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TITLE: Do Black Men with Metastatic Castration-Resistant Prostate Cancer Have Worse Outcomes Than White Patients? A Nationwide VA Study

PRINCIPAL INVESTIGATOR: Jun Gong, MD

CONTRACTING ORGANIZATION: Cedars-Sinai Medical Center

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Jun Gong, MD

E-Mail: Jun.Gong@cshs.org

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Cedars-Sinai Medical Center
8700 Beverly Blvd, MOT
Los Angeles, CA 90048
USA

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14. ABSTRACT

Black men have a higher prostate cancer (PC) risk and mortality than white men. Whether these differences are due to lack of access to care or more aggressive biology is debated. However, a few small studies suggested black men may actually have better outcomes than white men when treated with metastatic castration-resistant PC (mCRPC) drugs. We hypothesize that black men with mCRPC will have similar responses to modern mCRPC therapies but worse compliance; after accounting for poorer compliance, black men will actually have better responses to these therapies than white men. Our objective is, to create a true nation-wide cohort from the Veterans Affairs (VA) Health System. Our preliminary analyses identified 46,535 men treated with one of 6 drugs for mCRPC (Cabazitaxel, Docetaxel, Abiraterone, Enzalutamide, Radium-223, and Sipuleucel-T). We will 1. Determine drug efficacy among black and white men with mCRPC; 2. Determine drug compliance among black and white men with mCRPC; and 3. Determine drug efficacy among black and white men with mCRPC after accounting for compliance.

15. SUBJECT TERMS NONE LISTED

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INTRODUCTION

Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Black men have a higher prostate cancer (PC) risk and mortality vs. white men. Whether these differences are due to lack of access to care or more aggressive biology is debated. In an equal access setting, we found black men had more PC, higher-grade PC, and more recurrences after surgery, arguing for more aggressive disease in black men. However, though we found recurrences after surgery were greater in black men, after adjusting for baseline disease differences, race was unrelated to recurrence or long-term outcomes (metastasis or PC death). Similarly, among men who failed surgery and received androgen deprivation therapy (ADT), long-term outcomes were unrelated to race (Vidal et al, Cancer 2019). This suggests, that when baseline differences are accounted for and men receive equal treatments, black men can experience similar outcomes as white men. Whether this is true for men with metastatic castration-resistant prostate cancer (mCRPC) receiving one of the new life-prolonging therapies is unknown. For the first time, we will test whether properly treated mCRPC black men have similar (or better) responses than white men. Importantly, understanding treatment patterns, efficacy, and adherence of life prolonging therapies for mCRPC by race is necessary not only to design rationale approaches to reducing PC health disparities, but also to help clinicians trying to decide the best drug to give to a man newly diagnosed with mCRPC based on race. To fulfill this goal, we are creating a true nation-wide cohort from the Veterans Affairs (VA) Health System. Our preliminary analyses identified 39,925 men treated with one of 6 drugs for mCRPC (Cabazitaxel, Docetaxel, Abiraterone, Enzalutamide, Radium-223, and Sipuleucel-T).

KEYWORDS

Provide a brief list of keywords (limit to 20 words).

Prostate cancer; metastatic castration-resistant prostate cancer (mCRPC); race; Veterans

ACCOMPLISHMENTS

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

SOW Major Goals (as proposed in 2019):

STATEMENT OF WORK – 10/11/2018
PROPOSED START DATE October 1, 2019

Site 1: Cedars-Sinai Medical Ctr
8700 Beverly Blvd
Los Angeles 90048
Dr. Jun Gong

Site 2: Durham VA
Durham, NC 27707
PI: Jun Gong (JG)
Co-I: Stephen Freedland

Specific Aim 1: Determine drug efficacy among black and white men with mCRPC	Timeline	Site 1	Site 2
Major Task 1: Data Collection & Preparation	Months		
Subtask 1: Abstract data of all men with mCRPC	1-12	Dr. Gong	Data Operations Manager, Michael Burns, under JG supervision
Subtask 2: Create a SQL server database, managed using Microsoft SQL Management Studio	1-12	Dr. Gong	Michael Burns, under JG supervision
Milestone Achieved: Preparation of large dataset including drugs used	1-12		

Major Task 2: Statistical Analysis			
Subtask 1: Conduct statistical analyses	13-23	Dr. Gong	Jessica Janes, under JG supervision
Subtask 2: Interpret results	13-23	Drs. Gong, Freedland	Drs. Freedland, Gong
Subtask 3: Archive datasets for future analyses and future patient follow-up.	18-23	Dr. Gong	Michael Burns
Milestone Achieved: Create the largest dataset on mCRPC by race. Manuscript preparation			

Aim 1: Determine drug efficacy among black and white men with mCRPC. We will use the largest integrated health system in the US: The Veterans Health Administration. We will retrieve data on mCRPC therapies including Cabazitaxel, Docetaxel, Abiraterone, Enzalutamide to compare drug efficacy among black and white men. Too few men were treated with Radium-223 or Sipuleucel-T for analysis. Drug efficacy will be measured as PSA maximum decline. We hypothesize black and white men have similar responses to mCRPC therapies.

Major Task 1: 1-12 First Months (First Year Progress Report): Data collection and Preparation.

Major Task 2: 13-23 Months (Second Year Progress Report): Statistical Analysis.

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1. **Major Activities – *Aim 1***

As proposed in the SOW, in the first year of this award, we focused on the Tasks proposed for Aim 1, please see SOW for Aim 1 above. As the SOW indicates, in the first 12 months of this study we conducted Data Collection and Preparation for the study, a major, time-consuming work. Below we expand on the work completed so far:

a) Local Durham VA Health Care system IRB approval, as well as VA Informatics and Computing Infrastructure (VINCI) approval, have been obtained so that we may proceed with all study activities, with all personnel required to complete these tasks.

b) Data collection has been completed as concerns for the objectives of Aim 1, as planned in the SOW.

	Table 1. Number of Patients with mCRPC treated at the VA			
	No record or other race	**Black**	**White**	**Total x Treat**
Distinct Patients x Race	5,727	7,737	26,461	39,925
Number of Patients (Patients can be counted multiple times)				
Cabazitaxel	60	215	484	759
Docetaxel	4008	2818	13205	20031
Abiraterone	1276	2822	9768	13866
Enzalutamide	812	2054	6812	9678

Table 1 shows the preliminary numbers of all men available to us within VINCI, reflecting treatment for mCRPC at National VA centers, since January 1, 2000. The data queries developed for mCRPC drugs resulted in a dataset of 39,925 men; of these, 11,474 received first treatment of Abiraterone; 20,201 with Docetaxel; and 5,136 with Enzalutamide. As we anticipate that the majority of mCRPC men receiving therapy within the VA system are regular users, these 39,925 men will be our analytic cohort and represents the largest cohort ever studied for mCRPC health disparities.

This cohort was initially identified using prostate cancer diagnosis ICD codes. Patients with a prostate cancer diagnosis code were then evaluated for metastatic, castrate-resistant disease based on a series of queries that classify a patient as (1) metastatic, (2) castrate, and/or (3) castrate resistant. Castrate resistance is determined by comprehensively evaluating hormone therapy treatment cycles and/or an orchiectomy procedure in conjunction with PSA lab results.

Patients who received abiraterone and/or enzalutamide treatments were classified as mCRPC patients. Patients identified as mCPRC were further evaluated for receipt of cabazitaxel and/or docetaxel treatments.

Treatments were identified using a combination of CPT codes and pharmacy data.

c) In addition to the queries developed to determine the data in Table 1, queries have been developed to determine information across a variety of our data elements of interest, notably for: demographic data, including race and age; and certain lab(s)/lab results, including prostate specific antigen (PSA), variables that will be used in the statistical analysis.

d) The NLP race model our team developed for this project, is a regular expression, race classifier paradigm utilizing a majority vote approach to output final results; this strategy has been adopted because within an individual patient there may exist n number of provider notes, each of which may have race reported differently, dependent upon a variety of factors. In addition to the race model, a prostate cancer metastasis model has also been generated, trained, and developed, and which employs a binomial (positive, negative) logistic regression paradigm. This logistic regression model uses keywords and keyword modifiers, extracted through provider and scan/radiology note sentence parsing to then assign a classification of “positive” or “negative” scan.

Site 1: Cedars-Sinai Medical Ctr
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Los Angeles 90048
PI: Dr. Jun Gong

Site 2: Durham VA
Durham, NC 27707
PI: Jun Gong (JG)
Co-I: Stephen Freedland

Specific Aim 2: Determine drug compliance among black and white men with mCRPC			
Major Task 1: Prepare data for analysis drug compliance by race			
Subtask 1: Retrieve data on compliance by measuring the relative dose intensity, which is calculated as a function of dose and frequency of administration. We will also determine whether the duration of drug therapy and time until next therapy differs between black and white men.	6-12	Dr. Gong	Data Operations Manager, Michael Burns, under JG supervision
Subtask 2: Analyze data on whether drug compliance differs by race	13-24	Drs. Gong, Freedland	Jessica Janes, under JG supervision
Milestone(s) Achieved: Largest study ever to address drug compliance for mCRPC by race			
Specific Aim 3: Determine drug efficacy among black and white men with mCRPC after accounting for compliance.			
Major Task 1: Prepare data for analysis			
Subtask 1: Ascertain response to drug, measured as PSA maximum decline, after accounting for compliance. Subtask 2: Analyze data and adjust for potential confounders including age, comorbidities, socioeconomic status, VA center, but also Gleason score, and primary treatment received	10-14 14-24	Dr. Gong Freedland Dr. Gong Freedland	Drs. Freedland, Gong Jessica Janes, under Drs. Freedland, Gong supervision
Milestone(s) Achieved: Determine drug efficacy for mCRPC by race in the largest dataset ever created.			

Aim 2: Determine drug compliance among black and white men with mCRPC. Among men given a mCRPC life-prolonging drug, we will determine compliance by measuring the relative dose intensity, which is calculated as a function of dose and frequency of administration. We will also determine whether the duration of drug therapy and time until next therapy differs between black and white men. We hypothesize black men have reduced compliance to mCRPC therapies vs. white men.

Major Task 1:
Subtask 1: 1-6 Months (First Year Progress Report): Prepare data for analysis on drug compliance by race
Subtask 2: 13-23 Months (Second Year Progress Report): Statistical Analysis

1. **Major Activities – *Aim 2:***

As proposed in the SOW, in the first year of this award, we focused on the Tasks proposed to conduct in the first year of the award for Aim 2, as detailed in SOW above. As the SOW indicates, in the first 6 months of this study we conducted Data Preparation for analysis on drug compliance by race, a major, time-consuming work. Below we expand on the work completed so far:

a) We have retrieved data on compliance by measuring the relative dose intensity, which is calculated as a function of dose and frequency of administration.

b) We have calculated the duration of drug therapy and time until next therapy in each race group.

Aim 3: Determine drug efficacy among black and white men with mCRPC after accounting for compliance. Among the men described in Aims 1 and 2, we will analyze response to drug, measured as PSA maximum decline, *after* accounting for compliance. We hypothesize response to therapy after accounting for compliance, is better in black men compared to white men.

Major Task 1:
Subtask 1: 10-14 Months (First Year Progress Report): Prepare data for analysis
Subtask 2: 14-24 Months (Second Year Progress Report): Statistical Analysis

1. **Major Activities – *Aim 3:***

As proposed in the SOW, in the first year of this award, we focused on the Tasks proposed for Aim 3, as detailed in SOW for Aim 3 above. As the SOW indicates, in the first 14 months of this study we ascertained response to drug, measured as PSA maximum decline, after accounting for compliance. Below we expand on the work completed so far:

a) We determined the percent of patients experiencing a $\geq$ 30% maximum decline in PSA, a level that approaches surrogacy for explaining the survival benefits of androgen receptor (AR) targeted therapy and had a high degree of surrogacy for docetaxel treated patients.

2. **Specific Objectives – *Aims 1-3:***

The specific objectives for Aims 1-3 were to obtain all the data and create the database to conduct analysis. As described in Major Activities for Aim 1, we collected and prepared the data needed for the analysis of determining drug efficacy among black and white men with mCRPC; for Aim 2, we collected the data on compliance, the duration of drug therapy and time until next therapy in each race group; for Aim 3, we collected data on drug response by race group.

3. **Significant Results - *Aims 1-3:***

We have achieved significant results as scheduled in the SOW timeline, i.e. we have collected all data as expected. However, at this point, a comprehensive dataset has not been finalized. As stated in the SOW, we anticipate to conducting statistical analyses during the following year of this award. Prior to conducting the respective statistical analyses, we plan to update the dataset and cohort for this study to be inclusive of more contemporary patients. This will allow for an increase total cohort size and further supplement the results and manuscript with more up-to-date data.

Over the past year we have continued work on increasing the accuracy of our prostate cancer metastasis NLP model by reducing the false positive rate. This NLP model will now be re-run upon refresh of this cohort to identify metastatic patients more accurately moving forward.

4. Other achievements:

An additional study coordinator and additional biostatistician personnel have been onboarded to the Durham VA study team. These individuals will assist in carrying out the project efforts from here until study closure.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Ruixin Yang, our data scientist, has recently published a manuscript describing one of the machine learning models being used in this study. He worked under the guidance of Dr. Zachary Klaassen, a VA urologist.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We plan to refresh the study cohort to be inclusive of more contemporary patients and increase the size and accuracy of the dataset. After this, our next step will be to apply the queries and NLP models above-mentioned to the study cohort, to develop a comprehensive dataset. This is a computationally intensive process given the size of the cohort (~40,000 men) and complexity of the data returned, which will require considerable quality assurance. Once the dataset is generated, the PI and statistician will perform quality assurance measures and begin analysis. We anticipate the statistical analysis will be conducted well before the end of the following year of this grant.

IMPACT

D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal

disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

As we have not finished analyzing the data, no impact on society has yet been achieved. However, we expect our results will impact the treatment of late stage prostate cancer, specifically mCRPC for black Veterans.

Thus, nothing to report at this time.

CHANGES/PROBLEMS

The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Within the prior year we have postponed work on this project due to a required change in PI. This recent change in PI to Dr. Jun Gong has now been completed. While awaiting this change we have not completed any further work in the past few months after initial cohort identification while awaiting this PI change implementation and other requests. We awaited completion of this in order to pull the most updated cohort and follow-up data for analysis. In addition, prior to refreshing and finalizing the dataset we wished to further improve our NLP identification, limiting the number of false positives, which has now been completed.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

N/A

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

N/A

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

N/A

PRODUCTS

List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

The manuscripts listed below are related to this project, however, not directly funded with this DoD award. These studies, from our group, helped move the field forward in terms of mCRPC and racial disparities, the main topic of this award. Thus, this is why I have decided to include them in this report.

1. Validation of a genomic classifier for prediction of metastasis and prostate cancer-specific mortality in African-American men following radical prostatectomy in an equal access healthcare setting. Howard LE, Zhang J, Fishbane N, Hoedt AM, Klaassen Z, Spratt DE, Vidal AC, Lin D, Hitchins MP, You S, Freeman MR, Yamoah K, Davicioni E, **Freedland SJ**. Prostate Cancer Prostatic Dis. 2019 Dec 16. doi: 10.1038/s41391-019-0197-3. Online ahead of print. PMID: 31844180.
2. Racial Discrepancies in Overall Survival among Men Treated with ^{223}Radium. Zhao H, Howard LE, De Hoedt A, Terris MK, Amling CL, Kane CJ, Cooperberg MR, Aronson WJ, Klaassen Z, Polascik TJ, Vidal AC**, Freedland SJ.** J Urol. 2020 Feb;203(2):331-337. doi: 10.1097/JU.0000000000000524. Epub 2019 Sep 3. PMID: 31479407
3. Yang R, Zhu D, Howard LE, De Hoedt A, Williams SB, Freedland SJ, Klaassen Z. Identification of Patients With Metastatic Prostate Cancer With Natural Language Processing and Machine Learning. JCO Clin Cancer Inform. 2022 Oct;6:e2100071. doi: 10.1200/CCI.21.00071. PMID: 36215673.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

N/A

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

N/A

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

N/A

- **Technologies or techniques**
  N/A

- **Inventions, patent applications, and/or licenses**
  N/A

- **Other Products**
  N/A

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project? Site I

Name: *Jun Gong*
Project Role: *Principal Investigator*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: ***0.36***
Contribution to Project: *Leads the project*
Funding Support:
Name: *Candace Hamann*
Project Role: *Data Technician*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: ***0.72***
Contribution to Project: *Data processing*
Funding Support:
Name: *Stephen Freedland*
Project Role: *Co-Investigator*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: ***0.60***
Contribution to Project: *Guidance and expertise*
Funding Support:

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners? (Subcontract, Site 2)

Organization Name: Durham VA Health Care System (DVAHCS)/Institute for Medical Research (IMR)
Location of Organization: Durham, North Carolina
Partner's contribution to the project: The team at DVAHCS/IMR provides database development, protocol/regulatory, and data analysis support.

SPECIAL REPORTING REQUIREMENTS

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

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

APPENDICES

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