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TITLE:
Defining Mutations of DNA Repair Genes in Prostate Cancer Patients Towards Enhancing Treatment

PRINCIPAL INVESTIGATOR:
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RECIPIENT:
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Fort Detrick, Maryland 21702-5012

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DEFINING MUTATIONS OF DNA REPAIR GENES IN PROSTATE CANCER PATIENTS TOWARDS ENHANCING TREATMENT

DNA damage repair genes (DDRGS) are critical for protecting genome integrity and have been implicated in several cancer types. Recent genomic studies of metastatic castration resistant prostate cancer (mCRPC) highlight the contributions from mutations or copy number changes in DDRG alterations, including BRCA1, BRCA1, ATM, CHEK2, and MSH2. It has also been shown that prostate cancer (CaP) patients harboring inherited mutations in DDRGs may benefit from early targeted PARP inhibitor therapy. However, the association of germline mutations of DDRGS with earlier stage high risk CaP patients remains to be defined. Accumulating evidence suggest for increased association of BRCA2 mutations with more aggressive CaP. Our recent data show an association of increased frequency of BRCA2 gene mutations in CaP patients with African ancestry with elevated risk of developing metastasis. We hypothesize that AA CaP patients have an increased frequency of mutated DDRGS. We aim to assess blood derived germline DNAs of AA (N=300) and CA (N=300) CaP patients archived in USU-CPDR, Center of Excellence, for the association frequency all known DDRGs genomic alterations with disease aggressiveness (based on pathologic grade, pathologic stage, time to recurrence/metastasis, family history and African ancestry). The results will be assessed to refine patient stratification for specific targeted therapy. Longer term implication of this project will impact early targeted therapy to reduce of racial disparity in CaP, given a higher anticipated rate of DDRG mutations in AA CaP patients. Within the DOD context, outcome of this research strategy will be valuable for developing approaches to reduce mutagenic exposures of affected service members and have a broader impact on other inherited cancers.
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1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

This study, the first of its kind, will provide ground breaking data on inherited defects of genome associated with aggressive prostate cancer (CaP) with focus on comparative status of DNA damage repair genes (DDRGs) in African American (AA) and Caucasian American (CA) CaP patients treated under equal access MHS. DDRGs play a critical role in protecting genome integrity and have been implicated in several cancer types. Recent studies demonstrate that PARP inhibitors (inhibiting single strand DNA break repair), such as Olaparib, can slow progression-free survival and extend overall survival in patients with BRCA1/2 mutations.

The goal of this proposal is to identify and evaluate all DDRG germline mutations, along with other germline cancer driver mutations, in AA CaP patients, which may provide critical information for treatment stratification and targeted therapy of this disparately affected patient population.

A) Perform an in-depth evaluation of germline mutations in all DDRGs (over 100 genes), and other cancer driver genes, in a large DOD cohort of AA (N=300) and CA (N=300) CaP patients

B) Assess DDRG mutation data, with emphasis on understudied AA CaP, for association with clinical and pathological data, including disease progression, and evaluate how this information can refine patient stratification for specific targeted therapeutic options

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

Prostate cancer, DNA damage repair genes (DDRG), germline mutations, African American, racial disparity, therapeutic stratification, PARP inhibitors, disease progression, military healthcare system

3. 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.

Major Task 1: Perform an in-depth evaluation of germline mutations in all DRGs, and other cancer driver genes, in a large DOD cohort of AA and CA CaP patients

Subtasks: Evaluation of germline mutations in all DDRGs from multiple repair pathways, and other cancer driver genes, will be performed by whole genome/exome sequence analysis of archived blood DNA samples from AA (N=300), and control CA (N=300), CaP patients who underwent primary treatment at Walter Reed National Military Medical Center (WRNMMC) over the past 20 years (total N=600). Cases that are positive for germline mutations in any DDRGs will be further evaluated for somatic aberrations in the same genes using genomic DNA from matched prostate tumor specimens that are also archived at CPDR.
Major Task 2: Assess DRG mutation data, with emphasis on understudied AA CaP, for association with clinical and pathological data including disease progression, and evaluate how this information can refine patient stratification for specific targeted therapeutic options

Subtasks: All DDRG mutations will be evaluated for association with clinical and pathological data in both AA and CA CaP patients. Correlation with pathological grade and stage, as well as progression to recurrence and metastasis will be assessed. As an embedded additional focus, we will also analyze the DDRG mutation data to develop a metastasis predictive signature.

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.

Brief summary of the main steps:

• IRB protocol approval (March 2018)
• Postdoctoral Fellow recruited (April)
• Selection of the AA (N=300) and CA (N=300) patient cohorts by epidemiologist (May)
• Identification of the archived blood genomic DNA specimens (N=600) (May-June)
• Processing of the specimens by 200 cases at a time (100 AA and 100 CA) (June-July)
• QC of the specimens by Qubit (quantity) and Bioanalyzer (quality) assays (August)
• Diluting and aliquoting of the DNA samples for sequence analysis. Plates of the final QC-d DNA samples with the required concentration and amount were submitted for WGS to TAGC (September).
• Completion of the WGS at TAGC (October)
• WGS data analyses (QC and mutations) (November 2018 – May 2019)

The DNA samples submitted to TAGC were subjected to whole genome sequencing (WGS) using the top of the line NovaSeq (Illumina) platform.

600 PCR-free libraries were generated (using automation), 14 of 600 dropped out (97.6% success rate)

QC of the sequencing libraries prepared:

The successful libraries have an excellent quality based on DNA library metrics shown below (n=586). Figure 1 depicts the DNA library yields, and Figure 2 the library fragment length distribution (well over the requirement).
Figure 1. Sequencing library yield distribution

Figure 2. Sequencing library fragment length distribution
QC of the WGS sequence quality:

Whole genome **sequencing depth exceeded 37X** on average.

Mutation (SNP) analysis **identified 4 - 4.5 million SNPs** on average among samples.

Interestingly, there are **two apparent clusters** of samples within this cohort. These clusters are unassociated with sequencing depth indicating this is not a technical observation (Figure 3). Rather, these groups **associate with differential ancestry**, African American patients having higher number of SNPs.

*Figure 3. Number of SNPs form two clusters independent of depth*
Patient genotypes were projected onto principle components from reference populations. Patients were assigned a predicted ancestry based on their similarity to reference populations. Results show two large populations, a population with European ancestry and a population of African ancestry (Figure 4).

Figure 4 – DNA based prediction of patient ancestry

(AFR=African; EUR=European; AMR=American; EAS=East Asian; SAS=South Asian)

Sample ancestries were predicted by the “Peddy” program, which uses a machine learning model trained on individuals of diverse ancestries from the 1000 Genomes Project reference panel. The 584 samples of this project (square) are superimposed on 2504 from the 1000 genome samples (small dots) in the PCA plots (Figure 4).
33 ancestry mismatched samples were excluded from further analyses (Table 1). Remaining samples in AA and CA cohorts are represented by green numbers.

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*Table 1. Summary table of sample exclusion based on ancestry mismatches*

Using “ContEst” tool from Broad GATK package, 6 additional noisy samples were identified. Results from Illumina % noise sites and GATK ContEst are linearly correlated. We set ContEst at 5% as the QA cutoff. **17 samples were excluded due to higher than minimal noise level.**

*Figure 5. Combined analysis of noise, samples above the 5% cutoff line were excluded from further analysis*
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**Table 2. Clinical data and sample status summary**

Samples are sorted by race, age at diagnosis, progression to metastasis status, and Gleason grade. Excluded numbers are shown in the last column by categories. Final numbers of the best quality samples passing all QC/QA are shown under the “Freeze” column, these numbers are frozen (fixed) for the mutation analyses.
Interrogating a DNA Damage Response gene set (180 genes total) in this cohort we identified mutations in the blood that are predicted to have **non-silent effects on the protein** sequence (e.g. missense, nonsense, frameshift). Counting the number of mutant genes for each patient revealed variation in the cumulative burden across predicted ancestry groups. The African ancestry group presented with a significantly greater number of mutated genes than the European ancestry group (Figure 6).

**Figure 6. Mutation analysis of whole genome sequencing from patients with prostate cancer**

(AFRAfrican; EUR=European; AMR=American; EAS=East Asian)
Limiting to rare variants (sub 5% prevalence in this cohort), we repeated the above analysis. These results show that the African ancestry group continued to have a greater burden of rare variants in this cohort. In fact, the average number of mutations in patients with African ancestry was nearly twice compared to patients with European ancestry (Figure 7).

*Figure 7. Mutation analysis of whole genome sequencing from patients with prostate cancer, focusing on rare variants*

(AFRAfrican; EUR=European; AMR=American; EAS=East Asian)
Germline variants on 180 DNA repair genes were classified using ClinVar database and InterVar program. If a variant was called "Pathogenic" by either ClinVar or InterVar, it was considered "Pathogenic". (Figure 8).

Figure 8. Pathogenic germline variant carrier rate in prostate cancer cases
Fraction of cases carrying pathogenic variants in African Americans (left panel) and Caucasian Americans (right panel) are shown in bar plots.
As an initial comparison of germline mutations in AA with prostate cancer versus CA with prostate cancer, germline mutations were directly compared between these two groups. This preliminary analysis was restricted to predicted pathogenic mutations in DDRGs.

The number of DDRGs with germline mutation was 20 affecting 42 CA patients, and 15 affecting 84 AA patients in this cohort.

These data suggest for a dramatic difference in the frequency of germline mutations in DDRGs between AA and CA CaP patients. We detected more than twice higher frequency of germline mutations in AA patients (in 84 of 259, 32%) compared to CA patients (in 42 of 273, 15%).

The most frequently mutated genes were MLH3 (31), ATM (22) and XPC (14), all other DDRGs had mutations in less than 10 patients. Two of these three top genes (MLH3 and XPC) were unexpected based on literature data (using cohorts of primarily CA or other Caucasian patients). All three genes had germline mutations mostly in AA patients: MLH3 (in 27 AA and in 4 CA patients), ATM (in 20 AA and in 2 CA patients), XPC (in 14 AA patients and in zero CA patients).

On the other hand, FANCA was mutated only in CA patients in this cohort (in 8 CA and zero AA patients).

The distribution of mutation frequencies was also interesting and different between AA and CA cases.

In AA patients the top three DDRGs were dominant among the 15 DDRGs with germline mutation detected: MLH3 (27 patients), ATM (20 patients) and XPC (14 patients). That is 61 (72%) of 84 total cases with mutation in AA patients.

In the CA cases only one DDRG had germline mutation in more than 4 patients: FANCA (8 patients). That is 8 (19%) of 42 total cases with mutation in CA patients.

The “second tier” DDRGs (in terms of frequency) had mutations in 2-4 patients, relatively evenly distributed among AA (6 genes of the 15 total genes mutated) and CA (9 genes of the 20 total genes mutated). The “third tier” DDRGs had mutation in just one patient each in either (or both) AA and CA cases, somewhat more frequent event in CA (10 genes of 20 total genes mutated) than in AA (6 genes of 15 total genes mutated) patients.

Another unexpected result was the low frequency of germline mutations in the BRCA2 gene (1 in AA and zero in CA patients). Perhaps our cohort with early stage CaP (treated with radical prostatectomy, which is usually offered for patients with lower stage and grade localized disease) may be the reason for this.

These results reflect incident mutation rates in our prostate cancer cohort. We are currently developing methods to incorporate public domain genotyping from non-diseased individuals into this study. Challenges in this step involve normalizing our mutation data to available public domain data. Afterwards, we anticipate these results will identify race-adjusted markers of prostate cancer risk and outcome, rather than current race-associated incidence analysis.

As an illustration of how the different mutations are distributed within a gene we show the mutation map of the well characterized ATM gene (Figure 9).
Locations of pathogenic germline mutations and domains in ATM protein is shown by lollipop plots. Protein domains are obtained from Uniprot database. African American and Caucasian American cohorts are shown in the first and second panel, respectively.

In African American patients:

![Lollipop plot for African American patients]

- Telomere-length maintenance and DNA damage repair
- FAT domain
- Phosphatidylinositol 3- and 4-kinase
- FATC domain

In Caucasian American patients:

![Lollipop plot for Caucasian American patients]

- FAT domain
- Phosphatidylinositol 3- and 4-kinase
- FATC domain
- Telomere-length maintenance and DNA damage repair

**Figure 9. Pathogenic mutations in the ATM gene**

Blue lollipop: Non-synonymous substitution; Green lollipop: Synonymous substitution
The size of the lollipops is proportional with the number of mutations at that position.

**Conclusions:**

We stated in the introduction that “This study, the first of its kind, will provide ground breaking data on inherited defects of genome associated with aggressive prostate cancer (CaP) with focus on comparative status of DNA damage repair genes (DDRGs) in African American (AA) and Caucasian American (CA) CaP patients treated under equal access MHS.”

**In summary,** based on our data analyses so far (discussed above), we can already conclude that **there is a dramatic difference between AA and CA CaP patients in at least three aspects:** the overall frequency of DDRG germline mutations (35% in AA vs 15% in CA), the mutation distribution (frequently mutated DDRGs in 75% of AA vs in 19% of CA), and the DDRG spectrum with germline mutations (of the 20 DDRGs with mutation in CA only 8 overlaps with AA, and DDRG mutations with higher than 6% frequency were present only in AA patients: MLH3, ATM, XPC).
These results may provide critical information in the near future affecting treatment stratification and targeted therapy options for the disparately affected AA CaP patients.

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.”

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Although the goal of this project is not to provide training, the Postdoctoral Fellow is being provided with both training and other professional development opportunities.

Training: one-on-one laboratory work with the mentor and senior laboratory personnel

Professional development: local seminars and individual study

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.

During the next reporting period we will continue to closely follow our SOW tasks and timeline.

Main goals for the next quarter:

- Finalize the extensive mutation analysis for the selected DDRG genes (180) in all 532 patients with highest quality data (259 AA, 273 CA)
- Analyze the mutation data in the context of clinical and pathological patient data
- Isolate DNA from tumor tissue specimens of selected patients for somatic mutation analysis
4. IMPACT: Describe 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.

Nothing to Report

5. 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:

Change: The Principal Investigator was replaced by Dr. Inger Rosner
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.

Nothing to Report

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.

Nothing to Report

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

Nothing to Report

6. 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).

  **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).

Nothing to Report

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.

Nothing to Report

- 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.

Nothing to Report

- Technologies or techniques
Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report

- Inventions, patent applications, and/or licenses
Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report

- Other Products
Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - data or databases;
  - physical collections;
  - audio or video products;
  - software;
  - models;
• educational aids or curricula;
• instruments or equipment;
• research material (e.g., Germplasm; cell lines, DNA probes, animal models);
• clinical interventions;
• new business creation; and
• other.

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Name: Dr. Inger Rosner from November 2018
Project Role: Principal Investigator
Contribution to Project: Dr. Rosner have overseen the administrative and clinical aspects of the project, including IRB protocol approval, as well as contribute to the overall coordination of the project.

Name: Dr. Gyorgy Petrovics
Project Role: Co-Investigator
Contribution to Project: Dr. Petrovics has been involved in the coordination of the project, including laboratory work, WGS sequencing/analyses, and IRB protocol writing / approval processes.

Name: Dr. Jennifer Cullen
Project Role: Co-Investigator
Contribution to Project: Dr. Cullen developed the patient/specimen cohort selection for this research project.

Name: Dr. Kevin Babcock
Project Role: Postdoctoral Fellow
Contribution to Project: Dr. Babcock has been working on the QC and aliquoting of the blood DNA specimens.

Name: Ms. Lakshmi Ravindranath
Project Role: Senior Research Assistant
Contribution to Project: Ms. Ravindranath has been working on the QC and aliquoting of the blood DNA specimens.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state “Nothing to Report.”
If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Since the last report, there has been a change in PI. Dr. Shiv Srivastava is no longer with the Uniformed Services University (USU), Center for Prostate Disease Research (CPDR). Dr. Inger Rosner is now the current PI on this project.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state “Nothing to Report.” Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name: The American Genome Center (TAGC) at USU
Location of Organization: Bethesda, MD
Partner’s contribution to the project (identify one or more)
• Collaboration (e.g., partner’s staff work with project staff on the project);

All sequencing (WGS) and sequence data analysis is performed at TAGC. DDRG mutation data is transferred to CPDR for further analysis and validation.

8. 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.

See attached.

9. 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.
Defining mutations of DNA repair genes in prostate cancer patients towards enhancing treatment

LOG# DM160510

PI: Inger Rosner, M.D.  Org: Uniformed Services University  Award Amount: $741,632

Study/Product Aim(s)
Define and evaluate mutation spectrum of all known DNA damage repair genes (DDRGs) in archived specimens from African American (AA) and Caucasian American (CA) prostate cancer (CaP) patients for association with disease aggressiveness, and assess how this information can refine patient stratification for specific targeted therapeutic options.

Approach
Number of total subjects: N=600
- Task 1) Perform an in depth evaluation of germline mutations in all DDRGs in a large DOD cohort of AA and CA CaP patients
- Task 2) Assess DDRG mutation data, with emphasis on understudied AA CaP, for association with clinical and pathological data including disease progression, and evaluate how this information can refine patient stratification for specific targeted therapy

Accomplishments: DNA specimen QC’s have been completed for all 600 DNA specimen (300 AA and 300 CA). WGS of all 600 cases is also completed. Data analysis is in progress.

Timeline and Cost

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<td>Task 1</td>
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Estimated Budget ($K) $242K $247K $252K $741K

Goals/Milestones

CY17 Goals  ✓ Complete DNA QC on all 600 cases
CY18 Goals  ✓ Complete DNA sequencing on 50% of cases  ✓ Complete DNA sequencing on all remaining cases (600 total)  ✓ Complete 50% of sequence data analyses
CY19 Goals  ✓ Complete the majority of sequence data analyses on all cases  □ Complete all statistical and sequence data analyses and all validations  □ Publish conclusions

Comments/Challenges/Issues/Concerns
Due to lengthy process of IRB protocol approval (March 2018), we completed the 2017 and 2018 goals together in 2018.

Budget Expenditure to Date
Projected Expenditure: $741K  Actual Expenditure: $411K

Updated: (05/25/2019)