AWARD NUMBER: W81XWH-19-1-0303

TITLE: Genomic and Biological Risk Prediction of Aggressive and Lethal Prostate Cancer in African American Men

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REPORT DATE: August 2021

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
August 2021	Annual	01Aug2020-31Jul2021

4. TITLE AND SUBTITLE

Genomic and Biological Risk Prediction of Aggressive and Lethal Prostate Cancer in African American Men

5a. CONTRACT NUMBER
W81XWH-19-1-0303

5b. GRANT NUMBER
FY18 New Start PC180956

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The University of Miami Miller School of Medicine, Sylvester Comprehensive Cancer Center

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
None

14. ABSTRACT
Despite robust and consistent evidence showing African-American men have poorer prostate cancer-specific outcomes, risk stratification tools (based on prostate-specific antigen, Gleason score, and tumor stage) are not currently able to incorporate racial disparities in a clinically meaningful way and identifying which men are at an increased risk of lethal prostate cancer remains a major challenge to the field. To this end, the purpose of this project is to develop a novel genomic/biological risk prediction approach to prostate cancer in men of African descent by identifying and developing a genomic signature/risk-classifier that is predictive of aggressive and potentially lethal prostate cancer. The resulting genomic/biological signature could identify African-descent men most likely to be at risk of lethal prostate cancer. We proposed to do this by: Aim 1: Identify and validate scenarios where current prostate cancer risk assessment tools are least prognostic in African-American men. Aim 2: Identify and characterize the prostate cancer genomic risk profile in African-descent men compared with European-descent men, particularly in clinical scenarios identified in Aim 1. Aim 3: Incorporate the findings from AIMs 1 and 2 into the development of a genomic-risk classifier/biomarker signature that is targeted toward the prediction of aggressive and potentially lethal prostate cancer in men of African descent and to determine whether the signature adds prognostic value to current clinical nomograms. Preliminary work from this grant has demonstrated that there could be genomic differences observed by race, particularly in metastatic disease: in a study of over 2k patients, Black men were most likely to have AR alterations, DDR alterations, and alterations in targetable genes (Mahal, NEJM 2020). My more recent work in partnership with Foundation Medicine has shown in a study of nearly 12k patient with advanced PCa that there are ancestry-specific mutational landscapes were observed, however alteration prevalence in AR, DNA damage response pathway, and other actionable genes were similar across ancestry (this is currently under Review at Lancet).

15. SUBJECT TERMS
Prostate cancer, Disparities, Cancer Disparities, Genomics, Translational Epidemiology

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	9	19b. TELEPHONE NUMBER *(include area code)*

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1. Introduction

Despite robust evidence suggesting African-descent men have a higher risk of dying from prostate cancer compared to other men, clinical tools used to predict prognosis are not currently able to incorporate race to predict which men may be at the highest risk of lethal forms of prostate cancer. This is mostly due to genomic efforts being highly Eurocentric, which as a form of structural bias, has the potential to widen prostate cancer disparities. As such, clinical tools used to determine prognosis and guide treatment recommendations that have been developed based on studies that have historically underrepresented the African-descent population are still applied to men of African descent. These prognostic tools do poorly in predicting which men of African descent may be most at risk of lethal disease and therefore may contribute to disparities in prostate cancer outcomes. Furthermore, current prognostic tools/nomograms have proven to be suboptimal in predicting the patients with potentially inherently aggressive biology which may be at risk of lethal prostate cancer. To date, there are no specific risk prediction tools that have been developed for men of African descent, and the biology and genomics of prostate cancer in African-descent men is not well characterized. To this end, the purpose of this project is to develop a novel genomic/biological risk prediction approach to prostate cancer in men of African descent by identifying and developing a genomic signature that can predict for aggressive and potentially lethal prostate cancer. This project will utilize rich data from several large data sources and registries to evaluate the impact of genetic biomarkers and other clinical factors on the risk of lethal prostate cancer in men of African descent. The resulting genomic findings could help improve currently used clinical tools to identify African-descent men most likely to be at risk of lethal prostate cancer.

2. Keywords

Prostate cancer, Disparities, Cancer Disparities, Genomics, Translational Epidemiology, Community Outreach

3. Accomplishments

Please note that the project timeline has been altered for a few reasons that are described in greater detail under “Changes/Problems”: 1) I was recruited to The University of Miami Miller School of Medicine (UM), Sylvester Comprehensive Cancer Center (SCCC) as Assistant Director of Community Outreach and Engagement in the middle of the pandemic (July 2020) and therefore I put hiring on hold anticipating a transfer. 2) I had a 2 month leave for multiple surgeries due to a sinus surgery complication. 3) The week I returned from my two month leave, research operations were halted at DFCI due to the COVID pandemic. 4) I ultimately transferred to UM-SCCC in July, 2020—and in doing so, I requested an extension on my award period given I did not use any of my funds through these major barriers that occurred during the initial award period.

Regardless, through these hurdles, I was able to make significant progress through the transfer process and in my early time at UM-SCCC.

A. Regarding research specific tasks, the following provides updates on completed tasks related to the project.

	Specific Aim 1: To identify and validate scenarios where current prostate cancer risk assessment tools are least prognostic in African-American men.	
Major Task 1: Identify clinical scenarios where disparities are greatest and where current clinical nomograms are least prognostic in African-American men.	**Months**	**Status**
Subtask 1 (**for Aims 1-3**): Prepare Regulatory Documents.		
Coordinate with site for IRB protocol submission.	1-3	This was initially completed at DFCI and has now been completed at UM-SCCC after transfer

Coordinate with site for local IRB review.	1-3	This was initially completed at DFCI and is currently under review at UM-SCCC.
Coordinate with site for Military 2nd level IRB review (USAMRMC/ORP/HRPO)	1-6	Completed at UM.
Subtask 2: Coordinate data collection in preparation for data analysis.		
Milestone Achieved: Data collected, curated, and primed for analyses to address Aim 1.	6-9	Milestone achieved. We have collected data from AACR project GENIE and I have recently signed an agreement with Foundation Medicine to access over 12k prostate cancer samples, including over 1k men with African ancestry. This was used for analyses related to this study.
Subtask 3: Data Analysis		
Develop a comprehensive multivariable Fine-Gray competing risks regression model to evaluate the combined effects of clinical risk predictors on PCSM by race in various cohorts (described in Biostatistical plan) including SCORE (N>1000) and CPDR (N>4,000) cohorts.	9-12	Completed during transfer period.
Fit a model that uses the predictive score in existing models (that is, the summation of log relative hazards multiplied by the predictors) as the risk predictors. These analyses can help us understand the performance of existing clinical nomograms in African-descent populations.	9-12	Completed during transfer period.
Milestones Achieved: clinical scenarios where disparities are greatest are identified and results are reported in abstract and manuscript form. The findings inform areas of focus for Aims 2 and 3.	12	Completed during transfer period.
Specific Aim 2: To identify and characterize the prostate cancer genomic risk profile in African-descent men compared with European-descent men, particularly in clinical scenarios identified in Aim 1.		
Major Task 2: Characterize genomic risk profile in African-descent men.	**Months**	**Status**
Subtask 1: Prepare Regulatory Documents.		
Complete all tasks related to regulatory documents as listed above under Subtask 1, specific aim 1.	1-6	Ongoing, as per above
Subtask 2: Coordinate data collection in preparation for data analysis.		
Collect and curate data.	6-12	Completed, as per above
Milestone Achieved: Data collected, curated, and primed for analyses to address Aim 2.	12	Completed, as per above
Subtask 3: Data Analysis		
Develop relative African ancestry scores to address potential heterogeneity within the gene-pool of the African-descent population.	12-15	These analyses are now completed through collaboration with Foundation Medicine.
Use prostate cancer biosamples from the SCORE (N=775 banked tumor blocks for African-descent men) and CPDR (N=545 banked tumor blocks for African-descent men) cohorts to perform comparative genomic analysis of Gleason score-matched cases in tumors from African compared to European-descent patients and establish racial differences in genomic risk profiles, particularly in clinical scenarios identified in aim 1.	12-18	We ultimately increased the sample size to over 12k patients from Foundation Medicine's genomic database. These analyses are now completed through collaboration with Foundation Medicine.
Milestone Achieved: Similarities and/or differences in biomarker expression patterns will allow us to identify genetic factors that may contribute to disparities in aggressive prostate cancer. Any observed racial differences in biomarker expression patterns may lead to the discovery of a novel biomarker profile unique to men of African descent.	18	These analyses are now completed through collaboration with Foundation Medicine.
Milestone Achieved: The findings are reported in abstract and manuscript form.	18	Presented as a scientific abstract at ASCO 2021 as an oral abstract: "Ancestral characterization of the genomic landscape, comprehensive genomic profiling utilization, and treatment patterns may inform disparities in advanced prostate cancer: A large-scale analysis."
Specific Aim 3: To incorporate the findings from Aims 1 and 2 into the development of a genomic-risk classifier/biomarker signature that is targeted toward the prediction of aggressive and potentially lethal prostate cancer in men of African descent and to determine whether the signature adds prognostic value to current clinical nomograms.		
Major Task 3: Identify a genomic-risk classifier/biomarker signature for men of African descent.	**Months**	**Status**
Subtask 1: Prepare Regulatory Documents.		
Complete all tasks related to regulatory documents as listed above under Subtask 1, specific aim 1.	1-6	Completed as per above
Collect and curate data.	6-12	Completed, as per above
Milestone Achieved: Data collected, curated, and primed for analyses to address Aim 2.	12	Completed, as per above
Subtask 3: Data Analysis		
Utilize the transcript/gene expression and alternative splicing abundance measures to identify biomarkers that differ by race using logistic regression.	18-24	Planned for this final year of award
Combine the significant biomarkers, utilizing biological information and published literature to partially winnow the space of potential biomarkers, to create a gene signature.	18-24	Planned for this final year of award
Perform Time-dependent Receiver Operating Characteristic analyses.	18-24	Planned for this final year of award
Examine the incremental value of a biomarker for PCSM by evaluating the relationship of each biomarker one at a time with PCSM using Fine-Gray competing risks regression analysis adjusted for standard risk predictors.	18-24	Planned for this final year of award
Milestone Achieved: Discovery of novel tumor biomarker signature(s) for men of African descent that will be immediately translatable in the clinical setting as predictive tools.	24	Planned for this final year of award
Milestone Achieved: Publication of findings in abstract and manuscript form.	24	Planned for this final year of award

B. Furthermore, for training specific tasks, I have:

- Attended scientific research workshops to help develop a better understanding of biomarker development and cancer genetic epidemiology.
- Participated in a private and tailored educational curriculum to continue training in biomarker development and cancer genetic epidemiology.
- Received weekly formal didactic/teaching sessions (from my mentors) in applying methods from epidemiology, statistics, molecular biology, and classical genetics toward translational research.
- Collaborate with and acquire skills from Dr. Rebbeck's (mentor) close network of epidemiologists, biostatisticians, translational research scientists and clinicians, and basic scientists.
- Attended and presented research at weekly/monthly research group meetings. I now Host my own lab meetings with presentations at UM-SCCC.
- Prepared manuscripts relevant to biomarker development and cancer genetic epidemiology in prostate cancer disparities.

C. From the above described progress on goals, I was able to publish a major manuscript in NEJM:

1. Racial Differences in Genomic Profiling of Prostate Cancer. **Mahal BA**, Alshalalfa M, Kensler KH, Chowdhury-Paulino I, Kantoff P, Mucci LA, Schaeffer EM, Spratt D, Yamoah K, Nguyen PL, Rebbeck TR. **N Engl J Med.** 2020 Sep 10;383(11):1083-1085. doi: 10.1056/NEJMc2000069. PMID: 32905685

The study examined tumor genomic profiles across race in a novel diverse cohort. Specifically, next generation sequencing tumor genomic data obtained from patients treated for prostate cancer at either MSKCC or DFCI were extracted from the AACR Project GENIE-v7.0 registry (released January, 2020). Mutational profiles of 474 genes were examined by race (White, Black, Asian) and stage (primary versus metastatic)[4]. The Benjamini-Hochberg method was used to control for false discovery rate (FDR). Notable findings were that in In metastatic cases, 6.8% of Black men had >20 mutations. AR mutations occurred more often in Black (18.3%) compared with White men (8.1%, PropDiff 0.10[0.01-0.19], P=0.004). TP53 mutations occurred more often in Asian (62.0%) compared with Black (22.5%, PropDiff 0.40[0.21-0.58], P=0.008) and White men (36.4%, PropDiff 0.26[0.10-0.41], P=0.004). DNA repair and actionable gene mutations occurred more often in Black (22.5% and 26.7%, respectively) compared with White men (15.6%, PropDiff 0.07[-0.01 - 0.18], and 18.0%, PropDiff 0.09[0.00-0.20], respectively) (P=0.05 for both). BRAF mutations also occurred more often in Black compared with White men (7.0% versus 1.5%, PropDiff 0.05[0.00-0.10], P=0.002).

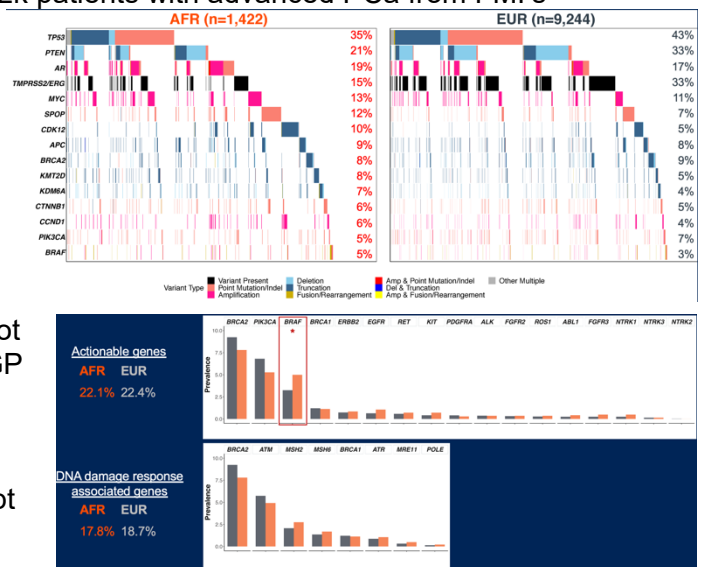
This work was also presented at the 2020 Prostate Cancer Foundation annual retreat and at the 2020 SUO (Society for Urological Oncology) meeting.

I have gained recognition for this work, and other accomplishments as a direct result of this work include me being invited to serve on several expert committees and panels, including The Lancet Commission on Prostate Cancer, American Cancer Society (ACS) National Advisory Team on Prostate Cancer Disparities, AdMeTech Blue Ribbon Expert Panel, and Prostate Cancer Foundation Disparities Working Group.

More recently, I was able to publish an oral abstract at ASCO:

2. **Ancestral characterization of the genomic landscape, comprehensive genomic profiling utilization, and treatment patterns may inform disparities in advanced prostate cancer: A large-scale analysis.** Smruthy Sivakumar, Jessica Kim Lee, Jay A. Moore, Julia Hopkins, Justin Newberg, Alexa Betzig Schrock, Randy Vince, Idalid Ivy Franco, Crystal Selesteen Seldon, JENNIFER MILLS, Jeffrey Michael Venstrom, Brandon Arvin Virgil Mahal. ASCO 2021 (Genitourinary Cancer- Prostate, Testicular, and Penile).

In this study, I have partnered with Foundation Medicine to characterize the genomic landscape, comprehensive genomic profiling (CGP) utilization patterns, and treatment patterns across ancestry in a large, diverse advanced PCa cohort. Specifically, examining nearly 12k patients with advanced PCa from FMI's genomic database, ancestry-specific mutational landscapes were observed, however alteration prevalence in AR, DNA damage response pathway, and other actionable genes were similar across ancestry (Figures to the right). Ancestry-specific mutational landscapes were observed, however alteration prevalence in AR, DNA damage response pathway, and other actionable genes were similar across ancestry. AFR men received CGP later in their treatment course and were less likely to go on trial after CGP. Ultimately, these findings suggest differences in biology may not be a significant driver of disparities in advanced PCa. Later CGP utilization and lower rate of clinical trial enrollment observed in AFR men could further impact genomics, outcomes, and ultimately disparities (this study was presented as a scientific oral at ASCO 2021 and has been submitted as a full manuscript and is under first round of **revisions at Lancet).**



4. Impact

The above described work suggests that though there may be race/ancestry specific genomic landscapes, clinically significant alterations likely to not account for prostate cancer disparities Later CGP utilization and lower rate of clinical trial enrollment observed in AFR men could further impact genomics, outcomes, and ultimately disparities. This could have implications for prognosis, therapy response, and enrollment of minority populations in clinical trials and precision oncology studies. Our future studies will incorporate fractional ancestry and attempt to develop genomic risk signatures across ancestry.

5. Changes/Problems

As described above, the project timeline has been altered for several reasons: 1) I was recruited to The University of Miami Miller School of Medicine (UM), Sylvester Comprehensive Cancer Center (SCCC) as Assistant Director of Community Outreach and Engagement and therefore I put hiring on hold anticipating a transfer. 2) I had a 2 month leave for multiple surgeries due to a sinus surgery complication. 3) The week I returned from my two month leave, research operations were halted at DFCI due to the COVID pandemic. 4) I ultimately transferred to UM-SCCC in July, 2020—and in doing so, I requested an extension on my award period given I did not use any of my funds through these major barriers that occurred during the initial award period.

Despite these challenges, I was able to work independently self-teach many critical aspects of bioinformatics, and through my transfer I was able to complete a major project as described above. Furthermore, given my transfer, it may be difficult for me to obtain specimens allocated to DFCI. Therefore, I formed a relationship with Foundation Medicine who I collaborated with to complete many aspects of this proposal (including analyses for over 12k prostate cancer samples).

Given these challenges, I did not spend funds during my first year, and requested a one-year extension.

6. Products

Publications:

1. Racial Differences in Genomic Profiling of Prostate Cancer. **Mahal BA**, Alshalalfa M, Kensler KH, Chowdhury-Paulino I, Kantoff P, Mucci LA, Schaeffer EM, Spratt D, Yamoah K, Nguyen PL, Rebbeck TR. **N Engl J Med.** 2020 Sep 10;383(11):1083-1085. doi: 10.1056/NEJMc2000069. PMID: 32905685
2. **Ancestral characterization of the genomic landscape, comprehensive genomic profiling utilization, and treatment patterns may inform disparities in advanced prostate cancer: A large-scale analysis.** Smruthy Sivakumar, Jessica Kim Lee, Jay A. Moore, Julia Hopkins, Justin Newberg, Alexa Betzig Schrock, Randy Vince, Idalid Ivy Franco, Crystal Selesteen Seldon, JENNIFER MILLS, Jeffrey Michael Venstrom, Brandon Arvin Virgil Mahal. ASCO 2021 (Genitourinary Cancer- Prostate, Testicular, and Penile).

7. Participants & Other Collaborating Organization

Name:	*Mohammed Alshalalfa, PhD*
Project Role:	*Computation Biologist/Bioinformatician/Collaborating Scientist*

Researcher Identifier (e.g. ORCID ID):	0000-0001-8405-3035
Nearest person month worked:	*5*
Contribution to Project:	*Mohammed has assisted with critical aspects of bioinformatics on this project.*
Funding Support:	*Mohammed is being funded by this project.*

Name:	*Foundation Medicine*
Project Role:	*Collaborating Organization*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0 (new relationship as of 12/2020)
Contribution to Project:	*Provided over 12k samples for analyses*
Funding Support:	*N/A*

8. Special Reporting Requirements

N/A

9. Appendices

The PDF documents for the publication described in “Products” is submitted along with this report.