

Supplementary Methods:

Participants

All veterans were eligible for participation in MVP. Consent to participate in MVP and permission to re-contact was provided after counseling by research staff and mailing of informational materials. Study participation included consenting to access the participant's electronic health records for research. The MVP received ethical and study protocol approval from the VA Central Institutional Review Board in accordance with the principles outlined in the Declaration of Helsinki.

Prostate Cancer Clinical Information

Each participant's electronic health record is integrated into the MVP biorepository. These records include International Classification of Diseases (ICD) diagnosis codes (ICD-9-CM and ICD-10-CM), procedure codes (ICD, Current Procedural Terminology, and Healthcare Common Procedure Coding (HCPCS)), laboratory values, medications, and clinical notes documenting VA care (inpatient and outpatient) and non-VA care paid for by the VA. Prostate cancer diagnosis, age at diagnosis, and date of last follow-up were retrieved from the VA Corporate Data Warehouse based on ICD codes and VA Central Cancer Registry data. Age at diagnosis of metastasis (nodal and/or distant, regardless of whether metastases were detected at diagnosis or at recurrence) was determined via a validated natural language processing tool and a search of individual participant's medical records in the Veterans Affairs system, as described previously¹. This tool was developed using data from over 1 million VA patients with prostate cancer; compared to manual chart review, the natural language processing tool had 92% sensitivity and 98% specificity for diagnosis of metastatic prostate cancer. To determine patients with metastatic prostate cancer at diagnosis, we identified patients with diagnosis of metastatic prostate cancer at a date within 1 year of first prostate cancer diagnosis. Cause and date of death was collected from National Death Index. Participants with ICD10 code "C61" as underlying cause of death were considered to have died from prostate cancer. Age of death was determined from difference between year of death and year of birth.

Metastatic Disease Only on Initial Staging

Analyses for association with metastatic disease were repeated using only metastases detected at initial staging (within one year of initial diagnosis).

Medical Care Outside the VA

Some veterans receive medical care outside of the VA system, which becomes more common when they become eligible for Medicare, typically at age 65. If they received no further care in the VA, they were censored in the analyses above at date of last follow-up. If they continue to receive even only some of their care at the VA, cancer diagnosis and staging should be documented in the VA health record, but there could plausibly be more omissions in documentation. To assess the possibility of an impact on results, we repeated univariable Cox proportional hazards analyses for association with age at diagnosis of prostate cancer and age at diagnosis of metastatic prostate cancer after excluding all MVP participants who enrolled in Medicare. This was done for the full cohort and for each racial/ethnic subgroup. Moreover, we repeated the multivariable analyses for prostate cancer and metastatic prostate cancer, adding a categorical variable to the model to indicate whether the participant enrolled in Medicare. As death outcomes were obtained from the National Death Index, analyses of fatal prostate cancer are not expected to be significantly affected by where the participant received healthcare services.

PSA Testing

PSA testing was not included in the MVP cohort study design, but many veterans do undergo PSA testing as part of their normal medical care. We collected PSA testing and result data from the VA medical records, including number of PSA tests, number of calendar years in which a PSA test

was performed, and age at first PSA test for all MVP participants. To evaluate the potential impact of PSA testing intensity on the primary analyses described above, we performed univariable Cox models with one of three different indices of PSA testing intensity: number of pre-diagnostic PSA tests, number of calendar years in which a pre-diagnostic PSA test was performed, and age at first pre-diagnostic PSA test. In each case, PSA tests in the two years immediately preceding a prostate cancer were excluded, where applicable. Each of these indices of PSA testing intensity was also added to the primary multivariable models (that include family history, race/ethnicity, and PHS290) to investigate any impact on those associations.

We also evaluated early baseline PSA, defined as any pre-diagnostic PSA test performed while the participant was between 40 and 49 years of age²⁻⁴. As before, to exclude PSA tests associated with a man presenting with symptoms, tests within the two years immediately preceding a prostate cancer diagnosis were excluded. We tested for univariable associations between the earliest PSA value obtained while the man was in the 40-49 years age range using Cox proportional hazards models. We also conducted our primary multivariable analysis (family history, race/ethnicity, and PHS290) in this subgroup of individuals with early baseline PSA, adding the early baseline PSA level to the model. Associations with each of the three clinical prostate cancer endpoints were investigated in the univariable and multivariable Cox proportional hazards models, as before.

Cox Proportional Hazards Analysis with Flexible, Group-Specific Thresholds

We chose to use fixed thresholds (instead of MVP-specific or subgroup-specific thresholds) because fixed thresholds have three key advantages. First, clinical implementation of a polygenic score would likely use fixed thresholds for simplicity of implementation, avoidance of errors, and to avoid strong dependence of test results on the accuracy of subgroups identification (e.g., in multiracial or admixed individuals). Second, comparison of results/performance across different research studies is facilitated by fixed thresholds. Third—and critical to the present study—fixed thresholds are necessary for a multivariable model where we seek to assess independent associations of the polygenic score after accounting for the population subgroups. However, it is important to understand that these thresholds are most consistent with whatever population they were defined in. For the present study, the fixed thresholds published previously were defined in a population of European genetic ancestry. Therefore, we also calculated HRs within the full MVP cohort and within each racial/ethnic subgroup using thresholds (lower 20%, middle 40%, upper 20%, upper 5%) of PHS290 within those subgroups (again, defined by PHS290 percentiles among men unaffected by prostate cancer and <70 years of age).

Genetic Ancestry and Genetic Principal Components

We chose self-reported race/ethnicity for the primary analyses because that is what is already available in clinic and used for current clinical guidelines. This approach allows the multivariable analyses to evaluate the relative potential impact of incorporating PHS290 in the clinical setting. However, if genotype data are available, other approaches like genetic ancestry are also of interest⁵⁻⁸. MVP participants have been assigned genetic ancestry groups based on previous analyses⁹. Briefly, a reference panel of 1000 Genomes Project¹⁰ and Human Genome Diversity Project¹¹ individuals was constructed for preliminary principal components analysis. Principal component loadings of reference panel were projected onto principal component loadings of MVP participant principal component loadings, and assignments were made based on a random forest classifier. We repeated the prostate cancer analyses described above using genetic ancestry groups instead of self-reported race/ethnicity. We also checked to see how much misclassification of race/ethnicity affected results. For Non-Hispanic White, African, Hispanic White and Asian men, we ran analysis only in men with matched genetic ancestry of European, African, American and Asian. We also repeated the above analyses when including the top 10 genetic principal components (i.e., not presuming any continental ancestry groups).

Observed vs. Predicted Risk

To illustrate the impact of PHS290 on lifetime risk, we measured the cumulative incidence (in the absence of death from another cause) of each of the three clinical endpoints. For comparison, we also estimated the predicted values based on the hazard ratios for each stratum of PHS290 by taking the observed outcomes from the average-risk stratum (PHS290 30-70th percentile) and multiplying by the estimated hazard ratio for the stratum of interest. We reported the observed and predicted incidence numbers for diagnosis of any PCa by age 70, after which diagnoses (but not

actual incidence) drop off because of less testing. We chose age 90 for metastatic PCa because of the impact of this condition (and its treatment) on quality of life. We also chose age 90 for fatal PCa. Additionally, observed vs. predicted cumulative incidence curves were generated.

Supplementary Results:

Metastatic Disease Only on Initial Staging

When analyses for the metastatic prostate cancer endpoint were repeated using only metastases detected at initial staging (i.e., within one year of prostate cancer diagnosis), the associations were very similar (**Supplemental Table 3**).

Medical Care Outside the VA

Univariable analyses of association of PHS290 with prostate cancer or metastasis yielded similar effect sizes after excluding men who eventually enrolled in Medicare (**Supplementary Table 4**). Likewise, addition of Medicare status to the multivariable analyses did not significantly impact effect size estimates for family history, race/ethnicity, or PHS290 (**Supplementary Table 11**). Men who enrolled in Medicare had equivalent risk for metastatic disease to men who did not enroll in Medicare (HR 1.00 [0.94-1.07]) and were slightly more likely to be diagnosed with prostate cancer (HR 1.10 [1.08-1.12]), suggesting the Medicare enrollment did not lead to major underreporting of these cancer endpoints in the VA medical records.

PSA Testing

On both univariable and multivariable analyses, increased PSA testing intensity was associated with decreased likelihood of prostate cancer, including metastatic and fatal prostate cancer (**Supplementary Tables 13-16**), regardless of the index of PSA testing intensity. When accounting for PSA testing intensity, PHS290, family history, and race/ethnicity each remained independently associated with the prostate cancer endpoints (**Supplementary Tables 13-15**).

There were 86,668 MVP participants who underwent a pre-diagnostic PSA test between the ages of 40 and 49 years (i.e., early baseline PSA), representing 14.7% of the full MVP cohort. On univariable analysis, early baseline PSA value (in ng/mL) was associated with each of the three prostate cancer endpoints, with similar effect sizes: HR 1.39 [1.31-1.48] for fatal prostate cancer, 1.34 [1.30-1.40] for metastatic prostate cancer, and 1.36 [1.33-1.40] for any prostate cancer (**Supplementary Table 17**). On multivariable analysis (accounting for family history, race/ethnicity, and PHS290), early baseline PSA level remained significantly associated with each of the endpoints (**Supplementary Table 18**). In this multivariable analysis, family history was only significantly associated with any prostate cancer. Both PHS290 and Black race were independently associated with any prostate cancer and with metastatic prostate cancer (with effect sizes similar to the multivariable without early baseline PSA), while the associations with fatal prostate cancer were no longer statistically significant.

Black men were more than twice as likely as non-Black men to have an early baseline PSA, but even among Black men, the proportion having early baseline PSA was <30% (**Supplementary Table 19**). Family history had little apparent impact on whether a man had early baseline PSA (13.0% of those with a family history of prostate cancer vs. 11.3% of those with no family history of prostate cancer and 20.5% of those with unknown family history). PHS290 was slightly *lower*, on average, among those who had early baseline PSA than among those with no early baseline PSA ($p < 10^{-16}$), though the mean PHS290 values were similar.

Cox Proportional Hazards Analysis with Flexible, Group-Specific Thresholds

When using subgroup-specific thresholds of PHS290 to calculate HRs, risk stratification (as indicated by magnitude of HRs) was similar to that using the fixed, previously defined thresholds (**Supplementary Table 2**). For example, among Black men, $HR_{80/20}$ for fatal PCa was 2.22 [95% CI: 1.69-2.99] when using Black-specific thresholds for the highest and lowest 20th percentiles, compared to 2.37 [95% CI: 1.73-3.29] when using the fixed, previously defined thresholds. However, the number of individuals and absolute risk in each group differed considerably by threshold. For example, while 20% of Black men had PHS290 in the bottom quintile when using Black-specific thresholds (as expected), only approximately 5% of Black men had PHS290 in the bottom quintile when using the fixed, previously defined thresholds (**Figure 3, Supplementary Figure 2**).

Genetic Ancestry and Genetic Principal Components

The genetic ancestry groups and self-reported race/ethnicity are compared in **Supplementary Table 6**, and basic participant characteristics within each genetic ancestry group are shown in **Supplementary Table 7**. Results of univariable analyses of PHS290 associations with the three prostate cancer endpoints within each genetic ancestry group were similar to those using race/ethnicity subgroups (**Supplementary Table 8**). There was little impact when the univariable analyses for PHS290 were limited to only those individuals with concordant race/ethnicity and genetic ancestry (**Supplementary Table 9**).

Adding the top 10 genetic principal components to the primary multivariable model (race/ethnicity, family history, and PHS290) did not substantially affect results for PHS290 or family history. However, after adding the genetic principal components, Black race was no longer independently associated with metastatic or fatal prostate cancer (**Supplementary Table 12**).

Observed vs. Predicted Risk

Observed and predicted lifetime risk results for each endpoint are shown in **Supplementary Table 20** and **Supplementary Figure 3**.

Supplementary References:

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Supplementary Tables:

Group	Clinical Endpoint	p	Hazard ratios			
			HR _{80/20}	HR _{20/50}	HR _{80/50}	HR _{95/50}
All (n=590,750)	Fatal Prostate Cancer	<10 ⁻¹⁶	4.42 [3.91-5.02]	0.48 [0.45-0.51]	2.12 [2.0-2.27]	3.0 [2.75-3.3]
Asian (n=6,644)		0.03	20.33 [2.4-503.26]	0.21 [0.04-0.64]	4.37 [1.52-21.31]	9.51 [1.89-96.34]
Black or African American (n=102,203)		<10 ⁻¹⁶	2.37 [1.73-3.29]	0.66 [0.56-0.77]	1.57 [1.33-1.85]	1.9 [1.5-2.42]
Hispanic White (n=27,651)		0.001	3.52 [1.72-6.95]	0.53 [0.38-0.76]	1.87 [1.31-2.64]	2.54 [1.49-4.23]
Native American (n=5,835)		0.008	10.94 [1.58-85.77]	0.31 [0.11-0.8]	3.41 [1.26-9.62]	6.03 [1.41-26.97]
Non-Hispanic White (n=420,473)		<10 ⁻¹⁶	4.37 [3.77-5.05]	0.48 [0.45-0.52]	2.11 [1.96-2.27]	3.0 [2.69-3.34]
Other (n=8,226)		0.002	7.66 [2.05-33.35]	0.36 [0.17-0.7]	2.78 [1.43-5.88]	4.58 [1.71-13.8]
Pacific Islander (n=3,246)		0.43	3.06 [0.31-175.49]	0.57 [0.08-1.8]	1.75 [0.55-13.44]	2.32 [0.4-51.41]
Unknown (n=16,472)		0.09	2.05 [0.9-4.54]	0.7 [0.48-1.05]	1.44 [0.95-2.16]	1.71 [0.93-3.07]
All (n=590,750)	Metastatic Prostate Cancer	<10 ⁻¹⁶	4.89 [4.57-5.21]	0.46 [0.44-0.47]	2.23 [2.16-2.31]	3.23 [3.07-3.39]
Asian (n=6,644)		<10 ⁻⁴	7.61 [2.64-19.07]	0.35 [0.22-0.61]	2.7 [1.61-4.22]	4.56 [2.07-9.22]
Black or African American (n=102,203)		<10 ⁻¹⁶	3.03 [2.62-3.51]	0.59 [0.55-0.63]	1.78 [1.65-1.92]	2.28 [2.05-2.54]
Hispanic White (n=27,651)		<10 ⁻⁷	2.92 [1.96-4.43]	0.58 [0.47-0.71]	1.71 [1.4-2.11]	2.22 [1.65-3.01]
Native American (n=5,835)		<10 ⁻⁴	4.98 [2.16-12.06]	0.46 [0.3-0.69]	2.28 [1.48-3.57]	3.34 [1.78-6.38]
Non-Hispanic White (n=420,473)		<10 ⁻¹⁶	4.62 [4.27-5.01]	0.47 [0.45-0.49]	2.17 [2.08-2.26]	3.13 [2.95-3.32]
Other (n=8,226)		<10 ⁻⁶	5.95 [3.02-11.48]	0.41 [0.3-0.58]	2.45 [1.74-3.43]	3.8 [2.27-6.26]
Pacific Islander (n=3,246)		0.4	1.77 [0.55-6.43]	0.75 [0.39-1.35]	1.33 [0.74-2.55]	1.53 [0.64-4.07]
Unknown (n=16,472)		<10 ⁻⁹	4.74 [2.97-7.47]	0.46 [0.37-0.58]	2.2 [1.74-2.78]	3.19 [2.25-4.51]
All (n=590,750)	Prostate Cancer	<10 ⁻¹⁶	5.2 [5.09-5.31]	0.44 [0.44-0.45]	2.31 [2.28-2.33]	3.39 [3.33-3.44]
Asian (n=6,644)		<10 ⁻¹⁶	5.32 [4.04-7.09]	0.43 [0.37-0.49]	2.27 [1.98-2.61]	3.49 [2.83-4.34]

Black or African American (n=102,203)	<10 ⁻¹⁶	3.22 [3.06-3.39]	0.57 [0.56-0.58]	1.83 [1.79-1.88]	2.39 [2.3-2.48]
Hispanic White (n=27,651)	<10 ⁻¹⁶	4.24 [3.74-4.85]	0.49 [0.45-0.52]	2.06 [1.93-2.2]	2.92 [2.66-3.22]
Native American (n=5,835)	<10 ⁻¹⁶	5.1 [4.04-6.55]	0.45 [0.4-0.51]	2.31 [2.05-2.62]	3.4 [2.85-4.12]
Non-Hispanic White (n=420,473)	<10 ⁻¹⁶	5.12 [4.99-5.26]	0.45 [0.44-0.45]	2.29 [2.26-2.32]	3.38 [3.31-3.44]
Other (n=8,226)	<10 ⁻¹⁶	5.52 [4.45-6.89]	0.43 [0.39-0.48]	2.36 [2.12-2.64]	3.59 [3.06-4.25]
Pacific Islander (n=3,246)	<10 ⁻¹⁰	3.58 [2.5-5.37]	0.53 [0.43-0.63]	1.9 [1.57-2.33]	2.6 [1.98-3.57]
Unknown (n=16,472)	<10 ⁻¹⁶	5.27 [4.39-6.3]	0.44 [0.4-0.48]	2.32 [2.12-2.55]	3.45 [3.0-3.94]

Supplementary Table 1: Association of PHS290 with any, metastatic and fatal prostate cancer with self-reported ethnicity/race groups. Cox Proportional-Hazards results from association with age at prostate cancer, metastatic prostate cancer and death from prostate cancer. *P*-values reported are from univariable models using PHS290 as the sole predictor variable. Hazard ratios (HRs) are shown comparing men in various percentiles of genetic risk. HR_{80/20}: highest 20% (≥80th percentile of PHS290, using previously published thresholds for men <70 years old and no diagnosis of cancer) vs. average risk (30-70th percentile). HR_{20/50}: lowest 20% (≤20th percentile) vs. average risk. HR_{80/50}: highest 20% vs. average risk. HR_{95/50}: highest 5% (≥95th percentile) vs. average risk. Numbers in brackets are 95% confidence intervals.

Race/Ethnicity	Clinical Endpoint	p	Hazard ratios			
			HR _{80/20}	HR _{20/50}	HR _{80/50}	HR _{95/50}
All (n=590,750)	Fatal Prostate Cancer	<10 ⁻¹⁶	4.37 [3.87-4.9]	0.47 [0.45-0.5]	2.07 [1.95-2.19]	2.92 [2.67-3.17]
Asian (n=6,644)		0.005	19.39 [3.08-427.85]	0.23 [0.05-0.57]	4.44 [1.77-20.89]	8.78 [2.29-82.7]
Black or African American (n=102,203)		<10 ⁻⁷	2.22 [1.69-2.99]	0.67 [0.58-0.77]	1.49 [1.3-1.72]	1.79 [1.46-2.22]
Hispanic White (n=27,651)		0.0003	3.44 [1.71-6.85]	0.54 [0.38-0.76]	1.84 [1.31-2.6]	2.46 [1.48-4.07]
Native American (n=5,835)		0.02	10.32 [1.53-75.77]	0.31 [0.11-0.81]	3.23 [1.24-8.69]	5.58 [1.37-23.9]
Non-Hispanic White (n=420,473)		<10 ⁻¹⁶	4.33 [3.73-4.98]	0.48 [0.45-0.52]	2.08 [1.93-2.23]	2.96 [2.65-3.28]
Other (n=8,226)		0.004	7.32 [1.85-27.79]	0.37 [0.19-0.73]	2.69 [1.36-5.28]	4.29 [1.56-11.32]
Pacific Islander (n=3,246)		0.42	2.77 [0.29-67.35]	0.6 [0.12-1.83]	1.65 [0.55-7.93]	2.11 [0.41-21.25]
Unknown (n=16,472)		0.07	2.05 [0.91-4.28]	0.7 [0.48-1.05]	1.43 [0.95-2.07]	1.69 [0.93-2.91]
All (n=590,750)		Metastatic Prostate Cancer	<10 ⁻¹⁶	4.91 [4.62-5.24]	0.45 [0.43-0.46]	2.19 [2.13-2.27]
Asian (n=6,644)	<10 ⁻⁵		7.2 [2.61-17.57]	0.37 [0.24-0.62]	2.7 [1.62-4.2]	4.24 [2.02-8.04]
Black or African American (n=102,203)	<10 ⁻¹⁶		2.81 [2.46-3.21]	0.59 [0.56-0.63]	1.67 [1.56-1.78]	2.12 [1.93-2.33]
Hispanic White (n=27,651)	<10 ⁻⁶		2.89 [1.92-4.28]	0.59 [0.48-0.72]	1.69 [1.38-2.06]	2.17 [1.61-2.9]
Native American (n=5,835)	0.0001		4.96 [2.32-11.69]	0.45 [0.29-0.66]	2.24 [1.52-3.46]	3.25 [1.83-6.07]
Non-Hispanic White (n=420,473)	<10 ⁻¹⁶		4.64 [4.28-5.04]	0.46 [0.44-0.48]	2.15 [2.07-2.24]	3.12 [2.93-3.31]
Other (n=8,226)	<10 ⁻⁶		5.88 [3.07-11.79]	0.41 [0.29-0.57]	2.42 [1.75-3.43]	3.66 [2.27-6.13]
Pacific Islander (n=3,246)	0.37		1.75 [0.53-6.16]	0.75 [0.4-1.37]	1.32 [0.73-2.46]	1.51 [0.62-3.72]
Unknown (n=16,472)	<10 ⁻¹⁰		4.75 [2.98-7.55]	0.46 [0.37-0.58]	2.18 [1.73-2.75]	3.14 [2.22-4.37]
All (n=590,750)	Prostate Cancer		<10 ⁻¹⁶	6.19 [6.03-6.36]	0.4 [0.39-0.4]	2.47 [2.43-2.5]
Asian (n=6,644)		<10 ⁻¹⁶	5.97 [4.34-8.5]	0.41 [0.35-0.48]	2.46 [2.09-2.94]	3.7 [2.88-4.78]

Black or African American (n=102,203)	<10 ⁻¹⁶	3.43 [3.26-3.61]	0.54 [0.52-0.55]	1.85 [1.8-1.9]	2.45 [2.36-2.54]
Hispanic White (n=27,651)	<10 ⁻¹⁶	4.8 [4.18-5.57]	0.45 [0.42-0.49]	2.18 [2.03-2.35]	3.14 [2.83-3.49]
Native American (n=5,835)	<10 ⁻¹⁶	5.78 [4.37-7.61]	0.42 [0.36-0.48]	2.42 [2.1-2.8]	3.61 [2.93-4.46]
Non-Hispanic White (n=420,473)	<10 ⁻¹⁶	6.09 [5.9-6.29]	0.41 [0.4-0.41]	2.47 [2.43-2.51]	3.79 [3.7-3.89]
Other (n=8,226)	<10 ⁻¹⁶	6.29 [4.89-7.99]	0.4 [0.35-0.45]	2.51 [2.21-2.83]	3.83 [3.17-4.63]
Pacific Islander (n=3,246)	<10 ⁻⁸	3.91 [2.53-6.0]	0.5 [0.4-0.63]	1.96 [1.59-2.44]	2.71 [1.98-3.75]
Unknown (n=16,472)	<10 ⁻¹⁶	6.33 [5.21-7.94]	0.4 [0.36-0.44]	2.52 [2.29-2.83]	3.86 [3.36-4.55]

Supplementary Table 2: Association of PHS290 with any, metastatic and fatal prostate cancer using MVP reference thresholds. Cox Proportional-Hazards results from association with age at prostate cancer, metastatic prostate cancer and death from prostate cancer. *P*-values reported are from univariable models using PHS290 as the sole predictor variable. Hazard ratios (HRs) are shown comparing men in various percentiles of genetic risk. HR_{80/20}: highest 20% (≥80th percentile of PHS290, using MVP group-specific thresholds for men <70 years old and no diagnosis of cancer) vs. average risk (30-70th percentile). HR_{20/50}: lowest 20% (≤20th percentile) vs. average risk. HR_{80/50}: highest 20% vs. average risk. HR_{95/50}: highest 5% (≥95th percentile) vs. average risk. Numbers in brackets are 95% confidence intervals. Race/ethnic groups are the same as described in the caption for Table 1.

Race/Ethnicity	Clinical Endpoint	p	Hazard ratios			
			HR _{80/20}	HR _{20/50}	HR _{80/50}	HR _{95/50}
All (n=590,750)	Metastatic Prostate Cancer (at diagnosis)	<10 ⁻¹⁶	3.97 [3.57-4.45]	0.51 [0.48-0.53]	2.01 [1.91-2.13]	2.78 [2.57-3.02]
Asian (n=6,644)		0.009	5.27 [1.42-19.46]	0.43 [0.22-0.83]	2.26 [1.19-4.27]	3.47 [1.3-9.08]
Black or African American (n=102,203)		<10 ⁻¹⁶	3.39 [2.68-4.34]	0.56 [0.49-0.62]	1.89 [1.67-2.14]	2.48 [2.08-2.98]
Hispanic White (n=27,651)		0.03	2.1 [1.07-4.24]	0.69 [0.49-0.97]	1.45 [1.03-2.06]	1.73 [1.05-2.93]
Native American (n=5,835)		0.06	3.7 [1.08-13.23]	0.53 [0.28-0.96]	1.96 [1.04-3.79]	2.67 [1.06-6.88]
Non-Hispanic White (n=420,473)		<10 ⁻¹⁶	3.49 [3.05-4.0]	0.54 [0.5-0.58]	1.88 [1.76-2.02]	2.54 [2.3-2.81]
Other (n=8,226)		0.04	3.34 [1.21-10.71]	0.55 [0.31-0.91]	1.84 [1.1-3.29]	2.47 [1.15-5.9]
Pacific Islander (n=3,246)		0.71	1.46 [0.2-15.22]	0.83 [0.26-2.23]	1.21 [0.45-3.93]	1.33 [0.3-7.81]
Unknown (n=16,472)		<10 ⁻⁶	5.81 [3.05-10.9]	0.42 [0.31-0.58]	2.44 [1.76-3.35]	3.71 [2.3-5.93]

Supplementary Table 3: Association of PHS290 with metastatic prostate cancer at diagnosis with self-reported ethnicity/race groups. Cox Proportional-Hazards results from association with age of metastatic prostate cancer at diagnosis. *P*-values reported are from univariable models using PHS290 as the sole predictor variable. Hazard ratios (HRs) are shown comparing men in various percentiles of genetic risk. HR_{80/20}: highest 20% (≥80th percentile of PHS290, using previously published thresholds for men <70 years old and no diagnosis of cancer) vs. average risk (30-70th percentile). HR_{20/50}: lowest 20% (≤20th percentile) vs. average risk. HR_{80/50}: highest 20% vs. average risk. HR_{95/50}: highest 5% (≥95th percentile) vs. average risk. Numbers in brackets are 95% confidence intervals.

Race/Ethnicity	Clinical Endpoint	p	Hazard ratios			
			HR _{80/20}	HR _{20/50}	HR _{80/50}	HR _{95/50}
All (n=93,583)	Metastatic Prostate Cancer	<10 ⁻¹⁶	5.18 [4.4-6.07]	0.44 [0.41-0.48]	2.3 [2.12-2.49]	3.38 [3.0-3.79]
Asian (n=975)		0.33	3.01 [0.55-16.36]	0.56 [0.22-1.37]	1.68 [0.76-3.7]	2.1 [0.67-6.73]
Black or African American (n=16,055)		<10 ⁻¹¹	3.65 [2.6-5.16]	0.53 [0.45-0.63]	1.95 [1.64-2.34]	2.6 [2.03-3.36]
Hispanic White (n=4,029)		<10 ⁻⁶	10.7 [4.24-29.58]	0.31 [0.18-0.48]	3.27 [2.05-5.43]	6.05 [3.01-13.03]
Native American (n=817)		0.12	3.66 [0.7-30.53]	0.52 [0.18-1.2]	1.91 [0.83-5.48]	2.55 [0.77-12.2]
Non-Hispanic White (n=67,987)		<10 ⁻¹⁶	4.51 [3.71-5.59]	0.48 [0.43-0.52]	2.14 [1.94-2.39]	3.08 [2.66-3.61]
Other (n=1,277)		0.03	5.3 [1.59-20.15]	0.43 [0.22-0.79]	2.26 [1.26-4.39]	3.53 [1.43-9.86]
Pacific Islander (n=509)		0.45	2.63 [0.28-38.36]	0.62 [0.16-1.88]	1.62 [0.52-6.12]	2.01 [0.39-13.79]
Unknown (n=1,935)		0.01	4.3 [1.59-12.35]	0.49 [0.3-0.8]	2.11 [1.27-3.68]	3.02 [1.42-6.74]
All (n=93,583)		Prostate Cancer	<10 ⁻¹⁶	5.45 [5.18-5.73]	0.43 [0.42-0.44]	2.36 [2.3-2.42]
Asian (n=975)	<10 ⁻⁴		5.69 [2.42-14.11]	0.4 [0.25-0.62]	2.26 [1.51-3.43]	3.23 [1.83-5.94]
Black or African American (n=16,055)	<10 ⁻¹⁶		3.68 [3.29-4.17]	0.53 [0.5-0.56]	1.96 [1.85-2.1]	2.62 [2.41-2.87]
Hispanic White (n=4,029)	<10 ⁻¹⁶		4.17 [2.99-5.93]	0.49 [0.41-0.58]	2.04 [1.73-2.43]	2.96 [2.29-3.86]
Native American (n=817)	<10 ⁻⁴		3.99 [2.14-7.7]	0.5 [0.36-0.68]	2.0 [1.45-2.8]	2.72 [1.73-4.37]
Non-Hispanic White (n=67,987)	<10 ⁻¹⁶		5.25 [4.94-5.57]	0.44 [0.43-0.45]	2.32 [2.24-2.39]	3.45 [3.29-3.61]
Other (n=1,277)	<10 ⁻⁷		4.23 [2.29-7.94]	0.48 [0.35-0.66]	2.03 [1.49-2.75]	2.98 [1.87-4.8]
Pacific Islander (n=509)	<10 ⁻³		5.05 [2.5-12.41]	0.45 [0.28-0.64]	2.25 [1.58-3.56]	3.22 [1.94-6.06]
Unknown (n=1,935)	<10 ⁻¹⁶		9.13 [5.6-14.96]	0.34 [0.27-0.43]	3.11 [2.42-4.01]	5.35 [3.64-7.78]

Supplementary Table 4: Association of PHS290 with any and metastatic prostate cancer after excluding Medicare enrollees. *P*-values reported are from univariable Cox proportional hazards models using PHS290 as the sole predictor variable. Hazard ratios (HRs) are shown comparing men in various percentiles of genetic risk. HR_{80/20}: highest 20% ($\geq 80^{\text{th}}$ percentile of PHS290, using previously published thresholds for men <70 years old and no diagnosis of cancer) vs. average risk (30-70th percentile). HR_{20/50}: lowest 20% ($\leq 20^{\text{th}}$ percentile) vs. average risk. HR_{80/50}: highest 20% vs. average risk. HR_{95/50}: highest 5% ($\geq 95^{\text{th}}$ percentile) vs. average risk. Numbers in brackets are 95% confidence intervals.

Genetic Ancestry

	Admixed American	African	Central/South Asian	East Asian	European	Middle Eastern	Unassigned	Total
Asian	118	28	277	6003	61	9	148	6644
Black/AA	1648	99716	58	163	378	44	196	102203
Hispanic White	24808	100	5	86	2500	14	138	27651
Native American	2699	401	6	48	2358	1	322	5835
Non-Hispanic White	405454	1133	9369	920	84	549	2964	420473
Other	1783	775	5410	109	35	42	72	8226
Pacific Islander	798	294	38	1336	614	6	160	3246
Unknown	7524	2550	5736	427	64	29	142	16472

Supplementary Table 5: Genetic ancestry assignments by self-reported ethnicity groups, n=590,750. Genetic ancestry assigned to participants in each self-reported ethnicity group. Individuals without assignment are labeled “Unassigned.”

	All	Admixed American	African	Central/South Asian	East Asian	European	Middle Eastern
Participants							
All participants	586,608 (375,763)	50,586 (24,961)	104,997 (48,308)	567 (225)	9,092 (4,680)	420,672 (297,152)	694 (437)
Prostate cancer	68,706 (49,073)	3,775 (2,358)	16,178 (8,717)	13 (8)	487 (329)	48,178 (37,602)	75 (59)
Metastases from prostate cancer	6,373 (4,250)	361 (215)	1,650 (822)	2 (0)	43 (29)	4,312 (3,181)	5 (3)
Death from prostate cancer	1,843 (1,302)	90 (46)	377 (196)	0 (0)	8 (5)	1,364 (1,051)	4 (4)
Age demographics							
Age at diagnosis, median and IQR	67 [62-72]	65 [60-70]	63 [58-68]	67 [62-69]	67 [61-72]	68 [63-73]	73 [67.5-78]
Age at last follow-up, median and IQR	664 [59-74]	59 [47-71]	62 [55-70]	49 [37-60]	56 [42-69]	68 [62-75]	66 [49.5-81]

Supplementary Table 6: Participant characteristics for genetic ancestry groups, n=586,608. Genetic ancestry groups were made based on PCA analysis on individual genotypes from Wendt et al. 4142 individuals were not assigned a genetic ancestry group and are excluded here.

		Hazard ratios				
Group	Clinical Endpoint	p	HR _{80/20}	HR _{20/50}	HR _{80/50}	HR _{95/50}
All (n=586,608)	Fatal Prostate Cancer	<10 ⁻¹⁶	4.39 [3.84-5.01]	0.48 [0.45-0.52]	2.12 [1.98-2.26]	2.99 [2.71-3.3]
Admixed American (50,586)		<10 ⁻⁵	4.3 [2.37-7.71]	0.48 [0.36-0.65]	2.08 [1.54-2.78]	2.96 [1.9-4.57]
African (n=104,997)		<10 ⁻⁷	2.35 [1.71-3.22]	0.66 [0.57-0.77]	1.56 [1.32-1.84]	1.89 [1.49-2.39]
Central/South Asian (n=567)		-	-	-	-	-
East Asian (n=9,092)		-	-	-	-	-
European (n=420,672)		<10 ⁻¹⁶	4.3 [3.7-4.99]	0.49 [0.45-0.52]	2.09 [1.94-2.26]	2.97 [2.65-3.31]
Middle Eastern (n=694)		-	-	-	-	-
All (n=586,608)		Metastatic Prostate Cancer	<10 ⁻¹⁶	4.87 [4.56-5.18]	0.46 [0.44-0.47]	2.23 [2.16-2.3]
Admixed American (50,586)	<10 ⁻¹⁶		4.01 [2.94-5.31]	0.5 [0.43-0.58]	2.01 [1.72-2.32]	2.81 [2.24-3.47]
African (n=104,997)	<10 ⁻¹⁶		2.96 [2.58-3.44]	0.59 [0.55-0.63]	1.76 [1.64-1.9]	2.25 [2.03-2.51]
Central/South Asian (n=567)	-		-	-	-	-
East Asian (n=9,092)	<10 ⁻⁴		6.51 [2.51-17.29]	0.38 [0.23-0.63]	2.51 [1.57-4.06]	4.06 [1.99-8.42]
European (n=420,672)	<10 ⁻¹⁶		4.6 [4.26-4.98]	0.47 [0.45-0.49]	2.16 [2.08-2.25]	3.12 [2.95-3.31]
Middle Eastern (n=694)	-		-	-	-	-
All (n=586,608)	Prostate Cancer		<10 ⁻¹⁶	5.19 [5.09-5.31]	0.44 [0.44-0.45]	2.3 [2.28-2.33]
Admixed American (50,586)		<10 ⁻¹⁶	4.36 [3.99-4.82]	0.48 [0.46-0.5]	2.09 [2.0-2.2]	3.0 [2.8-3.23]
African (n=104,997)		<10 ⁻¹⁶	3.21 [3.06-3.37]	0.57 [0.56-0.58]	1.84 [1.79-1.88]	2.39 [2.3-2.47]
Central/South Asian (n=567)		0.24	2.84 [0.52-13.39]	0.59 [0.27-1.37]	1.67 [0.72-3.6]	2.22 [0.61-7.17]
East Asian (n=9,092)		<10 ⁻¹⁶	4.23 [3.27-5.47]	0.48 [0.42-0.55]	2.03 [1.79-2.3]	2.94 [2.42-3.58]
European (n=420,672)		<10 ⁻¹⁶	5.13 [4.99-5.26]	0.45 [0.44-0.45]	2.29 [2.26-2.32]	3.38 [3.31-3.44]
Middle Eastern (n=694)		0.05	1.93 [1.01-3.77]	0.72 [0.52-1.0]	1.4 [1.0-1.95]	1.64 [1.0-2.74]

Supplementary Table 7: Association of PHS290 with any, metastatic and fatal prostate cancer using genetic ancestry groups. Cox Proportional-Hazards results from association with age at prostate cancer, metastatic prostate cancer and death from prostate cancer. *P*-values reported are from univariable models using PHS290 as the sole predictor variable. Hazard ratios (HRs) are shown comparing men in various percentiles of genetic risk. HR_{80/20}: highest 20% ($\geq 80^{\text{th}}$ percentile of PHS290, using previously published thresholds for men <70 years old and no diagnosis of cancer) vs. average risk (30-70th percentile). HR_{20/50}: lowest 20% ($\leq 20^{\text{th}}$ percentile) vs. average risk. HR_{80/50}: highest 20% vs. average risk. HR_{95/50}: highest 5% ($\geq 95^{\text{th}}$ percentile) vs. average risk. Numbers in brackets are 95% confidence intervals. For subgroup analyses with less than 10 events of the endpoint, the box is marked '-'. Genetic ancestry groups are the same as described in the caption for Supplementary Table 7.

Race/Ethnicity	Clinical Endpoint	p	Hazard ratios			
			HR _{80/20}	HR _{20/50}	HR _{80/50}	HR _{95/50}
Asian (n=6,006)	Fatal Prostate Cancer	0.03	21.35 [3.17-650.2]	0.21 [0.04-0.55]	4.44 [1.75-24.0]	9.6 [2.34-114.53]
Black or African American (n=99,734)		<10 ⁻⁷	2.36 [1.71-3.24]	0.66 [0.57-0.77]	1.56 [1.32-1.84]	1.9 [1.49-2.39]
Hispanic White (n=24,813)		0.001	3.87 [1.82-8.42]	0.51 [0.34-0.74]	1.96 [1.35-2.9]	2.72 [1.56-4.84]
Non-Hispanic White (n=405,540)		<10 ⁻¹⁶	4.41 [3.77-5.09]	0.48 [0.45-0.52]	2.12 [1.96-2.28]	3.02 [2.68-3.36]
Asian (n=6,006)	Metastatic Prostate Cancer	<10 ⁻⁵	9.61 [3.27-24.56]	0.31 [0.19-0.54]	3.01 [1.8-4.66]	5.32 [2.43-10.52]
Black or African American (n=99,734)		<10 ⁻¹⁶	2.97 [2.56-3.48]	0.59 [0.55-0.64]	1.76 [1.63-1.91]	2.25 [2.01-2.53]
Hispanic White (n=24,813)		<10 ⁻⁶	3.0 [2.04-4.62]	0.58 [0.46-0.7]	1.73 [1.43-2.15]	2.25 [1.69-3.1]
Non-Hispanic White (n=405,540)		<10 ⁻¹⁶	4.66 [4.25-5.03]	0.47 [0.45-0.49]	2.18 [2.08-2.27]	3.15 [2.94-3.33]
Asian (n=6,006)	Prostate Cancer	<10 ⁻¹⁶	5.28 [4.07-7.14]	0.43 [0.36-0.49]	2.25 [1.98-2.62]	3.42 [2.81-4.33]
Black or African American (n=99,734)		<10 ⁻¹⁶	3.2 [3.05-3.37]	0.57 [0.56-0.59]	1.83 [1.79-1.88]	2.38 [2.29-2.47]
Hispanic White (n=24,813)		<10 ⁻¹⁶	4.07 [3.55-4.65]	0.49 [0.46-0.53]	2.01 [1.88-2.16]	2.83 [2.55-3.13]
Non-Hispanic White (n=405,540)		<10 ⁻¹⁶	5.14 [5.0-5.27]	0.45 [0.44-0.45]	2.29 [2.26-2.32]	3.38 [3.32-3.45]

Supplementary Table 8: Association of PHS290 with any, metastatic and fatal prostate cancer using matched race/ethnicity and genetic ancestry groups. Cox Proportional-Hazards results from association with age at prostate cancer, metastatic prostate cancer and death from prostate cancer. *P*-values reported are from univariable models using PHS290 as the sole predictor variable. Hazard ratios (HRs) are shown comparing men in various percentiles of genetic risk. HR_{80/20}: highest 20% (≥80th percentile of PHS290, using previously published for men <70 years old and no diagnosis of cancer) vs. average risk (30-70th percentile). HR_{20/50}: lowest 20% (≤20th percentile) vs. average risk. HR_{80/50}: highest 20% vs. average risk. HR_{95/50}: highest 5% (≥95th percentile) vs. average risk. Numbers in brackets are 95% confidence intervals. Race/ethnic groups are individuals with matched genetic ancestry: e.g., Non-Hispanic White men with assigned European genetic ancestry, Black men with assigned African genetic ancestry.

Clinical Endpoint	Asian	Black or African American	Hispanic White	Native American	Other	Pacific Islander	Unknown
Fatal Prostate Cancer	0.48 [0.12-0.98]	2.53 [2.14-2.92]***	1.02 [0.68-1.43]	1.04 [0.34-2.0]	1.87 [1.04-2.8]	1.83 [0.0-4.87]	0.72 [0.0-1.88]
Metastatic Prostate Cancer	0.94 [0.59-1.38]	2.85 [2.64-3.08]***	1.29 [1.08-1.52]*	1.47 [1.02-2.02]	1.65 [1.28-2.07]*	1.19 [0.23-2.33]	1.49 [0.73-2.31]
Any Prostate Cancer	0.9 [0.8-1.01]	2.33 [2.28-2.38]***	1.06 [1.0-1.12]	1.1 [0.98-1.21]	1.18 [1.09-1.27]*	1.0 [0.76-1.29]	0.87 [0.7-1.04]

Supplementary Table 9: Association of self-reported race/ethnicity with three prostate cancer clinical endpoints. Hazard ratios (HRs) are shown from Cox proportional hazards models with race/ethnicity as the only predictor variable and Non-Hispanic White as the reference for each group. Numbers in brackets are 95% confidence intervals.

Clinical Endpoint	p Value	Family History
Fatal Prostate Cancer	1.83 [1.53-2.17]	<10 ⁻¹²
Metastatic Prostate Cancer	1.67 [1.52-1.83]	<10 ⁻¹⁶
Any Prostate Cancer	1.93 [1.88-1.99]	<10 ⁻¹⁶

Supplementary Table 10: Association of family history with three prostate cancer clinical endpoints. Hazard ratios (HRs) are shown from Cox proportional hazards models with family history as the only predictor variable. This analysis was limited to the 378,366 participants who provided family history information in baseline survey data. Numbers in brackets are 95% confidence intervals.

	PHS290	Family History	Race/Ethnicity							Medicare
Clinical Endpoints	HR _{80/20}	Family History	Asian	Black or African American	Hispanic White	Native American	Other	Pacific Islander	Unknown	Medicare
Metastatic Prostate Cancer	4.15 [3.82-4.55]***	1.53 [1.39-1.68]***	1.31 [0.83-1.91]	2.25 [2.08-2.43]***	1.32 [1.1-1.56]*	1.4 [0.97-1.92]	1.67 [1.29-2.09]*	1.14 [0.22-2.2]	1.52 [0.75-2.36]	1.0 [0.94-1.07]
Prostate Cancer	4.69 [4.57-4.82]***	1.78 [1.73-1.84]****	1.28 [1.15-1.42]*	1.82 [1.77-1.86]***	1.1 [1.04-1.16]*	1.04 [0.93-1.15]	1.19 [1.1-1.28]*	0.98 [0.73-1.24]	0.91 [0.74-1.09]	1.1 [1.08-1.12]***

Supplementary Table 11: Multivariable models combining self-reported Race/Ethnicity, Family History (FH), PHS290 and Medicare enrollment status for any and metastatic prostate cancer clinical endpoints. *P*-values reported are from multivariable Cox proportional hazards models using self-reported race/ethnicity, family history, PHS290, and Medicare eligibility status. For PHS290, effect size was illustrated via the hazard ratios: HR_{80/20} for the highest 20% vs. lowest 20% of genetic risk. As the thresholds for a multivariable model must be constant across racial/ethnic groups and regardless of family history status, the thresholds for percentiles of PHS290 were taken from previously published values of an independent dataset of men with European genetic ancestry <70 years old and who did not have prostate cancer. Hazard ratios for race/ethnicity were estimated using Non-Hispanic White as the reference. Hazard ratios for family history were for one or more first-degree relatives diagnosed with prostate cancer. This multivariable analysis was limited to the 378,366 participants who provided family history information in baseline survey data. Numbers in brackets are 95% confidence intervals. Significant predictors in the multivariable model are indicated by * ($p < 0.01$) and *** ($p < 10^{-16}$).

Clinical Endpoint	HR _{80/20}	Family History	Asian	Black or African American	Hispanic White	Native American	Non-Hispanic White	Other	Pacific Islander	Unknown
Fatal Prostate Cancer	4.07 [3.39-4.74]***	1.67 [1.39-1.98]*	0.68 [0.07-2.77]	1.31 [0.73-2.35]	1.16 [0.68-1.84]	1.02 [0.34-2.0]	Ref	1.97 [1.01-3.21]*	1.16 [0.0-5.51]	0.72 [0.0-1.92]
Metastatic Prostate Cancer	4.06 [3.74-4.44]***	1.53 [1.39-1.68]**	0.95 [0.35-2.26]	1.03 [0.76-1.39]	1.25 [0.96-1.6]	1.21 [0.83-1.68]	Ref	1.41 [1.07-1.86]	0.85 [0.16-1.95]	1.35 [0.66-2.13]
Any Prostate Cancer	4.67 [4.55-4.79]***	1.78 [1.73-1.84]***	1.28 [0.98-1.7]	1.15 [1.04-1.27]*	1.08 [1.0-1.17]	1.02 [0.9-1.13]	Ref	1.11 [1.02-1.21]	0.89 [0.64-1.23]	0.86 [0.69-1.03]
Clinical Endpoint	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
Fatal Prostate Cancer	0.11 [0.0-2.57]	0.26 [0.02-2.62]	0.56 [0.01-24.6]	0.08 [0.01-0.35]*	0.19 [0.01-2.88]	3.62 [0.1-119.93]	85.52 [0.18-167982.22]	0.01 [0.0-5.19]	3.14 [0.02-604.17]	3.42 [0.06-247.61]
Metastatic Prostate Cancer	0.01 [0.0-0.06]*	0.67 [0.18-2.34]	0.79 [0.09-6.75]	0.06 [0.02-0.14]*	1.01 [0.2-4.91]	5.77 [0.64-48.68]	0.42 [0.02-21.55]	0.47 [0.02-9.1]	5.73 [0.37-121.3]	0.18 [0.02-2.04]
Any Prostate Cancer	0.07 [0.04-0.13]***	0.5 [0.34-0.74]*	1.01 [0.53-1.92]	0.72 [0.55-0.96]	2.42 [1.52-3.87]*	2.51 [1.46-4.61]*	1.5 [0.58-4.5]	0.37 [0.16-0.89]	1.11 [0.45-2.71]	0.84 [0.41-1.8]

Supplementary Table 12: Multivariable models combining self-reported Race/Ethnicity, Family History, Top 10 Population Principal Components, and PHS290 for three prostate cancer clinical endpoints. Cox proportional hazards results for association with age at death from prostate cancer, age at diagnosis of metastatic prostate cancer, and age at diagnosis with prostate cancer. *P*-values reported are from multivariable models using race/ethnicity, family history, the top 10 population principal components, and PHS290. For PHS290, effect size was illustrated via the hazard ratio (HR_{80/20}) for the highest 20% vs. lowest 20% of genetic risk. Hazard ratios for racial/ethnic groups were estimated using Non-Hispanic White as the reference. Hazard ratios for family history were for one or more first-degree relatives diagnosed with prostate cancer. This analysis was limited to the 378,366 participants who provided family history information in baseline survey data. Numbers in brackets are 95% confidence intervals. Significant predictors in the multivariable model are indicated by * ($p < 0.01$), ** ($p < 10^{-10}$) and *** ($p < 10^{-16}$). PHS290 and family history remained significant after addition of the top 10 population principal components, but Black race was no longer independently associated with fatal or metastatic prostate cancer, implying this racial information was accounted for in the top 10 principal genetic components.

	PHS290	Family History	Race/Ethnicity							PSA intensity
Clinical Endpoint	HR _{80/20}	Family History	Asian	Black or African American	Hispanic White	Native American	Other	Pacific Islander	Unknown	# pre-diagnostic tests
Fatal Prostate Cancer	3.64 [3.14-4.23]***	1.59 [1.31-1.89]***	0.6 [0.14-1.26]	2.11 [1.76-2.44]***	1.08 [0.69-1.5]	1.06 [0.34-2.0]	2.07 [1.17-3.1]*	1.75 [0.0-4.82]	0.66 [0.0-1.74]	0.91 [0.89-0.92]***
Metastatic Prostate Cancer	3.52 [3.23-3.83]***	1.44 [1.3-1.6]***	1.14 [0.71-1.63]	2.47 [2.28-2.65]***	1.39 [1.15-1.65]*	1.56 [1.08-2.09]*	1.85 [1.43-2.32]*	1.18 [0.25-2.39]	1.31 [0.64-2.03]	0.89 [0.89-0.9]***
Prostate Cancer	4.13 [4.03-4.23]****	1.72 [1.67-1.77]***	1.08 [0.95-1.21]	2.27 [2.22-2.33]***	1.2 [1.14-1.27]***	1.24 [1.11-1.38]*	1.41 [1.31-1.52]***	1.04 [0.78-1.31]	0.71 [0.58-0.85]*	0.86 [0.86-0.86]***

Supplementary Table 13: Multivariable models combining self-reported Race/Ethnicity, Family History (FH), PHS290 and number of pre-diagnostic PSA tests for three prostate cancer clinical endpoints. Cox proportional hazards results for association with age at death from prostate cancer, at diagnosis of metastatic prostate cancer, and age at diagnosis with prostate cancer. Hazard ratios for PSA testing included number of pre-diagnostic tests (> 2 years before prostate cancer diagnosis for prostate cancer cases). This multivariable analysis was limited to the 378,366 participants who provided family history information in baseline survey data and had PSA information available. Numbers in brackets are 95% confidence intervals. Significant predictors in the multivariable model are indicated by * ($p < 0.01$) and *** ($p < 10^{-16}$).

	PHS290	Family History	Race/Ethnicity							PSA intensity
Clinical Endpoint	HR _{80/20}	Family History	Asian	Black or African American	Hispanic White	Native American	Other	Pacific Islander	Unknown	# PSA testing years
Fatal Prostate Cancer	3.52 [3.02-4.09]***	1.57 [1.3-1.87]***	0.59 [0.14-1.23]	2.11 [1.76-2.44]***	1.07 [0.69-1.5]	1.07 [0.34-2.02]	2.09 [1.18-3.12]*	1.73 [0.0-4.8]	0.65 [0.0-1.72]	0.87 [0.85-0.88]***
Metastatic Prostate Cancer	3.39 [3.11-3.69]***	1.42 [1.28-1.57]***	1.12 [0.7-1.6]	2.47 [2.29-2.66]***	1.39 [1.15-1.64]*	1.57 [1.09-2.1]*	1.87 [1.44-2.35]***	1.17 [0.25-2.36]	1.29 [0.63-2.01]	0.85 [0.85-0.86]***
Prostate Cancer	3.99 [3.89-4.09]***	1.7 [1.65-1.75]***	1.06 [0.93-1.19]	2.32 [2.26-2.38]***	1.2 [1.14-1.27]***	1.26 [1.13-1.4]*	1.44 [1.33-1.55]***	1.03 [0.77-1.3]	0.69 [0.57-0.83]*	0.81 [0.81-0.81]***

Supplementary Table 14: Multivariable models combining self-reported Race/Ethnicity, Family History (FH), PHS290 and number of calendar years with a pre-diagnostic PSA test for three prostate cancer clinical endpoints. Cox proportional hazards results for association with age at death from prostate cancer, at diagnosis of metastatic prostate cancer, and age at diagnosis with prostate cancer. Hazard ratios for PSA testing included number of pre-diagnostic tests (> 2 years before prostate cancer diagnosis for prostate cancer cases). This multivariable analysis was limited to the 378,366 participants who provided family history information in baseline survey data and had PSA information available. Numbers in brackets are 95% confidence intervals. Significant predictors in the multivariable model are indicated by *($p < 0.01$) and *** ($p < 10^{-16}$).

	PHS290	Family History	Race/Ethnicity							PSA intensity
Clinical Endpoint	HR _{80/20}	Family History	Asian	Black or African American	Hispanic White	Native American	Other	Pacific Islander	Unknown	Age at first PSA
Fatal Prostate Cancer	4.2 [3.61-4.9]***	1.66 [1.38-1.97]***	0.67 [0.16-1.39]	1.93 [1.61-2.24]***	1.03 [0.66-1.44]	0.94 [0.31-1.78]	1.83 [1.05-2.75]*	1.7 [0.0-4.55]	0.73 [0.0-1.91]	0.97 [0.97-0.98]***
Metastatic Prostate Cancer	4.16 [3.83-4.54]***	1.5 [1.35-1.66]***	1.28 [0.79-1.81]	2.08 [1.93-2.25]***	1.29 [1.07-1.54]*	1.3 [0.9-1.77]	1.54 [1.18-1.94]*	1.1 [0.23-2.22]	1.51 [0.74-2.35]	0.96 [0.96-0.97]***
Prostate Cancer	4.71 [4.59-4.82]***	1.77 [1.72-1.82]***	1.26 [1.12-1.41]*	1.75 [1.71-1.79]***	1.08 [1.02-1.14]*	1.0 [0.9-1.11]	1.14 [1.05-1.23]*	0.96 [0.72-1.2]	0.89 [0.73-1.06]	0.98 [0.98-0.99]***

Supplementary Table 15: Multivariable models combining self-reported Race/Ethnicity, Family History (FH), PHS290 and age at first PSA test for three prostate cancer clinical endpoints. Cox proportional hazards results for association with age at death from prostate cancer, at diagnosis of metastatic prostate cancer, and age at diagnosis with prostate cancer. Hazard ratios for PSA testing included number of pre-diagnostic tests (> 2 years before prostate cancer diagnosis for prostate cancer cases). This multivariable analysis was limited to the 378,366 participants who provided family history information in baseline survey data and had PSA information available. Numbers in brackets are 95% confidence intervals. Significant predictors in the multivariable model are indicated by *($p < 0.01$) and *** ($p < 10^{-16}$).

Race and ethnicity	Clinical Endpoint	PSA testing exposure					
		# prediagnostic tests		# PSA testing years		Age at first PSA	
		HR	p	HR	p	HR	p
All (n=590,750)	Fatal Prostate Cancer	0.88 [0.87-0.89]	<10 ⁻¹⁶	0.84 [0.83-0.85]	<10 ⁻¹⁶	0.98 [0.97-0.98]	<10 ⁻¹⁶
Asian (n=6,644)		0.95 [0.0-1.08]	0.67	0.88 [0.0-1.07]	0.43	1.03 [0.96-1.11]	0.57
Black or African American (n=102,203)		0.85 [0.83-0.88]	<10 ⁻¹⁶	0.8 [0.77-0.83]	<10 ⁻¹⁶	0.96 [0.94-0.97]	<10 ⁻⁸
Hispanic White (n=27,651)		0.84 [0.77-0.91]	<10 ⁻⁵	0.79 [0.7-0.86]	<10 ⁻⁶	0.97 [0.94-0.99]	0.03
Native American (n=5,835)		0.64 [0.0-0.86]	0.01	0.46 [0.0-0.71]	0.01	1.02 [0.97-1.07]	0.62
Non-Hispanic White (n=420,473)		0.89 [0.88-0.91]	<10 ⁻¹⁶	0.85 [0.84-0.87]	<10 ⁻¹⁶	0.98 [0.98-0.99]	<10 ⁻⁷
Other (n=8,226)		0.85 [0.72-0.94]	0.005	0.81 [0.65-0.92]	0.003	0.97 [0.9-1.02]	0.33
Pacific Islander (n=3,246)		0.63 [0.0-0.88]	0.1	0.61 [0.0-0.88]	0.09	1.04 [0.94-1.16]	0.53
Unknown (n=16,472)		0.85 [0.73-0.92]	<10 ⁻³	0.79 [0.66-0.88]	<10 ⁻³	0.99 [0.96-1.01]	0.36
All (n=590,750)		Metastatic Prostate Cancer	0.88 [0.87-0.88]	<10 ⁻¹⁶	0.83 [0.82-0.84]	<10 ⁻¹⁶	0.96 [0.96-0.97]
Asian (n=6,644)	0.93 [0.82-1.0]		0.06	0.88 [0.76-0.97]	0.01	1.01 [0.98-1.03]	0.73
Black or African American (n=102,203)	0.85 [0.84-0.86]		<10 ⁻¹⁶	0.8 [0.79-0.82]	<10 ⁻¹⁶	0.94 [0.94-0.95]	<10 ⁻¹⁶

Hispanic White (n=27,651)		0.85 [0.82-0.88]	<10 ⁻¹⁶	0.8 [0.76-0.84]	<10 ⁻¹⁶	0.97 [0.95-0.98]	<10 ⁻³
Native American (n=5,835)		0.79 [0.69-0.86]	<10 ⁻⁷	0.74 [0.64-0.81]	<10 ⁻⁷	1.0 [0.96-1.02]	0.85
Non-Hispanic White (n=420,473)		0.88 [0.87-0.89]	<10 ⁻¹⁶	0.84 [0.83-0.85]	<10 ⁻¹⁶	0.97 [0.97-0.98]	<10 ⁻¹⁶
Other (n=8,226)		0.87 [0.82-0.92]	<10 ⁻⁶	0.84 [0.77-0.89]	<10 ⁻⁶	0.93 [0.89-0.96]	<10 ⁻³
Pacific Islander (n=3,246)		0.75 [0.53-0.85]	<10 ⁻³	0.71 [0.51-0.82]	<10 ⁻³	1.03 [0.96-1.08]	0.42
Unknown (n=16,472)		0.82 [0.75-0.87]	<10 ⁻¹⁰	0.77 [0.69-0.83]	<10 ⁻¹¹	1.0 [0.98-1.01]	0.76
All (n=590,750)	Prostate Cancer	0.85 [0.85-0.85]	0	0.8 [0.8-0.8]	<10 ⁻¹⁶	0.98 [0.98-0.98]	<10 ⁻¹⁶
Asian (n=6,644)		0.87 [0.85-0.9]	1.93E-24	0.83 [0.8-0.86]	<10 ⁻¹⁶	0.99 [0.98-1.0]	0.33
Black or African American (n=102,203)		0.84 [0.83-0.84]	<10 ⁻¹⁶	0.78 [0.78-0.79]	<10 ⁻¹⁶	0.97 [0.97-0.98]	<10 ⁻¹⁶
Hispanic White (n=27,651)		0.83 [0.81-0.84]	<10 ⁻¹⁶	0.76 [0.75-0.77]	<10 ⁻¹⁶	0.98 [0.98-0.99]	<10 ⁻⁷
Native American (n=5,835)		0.83 [0.8-0.85]	<10 ⁻¹⁶	0.77 [0.74-0.79]	<10 ⁻¹⁶	0.99 [0.98-1.0]	0.07
Non-Hispanic White (n=420,473)		0.85 [0.85-0.85]	<10 ⁻¹⁶	0.8 [0.79-0.8]	<10 ⁻¹⁶	0.99 [0.99-0.99]	<10 ⁻¹⁶
Other (n=8,226)		0.85 [0.83-0.86]	<10 ⁻¹⁶	0.79 [0.77-0.81]	<10 ⁻¹⁶	0.97 [0.96-0.98]	<10 ⁻⁶
Pacific Islander (n=3,246)		0.85 [0.82-0.88]	<10 ⁻¹⁶	0.8 [0.77-0.83]	<10 ⁻¹⁶	0.99 [0.97-1.0]	0.12
Unknown (n=16,472)		0.83 [0.81-0.85]	<10 ⁻¹⁶	0.78 [0.76-0.8]	<10 ⁻¹⁶	0.99 [0.98-1.0]	0.01

Supplementary Table 16: Association of PSA testing intensity with any, metastatic and fatal prostate cancer. Cox Proportional Hazards model results from association with age at prostate cancer, metastatic prostate cancer (nodal or distant) and death from prostate cancer. *P*-values reported

are from univariable models using one of three different indices of PSA testing intensity as the sole predictor variable: number of pre-diagnostic PSA tests, number of calendar years with at least one pre-diagnostic PSA test, and age at first pre-diagnostic PSA test. In all analyses, PSA tests obtained within the two years immediately preceding a diagnosis of prostate cancer were excluded. Numbers in brackets are 95% confidence intervals.

Race/Ethnicity	Clinical Endpoint	PSA (ng/dl)	
		HR	P
All (n=94,639)	Fatal Prostate Cancer	1.39 [1.31-1.48]	<10 ⁻¹³
Asian (n=1,066)		-	-
Black or African American (n=31,608)		1.44 [1.36-1.54]	<10 ⁻¹²
Hispanic White (n=5,311)		-	-
Native American (n=1,096)		-	-
Non-Hispanic White (n=50,677)		1.28 [1.18-1.44]	0.01
Other (n=1,718)		-	-
Pacific Islander (n=725)		-	-
Unknown (n=2,438)		-	-
All (n=94,639)	Metastatic Prostate Cancer	1.34 [1.3-1.4]	<10 ⁻¹⁶
Asian (n=1,066)		-	-
Black or African American (n=31,608)		1.32 [1.28-1.39]	<10 ⁻¹⁶
Hispanic White (n=5,311)		-	-
Native American (n=1,096)		-	-
Non-Hispanic White (n=50,677)		1.31 [1.24-1.43]	<10 ⁻¹²
Other (n=1,718)		-	-
Pacific Islander (n=725)		-	-
Unknown (n=2,438)		-	-
All (n=94,639)	Prostate Cancer	1.36 [1.33-1.4]	<10 ⁻¹⁶
Asian (n=1,066)		1.44 [1.15-1.95]	0.01
Black or African American (n=31,608)		1.32 [1.28-1.38]	<10 ⁻¹⁶
Hispanic White (n=5,311)		1.39 [1.29-1.59]	<10 ⁻¹⁶
Native American (n=1,096)		1.79 [1.63-2.35]	<10 ⁻¹⁰
Non-Hispanic White (n=50,677)		1.41 [1.37-1.48]	<10 ⁻¹⁶
Other (n=1,718)		1.38 [1.32-2.15]	<10 ⁻¹³

Pacific Islander (n=725)	1.29 [1.02-2.44]	0.002
Unknown (n=2,438)	1.37 [1.25-2.08]	<10 ⁻¹²

Table 17: Univariable models for early baseline PSA (age 40-49 years) for three prostate cancer clinical endpoints, among the 16.0% of MVP participants with available early baseline PSA. Cox proportional hazards results for association of early baseline PSA level with age at death from prostate cancer, at diagnosis of metastatic prostate cancer, and age at diagnosis with prostate cancer. Hazard ratios for PSA testing included number of pre-diagnostic tests (> 2 years before prostate cancer diagnosis for prostate cancer cases). This analysis was limited to the 94,639 participants with available pre-diagnostic PSA information between age 40 and 49 years. Numbers in brackets are 95% confidence intervals. Significant predictors in the multivariable model are indicated by *($p < 0.01$) and *** ($p < 10^{-16}$). For subgroup analyses with less than 10 events of the endpoint, the box is marked '-'.

	PHS290	Family History	Race/Ethnicity							Early Baseline PSA
Clinical Endpoint	HR _{80/20}	Family History	Asian	Black or African American	Hispanic White	Native American	Other	Pacific Islander	Unknown	PSA
Fatal Prostate Cancer	1.2 [0.4-3.98]	1.41 [0.0-4.42]	-	1.02 [0.28-2.9]	-	-	-	-	-	1.38 [1.25-1.56]***
Metastatic Prostate Cancer	3.12 [1.95-5.12] *	1.62 [0.96-2.49]	-	2.5 [1.8-3.71]***	-	-	-	-	-	1.31 [1.26-1.42]***
Prostate Cancer	3.97 [3.48-4.53]***	2.13 [1.9-2.37]***	1.38 [0.63-2.31]	1.94 [1.75-2.15]***	1.01 [0.74-1.3]	0.94 [0.57-1.35]	1.14 [0.86-1.47]	0.45 [0.0-1.22]	1.38 [0.31-2.93]	1.32 [1.28-1.4]***

Supplementary Table 18: Multivariable models combining early baseline PSA (age 40-49 years) with self-reported Race/Ethnicity, Family History (FH), and PHS290 for three prostate cancer clinical endpoints, among the 7.9% of MVP participants with available early baseline PSA and family history information. Cox proportional hazards results for association with age at death from prostate cancer, at diagnosis of metastatic prostate cancer, and age at diagnosis with prostate cancer. Hazard ratios for PSA testing included number of pre-diagnostic tests (> 2 years before prostate cancer diagnosis for prostate cancer cases). This multivariable analysis was limited to the 46,470 participants with available pre-diagnostic PSA information between age 40 and 49 years and family history survey data. Numbers in brackets are 95% confidence intervals. Significant predictors in the multivariable model are indicated by *(p<0.01) and *** (p<10⁻¹⁶).

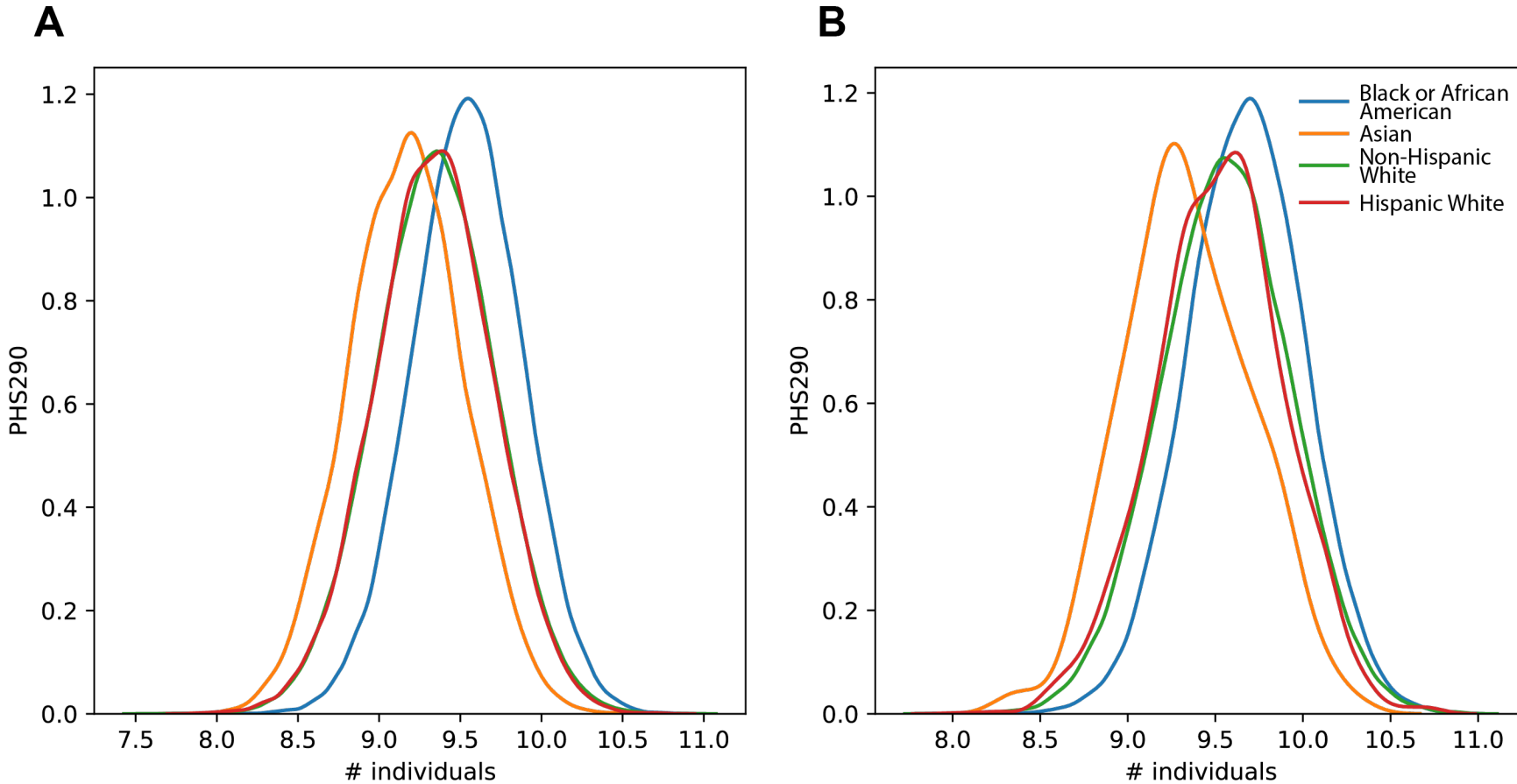
Risk Factor	Had Early Baseline PSA	No Early Baseline PSA
Family History of Prostate Cancer	3,963 (13.9%)	24,582 (86.1%)
No Family History of Prostate Cancer	32,507 (12.2%)	307,314 (87.8%)
Family History Unknown	48,169 (22.7%)	164,215 (77.3%)
Black	31,608 (30.9%)	70,595 (69.1%)
Not Black	63,031 (12.9%)	425,516 (87.1%)
Mean PHS290	9.43	9.39

Supplementary Table 19: Risk factor profiles of MVP participants with available early baseline PSA. Of the 590,750 participants included in the present study, 94,639 (16%) had an available pre-diagnostic early baseline PSA, defined as a PSA test performed while the participant had age 40-49 years and excluding any diagnostic PSA results (i.e., PSA tests within the two years preceding a prostate cancer diagnosis). Black men (self-identified as Black or African American) were more than twice as likely as non-Black men to have an early baseline PSA, but even among Black men, the proportion having early baseline PSA was <35%. Family history had little apparent impact on whether a man had early baseline PSA (13.9% for those with a family history of prostate cancer vs. 12.2% for those with no family history of prostate cancer and 22.7% for those with unknown family history). PHS290 was slightly *lower*, on average, among those who had early baseline PSA than among those with no early baseline PSA ($p < 10^{-16}$), though the mean PHS290 values were similar.

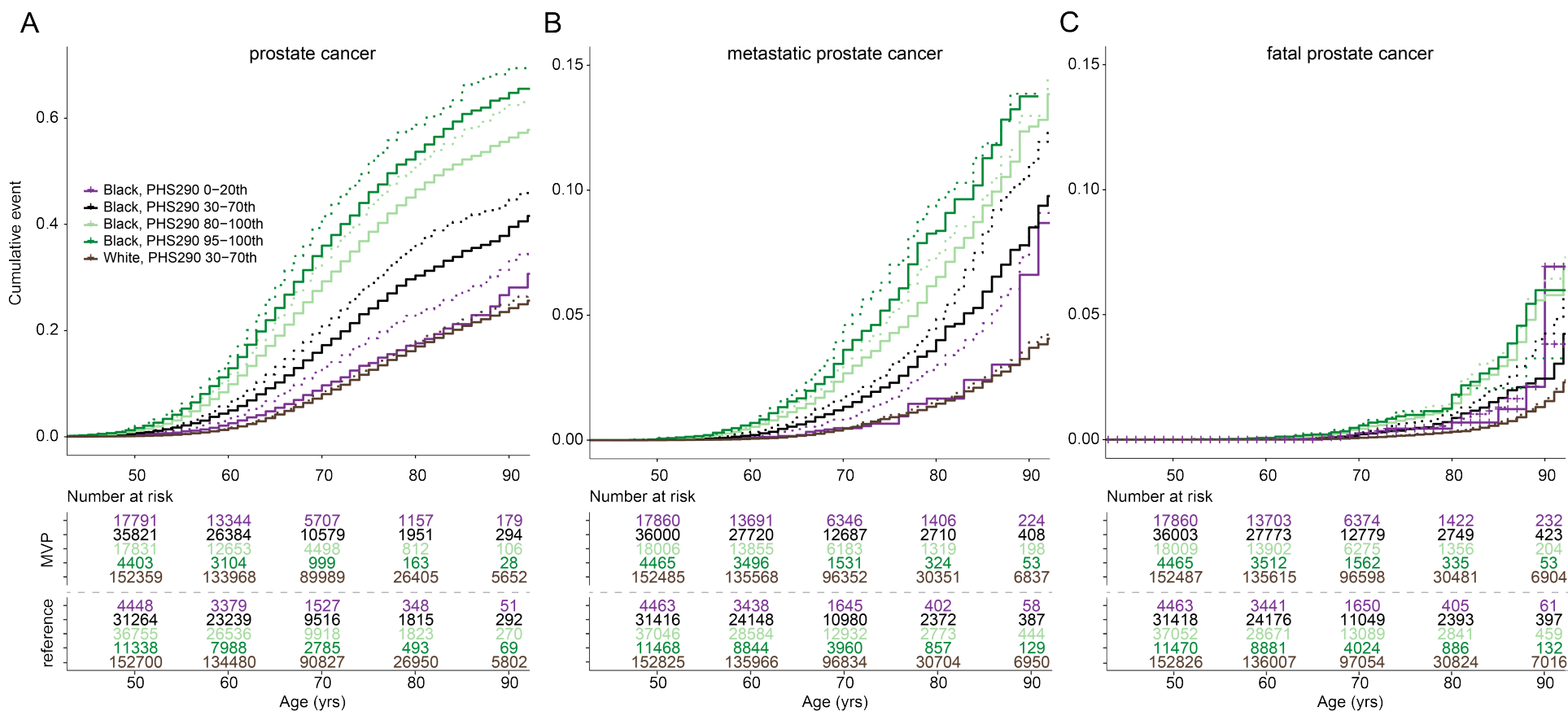
Clinical Endpoints	Observed vs. Predicted Cumulative Incidence			
	PHS290 0-20 th	PHS290 30-70 th	PHS290 80-100 th	PHS290 95-100 th
Fatal Prostate Cancer by age 90	1.1% vs. 0.8%	1.6% vs. N/A	3.8% vs. 3.5%	5.1% vs. 4.9%
Metastatic Prostate Cancer by age 90	2.0% vs. 1.9%	4.1% vs. N/A	8.2% vs. 9.2%	10.7% vs. 13.4%
Prostate Cancer by age 70	4.1% vs. 4.1%	9.3% vs. N/A	21.4% vs. 21.4%	29.3% vs. 31.4%

Supplementary Table 20: Observed and predicted cumulative incidence at relevant ages. Observed vs. predicted incidence within each stratum of PHS90 of any prostate cancer by age 70, metastatic prostate cancer by age 90, and fatal prostate cancer by age 90. Predicted values were based on the hazard ratios for each stratum of PHS290 by taking the observed outcomes from the average-risk stratum (PHS290 30-70th percentile) and multiplying by the estimated hazard ratio for the stratum of interest.

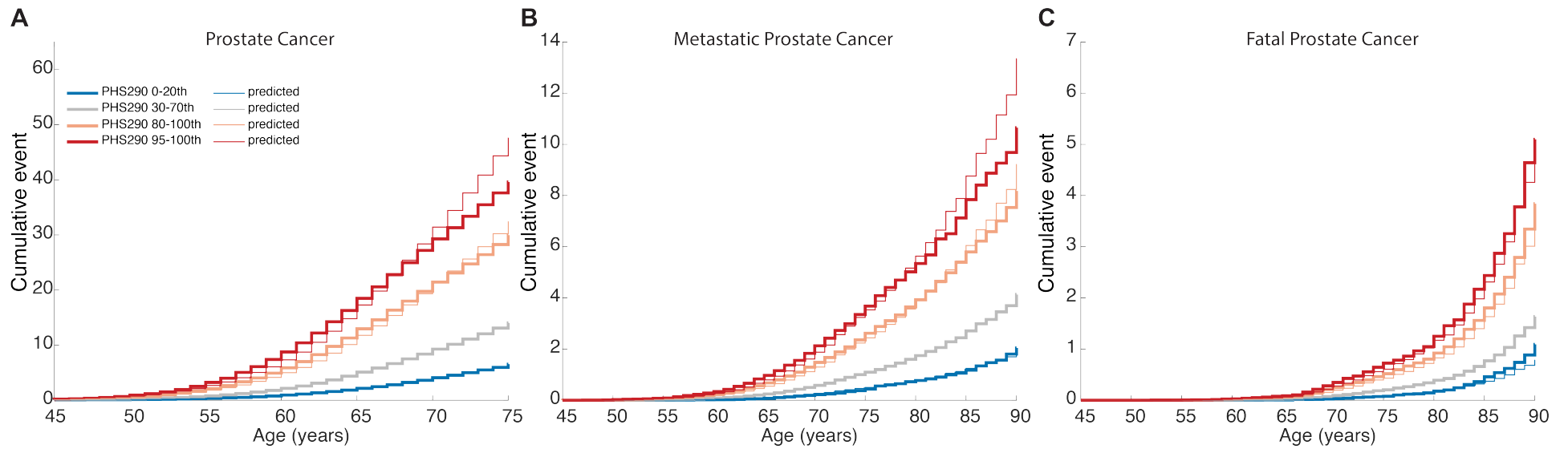
Supplementary Figures:



Supplementary Figure 1. (A) PHS290 score density plot in prostate cancer controls for White Non-Hispanic, Black or African American, Hispanic White and Asian self-reported race/ethnicity groups. **(B)** PHS290 score density plot in prostate cancer cases for White Non-Hispanic, Black or African American, Hispanic White and Asian self-reported race/ethnicity groups. These plots do not account for age. Intriguingly, typical PHS290 scores differed between racial/ethnic groups, with the mean PHS290 slightly higher among Black men and slightly lower among East Asian men, compared to Hispanic and Non-Hispanic White men. These shifts in PHS290 distribution are consistent with reported differences in PCa incidence across racial groups^{12–16} and with a previous polygenic risk meta-analysis⁸. Higher overall PHS290 scores in African ancestry group may point to true differences in PCa risk but could also be inflated by minor allele frequency (MAF) differences between ancestry groups. Incorporating approaches for local ancestry and admixture can also boost genetic model performance and should be explored further to improve the predictive accuracy of polygenic scores¹⁷.



Supplementary Figure 2: Comparing previously published population thresholds for percentile groups to race-specific thresholds. Cause-specific cumulative incidence for Black or African American (Black/AA) men in several PHS290 strata compared with average-risk Non-Hispanic White (PHS290 30-70th percentiles) within MVP, stratified by PHS290 using reference thresholds (solid) and group-specific thresholds (dotted), for **(A)** any prostate cancer, **(B)** metastatic prostate cancer and **(C)** fatal prostate cancer. For the solid curves, percentiles of PHS290 were defined previously in an independent dataset comprised of men of European genetic ancestry. This strategy allows direct comparison of absolute values of PHS290 across groups (and makes possible multivariable analyses), but one cannot suppose that 20% of Black men will be in the 0-20th stratum because Black men, on average, have higher PHS290 values than White men. For the dotted curves, percentiles were defined within each subgroup of MVP: i.e., “Black, PHS290 0-20th” represents Black men whose PHS290 is <20th percentile of Black MVP participants <70 years old and without prostate cancer.



Supplementary Figure 3: Observed vs. Predicted Risk. Cause-specific cumulative incidence for **(A)** prostate cancer, **(B)** metastatic prostate cancer and **(C)** fatal prostate cancer. Thick solid lines are the observed incidence for the PHS290 strata of the corresponding color. Thin solid lines are the predicted incidence for the corresponding PHS290 strata based on the HRs estimated in the univariable models (**Table 2**).