NA ancestry + Log2(PSA) + Prostate Volume + Abnormal DRE	72.912	61.334, 84.490	75.744	68.780, 82.708	74.328
WA ancestry + Log2(PSA) + Prostate Volume + Abnormal DRE	72.692	61.092, 84.292	75.862	68.876, 82.847	74.277
NA ancestry + Log2(PSA) + Prostate Volume + Abnormal DRE	72.418	60.564, 84.271	76.302	69.418, 83.187	74.360
WA ancestry + Log2(PSA) + Prostate Volume + Abnormal DRE + Prior Biopsy	72.088	60.412, 83.764	74.001	66.726, 81.277	73.045
<i>With Ancestry & Without Volume (Aim 2B)</i>					
NA ancestry + Log2(PSA) + Abnormal DRE	66.374	53.440, 79.307	72.934	65.601, 80.267	69.654
WA ancestry + NA ancestry + Log2(PSA) + Abnormal DRE	67.198	55.065, 79.330	71.827	64.170, 79.484	69.513
WA ancestry + Log2(PSA) + Abnormal DRE	67.198	55.083, 79.312	71.661	63.854, 79.467	69.430
WA ancestry + NA ancestry + Log2(PSA) + Abnormal DRE + Prior Biopsy	66.319	53.441, 79.197	69.301	61.453, 77.149	67.810

Note: Models include clinical variables alone, with prostate volume or genetic ancestry variables or with both ancestry and volume variables. Bolded models refers to preferred models for each sub-type. PSA: prostate specific antigen; DRE: digital rectal exam of the prostate, Prior biopsy is having a history of 1 or more previous negative prostate biopsies (yes/no); prostate volume is measured in cm³; NA: Native American ancestry; WA: West African ancestry.

Results: The best performing models with prostate volume included are actually better without the WA or NA ancestry variables added. The best performing model in Blacks without prostate volume only has two variables: serum PSA and abnormal DRE. When added to this model, Native American ancestry and West African ancestry numerically increases the AUC minimally but is not statistically higher than the log₂(PSA) + Abnormal DRE model.

Conclusion: Pending the results from the rest of the genetic ancestry estimates, preliminarily it appears that neither West African nor Native American ancestry augments the predictive accuracy of the risk calculators for GG2-5 PCa.

Major Task 7: Enroll participants

Current Objectives: Enroll 400 Black men from outpatient Urology clinics. Complete data entry and database management. Transfer buffy coat to Dr. Kittles' laboratory for genetic ancestry estimation.

Results: A total of 364 participants were enrolled out of the anticipated 400 enrollees across the three sites. We completed enrollment on October 14, 2021. We sent blood only everyone who provided a blood sample. The last batch of 75 buffy coats were sent on December 8, 2021

Accomplishments: We enrolled 364 participants across the 3 sites. This will achieve 91% enrollment. 354 have complete biopsy data as 10 did not complete their biopsy despite coming to clinic

Data entry is up to date at Northwestern University and University of Illinois at Chicago. Stroger data is being re-entered from the survey data and the electronic health records. This is on track to be completed by August 31, 2021.

Dr. Kittles' laboratory has received the latest batch of 75 whole blood based germline DNA samples from our lab on 12-8-21. Thus, we have sent germline DNA on all the remaining participants. We should receive the results by January 31, 2022.

Discussion: Due to the COVID-19 pandemic, we were only able to recruit 9 participants in Year 3 from September 2019 through September 2020. We chose to continue to pay our co-investigators and coordinators during the pandemic year when coordinators were not allowed in the clinics. The no cost extension period fortunately allowed us to approach our goal recruitment numbers.

Database quality was concerning at John H. Stroger due to coordinator turnover. We have since hired 2 new research coordinators (Victoria Reyes and Anand Bankapur) at Stroger who are manually re-entering and validating data from the electronic health records. This was completed by December 5th, 2021.

We were using saliva kits to extract DNA and then whole blood based DNA extraction initially in the study grant period. Both processes led to RNA and protein contamination of the DNA that led to poor quality genotyping for the imputed ancestry estimates that Dr. Kittles uses to estimate continental ancestry composition. We had to do significant troubleshooting to discover the cause and ultimately had to dilute down the DNA to 20ng/microliter and this allowed for high-quality DNA and call rates >95% on the genotyping. There are 75 samples still left to run which have been sent to Dr. Kittles' lab at City of Hope. SO far, 67 samples were not salvageable, and we do not have ancestry estimates on these patients (76.8% genotype success rate = 222 samples with ancestry data /289 recruited patients with samples processed by the Kittles lab). We estimate that we will have success with the remaining 75 samples (i.e. $297/364 = 81.6\%$) since buffy coat performs well for DNA extraction in the Kittles lab.

Major Task 8: Conduct data analysis

The subtasks for this Major Task were to the draft an initial analysis plan and then to conduct the analyses for the 3 Specific Aims.

This is done preliminarily but we are awaiting the 75 genetic ancestry results from Dr. Kittles' lab to finalize the models and compare the accuracy amongst them.

Major Task 9: Prepare manuscripts and presentations

We were planning to submit a couple abstracts and then prepare 3 manuscripts to focus on Aim 1, then Aim 2 and finally Aim 3.

We have revised this plan since we have a smaller development cohort. We published 4 abstracts related to this data. We published the Aim 1 findings in 2019. We decided to combine the Aim 2 and Aim 3 papers into one manuscript.

Abstracts/Poster presentations:

1. Stinson J, Kittles R, **Murphy AB**. Native American and West African Ancestry are Associated with Prostate Biopsy Outcomes. Student National Medical Association Annual Conference. April 1, 2018.
2. Stinson J, **Murphy AB**, Nettey OS, Ruden M, Gogana P, Dixon MA, Hollowell CMP, Sharifi R, Catalona WJ, Kajdacsy-Balla A, Macias V, Kittles RA. Native American and West African Ancestry are Associated with Risk of Significant Prostate Cancer Among Racially Diverse Men Undergoing Prostate Biopsy. North Central Section of the AUA, Inc. Meeting. September 5 - 8, 2018
3. Nettey OS, David L, Walker AJ, Park SY, Jovanovic B, Rydland K, Kittles R, Lleras C, **Murphy AB**. Neighborhood Associated Exposures and Socioeconomic Factors are Associated with Prostate Biopsy Outcomes. The Journal of Urology, no. 4 (2018).
4. Nettey O, Walker A, Keeter MK, Nugooru A, Martin IK, Ruden M, Gogana P, Dixon MA, Osuma T, Hollowell CMP, Sharifi R, Abern MR, **Gann P**, Sekosan M, Yang M, Catalona W, Meeks J, Kajdacsy-Balla A, Macias V, Kittles R, **Murphy A**. Black Race Predicts Significant Prostate Cancer Independent of Clinical Setting, and Clinical and Socioeconomic Risk Factors: evidence for a biological basis of disparities. The Journal of Urology, no. 4 (2018).

Aim 1 manuscript citation:

Carbunaru S, Nettey OS, Gogana P, Helenowski IB, Jovanovic B, Ruden M, Hollowell CMP, Sharifi R, Kittles RA, Schaeffer E, **Gann P**, **Murphy AB**. A comparative effectiveness analysis of the PBCG vs. PCPT risks calculators in a multi-ethnic cohort. BMC Urol. 2019 Nov 27;19(1):121. doi: 10.1186/s12894-019-0553-6. PMID: 31771578; PMCID: PMC6880480.

We believe combining the analyses for Aim 2 and 3 will make for a stronger paper if we include the internal and external validation data along with the rationale for development of these risk calculator models. Therefore, there will only be two major publications. We have published Aim 1 findings in 2019. We are preparing the Aim 2 and 3-focused manuscript for *The Journal of Urology* for submission in mid-February 2022.

4. KEY RESEARCH ACCOMPLISHMENTS: *Bulleted list of key research accomplishments emanating from this research. Project milestones, such as simply completing proposed experiments, are not acceptable as key research accomplishments. Key research accomplishments are those that have contributed to the major goals and objectives and that have potential impact on the research field.*

- We published our Aim 1 publication which showed that the new Prostate Biopsy Collaborative Group risk calculator is inferior to the Prostate Cancer Prevention Trial risk calculator for Black men.
- We completed enrollment on the first ever study to develop a prostate cancer risk calculator tailored for men of West African ancestry in the US, to our knowledge.
- We have demonstrated that we can successfully accrue Black men across a multitude of clinical settings and accomplish enrollment of >100 Black men each year, including from public and safety net hospitals, excluding the COVID 19 pandemic timeframe with no recruitment.

- We have contributed new insight into how inclusion of Black men into a study is not enough to ensure risk calculator prediction accuracy and highlights the need for specific sub-group analysis.
- We have improved our planned data analyses based on 2 newer manuscripts that developed new prostate cancer risk calculators (Ankerst DP et al and Presti D et al). Hence, we are comparing our tailored calculator to the original PCPT 2.0 RC along with the Kaiser Permanente Prostate Cancer RC and the Prostate Biopsy Collaborative Group RC. Our Aim 2 and Aim 3 analyses are underway. We finalized the Development cohort database. We have finalized the Validation cohort database pending 75 genetic ancestry results so that we may lock this database this month (estimated date: 1-31-2022).

5. CONCLUSION: Summarize the importance and/or implications with respect to medical and /or military significance of the completed research including distinctive contributions, innovations, or changes in practice or behavior that has come about as a result of the project. A brief description of future plans to accomplish the goals and objectives shall also be included.

Conclusion: The study demonstrated that the impact of risk calculators such as PCPT and PBCG risk calculators will differ, depending on the prevalence of the population in which it is deployed. The PCPT led to an increased number of avoidable biopsies in Blacks compared to PBCG at the 30% risk threshold (68% vs. 28% of all patients) with roughly similar rates of missed GG2-5 PCa (23% vs. 20%). Overall, the PBCG is fairly accurate in Black men, but overestimates risk and exposes Blacks to excessive unnecessary prostate biopsies. The PCPT RC 2.0, though older and developed in a PCa screening cohort, avoids more unnecessary biopsies than the PBCG RC in Black men. There is a need for improved risk calculators in this population.

Our Aim 1 publication also highlights the challenge involved in using race adjusted models that add a static term to a regression model. The forthcoming Aim 2 and 3 results published from this DOD-funded Study should impact how clinicians counsel Black men during the difficult decision process around biopsy decisions for detection of GG2-5 PCa. It is also our hope that future studies will focus on the clinical validation of our risk calculator in larger external cohorts with Black men.

We have created a PCa risk calculator for Black men and tested it as described in Aim 2A and 2B. Future work will incorporate prostate MRI PIRADS score and Prostate Health Index assay results into the risk calculators.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts. Each entry shall include the author(s), article title, journal name, book title, editors(s), publisher, volume number, page number(s), date, DOI, PMID, and/or ISBN.

Lay/Professional Press (6):

1. University of Chicago, Radio Host: Dorianne Miller MD, WVON 1690 AM, Topic: African Americans and Prostate Cancer Risk. 2018.
2. BlackDoctors.org, Facebook Live Event, Host: Sandria Washington, Topic: African American Men and Prostate Cancer Screening Recommendations. 2018.
3. WVON 1690AM, Radio Appearance, Topic: AA Men's Prostate and Sexual Health. Jan 5, 2019.
4. Munir Muhammad Show. Live cable show with call-in. June 19, 2019.

5. ABC Channel 10. Spokesperson for Prostate Cancer Foundation in Prostate Cancer Awareness Month. Facebook Live show with call-in. September 3, 2020.
6. Steve Harvey Show WHUR 96.3 FM. "The Importance of Prostate Cancer Screening in Black Men." June 17, 2021.

Peer-Reviewed Scientific Journals (4):

Direct:

1. Carbutaru S, Netley OS, Gogana P, Helenowski IB, Jovanovic B, Ruden M, Hollowell CMP, Sharifi R, Kittles RA, Schaeffer E, **Gann P, Murphy AB**. A comparative effectiveness analysis of the PBCG vs. PCPT risks calculators in a multi-ethnic cohort. *BMC Urol*. 2019 Nov 27;19(1):121. doi: 10.1186/s12894-019-0553-6. PMID: 31771578; PMCID: PMC6880480.

Indirect:

2. Press DJ, Shariff-Marco S, Lichtensztajn DY, Lauderdale D, **Murphy AB**, Inamdar PP, DeRouen MC, Hamilton AS, Yang J, Lin K, Hedeker D, Haiman CA, Cheng I, Gomez SL. Contributions of Social Factors to Disparities in Prostate Cancer Risk Profiles among Black Men and Non-Hispanic White Men with Prostate Cancer in California. *Cancer Epidemiol Biomarkers Prev*. 2021 Nov 30. doi: 10.1158/1055-9965.EPI-21-0697. Epub ahead of print. PMID: 34853020.
3. Babajide R, Carbutaru S, Netley OS, Watson KS, Holloway-Beth A, McDowell T, Ben Levi J, Murray M, Stinson J, Hollowell CMP, Dalton DP, Moore L, Kittles RA, **Gann PH, Schaeffer EM, Murphy AB**. Performance of Prostate Health Index in Biopsy Naïve Black Men. *J Urol*. 2021 Mar;205(3):718-724. doi: 10.1097/JU.0000000000001453. Epub 2020 Oct 26. PMID: 33103942; PMCID: PMC8320068.
4. **Murphy AB**, Carbutaru S, Netley OS, Gornbein C, Dixon MA, Macias V, Sharifi R, Kittles RA, Yang X, Kajdacsy-Balla A, **Gann P**. A 17-Gene Panel Genomic Prostate Score Has Similar Predictive Accuracy for Adverse Pathology at Radical Prostatectomy in African American and European American Men. *Urology*. 2020 Aug;142:166-173. doi: 10.1016/j.urology.2020.01.052. Epub 2020 Apr 8. PMID: 32277993; PMCID: PMC7387177.

Invited Articles 1:

1. Esdaille AR, Ibilbor C, Holmes A 2nd, Palmer NR, **Murphy AB**. Access and Representation: A Narrative Review of the Disparities in Access to Clinical Trials and Precision Oncology in Black men with Prostate Cancer. *Urology*. 2021 Sep 25:S0090-4295(21)00893-1. doi: 10.1016/j.urology.2021.09.004. Epub ahead of print. PMID: 34582887.

Abstracts/Poster presentations:

5. Stinson J, Kittles R, **Murphy AB**. Native American and West African Ancestry are Associated with Prostate Biopsy Outcomes. Student National Medical Association Annual Conference. April 1, 2018.
6. Stinson J, **Murphy AB**, Netley OS, Ruden M, Gogana P, Dixon MA, Hollowell CMP, Sharifi R, Catalona WJ, Kajdacsy-Balla A, Macias V, Kittles RA. Native American and West African Ancestry are Associated with Risk of Significant Prostate Cancer Among Racially Diverse Men Undergoing Prostate Biopsy. North Central Section of the AUA, Inc. Meeting. September 5 - 8, 2018

7. Nettey OS, David L, Walker AJ, Park SY, Jovanovic B, Rydland K, Kittles R, Lleras C, **Murphy AB**. Neighborhood Associated Exposures and Socioeconomic Factors are Associated with Prostate Biopsy Outcomes. The Journal of Urology, no. 4 (2018).
8. Nettey O, Walker A, Keeter MK, Nugooru A, Martin IK, Ruden M, Gogana P, Dixon MA, Osuma T, Hollowell CMP, Sharifi R, Abern MR, **Gann P**, Sekosan M, Yang M, Catalona W, Meeks J, Kajdacsy-Balla A, Macias V, Kittles R, **Murphy A**. Black Race Predicts Significant Prostate Cancer Independent of Clinical Setting, and Clinical and Socioeconomic Risk Factors: evidence for a biological basis of disparities. The Journal of Urology, no. 4 (2018)

List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk () if presentation produced a manuscript.*

1. **Murphy AB**, Carbanaru S, Abern M, Hollowell C, Sharifi R, King-Lee P, **Gann P** (2019). ENACT: a randomized trial assessing the impact of the Oncotype DX Prostate Cancer Assay on treatment decision in a racially diverse population of men eligible for active surveillance. 12th AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, San Francisco, CA.
2. Carbanaru S, Nettey O, Watson K, Holloway-Beth A, McDowell T, Ben Levi J, Murray M, Hollowell C, Schaeffer E, **Gann P**, Moore L, **Murphy AB** (2019). Performance of the prostate health index (PHI) assay in Black men. 12th AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, San Francisco, CA.
3. Carbanaru A, Macias V, Nettey O, Yang X, Sharifi R, Dixon M, Gornbein C, Jovanovic B, Kajdacsy-Balla A, **Gann P**, **Murphy AB**. (2019) Oncotype DX assay has similar predictive accuracy for adverse pathology at radical prostatectomy in African American and European American men. 12th AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, San Francisco, CA.
4. Nettey OS, David L, Walker AJ, Park SY, Jovanovic B, Rydland K, Kittles R, Lleras C, **Murphy AB**. Neighborhood Associated Exposures and Socioeconomic Factors are Associated with Prostate Biopsy Outcomes. The Journal of Urology, no. 4 (2018).
5. Nettey O, Walker A, Keeter MK, Nugooru A, Martin IK, Ruden M, Gogana P, Dixon MA, Osuma T, Hollowell CMP, Sharifi R, Abern MR, **Gann P**, Sekosan M, Yang M, Catalona W, Meeks J, Kajdacsy-Balla A, Macias V, Kittles R, **Murphy A**. Black Race Predicts Significant Prostate Cancer Independent of Clinical Setting, and Clinical and Socioeconomic Risk Factors: evidence for a biological basis of disparities. The Journal of Urology, no. 4 (2018)
6. Stinson J, Kittles R, **Murphy AB**. Native American and West African Ancestry are Associated with Prostate Biopsy Outcomes. Student National Medical Association Annual Conference. April 1, 2018.
7. Stinson J, **Murphy AB**, Nettey OS, Ruden M, Gogana P, Dixon MA, Hollowell CMP, Sharifi R, Catalona WJ, Kajdacsy-Balla A, Macias V, Kittles RA. Native American and West African Ancestry are Associated with Risk of Significant Prostate Cancer Among Racially Diverse Men Undergoing Prostate Biopsy. North Central Section of the AUA, Inc. Meeting. September 5 - 8, 2018.

8. Kundu S, Wong V, Victorson D, Burns J, Guitierrez S, McVary K, Schaeffer EM, Psutka SP, Meeks J, Schaeffer AJ, **Murphy A**, Cella D. [The impact of race on perceptions of anxiety after radical prostatectomy](#). *Journal of Clinical Oncology* 2017 35:6_suppl, e538-e538.

9. Batai K, **Murphy AB**, Shah E, Kittles RA. Effect modifications of vitamin D receptor common polymorphisms association with prostate cancer by serum vitamin D related behavioral and biological factors. The American Association for Cancer Research (AACR) annual meeting in Washington, D.C. April 1-5, 2017.

7. INVENTIONS, PATENTS AND LICENSES: List all inventions made and patents and licenses applied for and/or issued. Each entry shall include the inventor(s), invention title, patent application number, filing date, patent number if issued, patent issued date, national, or international.

None.

8. REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. This list may include development of prototypes, computer programs and/or software (such as databases and animal models, etc.) or similar products that may be commercialized.

None yet. Our R code for the prostate cancer risk calculators will be downloaded onto a free website, like the risk calculators for PCPT, PBCG and KPPC, once peer reviewed and accepted.

9. OTHER ACHIEVEMENTS: This list may include degrees obtained that are supported by this award, development of cell lines, tissue or serum repositories, funding applied for based on work supported by this award, and employment or research opportunities applied for and/or received based on experience/training supported by this award.

Based on our team's collaboration we have begun to develop other grant proposals using this network of clinicians and basic and social scientists. We submitted grants to the NCI and obtained an R01 to validate two PCa biomarkers, Prostate Health Index and Prostate MRI, in 500 Black and Hispanic men. We were successful in obtaining DOD funding to continue follow-up of the other partnering study from fiscal year 2014 W81XWH-15-1-0534 (the ENACT clinical trial cohort) and enroll a new cohort to study enhanced measures for monitoring Black men on AS. The new project is a Translational Science Award from the CDMRP Prostate Cancer Research Program: PC200229P2 - "Expanding an Active Surveillance Cohort to Improve Survivorship for Black Men with Favorable-Risk Prostate Cancer", Initiating PI: Adam Murphy, Partnering PI: Peter Gann.

10. REFERENCES: List all references pertinent to the report using a standard journal format (i.e., format used in Science, Military Medicine, etc.).

Presti J Jr., Alexeeff S, Horton B, Prausnitz S, Avins AL. Prospective development of a prostate cancer risk calculator in a racially diverse population: The Kaiser Permanente Prostate Cancer Risk Calculator. *Urol Oncol.* 2020 Nov;38(11):847.e1-847.e8.

11. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Appendices 1-4:

Direct Publications

1. Carbanaru S, Netter OS, Gogana P, Helenowski IB, Jovanovic B, Ruden M, Hollowell CMP, Sharifi R, Kittles RA, Schaeffer E, **Gann P, Murphy AB**. A comparative effectiveness analysis of the PBCG vs. PCPT risks calculators in a multi-ethnic cohort. BMC Urol. 2019 Nov 27;19(1):121. doi: 10.1186/s12894-019-0553-6. PMID: 31771578; PMCID: PMC6880480.

Indirect Publications

2. Press DJ, Shariff-Marco S, Lichtensztajn DY, Lauderdale D, **Murphy AB**, Inamdar PP, DeRouen MC, Hamilton AS, Yang J, Lin K, Hedeker D, Haiman CA, Cheng I, Gomez SL. Contributions of Social Factors to Disparities in Prostate Cancer Risk Profiles among Black Men and Non-Hispanic White Men with Prostate Cancer in California. Cancer Epidemiol Biomarkers Prev. 2021 Nov 30. doi: 10.1158/1055-9965.EPI-21-0697. Epub ahead of print. PMID: 34853020.
3. Babajide R, Carbanaru S, Netter OS, Watson KS, Holloway-Beth A, McDowell T, Ben Levi J, Murray M, Stinson J, Hollowell CMP, Dalton DP, Moore L, Kittles RA, **Gann PH, Schaeffer EM, Murphy AB**. Performance of Prostate Health Index in Biopsy Naïve Black Men. J Urol. 2021 Mar;205(3):718-724. doi: 10.1097/JU.0000000000001453. Epub 2020 Oct 26. PMID: 33103942; PMCID: PMC8320068.
4. **Murphy AB**, Carbanaru S, Netter OS, Gornbein C, Dixon MA, Macias V, Sharifi R, Kittles RA, Yang X, Kajdacsy-Balla A, **Gann P**. A 17-Gene Panel Genomic Prostate Score Has Similar Predictive Accuracy for Adverse Pathology at Radical Prostatectomy in African American and European American Men. Urology. 2020 Aug;142:166-173. doi: 10.1016/j.urology.2020.01.052. Epub 2020 Apr 8. PMID: 32277993; PMCID: PMC7387177.

TRAINING OR FELLOWSHIP AWARDS: For training or fellowship awards, in addition to the elements outlined above, include a brief description of opportunities for training and professional development. Training activities may include, for example, courses or one-on-one work with a mentor. Professional development activities may include workshops, conferences, seminars, and study groups.

Not Applicable

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

We are submitting a duplicative report for both the Initiating (Adam B. Murphy MD, MBA, MSCI) and Partnering PI (Peter H. Gann MD, ScD). Please see the attached documentation.

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

Not Applicable

MARKING OF PROPRIETARY INFORMATION: Data that was developed partially or exclusively at private expense shall be marked as "Proprietary Data" and Distribution Statement B included on the cover page of the report. Federal government approval is required before including Distribution Statement B. The recipient/PI shall coordinate with the GOR to obtain approval. Reports not properly marked for limitation will be distributed as Approved for Public Release. It is the responsibility of the Principal Investigator to advise the GOR when restricted limitation assigned to a document can be downgraded to "Approved for Public Release." DO NOT USE THE WORD "CONFIDENTIAL" WHEN MARKING DOCUMENTS. See term entitled "Intangible Property – Data and Software Requirements" and

https://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting for additional information.

Not Applicable

14. ABSTRACT:

Black men represent a high-risk group for prostate cancer. Prostate Cancer risk calculators are used to help in biopsy decision making. Currently, most of the prostate cancer risk calculators have been developed in cohorts with 0-12% enrollment of Black men and no study has performed an adequate assessment of their accuracy in Black men. Because West African ancestry has been associated with risk of prostate cancer and aggressive prostate cancer, it may be an independent risk factor for potentially lethal prostate cancer but has never been incorporated into a risk prediction model. Given this, we aimed to develop and validate a Black-race tailored risk calculator to address this critical need.

For Aim 1, we will first compare the accuracy of the Prostate Cancer Prevention Trial Risk Calculator (PCPT RC) & the Prostate Biopsy Collaborative Group Risk Calculator (PBCG RC) in 463 Black, 355 White and 136 Other race men using standard measures including discrimination (area under the curve), calibration, and by calculating the number of missed high-grade PCas and avoided biopsies in men who previously had enrolled in our observational study exploring associations between vitamin D deficiency and aggressive PCa. These men had at least a 12-core prostate biopsy in our institutions with available clinical and pathological data and provided DNA for future research.

For Aim 2, we used a subset of the 463 Black men (n=393) that had PSA <50ng/ml and complete data. Prior studies have identified 31 variables that are predictive of overall Gleason grade group 1-5 prostate cancer (GG1-5 PCa) or clinically significant GG2-5 PCa. These were used to generate the data for this report though we are awaiting 75 genetic ancestry results prior to finalizing the Validation cohort database for the pending manuscript. For this report, we developed 2 binary logistic regression models to predict GG2-5 PCa vs. negative biopsy or GG1 PCa. One model will contain prostate volume based measures (e.g. PSA density, prostate volume) and one model will not, since prostate MRI is not used in many medical centers and since transrectal ultrasound is not done routinely unless they're undergoing prostate biopsy.

We divided the 393 men into a development cohort (n=275, 70%) and an internal validation cohort (n=118, 30%) to create and preliminarily validate the binary logistic regression models. We tested models using the same covariates in the PCPT and PBCG risk calculators and created new models using forward selection, backward selection, and a combined iterative approach to select among the 31 literature-identified covariates that best predict potentially lethal GG2-5 PCa. The top 2 best performing models (with and without prostate volume based data) were then internally and externally validated using discrimination (area under the curve) for this report.

For the actual manuscript, we will take the 2 models with the highest discrimination and compare them with the PCPT, PBCG and KPPC RCs for net benefit from 5-40% risk threshold for GG2-5 PCa. The models will also be compared for calibration, specificity, and number of missed GG2-5 PCas at $\geq 90\%$ and $\geq 95\%$ sensitivity. For the external validation of Aim 2, we prospectively recruited 364 of a desired 400 Black men to test the accuracy of the 2 Black race-tailored models in men undergoing prostate biopsy in Chicago area Urology clinics. Though we have 75 pending genetic ancestry estimates for the Validation cohort, we preliminarily analyzed the data for this report to compare the area under the curve estimates with 95% confidence intervals for the Black tailored RC and the 3 publicly available models.

For Aim 3, we have genotyped 222 of 364 patients' germline DNA for ancestry informative markers to determine their percentages of genetic West African, Native American and European ancestry; 67 samples had poor genotyping and 75 samples are pending results. Next, we will add the degree of West African and Native American ancestry into the 2 best performing Aim 2 models and repeat the assessment of the discrimination. If there is a significant improvement in AUC, we will also calculate the net benefit and missed

GG2-5 cancers at a $\geq 90\%$ and $\geq 95\%$ sensitivity. We will determine if genetic ancestry is an independent predictor of GG2-5 PCa and if it improves the accuracy of our PCa risk calculator models.

Our hypothesis is that we can create a superiorly performing RC for potentially lethal GG2-5 PCa tailored to Black men, which will be tested with the following Specific Aims:

- 1) Test the accuracy of the PCPT RC 2.0 for predicting the presence of significant GG2-5 PCa in a retrospective cohort of Black and White men undergoing prostate biopsy

Progress: DONE. This manuscript is published in BMC Urology.

- 2A) Develop and validate a Black race-tailored pre-biopsy regression model for the prediction of potentially lethal GG2-5 PCa

Progress: DONE. This will be combined with the publications for Aim 2B and Aim 3.

- 2B) Determine if adding genetic West African ancestry to the best performing Black race-tailored model improves prediction performance

Progress: DONE. This will be combined with the publications for Aim 2A and Aim 3.

- 3) Test the prediction accuracy of the PCPT RC and the Black race-tailored model in a prospective cohort of Black men undergoing prostate biopsy.

Progress: Our team is waiting for 75 genetic ancestry results from Dr. Kittles' laboratory for the prospective validation cohort to finalize the analysis. The remainder of the data is complete, and we have performed an interim analysis for this Final report. This analysis will be repeated once the 75 ancestry results have been added to the database and we will evaluate calibration, net benefit, and specificity at $\geq 90\%$ and $\geq 95\%$ sensitivity.

RESEARCH ARTICLE

Open Access



A comparative effectiveness analysis of the PBCG vs. PCPT risks calculators in a multi-ethnic cohort

Samuel Carbunaru^{1†}, Oluwarotimi S. Netthey^{1†}, Pooja Gogana¹, Irene B. Helenowski², Borko Jovanovic², Maria Ruden³, Courtney M. P. Hollowell⁴, Roohollah Sharifi^{5,6}, Rick A. Kittles⁷, Edward Schaeffer¹, Peter Gann⁸ and Adam B. Murphy^{1,4,5*}

Abstract

Background: Predictive models that take race into account like the Prostate Cancer Prevention Trial Risk Calculator 2.0 (PCPT RC) and the new Prostate Biopsy Collaborative Group (PBCG) RC have been developed to equitably mitigate the overdiagnosis of prostate specific antigen (PSA) screening. Few studies have compared the performance of both calculators across racial groups.

Methods: From 1485 prospectively recruited participants, 954 men were identified undergoing initial prostate biopsy for abnormal PSA or digital rectal examination in five Chicago hospitals between 2009 and 2014. Discrimination, calibration, and frequency of avoided biopsies were calculated to assess the performance of both risk calculators.

Results: Of 954 participants, 463 (48.5%) were Black, 355 (37.2%) were White, and 136 (14.2%) identified as Other. Biopsy results were as follows: 310 (32.5%) exhibited no cancer, 323 (33.9%) indolent prostate cancer, and 321 (33.6%) clinically significant prostate cancer (csPCa). Differences in area under the curve (AUC)s for the detection of csPCa between PCPT and PBCG were not statistically different across all racial groups. PBCG did not improve calibration plots in Blacks and Others, as it showed higher levels of overprediction at most risk thresholds. PCPT led to an increased number of avoidable biopsies in minorities compared to PBCG at the 30% threshold (68% vs. 28% of all patients) with roughly similar rates of missed csPCa (23% vs. 20%).

Conclusion: Significant improvements were noticed in PBCG's calibrations and net benefits in Whites compared to PCPT. Since PBCG's improvements in Blacks are disputable and potentially biases a greater number of low risk Black and Other men towards unnecessary biopsies, PCPT may lead to better biopsy decisions in racial minority groups. Further comparisons of commonly used risk calculators across racial groups is warranted to minimize excessive biopsies and overdiagnosis in ethnic minorities.

Keywords: Prostate biopsy collaborative group risk calculator, Prostate Cancer prevention trial risk calculator 2.0, Prostate cancer risk prediction, Risk calculator, African American validation

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Background

Prostate cancer (PCa) is the leading malignancy amongst men with 164,690 new diagnoses in the United States in 2018 [1]. Prostate specific antigen (PSA) screening has reduced PCa specific mortality by ~50% [2]. Approximately 1 million biopsies are performed in the US each year, however, 54% of them are negative and another 25% reveal presumably indolent PCa [3, 4]. Complications of prostate biopsy are not uncommon and should be considered. Infectious complications affect 0.1 to 7.0% of patients, followed by sepsis ranging from 0.3 to 3.1% [5]. To mitigate screening harms, several predictive risk calculators (RCs) have been developed to help men make informed decisions about biopsy and better identify men who are likely to have clinically significant PCa. However, it is unclear if commonly used RCs are appropriately calibrated to identify racial minorities who can avoid unnecessary biopsies. While racial disparities in PCa between US Blacks and Whites have diminished over the past decades, there are still considerable differences [6]. Black men present with higher PSA levels, are at higher risk of developing clinically significant PCa (csPCa), and have higher mortality rates compared to Whites [7, 8]. The commonly used Prostate Cancer Prevention Trial 2.0 (PCPT) and the new Prostate Biopsy Collaborative Group (PBCG) RCs both take race into consideration, but were developed in largely European ancestry populations [9, 10].

This study compares the PBCG and PCPT RCs across racial groups using discrimination and calibration statistics, as well as the frequency of avoided biopsies and missed csPCa in an urban, multi-racial cohort.

Methods

Study participants

Following institutional review board approval at Northwestern University, University of Chicago, University of Illinois at Chicago, Jesse Brown VA Medical Center and Cook County Health from 2009 to 2014, 954 consecutive ambulatory men from urology clinics at two privately funded and three publicly funded institutions were enrolled in a cross-sectional study evaluating the association between vitamin D status and prostate biopsy outcomes [11]. Patients were deemed eligible if they were undergoing their first prostate biopsy for an abnormal PSA level or digital rectal exam (DRE). All patients provided written informed consent.

Data collection

A self-administered questionnaire confirmed self-reported race & ethnicity, demographics, and medical history. Histologic diagnosis, DRE, and imaging reports were evaluated to determine disease stage according to American Joint Committee on Cancer TNM (tumor, node, metastasis)

staging system [2]. All patients underwent a transrectal ultrasound guided biopsy with at least a 10-core biopsy with a median of 12 cores. Biopsies were read by three experienced uropathologists at Northwestern (XY) and at the University of Illinois at Chicago (ABJ and VM).

Statistical analysis

Descriptive statistics were used to characterize important covariates including age, race, PSA, PSA density, prostate volume, body mass index (BMI), alcohol and smoking use, income, family history of PCa, marital status, abnormal DRE, college completion, 5 alpha-reductase inhibitor (5-ARI) use, and the clinical diagnosis of benign prostatic hyperplasia (BPH). To compare groups, Student's *t*-tests or nonparametric Wilcoxon-Mann tests were performed for continuous variables, and Pearson- χ^2 tests were used for categorical variables.

The PCPT RC 2.0 [10] and PBCG [9] were applied, as provided in R package, to estimate the risk of overall PCa and csPCa (defined as Gleason $\geq 3 + 4$) for each participant using PSA, DRE, first-degree family history of PCa (father, brother or son ever diagnosed with PCa) and history of a prior negative prostate biopsy. All patients had no prior prostate biopsy as they were recruited at time of initial biopsy. Categories for self-reported race included Black/African American, White/Caucasian, Hispanic and Other. Because published logistic regression coefficients in the PCPT RC [10] computed probabilities by race similarly for 'Hispanic' and 'Other', we categorized all participants who were non-Black and non-White as 'Other' in our analysis. For participants with unknown family history or DRE status, "Do not know" and "Not performed or not sure", respectively, were used following the recommendation by the online RCs. Percent free PSA, PCA3, and TMPRSS ERG were not included in the risk calculations since the test was not routinely ordered for all participants. The primary endpoints were the presence of any prostate adenocarcinoma and the presence of Gleason $\geq 3 + 4$ PCa on prostate biopsy. Of the Gleason 6 tumors, 77% were very low to low risk according to NCCN guidelines [12].

Discrimination was calculated by quantifying the non-parametric area under the receiver operating characteristics curve (AUC). AUC was calculated for PBCG and PCPT by race (Black, White, Other). We were powered to detect a 7% AUC difference between PCPT and PBCG in Blacks and Whites at $\alpha = 5\%$ with greater than 99% power. For Other men we achieved a 76% power. We assumed a PCPT AUC of 0.60 with a one-sided α of 0.05, and a 0.95 correlation between PCPT and PBCG for both positive and negative results.

Calibration curves were generated by plotting the predictions generated by the PBCG and PCPT RC on the *x*-axis in deciles and the observed outcomes for men in

that decile on the y -axis. In the calibration plot, the 45-degree line represents perfectly calibrated predictions. A Hosmer-Lemeshow test for goodness-of-fit was performed to assess the quality of the calibration of each risk calculator.

Decision curve analysis (DCA) is a graphical statistical method that plots a population's net benefit from a RC on the y -axis over a variety of probabilities for the calculator detecting true disease on the x -axis [13]. Patients and providers usually have individual *probability thresholds* of disease detection above which they would undergo or recommend the biopsy that range between 5 and 40% [14–17]. The probability threshold can be used to estimate how a decision maker might weigh the relative benefit of appropriate treatment compared to the potential harms of undergoing unnecessary biopsy. The net benefit of PBCG and PCPT has not been compared across race previously.

The net benefits were compared using the following biopsy strategies: Biopsy All men, Biopsy based on PBCG

Thresholds, and Biopsy based on PCPT Thresholds. For the Biopsy All men curve, an exchange rate of 1/9 was used (as in Vickers et al.'s analysis of PCa biomarkers [18]), meaning we are willing to perform nine unnecessary biopsies to detect one case of csPCa.

Statistical analyses were performed using Excel, SPSS 24 (IBM Corporation 2016, United States), R 3.3.3., SAS v9.4 (SAS Institute, Cary, NC, USA), and Stata 12.1 (StataCorp, 2011, College Station, TX).

Results

Demographics

In total, 954 men with elevated PSA levels or abnormal DRE results underwent an initial transrectal ultrasound guided prostate biopsy during 2009–2014 (see Table 1). The sample included men who self-reported as Black (463, 48.5%), White (355, 37.2%), and Other races (136, 14.2%). The Other racial group included Hispanic ($n = 103$, 75.7%), Asian ($n = 28$) and Middle Eastern men

Table 1 Patient sociodemographic characteristics and clinical risk factors by race

Continuous Variables	Black ($n = 463$) Median [IQR]	White ($n = 355$) Median [IQR]	Other ($n = 136$) Median [IQR]	p Value ¹
Age, years	61.0 [57.0, 67.0]	62.0 [58.0, 67.0]	62.0 [57.0, 67.0]	0.47
BMI, kg/m ²	27.8 [24.5, 31.8]	27.5 [25.0, 30.6]	27.4 [24.2, 30.3]	0.56
PSA, ng/ml	7.8 [5.3, 15.5]	4.8 [3.6, 7.3]	7.2 [5.1, 12.4]	< 0.001
Prostate Volume, cm ³	39.5 [28.8, 55.4]	39.5 [29.7, 51.0]	48.7 [30.0, 69.4]	< 0.001
PSA density, ng/cm ³	0.23 [0.12, 0.43]	0.13 [0.09, 0.20]	0.18 [0.11, 0.32]	< 0.001
PCPT csPCa Risk, %	25.0 [17.0, 40.0]	7.0 [5.0, 12.0]	11.5 [7.0, 18.0]	< 0.001
PBCG csPCa Risk, %	45.0 [31.0, 65.0]	26.0 [18.0, 41.0]	37.5 [22.0, 54.2]	< 0.001
Categorical Variables	Black n (%)	White n (%)	Other n (%)	p Value ²
Clinical Risk Factors				
Family History of PCa	93 (20.1)	88 (24.8)	21 (15.4)	0.055
Abnormal DRE	140 (30.3)	112 (31.5)	43 (31.3)	0.92
BPH/LUTS	151 (32.6)	135 (38.0)	66 (48.5)	0.003
5-ARI Use (current)	43 (9.3)	19 (5.4)	26 (19.1)	< 0.001
Substance Use History				
Heavy Smoking (>1ppd)	29 (6.4)	19 (5.4)	1 (0.7)	0.034
Heavy Alcohol Use (> 10 drinks/week)	30 (6.6)	46 (13.0)	5 (3.7)	< 0.001
Demographic Factors				
Married	192 (42.1)	269 (76.2)	105 (77.2)	< 0.001
College Completion	165 (36.2)	248 (70.3)	46 (33.8)	< 0.001
Income < \$30,000	161 (43.9)	39 (12.0)	42 (55.2)	< 0.001
Biopsy Outcomes				
Indolent Cancer	167 (36.1)	118 (33.2)	38 (27.9)	0.20
Clinically Significant Cancer	175 (37.8)	120 (33.8)	26 (19.1)	< 0.001
No Cancer	121 (26.1)	117 (33.0)	72 (52.9)	< 0.001

¹Using Kruskal-Wallis tests; ²Using Pearson- χ^2 tests; ³ χ^2 trend test. Bold type indicates p values < 0.05. Abbreviations: BMI body mass Index, PSA prostate specific antigen, BPH/LUTS clinical diagnosis of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms, DRE digital rectal examination, csPCa clinically significant prostate cancer, PBCG Prostate Biopsy Collaborative Group, PCPT Prostate Cancer Prevention Trial, ppd pack per day

($n = 5$). All groups had a comparable age ($p = 0.47$) and BMI ($p = 0.56$). Black men had higher pre-biopsy PSA values and density (both $p < 0.001$).

Of the 954 biopsies, 310 (32.5%) were negative for PCa, 323 (33.9%) were positive for indolent PCa, and 321 (33.6%) demonstrated csPCa. Black men were more often diagnosed with overall PCa (73.9%) and csPCa (37.8%) on biopsy than White or Other men (both $p < 0.001$). A comparison of median risk scores shows that Blacks had higher risk scores for csPCa compared to White and Other men in both PCPT and PBCG ($p < 0.001$).

Discrimination/calibration

Statistically, there was no difference in the AUCs between PBCG and PCPT for overall PCa when all men are included. The AUC for csPCa was 0.64 (95% CI: 0.61–0.68) for PCPT and 0.65 (95% CI: 0.62–0.68) for PBCG ($p = 0.27$). The AUCs slightly improved with PBCG in Whites (0.64 vs. 0.66; $p = 0.07$) and Blacks (0.67 vs. 0.68; $p = 0.25$), but not in Others (0.64 vs. 0.64;

$p = 0.81$); yet, none of these differences were statistically significant.

Figure 1 depicts the calibration and distribution plots for csPCa by racial group. The PBCG calculator results in a broader distribution of men in all racial groups, as opposed to the PCPT RC where most men are clustered in the lower risk deciles ($< 30\%$). The PBCG calibration in all men outperforms PCPT at the $< 30\%$ range, while the PCPT is better calibrated at $\geq 30\%$ risk deciles. It is unclear if the improved calibration at probabilities $\geq 30\%$ is clinically significant since most men will opt for biopsy at $> 30\%$ risk [16]. For Blacks and Others PCPT seems to be better calibrated, as PBCG over-predicts csPCa across most risk thresholds. In Whites, however, the opposite is seen with PBCG being better calibrated, since PCPT underestimates the risk of csPCa in the 10–60% range. After performing a Hosmer-Lemeshow test for goodness-of-fit, no statistically significant changes were detected in calibration plots between PCPT and PBCG in any racial group: Blacks ($p = 0.15$), Whites ($p = 0.08$), and Others ($p = 0.07$).

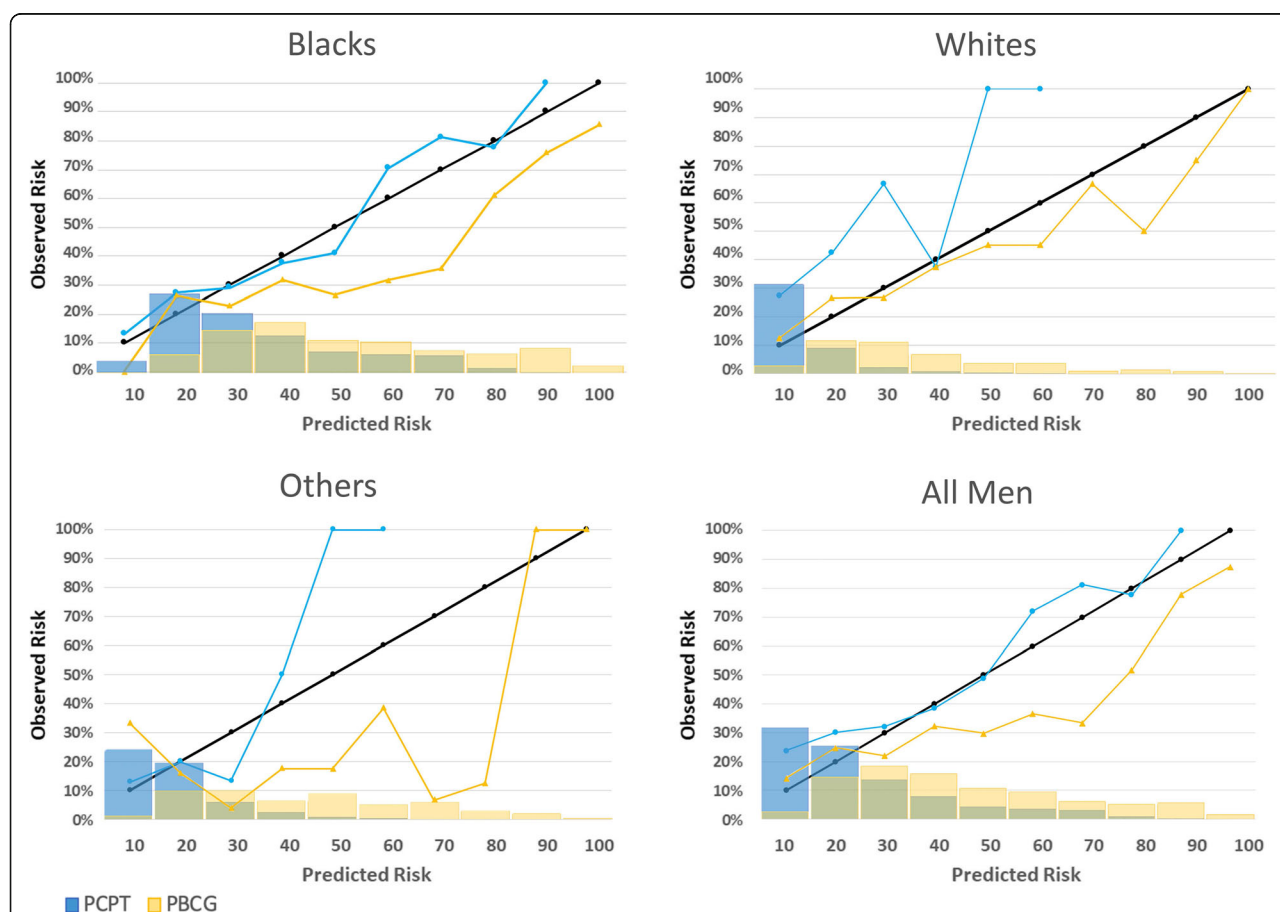


Fig. 1 Race-stratified calibration curves and the risk probability distribution histograms for clinically significant prostate cancer for PBCG and PCPT risk calculators. PCPT = Prostate Cancer Prevention Trial risk calculator; PBCG = Prostate Biopsy Collaborative Group risk calculator; Blue lines and histograms = PCPT; Yellow lines and histograms = PBCG; Black lines = 45-degree line representing perfect calibration

Number of avoided biopsies and missed clinically significant prostate cancer

Figure 2 presents the theoretical number of biopsies avoided and missed csPCa at the $\geq 10\%$ and $\geq 30\%$ risk thresholds.

At the $\geq 10\%$ threshold, assuming no biopsies are performed below this threshold, the number of biopsies avoided with the PCPT RC for All men is 336/954 (35%) compared to 28/954 (3%) with PBCG. The PCPT RC, however, missed 80 (24%) csPCas compared to 4 (14%) csPCas when using PBCG. Few Black men fall below the 10% risk threshold, so the number of avoided biopsies is small with both calculators. The difference is particularly prominent in Whites where the percentage of biopsies avoided is ten-fold higher with PCPT relative to PBCG (71% vs 7%).

At the $\geq 30\%$ threshold in All men, 748 (78%) biopsies are avoided using PCPT compared to 376 (39%) with PBCG, and the number of missed csPCa is 207 (28%) and 85 (23%), respectively. Black and Other men demonstrate a similar trend, where more than twice as many biopsies are avoided using PCPT with similar rates of missed csPCa (27% vs. 24% in Blacks; and 16% vs. 11% in Others).

Unnecessary biopsies in low risk men

The proportion of low risk men (i.e. men with PSA < 10 ng/mL and either Gleason 6 tumors or no cancer) who underwent unnecessary biopsies was assessed by racial group. At a threshold of $\geq 10\%$, assuming that men with higher scores are biopsied, 250/487 (51%) low risk men would have undergone a biopsy with PCPT and 466 (96%) with PBCG. Almost all low risk Black men are biopsied with both PCPT (92%) and PBCG (99.5%). For Whites and Others, the proportion of low risk men biopsied with PCPT is much lower relative to PBCG (see Additional file 1).

At the $\geq 30\%$ threshold, PCPT would spare most low risk men a biopsy and only subject 5% to a prostate biopsy, while 42% are still biopsied with PBCG. In Blacks, the number of low risk men biopsied substantially decreases to 25 (12%) with PCPT, but continues to remain high with PBCG at 121 (59%). There were no White and Other men biopsied with PCPT, while 27 and 38% were biopsied using PBCG, respectively. The increase in risk scores seen in PBCG does not spare low risk men, resulting in many unnecessary biopsies performed in men with indolent or no PCa.

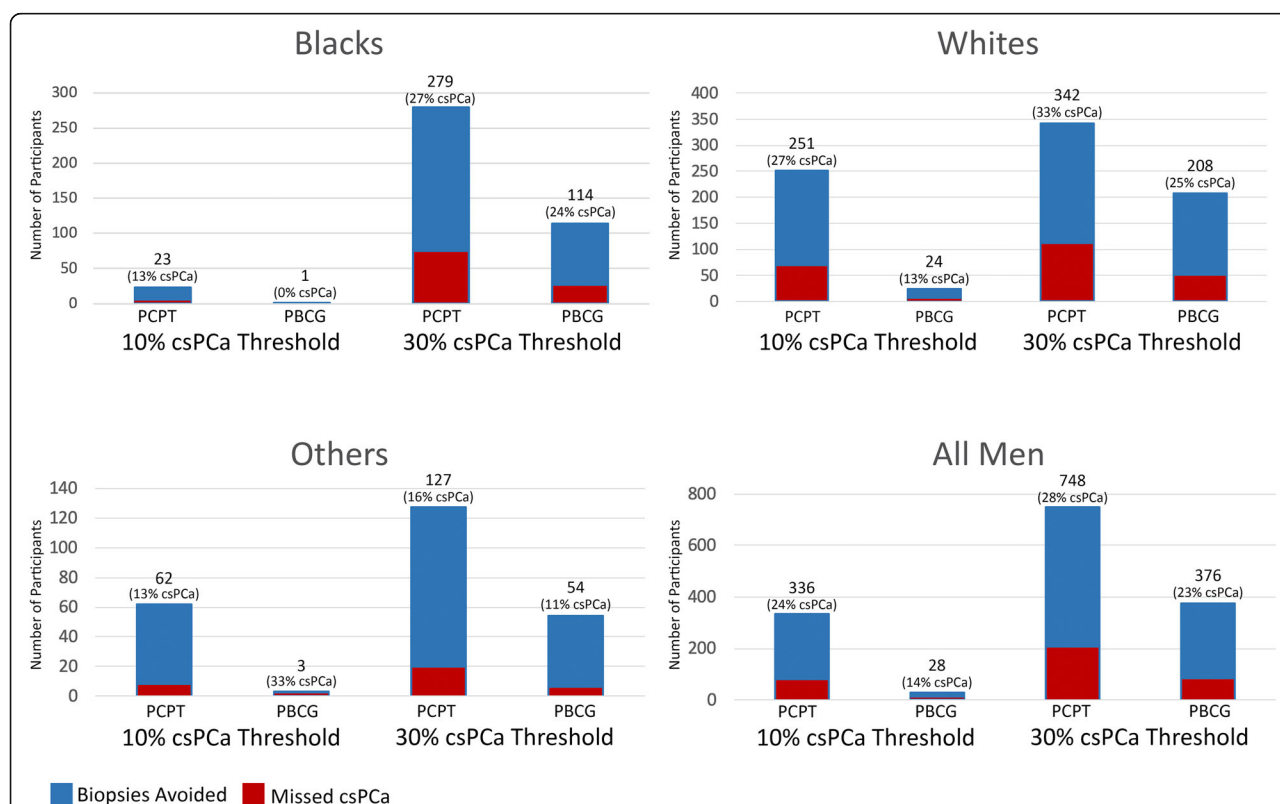


Fig. 2 Theoretical number of avoided biopsies and missed clinically significant cancers at the 10 and 30% predictive thresholds by race. PCPT = Prostate Cancer Prevention Trial risk calculator; PBCG = Prostate Biopsy Collaborative Group risk calculator; csPCa = clinically significant prostate cancer. Blue bar: Total number of biopsies avoided; Red bar: Missed clinically significant prostate cancer

Decision curve analysis: net benefit

The net benefit of each risk model is displayed graphically in Fig. 3. When calculating the net benefit analysis for All men, we note that the net benefit for PBCG is higher than PCPT at low threshold probabilities; however, neither RC shows higher net benefit than the Biopsy All men strategy at thresholds below 25%. At the higher risk thresholds (> 30%), PCPT surpasses the net benefit of PBCG.

These results differ vastly by race. Black men show similar trends as the ones described above with PBCG having higher net benefits than PCPT at lower thresholds, but not at thresholds above 30%. White men show a more pronounced improvement with PBCG across all thresholds. In Other men, the opposite is seen with PCPT showing higher net benefit than PBCG throughout all thresholds. Overall, PBCG demonstrates improved net benefits below the 30% threshold in Whites and, to lesser extent, in Blacks, but not in Others.

Discussion

Discrimination between PBCG and PCPT was not statistically different for overall or csPCa ($p = 0.27$). Although

Ankerst et al. did show a statistically significant 3% improvement in PBCG over PCPT on both the internal and external validation [9], our study was not powered to detect this difference. The PCPT RC has been mostly validated in populations of European descent, which might not be representative of the demographics in the United States. The PCPT 2.0 risk calculator development cohort included 219 (3.3%) Blacks, but did not report the AUCs for csPCa by race. This study includes a multi-racial cohort of men recruited from five institutions in a large metropolitan city. Few studies have evaluated the performance of the PCPT RC in diverse populations. The Durham VA (North Carolina) cohort enrolled high numbers of Black men (45%) and demonstrated an AUC of 0.74 [19]. The Cleveland Clinic cohort was composed of 13% Black men and had an AUC of 0.64 [19]. Lastly, the SABOR Cohort from San Antonio, Texas compared PCPT across racial groups and showed that PCPT performs best in Black men compared to other races (AUC 0.80 vs. 0.66, $p = 0.02$) [20]. The AUC for Blacks in our study (0.67) was notably lower than SABOR's and Durham's, and similar to the Cleveland Clinic's cohort.

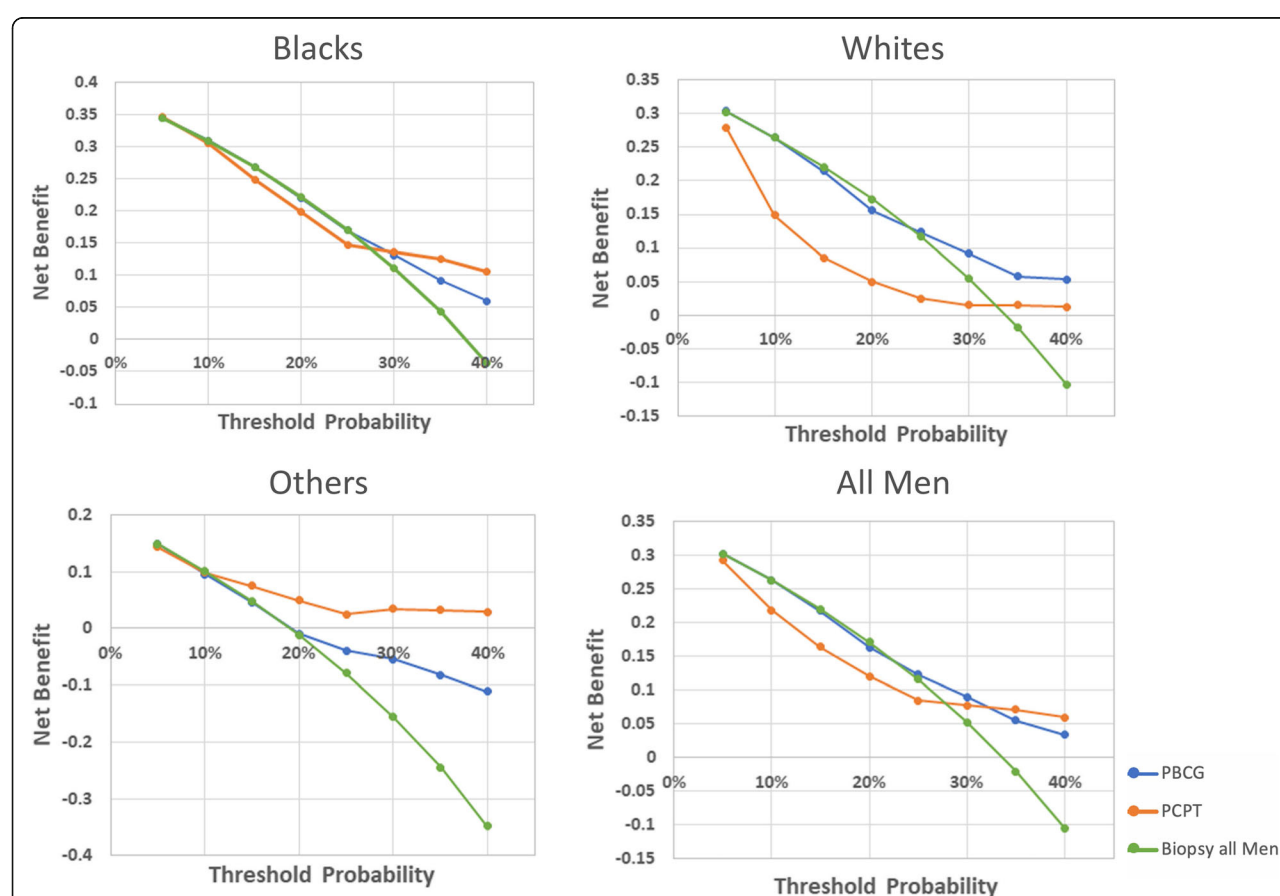


Fig. 3 Net Benefit curves for clinically significant prostate cancer prediction comparing PBCG to PCPT and the Biopsy all Men strategy by race. PCPT = Prostate Cancer Prevention Trial risk calculator; PBCG = Prostate Biopsy Collaborative Group risk calculator. Green line = Biopsy All men (assuming an exchange rate = 1/9); Orange line = Biopsy based on the probability risk thresholds of the PCPT risk calculator; Blue line = Biopsy based on the probability risk thresholds of the PBCG risk calculator

Like SABOR's, the AUC for Blacks in our cohort was slightly higher than Whites' (0.64), although this was not statistically significant.

In terms of the calibration curves, PBCG's calibrations in White men appear to be superior to PCPT. Blacks and Others show a different trend, where PCPT appears better calibrated since PBCG overestimates the rates of csPCa. Ankerst et al.'s validations also show a widened distribution for PBCG across all thresholds [9]. Their results are similar to the calibration plots we obtained for csPCa in our White population, but not in our minority groups. Since their internal and external validations had a non-Black population of 87% and 99.7%, their results come from a more racially homogeneous sample [9], which might explain these discrepancies. To our knowledge, no other studies have validated PBCG in a racially diverse cohort.

The cutoff most urologists use to decide if a patient should undergo a biopsy lies somewhere between the 5–30% threshold [18]. Therefore, this range is where nomograms serve the greatest clinical utility. At the 30% threshold, PCPT results in more than twice the amount of avoided biopsies with similar rates of missed csPCa in Blacks and Others (see Fig. 2). In addition, despite similar frequencies of indolent PCa and negative biopsy in Blacks and Whites (62.2% vs. 66.2%, $p = 0.24$), PBCG disproportionally biases more low risk Black men towards unnecessary biopsies (59% low risk men missed) relative to White men (27% missed).

The net benefits and clinical utility of different strategies vary widely by race, as seen in Fig. 3. In our data, White men and Black men seem to have higher net benefit with PBCG at relevant thresholds between 0 and 25%. For Others, PCPT has higher net benefit across all thresholds, which might be due their lower prevalence of csPCa compared to Blacks and Whites. Below the 30% threshold, the PBCG RC shows no greater benefit than the "Biopsy All strategy" in Black and White men, indicating that the conservative cutoff of 10% might not have any clinical benefit to avoid unnecessary biopsies.

Our comparison of PBCG vs. PCPT concurs with the study published by Ankerst et al. in that PBCG has higher discrimination [9], though not statistically significant in our smaller sample. However, we find that the performance of both calculators varies widely by race. Unfortunately, Ankerst et al. did not include an analysis on how the calibration or net benefit plots differ by racial groups. Although the PBCG RC was developed in a cohort with 13% Blacks, the validation study only included 33 (0.3%) Blacks in the cohort. Our results coincide with Ankerst et al. in that PBCG results in significant improvements compared to PCPT in Whites; yet, we find that the PBCG RC results in overprediction of PCa and a significant increase in the number of unnecessary biopsies in racial

minorities. Given that PCPT was of higher accuracy in Blacks in prior validations, it may be prudent to continue to use it in biopsy decision making for Blacks. This should be compared in future studies using other diverse cohorts.

With the increasing popularity of multiparametric magnetic resonance imaging (mpMRI) as a PCa detection method, many are doubting the current need for risk calculators or are incorporating mpMRI PIRADS scores into them [21]. There is substantial evidence supporting the advantage of mpMRI, as it has been shown to avoid biopsies in around 28% of men and subsequently decrease the overdiagnoses of indolent PCa [15]. However, the adoption of mpMRI would add approximately \$3 billion annually, meaning that this diagnostic test would account for 15% of all PCa related cost [22]. The use of mpMRI has become common practice in large academic institutions; however, 70% of community hospitals have not adopted such practice and 75% of hospitals perform few mpMRI (< 20 mpMRI/month) [22]. Currently, a patient's geographic location (non-urban settings) and insurance type (health maintenance organizations) greatly reduce their chances of having access to a mpMRI [22, 23]. The accuracy of mpMRI in community settings is also risky with only 55% concordance between community and expert academic radiologists [24]. While mpMRIs show promising results, the need for predictive nomograms is still warranted in areas of the country that face barriers in the implementation of mpMRIs.

This study has several limitations that should be noted. The recruitment was done in tertiary and publicly funded medical centers in a large metropolitan city. Our population was recruited from the outpatient Urology clinics between 2009 and 2014 and Gleason grading has shifted several Gleason 6's to Gleason 7 tumors limiting generalizability to our contemporary patients [25]. Our Gleason 6 tumors were consistent with NCCN very low or low risk group in 77% of cases. There were low numbers of non-Black minorities enrolled, which limits power and prevents subgroup analyses of Hispanics, Asians and other ethnic groups. The PCPT RC can accommodate biomarkers that we did not account for like PCA3, free PSA, and TMPRSS2-ERG [26].

Conclusions

Since PBCG's improvements in Blacks are disputable and potentially biases a greater number of low risk Black and Other men towards unnecessary biopsies, PCPT may lead to better biopsy decisions in racial minority groups. Further validation studies in racially diverse cohorts are warranted to mitigate the harms of PSA screening in ethnic minorities.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12894-019-0553-6>.

Additional file 1. Percentage of low risk men who underwent an unnecessary prostate biopsy at the 10 and 30% risk thresholds stratified by race. Low risk Men includes men with PSA < 10 ng/mL and either a negative biopsy ($n = 238$) or Gleason 3 + 3 prostate cancer and less than clinical T3a ($n = 249$); PCPT = Prostate Cancer Prevention Trial Risk Calculator; PBCG = Prostate Biopsy Collaborative Group Risk Calculator.

Abbreviations

5-ARI: 5 alpha-reductase inhibitor; AUC: Area Under the Receiver Operating Characteristics Curve; BMI: Body Mass Index; BPH: Benign Prostatic Hyperplasia; csPCa: Clinically Significant Prostate Cancer; DCA: Decision Curve Analysis; DRE: Digital Rectal Exam; PBCG: Prostate Biopsy Collaborative Group; PCa: Prostate Cancer; PCPT: Prostate Cancer Prevention Trial 2.0; PSA: Prostate Specific Antigen; RC: Risk Calculators

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Authors' contributions

SC, OSN, ABM were major contributors in writing the manuscript. SC, OSN, IBH, BJ analyzed and interpreted the data. PG1 aided in the acquisition of data and data analysis plan. MR aided in data acquisition and data quality control. CMPH, RAK aided in editing the manuscript and data acquisition. RS aided in data acquisition and patient recruitment. ES made contributions in the design of the study, acquiring study funding, and drafting the data analysis plan. PG2 substantially developed the data analysis plan and revised the manuscript. All authors read and approved the final version of the submitted manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Data was obtained from our prospectively maintained and institutional review board-approved dataset at Northwestern University (STU00005398). The participants were also recruited after institutional review board-approval at University of Chicago (16811B), Jesse Brown VA Medical Center (5R01MD007105-03), Cook County Health (08-174) and University of Illinois at Chicago (2010-0951). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Contributions of Social Factors to Disparities in Prostate Cancer Risk Profiles among Black Men and Non-Hispanic White Men with Prostate Cancer in California

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ABSTRACT

Background: Black men are more likely than Non-Hispanic White (NHW) men to be diagnosed with high-risk prostate cancer. We examined the extent to which social factors were associated with differences in prostate cancer risk profiles between Black men and NHW men [using a modification to the original D'Amico risk groups based on prostate specific antigen (PSA), Gleason score (GS), and TNM stage (stage)], based on individual and combined clinicopathologic characteristics.

Methods: We conducted a cross-sectional population-based study of 23,555 Black men and 146,889 NHW men diagnosed with prostate cancer in the California Cancer Registry from 2004 to 2017. We conducted multivariable logistic regression to examine the association of year of diagnosis, block group-level neighborhood socioeconomic status (nSES), marital status, and insurance type

on differences in prostate cancer risk profiles between Black and NHW men.

Results: High PSA (>20 ng/mL), GS, stage, individually and combined prostate cancer risk profiles were more common among Black men versus NHW men. In fully adjusted models, relative to NHW men, we observed a persistent 67% increased odds of high PSA among Black men. nSES was the factor most strongly associated with racial disparity in high PSA, accounting for 25% of the difference. Marital status was the factor that was second most associated with a racial disparity.

Conclusions: nSES was the factor most strongly associated with racial disparities in high PSA prostate cancer.

Impact: The influence of nSES on racial disparities in PSA, GS, stage, and prostate cancer risk profiles warrants further consideration.

Introduction

Prostate cancer is the most common cancer among men in the United States. In 2021, Black men are projected to experience 1.8 times the incidence and 2.1 times the mortality as non-Hispanic White (NHW) men (1). Prostate-specific antigen (PSA), Gleason score (GS), and stage are prognostic factors of prostate cancer, which together can be used to indicate prostate cancer risk profile for clinical decision-

making (2). Black men with prostate cancer present with higher PSA levels on average compared with other racial groups, and for a given level of PSA, Black men have larger tumor volumes than NHW men (3–6). In California, we previously reported a 60% higher age-adjusted prostate cancer mortality among Black men relative to NHW men, which was reduced to the null after adjustment for tumor, sociodemographic, institutional, and neighborhood characteristics (7). However, it remains unclear what factors contribute to the higher risk of advanced prostate cancer at diagnosis among Black men.

Social determinants of disparities in cancer outcomes (e.g., clinicopathologic presentation, diagnosis, treatment, and survival; ref. 8) are complex and intersecting. What we observe as racial disparities—adverse health consequences of racism for historically marginalized racial groups—may partially reflect overlapping inequities across other social factors associated with cancer outcomes (7, 9–13). Individuals who reside in resource-poor settings as measured by low neighborhood socioeconomic status (nSES) are more likely to experience social isolation, stressors, have reduced access to medical and social services (14–22) and also experience disparate prostate cancer outcomes (2, 7, 23). In addition, patient-level social factors including health insurance status type and marital status are associated with disease stage and mortality (7, 24). Determining the relative contribution of intersecting social factors (at the individual- and contextual-level) to prostate cancer risk is an area of ongoing investigation (2, 7, 23, 25). To our knowledge, only one study has evaluated associations between these factors (in addition to race) and risk of advanced prostate cancer at diagnosis (2). Elucidating these factors may provide insight to mitigate the Black-White racial disparity in prostate cancer survival. To further examine intersecting social factors that may impact prostate cancer risk profile, we conducted a population-based study using California Cancer Registry (CCR) data of Black men and NHW men in California with prostate cancer from

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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2004 to 2017 with detailed information on PSA, GS, and stage, in addition to information on individual characteristics (age at and year of diagnosis, marital status, insurance status) and nSES.

Materials and Methods

Study population

From the CCR, we identified 25,886 Black men and 160,897 NHW men residing in California diagnosed with first primary invasive prostate cancer [International Classification of Disease for Oncology, 3rd edition [ICD-O-3] site code C619; ref. 26] during the period January 1, 2004 to December 31, 2017. The population-based CCR comprises three regional registries that are a part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, which maintains the highest level of registry data quality and accuracy. We limited the earliest year of diagnosis to 2004 since PSA and GS were incomplete in cancer registry data before 2004 (27). We limited the study to men with pathologically confirmed adenocarcinoma or other prostate cancer histology (ICD-O-3 morphology codes 8000–8110, 8140–8576, 8940–8950, and 8980–8981; ref. 26). The final cross-sectional study population included 23,555 Black men and 146,889 NHW men; however, slightly different numbers of cases were included for each outcome studied on the basis of data availability. Specifically, the study samples with complete data for each prostate cancer risk profile outcome included: PSA data for 21,643 Black men and 131,755 NHW men; GS data for 22,255 Black men and 138,393 NHW men; clinical stage data for 22,854 Black men and 142,487 NHW men; and combined risk profile data for 21,658 Black men and 132,050 NHW men. A flow diagram is presented in Supplementary Fig. S1.

Variables

Independent variables

Race/ethnicity was classified as NHW for White men who were also non-Hispanic and Black for Black/African American men who were either Hispanic or non-Hispanic. Insurance type was defined as primary payer (no insurance, private, Medicare only, any public/Medicaid/military, and unknown or missing) based on the last report received by the cancer registry for a given diagnosis. nSES was measured using a previously defined composite index score developed by principal components analyses of 2000 Census (for diagnoses 2004–2005) or 2008 to 2012 American Community Survey (for diagnoses 2006–2017) data on education, occupation, employment, household income, poverty, and rent and house values (28,29) linked to the census block group. Address of residence at time of diagnosis was geocoded and used to assign a census block group. Each cancer case was assigned to a census block group nSES quintile based on the statewide distribution of nSES scores, separately derived for 2000 and 2010. Registry information on individual characteristics (age and year of diagnosis, marital status, insurance type based on primary payer, and residence at diagnosis) were abstracted from the medical record.

Outcome variables

We used CCR data items on PSA, GS, and American Joint Committee on Cancer stage (27) to categorize men into “low,” “intermediate,” and “high” prostate cancer risk groups based on a modification of D'Amico risk groups (30) and National Comprehensive Cancer Network (NCCN) risk categories (31), using stage, GS, and PSA. Low included low-risk (N0 and M0 and T1/T2a and Gleason ≤ 6 and PSA < 10 ng/mL) and intermediate-risk (N0 and M0 and T2b/T2c or biopsy Gleason 7 or PSA 10–20 ng/mL); and high included high-risk (T3/T4 or Gleason 8+ or PSA > 20 ng/mL or N1 or M1). For primary analyses,

the overall combined risk group was dichotomized between low and high, with the intermediate group combined with the low group. In secondary analyses, we also examined risk stratification within each of the risk group component measures based on three categories within each component: PSA < 10 ng/mL (low), 10–20 ng/mL (intermediate), > 20 ng/mL (high); GS < 7 (low), 7 (intermediate), ≥ 8 (high); and stage T1/T2a (low); T2b/T2c (intermediate); T3/T4 or N1 or M1 (high).

Statistical analyses

Descriptive analyses of prostate cancer prognostic factors and patient characteristics by race were assessed by comparing frequencies and percent. Chi-squared tests were performed, but considered of limited practical utility due to the large sample size. To examine racial disparities in risk of advanced prostate cancer for each prostate cancer prognostic factor (i.e., PSA, stage, GS, and combined risk), we used multivariable logistic regression to estimate ORs and 95% confidence intervals (CI) across race, with NHW as the reference and each prostate cancer prognostic factor as the outcome in separate models. Classifications of prostate cancer prognostic factors were analyzed as binary variables with low and intermediate categories combined. Each multivariable model was sequentially adjusted for age at diagnosis, year of diagnosis, marital status, insurance type, and nSES. To examine whether observed differences in Black-NHW ORs were independent of other prognostic factors included in the overall combined prostate cancer risk profile, we developed a series of models, as follows:

- Binary PSA as the outcome (≤ 20 vs. > 20). Fully adjusted models were stratified by binary GS (≤ 7 vs. ≥ 8) and binary stage (T1/T2a, T2b/T2c vs. T3/T4 or N1 or M1).
- Binary GS as the outcome. Fully adjusted models were stratified by binary PSA and binary stage.
- Binary stage was the outcome. Fully adjusted models were stratified by binary PSA and binary GS.
- Binary combined risk as the outcome. These models were not stratified.

To assess potential differences within prostate cancer prognostic factor groupings, we also developed fully adjusted multinomial logistic regression models using the three risk group categories as in our prior research (2), using the low categories as the reference group.

To examine the relative influence of each covariable (i.e., age at diagnosis, year of diagnosis, insurance type, marital status, and nSES) on observed Black-NHW disparities in prostate cancer risk combined and separately we used a previously developed method (32). Briefly, the baseline model included race plus age. The prostate cancer risk disparity for a particular model was

$$D = \sqrt{(\sum n_i \{\beta_i - \bar{\beta}_\bullet\}^2) / \sum n_i}$$
the sample-size weighted standard deviation of OR estimate for Black men relative to NHW men. Here, β_i is the log_e OR estimate of Black men relative to NHW men, n_i is the sample size of Black men, and $\bar{\beta}_\bullet$ is the sample size-weighted mean for β_i . The relative influence was then defined as $\{(D_- - D_+) / D_0\} \times 100$ in which D_0 was the OR from the baseline model, D_- was the OR from the model without the covariable of interest, and D_+ was the OR from the model with the covariable of interest. In the multivariable context, D_- was the OR from the model with the covariable of interest, and D_+ was the OR from the model without the covariable of interest. The influence of each covariable on Black-NHW disparities first was tested in a base model to identify univariable influence: race plus age plus covariable. Covariables were then ranked in order of their

univariable influence on prostate cancer risk disparities (i.e., by how much the logistic regression OR predicting prostate cancer risk decreased when included in the base model), sequentially added to the baseline model by the univariable influence rank order, sequentially assessing the change in OR as a measure of the relative change in Black-NHW disparity (i.e., the proportion of the total disparity contributed by that covariable, after accounting for previously added covariables). We also obtained a measure of multivariable influence comparing the baseline model and the multivariable models including all covariables except for the covariable of interest. The process was performed separately for each prognostic factor of prostate cancer risk profile outcome. To check the robustness of the findings, we used the approach described in Gelman 2008 (33) to standardize covariates, and found that the results did not change using this approach; thus, we only present the first set of results.

To examine the possibility that ORs were an overestimate of risk ratios (RR), we calculated RRs and compared them with ORs, using the equation: $RR = \frac{OR}{(1 - prev_0) + (OR \times prev_0)}$, where $prev_0$ is the prevalence of the outcome among NHW men. In addition, we generated multiple imputations of missing covariable data, re-ran the multinomial regression analyses with these imputed values, and compared our models with and without multiple imputations to assess whether results differed between models with and without imputed values for missing covariables. In addition, we imputed missing outcome data based on covariables in the model using discriminant function method (https://documentation.sas.com/doc/en/pgmsascdc/9.4_3.4/statug/statug_mi_details09.htm). Given that the maximum percentage of missing outcome is 10%, we generated 10 multiple imputation samples to achieve 99% efficiency. We re-ran multinomial regression analyses with these imputed data, and the OR estimates from models with and without multiple imputations were compared with assess whether results differed between models with and without missing values in outcome variables. We did not perform multiple comparisons tests.

This study was based on de-identified cancer registry data collected as part of the California statewide cancer registry reporting mandate. The analyses is approved for human subjects research through the Greater Bay Area Cancer Registry Institutional Review Board protocol at the University of California. All statistical comparisons were two-sided. We used SAS 9.4 for multivariable logistic regression analyses.

Results

Descriptive characteristics

Descriptive characteristics for the 23,555 Black men and 146,889 NHW men diagnosed with prostate cancer from 2004 to 2017 are presented in Table 1. The age range of the cohort was 21 to 102 years. Black men with prostate cancer had higher proportions of high risk prostate cancer categories than NHW men (i.e., within the components of PSA, GS, stage, as well as for combined risk). Differences were greatest for high PSA (>20 ng/mL; Black men: 16.3%; NHW men: 9.8%). Black men were more often diagnosed at younger age (<55 years) compared with White men (16.2% and 8.6% respectively). In comparison to NHW men, Black men were more likely to reside in lowest SES neighborhoods (24.2% compared with 6.6%), more likely to be unmarried (41.7% compared with 24.2%), less likely to have Medicare insurance (13.2% compared with 23.7%), and more likely to have public insurance (28.9% compared with 19.1%). All frequencies examined χ^2 p-values < 0.001. Higher proportions of worse prognosis for each factor were observed for Black men relative to NHW men, for older men

relative to younger men, for widowed men, for men residing in lower SES neighborhoods, and for men with unknown or missing insurance status. Supplementary Table S1 provides characteristics of men with missing prostate cancer outcome data by age. We observed some indication that data were missing not at random.

Black-NHW disparities in prostate cancer risk profiles at diagnosis

Figure 1 and Supplementary Table S2 provide results from multivariable models for the association between all covariables and each of the binary prostate cancer risk outcomes assessed. Black men had increased odds of high PSA, GS, stage, and combined risk, compared with NHW men (65%, 13%, 12%, and 27% increases, respectively). Further adjusting for GS and stage had no impact on the increased odds of high PSA among Black men relative to NHW men (OR, 1.67; 95% CI, 1.59–1.75; $P < 0.001$). However, the increased odds of high GS and high stage among Black men was attenuated to the null and beyond the null, respectively, when we include all specific risk measures in a single model. In these models, high PSA was strongly associated with high GS and high stage tumors; the OR for the association of PSA with GS was 6.27 (95% CI, 6.04–6.50; $P < 0.001$) in the model with high GS as the outcome; and the OR for the association of PSA with stage was 7.41 (95% CI, 7.12–7.73; $P < 0.001$) in the model with high stage as the outcome.

Table 2 shows results of fully adjusted models of the racial disparity considering three categories of risk for each specific prostate cancer risk measure to assess the pattern of the racial disparity across the three categories; with low risk as the referent. The most prominent disparity was evident for PSA; compared with NHW men, Black men had 40% increased odds of intermediate versus low PSA (OR, 1.37; 95% CI, 1.29–1.45) and nearly twice the odds of high versus low PSA (OR, 1.96; 95% CI, 1.86–2.06), even with adjustment for GS and stage. This pattern was not observed for GS for which, compared with NHW men, Black men had equivalent odds of high versus low GS after adjustment for PSA (OR, 1.00; 95% CI, 0.96–1.05). For stage, we observed inverse associations between intermediate versus low stage (OR, 0.78; 95% CI, 0.75–0.81) and high versus low stage (OR, 0.84; 95% CI, 0.80–0.88), suggesting that Black men were less likely than NHW men to present with intermediate or high stage disease after adjustment for PSA. Comparison of these results with those from the multiple imputations revealed <1% differences in ORs for all models. Black-NHW disparities in high PSA persisted across all stratified analyses; whereas attenuations to the null were observed for high GS and high stage when stratified by low PSA disease and beyond the null when stratified by high PSA (Fig. 1; Supplementary Table S3). We did not observe substantial differences in the OR and RR calculations (Supplementary Table S4).

Relative influence of covariables on Black-NHW disparities

Results of models to assess relative influence of covariables on Black-NHW disparities in prostate cancer risk profiles are provided in Fig. 2. The age-adjusted odds of high versus low/intermediate PSA prostate cancer among Black men were 2.14 times those of NHW men (95% CI, 2.06–2.23). A large proportion of this racial disparity in PSA was attributable to nSES, which accounted for about 25.4% of the Black-NHW disparity in multivariable models. An additional 10.8% was explained by differences in marital status, and 4.9% was explained by differences in insurance status. Similarly, the largest proportion of the Black-NHW disparity in high GS, stage, and combined risk disease in multivariable models were attributable to differences in nSES, followed by marital status.

Table 1. Patient demographic and prostate cancer (PCa) characteristics among 23,555 Black men and 146,889 NHW men diagnosed with first primary invasive prostate cancer from 2004 to 2017 in California.

Patient and PCa characteristics	Race				Total
	NHW men		Black men		
	<i>n</i>	Col (%)	<i>n</i>	Col (%)	
PCa prognostic factor ^a					
Prostate-specific antigen (PSA) category					
Low (<10 ng/mL)	96,042	65.3	13,669	58.0	109,711
Intermediate (10 to <20 ng/mL)	21,283	14.4	4,139	17.6	25,422
High (20+ ng/mL)	14,430	9.8	3,835	16.3	18,265
Missing	15,134	10.3	1,912	8.1	17,046
Gleason score (GS) risk category					
Low (<7)	57,430	39.1	8,648	36.7	66,078
Intermediate (7)	57,581	39.2	9,689	41.1	67,270
High (8+)	23,382	15.9	3,918	16.6	27,300
Missing	8,496	5.8	1,300	5.5	9,796
Stage risk category					
Low (N0, M0, and T1/T2a)	89,814	61.1	15,068	63.9	104,882
Intermediate (N0, M0, and T2b/T2c)	35,143	23.9	4,615	19.6	39,758
High (N1, M1, and/ or T3a+)	17,443	11.9	3,161	13.4	20,604
Missing	4,489	3.1	711	3.0	5,200
Combined National Comprehensive Cancer Network (NCCN) PCa risk category					
Low	34,245	23.3	5,233	22.2	39,478
Intermediate	63,265	43.1	9,862	41.9	73,127
High	34,540	23.5	6,563	27.9	41,103
Missing	14,839	10.1	1,897	8.1	16,736
Individual characteristics					
Age at diagnosis (years)					
<55	12,555	8.6	3,818	16.2	16,373
55–64	48,011	32.7	9,288	39.4	57,299
65–74	57,038	38.8	7,681	32.6	64,719
75+	29,285	19.9	2,768	11.8	32,053
Year of diagnosis					
2004	12,008	8.2	1,664	7.1	13,672
2005	10,632	7.2	1,607	6.8	12,239
2006	12,056	8.2	1,809	7.7	13,865
2007	12,903	8.8	1,930	8.2	14,833
2008	11,964	8.1	1,811	7.7	13,775
2009	11,556	7.9	1,870	7.9	13,426
2010	11,350	7.7	1,893	8.0	13,243
2011	11,485	7.8	1,837	7.8	13,322
2012	9,499	6.5	1,729	7.3	11,228
2013	9,138	6.2	1,637	7.0	10,775
2014	8,328	5.7	1,418	6.0	9,746
2015	8,605	5.9	1,431	6.1	10,036
2016	8,580	5.8	1,414	6.0	9,994
2017	8,785	6.0	1,505	6.4	10,290
Marital status					
Single, never married ^b	15,538	10.6	5,059	21.5	20,597
Married	100,470	68.4	12,170	51.7	112,640
Separated	1,032	0.7	474	2.0	1,506
Divorced	9,621	6.6	2,242	9.5	11,863
Widowed	5,830	4.0	939	4.0	6,769
Unknown	14,398	9.8	2,671	11.3	17,069
Insurance type ^c					
No insurance	1,139	0.8	336	1.4	1,475
Private	76,285	51.9	12,500	53.1	88,785
Medicare only	34,767	23.7	3,100	13.2	37,867
Any public/medicaid/military	28,116	19.1	6,795	28.9	34,911
Unknown or missing	6,582	4.5	824	3.5	7,406

(Continued on the following page)

Table 1. Patient demographic and prostate cancer (PCa) characteristics among 23,555 Black men and 146,889 NHW men diagnosed with first primary invasive prostate cancer from 2004 to 2017 in California. (Cont'd)

Patient and PCa characteristics	Race				Total
	NHW men		Black men		
	<i>n</i>	Col (%)	<i>n</i>	Col (%)	
Neighborhood characteristics					
nSES at diagnosis					
Quintile 1 (low)	9,619	6.6	5,689	24.2	15,308
Q2	19,776	13.5	5,540	23.5	25,316
Q3	29,076	19.8	4,957	21.0	34,033
Q4	37,767	25.7	4,538	19.3	42,305
Quintile 5 (high)	50,651	34.5	2,831	12.0	53,482
Total	146,889	100.0	23,555	100.0	170,444

Note: All χ^2 *P* values < 0.001.

^aPCa risk profile stratification criteria based on the NCCN classification using TNM stage, GS, and PSA level. Low included low-risk (T1/T2a and GS $\leq$ 6 and PSA <10 ng/mL) and intermediate-risk (N0 and M0 and T2b/T2c or biopsy GS 7 or PSA 10–20 ng/mL); and high included high-risk (T3/T4 or GS 8+ or PSA >20 ng/mL or N1 or metastatic M1).

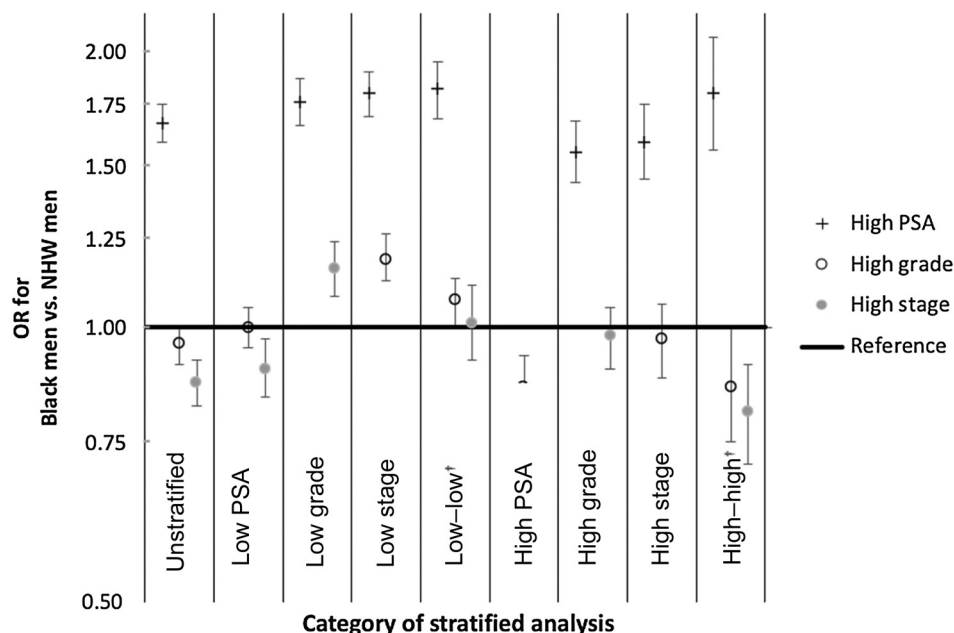
^bSingle, never married included unmarried or domestic partner (same sex or opposite sex, registered or unregistered other than common law marriage).

^cPrimary payer at diagnosis.

Discussion

To examine the extent to which social factors contribute to racial disparities in prostate cancer risk profiles as defined by PSA, GS, clinical stage, and combined risk, we conducted a population-based study of all Black men and NHW men diagnosed with first primary invasive prostate cancer in California from 2004 to 2017. NSES was the most influential factor contributing to age-adjusted racial disparities in prostate cancer risk profile among Black men relative to NHW men for

PSA, GS, stage, and combined risk; followed by marital status. Future studies are needed to elucidate the role of nSES and marital status in prostate cancer risk profile at diagnosis. Specific areas of interest include a careful consideration of what nSES may be measuring, how that may be driving racial disparities in high PSA prostate cancer in particular—including an increased understanding of the intersection of social factors of racism, social isolation, social stressors, and specific neighborhood factors—and whether such racial disparities in high

**Figure 1.**

OR of PCa risk profiles for Black men relative to NHW men among men diagnosed with PCa from 2004 to 2017 in California using three risk categorizations (PSA^a, GS^b, and stage^c), fully adjusted models series of stratified models defined by PSA^a, GS, and stage^c. All models adjusted for age at diagnosis, year of diagnosis, marital status, insurance type, and nSES. Unstratified model for outcome of PSA additionally adjusted for GS and stage (low and high). Unstratified model for outcome of GS additionally adjusted for PSA and stage (low and high). Unstratified model for outcome of stage additionally adjusted for PSA and GS (low and high). †, Low-low and high-high represent the strata for which the outcome is not modeled [i.e., for high PSA: low stage and low GS (low-low) and high stage and high GS (high-high); for high GS: low PSA and low stage (low-low) and high PSA and high stage (high-high); and for high stage: low PSA and low GS (low-low) and high PSA and high GS (high-high)]. ^aPSA risk category low ($\leq$ 20 ng/mL) vs. high (>20 ng/mL). ^bGS risk category low (<8) vs. high (8+). ^cStage risk categories low (N0, M0, and <T2b) and high (N1, M1, and/ or T3a+).

Table 2. OR of PCa risk profiles among Black men relative to NHW men with outcomes of high PSA,^a GS,^b and stage^c disease among California residents with PCa from 2004 to 2017, by race

PCa risk profile outcome modeled	OR for Black men relative to NHW men				N ^d
	Intermediate vs. low		High vs. low		
	OR	(95% CI)	OR	(95% CI)	
PSA ^a	1.40	(1.35–1.46)	1.96	(1.86–2.06)	153,398
GS ^b	1.12	(1.08–1.15)	1.00	(0.96–1.05)	160,648
Stage ^c	0.78	(0.75–0.81)	0.84	(0.80–0.88)	165,244 ^e
Combined National Comprehensive Cancer Network (NCCN) PCa risk category ^f	1.09	(1.05–1.13)	1.35	(1.29–1.41)	153,708

Note: All models adjusted for age at diagnosis (years), year of diagnosis, marital status, insurance type, and nSES. Model for outcome of PSA adjusted for GS (low, intermediate, high), and stage (low, intermediate, and high). Model for outcome of GS adjusted for PSA (low, intermediate, high). Model for outcome of stage adjusted for PSA (low, intermediate, high).

^aPSA risk category low (<10 ng/mL), intermediate (10–20 ng/mL), and high (>20 ng/mL).

^bGS risk category low (<7), intermediate (7), and high (8+).

^cStage risk categories low (NO, MO, and T1/T2a), intermediate (NO, MO, and T2b/T2c) and high (N1, M1, and/ or T3/T4).

^dModels with PSA outcomes exclude men with missing data on PSA. Models with GS outcomes exclude men with missing data on PSA or GS. Models with outcomes of stage exclude men with missing data on PSA or stage.

^eExcludes $n = 97$ (0.06%) for whom N stage and M stage are missing. These men were inferred to not have nodal involvement or metastases in binomial analyses.

^fPCa risk stratification criteria based on the NCCN classification using TNM stage, GS, and PSA level. Low included low-risk (T1/T2a and GS ≤ 6 and PSA <10 ng/mL) and intermediate-risk (T2b/T2c or biopsy GS 7 or PSA 10–20 ng/mL); and high included high-risk (T3/T4 or GS 8+ or PSA >20 ng/mL or N1 or M1).

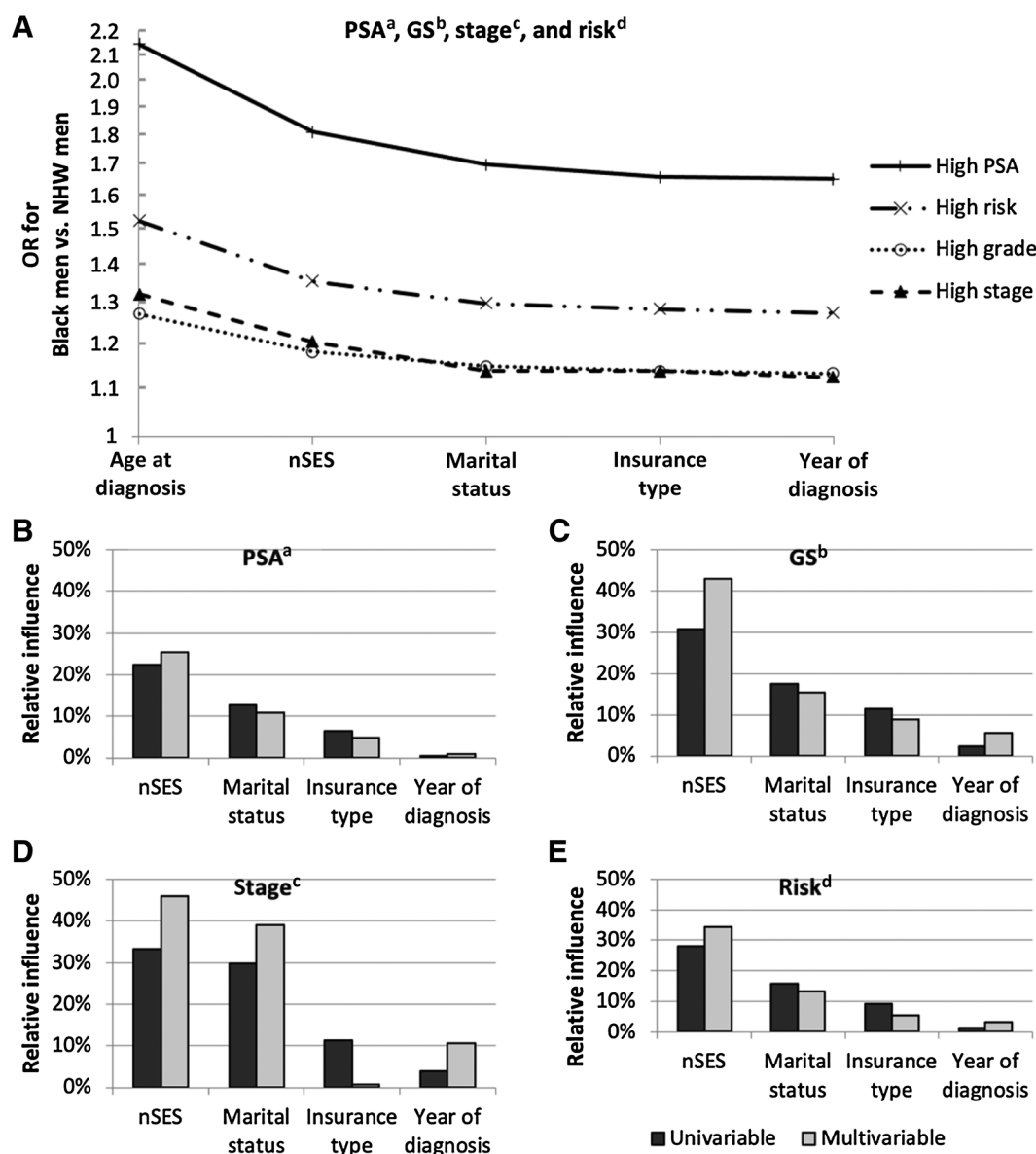
PSA prostate cancer are associated with worse survival outcomes after controlling for stage and GS.

Increased serum PSA, an androgen-regulated glycoprotein molecule involved in the liquefaction of seminal fluid, is a prognostic factor of prostate cancer risk (34–36). Higher PSA among Black men relative to White men has been under investigation for decades (3, 5). Some have speculated that higher PSA levels among Black men in comparison to NHW men at diagnosis of nonmetastatic prostate cancer may be due to higher tumor cell burden or screening detection later in the clinical course (i.e., differential disease courses) (37). Tumor volume, inflammation, number, or cores positive and percentage of the higher versus lower GS components are reasons why patients could have the same stage and GS but a higher risk profile prostate cancer. Other nonmalignant clinical correlates of increased serum PSA include increasing age, larger prostate volume, infection or trauma to the prostate, and medical procedures that interfere with the prostate gland (38–42). It is therefore unclear whether high PSA among Black men compared with NHW men at diagnosis in our study is due to differences in underlying tumor biology, PSA expression, or racial differences in PSA-based screening.

There are biological differences in high PSA at prostate cancer diagnosis, which warrants further study because the majority of genetic research on prostate cancer to date has been conducted among White men. Recent work has indicated that certain *Kallikrein* polymorphisms are associated with PSA levels in Black men but not NHW men (43). Additional studies are necessary to elucidate mechanisms for biological differences in prostate cancer risk profiles observed between Black men and NHW men that are due to genetic ancestry versus social factors. Moreover, biological differences may be due to underlying germline genetics or epigenetic expression in response to the embedding of racism. An example of one such study that considers the full breadth of factors that may contribute to racial disparities in prostate cancer outcomes is our national, multicenter study; Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers and Social Stress (RESPOND), currently in the field. In RESPOND, we are conducting the largest coordinated research effort to date to study multilevel

determinants of enduring racial disparities in prostate cancer among US Black men. We conceptualize increased risk of aggressive prostate cancer and prostate cancer mortality among Black men in the United States as a combination of underlying germline genetics and the experience of racism through individual- and neighborhood-level social stressors across the lifecourse that “get under the skin” to cause biological vulnerability in somatic profiles, tumor inflammation, and other potential mechanisms.

Disparities in PSA-based screening across populations may also contribute to high PSA among Black men at prostate cancer diagnosis. Although best available crude prevalence estimates for PSA screening are comparable between Black men and NHW men of age 40+ years in California (44, 45), these estimates may not accurately reflect PSA screening prevalence for more recent years included in our study, or relevant PSA screening behavior. Multiple PSA tests need to occur to detect prostate cancer early and it is unknown how many PSA tests Black men receive over time relative to NHW men. In our study, delayed diagnosis among Black men relative to NHW men resulting from differential longitudinal screening frequencies may have had a stronger impact on rates of high PSA at prostate cancer diagnosis than on high GS at diagnosis since prostate cancer among Black men tend to produce more PSA per tumor volume. Higher GS is generally considered to be less susceptible to early detection. We performed sensitivity analyses to examine whether Black-NHW disparities in high risk profile prostate cancer were driven by changes in screening behavior following the 2012 United States Preventive Services Task Force (USPSTF) recommendation that clinicians should not screen men who do not express a preference for screening (46). We observed fewer men with prostate cancer and proportionally more advanced prostate cancer diagnosed in 2013 to 2017 than in preceding years for both racial groups, but adjustment for a period effect of year of diagnosis 2004 to 2012 versus 2013 to 2017 did not result in changes in Black-NHW odds ratio estimates for PSA, GS, stage or prostate cancer risk of more than 1% (Supplementary Table S5). These suggest that our main findings were likely not impacted by changes in screening behavior following the 2012 USPSTF recommendations.

**Figure 2.**

A, OR of PCa risk profiles (PSA,^a GS,^b stage,^c and combined risk^d) for Black men compared with NHW men, for a sequence of logistic regression models, the leftmost of which includes racial/ethnic group alone adjusted for age at diagnosis, where variables are added in the order of their univariable significance, and where the rightmost represents the full baseline model. **B–E**, Univariable and multivariable relative influence of individual variables in the baseline model for prostate cancer risk profile outcomes. ^aPSA risk category low (≤ 20 ng/mL) vs. high (> 20 ng/mL). ^bGS risk category low (< 8) vs. high (≥ 8). ^cStage risk categories low (N0, M0, and $< T2b$) and high (N1, M1, and/or $\geq T2b$). ^dPCa risk stratification criteria based on the NCCN classification using TNM stage, GS, and PSA level. Low included low-risk (N0 and M0 and $T1/T2a$ and $GS \leq 6$ and $PSA < 10$ ng/mL) and intermediate-risk (N0 and M0 and $T2b/T2c$ or biopsy $GS 7$ or $PSA 10–20$ ng/mL), and high included high-risk ($T3/T4$ or $GS 8+$ or $PSA > 20$ ng/mL or N1 or M1).

Our study is strengthened by the legal mandate in California for routine collection of tumor and patient characteristics on all persons with cancer in California. As part of the SEER registry program, component registries of the CCR meets stringent standards for quality, timeliness, and completeness. Hence, our study is less prone to reporting and selection biases than studies within specific healthcare systems or patient populations. We utilized composite indices for measuring nSES that did not require patient report, which enabled us to provide evidence that nSES is a

primary contributor to Black-NHW disparities in advanced prostate cancer.

Our study was subject to limitations common to cancer registry-based analyses including lack of individual-level data on SES, family history of cancer, and lifestyle factors. We were unable to control for obesity, which is positively associated with GS (47), negatively associated with PSA (48), and disproportionately high in California for Black men relative to NHW men (e.g., 35.4% vs. 25.2%, respectively, in the California Health Interview Survey; ref. 49). Another limitation of

SEER data is inability to identify whether men were diagnosed with prostate cancer following routine screening or based on a symptomatic indication. An additional limitation of cancer registry data is lack of information regarding prior residences or length at residence, which may be related to prostate cancer risk profiles. We also lacked data on tumor volume, prostate size, and number and involvement of biopsy cores. Furthermore, our single PSA test result lacked potentially important information such as PSA kinetics (PSA velocity and doubling time) and free-to-total PSA ratio; potentially important predictors of prostate cancer risk profile (35, 36, 50). In addition, we observed some indication of nonrandom missingness in prostate cancer risk profile outcome variables. The largest proportion of missing prostate cancer risk profile data were observed among men with unknown or missing insurance status. However, men with missing or unknown insurance status comprised <5% of the overall sample. A recent study examining potential exclusion bias due to missing data when grouping prostate cancer cases using this D'Amico risk stratification in SEER data, found that tumor characteristics among men with missing prostate cancer risk profile data were similar to those with complete data for risk profile (51). Our observation of <1% differences in the ORs between our models with and without multiple imputations provided evidence that our findings were likely not biased due to missing data.

Our findings suggest that racial disparities in high-risk prostate cancer among Black men relative to NHW men may be influenced in part by differences in nSES. These findings are consistent with previous findings of high prostate cancer risk profiles for men in the lowest nSES quintile (2) and worse prostate cancer survival among Black men than White men, which was attenuated by adjustment for nSES (23). Our findings that marital status contributes to racial disparities in high-risk prostate cancer among Black men relative to White men is consistent with findings that marital status is an independent and strong predictor of prostate cancer survival, and a moderator of racial disparities therein (7, 24). We interpret our findings for nSES and marital status in light of emerging evidence that prostate cancer develops through complex interactions at the biological, individual, and social levels (10, 23, 52, 53). Further work is necessary to elucidate potentially relevant adverse exposures among Black men residing in low nSES neighborhoods, such as perceived racism and social stress, how such factors may contribute to high-risk prostate cancer profiles. Furthermore, the association between high-risk prostate cancer at diagnosis and unmarried status warrants additional investigation, possibly to inform social support resources for health disparities populations.

Authors' Disclosures

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Authors' Contributions

D.J. Press: Conceptualization, data curation, formal analysis, investigation, visualization, methodology, writing—original draft, writing—review and editing. **S. Shariff-Marco:** Resources, methodology, writing—review and editing. **D.Y. Lichtensztajn:** Data curation, formal analysis, methodology, writing—review and editing. **D. Lauderdale:** Conceptualization, methodology, writing—review and editing. **A.B. Murphy:** Conceptualization, methodology, writing—review and editing. **P.P. Inamdar:** Data curation, formal analysis, methodology, writing—review and editing. **M.C. DeRouen:** Methodology, writing—review and editing. **A.S. Hamilton:** Funding acquisition, methodology, writing—review and editing. **J. Yang:** Methodology, writing—review and editing. **K. Lin:** Formal analysis, validation, investigation. **D. Hedeker:** Methodology, writing—review and editing. **C.A. Haiman:** Resources, funding acquisition, methodology, writing—review and editing. **I. Cheng:** Conceptualization, resources, methodology, writing—review and editing. **S.L. Gomez:** Conceptualization, resources, supervision, funding acquisition, methodology, project administration, writing—review and editing.

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Contributions of Social Factors to Disparities in Prostate Cancer Risk Profiles among Black Men and Non-Hispanic White Men with Prostate Cancer in California

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APPENDIX 3

Performance of Prostate Health Index in Biopsy Naïve Black Men

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Abstract

Purpose: The Prostate Health Index is validated for prostate cancer detection but has not been well validated for Gleason grade group 2-5 prostate cancer detection in Black men. We hypothesize that the Prostate Health Index has greater accuracy than prostate specific antigen for detection of Gleason grade group 2-5 prostate cancer. We estimated probability of overall and Gleason grade group 2-5 prostate cancer across previously established Prostate Health Index ranges and identified Prostate Health Index cutoffs that maximize specificity for Gleason grade group 2-5 prostate cancer with sensitivity >90%.

Materials and Methods: We recruited a “cancer-free” Black control cohort (135 patients) and a cohort of biopsy naïve Black men (158) biopsied for elevated prostate specific antigen. Descriptive statistics compared the prostate cancer cases and controls and the frequency of Gleason grade group 2-5 prostate cancer across Prostate Health Index scores. Receiver operating characteristics compared the discrimination of prostate specific antigen, Prostate Health Index and other prostate specific antigen related biomarkers. Sensitivity and specificity for Gleason grade group 2-5 prostate cancer detection were assessed at prostate specific antigen and Prostate Health Index thresholds alone and in series.

Results: Of biopsied subjects 32.9% had Gleason grade group 2-5 prostate cancer. In Blacks with prostate specific antigen from 4.0–10.0 ng/ml, Prostate Health Index and prostate specific antigen had similar discrimination for Gleason grade group 2-5 prostate cancer (0.63 vs 0.57, $p=0.27$). In Blacks with prostate specific antigen ≤ 10.0 , a threshold of prostate specific antigen ≥ 4.0 had 90.4% sensitivity for Gleason grade group 2-5 prostate cancer; a threshold of prostate specific antigen ≥ 4.0 with Prostate Health Index ≥ 35.0 in series avoided unnecessary biopsy in 33.0% of men but missed 17.3% of Gleason grade group 2-5 prostate cancer. Prostate specific antigen ≥ 4.0 with Prostate Health Index ≥ 28.0 in series spared biopsy in 17.9%, while maintaining 90.4% sensitivity of Gleason grade group 2-5 prostate cancer.

Conclusions: The Prostate Health Index has moderate accuracy in detecting Gleason grade group 2-5 prostate cancer in Blacks, but Prostate Health Index ≥ 28.0 can be safely used to avoid some unnecessary biopsies in Blacks.

Keywords

prostatic neoplasms; African Americans; biomarkers; sensitivity and specificity; comparative effectiveness research

PROSTATE specific antigen testing has led to improved detection of prostate cancer and a reduction in prostate cancer specific mortality.¹ However, the poor specificity results in excessive biopsies in over 50% of men (ie negative biopsies and indolent prostate cancer).^{2,3} Post-biopsy sepsis and hospitalization occur in 1%–3% of biopsies.⁴ Over detection of indolent prostate cancer causes overtreatment and morbidity, and generates high health care

costs.⁵ Given the limitations and risks of prostate specific antigen screening, there is growing interest in new screening tests that accurately detect clinically significant Gleason grade group 2-5 prostate cancer (ie Gleason score $\geq 3+4$) and help men avoid unnecessary biopsies (through improved specificity).

In 2012, the FDA approved the Prostate Health Index, a biomarker with increased specificity for PCa detection in the diagnostic gray zone of PSA from 4.0–10.0 ng/ml with normal digital rectal examination.⁶ The PHI assay uses a composite of total PSA, free PSA and p2PSA.⁷ Several multicenter studies have shown that PHI outperforms PSA in the detection of PCa^{7–14} with some studies demonstrating PHI's increased accuracy for GG 2-5 PCa in men within the diagnostic PSA gray zone.^{8,14} It has been determined that PHI should not be used for primary screening in the general population, but instead as a reflex confirmatory test, using a threshold of PHI ≥ 35.0 for biopsy decisions.¹⁰ Validation studies in diverse populations have suggested varying optimal cut points for PHI across ethnic groups.^{15,16} For instance, at a sensitivity of 90%, reported PHI cutoffs include 28.6 for European Americans,¹² 26.5 for Asian Americans¹⁷ and 31.6 for European Whites.¹⁸ Few studies have evaluated the performance of PHI in detecting GG 2-5 PCa in Black cohorts,¹⁹ so its generalizability in this population remains unestablished. Given the high risk of PCa in Black men, PHI should be validated in this population.^{20,21}

We hypothesize that the accuracy of PHI in GG 2-5 PCa detection is greater than PSA in biopsy naïve Black men. Our secondary objectives were to 1) assess the prevalence of GG 2-5 PCa in Black men across assay reported PHI scores, and 2) assess the overall sensitivity and specificity for GG 2-5 PCa in Black men of PSA and PHI thresholds alone and of PHI when paired with a PSA ≥ 4.0 ng/ml threshold.^{7,12,22,23}

METHODS

Study Population

This study utilizes 2 different cohorts recruited in Chicago, Illinois. Research coordinators administered a survey that captured sociodemographic information, substance use, and family and medical history to both cohorts. The first cohort of “cancer-free” controls included 139 self-reported Black men, age 40–79 years. They were recruited from community PCa screening events in Chicago, Illinois from 2018–2019 through the social networks of 8 Black Citizen Scientists who were interested in Black men's health (Black Citizen Scientists Study). Controls did not undergo assessment of prostate volume or prostate biopsy unless referred by their physician for PB (3). Men with PSA ≥ 4.0 ng/ml (13) were tracked for 1 year for PSAs or biopsies (1) that occurred after enrollment. Coordinators collected information on repeat PSA, potential biopsies and PCa diagnoses by administering a 1-page survey 12 months after enrollment for the BCS cohort. Four men were excluded for PSA >10.0 ng/ml (3) or subsequent PCa diagnosis (1), leaving 135 for analysis. Men with a history of 5-alpha reductase inhibitor use, prior PB, abnormal DRE, and men with PSA >10.0 ng/ml were excluded from the cohort in order to establish median levels of PHI in “cancer-free” controls (135).

The second cohort, the PHI Biopsy Study, comprised 158 Black men, age 40–79 years, referred to outpatient urology clinics at Northwestern Memorial, John H. Stroger, or University of Illinois at Chicago Hospitals for elevated PSA between February 2017 and January 2020. Coordinators administered the same sociodemographic and medical history survey immediately before the biopsy. Coordinators then reviewed the electronic health records of each participant 1 month and 12 months after the biopsy to collect information on repeat PSAs, PB pathology reports, imaging and clinical stage (if cancer was present). Men underwent PHI testing immediately prior to the initial TRUS guided PB. Men with a history of 5-alpha reductase inhibitor use, prior PB, abnormal DRE, and men with PSA >10.0 ng/ml were excluded from the cohort.

For the study we include all men with PSA ≤10.0 ng/ml but for the comparison of AUC between PHI and PSA, we limited it to the 4.0–10.0 ng/ml range (142), consistent with its FDA approval. Other studies have varied the inclusion criteria to include men with PSA as low as 2.0 ng/ml, and we similarly included PSA levels below 4.0 ng/ml to evaluate the impact of various PSA thresholds on sensitivity and specificity. Coordinators administered the same sociodemographic and medical history survey immediately before the biopsy. Coordinators then reviewed the electronic health records 12 months after the biopsy to collect information on repeat PSAs, PB pathology reports, imaging and clinical stage (if cancer was present). Baseline demographic and clinical data included age, race, family history of PCa, suspicious DRE, referral PSA level and the PSA related biomarkers in the PHI assay along with the PHI score.

The Beckman Coulter Access® 2 immunoassay analyzer (Beckman Coulter, Brea, California, USA) was used to measure serum PSA, fPSA and p2PSA. PHI was calculated by the assay as $(p2PSA/fPSA) \times (PSA^{1/2})$, and % fPSA was defined as $(fPSA/PSA) \times 100$.

As supplementary data, we provide the normal age specific ranges of PHI in community dwelling Black, “cancer-free” controls (supplementary table, <https://www.jurology.com>). We also include the AUC data for GG 1-5 PCa using PSA, PHI and the PSA related biomarkers.

IRB Approval

The BCS study was approved by the institutional review boards at Northwestern University, University of Illinois at Chicago and Northeastern Illinois University (IRB No. STU00206075). The PBS was approved by the IRBs at Northwestern University, University of Illinois at Chicago and Cook County Health (IRB No. STU0020425).

Pathological Review

Pathological assessment of biopsy specimens was performed by expert uropathologists in accordance with the 2016 International Society of Urological Pathology Consensus Conference, ie GG 1: Gleason score ≤6; GG 2: Gleason score 3+4=7; GG 3: Gleason score 4+3=7; GG 4: Gleason score=8; and GG 5: Gleason score=9–10.²⁴ The primary outcome was GG 2-5 PCa.

Statistical Analysis

Statistical comparisons were made using the chi-square test for proportions; comparisons of medians and IQRs were made with medians test for continuous variables. Receiver operating characteristic curves were constructed for nonparametric data to compare the AUC of the referral PSA, PHI and other PSA related biomarkers for GG 2-5 PCa and GG 1-5 PCa (supplementary figure, <https://www.jurology.com>) in men with PSA from 4.0–10.0 ng/ml using the Kolmogorov-Smirnov test.

For objective 1, the percentages of men with overall and GG 2-5 PCa were reported across previously established PHI score ranges. For comparison, we include the estimated probabilities of overall PCa from the PHI assay report.⁶

For objective 2, thresholds of PSA (from 2.0–6.0) and PHI (from 20–55) were generated, and the specificities for GG 2-5 PCa were compared at $\geq 90\%$, and $\geq 95\%$ sensitivity among biopsy subjects. For brevity, we include only thresholds of PHI where sensitivity was $\geq 90\%$. Since PSA ≥ 4.0 ng/ml is the standard in the U.S.,²² we tested the impact of using various PHI thresholds after serum PSA ≥ 4.0 ng/ml on sensitivity and specificity for GG 2-5 PCa in the biopsy subjects. To estimate the impact of these thresholds on a Black screening population, we used the PHI and PSA results of the BCS cohort to determine the percentage of “cancer-free” controls that would exceed each threshold and be referred to urologists for a PB. We used the PSA in the PHI assay since these men were recruited in community PCa screening events.

Based on data from Loeb, de la Calle and Nordström et al, we powered this study for comparing the discrimination of PHI and PSA in GG 2-5 PCa detection in Blacks.^{8,12,14} Assuming an AUC of 0.60 for PSA, with 142 Black men, and a difference of 0.12 in AUC, we are powered at 82% with a 2-sided alpha of 0.05.

All comparisons were 2-sided and p values < 0.05 indicated statistical significance. Statistical analysis was performed using SPSS® 25 and MedCalc® 19.0.5.

RESULTS

Demographics and Distribution

The study included 158 Black men from the PBS cohort and 135 men from the BCS cohort who were included as “cancer-free” controls (table 1). Compared to the controls, men in the PBS cohort were older (median age 60.0 vs 55.0 years), had higher PSA levels and PHI scores, and had greater frequencies of family history of PCa and personal history of benign prostatic hyperplasia/lower urinary tract symptoms (benign prostatic hyperplasia/lower urinary tract symptoms, all p > 0.01).

In the PBS group, using the same PHI categories that are included in the PHI report,⁶ the risk of overall and GG 2-5 PCa for Blacks increases with higher scores (table 2). Black men with PHI scores between 27.0–35.9, 36.0–54.9, and ≥ 55.0 had a PCa prevalence of 45.5%, 51.3%, and 65.8% and had GG 2-5 PCa in 18.2%, 35.1%, and 39.5%, respectively. No Black men with PHI < 27.0 (7) had biopsy proven PCa. Notably, Blacks in the PBS had higher rates

of PCa in every category than the population used to validate PHI⁷ for PHI scores above 27.0.

Median PHI scores and PSA levels in the BCS cohort by decade of age are presented in the supplementary table (<https://www.jurology.com>). There was a threefold increase in PSA from men aged 40–49 years (0.69 ng/ml) to men aged 70–79 years (2.11 ng/ml). The PHI score, however, remained relatively constant across all 4 age groups (median range 18.12–22.12).

Discrimination Analysis

For the discrimination analysis of GG 2-5 PCa, we included men in the PBS cohort with PSA from 4.0–10.0 ng/ml and normal DRE, since this is the FDA approved indication. PHI was statistically similar to PSA in the detection of GG 2-5 PCa in Black men (AUC 0.63 vs 0.57, $p = 0.27$). PHI density (AUC 0.74) and PSA density (AUC 0.74) both showed statistically greater accuracy in detecting GG 2-5 PCa relative to PSA and PHI (see figure).

A secondary discrimination analysis of overall PCa was performed using the PBS population. For overall PCa as well, PHI was statistically similar to PSA in the detection of GG 1-5 PCa (AUC 0.66 vs 0.64, $p = 0.75$). PSA density (AUC 0.75) was statistically more accurate than PSA in detecting overall PCa, however, while PHI density had a higher AUC than PSA (AUC 0.73) it was not a statistically significant difference ($p = 0.11$, supplementary figure, <https://www.jurology.com>).

Sensitivity and Specificity Analysis

Sensitivity and specificity were calculated for detecting GG 2-5 PCa using varied thresholds of PSA and PHI alone and in series (table 3) to achieve $\geq 90\%$ and $\geq 95\%$ sensitivity for GG 2-5 PCa. To estimate the impact on screening healthy Black men, we calculated the percentage of the BCS “cancer-free” controls that would exceed each threshold (ie have a false-positive test) and undergo a theoretically unnecessary biopsy. A sensitivity of 90.4% is achieved with a PHI threshold of ≥ 35.0 , a PSA threshold of ≥ 4.0 ng/ml, and a PSA ≥ 4.0 ng/ml with PHI ≥ 28.0 in series. These correspond to specificities of 26.2%, 10.4% and 17.9%, respectively, which are proxies for avoidable biopsies. However, these thresholds would lead to biopsies in 17.8%, 6.7%, and 5.9% of “cancer-free” controls, respectively. The current standard of care combines the screening threshold of PSA ≥ 4.0 and PHI ≥ 35.0 and captures only 82.7% of GG 2-5 PCa, but spares 35 (33.0%) men an unnecessary biopsy. This also causes 8 (5.9%) unnecessary biopsies among “cancer-free” controls. Meanwhile, using the screening threshold of PSA ≥ 4.0 ng/ml with PHI ≥ 28.0 maintains the same sensitivity as PSA ≥ 4.0 ng/ml alone, 90.4% for GG 2-5 PCa, and spares 28 (17.9%) men an unnecessary biopsy.

DISCUSSION

Black men have higher rates of overall PCa compared to the general population across several PHI risk groups relative to the data that is provided by the PHI assay. In Black men, PHI is moderately accurate at detection of GG 2-5 PCa (AUC 0.63) and overall PCa (AUC 0.66, supplementary figure, <https://www.jurology.com>), but is not superior to PSA in either

outcome (both $p > 0.25$). When used alone, PSA ≥ 4.0 ng/ml threshold only has 90.4% sensitivity, while PHI ≥ 28.0 has 100% sensitivity; use of PHI as an initial screening test would subject $>25\%$ of “cancer-free” controls to unnecessary biopsies. When combined with the standard PSA ≥ 4.0 ng/ml threshold, PHI ≥ 28.0 only increases specificity to 17.9% while maintaining 90.4% sensitivity.

Currently, PHI scores are reported in 4 distinct “risk categories”: 0–26.9, 27.0–35.9, 36.0–54.9, and >55.0 . The PHI report lists the probability of PCa on biopsy as 9.8%, 16.8%, 33.3%, and 50.1%, respectively.⁶ Our data show that Black men have a higher prevalence of PCa within each risk category above 26.9 (table 2). In response to the higher prevalence of GG 2-5 PCa in Blacks, a lower PHI threshold in this group is needed to reduce false negatives.

PHI performed poorly in Black men compared to the external literature on GG 2-5 PCa. In a manuscript by de la Calle et al,⁸ the AUC of PHI for GG 2-5 PCa in a mostly nonBlack cohort was 0.81 in their primary cohort (561) and AUC of 0.78 in their validation cohort (395). A paper by Loeb et al showed an AUC of 0.70 for PHI with GG 2-5 PCa, but 21% of men had prior negative biopsies.¹² Another manuscript by Tosoian et al also showed an AUC of 0.77 for GG 2-5 PCa, but included men with prior biopsies.²² In Swedish biopsy naïve men, they also found a lower AUC of 0.71 for GG 2-5 PCa relative to studies including prior negative biopsies.¹⁴ In our study, the AUC for PHI was also not statistically different than the AUC for PSA (AUC 0.63 vs 0.57, $p=0.27$). Notably, our lower AUCs relates to the fairly modest increase in specificity of PHI in men with elevated PSA ≥ 4.0 ng/ml. This renders PHI somewhat less useful as a reflex test in this high risk population.

PHI density and PSA density have higher AUC and are more accurate than PSA and PHI for predicting GG 2-5 PCa ($p < 0.05$ for both comparisons with PHI, data not shown). However, many Black men do not have access to prostate MRI²⁵ and will likely not undergo TRUS for volume measurement without a concomitant PB. Hence, PHI seems to be the most practical reflex test.

Using PSA ≥ 4.0 ng/ml alone as a screening test missed 9.6% of GG 2-5 PCa in Black men in the study population and spared 10.4% of men an unnecessary PB. The current standard of care in the NCCN Guidelines® recommends reflex testing using thresholds of PSA ≥ 4.0 ng/ml and PHI ≥ 35.0 .²³ This missed 17.3% of GG 2-5 PCa in Black men (82.7% sensitivity), but potentially allowed 33.0% of men to avoid an unnecessary PB. To maintain sensitivity above 90%, using a threshold of PHI ≥ 28.0 following a threshold of referral PSA ≥ 4.0 ng/ml avoids unnecessary biopsy in an additional 7.5% of men compared to PSA ≥ 4.0 ng/ml alone (17.9%) without missing any additional cases of GG 2-5 PCa (90.4% sensitivity). We highlight this 28.0 threshold as a preliminary suggestion for PCa screening in biopsy naïve Black men as they have a higher PCa mortality rate and lower rate of insurance and may not return for a repeat PSA in a year.²⁶ Hence, increasing sensitivity with PHI ≥ 28.0 may be of higher import than the gains in specificity using the 35.0 threshold.

The percentage of avoided unnecessary biopsies with PHI in Black men appears to be notably lower than previously reported values in other population groups based on GG 2-5

PCa detection.¹² For instance, in a mostly nonBlack cohort, Loeb et al reported that a PHI threshold of 28.6 leads to 30% of unnecessary biopsies avoided.¹² Another paper by Chiu et al reported that, maintaining a sensitivity of 90%, PHI as a reflex test avoided unnecessary biopsies in 40% of men.¹⁶ However, in our Black biopsy patients, the specificity of PHI was only 17.9%. A PHI threshold of 27.0 has also been suggested to trigger a multiparametric magnetic resonance imaging of the prostate, but only 7.8% (25) of the entire PHI Biopsy Cohort had a PHI below 27.0.²² In centers that integrate multiparametric MRI in their practice, such low PHI thresholds might not meaningfully reduce unnecessary MRIs for Black men with elevated PSA in the diagnostic gray zone. It is likely that the high sensitivity of multiparametric MRI and moderate specificity would be a useful adjunct to PHI in helping men avoid unnecessary biopsies, but insurance constraints limit its widespread use.^{27,28}

As previously established, median PSA increases with age, while PHI does not need age adjustment in Blacks (supplementary table, <https://www.jurology.com>).²⁹

Several limitations in this study should be noted. The study population was selected for PB based on a screening PSA, which potentially introduces a selection bias. We use a PSA ≥ 4.0 ng/ml threshold for our basis of comparison since this is considered standard in the U.S. The PSA ≥ 4.0 ng/ml threshold misses 9.6% of GG 2-5 PCa in Black men.²³ The population in this study was relatively small, recruited from Chicago communities and tertiary and publicly funded medical centers, and included exclusively Black men, which limits the generalizability of our results. Our findings should be validated in a larger cohort. The controls did not undergo rectal exam or PB as they were recruited from community sites, but were followed for 1 year and all men with elevated PSA were linked to care. Also, standard TRUS biopsies were performed, which has lower sensitivity than saturation or MRI-guided biopsies, which could lead to misclassification bias.^{27,28} Furthermore, because the median age of the controls was 5 years younger than men in the PBS cohort, the percentage of controls exceeding screening thresholds may be underestimated.

CONCLUSIONS

Compared to the PHI assay report for PCa prevalence by PHI risk group, Black men have a much higher overall prevalence of PCa. PHI does not appear to be more accurate than PSA for detection of GG 2-5 PCa in Black men and only avoids 7.5% more unnecessary PBs. We propose a PHI ≥ 28.0 cut point that maintains high sensitivity and can avoid a modest proportion of unnecessary biopsies in Black men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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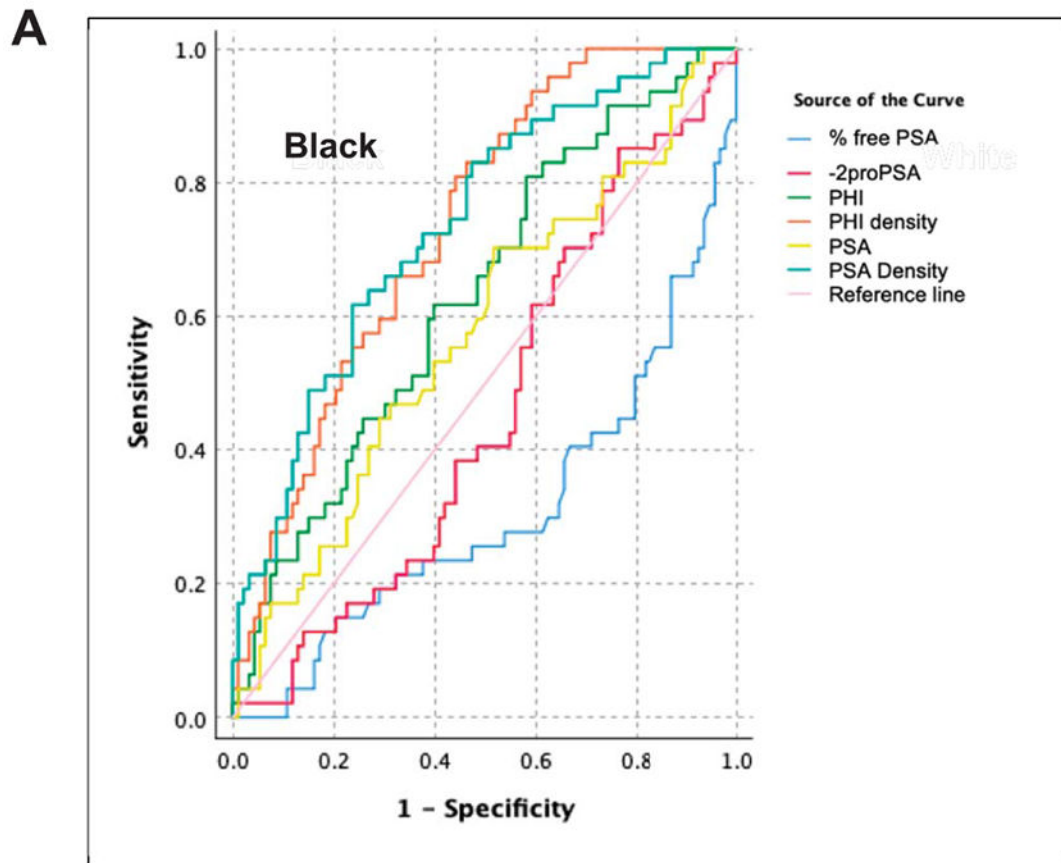
Abbreviations and Acronyms

BCS	Black Citizen Scientists
DRE	digital rectal examination of the prostate
FDA	U.S. Food and Drug Administration
fPSA	free PSA
GG	Gleason grade group
MRI	magnetic resonance imaging
p2PSA	⁻² proPSA
PB	prostate biopsy
PBS	PHI Biopsy Study
PCa	prostate cancer
PHI	Prostate Health Index
PSA	prostate specific antigen
TRUS	transrectal ultrasound

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B

Biomarker	AUC (95% CI) (n =142)	P-value Biomarker v. PSA ¹
PHI	0.63 (0.54-0.73)	0.27
PSA	0.57 (0.47-0.68)	-
% free PSA	0.31 (0.21-0.40)	0.002
[-2]proPSA	0.46 (0.36-0.56)	0.04
PSA Density	0.74 (0.65-0.82)	<0.001
PHI Density	0.74 (0.65-0.82)	0.004

Receiver operating curves for PSA vs PSA related biomarkers for detection of Gleason grade group 2-5 prostate cancer in men with PSA 4.0–10.0 ng/ml. *A*, receiver operating characteristic curves are drawn for PHI, PSA, % free PSA, ⁻²proPSA, PSA density and PHI density in men with PSA 4.0–10.0 ng/ml. *B*, area under receiver operating characteristic curve for detection of GG 2-5 prostate cancer is shown for each biomarker in men with PSA 4.0–10.0 ng/ml. Biomarkers were log-transformed. p Values were compared between biomarkers and PSA. Bold font indicates AUC comparisons with p values less than 0.05.

Table 1

Clinical characteristics by study population

	Citizen Scientists Study	PHI Biopsy Study	Neg Biopsy/GG 1 PCa	PHI Biopsy Study	GG 2-5 PCa	p Value
No. pts	135	106		52		
Continuous variables (median/IQR): *						
Age (yrs)	55.0 (48.0, 60.0)	60.0 (56.0, 64.0)		60.5 (54.3, 64.8)		<0.001
Body mass index (kg/m ²)	27.9 (25.4, 31.6)	30.0 (26.6, 34.0)		28.7 (25.2, 31.6)		0.049
PSA (ng/ml)	0.91 (0.45, 2.1)	5.6 (4.7, 7.6)		6.5 (4.6, 7.74)		<0.001
PHI	19.8 (13.3, 28.2)	51.9 (34.7, 70.1)		63.6 (48.7, 94.8)		<0.001
% Free PSA	24.1 (16.7, 35.2)	14.8 (10.4, 20.2)		9.3 (6.0, 14.5)		<0.001
⁻² proPSA	5.0 (2.9, 8.5)	17.4 (10.3, 27.3)		16.1 (11.5, 23.8)		<0.001
Prostate vol (cm ³)	-	42.4 (32.7, 59.5)		29.5 (22.1, 43.0)		<0.001
PSA density (ng/ml/cm ³)	-	0.12 (0.09, 0.17)		0.18 (0.13, 0.31)		<0.001
PHI density	-	1.17 (0.66, 1.79)		2.00 (1.38, 3.39)		<0.001
Categorical variables (No./%): †						
Family history of PCa	11 (8.1)	21 (19.8)		8 (15.4)		0.03
History of benign prostatic hyperplasia	3 (2.2)	20 (18.9)		8 (15.4)		<0.001
PHI ≥35.0	24 (17.8)	78 (73.6)		47 (90.4)		<0.001
PSA <4 ng/ml	126 (93.3)	11 (10.4)		5 (9.6)		<0.001
PSA 4–10 ng/ml	9 (6.7)	95 (89.6)		47 (90.4)		<0.001
Currently married	39 (28.9)	40 (37.7)		26 (50.0)		0.04
Income <\$30,000	69 (51.1)	69 (65.1)		18 (34.6)		0.001
Current smoking	42 (31.1)	35 (33.0)		18 (34.6)		0.85
Heavy drinking	12 (8.9)	6 (5.7)		8 (15.4)		0.12

Bold type indicates p <0.05.

* Independent sample medians test.

† Chi-square test.

Table 2.

Probability of overall and Gleason grade group 2-5 prostate cancer based on PHI results with PSA 4.0–10.0 ng/ml

PHI Range	Probability of PCa (95% CI) *	Probability of PCa in Blacks (142)	Probability of GG 2-5 PCa in Blacks (142)
0–26.9	9.8% (5.2%–15.4%)	0.0% (0/7)	0.0% (0/7)
27.0–35.9	16.8% (11.3%–22.2%)	45.5% (10/22)	18.2% (4/22)
36.0–54.9	33.3% (26.8%–39.9%)	51.3% (19/37)	35.1% (13/37)
≥55.0	50.1% (39.8%–61.0%)	65.8% (50/76)	39.5% (30/76)

* Based on Hybritech PHI assay.

Table 3.

Sensitivity and specificity for Gleason grade group 2-5 prostate cancer of PSA and PHI alone and in series with PSA ≤ 10.0 ng/ml

Biopsy Strategy	Sensitivity-Blacks in Biopsy Cohort	Specificity-Blacks in Biopsy Cohort	"Cancer-Free" Controls Exceeding Threshold
No. pts	158	158	135
PSA alone (%):			
≥ 3.0	100.0	4.7	11.1
≥ 3.5	96.2	6.6	8.1
≥ 4.0	90.4	10.4	6.7
≥ 5.0	71.2	33.0	4.4
≥ 6.0	51.9	33.0	1.5
PHI alone (%):			
≥ 27.0	100.0	9.4	31.1
≥ 28.0	100.0	10.4	25.9
≥ 28.6	98.1	10.4	23.7
≥ 29.0	96.2	10.4	23.7
≥ 30.0	94.2	15.1	22.2
≥ 31.0	92.3	18.9	21.5
≥ 32.0	92.3	19.8	21.5
≥ 33.0	90.4	21.7	20.0
≥ 34.0	90.4	22.6	18.5
≥ 35.0	90.4	26.2	17.8
PSA+PHI in series (%):			
PSA ≥ 4.0 , PHI ≥ 27.0	90.4	17.0	5.9
PSA ≥ 4.0 , PHI ≥ 28.0	90.4	17.9	5.9
PSA ≥ 4.0 , PHI ≥ 28.6	88.5	17.9	5.9
PSA ≥ 4.0 , PHI ≥ 29.0	88.5	17.9	5.9
PSA ≥ 4.0 , PHI ≥ 30.0	86.5	21.7	5.9
PSA ≥ 4.0 , PHI ≥ 31.0	84.6	25.5	5.9
PSA ≥ 4.0 , PHI ≥ 32.0	84.6	26.4	5.9
PSA ≥ 4.0 , PHI ≥ 33.0	82.7	28.3	5.9
PSA ≥ 4.0 , PHI ≥ 34.0	82.7	29.2	5.9
PSA ≥ 4.0 , PHI 35.0	82.7	33.0	5.9

Sensitivity reflects percentage of Gleason grade group 2-5 prostate cancers detected at each threshold. Specificity reflects percentage of men with negative biopsy or indolent cancer who would avoid biopsy at each threshold. Proportion of controls exceeding threshold reflects percentage of "cancer-free" controls who would have a false-positive test and be referred for biopsy at each threshold. Serum PSA for "cancer-free" controls is from Hybritech PHI assay at community screening. PSA for PHI Biopsy cohort is from referral PSA, which uses Beckman Coulter PSA assay in over 95% of cases.



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APPENDIX 4

A 17-Gene Panel Genomic Prostate Score has Similar Predictive Accuracy for Adverse Pathology at Radical Prostatectomy in African American and European American Men

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Abstract

Objective: To validate the 17-gene Oncotype DX Genomic Prostate Score (GPS) as a predictor of adverse pathology (AP) in African American (AA) men and to assess the distribution of GPS in AA and European American (EA) men with localized prostate cancer.

Methods: The study populations were derived from two multi-institutional observational studies. Between February 2009 and September 2014, AA and EA men who elected immediate radical prostatectomy after a ≥ 10 -core transrectal ultrasound biopsy were included in the study. Logistic regressions, area under the receiver operating characteristic curves (AUC), calibration curves, and predictive values were used to compare the accuracy of GPS. AP was defined as primary Gleason grade 4, presence of any Gleason pattern 5, and/or non-organ-confined disease ($\geq pT3aN0M0$) at radical prostatectomy.

Results: Overall, 96 AA and 76 EA men were selected and 46 (26.7%) had AP. GPS result was a significant predictor of AP (odds ratio per 20 GPS units [OR/20 units] in AA: 4.58; 95% confidence interval (CI) 1.8-11.5, $p=0.001$; and EA: 4.88; 95% CI 1.8-13.5, $p=0.002$). On

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multivariate analysis, there was no significant interaction between GPS and race ($p > 0.10$). GPS remained significant in models adjusted for either National Comprehensive Cancer Network (NCCN) risk group or Cancer of the Prostate Risk Assessment (CAPRA) score. In race-stratified models, AUC for GPS/20 units was 0.69 for AAs vs. 0.74 for EAs ($p = 0.79$). The GPS distributions were not statistically different by race (all $p > 0.05$).

Conclusion: In this clinical validation study, the Oncotype DX GPS is an independent predictor of AP at prostatectomy in AA and EA men with similar predictive accuracy and distributions.

Keywords

Oncotype DX; GPS score; prostate cancer biomarkers; African American; biomarker validation; active surveillance

Introduction

Only 16% of clinically localized prostate cancer (PCa) cases progress to cause mortality¹. Active surveillance (AS) has been deployed as a way to manage very low to intermediate risk PCa and preserve quality of life by delaying treatment (i.e. radical prostatectomy (RP) or radiotherapy), while monitoring patients' PCa progression by using serial PSA measurements, rectal examinations and prostate biopsies². Overtreatment of biologically indolent disease results in substantial cost and unnecessary morbidity, which has led to some authorities doubting the value of routine screening^{3,4}. Serum, urinary and tissue biomarkers are increasingly used to predict tumor aggressiveness and risk stratify patients who may elect AS⁵.

The Oncotype DX (ODX) Prostate Cancer Assay is a clinically validated assay based on the expression of 12 informative cancer-related genes relative to 5 housekeeping genes using tumor epithelium RNA macro-dissected from formalin fixed paraffin embedded needle biopsy specimens⁶. The expression values are weighted and added to provide a Genomic Prostate Score (GPS) for each patient's tumor. The ODX report displays the patient's GPS score on a normal GPS distribution for men within the same National Comprehensive Cancer Network (NCCN) risk group to see how an individual patient compares to the others and provides an estimated probability of adverse pathology (AP) at the time of RP. Validations of GPS have been limited to largely European ancestry populations⁷. Few studies have validated the GPS in African American (AA) men⁸. Among PCa patients, AA with low risk PCa have increased rates of AP and varied prostate tumor expression, especially in the androgen signaling pathway⁹⁻¹⁴. In the publication by Cullen et al., 82 AA men were included in their analysis of AP and GPS. They found similar GPS distributions by race but a lower odds ratio for AP prediction in AAs relative to EAs (OR: 2.86 vs. 4.05). These data suggest that the ODX assay may have different predictive accuracy between AA and EA men eligible for AS⁸. In the present study, we aim to compare the accuracy of GPS as a predictor of AP in AA and EA men with clinically localized PCa who underwent RP. We will additionally compare the distributions of GPS score between AA and EA men.

Materials and Methods

Study Population

The study populations were derived from 2 related observational studies investigating the associations between vitamin D status (serum and prostatic) and aggressive PCa called *Biological and Environmental Mediators of Vitamin D and Prostate Cancer Risk* (Vitamin D study, n = 95) and *Vitamin D Effects on Apoptosis and Proliferation* (Apoptosis study, n = 77). Both studies were institutional review board approved at Northwestern University and Jesse Brown VA Medical Center. The Vitamin D study accrued 954 men immediately before prostate biopsy from 2009-2014 and the second study accrued 191 men after they chose RP for primary treatment of their clinically localized PCa from 2013-2018. We compared the baseline characteristics of the Apoptosis and the Vitamin D study cohorts using nonparametric Mann-Whitney tests for continuous variables and Pearson- χ^2 tests for categorical variables (see supplementary table 1). All men had ≥ 10 core transrectal ultrasound (TRUS) guided prostate needle biopsies and targeted the peripheral zone. Due to our recruitment period, MRI was not used before biopsy or before prostatectomy. Participants were the subset of 40-79y/o men who were NCCN very low to unfavorable intermediate risk, selfidentified as AA (non-Hispanic Black/African American) or EA (non-Hispanic White), had available biopsy tumor blocks, had undergone RP at our sites, and consented to the use of their data and specimen for future PCa research. There were 208 AAs and 152 EAs who fit eligibility criteria for this protocol and had their DNA extracted for ancestry estimation. Of these men, 96 AA and 76 EA provided consent and had available and adequate biopsy cores with ≥ 0.7 mm tumor in the highest Gleason grade core. Exclusion criteria included delay in RP > 12 months and prior therapy for PCa such as pelvic- or prostate-focused external beam or interstitial seed radiotherapy, orchiectomy, androgen deprivation therapy, high-intensity focused ultrasound therapy, or cryotherapy. In addition, six AA men with PSA > 20.00 ng/ml as their high-risk feature had an ODX assay performed to assess AA's GPS distribution in this subgroup. All patients provided written informed consent.

Pathology

Biopsies were selected where the dominant tumor nodule had at least 0.7mm of tumor length in the core containing the highest Gleason score. Both the prostate biopsy and RP tumor blocks were de-identified by adhering new labels on all slides with study ID number for all eligible subjects. Biopsy and prostatectomy specimen were read in separate sessions for centralized review by 3 experienced uropathologists at both sites in accordance with the 2014 International Society of Urological Pathology Consensus guidelines: Gleason Grade Group (GG)1 = Gleason score ≤ 6 ; GG2 = Gleason score 3+4 = 7; GG3 = Gleason score 4+3 = 7; GG4 = Gleason score 8; and GG5 = Gleason score 9–10¹⁵. Biopsy tumor blocks were submitted to the Genomic Health Inc. laboratory (Redwood City, CA) and were manually macrodissected as previously described^{6, 8}.

Statistical Methods

Descriptive statistics were used to compare notable clinical, demographic, and cancer related covariates. Genetic West African ancestry was also compared to ensure accurate racial

stratification. AP was defined as primary Gleason grade 4, presence of any Gleason pattern 5, and/or non-organ-confined disease ($\geq$ pT3aN0M0) at RP. To compare racial groups, nonparametric Mann-Whitney tests were performed for continuous variables, and Pearson- χ^2 tests were used for categorical variables.

Our prespecified objectives were to compare the GPS distributions between EA and AA men and the associations of GPS testing with AP in the pathologic specimen with NCCN very low-, low-, favorable intermediate- and unfavorable intermediate-risk who elected RP¹⁶. The association of GPS and AP was evaluated using bivariate and multivariate logistic regression models to compare the odds ratios. GPS was explored as a continuous variable with GPS score divide by 20¹⁷. Multiplicative interactions tested for differential prediction of GPS accuracy by race (AA vs. EA). Receiver operating characteristic (ROC) curves were used to compare accuracy of models adjusted for GPS/20 and NCCN risk group or CAPRA score for prediction of AP. Additionally, in a post-hoc analysis, the accuracy of the ODX assay was compared to the Memorial Sloan Kettering Cancer Calculator (MSKCC) for the prediction of non-organ confined PCa since this is already available at no cost. We were powered to detect a 10% AUC difference between AA and EA with 80% power, assuming an AUC of 0.72 for GPS in EAs⁸. An alpha <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 25 (IBM Corporation 2016, United States).

Results

Of 172 subjects, 96 (55.8%) identified as AA ($N_{NMH} = 21/N_{VA} = 75$) and 76 (44.2%) as EA ($N_{NMH} = 58/N_{VA} = 18$). Median age was 61.5 years and a total of 46 men (26.7%) had AP. NCCN risk groups at biopsy were as follows: 40% very low to low risk, 39% favorable intermediate risk, and 21% unfavorable intermediate risk. Compared to EA men, AAs had higher PSA (6.0ng/mL vs. 4.6ng/mL), PSA density (0.16ng/cm³ vs. 0.12ng/cm³), CAPRA scores (3.0 vs. 2.0), and greater frequencies of current smoking (25.0% vs. 2.7%) (all $p < 0.001$). On univariate analysis, there were no statistical differences between racial groups in GPS, AP rates, pathological staging, age, family history of PCa, abnormal DRE, 5- α reductase inhibitor use, high school completion, and income less than \$30,000/year (see Table 1). Although the study populations statistically differed in some clinical parameters, the rate of AP was similar in both groups: 24.7% for Vitamin D vs. 29.3% for Apoptosis study (supplementary table 1). The other parameters were clinically in line with AS cohorts and the distributions of NCCN risk strata were not statistically different.

The distribution of biopsy and pathological Gleason score by race is depicted in Table 2. Overall 85 (48.3%) subjects had a Gleason score of 3+3 PCa, out of which 39 (45.9%) were AA and 46 (54.1%) were EA men. AAs had a 43.6% rate of upgrading from Gleason 3+3 to Gleason 7-10. GPS scores across strata of NCCN risk groups by race is illustrated in Table 3 and Supplementary Figure 1. AA men with NCCN high-risk PCa were included for the purposes of assessing the distribution of GPS by risk group. Similar median GPS scores were observed for both racial groups, with GPS score increasing with higher NCCN risk groups. The rate of AP was substantially higher in EA men in the favorable intermediate (43.8% vs. 14.3%) and unfavorable intermediate (66.7% vs. 50.0%) risk groups relative to their AA counterparts. In line with this, the GPS scores were also higher or more varied for

the EA men in the favorable and unfavorable intermediate risk groups, though differences were not statistically significant. To evaluate the GPS range in higher risk AAs, we also included 6 AA men with NCCN high risk PCa by PSA, out of which 5 (83.3%) demonstrated AP. No EA men were staged as high risk.

On the binary logistic regressions for AP at prostatectomy, GPS score was coded as a continuous variable divided by 20 [GPS/20] to assess the odds ratio per 20-point increase as in the publication by Cullen et al⁸. GPS/20 was a significant predictor of AP in both racial groups with an odds ratio in AA of 4.58 (95% CI 1.8-11.5, $P=0.001$) and in EA of 4.88 (95% CI 1.8-13.5, $p=0.002$). GPS/20 remained significant after adjustment for CAPRA score (2.55, $p=0.17$) and NCCN risk group (3.65, $p<0.001$). The interaction term of GPS/20 with race was not significant in both the CAPRA ($p=0.38$) and the NCCN ($p=0.53$) model.

ROC curves assessed the accuracy of 5 binary logistic regression models: 1) GPS/20 alone; 2) NCCN risk group as a four-level ordinal variable (i.e. very low, low, favorable intermediate, and unfavorable intermediate) alone; 3) NCCN risk group with GPS/20; 4) CAPRA score (continuous from 0-10¹⁸) alone; and 5) CAPRA score with GPS/20. Using GPS/20 alone, the area under the receiver operating characteristics curve (AUCs) was 0.74 (SE: 0.60-0.88) in EA and 0.69 (SE: 0.56-0.81) in AA men ($p=0.79$). The CAPRA model with GPS/20 had an AUC of 0.91 (0.84-0.98) in EA and 0.85 (SE: 0.75-0.94) in AA. The NCCN model, as used in the clinical assay, had an AUC of 0.81 (SE: 0.69-0.93) in EA and 0.76 (SE: 0.64-0.88) in AA ($p=0.77$) (see Figure 1).

The calibrations of the CAPRA risk model with GPS varied by race. In AAs, the model slightly underestimated the risk of AP in the 0-20% threshold, yet in EAs the model was well-calibrated through the 0-30% threshold. The NCCN risk model with GPS was fairly well calibrated for AA men. The differences between the CAPRA and NCCN models, however, were not significant in either racial group (AA: $p=0.87$, EA: $p=0.29$) (see Supplementary Figure 2).

In terms of its clinical application, at a 95% sensitivity the overall positive predictive value (PV) for the NCCN + GPS/20 model was 29% and the negative PV was 92%. No major differences were noted between racial groups. At a 90% sensitivity, the NCCN + GPS/20 model yielded a 29% positive and an 87% negative PV.

We compared the ODX assay and the MSKCC¹⁹ for their prediction of non-organ confined prostate cancer at radical prostatectomy. Based on AUC curves, the MSKCC significantly outperformed the ODX assay for this adverse pathologic feature (AUC: 0.86 vs. 0.74, $p=0.015$). Moreover, ODX GPS score did not add to the accuracy of the calculator (supplementary figure 3).

Discussion

This provides confirmatory evidence of the GPS score as an independent predictor of AP at RP in both AA and EA men with similar distributions and odds ratios by race. We believe this indicates that the Oncotype DX Assay is clinically valid for determining risk of AP independent of clinical risk factors with a high negative predictive value. Results of

calibration analyses suggest that the GPS model with NCCN risk groups works well in predicting AP in the 0-30% range. In addition, we observe that GPS score distributions were similar for both AA and EA men across NCCN levels. This would suggest that tumor aggressiveness is similar stage for stage between EAs and AAs. In fact, similar GPS distributions were also seen with the ODX validation in 82 AAs and 305 EAs from Walter Reed and Madigan Army Medical Center⁸. Notably, both AA validations involved patient samples from 'equal access' sites where differences between EA and AA men in income and educational level are less pronounced. This is somewhat counter-intuitive given that AAs are known to harbor more aggressive PCa when eligible for AS⁹. However, our calibration plots demonstrate that the ODX assay with CAPRA under-estimated the rate of AP in AA men in the range from 0-20%. Despite similar distributions, ODX may benefit from re-calibration in this important prediction range to better match the actual rate of AP.

In the real world, AA men are less likely to be treated with AS²⁰. Overall, ODX should allow AA men to confidently avoid active treatment when eligible for AS despite their increased risk of harboring AP⁹. Similar to MRI, the evidence provided in this study shows that the ODX assay may improve the safety of AS in AA men through improved patient selection²¹. The evidence provided in this study shows that GPS can provide orthogonal data to patients eligible for AS to facilitate their treatment decisions.

Several studies have described GPS as a strong independent predictor of AP in low to intermediate risk men^{8,22,23}. The assay can increase urologists' confidence when providing treatment recommendations for very low to low-intermediate risk patients, leading to increased uptake of AS²⁴. In a prospective cohort, patients that received GPS scores were more likely to select AS and 96% reported finding the test useful²⁵.

Few studies have analyzed the predictive accuracy of GPS in AAs. AA men eligible for AS progress more often and may harbor adverse pathologic features compared to EA men, which has led to an under-utilization of AS among AAs^{9,26-29}. It was plausible that the GPS variables would not predict as well in AAs since there are known genetic and molecular differences between AA and EA PCas including: increased androgen signaling, differences in frequency of TMPRSS-ERG fusions and differences in tumor gene expression patterns^{12,30,31}. On bivariate analysis, GPS prediction of AP proved to be similarly strong in both racial groups ([OR/20 units] in AA: 4.58, $p=0.001$; and EA: 4.88; $p=0.002$). Our results are consistent with Cullen et al.'s study which included 82 (20.4%) AA men in its cohort and demonstrated a statistically significant association between GPS and AP in both EAs and AAs: OR/20 4.05 and 2.86, respectively. Furthermore, similarly to Klein et al.'s large validation study, GPS/20 remained significant in multivariate analyses adjusting for CAPRA score and NCCN risk groups²³. To our knowledge, this is the largest study to evaluate the accuracy of GPS in AA populations. Future studies with greater AA samples should externally validate our findings.

In our comparison of the ODX assay and the MSKCC calculator, it appears that the risk calculator outperforms the ODX assay for the prediction of non-organ confined PCa. The ODX GPS score did not provide orthogonal data to the calculator in our cohort. The benefit of the ODX assay over the MSKCC calculator is that it also predicts whether the patient

harbors more aggressive Gleason patterns in the prostate, which is an important endpoint for AS patients. A future comparison between the ODX assay and prostate multi-parametric MRI could be assessed in men that have undergone both tests to predict the presence of a higher grade and higher stage tumor given their similar costs

Several limitations in the study should be noted. First, this is a retrospective analysis of multi-center studies where eligible AS men with available biopsy specimen were selected from a tertiary and VA medical center in a large metropolitan city, which might affect generalizability. Although we prospectively enrolled consecutive men in the parent cohorts we cannot rule out selection or spectrum bias. Our selection criteria most likely reduced any racial differences in risk factors. This is a common problem with retrospective biomarker validation in populations with diverse racial and socioeconomic characteristics. However, our demographic and clinical data suggests that these men are typical for their NCCN risk strata and AS cohorts, and while the selection criteria reduced racial differences in terms of risk, this would not necessarily introduce bias regarding the effect of race on GPS accuracy. Moreover, we conducted centralized pathologic review and blinded the pathologists to the race and clinical data of the participants. Second, 19 AS eligible men had insufficient tumor for the assay, which limited our AA men and possibly introduced a bias. Third, many of the biopsies were performed between 2009-2014 definitions of unfavorable risk PCa were not popular and centralized review upgraded several men, which led to our inclusion of unfavorable intermediate risk men in the sample. Our population was partially recruited prior to the widespread adoption of AS in EA men and increased concern regarding the safety of AS in AA men. Therefore, we recommend repeating our study design in a completely contemporary cohort. Lastly, the population size was relatively small, and limited our ability to include other ethnic/racial groups. In addition, GPS now reports risk of metastasis and death which was unable to be validated due to insufficient follow up time²³.

Conclusion

In summary, the ODX Genomic Prostate Score has similar predictive accuracy for AP at RP in AA and EA men with very low-, low-, and intermediate-risk PCa. This establishes that Oncotype Dx assay can provide patients eligible for AS with orthogonal data to clinical factors to support treatment decisions. Future studies investigating the impact of these assays on patient treatment choice, especially in high-risk populations with potentially low health literacy is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

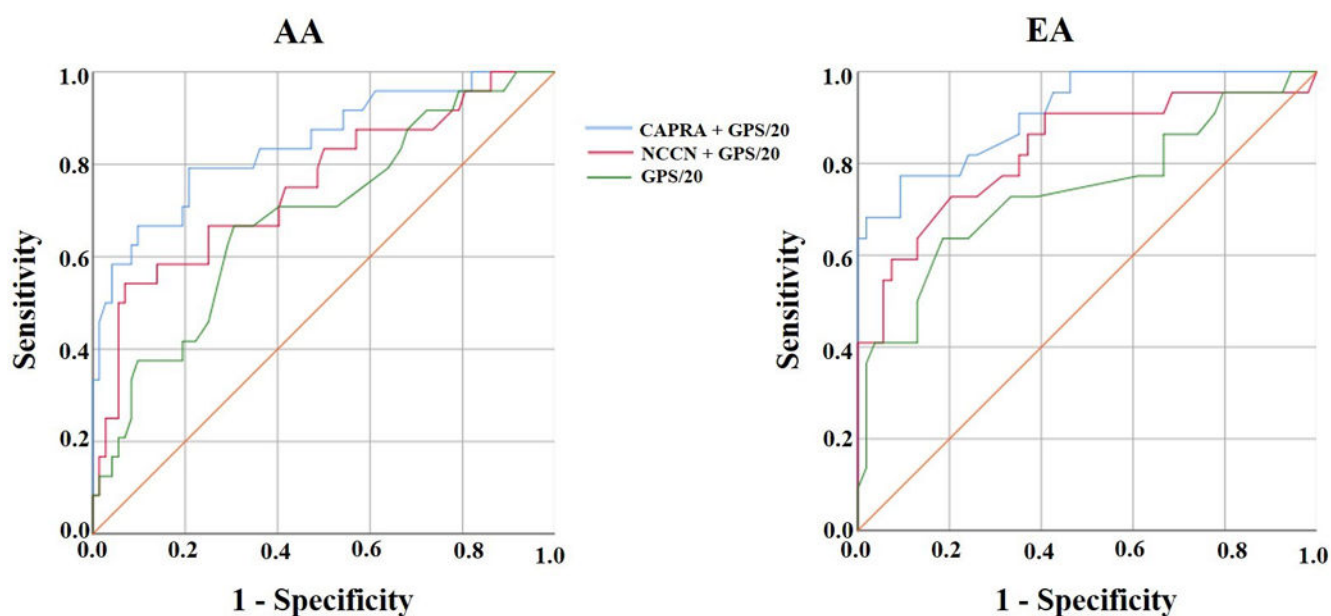
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Binary Logistic Risk Models	AA (n=96)	EA (n=76)	p-value
GPS alone	0.687 (0.56-0.81)	0.739 (0.60-0.88)	0.79
NCCN risk group	0.712 (0.59-0.84)	0.750 (0.63-0.87)	0.82
NCCN risk group with GPS	0.759 (0.64-0.88)	0.812 (0.69-0.93)	0.77
CAPRA	0.836 (0.73-0.94)	0.888 (0.80-0.98)	0.73
CAPRA with GPS	0.845 (0.75-0.94)	0.910 (0.84-0.98)	0.59

Figure 1.

Prediction of adverse pathology at prostatectomy in univariate and multivariate analyses.

Legend 1a: Blue line = GPS with CAPRA model. Red Line = GPS with NCCN model.

Green line = GPS alone.

Legend 1b: AUCs for all 5 models stratified by race.

Table 1.

Clinical & Socioeconomic Factors by Racial Groups.

Continuous Variables	AA (n = 96)	EA (n = 76)	p-value ¹
	Median [IQR]	Median [IQR]	
Age, years	61.5 [57.5, 67.0]	62.0 [59.0, 66.8]	0.78
BMI, kg/m ²	28.1 [25.8, 30.8]	27.4 [26.0, 29.9]	0.34
West African Ancestry, %	78.6% [67.5%, 85.8%]	4.0% [1.7%, 6.6%]	<0.001
PSA, ng/ml	6.0 [4.5, 8.9]	4.6 [3.85, 7.14]	<0.001
PSA density, ng/cm ³	0.16 [0.10, 0.24]	0.12 [0.08, 0.19]	<0.001
CAPRA	3.0 [2.0, 4.0]	2.0 [1.0, 3.0]	<0.001
GPS	29.5 [23.3, 37.5]	27.0 [23.0, 35.0]	0.27
Number of Positive Cores	3.0 [2.0, 6.0]	2/0 [1.0, 4.0]	0.004
Percent of Positive Cores	27.9% [16.7%, 45.7%]	17/4% [8.3%, 3.3%]	0.001
Categorical Variables	AA n (%)	EA n (%)	p-value ²
<u>Pre-orostatectomy</u>			
Current Smoking	24/96 (25.0)	2/74 (2.7)	<0.001
High school completion	76/95 (80.0)	59/74 (79.7)	0.96
Income < \$30,000/year	24/95 (25.2)	11/71 (15.5)	0.13
FHx of PCa	27/96 (28.1)	16/76 (21.1)	0.35
Abnormal DRE	17/96 (17.7)	19/76 (25.0)	0.24
5 α -reductase inhibitor use	1/96 (1.0)	3 (3.9)	0.19
NCCN Risk Group			
Very Low/Low	31 (32.3)	38 (50.0)	0.02
Favorable Intermediate	35 (36.5)	32 (42.1)	0.45
Unfavorable Intermediate	30 (31.2)	6 (7.9)	<0.001
<u>Post-prostatectomy</u>			
Adverse Pathology	24/96 (25.0)	22/76 (28.9)	0.56
Pathology Staging			
T2a-T2b	8 (8.3)	6 (7.9)	0.97
T2c	71 (74.0)	54 (71.1)	0.67
T3a-T3b	17 (17.7)	16 (21.0)	0.58

¹Using Mann-Whitney tests²Using χ^2 tests; Bold type indicates p values <0.05

Abbreviations: AA: African American; EA: European American; BMI: Body Mass Index; PSA: Prostate Specific Antigen; CAPRA: Cancer of the Prostate Risk Assessment; GPS: Genomic Prostate Score; FHx of PCa: 1st degree Family History of Prostate cancer; DRE: digital rectal examination; NCCN: National Comprehensive Cancer Network.

Table 2.

Distribution of Biopsy and Radical Prostatectomy Gleason Grade by Race.

<u>African American men</u>							
Radical Prostatectomy Gleason Grade							
	<u>3+3</u>	<u>3+4</u>	<u>4+3</u>	<u>≥4+4</u>	Total	Gleason Upgrade %	
	<u>3+3</u>	22	12	4	1	39 (40.6%)	43.6%
Biopsy Gleason Grade	<u>3+4</u>	2	31	5	2	40 (41.7%)	17.5%
	<u>4+3</u>	-	6	9	2	17 (17.7%)	11.8%
<u>European American men</u>							
Radical Prostatectomy Gleason Grade							
	<u>3+3</u>	<u>3+4</u>	<u>4+3</u>	<u>≥4+4</u>	Total	Gleason Upgrade %	
	<u>3+3</u>	35	4	5	2	46 (60.5%)	23.9%
Biopsy Gleason Grade	<u>3+4</u>	5	15	9	1	30 (39.5%)	33.3%
	<u>4+3</u>	-	-	-	-	-	-

Table 3.

Race-stratified distribution of GPS and Adverse Pathology at Prostatectomy by NCCN Risk Group.

NCCN Risk Group	GPS Distribution Median [IQR]				Adverse Pathology n (%)			
	All N=178	AA N=102	EA N=76	p-value ¹	All N=178	AA N=102	EA N=76	p-value ²
Very Low/Low N=69	27.0 [20.0,33.5]	27.0 [20.0,34.0]	27.0 [19.8,32.3]	0.51	8/69 (11.6%)	4/31 (12.9%)	4/38 (10.5%)	1.00
Favorable Intermediate N=67	31.0 [26.0,40.0]	30.0 [24.0,40.0]	31.0 [27.0,39.5]	0.47	19/67 (28.4%)	5/35 (14.3%)	14/32 (43.8%)	0.01
Unfavorable Intermediate N=36	35.0 [25.5,43.3]	35.00 [26.5,41.8]	35.0 [17.3,54.0]	0.89	19/36 (52.8%)	15/30 (50.0%)	4/6 (66.7%)	0.66
High N=6	40.0 [36.8,46.5]	40.0 [36.8,46.5]	-	-	5/6 (83.3%)	5/6 (83.3%)	0 (0%)	-

¹Using Mann-Whitney tests²Using Fisher's exact test.

Abbreviations: AA: African American; EA: European American; GPS: Genomic Prostate Score; NCCN: National Comprehensive Cancer Network; AA: African American; EA: European American.