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TITLE: Reduction of Lethal Prostate Cancer Disparities in Underserved Hispanic/
Latino Populations

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14. ABSTRACT The proposed project will advance research into the biology of lethal prostate cancer (PCa) and reduce the burden of lethal PCa health disparities in Puerto Rican Hispanic/Latino men (PR H/L) through the following aims: Aim 1: Identify the genomic alterations and mutation signatures that characterize lethal PCa in PR Hispanic/Latino (PR H/L) men. Aim 2: Studying the lethal PCa phenotype in terms of overall DNA repair capacity (DRC) levels using lymphocytes as surrogate markers to develop a potential biomarker for identifying men at high-risk. Aim 3: To increase PCa awareness and screening in PR communities with high African ancestry and high PCa mortality rates. During this funding period, the molecular analysis for 25 prostate tumors from PR H/L men was completed: WES and RNA sequencing data are available for 14 and 25 tumors, respectively. Through RNA-seq, 31 DNA repair genes whose expression correlated with that of the androgen receptor gene were identified (P < 0.0003). For Aim 2, 85 samples were analyzed for DRC values including cases and controls. Significant differences were observed when comparing cases and controls (p<0.001). When stratifying by disease aggressiveness, significant differences were observed when comparing controls with the four PCa groups (p<0.0001). Standardization for the DNA repair assay to measure homologous recombination was completed. For Aim 3, the Community Advisory Committee (CAC) was established. A manuscript with data from Aim 3 is currently under review. Several oral presentations and posters regarding the data from Aims 2 and 3 were presented at local meetings.					
15. SUBJECT TERMS Lethal prostate cancer, Hispanic/Latino, Puerto Rico, genomics, DNA repair, tumor, blood, community outreach, education, screening, African ancestry, mortality					
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1. INTRODUCTION:

Puerto Rico is a United States (US) Territory located in the Caribbean with an estimated population of 3,200,000 inhabitants. Puerto Ricans are particularly vulnerable to cancer disparities because of socioeconomic inequalities. In 2020, approximately 44% of the population in Puerto Rico lived in poverty, compared with 17% of US Hispanics and 9% of Non-Hispanic Whites (NHW) living in the continental US. China *et al.* (2017) reported that Hispanic/Latino (H/L) subgroups have different prostate cancer-specific mortality (PCSM) rates when compared to NHW and non-Hispanic Black (NHB) men, using data from 2000-2013 that included 486,865 men. Prostate Cancer (PCa) incidence and mortality rates in H/L men were similar to NHW; however, Puerto Rican Hispanic/Latino (PR H/L) men had significantly higher PCSM than NHW and had the highest mortality among Hispanic subgroups. In 2018, the general PCa incidence rate in Puerto Rico was 145.2 cases per 100,000 population and an age-adjusted mortality rate of 18.2 deaths per 100,000 population (Figure 1). However, at the regional level, differences in incidence and mortality were identified among those living in the south (Ponce Region) and east (Fajardo Region) parts of Puerto Rico. Most recent data shows that both areas have the highest age-adjusted mortality rate with 23.7 and 22.4 deaths per 100,000 population, respectively (Figure 1B). As shown in Figure 1, the study's target municipality, Patillas, (Aim 3) is part of the Ponce region, which is one of the two regions of Puerto Rico with the highest PCa mortality rates (19.7-23.9). The study's other two target municipalities (Maunabo and Las Piedras) are part of the Caguas region, which has the second highest PCa mortality rates (18.3-19.6), as shown in Figure 1. With regards to incidence, recent data also illustrates a similar scenario in which the Ponce and Caguas Health regions are the two regions with the highest PCa incidence rates (151.7- 162.6), as shown in Figure 1.

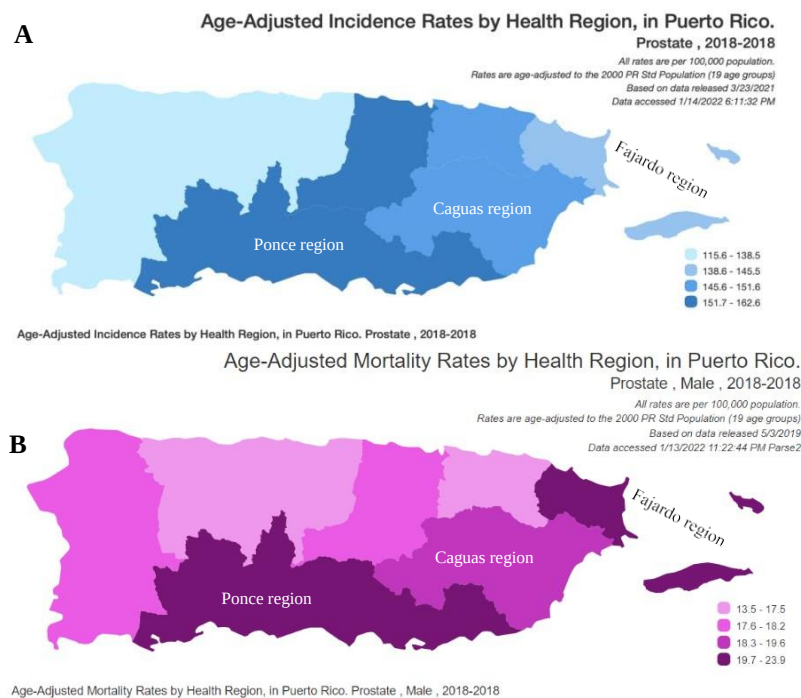


Figure 1. Age-Adjusted Incidence and Mortality Rates by Health Region in Puerto Rico- Prostate Cancer, 2018. Note: Names of regions added by research team to illustrate regions for this report. Source: Puerto Rico Cancer Registry. [Tasas y Mapas \(rcpr.org\)](https://rcpr.org)

2. KEYWORDS:

Lethal prostate cancer, Hispanic/Latino, Puerto Rico, genomics, DNA repair, tumor, blood, community outreach, education, screening, African ancestry, mortality

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The study team aims to significantly advance research in the biology of lethal prostate cancer (PCa) and reduce the burden of lethal PCa health disparities in Puerto Rican Hispanic/Latino (PR H/L) men. PCa is the most prevalent cancer, both in terms of incidence and mortality in Puerto Rico. The long-term goal of this study is to reduce lethal prostate cancer disparities in PR H/L men by 1) identifying genetic and genomic differences in the PR H/L population, the study team expects to gain insight into why PR H/L men have the highest PCa mortality among all Hispanic subgroups in the United States (US), and; 2) engaging the community as research partners, the team expects to gain knowledge as to specific social, psychological, and cultural factors that may represent barriers to PCa education and screening. These goals are presented in the SOW through the following three Specific Aims:

Aim 1: Identify the genomic alterations and mutation signatures that characterize lethal prostate cancer in Puerto Rican Hispanic/Latino (PR H/L) men.

Aim 2: Studying the lethal prostate cancer phenotype in terms of overall DNA repair capacity (DRC) levels using lymphocytes as surrogate markers to develop a potential biomarker for identifying men at high risk.

Aim 3: To increase PCa awareness and screening in Puerto Rican communities with high African ancestry and high PCa mortality rates.

What was accomplished under these goals?

Specific objectives for Specific Aim 1

Aim 1: Identify the genomic alterations and mutation signatures that characterize lethal prostate cancer in Puerto Rican Hispanic/Latino (PR H/L) men. Hypothesis: PR H/L men with stronger African ancestry will be enriched for somatic mutations and signature profiles associated with a higher aggressiveness of lethal PCa as measured by Gleason scores and metastasis.

Specific Aim 1: Identify the genomic alterations and mutation signatures that characterize lethal prostate cancer in Puerto Rican Hispanic/Latino (PR H/L) men.	Months	Percentage of completion
Task 1: Recruitment, tissue collection, processing, and data analysis		
Subtask 1: Study start-up procedures, including approval from USAMRDCORP HRPO and IRB prior to work involving human subjects.	1-3	100%
Subtask 2: Recruit PR H/L men with PCa (n =150), send to ORIEN for QC, WES and RNA-sequencing. Expect 10 participants per month.	3-18	63%
Subtask 3: DNA extraction from whole blood and GWAS array genotyping.	3-18	63%
Subtask 4: Request WES data to the Tissue and Data Sharing committee of the PRBB.	6, 22	50%*
Subtask 5: Genotyping of genome-wide SNP array for ancestry analysis.	6-20	63%

*Instead of placing 2 requests at month 6 and 22, we have been receiving data on a rolling basis which means that we download and analyze the data as soon as it is released.

Major activities

The team proposed to characterize genomic alterations (genes mutated, types of mutations, mutation burden, fusion genes) and mutational signatures (the combinations of genomic changes resulting from specific mutagenesis processes) in tumors from PR H/L men, comparing tumors with favorable Gleason Scores (GS) to lethal, advanced stage PCa including those

with Gleason scores ≥ 8 , and metastatic castration-resistant prostate cancer (mCRPC) both classified as high-risk by the 2020 National Comprehensive Cancer Network Guidelines for Advanced Stage Prostate Cancer (NCCN PCA, nccn.org/patients/guidelines). The ancestral composition of the cohort will also be measured to allow the clustering of samples according to their African, European, and Indigenous American ancestral composition. PR H/L data will be compared to US existing datasets: non-Hispanic white (NHW) and non-Hispanic blacks (NHB). As presented in the proposal's statement of work (SOW), this aim was divided into five subtasks which are summarized below.

Goals related to Subtask 1.1: Study start-up procedures, including approval from USAMRDC ORPHRPO and IRB prior to work involving human subjects

Additional recruitment site: As proposed in the previous technical report, we have established a collaboration with Dr. William Roman, a urologist located in the West area of PR (Mayaguez, PR). The main objective is to increase the number of patients with prostate tumors with high GS. Dr. Roman and his staff identified 15 patients that fit our study criteria and the criteria from ORIEN. These patients with GS ≥ 8 have undergone surgery within the past three years. Once the patients were identified, a member of Dr. Roman's staff called them to ask whether they were interested in participating in our study. Once the patients agreed, a list of patients' names and phone numbers was sent on an encrypted file to Sonia Abac, RN, the recruiting nurse from the Puerto Rico Biobank (PRBB). She administered the PRBB's informed consent to the patients over the phone, and 10 out of 15 patients consented to participate. Currently, we are working on logistics to gather evidence of the patient's consent on paper and obtain the tissue specimens' release from the pathology laboratory. The inclusion of Dr. Roman's clinical practice as a new recruitment site was submitted as an amendment to the IRB protocol for this project. This amendment was approved on December 9, 2022.

Access to biopsy samples from mCRP tumors: To move forward with the proposed pilot project for the sequencing of mCRPC transrectal core biopsy samples, we have established collaboration with CorePlus Servicios Clínicos y Patológicos, LLC. After several meetings between Mr. Mariano de Socaraz (CEO CorePlus), Dr. Ruiz-Deyá (Co-PI), and Dr. Jaime Matta (PI), a Memorandum of Understanding (MOU) between Ponce Medical School Foundation, Inc. and CorePlus was signed by the President (Dr. Kenira Thompson) on June 7, 2023. After signing the MOU, an amendment was submitted to the IRB protocol for this project, which was approved on July 5, 2023. Dr. Matta and his staff have met continuously with Mr. de Socaraz and Erik Gustafson, Ph.D. (Vice President of Clinical Services at CorePlus). Through these meetings, we have received confirmation that CorePlus holds the transrectal biopsy core specimens for 4 of the mCRPC patients previously recruited through the PRBB. Recently, the team and Dr. Juan Santa, pathologist and Medical Director at CorePlus, identified the best FFPE blocks for sequencing from each patient. The criteria for choosing these blocks are that they represent the highest GS for each patient and a cellularity of $>20\%$. This has proven challenging for some of the blocks; however, higher cellularity will improve the chances of success of this pilot project. The pathology slides from these patients were received in the laboratory of Dr. Matta on August 7, 2023.

Goals related to Subtask 1.2: Recruit PR H/L men with PCa ($n = 150$), send to ORIEN (for QC, whole exome sequencing and RNA-sequencing. Expect 10 participants per month.)

Overview of the processes: Enrollment of tumors from prostate cancer patients is ongoing through the Puerto Rico BioBank (PRBB) protocol. In brief, the PRBB works jointly with the Urology clinical team headed by Dr. Ruiz-Deyá (Co-PI) to identify eligible patients, consent, and collect biospecimens. Additional support is provided by three additional urologists based at Urocentro del Sur. As stated above, since January 2023, an additional recruitment site was added to facilitate the collection of high GS tumors. The PRBB collaborates with the Oncology Research Information Exchange Network (ORIEN) for evaluation of the clinical data biospecimens and clinical data.

We have completed our recruitment efforts for GS low- to intermediate with 94 patients with GS low ($3+3=6$), and 27 patients with GS intermediate ($4+3=7$) (Figure 2). Our objective was 50 for these 2 categories combined. We have continued our strategy of focusing on patients with aggressive tumors. As a result, we now have consented 17 patients with GS high (8 and above), and 19

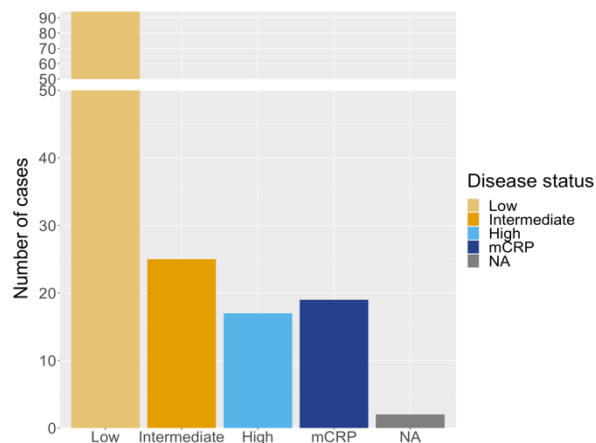


Figure 2. Distribution of the patients consented for Aim 1, grouped by disease status defined as Low Gleason Score (GS) ($6, 3+3=6$), intermediate GS ($4+3=7$), and high GS ($8+$), metastatic castrate resistant prostate cancer (mCRPC).

mCRPC. This represents 39% and 34% of our objective for these categories.

Given that this strategy has proven successful in the past six months, we will continue as follow:

- Rather than consenting unselected PCa patients on a rolling basis, the clinical team will continue to target patients with aggressive disease.
- As discussed in the prior technical report and briefly summarized above, we have initiated the recruitment of mCRPC patients for which surgical specimens are not available. We are developing the protocol for obtaining nucleic acids and sequencing using transrectal core biopsy samples. This is accomplished through a collaboration with the Quantitative Sciences Core (QSC, U54 PACHE Partnership) and the Cancer Genomics lab at PHSU. This idea is supported by recent evidence in the literature demonstrating that prostate tumor biopsy samples constitute an adequate source of material for whole genome molecular analysis (Nat Commun. 2019 Nov 20;10(1):5251. doi: 10.1038/s41467-019-13084-7). This approach will allow to capture aggressive and metastatic cases that are not undergoing surgery but for which biopsy samples are available. As this grant's budget does not include funds for such analysis, alternative funds have been identified through the QSC. Since the last technical report, 19 patients with a diagnosis of mCRPC have been consented and work is underway to obtain specimens.

Goals related to Subtask 1.3: DNA extraction from whole blood and GWAS array genotyping

Overview of the processes: Once the patients are consented to participate in the study and donate their tissues, a blood sample is also collected. Germ-line DNA (gDNA) from matching blood is extracted using a standard protocol from the manufacturer (PAXgene Blood DNA system, Qiagen). The gDNA obtained is used for ancestry analysis (Subtask 1.5). Germ-line DNA is extracted on a rolling basis for all patients consented for aim#1 and aim#2. The results of the preliminary analysis of the ancestry analysis derived from germ-line genotyping is presented in Subtask 1.5.

Goals related to Subtask 1.4: Request Whole Exome Sequencing data to the Tissue and Data Sharing committee of the Puerto Rico Biobank.

Overview of the processes: Through the collaboration with ORIEN, nucleic acids are extracted from tumors and blood. This material is used for whole exome sequencing (WES) (tumor DNA and germline DNA to control for inherited variants) and RNA sequencing (tumor RNA). The data is then shared with the study team for analysis.

- In previous reports, we presented the initial analysis of the molecular analysis for 14 prostate tumors from H/L men from Puerto Rico (*this data is below*). After QC steps, WES and RNA sequencing data is available for 11 and 14 tumors, respectively. In the current report, we are presenting molecular data from 14 WES and 25 RNA-seq.
- An additional shipment of 19 additional prostate cancer tumors was sent to ORIEN for processing in January 2022.
- In the summer of 2022, all sequencing processes at ORIEN were paused due to technical difficulties. In the previous report, we expected sequencing activities to resume in March 2023. We are hereby confirming that these activities have resumed in May 2023 as planned and that samples from the Puerto Rican tumors consented for this proposal are in queue.
- The analysis pipelines for somatic mutations, mutational signatures and gene fusion events identification have been developed and have been implemented to analyze the sequencing data presented in this report.
- There was an initial request for molecular data before month 6 of the grant and for which preliminary data was presented in prior technical reports. We are now presenting analysis of 14 WES and 25 RNA seq datasets.

Preliminary findings: molecular profiling of PCa tumors in Puerto Rican patients as of August 2023

Analysis of tumor mutational burden (TMB): The tumor mutational burden refers to how many coding mutations (non-synonymous mutations within 30Mb of exonic regions) are found in the tumor of a patient. The number of mutations per tumor ranged from 1 to 47, with an average of 20.57. The tumor mutation burden (TMB) is calculated as the number of mutations per 1 million base pairs (1Mb). The tumor mutation burden appears higher in intermediate compared to low GS tumors; however, this is not statistically significant ($P_{\text{Kruskal-Wallis}} = 0.1187$) (Figure 3).

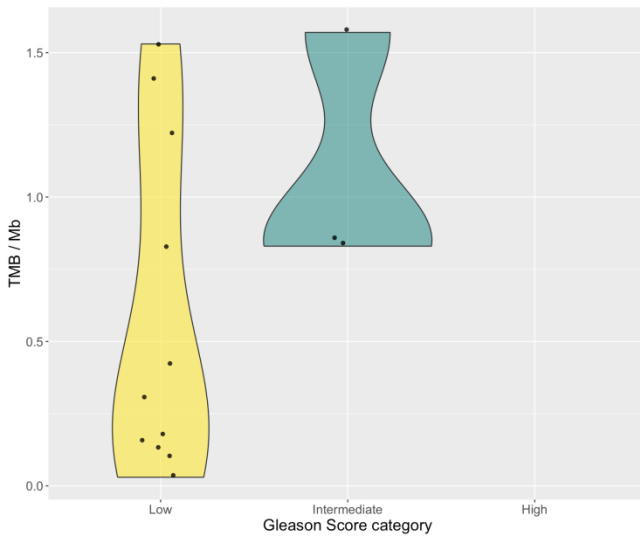


Figure 3. Tumor mutational burden (TMB) in 14 PCa tumors grouped by Gleason Score (GS) category: low (GS6 and GS7(3+4)), intermediate (GS7(4+3)) and high (GS $\geq$ 8). WES data is not yet available for high GS tumors.

Somatic mutations. Driver mutations are observed in 3 out of 14 tumors in the genes *ATM* (1 sample, 7%), *FOXA1* (1 sample, 7%), *KMT2C* (1 sample, 7%). A truncating mutation of unknown significance was also observed in the gene and *PTEN* (1 sample, 7%) (Figure 4).

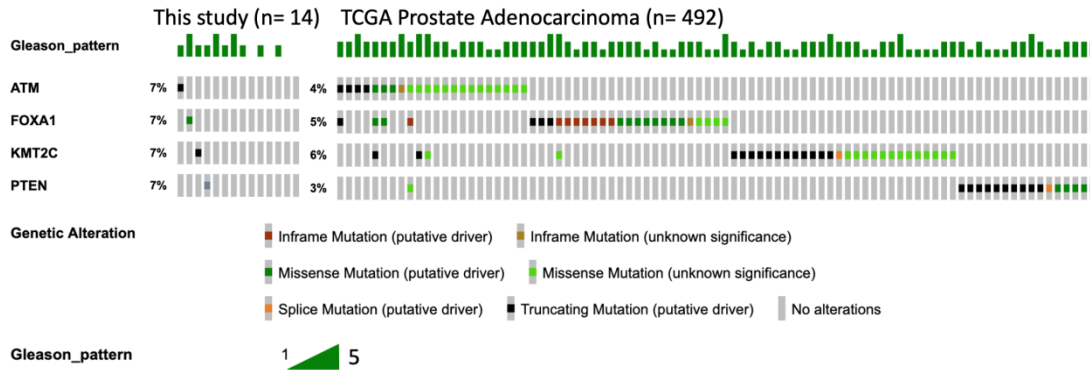


Figure 4. Somatic mutations identified in known driver genes in this study (n=14) compared to The Cancer Genome Atlas (TCGA) prostate adenocarcinoma (n=492) presented along Gleason Score patterns.

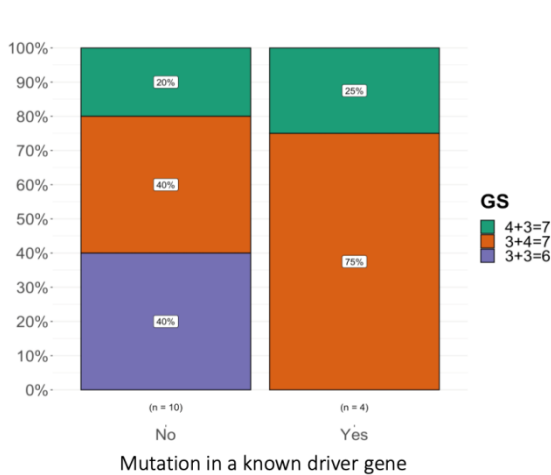


Figure 5. Distribution of the tumors for which a mutation in a driver gene (putative driver or truncating mutation of unknown significance) was detected grouped by Gleason scores.

Interestingly, no mutation in driver genes were detected in the most indolent tumors (GS6) (Figure 5). There was no significant difference in the frequency of mutations in a driver gene in tumors grouped by Gleason score ($P_{\text{Fisher}} = 0.335$).

Mutational signatures. We performed analysis of the mutational signatures based on the classifications previously described in (*Nature* 2013 **500**, 415–421, <https://doi.org/10.1038/nature12477>). After grouping the signature by etiology, we identified weak to moderate evidence of Base Excision Repair (BER) and Mismatch Repair (MMR) deficiencies in 4 and 2 tumors, respectively (Figure 6). In addition, one tumor exhibited traces of homologous repair deficiency.

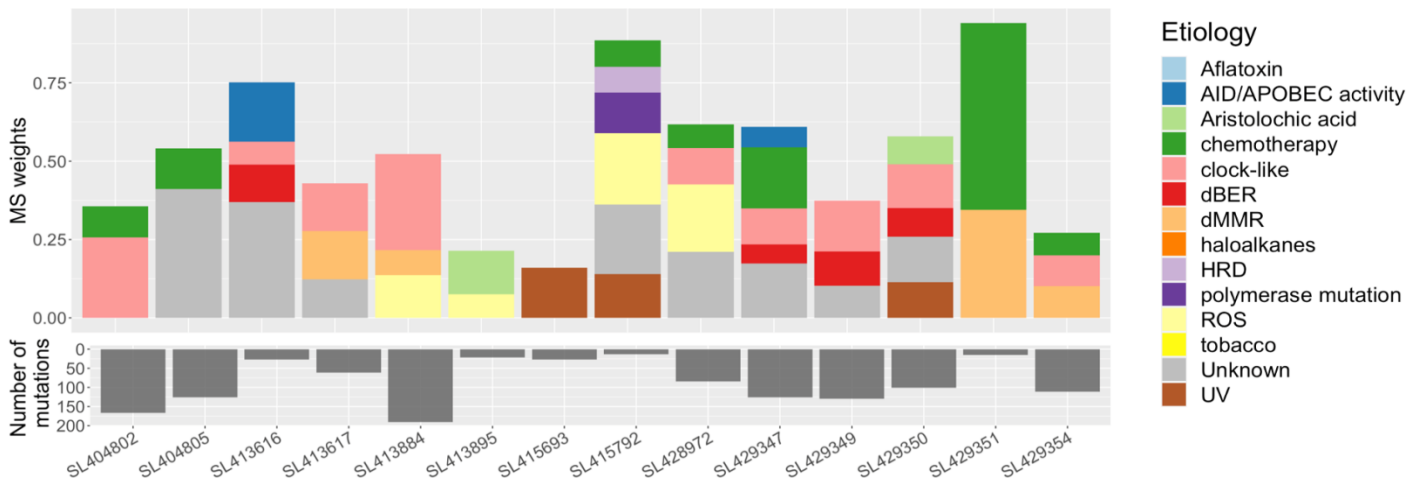


Figure 6. Mutational signature (MS) weights in 14 tumor (top pane), after grouping MS by etiology and number of mutations from which MS were determined (bottom pane).

Gene expression signatures. With the availability of RNA-sequencing data from 25 tumors, we have started exploring the relationship between changes in gene expression levels and Gleason score. The androgen receptor gene plays a prominent role in the development and progression of prostate cancer, especially in the molecular consequences of development of resistance to androgen deprivation therapy. While WES data allows detecting changes such as point mutations resulting in structural or coding changes in the protein, RNA sequencing allows to measure changes in the levels of expression. When compared to tumors of low (6 or 3+4=7) or intermediate (4+3=7), tumors with a high GS (≥ 8) tended to show increased AR expression (Figure 7). While this trend does not reach statistical significance ($P = 0.1089$) and needs to be confirmed with a larger sample, it is consistent with what has been observed in the literature.

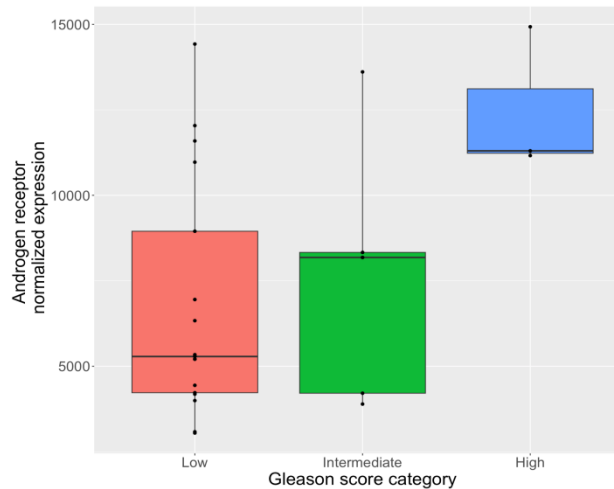


Figure 7. Androgen receptor (AR) gene expression in 25 prostate tumors grouped by Gleason score (GS) category: low (GS6 and GS7(3+4)), intermediate (GS7(4+3)) and high (GS ≥ 8).

Previous studies have reported a crosstalk between androgen signaling and DNA damage response and DNA repair through regulation of gene expression levels in response to androgen. Out of a group of 168 DNA damage response and DNA repair genes, we identified 31 genes whose expression correlated with that of the androgen receptor genes ($P < 0.0003$). As illustrated in Figure 8, high and intermediate Gleason score tumors are more likely to be characterized by a signature of high expression of the 31 AR-associated DNA damage response/DNA repair genes.

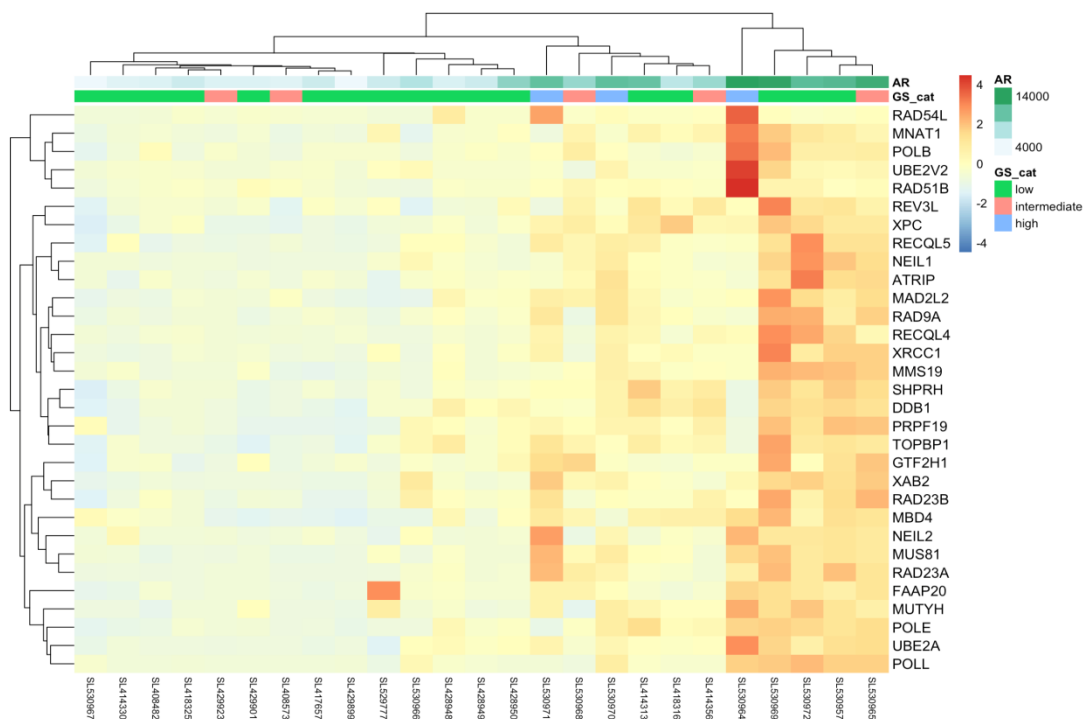


Figure 8. Heatmap representing the gene expression levels of 31 DNA damage response and DNA repair genes that were significantly correlated with Androgen Receptor gene expression levels. Gleason scores were stratified into: low (GS6 and GS7(3+4)), intermediate (GS7(4+3)) and high (GS $\geq$ 8).

Goals Related To Subtask 1.5: Genotyping of genome-wide SNP array For ancestry analysis.

Overview of the processes: Using DNA extracted from blood, genome-wide genotyping is performed using the Affymetrix UK Axiom Biobank array. This data allows accurate estimation of the genetic ancestry for each patient. Ancestry analysis allows the team to quantify the contribution of the genome from each ancestral population and to cluster individuals based on their genetic characteristics.

- In February of 2022, we reported the successful genotyping of 6 samples. Since then, genotyping was completed for an additional 128 samples (from aim#1 and aim#2) using the Affymetrix UK Axiom Biobank array. After QC, 538,589 genetic variants remained with a total genotyping rate of 0.999808. Ancestry proportions were determined using the ADMIXTURE software using 1000 Genomes populations as references. Preliminary analysis of this data is presented below.
- Additional samples accrued are being genotyped and analyzed on a rolling basis. The next batch of genotyping (94 samples) is planned for September 2023. Preliminary findings of the ancestry data were presented in the previous technical report (January 2023).

Preliminary findings: ancestral composition of non-cancer controls and PCa cancers patients in Puerto Rican patients as of January 2023

Ancestral composition of the cohort. As expected, the patients cluster with the 1000 Genomes Puerto Rico population. It is noteworthy that the patients analyzed to date represent the full spectrum of ancestry composition observed in Puerto Rico including individuals of high African ancestry, overlapping admixed Africans from the Caribbean (Figure 9).

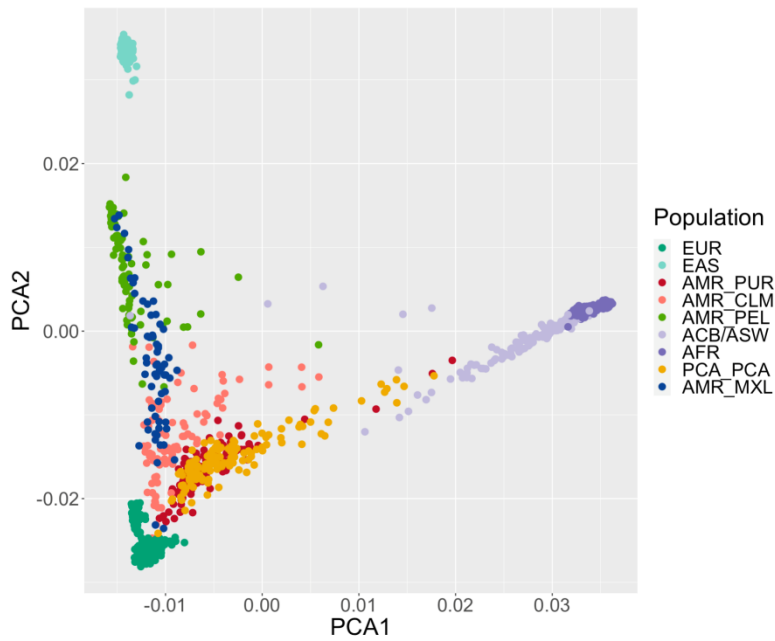


Figure 9. Visualization of the population structure from germ-line genetic variation using the first two components from principal component analysis for the study prostate cancer patients in reference to populations of the 1000 Genomes Project. Patients from the current study are represented in yellow and labeled DoD PCA. Reference 1000 Genomes populations are: ACB African Caribbean in Barbados, AFR African, ASW Americans of African Ancestry in SW US, CLM Colombian in Medellin Colombia, EAS East Asians, EUR Europeans, Mexican Ancestry from Los Angeles, California, PEL Peruvians from

Association of ancestry proportions and disease status. We have compared the ancestry composition of non-cancer controls, and prostate cancer patients grouped by diseases type as defined by low to intermediate GS (6, 7), high GS (8+) and mCRPC. Although the data is preliminary, interesting trends arise. Notably, disease status and severity showed an association with proportions of indigenous American ancestry (Table 1 and Figure 10, $P < 0.05$). Specifically, higher proportions of IA ancestry were observed in controls and showed incremental decreases in cases and more aggressive disease. Although not statistically significant in the sample currently available, an inverse trend was observed for African ancestry. The latter is consistent with established evidence that African American men are more likely to be diagnosed with a more aggressive disease than non-Hispanic whites.

Table 1. Comparison of African, European and Indigenous American global ancestry proportions in non-cancer controls and prostate cancer patients grouped by disease status.

Ancestral component	Mean (SD)				P^1
	Controls (n=16)	Low to Int. GS (n=67)	High GS (n=37)	mCRPC (n=1)	
AFR	0.172 (0.156)	0.205 (0.117)	0.219 (0.143)	0.355 (NA)	ns
EUR	0.651 (0.060)	0.632 (0.110)	0.629 (0.124)	0.502 (NA)	ns
IA	0.174 (0.033)	0.157 (0.040)	0.146 (0.040)	0.143 (NA)	0.048*

¹ P Kruskal-Wallis test, excluding mCRPC disease category because of sample size of $n = 1$. Low to intermediate GS (6, 7), high GS (≥ 8).

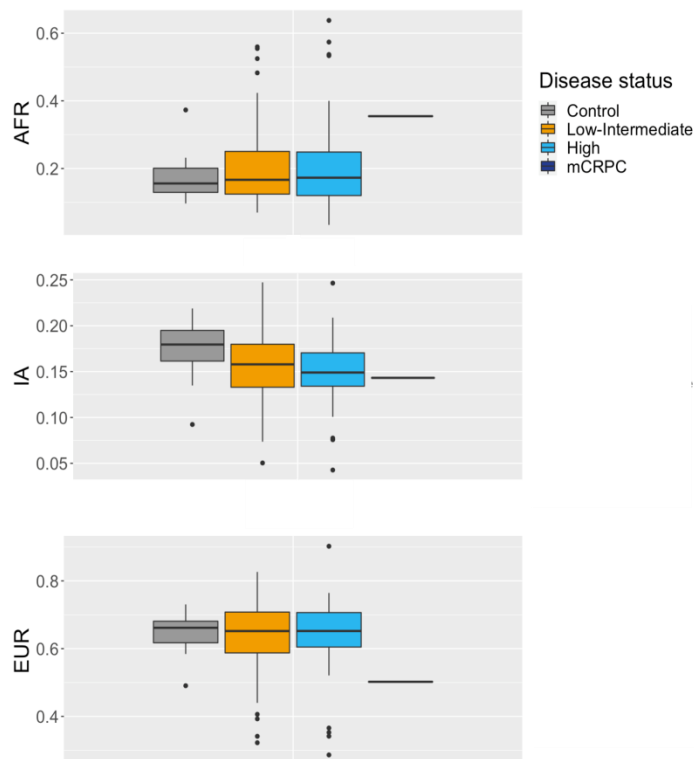


Figure 10. Proportion of the genome of African (AFR), Indigenous American (IA), and European (EUR) origins in controls and prostate cancer patients (Aims 1 and 2) grouped by disease categories (low to intermediate Gleason Score (GS), high GS and metastatic castrate resistant prostate cancer (mCRPC)).

Specific objectives for Specific Aim 2

Aim 2: Studying the lethal prostate cancer phenotype in terms of overall DNA repair capacity (DRC) levels using lymphocytes as surrogate markers to develop a potential biomarker for identifying men at high-risk. Hypothesis 1: PR H/L men with PCa will have lower DRC levels than controls without PCa in terms of three repair pathways associated with PCa. Hypothesis 2: Varying levels of overall DRC will be detected among the subgroups of PR H/L men with PCa based on Gleason score.

Specific Aim 2: Studying the lethal prostate cancer phenotype in terms of overall DNA repair capacity (DRC) levels using lymphocytes as surrogate markers to develop a potential biomarker for identifying men at high-risk.	Months	Percentage of completion
Task 2: Blood collection and lymphocyte isolation for DRC experiments		
Subtask 1: Recruit PR H/L men with (n=124) and without (n=31) PCa.	3-12	90%
Subtask 2: Draw blood to isolate lymphocytes for storage.	6-12	90%
Subtask 3: Measure DRC levels through the nucleotide excision repair pathways using the CometChip assay.	7-33	54%
Subtask 4: Measure DRC levels through the homologous recombination pathway using the CometChip assay.	7-33	15%
Subtask 5: Data analysis.	7-36	35%
Subtask 6: Prepare abstracts and manuscripts based on Aim 2 data.	33-36	50%

Goals related to Subtask 2.1: Recruit PR H/L men with (n=124) and without (n=31) PCa.

During this reporting period, the major goal was to continue recruiting Puerto Rican Hispanic/Latino men with (cases) and without (controls) prostate cancer. Cases included men with pathologically confirmed primary tumors with (1) Gleason ≤ 6 , (2) Gleason 7, and (3) Gleason >8 ; including a study group of (4) metastatic-castrate resistant prostate cancer (mCRPC). A total of 39 prostate cancer patients were recruited, and their blood was collected for lymphocyte isolation. During this reporting period, we were able to recruit participants for all prostate cancer study groups: Gleason ≤ 6 (n=10), Gleason 7 (n=17), and mCRPC (n=3) (Figure 11). Of all the patients recruited, 9 participants are still in the pipeline for data abstraction. The recruitment sample distribution is described in Figure 11. The recruitment for study groups of Gleason 7 and ≥ 8 has been completed.

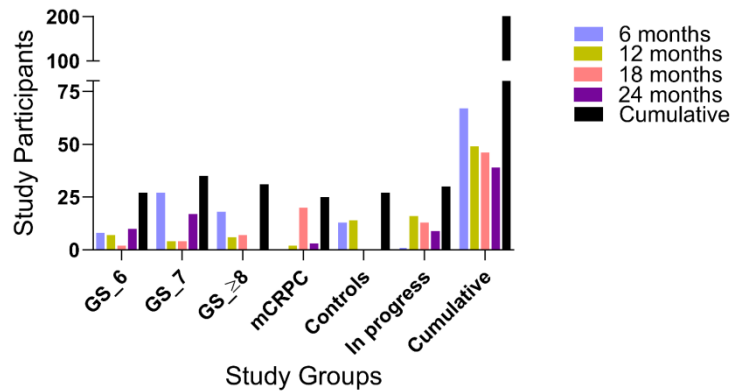


Figure 11. Recruitment of study participants at 6, 12, 18, and 24 months for Aim 2. Bars represent the number of participants recruited for each study group including: GS6, GS7, GS ≥ 8 , mCRPC, and controls. Participants with clinical data abstraction pending are included as in progress. Cumulative recruitment for each study groups is also included. The total recruitment for each category is represented in black bars.

Goals related to Subtask 2.2: Draw blood to isolate lymphocytes for storage.

This subtask included the blood collection from the study participants recruited with the collaboration of the Puerto Rico Biobank (PRBB) at Dr. Gilberto Ruiz-Deyá's clinical practice and Urocentro del Sur. The blood samples were drawn by the study consenters (Drs. Marie Ramirez and Wilzaida Perez) and collected by Dr. Jaime Matta's laboratory staff (Dr. Carmen Ortiz and Jarline Encarnación, MS). The blood samples collected were processed at the Matta laboratory at Ponce Health Sciences University (PHSU) using BD Vacutainer® CPT™ Mononuclear Cell Preparation Tubes. The lymphocytes obtained from each blood sample were preserved using the appropriate freezing media and stored in the -80° C freezer at the Matta laboratory at PHSU.

Goals related to Subtask 2.3: Measure DRC levels through the nucleotide excision repair pathways using the CometChip assay.

The goal of this subtask is to measure the DNA repair capacity, through the nucleotide excision repair (NER), of the study participants using lymphocytes as surrogate markers. To achieve this goal, the lymphocytes previously frozen and stored were thawed and seeded in cell culture flasks for cell growth and expansion. After allowing the participant's cells to grow for a week, the cells are counted to measure cell concentration and viability before performing the DNA repair measurements as previously published (Ortiz-Sanchez et al. 2022). After ensuring that the cell cultures for each participant have the appropriate viability ($>70\%$) and concentration ($>4 \times 10^5$ cells/mL), the DNA repair experiments were performed using the CometChip assay. The activities for this subtask have continued consistently throughout this period. During this reporting period, we obtained the DNA repair measurements for the first 13 mCRPC patients. *This is the first available phenotypic DNA repair data for mCRPC patients available for any population.*

Goals related to Subtask 2.4: Measure DRC levels through the homologous recombination pathway using the CometChip assay.

The main goal for this subtask is the assessment of DNA repair capacity values in the study participants through the homologous recombination repair (HRR) pathway. During this period, we completed the assay standardization to measure DNA repair through this pathway. We continued to successfully grow and expand the cell lines used as internal controls for the assay. These cell lines were previously acquired from Trevigen, Inc. and have knockdown of genes involved in the HRR pathway. These cell lines include Knockdown (KD) control cell line (wild type) and cells with KD in *XRCC3* and *BRCA1* (XRCC3-KD and BRCA1-KD). Hydroxyurea was used as the inducer of the pathway. Therefore, the activities for this period included standardization of the appropriate hydroxyurea concentration and exposure time to induce DNA damage through HRR, and selection of the appropriate time point for HRR to occur. These experiments were performed on the KD cell lines previously mentioned.

Goals related to Subtask 2.5: Data analysis.

During this reporting period, this subtask included the data analysis of the new data collected from the DNA repair capacity measurements performed through the NER pathway. The data analysis included the epidemiological and clinical

data of the participants in the DNA repair experiments. In addition, comparisons of DNA repair capacity values were performed between PCa cases and controls. Moreover, the DNA repair values were compared among the study groups including controls and cases with Gleason ≤ 6 , Gleason 7, Gleason > 8 , and the mCRPC group.

Goals related to Subtask 2.6: Prepare abstracts and manuscripts based on Aim 2 data.

Although this subtask was planned for months 33-36, we continued to make progress during this funding period. Under this subtask, an abstract was prepared for the FLASCO 12th Annual Puerto Rico Oncology Symposium held on February 3, 2023, at the Sheraton Puerto Rico Hotel & Casino (San Juan, PR). Two abstracts were presented at the 18th PHSU/PRI Annual Scientific Conference/2nd RCMi Symposium in Health Disparities, held on May 6, 2023. The data was also presented as an oral presentation by Dr. Jaime Matta, who Chaired a prostate cancer panel at that symposium in which Dr. Gilberto Ruiz-Deya and Dr. Julio Jimenez also participated.

What was accomplished under these goals?

Major activities

- During this reporting period, we have been actively recruiting prostate cancer cases at both recruitment sites: Dr. Ruiz-Deyá's clinical practice and UroCentro del Sur. The recruitment logistics coordinated along with the Puerto Rico Biobank (PRBB) have been effective in continuing with participant recruitment.
- Regarding DNA repair experiments, a total of 85 study participants, including prostate cancer cases (**n=63**) and controls (**n=22**), were successfully included in the experiments, and DNA repair values were successfully measured.
- To complete the optimization of the DNA repair assay to measure homologous recombination repair (HRR), the cell lines used as internal controls for the assay were grown and expanded to perform the standardization process. These cell lines, previously acquired from Trevigen, Inc., have knockdown on different genes involved in this pathway, including *XRCC3* and *BRCA1*. The rationale is to prove that our standardized process will allow us to detect varying HRR capacity levels on these knockdown cell lines. Due to the genetic modification of these cell lines, we expect them to have varying levels of HRR. KD control (wild type) cell line is expected to be a model for normal HRR, while *XRCC3*-KD will have a medium HRR. The *BRCA1*-KD cell line is expected to have the lowest HRR capacity. For this assay, the three cell lines were loaded on the Chip. A non-toxic concentration of 16 mM was used to induce the HRR pathway for 2 hours. After treatment, the cells were allowed to repair for 2 hours, and after the repair period, lysis and neutral electrophoresis were performed.
- As a result of different analyses performed with the data from the study participants, two abstracts were prepared and presented at local meetings.
 - Abstract 1: The CometChip technology as a promising tool for the analysis of DNA repair capacity in clinical samples from cancer patients. (Poster presentation at FLASCO Annual Meeting)
 - Abstract 2: Prostate Cancer Under 40: A Case Report. (Poster presentation at the FLASCO Annual Meeting and the 18th PHSU/PRI Annual Scientific Conference/2nd RCMi Symposium in Health Disparities)

Significant results or key outcomes

- A total of 39 prostate cancer patients were recruited during this reporting period for the different study groups based on the Gleason score. During this reporting period, we were able to continue with the identification of mCRPC patients; three additional patients were recruited during this period. Since this type of patient is difficult to identify and requires the collaboration of the urologist and the oncologist to collect the necessary information for the final diagnosis, every patient identified represents significant progress for this aim. Also, we completed the recruitment for two of the five study groups included in this aim: Gleason 7 and ≥ 8 . The identification of mCRPC patients proves that our recruitment strategy has been successful thanks to the close communication between the clinical staff at Dr. Ruiz-Deyá's office and UroCentro del Sur and the study team.
- Regarding DNA repair measurements through the nucleotide excision repair (NER) pathway, a total of **85 participants** have been evaluated, including prostate cancer cases (**n=63**) and controls (**n=22**). The DNA repair measurements were performed using the CometChip technology standardized and adapted by Dr. Ortiz to measure DNA repair through the NER pathway. Upon increasing the number of samples analyzed for DNA repair, the differences between prostate cancer cases and controls are still clear. The mean DRC value for the control group was 18.34%, and for the cases, it was 8.25%. This represents a statistically significant reduction in DRC levels of 45% in patients with PCa compared to the controls ($p < 0.0001$, Mann Whitney test).

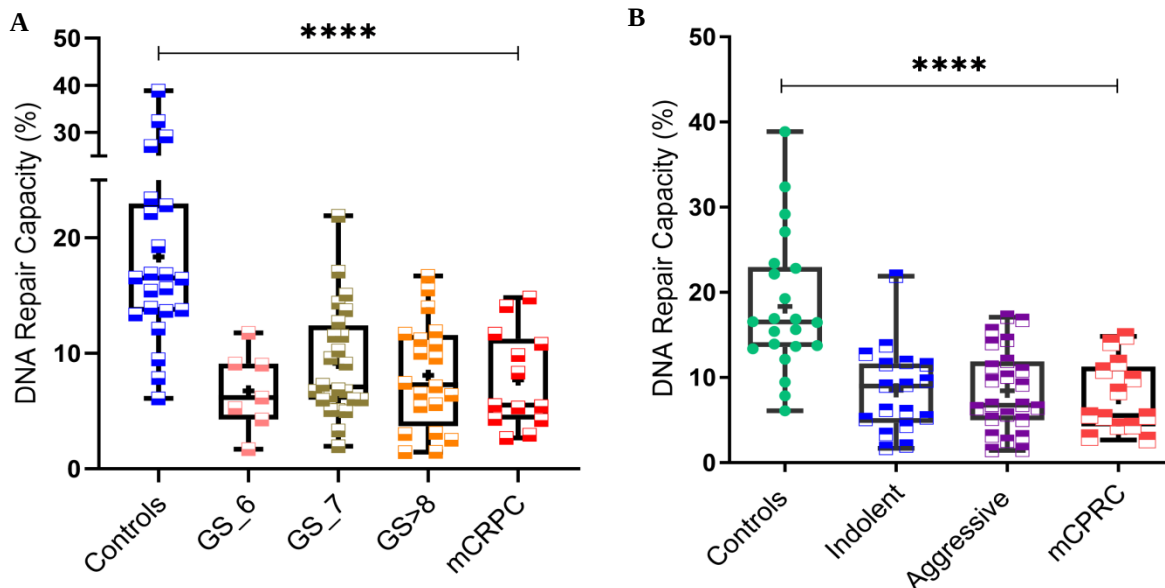


Figure 12. Overall DNA repair capacity in prostate cancer patients and controls. Sample distribution **(A)** among study groups including: controls (n , and prostate cancer cases with tumors with GS 6, GS 7, GS ≤ 8 , and mCRPC, **(B)** by disease aggressiveness. Based on their Gleason scores, the tumors from PCa cases were stratified into indolent ($n = 17$) and aggressive ($n = 23$). Symbols represent individual DRC values. Mean DRC value for each group is represented with a plus (+) sign. Asterisk (****) denotes statistical significance ($p < 0.001$, Kruskal–Wallis test).

- Increasing the sample size during this reporting period effectively allowed us to perform comparisons based on the Gleason Score (GS) (Figure 12A). The stratification by GS were: GS6 ($n=7$), GS7 ($n=23$), GS ≥ 8 ($n=20$), and mCRPC patients ($n=13$). Significant differences were found when comparing the DRC values of the controls with any other of the four PCa patient groups ($p < 0.0001$, Kruskal-Wallis test). Specifically, the mean for the GS6 was 6.75%, while for the GS7, it was 9.14%. For the GS ≥ 8 group, the mean DRC value was 8.08%, and for the mCRPC group, it was 7.70%. The median DRC values were 16.52%, 6.17%, 7.09%, 7.29%, and 5.53% for controls, GS6, GS7, GS ≥ 8 , and mCRPC patients, respectively (Figure 12A).
- Additional analyses were performed by stratifying prostate cancer patients based on disease aggressiveness (Figure 12B). Indolent cases included GS6 and GS7(3+4) while aggressive cases included GS7(4+3) and GS ≥ 8 . Significant differences were observed when comparing the control and indolent, aggressive, and mCRPC groups. The mean DRC value for the control group was 18.34%, as previously mentioned. As for the indolent cases, the mean DRC value was 8.51%, while for the aggressive cases, it was 8.43%. This represents a significant reduction of 54% in DRC levels in both groups compared with the controls. The mean DRC value for the mCRPC group was 7.7%, as previously mentioned. This represents a significant reduction of 58% in DRC levels compared to the controls. The median DRC value for the indolent cases was 9.01%, while for the aggressive cases, it was 6.74%.
- When performing a multiple comparisons analysis, significant differences were only observed between the control group and any of the other four study groups, as shown in Table 2.

Table 2. Multiple comparisons analysis of DRC values among study groups.

Study groups		Mean DRC Difference (%)	Significance	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
Controls	Indolent PCa	9.77	<0.0001	5.07	14.47
	Aggressive PCa	10.08	<0.0001	5.69	14.46
	mCRPC	10.64	<0.0001	5.25	16.02
Indolent PCa	Controls	-9.76	<0.0001	-14.47	-5.07
	Aggressive PCa	0.31	1.000	-4.13	4.75
	mCRPC	0.87	1.000	-4.56	6.30
Aggressive PCa	Controls	-10.07	<0.0001	-14.46	-5.69
	Indolent PCa	-0.31	1.000	-4.75	4.13
	mCRPC	0.56	1.000	-4.61	5.73
mCRPC	Controls	-10.64	<0.0001	-16.02	-5.25
	Indolent PCa	-0.87	1.000	-6.30	4.56
	Aggressive PCa	-0.56	1.000	-5.73	4.61

- The optimization for the assay to **measure** DNA repair through the homologous recombination repair (HRR) pathway was completed during this period. Although in our previous report, we explored the possibility of using a low concentration (2 mM) of hydroxyurea for 24 hours, we decided to use a higher concentration in a shorter exposure time. This decision was made considering the best experimental approach to avoid the reduction of cell viability of the primary lymphocytes, which are the cells used as surrogate markers of the overall DRC. Therefore, we decided to use 16 mM of hydroxyurea with an exposure time of 2 hours. This approach provided us with the conditions of the HR induction without reducing the cell viability.
- For measurements of the HRR pathway, the cells of interest (KD control, XRCC3-KD, and BRCA1-KD) were seeded in the Chip at a density of 1×10^5 cells/mL. Four experimental conditions were included for each cell line: untreated, aphidicolin C (APC) treatment, hydroxyurea treatment, and a combination of APC and hydroxyurea. APC was added in a concentration of 15 μ M for 30 minutes. Hydroxyurea was added at 16 mM concentration for 2 hours. All treatments were performed on the Chip and incubated at 37 °C in a CO₂ incubator. After completion of the corresponding exposure times, the cells were washed with 1X PBS, and the CometChip assay protocol was performed as instructed by the manufacturer. Neutral conditions were used during the electrophoresis process to detect double-strand DNA damage. After the electrophoresis, the nuclei were stained with a DNA intercalating dye (YOYO-1), and several images were acquired from the different experimental conditions using the EVOS Imaging system M7000 (Life Technologies). A total of 50 comets were evaluated for each condition. Every experimental condition was analyzed in triplicates. The tail moment (TM) was used to measure double-strand DNA damage for each experimental condition. DRC through HR was calculated using the percent of the tail moment of the samples with the different treatments using the following equation:
 - $DRC = \%TM (APC + HU) - \%TM (HU) - \%TM (APC)$, where TM is the tail moment.
- As can be seen in Figure 13, through our method, we were able to detect varying levels of HRR successfully. The mean DRC value for the KD control (wild type) cell line was 17.45 % ($\pm$ 3.04%). As for the XRCC3-KD and BRCA1-KD cell lines, the mean DRC values were 9.37% ($\pm$ 3.20%) and 3.82 ($\pm$ 1.89%), respectively. Differences in DRC through HR were statistically significant ($p < 0.01$) using a One-way ANOVA test.

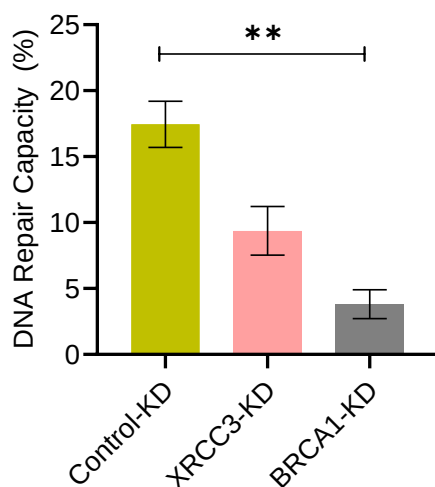


Figure 13. Assessment of the DNA repair capacity in human cell lines with deficiencies in homologous recombination using the CometChip assay. Each bar represents the mean $\pm$ SD of three independent experiments. Asterisks denote statistical significance: (**) $p < 0.01$.

Key outcomes

- During this reporting period, we were able to recruit 39 additional prostate cancer patients successfully. The recruitment for GS7 and GS $\geq$ 8 groups was completed during this reporting period.
- A total of 85 samples were analyzed for overall DNA repair capacity values through NER, including cases and controls. Significant differences were found when comparing the DRC values of the controls with any other of the study groups ($p < 0.0001$, Kruskal-Wallis test). In terms of tumor aggressiveness, no significant differences were observed when comparing the DRC values of patients with aggressive and indolent tumors. However, the case-control difference is still reflected in the results regardless of the tumor aggressiveness.
- The standardization of our assay to measure HR was completed using the internal control cell lines. Our results show that using the parameters established in our laboratory, we can successfully detect varying levels of HR.
- Two abstracts for poster presentations were submitted and presented at the local meetings, including the FLASCO 12th Annual Meeting and the 18th PHSU/PRI Annual Scientific Conference/2nd RCMI Symposium in Health Disparities. Three oral presentations related to this study were presented by Drs. Ruiz-Deya, Matta and Jimenez in the PHSU/PRI Annual Scientific Conference as part of a prostate cancer panel.

Specific objectives for Specific Aim 3

Aim 3: To increase PCa awareness and screening in Puerto Rican communities with high African ancestry and high PCa mortality rates. Hypothesis 4: The integration of a culturally based Community-Engagement Educational Plan (CEEP) will increase PCa awareness and screening by promoting healthy behaviors through education and outreach activities among PR communities with high African ancestry and PCa mortality rates.

Specific Aim 3: To increase PCa awareness and screening in Puerto Rico communities with high African ancestry and high PCa mortality rates.	Months	Percentage of completion
Task 3: Community assessment to explore knowledge, cultural beliefs, and perceived risk toward PCa (Exploratory mixed method study).		
Subtask 1: Request for institutional IRB approval prior to evaluation of men from the communities of Maunabo, Las Piedras and Patillas, PR.	1-3	100%
Subtask 2: Recruitment of participants and conduct focus groups	4-8	100%
Subtask 3: Focus group data analysis.	9-12	100%
Subtask 4: Design and pilot test of the questionnaire for the survey	13-15	100%
Subtask 5: Recruitment of survey participants (on-site).	16-25	61%*

* Survey recruitment in process. Currently, dates are planned to recruit the remaining participants in Maunabo, and Las Piedras. Recruitment is expected to be completed in the months 26-27 (N=92/39%).

What was accomplished under these goals?

Goals related to Subtask 3.1: Request for institutional IRB approval prior to evaluation of men from communities of Maunabo, Las Piedras, and Patillas, PR.

As mentioned in the previous reports, the renewal of the PSHU IRB was received on February 14, 2022. The renewal was granted to the objectives and activities contemplated under Aim 3. Even though the contagion rates of Covid-19 have had periods of leave, protection measures continue to be considered by state measures. As anticipated, no issues arose during the 2020-2023 IRB renewal process.

Goals related to Subtask 3.2: Recruit participants and conduct focus groups.

As planned through SOW 3.2 subtask, all planned focus groups corresponding to the qualitative phase were completed. The recruitment strategy focused on community engagement was successful. The sociodemographic characteristics of the participants conform to the main objective of Aim 3, to educate underserved communities in three regions of Puerto Rico with high rates of incidence and mortality of prostate cancer for the prevention of prostate cancer. During this recruitment process, leaders from each region were identified (Las Piedras, Maunabo, and Patillas) with whom communication has been maintained.

Goals related to Subtask 3.3: Focus group data analysis (survey).

As mentioned previously, the information from the focus group analyses informed and guided the selection of pre-existing surveys as it helped to identify additional questions to be included to collect sensitive information to our target population and project goal. A meeting was held between the Aim 3 team to discuss the Final Report and the manuscript to identify themes and sub-themes included as questions in the survey (quantitative phase of the evaluation). In preparation for the survey recruitment, communication was maintained with the leaders who collaborated during Community Engagement and Educational Intervention Activities and the focus groups held in the towns of Patillas, Las Piedras, and Maunabo.

Goals related to Subtask 3.4: Design and pilot test of the questionnaire for the survey.

- In preparation for the development of the Community Participation Educational Plan (CEEP), and once the qualitative phase is finished, we focus on the development of a questionnaire aimed at completing the quantitative degree of the study to achieve a comprehensive understanding of the phenomenon studied (method mixed exploratory sequential). Through this approach, we seek different but complementary information on the topics studied.
- Categories that emerged from the qualitative analysis (focus groups) and questionnaires used in the Hispanic population were integrated to develop a survey to complete the quantitative phase to explore information on knowledge, self-care behaviors, social determinants of health, health literacy, and learning preferences in health education.
- The CAC members reviewed the questionnaire to ensure it was culturally adapted to their communities and of easy comprehension for the potential participants.

Goals related to Subtask 3.5: Recruitment of survey participants.

Community Engagement

- To ensure effective project management and oversight of tasks, activities, and responsibilities, Dr. Julio Jimenez and Milton Rodriguez Padilla (RA) held weekly meetings to establish coordination for the quantitative component of the project. These meetings served as a platform for organizing community visits, facilitating communication with key stakeholders involved in interventions, preparing the recruitment plan, and ensuring compliance with IRB requirements.
- To achieve the target of gathering data from 150 participants in the municipalities of Patillas, Maunabo, and Las Piedras, strategic visits were scheduled to engage with local community leaders. We expect these local community leaders will be pivotal in participant recruitment and share valuable insights on effective data collection strategies. The initial visit took place in Patillas, where discussions were held with community leader Ruth Reyes and three volunteers from the Foundation "Los Buenos de Patillas." A comprehensive exchange of ideas focused on recruitment strategies tailored to locations frequented by our project's target population.

- During the engagement in Maunabo, a meeting was conducted with the community leader Paula Lebron. The meeting facilitated the identification of additional community leaders who demonstrated a strong potential for supporting the promotion of data collection and future educational events. Furthermore, discussions centered around resource allocation for participants dedicating their time to complete the survey. Notably, the meeting served as an opportunity to identify individuals of interest who could actively contribute to the composition of the Community Advisory Committee (CAC). To streamline future interactions with the municipality, a contact directory was established.

- Finally, communication channels were reopened with leaders in the Las Piedras. These connections played a crucial role in participant identification and data collection endeavors. Among the leaders, we identified the municipal employee Juana Colon, who guided optimal strategies to recruit 50 participants within their jurisdiction. Furthermore, insightful contacts were shared, including Dr. Willyson Velázquez, who expressed a genuine interest in the project and extended support in multiple capacities. Dr. Velázquez generously offered their clinical facility as a venue for participant identification and data collection while also accepting a role within the Community Advisory Committee (CAC).

Community Advisory Committee (CAC)

- The involvement of the CACs in community-based health education programs is valuable for identifying needs, accessing issues in the target population, promoting healthy behaviors, and increasing participants recruitment rates, among other tasks. One of the key objectives of the project is to establish a Community Advisory Committee that serves as a resource, leveraging the expertise and knowledge of its members to address pertinent issues and provide crucial insights for the implementation of effective and contextually relevant interventions within their respective communities. A recruitment process resulted in the selection of three participants from the municipality of Patillas, two participants from the municipality of Maunabo, and two participants from the municipality of Las Piedras. This diverse group encompasses community leaders, prostate cancer survivors, and a primary care physician, ensuring a well-rounded representation of key stakeholders who bring invaluable perspectives to the committee.

Data Collection

- From March to May 2023, the data collection instrument for the quantitative component of the project was developed. Pre-validated scales and other relevant items to the target population were utilized. While the instrument was translated into English to comply with IRB requirements, the Spanish version was culturally adapted to the context of Puerto Rico. The instrument was edited by Dr. Melissa Marzán, Dr. Julio Jiménez, and Dr. Jaime Matta. Furthermore, it underwent reviews by Luis Arroyo (RA), Milton Rodríguez (RA), and Juan Derieux (volunteer student).

- REDCap serves as the institutional platform where the data collection instrument will be hosted, allowing participants to complete it virtually if desired. The platform was chosen as it will also be utilized for conducting relevant statistical analyses after data collection.

- To meet PSBU IRB requirements, a promotion designed for data collection in the communities was submitted. Additionally, the informed consent form for self-administered questionnaires and the final revised questionnaire was also submitted for review. All submitted documents have been approved by the IRB and are ready for use.

- In July 2023, we initiated the recruitment activities by coordinating visits to the municipalities, guided by our community leaders. Before the visits, we arranged suitable recruitment spaces in the municipalities, decided on schedules, recruited volunteers to support the activities, promoted community events, and printed the data collection instruments.

- The first activity took place in Patillas on July 1, at a baseball park, where the organization "Los Buenos de Patillas" hosted a community gathering. Dr. Julio Jiménez had the opportunity to address the attendees, introduce the project, and explain our purpose for that day. We collected data from 13 participants. In this municipality, a second data collection activity on July 9th was conducted to reach our target of 50 participants. On this occasion, we visited the churches in Patillas. Just like the first activity, we had the opportunity to present the project and our

purpose for two Sunday masses. We completed the survey with 44 participants, successfully achieving the goal of 50 participants in Patillas.

- For the Municipality of Maunabo, we identified churches as the most effective points for data collection. We conducted two activities on July 2 after the Sunday masses at 9 AM and 11 AM. During both sessions, we were given time in the announcements to present the project and our purpose for the event. Between the two masses, we collected data from 26 participants. Due to the success of these activities, we coordinated a data collection event to achieve our target of 50 interviews. On July 30th an additional event was held in a church in Maunabo, recruiting 16 more participants.

- As agreed with Dr. Willyson Velazquez, we printed and delivered 30 questionnaires and informed consent to the Municipality of Las Piedras. The medical assistants of Dr. Velazquez will be conducting approximately six interviews per day with recurring participants who visit the office. It is anticipated that this effort may be sufficient to reach the goal of 50 interviews in the municipality, as the office has a substantial number of eligible participants to complete the questionnaire.

- As of August 8, 2023, 92 out of 150 participants were recruited (61%). Currently, dates are planned to recruit the remaining participants in Maunabo and Las Piedras. Recruitment is expected to be completed in the months 26-27 (N=92/39%).

Significant results or key outcomes

- One of the main outcomes of the visits to Maunabo, Patillas, and Las Piedras was the establishment of a Community Advisory Committee (CAC) by recruiting participants. It is anticipated that this team will meet at least three times during the current year.

- Another notable achievement was the beginning of data collection. We have currently recruited over 70 participants from Patillas and Maunabo, with the expectation of concluding the data collection within the coming month.

- Engagements were made with the communities we started working with. During the visits, collaborative relationships with groups and individuals with whom we had already established connections during the qualitative phase were strengthened, and new opportunities for collaboration were created.

- A research paper titled "Barriers to Prostate Cancer Screenings in Three Communities in Southeastern PR" was developed. The work has been resubmitted to a scientific journal (Journal of Cancer Education), and we await publication in the coming months.

- The data collection instrument, informed consent, and recruitment promotional materials were completed and tailored to our priority population. These documents have been approved by the Institutional Review Board (IRB) and are ready for use.

- The team for the quantitative phase of the project was strengthened by adding a new research assistant and a doctoral student with expertise in community-based educational interventions.

- The team for the quantitative phase of the project was strengthened by adding a new research assistant, a summer student of medicine, and a doctoral student with expertise in community-based educational interventions.

Conclusions

Based on the achievements of the various project components, the team was prepared to commence the data collection phase. The weekly, bi-weekly, and monthly meetings with the team for the development and review of our instrument facilitated the process and yielded a robust and culturally adapted product. Furthermore, adapting the instrument to a virtual format using the REDCap platform allows for broader recruitment, providing a user-friendly and easily manageable platform for remote participants to complete the questionnaire. Community visits continue to reaffirm the significance of our presence in the communities, fostering collaborative relationships and ensuring success in the data collection phase. Moreover, establishing the Community Advisory Committee (CAC) places us in

an advantageous position, as we have community experts who will guide the path for data collection. Including new members experienced in implementing educational interventions in communities strengthens the effort in creating the educational module that will be delivered to the communities following the analysis of the collected data. Additionally, the findings from the qualitative phase supported the development of the data collection instrument and informed the presentations given at scientific forums and the ongoing work on papers. As a result, we started the data collection, and within two weeks, we completed half of our 150 participants' goal.

What opportunities for training and professional development has the project provided?

- Third-year medical student, Swizel Tevenal, has served as a summer research trainee. She has been part of a 10-week research training program focused on: scientific literature review, data collection, data entry and data analysis techniques, qualitative research strategies, field recruitment activities, and scientific dissemination strategies. As part of her work, she will present on August 3, 2023, a poster presentation at the CAPAC (Cancer Prevention and Control Research Training Program) Closing Session to be held in San Juan, PR. Dr. Melissa Marzan serves as a primary mentor.
- Juan Derieux is a second-year student of the doctoral program in Clinical Psychology (Ph.D.), who has joined the team in activities related to poster preparation, the development of the survey instrument, data collection, and data entry into REDCap. During this period, Juan Derieux received training in the use of REDCap.

Training for new team members

- The recruitment of a Research Assistant (Milton Rodriguez), a summer medical student (Swizel Tevenal) and a doctoral Ph.D. student (Juan Derieux) in Clinical psychology provided an opportunity for the new members to receive training in Social and Behavioral Sciences and research involving human subjects, among other relevant topics. All members obtained CITI certifications to continue conducting research on the project. Additionally, Milton Rodríguez (RA) received training in the REDCap platform for data collection instrument development and mentorship from Dr. Melissa Marzán.

How were the results disseminated to communities of interest?

- The manuscript "Barriers to prostate cancer screening in three communities in southeastern Puerto Rico" has been resubmitted to a peer-reviewed journal; Journal of Cancer Education, currently under review.
 - Response to Critiques to be submitted on August 15, 2023.
 - Luis A. Arroyo-Andújar, Jaime Matta, Nicole Ryan, Gustavo Ronda, Eddiel Hernandez, Melissa Marzan-Rodriguez, & Julio Jimenez. Structural and individual barriers to prostate cancer screening in three towns in southeastern Puerto Rico.
- In May 7, 2023, Dr. Julio Jiménez and Dr. Jaime Matta shared preliminary findings from the first phase of the project at the Ponce Health Sciences University Annual Scientific Conference in a Prostate Cancer panel.
- At the same conference, Luis Arroyo (RA) and Juan Derieux presented a poster titled " "Machismo" as a Cultural Construct affecting behavior toward Prostate Cancer Screening." Two additional posters were presented from the data obtained on Aim 2.
- During the reporting period, we have established collaborative relationships with the outreach core of the U54 PHSU-MCC partnership project. During the reported period, we have established collaborative relationships with the U54 PHSU-MCC Partnership Project Outreach Core. Through health fairs in the towns of Maricao and Ponce, informative material on the Lethal Cancer Project has been distributed, impacting one hundred and thirty people. These materials were also disseminated in a health fair organized by the Puerto Rico Health Department in Patillas on August 5, 2023. This is one of the three towns in our study.
- Dr. Julio Jiménez hosts a local TV program called "Tu Salud Informa," which is broadcast on Puerto Rican television. The project research team regularly utilizes this platform to disseminate educational information about prostate cancer, screening, and research findings to the public.
- Summer Research Trainee submit a poster presentation for CAPAC Closing Section:

What do you plan to do during the next reporting period to accomplish the goals?

Aim 1

- The clinical team will continue to target patients with aggressive disease on the original recruitment sites and on the recently added recruitment site at Dr. Roman's office in Mayaguez, PR. In addition, there are plans to contact Southern Pathology (Ponce, PR) for availability of aggressive tumor samples whose surgeries have been done at San Lucas Hospital (Dr. G. Ruiz-Deya) or in Bella Vista Hospital (Mayaguez, Dr. W. Roman). Once these tumors are identified, these patients will be cited by their respective urologists by appointment in order to obtain Informed Consent and administer the questionnaire used for the ORIEN protocol.
- Begin with the proposed pilot project using transrectal core biopsy samples as a source of RNA/DNA to perform WES and RNA-seq analysis.
- Continue to identify patients with mCRPC to increase the numbers of patients on this study group.

Aim 2

- Continue with the recruitment of prostate cancer patients and controls to complete the recruitment goal of 155 participants. The coordination of the recruitment logistics with the PRBB will continue to be crucial for the achievement of this goal.
- Continue to perform the DNA repair measurements through the NER pathway.
- We will begin to perform the DNA repair measurements through the homologous recombination pathway using the recently standardized methodology.

Aim 3

- During the upcoming reporting period, it is anticipated that the data collection phase will be completed through ongoing visits to the priority municipalities.
- Additionally, the manually collected data is expected to be entered into the REDCap platform to facilitate quantitative data analysis.
- With the statistical analyses conducted by Dr. Melissa Marzán and complemented by the results from the qualitative phase, the educational materials will be developed under the guidance of Dr. Julio Jiménez, Milton Rodríguez (RA), and Juan Derieux.
- The Community Advisory Committee (CAC) will convene three times during the remaining duration of the project to provide updates on the interventions and remaining project activities.
- Finally, at least two educational interventions are expected to be conducted in each of the municipalities where data was collected.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

As planned for the quantitative phase of the project, the development, revision, cultural adaptation, and approval by the Institutional Review Board (IRB) of the data collection instrument have been successfully accomplished.

What was the impact on other disciplines?

Nothing to report currently.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

The engagement with leaders and community organizations regarding prostate cancer incidence and the importance of taking action has cultivated an interest in the subject matter and prompted individuals to work together for the well-being of their communities. The community visits and meetings have generated open conversations among prostate cancer survivors regarding their personal experiences upon receiving a diagnosis. These spaces have served as a source of inspiration, compelling community members to actively participate in the project, as is exemplified by their involvement in the Community Advisory Committee (CAC).

5. CHANGES/PROBLEMS**Changes in approach and reasons for change**

Nothing to report.

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

While significant delays in data collection are not anticipated, the implementation of a pilot study where members of the Community Advisory Committee (CAC) provided their feedback on the data collection instrument before commencing data collection took the month of June 2023 and slightly delayed the data collection to July.

Changes that had a significant impact on expenditures

Nothing to report.

Changes at the team members

- As mentioned in the previous report, it was expected to replace RA Nicole Ryan with a new research assistant, and this objective was achieved by incorporating Milton Rodríguez into the research team. In March 2023, Milton Rodríguez Padilla joined the team as a research assistant. Mr. Rodríguez holds a master's degree in public health education. Furthermore, he has prior experience as a research assistant in topics related to HIV and other public health issues at the University of Puerto Rico Medical Sciences Campus. His contribution to the team is expected to facilitate the development of educational interventions to be carried out in Patillas, Maunabo, and Las Piedras.
- An accomplishment of the project was the recruitment of Juan Derieux. Mr. Derieux is a doctoral student in psychology with a background in arts and theater. His inclusion in the team as a volunteer is expected to provide him with research experience that complements his doctoral studies while also contributing to the development of educational materials that will be disseminated after the completion of the quantitative component. Like the research assistant, Derieux has undergone training in research involving human subjects.
- Swizel Tevenal joins the project as a new team member during the summer. She is a medical student from PHSU and is undertaking a full-time practical experience as part of her summer tasks. In the project, Swizel has demonstrated exceptional skills in gathering and entering data in REDCap. Furthermore, she has actively taken part in training sessions focused on data management and qualitative research strategies, which were conducted by Luis Arroyo Andujar.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

Publications, conference papers, and presentations

Poster Presentations

1. Bernaschina-Rivera SA, Matta J, Encarnacion J, Ortiz-Sánchez C, Bernaschina-Bobadilla CP. Prostate Cancer Under 40: A Case Report. *18th PHSU/PRI Annual Scientific Conference/2st RCMI Symposium in Health Disparities*, May 6, 2023. Poster presentation.
2. Matta J, Cruz-Correa M, Encarnación-Medina J, Montes I, Ortiz-Sánchez C. The CometChip technology as a promising tool for the analysis of DNA repair capacity in clinical samples from cancer patients. *FLASCO 12th Annual Puerto Rico Oncology Symposium*, February 3, 2023. Poster presentation.

Oral Presentations

1. Matta, J. Reduction of lethal prostate cancer disparities in Puerto Rican populations. *18th PHSU/PRI Annual Scientific Conference/2st RCMI Symposium in Health Disparities*, May 6, 2023.
2. Ruiz-Deya, G. Current Clinical Tests for Prostate Cancer Detection. *18th PHSU/PRI Annual Scientific Conference/2st RCMI Symposium in Health Disparities*, May 6, 2023.
3. Jimenez, J. Health Determinants of Prostate Cancer in Puerto Rico. *18th PHSU/PRI Annual Scientific Conference/2st RCMI Symposium in Health Disparities*, May 6, 2023.

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

- As mentioned previously, a presentation was conducted at the Ponce Health Science University (PHSU) and Ponce Research Institute (PRI)'s 18th Annual Scientific Conference and 2nd RCMI Symposium. The presentation provided an overview of the project and highlighted the achievements in its implementation to the PHSU faculty students who participated in the presentation. The entire project team was present, and the presentation was delivered in both English and Spanish to accommodate the members of the Community Advisory Committee (CAC).
- During the conference, the team presented the poster "Sexism as a cultural construct affecting behavior towards prostate cancer screening." The poster showcased findings related to the focus groups conducted in the qualitative component of the project. Special attention was given to machismo as a barrier to prostate cancer prevention among men in southeastern Puerto Rico. As part of the poster recommendations, the development of educational strategies to promote prostate cancer screening that consider sociocultural factors associated with masculine gender roles was suggested.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Jaime Matta, PhD

Project Role: Co-PI

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 24

Contribution to Project:

Dr. Matta has overseen the day-to-day operation of the DoD study. He has provided oversight and leadership, planning, coordination to all aspects of the project together with Dr. Ruiz Deya, also PI. He continually monitored all aspects of the study and intervened when necessary to ensure timely accrual and completion of the study Aims. Dr. Matta meets regularly with the co-investigators, one consultant, and key personnel for each aim on a monthly basis. He has also worked on the preparation and revision of the semi-annual and annual technical reports. He is responsible for compliance with all DoD guidelines for the use of Human Subjects (HRPO) and PHSU IRB guidelines. Matta is responsible for dissemination of results to the scientific community including presentation at seminars, national/international scientific meetings, preparation of publications for peer-reviewed journals, and regular progress reports to the DoD. He worked on the preparation of the manuscript recently published and, in the supervision of the summer medical students. He has been involved in meetings and discussions with the research team including Dr. Ruiz-Deya and with CorePlus in developing a plan to recruit aggressive tumors during this period.

Name: Gilberto Ruiz-Deya, MD

Project Role: Co-PI

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 24

Contribution to Project:

Dr. Ruiz-Deya has been responsible for oversight of all clinical aspects of the project related to patient recruitment and interpretation of clinical data. He has been involved in the identification of study participants for recruitment through the PRBB. Dr. Ruiz-Deya provides supervision of the study consenters (Drs. Ramirez and Velez). He meets regularly with Dr. Matta to discuss the progress of the recruitment for Specific Aims 1 and 2. He has been involved in meetings and discussions with the research team and with CorePlus and one urologist from the west coast in developing a plan to recruit aggressive tumors during this period.

Name: Carmen Ortiz, PhD

Project Role: Postdoctoral Researcher and Program Manager

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 24

Contribution to Project:

Dr. Ortiz meets weekly with Dr. Matta and monthly with all of the co-investigators for Specific Aims 1 and 3. She has been collecting the blood samples at the recruitment sites once they are drawn by the study consenters. She has met regularly with the Data Abstractor from the PRBB assigned for this study. She has constructed and continuously updated the recruitment database with important information regarding the samples collected (i.e. study ID, date of recruitment, cell concentration, cell viability, recruitment site). She has performed the DNA repair capacity experiments with the participants' samples using the CometChip technology, acquired fluorescence images for each sample, and performed the quantitative analysis using the CometAssay software to finally obtain the DNA repair capacity values. She supervised and mentored the MD summer students during their summer rotations and provided feedback for their abstracts and oral presentations. Dr. Ortiz has been responsible for the preparation and submission

of the required documents for the renewal of the IRB at PHSU. Dr. Ortiz has been responsible for the standardization process of the assay to measure DNA repair through HR.

Name: Jarline Encarnación, MS

Project Role: Laboratory Supervisor (Matta's laboratory)

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 24, in-kind

Contribution to Project: Ms. Encarnación has provided support to Dr. Ortiz on the processes of collection of blood samples at the recruitment sites, processing of the blood samples for lymphocyte isolation and storage, and on different steps during the DNA repair experiments. She has thawed and cultured the patient's lymphocytes for the DNA repair experiments. Along with Dr. Ortiz, she supervised the MD summer students during their summer rotations. She performed the statistical analyses for the data collected on Aim 2 that were included on the manuscript.

Name: Julie Dutil, PhD

Project Role: Co-Investigator

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 12

Contribution to Project:

Dr. Dutil has overseen and integrated all genomic analyses for Aim 1 that has been performed so far on 11 PCa tumors. Specifically, she has conducted quality control of germ-line genome-wide genotyping array data and ancestry analysis. In collaboration with Dr. Teer (MCC), she has prioritized somatic mutations of interest and compared mutation frequencies across risk groups and ethnicity/ancestry associated group and analysis of gene expression signatures by RNA-Seq. She has worked closely with Dr. Teer and participated in monthly meetings with Drs. Matta, Ortiz, and Park.

Name: Jamie Teer, PhD

Project Role: Co-Investigator, Moffitt Cancer Center

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 12

Contribution to Project:

Dr. Teer has conducted quality controls of whole exome sequencing (WES) data (14 tumors) and RNAsequencing data (25 tumors) studied so far in Aim 1. Dr. Teer has been responsible for the analysis resulting in the identification of tumor mutational burden, somatic mutations in the PCa tumors from Puerto Rico. He has worked closely with Dr. Dutil and participated in monthly meetings with Drs. Matta, Ortiz, Dutil, and Park.

Name: Julio Jiménez, MD

Project Role: Aim 3 Project Co-Investigator

Nearest person month worked: 24

Contribution to Project:

During this work period, Dr. Jiménez has actively coordinated community visits to maintain existing collaborations in the municipalities and establish new partnerships that support data collection efforts. He has also overseen identifying and recruiting participants for the Community Advisory Committee (CAC). Furthermore, Dr. Jiménez has overseen tasks related to the development of the data collection instrument and guided research assistants in recruitment and data dissemination activities. Additionally, Dr. Jiménez has coordinated preparation meetings for activities in this reporting period, provided mentorship to the doctoral student, and led efforts in disseminating qualitative phase data.

Name: Melissa Marzan, DrPH

Project Role: Aim 3 Project Co-Investigator

Nearest person month worked: 24

Contribution to Project:

Dr. Melissa Marzán has been leading the efforts in developing manuscripts for publication in scientific journals and academic forums, focusing on the findings from the qualitative phase of the project. She has also played a key role in recruiting a new research assistant and guided Mr. Rodríguez in the human subject's research training. Additionally, Dr. Marzán has been conducting bi-weekly coordination meetings for the quantitative phase of the project and has provided support and oversight to ensure the successful completion of the proposed tasks. She has offered guidance

in adapting the quantitative data collection instrument and integrating it into the REDCap platform. Furthermore, Dr. Marzán has assisted in the development of the technical report.

Name: Milton Rodríguez Padilla, MPHE

Project Role: Aim 3 Project Research Assistant

Nearest person month worked: 03

Contribution to Project:

Milton Rodríguez, along with Dr. Jiménez, has been responsible for community outreach to maintain collaborations with community leaders, aiming to achieve the goal of recruiting 150 participants. As part of this effort, Mr. Rodríguez has participated in visits to the municipalities of Maunabo and Patillas. From these visits, he has compiled a directory of contacts to implement the quantitative phase. He has provided ongoing support to participants in forming the CAC group, which was successfully formed last month. He has also contributed to the development, review, and editing of the questionnaire that will be used for data collection. In addition, Mr. Rodríguez has reviewed the informed consent document, created recruitment promotions, and adapted the data collection instrument to the REDCap platform.

Name: Luis A. Arroyo Andújar, MPH, MA

Project Role: Aim 3 Project Qualitative Research Assistant

Nearest person month worked: 24

Contribution to Project:

Mr. Arroyo has supported the development of the data collection instrument for the quantitative phase of the project. Among the tasks related to the instrument, Mr. Arroyo has reviewed the original document, translated it into English, and culturally adapted it to the context of Puerto Rico. Alongside Dr. Marzán, Mr. Arroyo has led efforts to create a new manuscript presenting the findings from the focus groups in which he participated. He was also primarily responsible for presenting a poster titled "Sexism as a cultural construct affecting behavior towards prostate cancer screening." Arroyo has been involved in planning meetings for the quantitative phase and will actively participate in data collection in the community.

Name: Jong Park, PhD

Project Role: Consultant

Researcher Identifier (e.g. ORCID ID): 0000-0002-6384-6447

Nearest person month worked: 24

Contribution to Project:

Dr. Park provided his services as a consultant for this project. Park and the Co-PIs work towards obtaining WES data from Hispanic patients from MCC. He attended monthly meetings related to Aim 1.

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?

GuPRE Community Center in Patillas, Puerto Rico, is a non-profit community center run by an alliance of community members and leaders of Patillas. Currently, the leader of this alliance is the study team's community liaison, Dr. Ruth Reyes. Their contribution to the project has been in-kind support, facilities, collaboration, and recruitment.

Community Development Office from Las Piedras Municipality, located in Las Piedras, Puerto Rico, is a local government agency that provides direct and in-kind support to Las Piedras' local community non-profits, as well as community leaders and activities. Currently, our contact liaison for this alliance is Mrs. Juanita Castro. Their contribution to the project has been in-kind support, facilities, collaboration, and recruitment.

The non-profit community institution CESSA, for its acronym in Spanish (Centro Educativo Sico-Social de Ayuda Incorporada), and Parroquia San Isidro Labrador and Parroquia Santa María de la Cabeza. All three are in Maunabo, Puerto Rico. These local institutions work together to serve the community of Maunabo. These three institutions provided in-kind support and collaboration and aided in recruiting focus group participants. Parroquia San Isidro Labrador also collaborated with the project by providing a facility to conduct focus groups. Our main contact in these institutions was Mrs. Paula "Sherry" Lebrón.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS:

Reduction of Lethal Prostate Cancer Disparities in Underserved Hispanic/Latino Populations

PC200176

Award Number: W81XWH2110241

PI: Jaime L. Matta, PhD

Org: Ponce Medical School Foundation, Inc.

Award Amount: \$1,174,652

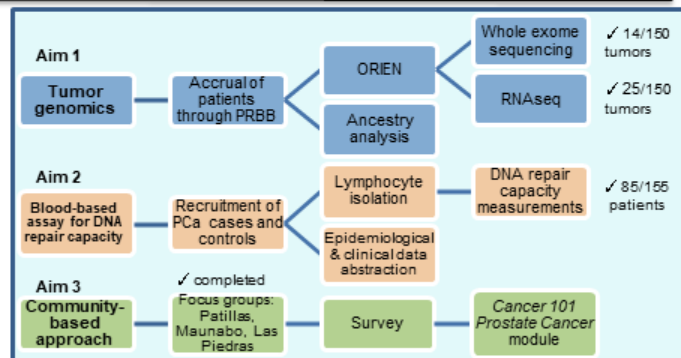


Study/Product Aim(s)

- Aim 1: Identify the genomic alterations and mutation signatures that characterize lethal PCA in PR Hispanic/Latino (PR H/L) men.
- Aim 2: Studying the lethal PCA phenotype in terms of overall DNA repair capacity (DRC) levels using lymphocytes as surrogate markers to develop a potential biomarker for identifying men at high-risk.
- Aim 3: To increase PCA awareness and screening in PR communities with high African ancestry and high PCA mortality rates.

Approach

The study team aims to significantly advance research in the biology of lethal prostate cancer (PCA) and reduce the burden of lethal PCA health disparities in Puerto Rican Hispanic/Latino (PR H/L) men. PCA is the most prevalent cancer, both in terms of incidence and mortality in Puerto Rico. The long-term goal of this study is to reduce lethal PCA disparities in PR H/L men by: 1) identifying genetic and genomic differences in the PR H/L population, the study team expects to gain insight into why PR H/L men have the highest PCA mortality among all Hispanic subgroups in the United States (US), and; 2) engaging the community as research partners, the team expects to gain knowledge as to specific social, psychological, and cultural factors that may represent barriers to PCA education and screening.



Molecular analysis for 14 prostate tumors from PR H/L men was completed: WES and RNA sequencing data are available for 14 and 25 tumors, respectively. Significant differences were observed in DRC between cases and controls and by disease aggressiveness. Focus groups (6) were performed with a response rate of 105% and key topics regarding PCA were identified.

Timeline and Cost

Activities	CY	21	22	23	24
Specific Aim 1					
Specific Aim 2					
Specific Aim 3					
Estimated Budget (\$K)		\$391K	\$391K	\$391K	\$391K

Updated: August 11, 2023

Goals/Milestones

CY21 Goals

- ☑ IRB approval
- ☑ Begin with recruitment for Aim 1 and 2, and for focus groups (Aim 3)

CY22 Goals

- ☑ Complete with recruitment for Aim 1 and 2.
- ☑ Request WES data, perform ancestry analysis.
- ☑ Measure DRC levels through NER.
- ☑ Focus groups data analysis.

CY23 Goals

- ☑ Analysis of WES and RNA-seq data
- ☑ Measure DRC levels through NER
- ☑ Standardization of the DRC assay to measure HRR
- ☑ Recruitment of survey participants

CY24 Goals

- ☐ Measure DRC levels through NER and HR; perform analysis and manuscript submission
- ☐ Perform interviews for evaluation of implementations strategies, interview data analysis, and manuscript preparation for Aim 3

Comments/Challenges/Issues/Concerns

- Nothing to report

Budget Expenditure to Date

Projected Expenditure: \$133,956.45

Actual Expenditure: \$1,040,695.55

9. APPENDICES:

Goals related to Subtask 3.5:

On July 1st, we started implementing the activities to complete Subtask 3.5. The first activity occurred in Patillas on July 1, 2023, at a baseball park, where the organization "Los Buenos de Patillas" hosted a community gathering. We collected data from 13 participants. In this municipality, a second data collection event was held on July 9th, where we recruited 44 participants, completing our efforts in this municipality. For Maunabo, we held events at churches of the municipality on July 2 and July 30. A total of 42 participants completed the survey, leaving us with 8 more participants to recruit. In Las Piedras, Dr. Willyson Velazquez will support the recruitment in his medical office. Data from this initiative is yet to be reported. As of August 8, 2023, a total of 92 out of 150 participants were recruited (61%).