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Actionable Genomic Alterations in Prostate Cancer Among Black and White United States Veterans

Luca F. Valle[1,2,‡], **Nicholas G. Nickols**[*,1,2,3,4,‡], **Ryan Hausler**[5,6], **Patrick R. Alba**[5,7], **Tori Anglin-Foote**[5], **Cristina Perez**[5], **Kosj Yamoah**[8,9], **Brent S. Rose**[10,11], **Michael J. Kelley**[12,13], **Scott L. DuVall**[5,7], **Isla P. Garraway**[1,3,4], **Kara N. Maxwell**[6,14,15], **Julie A. Lynch**[5,7,16]

[1]Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA, USA
[2]Department of Radiation Oncology, David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA, USA
[3]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA
[4]Department of Urology, David Geffen School of Medicine at the University of California, Los Angeles, CA, USA
[5]Department of Veterans Affairs Informatics and Computing Infrastructure, Department of Veterans Affairs Salt Lake City Health Care System, Salt Lake City, UT, USA
[6]Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[7]Division of Epidemiology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA
[8]Department of Radiation Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA
[9]James A. Haley Veterans' Hospital, Tampa, FL, USA
[10]Department of Radiation Oncology, University of California, San Diego, CA, USA
[11]Veterans Affairs San Diego Healthcare System, San Diego, CA
[12]Duke University Medical Center, Durham, NC, USA
[13]Department of Veteran Affairs Medical Center, Durham, NC, USA
[14]Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA
[15]Abramson Cancer Center, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[16]Department of Nursing and Health Sciences, University of Massachusetts, Boston, MA, USA

*Corresponding author: Nicholas G. Nickols, MD, PhD, VA Greater Los Angeles Healthcare System, West Los Angeles VA, Department of Radiation Oncology, 11301 Wilshire Boulevard, Building 500, Los Angeles, CA 90073, USA. Email: nicholas.nickols@va.gov
‡Contributed equally.

Abstract

Black Veterans have higher a incidence of localized and metastatic prostate cancer compared to White Veterans yet are underrepresented in reports of frequencies of somatic and germline alterations. This retrospective analysis of somatic and putative germline alterations was conducted in a large cohort of Veterans with prostate cancer (N = 835 Black, 1613 White) who underwent next generation sequencing through the VA Precision Oncology Program, which facilitates molecular testing for Veterans with metastatic cancer. No differences were observed in gene alterations for FDA approved targetable therapies (13.5% in Black Veterans vs. 15.5% in White Veterans, P = .21), nor in any potentially actionable alterations (25.5% vs. 28.7%, P =.1). Black Veterans had higher rates of *BRAF* (5.5% vs. 2.6%, P < .001) alterations, White Veterans *TMPRSS2* fusions (27.2% vs. 11.7%, P < .0001). Putative germline alteration rates were higher in White Veterans (12.0% vs. 6.1%, P < .0001). Racial disparities in outcome are unlikely attributable to acquired somatic alterations in actionable pathways.

Key words: metastatic prostate cancer; actionable alterations; next-generation sequencing; disparities; race.

Veterans self-identifying as Black/African American have a higher incidence of both localized (M0) and de novo metastatic (M1) PCa compared to White Veterans.[1] Next Generation Sequencing (NGS) is recommended for all Veterans with metastatic PCa to identify actionable alterations targetable with approved therapies. Prior studies comparing racial differences in the frequency of somatic alterations in patients with metastatic PCa are mixed, though the representation of Black patients has been low. We evaluate differences in actionable genomic profiles between Black and White Veterans with metastatic PCa in a cohort with the largest total and proportional representation of Black patients in the published literature.

We retrospectively analyzed Veterans who underwent clinical tumor genomic sequencing for a submitted diagnosis of PCa as part of the National Precision Oncology Program (NPOP) sequencing initiative[2] between January 2015 and February 2022. Race and ethnicity were self-reported by Veterans. Race categories in this analysis were Black/African American and White. For Black Veterans, Hispanic and non-Hispanic ethnicities were included. For White Veterans, only non-Hispanic ethnicities were included. FFPE tissue submitted for sequencing included prostate biopsies, prostatectomy specimens, and prostate cancer metastases. Foundation Medicine, Personalis, and Personal Genome Diagnostics (PGDx) platforms were

Table 1. Characteristics of patients with prostate cancer who underwent tumor sequencing.

Characteristics	White (*n* = 1613)		Black (*n* = 835)		*P*-value
	Number	%	Number	%	
Vital status as of 3/15/2022					
Deceased	661	41.0	310	37.1	.0673
Lab					
Foundation medicine	1349	83.6	692	82.9	.0024
Personalis	89	5.5	73	8.7	
PGDX	175	10.8	70	8.4	
Age					
Mean (SD)	73.2 (7.6)		69.6 (8.1)		
Category (age group at index)					
18-49	*	*	*	*	<.0001
50-54	16	1.0	19	2.3	
55-59	47	2.9	45	5.4	
60-64	101	6.3	140	16.8	
65-69	216	13.4	187	22.4	
70-74	534	33.1	218	26.1	
75-79	403	25.0	126	15.1	
80 to older	292	18.1	97	11.6	
Marital status					
Other	699	43.3	505	60.5	<.0001
Married	914	56.7	330	39.5	
Residential urban/rural					
Urban	1025	63.5	716	85.7	<.0001
Rural	588	36.5	119	14.3	
Medicaid eligible					
No	1598	99.1	813	97.4	.0024
Yes	15	0.9	22	2.6	
Type of VHA benefits					
Non-service-connected veteran	36	2.2	21	2.5	.0016
10%-39%	191	11.8	100	12.0	
40%-59%	59	3.7	25	3.0	
60%-89%	98	6.1	89	10.7	
90+	1229	76.2	600	71.9	
Potential exposure to agent orange					
No	1210	75.0	743	89.0	<.0001
Yes	403	25.0	92	11.0	
Branch of service					
Other or missing	292	18.1	105	12.6	<.0001
Air force	191	11.8	105	12.6	
Army	688	42.7	431	51.6	
Coast guard	12	0.7	*	*	
Marine corps	154	9.5	97	11.6	
Navy	276	17.1	96	11.5	
Service period					
Other or unknown	*	*	*	*	<.0001
Pre-Korean (WWI, WWII, and Pre-Korean)	12	0.7	*	*	
Korean	96	6.0	37	4.4	
Post-Korean	75	4.6	14	1.7	
Vietnam	1191	73.8	499	59.8	
Post-Vietnam	148	9.2	176	21.1	
Persian Gulf War	89	5.5	104	12.5	

*Less than 11 patients were observed. Statistical comparisons by Chi squared test.

deployed for sequencing, but only commonly reported genes were considered in this analysis. When multiple specimens from the same patient were sequenced, only the most recently sequenced specimen was analyzed. Alterations were defined as "likely oncogenic/oncogenic" according to described criteria (Supplementary Methods, Supplementary Tables S1, S2).

Likely oncogenic/oncogenic alterations were categorized as "FDA Approved," (alterations in genes targetable by drugs with FDA-approved indications in metastatic PCa. Supplementary Table S3) or "Any Actionable," (alterations in genes targetable by any drug), including targeted agents with FDA approval for another indication. In addition, putative germline alterations were defined as oncogenic/likely oncogenic variants if variant allele frequency exceeded 30% (VAF >30%) in genes identified by the ESMO Precision Medicine Working Group.[3] Fisher's exact test and Chi squared test compared differences among White versus Black Veterans.

NGS results from 2448 Veterans were available for analysis, 1613 (66%) White and 835 (34%) Black (Table 1, Supplementary Table S4). The cohort was balanced for vital status, but Black Veterans were younger, more likely to be unmarried, Medicaid eligible, and reside in an urban setting, and less likely to report Agent Orange exposure.

White Veterans had higher rates of *TMPRSS2-ERG* fusions (27.2% vs. 11.7% of tested patients, $P < .001$). No differences were observed in *TP53* or *AR* alteration rates (Fig. 1; Table 2). Oncogenic alteration rates were not different in the "FDA Approved" gene category for White vs. Black Veterans (15.5% vs. 13.7, $P = 0.2$), respectively, owing to similar rates of alterations in DDR genes, MMR genes, TMB status, and MSI status. Similarly, there was no difference in the rates of "Any Actionable" alterations (28.7% vs. 25.5%, $P = 0.1$). Black Veterans displayed higher rates of *BRAF* (5.5% vs. 2.6%, $P < .001$) oncogenic alterations. White Veterans had
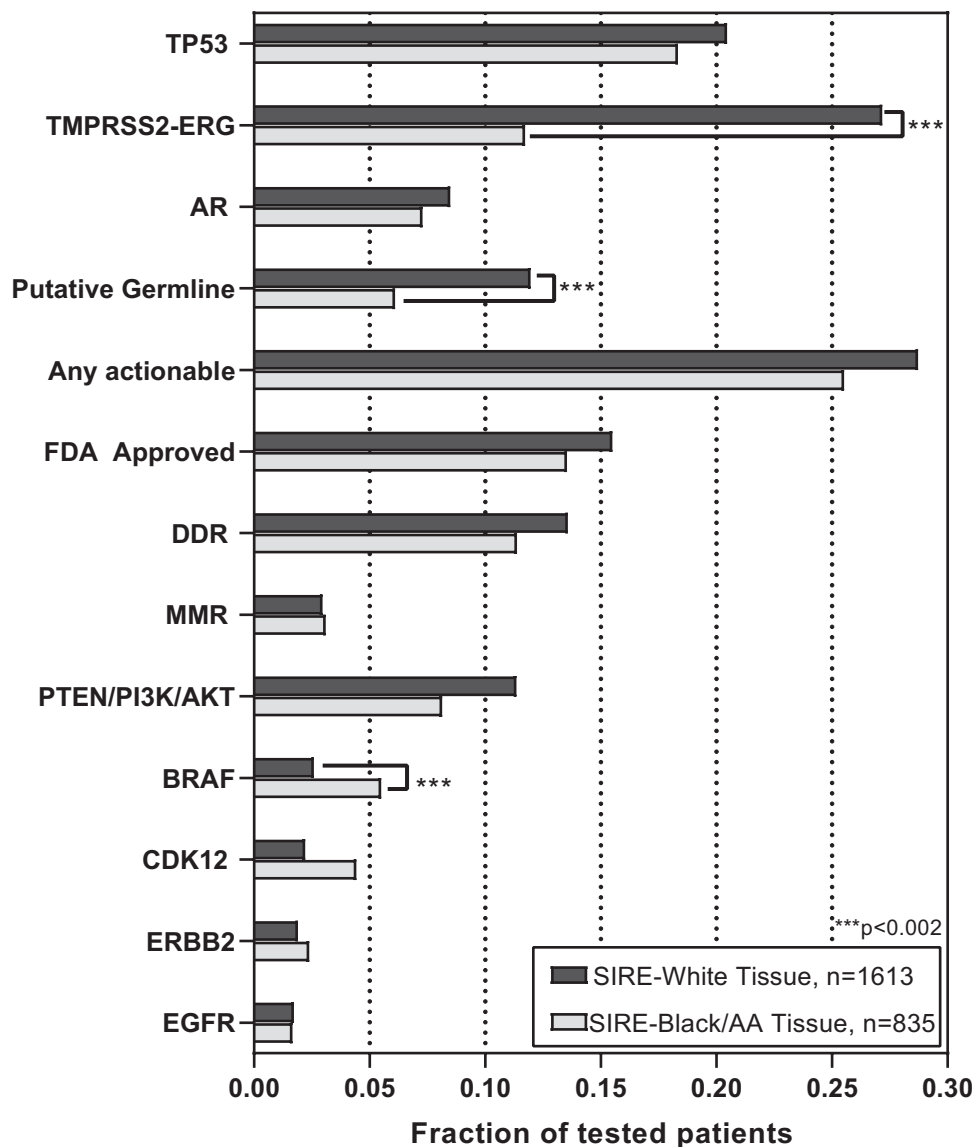

Figure 1. Alteration profiles in Black vs. White Veterans with metastatic prostate cancer. Alteration rates for the listed genes or gene groupings according to the fraction of total patients tested for that particular gene. "MMR" deficiency was defined as oncogenic alterations (short variants or copy number loss) in *MLH1, MSH2, MSH6 or PMS2*; MSI-High status on report; or TMB-High status on report. "DDR" deficiency was defined as oncogenic alterations (short variants or copy number loss) in *ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FANCA, FANCL, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, or RAD54L*. "Any Actionable" further included oncogenic alterations in *BRAF, PTEN, PI3KCA, AKT, CDK12, ERBB2, EGFT, IDH1, CHKN2A, NTRK1/2/3, ALK, FGFR1/2/3, KIT, PDGFRA, RET, and ROS1*. Short variants in *TP53, AR*, and *TMPRSS2* fusions were not considered actionable but reported. Tabulation of this data is available in Supplementary Table S5. ***Refers to the Bonferroni corrected significance threshold $P < .002$.

Table 2. Comparison of rates of genomic alterations between White and Black Veterans.

	SIRE-White		SIRE-Black/AA		*P*-value (8)	% change (W-B)
	n	% of 1613	*n*	% of 835		
TP53	331	20.52	154	18.44	.2181	2.1
TMPRSS2-ERG	438	27.15	98	11.74	<.0001*	15.4
DDR (1)	219	13.58	95	11.38	.1264	2.2
PTEN/PI3K/AKT	183	11.35	68	8.14	.0138	3.2
AR	137	8.49	61	7.31	.3481	1.2
BRAF	42	2.60	46	5.51	.0005*	–2.9
PTEN	97	6.01	39	4.6	.1925	1.3
CDK12	36	2.23	37	4.43	.0036	–2.2
MMRd (2)	48	2.98	26	3.11	.901	–0.1
ERBB2	31	1.92	20	2.40	.457	–0.5
EGFR	28	1.74	14	1.68	1	0.1
CDKN2A	14	0.87	<11	<1.3	N/A	0.0
FGFR (3)	<11	<0.7	<11	<1.3	N/A	–0.5
IDH1	<12	<0.7	<11	<1.3	N/A	–0.2
PDGFRA	<13	<0.7	<11	<1.3	N/A	0.0
RET	12	0.74	<11	<1.3	N/A	0.5
ROS1	<11	<0.7	<11	<1.3	N/A	–0.2
NTRK (4)	<11	<0.7	<11	<1.3	N/A	0.1
ALK	<11	<0.7	<11	<1.3	N/A	0.1
KIT	13	0.81	<11	<1.3	N/A	0.7
ABL1	<11	<0.7	<11	<1.3	N/A	0.3
Any actionable (5)	463	28.70	213	25.51	.0953	3.2
FDA approved (6)	250	15.50	113	13.53	.2079	2.0
Putative Germline (7)	193	11.97	51	6.11	<.0001*	5.9

(1) DDR: LP/P alteration in ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FANCA, FANCL, NBN, PALB2, RAD51, RAD51B RAD51C, RAD51D, RAD54L.
(2) MMR deficiency = LP/P alteration in MLH1, MSH2, MSH6, PMS2 and/or MSI-H and/or TMB-H.
(3) FGFR: LP/P alteration in FGFR2, FGFR3.
(4) NTRK: LP/P alteration in NTRK1, NTRK2, NTRK3.
(5) Any actionable: LP/P alteration in DDR, MMRd, ABL1, AKT, BRAF, CDK12, ERBB2, EGFR, IDH1, CDKN2A, NTRK, ALK, FGFR, KIT, PDGFRA, PI3KCA, PTEN, RET, ROS1.
(6) FDA approved: LP/P alteration in MMR deficiency + DDR.
(7) Putative germline = LP/P alteration with VAF>30% in ESMO guideline gene.
(8) *Refers to the Bonferroni corrected value significance level $P < .002$.

higher rates of putative germline alterations (12.0% vs. 6.1%, $P < .001$) compared to Black Veterans.

To our knowledge, this cohort has the largest total and proportional representation of Black men with PCa who underwent NGS to date. Defined narrowly or broadly, actionable alterations do not differ between Black and White Veterans, suggesting current therapeutic strategies based on actionable alterations are likely equally beneficial for Black and White patients. Additionally, differences in somatic alterations are likely insufficient to explain the race-based disparities in the incidence and outcomes of metastatic PCa.

Our findings are consistent with a prior study,[4] which evaluated a mixed population of 861 metastatic and non-metastatic men with PCa. Though only 250 Black men were included in their cohort, they found a similar proportion of actionable alterations between White and Black patients. A separate comparative analysis[5] evaluated sequencing data from 165 Black men and similarly uncovered no differences in rates of DDR alterations. Also consistent with our findings, *TMPRSS2* rearrangements were less common in patients of African ancestry compared to those of European ancestry, a finding that has been recapitulated across multiple studies.[5-7] In contrast, another study reported greater rates of actionable alterations in the metastatic tumors of 71 Black men compared to those of 801 White men.[8] It is possible that the low representation of Black men in that analysis contributed to an over-emphasis of the rates of potentially actionable alterations.

The almost two-fold difference in putative germline variants by race is striking. Annotation databases lack representation of men of African ancestry making it difficult to properly annotate and identify germline variants in this population. However, given that most putative germline variants were truncating variants, differential inclusion in annotation databases is unlikely explain this difference entirely.

Limitations include the lack of annotation to distinguish if sequenced tissue was from metastases versus primary tissue, the potential phenotypic heterogeneity of this metastatic cohort, and our inability to correlate corresponding clinicopathologic data such as tumor burden and castrate sensitivity with genomic findings. Importantly, our primary analysis of actionable mutation

rates should not be affected by different proportions of primary versus metastatic tissue because DDR alterations and MSI are truncal alterations.[9-11] While sequencing was accomplished using multiple platforms, our analysis was restricted to commonly reported genes across all platforms to maintain a robust analysis. We feel that the benefits of reporting genomic sequencing data with a high total and proportional representation of Black patients outweigh these limitations, given the critical need to understand race-based drivers of PCa disparities.

Our work adds the largest NGS analysis of Black patients with PCa and suggests that clinically actionable alteration rates do not vary with race. Thus, racial disparities in outcome are unlikely attributable to acquired somatic alterations in currently known actionable pathways, though we cannot exclude the possibility that unknown actionable pathways play a role. We echo others[12] in underscoring the importance of diverse and equitable representation in studies seeking to characterize cancer genomic profiles. This is especially true in the context of a relatively lower mutation rate of PCa, where conclusions from comparative studies with low Black representation may provide an incomplete picture of the true tumor mutational landscape in this population. Ultimately, we support genomic sequencing efforts for Veterans with advanced PCa in service of improving patient selection for targeted therapies and simultaneously encourage complementary strategies that address modifiable cancer risk factors, healthcare access, social determinants of health, and other interactions with genomics to address disparities in cancer outcomes.

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Conflict of Interest

Nicholas G. Nickols reported research support from Lantheus, Janssen, and Bayer, and consulting for PrimeFour outside the scope of the present work. Michael J. Kelley reported research support from Novartis, AstraZeneca, Bristol-Myers Squibb, Regeneron, and Genentech. Scott L. DuVall and Julie A Lynch reported research support from Alnylam Pharmaceuticals, Inc, Astellas Pharma, Inc, AstraZeneca Pharmaceuticals LP, Biodesix, Boehringer Ingelheim International GmbH, Celgene Corporation, Eli Lilly and Company, Genentech Inc., Gilead Sciences Inc., GlaxoSmithKline PLC, Innocrin Pharmaceuticals Inc., IQVIA Inc., Janssen Pharmaceuticals, Inc., Kantar Health, MDxHealth, Merck & Co., Inc., Myriad Genetic Laboratories, Inc., Novartis International AG, and Parexel International Corporation through the University of Utah or Western Institute for Veteran Research outside the submitted work. The other authors indicated no financial relationships.

Author Contributions

Conception/design: N.G.N., I.P.G., K.N.M., J.A.L. Provision of study material or patients: M.J.K., S.L.D., I.P.G., J.A.L. Collection and/or assembly of data: R.H., P.R.A., T.A.F., C.P., M.J.K., S.L.D., J.A.L. Data analysis and interpretation: L.F.V., N.G.N., R.H., P.R.A., T.A.F., C.P., K.Y., B.S.R., M.J.K., S.L.D., I.P.G., K.N.M., J.A.L. Manuscript writing: N.G.N., L.F.V., K.Y., B.S.R., M.J.K., I.P.G., K.N.M., J.A.L. Final approval of manuscript: All authors.

Data Availability

The data underlying this article cannot be shared publicly due to privacy.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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