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TITLE: Clinical Qualification of DNA Repair Defects as Biomarkers in Metastatic Prostate Cancer Using Integrated Genomics and Tissue-Based Functional Assays

PRINCIPAL INVESTIGATOR: Joaquin Mateo

CONTRACTING ORGANIZATION: Vall d'Hebron Institute of Oncology
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Dr. Joaquin Mateo, , Colin Pritchard, David Olmos

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14. ABSTRACT

We and others previously described an enrichment for somatic and germline alterations in DNA damage repair (DDR) genes among men with metastatic prostate cancer. Several recent clinical studies have indicated many of these patients could benefit from precision medicine strategies with PARP inhibitors and DNA damaging agents. In this project, our teams would investigate genomic, transcriptomic and protein-related functional signatures for a more accurate sub-classification of prostate cancers associated to DDR defects, aiming for a more precise patient care. The project is divided in 3 main aims: 1) testing the prognostic value of somatic DDR defects in a retrospective cohort of tumor biopsies, 2) developing multi-omics signatures based on prospective analyses of metastatic biopsies and 3) clinical validation of these biomarkers in a clinical trial using carboplatin as DNA damaging chemotherapy.

15. SUBJECT TERMS

None Listed

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1. **INTRODUCTION:**

We and others previously described an enrichment for somatic and germline alterations in DNA damage repair (DDR) genes among men with metastatic prostate cancer. Several recent clinical studies have indicated many of these patients could benefit from precision medicine strategies with PARP inhibitors and DNA damaging agents. In this project, our teams would investigate genomic, transcriptomic and protein-related functional signatures for a more accurate sub-classification of prostate cancers associated to DDR defects, aiming for a more precise patient care. The project is divided in 3 main aims: 1) testing the prognostic value of somatic DDR defects in a retrospective cohort of tumor biopsies, 2) developing multi-omics signatures based on prospective analyses of metastatic biopsies and 3) clinical validation of these biomarkers in a clinical trial using carboplatin as DNA damaging chemotherapy.

2. **KEYWORDS:**

Genomics; Whole-exome sequencing; RNAseq; Precision Medicine; DNA repair; BRCA; PARP inhibitors; platinum chemotherapy; clinical trial.

3. **ACCOMPLISHMENTS:** .

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.

Specific Aim 1 – To correlate the presence or absence of somatic/germline alterations in DNA repair genes with overall survival from mCRPC, and specific response to taxanes, Abiraterone, Enzalutamide, and Rd223, in samples from a prospective study.

Major Task 1: Targeted NGS on all study samples	**Timeline (Months)**	**Completed (%)**
Preparation of tumor biopsies for DNA extraction	0-12	100%
Milestone 1.1 – Shipment of samples to UW Laboratory (batches)	3 to 15	60%
Library preparation for targeted NGS	3 to 20	60%
Sequencing of all samples from the PROREPAIR-B study	3 to 20	60%
Variant calling, bioinformatics analysis	3 to 20	60%

	Timeline (Months)	Completed (%)
Milestone 1.2 – Classification of each patients as "positive" or "negative" for each of the biomarkers of interest (BRCA1, BRCA2, ATM, PALB2)		
Sequencing data analysis board: identification of putative relevant calls for patient care and relatives' risk of cancer	3 to 20	60%
Statistical analysis: correlation of genomic biomarkers with previously annotated clinical outcome data	22	No
Milestone 1.3 – Data analysis and interpretation, Manuscript Preparation	24	No
Milestone 1. 4 - F2F meeting among participating sites to discuss progress	12	100%

Specific Aim 2 – To optimize tissue-based tests of HR functionality samples for CRPC samples, and study the correlation with genomic aberrations in HR genes.

Major Task 2: Acquisition of bone marrow metastatic biopsies	**Timeline (Months)**	**Completed (%)**
Harmonization of tissue acquisition protocol among participating sites	1 to 2	100%
Collection of 100 metastatic biopsies, samples are sent to sites 2 and 3	3 to 22	60%
Milestone 2.1 – Sample acquisition completed	23	60%
Major Task 3: Whole-exome sequencing studies		
DNA extraction from tumor and germline DNA	6 to 24	80%
Whole exome sequencing studies	12 to 26	25%
Variant calling, bioinformatics analysis	12 to 28	25%
Sequencing data analysis board: identification of putative relevant calls for patient care and relatives' risk of cancer	6 to 30	10%
Major Task 4: Expression profiling studies		
RNA extraction from frozen core of biopsies	6-24	15%

RNA-seq studies	9 to 26	10%
Bioinformatics analysis	12 to 28	10%
Major Task 5: Immunofluorescence studies		
Sample preparation	8 to 30	50%
Immunofluorescence studies	10 to 30	50%
Milestone 5.1 – Integrated analysis of sequencing and IF data	32	25%
Milestone 5.2 – Data analysis and interpretation, Manuscript Preparation	34	0%

Specific Aim 3 To clinically qualify this HR functional test in a clinical trial of carboplatin in CRPC

Major Task 6: Clinical Trial Set Up	**Timeline (Months)**	**Completed (%)**
Clinical Trial Protocol Writing and Development	1 to 5	100%
Submission of clinical trial protocol to local ethics and regulatory bodies	5	100%
Set up of clinical sites participating in the trial		90%
Milestone 6.1 – First patient enrolled in the clinical trial	12	0%
Major Task 7: Clinical Trial conduction		
Patient recruitment	12 to 30	0%
Continuous data monitoring	12-36	0%
Trial-related biopsy acquisition	12 to 30	0%
Milestone 7.1 Recruitment completed for cohort 1	26	0%
Milestone 7.2 Recruitment completed for cohort 2, stage 1	22	0%

Recruitment for cohort 2, stage 2 (depending on results from stage 1)	23-30	0%
Milestone 7.3 Recruitment completed for cohort 2, stage 2	30	0%
Major Task 7: Biomarker studies in trials samples		
Preparation of trial related biopsies for NGS studies	12 to 30	0%
Targeted sequencing in trial-related biopsies	12 to 30	0%
Variant calling, bioinformatics analysis	12 to 30	0%
Immunofluorescence studies	12 to 30	0%
Sequencing data analysis board: identification of putative relevant calls for patient care and relatives' risk of cancer	12 to 30	0%
Milestone 7.1 – Integrated analysis of clinical and biomarker data	34	0%
Milestone 7.2 – Data analysis and interpretation, Manuscript Preparation	36	25%

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.

Specific Aim 1 – To correlate the presence or absence of somatic/germline alterations in DNA repair genes with overall survival from mCRPC, and specific response to taxanes, Abiraterone, Enzalutamide, and Rd223, in samples from a prospective study.

Major Task 1: Targeted NGS on all study samples

To date, 4 batches of samples have been sent from CNIO to the UW site and UW-OncoPlex sequencing and 97 have had sequencing using our more optimized low input protocols as outlined below. Of these, 70 had adequate studies to call mutations despite very low input quantities and low DNA quality. Among these 7 had *BRCA2* mutations, 5 had *ATM* mutations, 1 had an *NBN*

mutation, 2 had *CHEK2* mutations, 2 had *MUTYH* mutations, 1 had a FANCA mutation, and 1 had a FANCC mutation (**Table**).

Table: Prostate Cancer Samples with DNA Repair Gene Mutations Detected by UW-OncoPlex

CNIO_OLM_ID	UW Dataset_ID	DNA Repair Gene Mutation	Interpretation
OLM_03.035	198R16_H02_OPXv5_NB0187	**ATM**	POSITIVE for a pathogenic ATM mutation with associated LOH (p.R521*), CHD1 focal homozygous copy loss, possible MYC amplification
CNIOUW 012	272R10_B02_OPXv6_NA0414	**ATM**	POSITIVE for a pathogenic ATM mutation (p.R531*) with LOH (bi-allelic), CHD1 homozygous copy loss (bi-allelic), possible MYC amplification
CNIOUW 028	276R04_D01_OPXv6_NB0352	**ATM**	POSITIVE for two pathogenic ATM mutations (bi-allelic).
OLM,03.012	281R08_H01_OPXv6_NB0365	**ATM**	POSITIVE for ATM exon 25-63 del mutation with LOH (bi-allelic), CHD1 homozygous copy loss, SPOP p.F102I mutation
OLM_03.047	198R17_A03_OPXv5_NB0187	**ATM VUS**	POSITIVE for a pathogenic TP53 mutation, ATM VUS in the FAT domain (p.I2401T), and PTEN copy loss
OLM_01.006	198R01_A01_OPXv5_NB0187	**BRCA2**	POSITIVE for BRCA2 copy loss, cannot determine if 1 or 2 copies. Possible MYC amplification.
OLM_01.039	198R07_G01_OPXv5_NB0187	**BRCA2**	POSITIVE for a pathogenic mutation in BRCA2 (c.6650_6654del); cannot tell if germline or somatic
CNIOUW 005	272R03_C01_OPXv6_NA0414	**BRCA2**	POSITIVE for BRCA2 focal deletion (favor bi-allelic) and FOXA1 mutation
CNIOUW 018	275R06_F01_OPXv6_NB0350	**BRCA2**	POSITIVE for BRCA2 exon 1-24 deletion + LOH (bi-allelic) and possible MYC amplification.
CNIOUW 032	276R08_H01_OPXv6_NB0352	**BRCA2**	POSITIVE for a pathogenic BRCA2 mutation (c.3264dup), with possible BRCA2 copy loss.
OLM,FIVO.012	286R25_A04_OPXv6_NB0365	**BRCA2**	POSITIVE for a pathogenic BRCA2 mutation (cannot determine if mono-allelic or bi-allelic)
OLM,02.007	281R11_C02_OPXv6_NB0365	**BRCA2?**	POSITIVE for TP53 mutation, BRCA2 single copy loss, possible MYC amplification, and additional alterations
OLM,03.065	286R23_G03_OPXv6_NB0365	**CDK12**	POSITIVE for CDK12 bi-allelic pathogenic mutation with associated tandem duplication signature, MYC amplification, FOXA1 mutation
OLM,02.009	281R01_A01_OPXv6_NB0365	**CHEK2**	POSITIVE for a pathogenic mutation in CHEK2 (exon 11-12 deletion), cannot determine if mono- or bi-allelic
CNIOUW 034	277R02_B01_OPXv6_NB0354	**CHEK2 VUS**	POSITIVE for SPOP p.F102C mutation, KDM6A mutation, MYC amplification, and CHEK2 VUS.
OLM,FIVO.228	286R37_E05_OPXv6_NB0365	**FANCA**	POSITIVE for FANCA pathogenic mutation (cannot tell if mono-allelic or bi-allelic), TP53 mutation, and additional alterations
CNIOUW 039	277R07_G01_OPXv6_NB0354	**FANCC**	POSITIVE for a pathogenic mutation in FANCC (c.455dup, carrier only)
OLM_02.033	198R12_D02_OPXv5_NB0187	**MLH1, MSI-high**	MSI-high due to MLH1 loss, high total mutation burden.
CNIOUW 010	272R08_H01_OPXv6_NA0414	**MSI/MMRd**	MSI-high likely (limited analysis due to low sample quality)
CNIOUW 033	277R01_A01_OPXv6_NB0354	**MUTYH (carrier)**	POSITIVE for a pathogenic mutation in MUTYH (p.G396D, carrier only)
CNIOUW 009	272R07_G01_OPXv6_NA0414	**MUTYH (carrier)**	POSITIVE for a pathogenic mutation in MUTYH (p.G396D, carrier only)
OLM,FIVO.009	286R32_H04_OPXv6_NB0365	**MUTYH (carrier), I**	POSITIVE for germline heterozygous MUTYH mutation (p.Y179C carrier), TP53 mutation, BRCA2 single copy loss, and additional alterations
CNIOUW 008	272R06_F01_OPXv6_NA0414	**NBN**	POSITIVE for a pathogenic mutation in NBN (p.R43*)

HRPO approvals: The research for Aim 1 at Site 1 (UW) was determined to be not human subjects by the UW IRB, with HRPO concurrence on 10/17/2018. This facilitated use of de-identified samples from Site 2 in year 1 and year 2 for optimization of the UW-OncoPlex sequencing assay in the context of limited sample quantity. HRPO approval was obtained at Site 2 (CNIO) on 9/30/19 for research on aims 1 and 2.

In years 1 and 2 Site 1 (UW) received representative de-identified extracted DNA specimens from the Site 2 (CNIO) for UW-OncoPlex sequencing in batches to optimize sequencing protocols.

Many of the samples had low amounts of residual DNA remaining (<250ng). There is availability of pre-capture libraries for most of the samples. To facilitate adequate performance on these low input samples we undertook three parallel development efforts in year 1 to modify and re-validate the UW-OncoPlex assay for clinical use with low-input samples anticipated from the PROREPAIR trial as part of this work.

The first approach was to validate pre-capture libraries from Site 2 for use with UW-OncoPlex. To evaluate and validate pre-capture libraries as a sample type for UW-OncoPlex pilot samples were sent to Site 1 (UW) from Site 2 (CNIO) with matched pre-cap libraries and extracted DNA. We are currently working closely with our bioinformatics team, wet-bench staff to work out the protocol to run and analyze these pre-cap library samples on our platform. Briefly, the samples are quantified on the Agilent Tape Station and pooled together for hybridization along with a HapMap control (NA12878). They are hybridized with latest UW-OncoPlex (version 6) capture, using an IDT xGen protocol. The pool is loaded on an Illumina instrument (PE101 + 8bp index read). Since the samples were previously barcoded with 6bp indexes, we added "NN" to the end of the sequences for the MiSeq sample sheet, which would allow demultiplexing and analysis of both the 6bp and 8bp indexes in the pool. Using this protocol we have successfully sequenced four pre-capture libraries, however the sequencing quality is not yet adequate using pre-capture libraries. To troubleshoot, we

are attempting more pre-capture libraries with higher DNA quantity. In parallel we focused on testing samples with >250ng input DNA, prioritizing patients with radical prostatectomy first.

The second approach was to modify and re-validate the UW-OncoPlex sequencing assay for use with Nextera NextFlex enzymatic tagmentation-based sequencing library preparation rather than using DNA shearing with the Covaris. This NextFlex method allows the assay to take as little as 10ng DNA input rather than the 250ng input desired with Covaris shearing method. Also, less DNA is lost in wash steps using the NextFlex method. Briefly, to validate this method at Site 1, we selected a total of 57 tumor DNA samples that had been previously characterized by UW-OncoPlex and re-ran these using the Nextera low input protocol. All reportable mutations, copy number variants, and structural variants were identified using the Nextera protocol. Between run and within reproducibility was assessed for 3 tumor samples and for the NA12878 HapMap control with perfect concordance. MSI status was also 100% concordant. An example of the qualitive concordance of copy number calling is given in the Figure below.

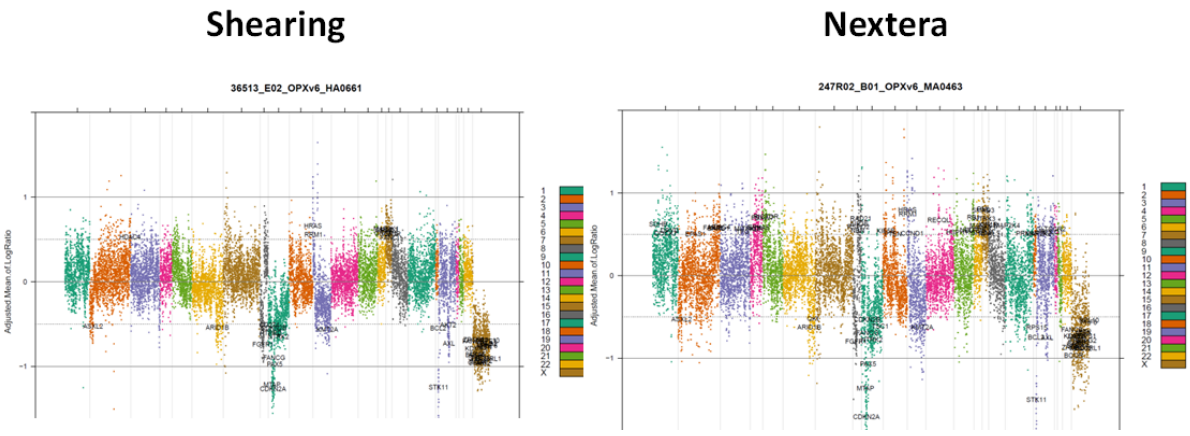


Figure: Comparison of copy number calling between the standard shearing and low input Nextera UW-OncoPlex sequencing. We observed high qualitative and quantitative concordance between the standard shearing-based library prep and Nextera low input library preparation for the UW-OncoPlex assay.

Finally, as a third approach if needed, we will explore testing plasma cell-free DNA for patients <250ng input DNA remaining. The CNIO group at Site 2 has frozen plasma available from most of these patients and is currently exploring whether it may be feasible to use these samples. The UW-OncoPlex assay has recently been extensively clinically-validated for use with plasma cell-free DNA in patients with metastatic prostate cancer (Schweizer et al. 2019 PMID:30865311, DOD support acknowledged). In parallel, and for those PROREAPIR-B cases without cell-free DNA samples and poor quantity/quality DNA yields, Site 2 (CNIO) will explore to complement the results with shallow whole genome sequencing (WGS) which may yield results satisfactory enough to detect chromosomal deletions which cause loss of function in the genes of interest, in some genes as *BRCA2* this large deletion are the commonest somatic change. At the present a small cross validation of both UW-OncoPlex sequencing at site 1 and shallow WGS has been completed as part of an initial PROREPAIR report in ASCO and ESMO annual meetings (Lozano et al. doi: 10.1200/JCO.2020.38.15_suppl.5511; Lozano et al. doi: doi.org/10.1016/j.annonc.2020.08.872, DOD support acknowledged) and which manuscript will be submitted shortly.

Summary of progress on milestones related to Aim 1 in Year 2

Milestone 1.1 Shipment of samples From CNIO laboratory to UW laboratory (batches) (Month 3-15): In summary, in year 2 two large batches of samples were shipped from CNIO to the UW Laboratory, focusing on samples with the highest quantity of residual DNA. Batches of de-identified samples were initially shipped for the purpose of assay and protocol optimization from Site 2 to Site 1 in year 1 (not human subjects research) while HRPO approval at site 2 was pending. The PROREPAIR-B trial in which aim 1 was based, was an already approved and completed protocol in Spain. There were some unanticipated delays in obtaining HRPO approvals at Site 2 (CNIO) due in part to requirements of independent evaluation of this work by our reference IRB, and review of several iterations of verified English translations from original study documents produced in Spanish between January and July 2019. After submission of the final required documents in July 2018, HRPO approval at Site 2 (CNIO) was granted on September 30th, 2019.

Since receiving HRPO approval at Site 2 (CNIO), 217 samples were reviewed by a trained GU pathologist, macro-dissected from tumor sections and processed for DNA extraction at the CNIO Lab. These were archived biopsies from multiple participating sites (38) which were obtained primary for pathology diagnosis a median of 2 years (range 4-21 years) before developing mCRPC and entering the study the tumor tissue availability was scarce in many previously devastated tumour blocks, or the DNA quantity and quality yield by these samples was low in most cases. After discussion with the Site 1 UW laboratory, and following progress in improving the UW-OncoPlex assay to work with samples with lower DNA quantity/quality as expected from PROREPAIR-B FFPE sample collection. Shipments were organised according to quality/quantity starting with best samples from initial 120 extracted samples.

Milestone 1.2 – Classification of each patients as "positive" or "negative" for each of the biomarkers of interest (BRCA1, BRCA2, ATM, PALB2): To date, we have identified 23 patients as "positive for the biomarker" of interest, using sequencing done at site 1 (see Table 1).

Milestone 1.3 – Data analysis and interpretation, Manuscript Preparation (24 months; Site 1, 2 and 3):
Two initial communications related to aim 1 have already been presented at international meetings in which the DOD funding has been acknowledged:

1. Meeting: 27th Prostate Cancer Foundation Scientific Retreat, October 20-23, 2020
- Title: *Association between BRCA2 alterations and intraductal and cribriform histologies in prostate cancer*
- Authors: E. Castro, D.C. Salles; R. Lozano, H. Thorne, F. López-Campos, J. Rubio-Briones, Ana M. Gutierrez-Pecharroman, M.I. Pacheco, T. Garcés, N. Romero-Laorden, F. Zambrana1, P.P. López-Campos, S. Sandhu, **J. Mateo, C. Pritchard**, E. Antonarakis, **D. Olmos**, T. Lotan.
- Reference: https://www.morressier.com/article/association-brca2-alterations-intraductal-cribriform-histologies-prostate-cancer/5f69edb69b74b699bf38c600?

2. Meeting: European Society of Medical Oncology annual meeting 2020, September 19-21, 2020 (also presented at the American Society of Clinical Oncology annual meeting, May 27-Jun 1, 2020)

- Title: *Clinical impact of somatic alterations in prostate cancer patients with and without previously known germline BRCA1/2 mutations: Results from PROREPAIR study*
- Authors: R. Lozano Mejorada, E. Castro Marcos, I.M. Aragon, H. Thorne, F. Lopez Campos, A. Sanz, C. Alonso, U. Anido, M.J. Juan Fita, A.M. Gutierrez Pecharromán, M. Ramirez-Backhaus, J. Balmana, I. Chirivella Gonzalez, G. Llort, N. Romero Laorden, S. Arevalo Lobera, J. Rubio Briones, **J. Mateo, C.C. Pritchard,** S. Sandhu, **D. Olmos Hidalgo**
- Reference: https://doi.org/10.1016/j.annonc.2020.08.872

A manuscript based on the PROREPAIR samples and the results in abstract 1 have been submitted before this summary to European Journal of Cancer, and a manuscript related to the second communication is currently in preparation. In both cases the DOD funding will be acknowledge.

Milestone 1. 4 - F2F meeting among participating sites to discuss progress (12 months; Site 1, 2 and 3): A project Kick-Off meeting with three PIs (Pritchard, Olmos, and Mateo) and with some co-investigators (Cheng and Castro) was held in San Diego, CA in Oct 2018. An end-of-year 1 meeting to discuss progress was held Oct 25th 2019 in San Diego, California, that included the three PIs, according to the planned timelines. A grant review meeting that included the three partnering PIs and key team members was held September 21, 2020.

Specific Aim 2 – To optimize tissue-based tests of HR functionality samples for CRPC samples, and study the correlation with genomic aberrations in HR genes.

Major Task 2: Acquisition of bone marrow metastatic biopsies

For Site 2 (CNIO): IRB approval for the participation of site 2 at this major task (2.2) was received on November 26th, 2018 with the approval to proceed with aim 1. As outlined in the section above HRPO approval for aim 1 and 2 was received September 30th, 2019.

For Site 3 (VHIO), the research protocol for acquisition and analysis of patient biopsies was approved by the local ethics board. As of 15th Oct 2020, 127 patients have been consented for consideration of biopsies. After discussion of suitability with interventional radiology, 42 patients have successfully undergone a metastatic biopsy procedure, collecting at least 1 fresh frozen core and 1 FFPE core for the study. Additionally, archival prostate primary tumor biopsy material has been retrieved from the diagnostic hospital for 78/127 cases. Saliva samples for correlative germline analyses were collected for all patients at the time of consent.

Major Task 3: Whole-exome sequencing studies

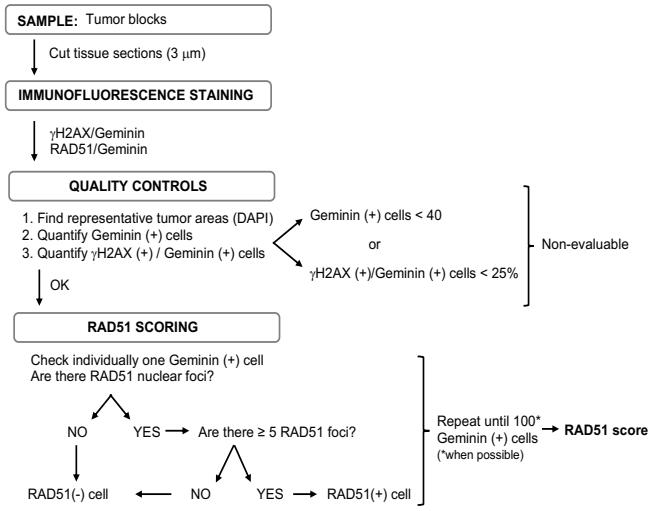
DNA has been extracted from both tumor and saliva samples for 50% of cases, and low-pass whole-genome sequencing has been performed in all of them. Samples with a tumor content over 20%, estimated by low-pass WGS bioinformatics analysis have been selected for WES. We started capturing libraries for WES for these samples in Sept 2020.

Major Task 4: Expression profiling studies

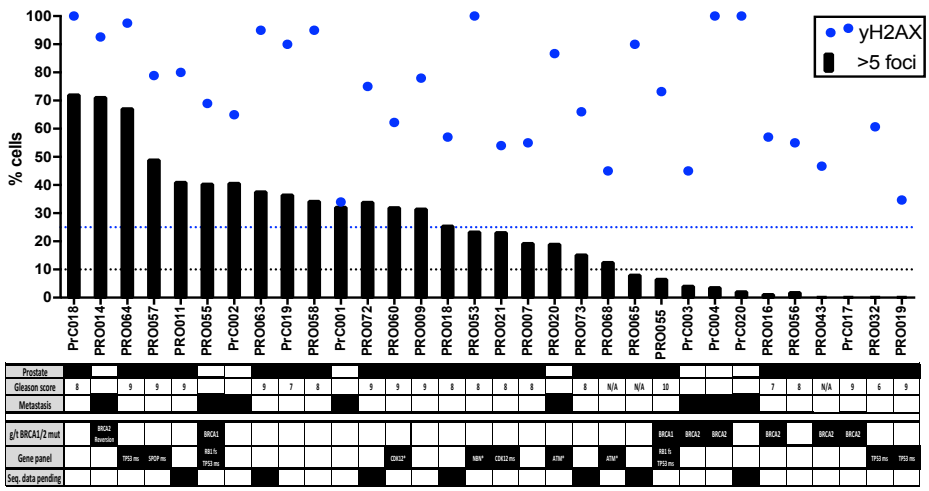
RNA from the frozen blocks of the metastatic biopsies is being extracted, this task has been started in Sept 2020. Unfortunately, this represents a significant delayed from the original planned calendar, resulting from the complete shutdown of our lab at site 3 (VHIO) for over 3 months and later partial re-opening, due to the COVID19 pandemic-related restrictions, that made us prioritize other projects with prospective sample collection. Similarly, work for this task at site 2 (CNIO) was severely disrupted due to the Covid-19 pandemic in Spain, the lab was closed from March 7th, 2020 until July 1st, 2020 under the government regulations. Since July 1st, Site 2 team has been allowed to work on site with a restriction of 50% of personnel. Then for this aim at site 2 (CNIO) the focus has been to revaluate the proposed approach for transcriptomic analyses based on RNAseq using in silico data and samples from other projects to optimize extraction form this precious samples (this protocols are shared between Site 2 and 3-CNIO and VHIO) and RNAseq library generation process.

Major Task 5: Immunofluorescence studies

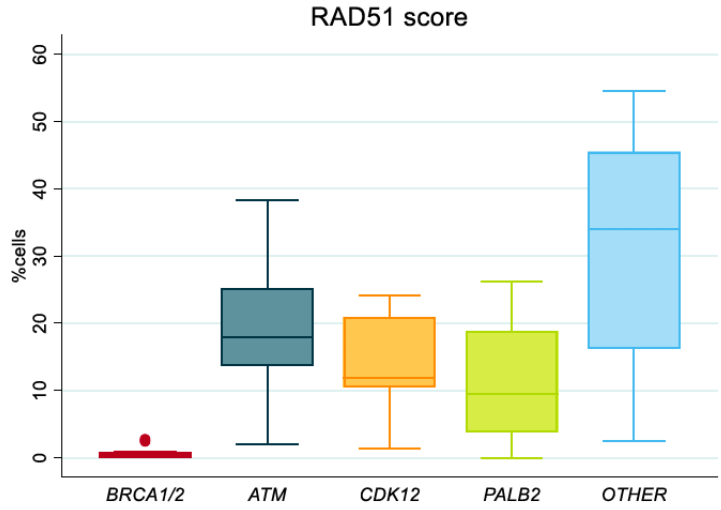
As planned, we have re-optimized now an IF-based test initially developed in breast cancer patient-derived xenoimplant models and then validated in breast cancer biopsies (Cruz et al, Ann Onc 2018; Castroviejo-Bermejo et al, EMBO Med 2019). We are using FFPE slides from prostate cancer primary and metastatic biopsies. An overview of the assay procedure and interpretation workflow is presented below:



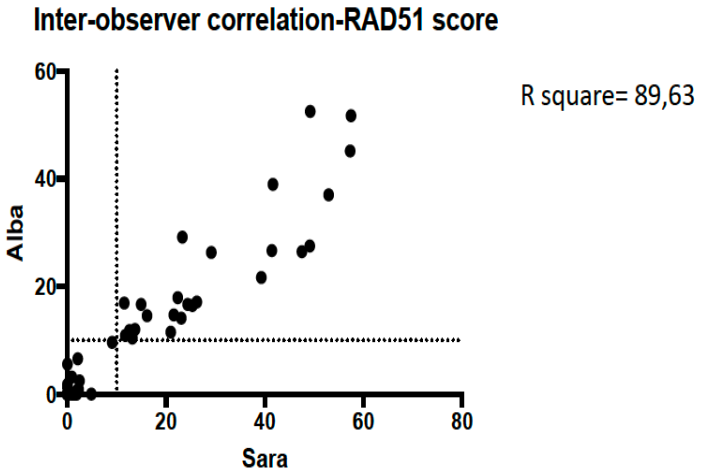
In Year 1, we presented results on a first cohort of 32 samples (results below), suggesting the assay is capable of identifying prostate cancers with *BRCA2* mutations:



In this second year, we have validated the assays using primary and metastatic biopsies from 52 patients with known DNA repair mutations who participated in clinical trials of PARPi. In the boxplot below, we show that every single case with BRCA1/2 mutations (n=16) presents negativity for RAD51 foci by immunofluorescence, whereas cases with mutations in other genes related with HR, such as ATM (n=10) and CDK12 (n=10), present positive foci for RAD51 but with significantly lower median values than those patients with no mutations in core HRR genes (n=13). At present, we are pursuing clinical outcome correlations for these results, that will be critical for the use of this assay in the clinical trial.



Additionally, we have analyzed the inter-reader reproducibility of the assay, finding a 100% concordance using a dycotomic positive/negative calling, and high correlation (R=0.896) using a continuoius variable calling between two blinded operators. At present, we are working in automatizing the reporting of results, in collaboration with our Pathology core services at VHIO; in order to expedit the development of the assay, we have now employed a pathologist (Dr Maria Urbanowicz) who work part-time in this project, but costs of this additional personnel will be covered by other sources, and not from this award.



Summary of progress on milestones related to Aim 2 in Year 2

Milestone 2.1 – Sample acquisition completed (month 23): Not completed, currently at 60%
***Milestone 5.1 – Integrated analysis of sequencing and IF data* (*month 32*): Not due yet.**
***Milestone 5.2 – Data analysis and interpretation, Manuscript (month 34):* Not due yet.**

Specific Aim 3 – To clinically qualify this HR functional test in a clinical trial of carboplatin in CRPC

Major Task 6: Clinical Trial Set Up

In year 1, we completed the trial protocol which was initially submitted to site 2 reference IRB (CEI Provincial de Malaga) and the AEMPS (Spanish regulatory agency) and initial review and proposed amendments were received by October 2020. The protocol was submitted to the HRPO before regulatory submission, but final feedback from HRPO was received in January 2020. These feedback were implemented together with the initial feedback from reference IRB and AEMPS and resubmitted for evaluation to both. Final IRB and AEMPS approvals of amended clinical trial documents were granted on March 27th and April 20th, 2020, respectively. The original documents and their verified translations of these documents were submitted to HRPO.

Following these approvals contract negotiations with participating sites were initiated by the CNIO team from July 1st, 2020, as the trial office was also in shutdown until July due to the government restrictions related to the COVID pandemic and the effects in the Spanish National Health System.

Currently, the trial set up at the participating clinical sites is at different stages:

Contracts negotiation review completed and pending on sponsor and participating institution legal signatures:

- Hospitales Universitarios Virgen de la Victoria and Regional de Málaga (CNIO clinical site)
- Hospital Clínico San Carlos, Madrid
- Hospital Universitario de Santiago, Santiago de Compostela

Reviewed contracts pending on final signatures:

- Instituto Oncológico de Donostia, San Sebastian
- Hospital Universitario Vall D'Hebron, Barcelona (Site 3)
- Hospital Universitario 12 de Octubre, Madrid
- Hospital Universitario La Princesa, Madrid
- Hospital Provincial de Castellon
- Centro Oncológico de Galicia, La Coruña
- Hospital del Mar, Barcelona

Initial contract review ongoing:

- Instituto Valenciano de Oncología, Valencia
- Hospital Universitario Puerta del Hierro, Madrid
- Instituto Catalan de Oncología, L'Hospitalet
- Instituto Catalan de Oncología, Badalona

While we were aiming for the first patient to be enrolled in the trial before the end of 2020, the first trimester of year 3.

During this time as part of this task the CNIO team has also completed the design of an electronic Clinical research form, a statistical analysis plan for the study and a manual of samples handling and procedures as part of the study materials for the participating sites personnel. We have also gathered regulatory documentation on the ICH-GCP training certification and CVs for the researchers participating at each site and this documentation has also been provided to the HRP.

Major Task 7: Clinical Trial conduction

Trial conduction has not been initiated pending on completing contracts signatures with the participating sites. On other hand pre-initiation on site or virtual visits to train and evaluate the research team at each trail site has been completed.

Major Task 8: Biomarker studies in trials samples

Tasks 7 and 8 are planned for Years 2 and 3 of the award, and hence have not been yet initiated as they depend on clinical trial activation.

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.

- **Site 1 (UW):** Gavin Ha, PhD recent junior faculty member recruit at the Fred Hutchinson Cancer Center who had collaborated with the Pritchard site on the UW-OncoPlex assay was awarded a 2019 Prostate Cancer Foundation Young Investigator Award. Jonathan Reichel, PhD, a postdoctoral fellow in the Pritchard group has received mentorship in bioinformatics for UW-OncoPlex. In June 2020, Heather Cheng, MD, PhD, co-investigator received a special NCI career development award for Cancer Clinical Investigator Team Leadership to make complex cancer research information more approachable. A Laboratory Medicine Masters Student, Mohammad Adil has begun training to learn how to analyze UW-OncoPlex data.

- **Site 2 (CNIO):** Elena Castro, MD, PhD, investigator at site 2 was awarded a Juan Rodés Clinician Scientist fellowship from ISCIII (Spanish NIH) to continue working in the area of this project and DNA repair in Prostate Cancer during Year 1. At year 2, her fellowship was evaluated and renewed for an additional year

- **Site 3 (VHIO):**Sara Arce, laboratory technician at Site 3 participating in this project, has been awarded a PhD fellowship to conduct her PhD in part related to this project under the mentorship of PI J. Mateo, and her role as technician in this project was taken over by Sarai Cordoba, PhD.

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.

- **Site 1 (UW):** Nothing to report.

- **Site 2 (CNIO):** This project has been discussed with other projects at a virtual Patient Engagement Event hold in Málaga in September 2020 co-organized by the CNIO team and

the CRIS foundation, a cancer research charity. The attendance to this virtual meeting was estimated in 115.

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- **Site 3 (VHIO):** In this Year 2, PI J Mateo participated during Sept 2020 in a virtual symposium for cancer patients organized by the Spanish Society Against Cancer (AECC) presenting results from this and other projects from his lab focusing in genomic stratification of advanced prostate cancer.

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.

Site 1 (UW): For Aim 1, we anticipate completing UW-OncoPlex testing for PROREPAIR-B samples where adequate DNA is available. For Aim 3, we anticipate beginning to receive samples for targeted sequencing from Site 3. We will shift our focus to data analysis and manuscript preparation.

Site 2 (CNIO): For aim 1, Site 2 (CNIO) is increasing communication with Site 1 (UW) where samples will be analyzed in order to ensure completion of this aim in year 2. Extra resources (more pathology and technicians' hours) to accelerate samples review and initial processing at CNIO have been put in place during year 2 and when Covid19 pandemia regulations allowed.

For aim 2, after HRPO approval at our site activation for this aim, we will accelerate ru contribution the recruitment of patients and samples for aim 2. We will also plan to start with the RNA expression analyses along the second part of year 2.

For aim 3, we expect to enroll the first patient on the trial during the first 3 months of year 3, and we already have discussed with CDMRP the need of a non-funded time extension of this aim.

Site 3 (VHIO): For aim 2 we anticipate comleting WES and IF studies on all samples, as well as extracting RNA for the RNAseq studies to be conducted at Site 2. We anticipate a delay in delivering final results from Aim 2 due to the COVID-related lockdown earlier this year. For aim 3 we anticipate the patient recruitment on the biomarker-driven clinical trial sponsored by Site 2, which also has been delayed due to the COVID-related restrictions..

4. IMPACT

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 during.

5. CHANGES/PROBLEMS:

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.

The current COVID-19 pandemic we are suffering worldwide has impacted the progress of this project at different levels: firstly, as our laboratories have been working at reduced capacity, or even under strict lockdown for some time, some of the analysis have been delayed. Secondly, the capacity to pursue research biopsies from patients at Site 2 and 3 were severely reduced during the period March-July due to the restrictions in our hospitals and the need for reducing the non-COVID related clinical activities and concerns about patient safety. At present, our sites still suffer from some limitations with regards to pursuing research biopsies, albeit not as strict as during Q2-Q3 2020. However, it is envisioned the second wave of COVID cases, currently affecting Europe severely may result again in more strict restrictions to the acquisition of research biopsies in the next few months. Last, the lockdown also has reduced the activates of our trials offices, delaying the setup of the clinical trial in Aim 3.
In order to minimize the impact of these restrictions in our progress, we have implemented diverse measures such as: 1) pursuing the validation of RAD51 IF assay in a separate cohort of metastatic biopsies with targeted genomics data available at Site 3; 2) prioritize exploiting publically available transcriptomics databases, so the analysis can be conducted faster once we acquire the necessary biopsies.

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.
As described above for Aim 1, we are developing protocols and alternative strategies for use with low input DNA quantity as many of the PROREPAIR-B samples have limited DNA. In parallel, we are prioritizing sequencing of samples from patients with high input DNA.

As described in Aim 3, the activation of the clinical trial of embedded in this project and key for al tasks in this aim has been severely delayed due to the Covid19 pandemic. We also expect that initial recruitment will be seriously impacted until mid 2021 (year 3). To minimize this impact, we are already planning to allow the inclusion of patients based on the biomarker results of diagnostic biopsies following the results that are being generated by site 3 in Aim 2. We are also increasing communication with the investigators at the participating sites in order to increase the commitment to the project. Nonetheless, we may need to request a no-cost extension next year for the clinical trial completion.

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.

None

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
Not applicable

Significant changes in use or care of vertebrate animals
Not applicable

Significant changes in use of biohazards and/or select agents
Not applicable

6. PRODUCTS:

- **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).*

  Schweizer MT, Gulati R, Beightol M, Konnick EQ, Cheng HH, Klemfuss N, DeSarkar N, Yu EY, Montgomery RB, Nelson PS, and **Pritchard CC**. Clinical determinants for successful circulating tumor DNA analysis in prostate cancer. Prostate; 79: 2019; 701-708; published; acknowledgement of federal support (yes).

  Schweizer MT, Antonarakis ES, Bismar TA, Guedes LB, Cheng HH, Tretiakova MS, Vakar-Lopez F, Klemfuss N, Konnick EQ, Mostaghel EA, Hsieh AC, Nelson PS, Yu EY, Montgomery RB, True LD, Epstein JI, Lotan TL, and **Pritchard CC**. Genomic Characterization of Prostatic Ductal Adenocarcinoma Identifies a High Prevalence of DNA Repair Gene Mutations. JCO Precis Oncol. 2019; PMID: 31123724; published; acknowledgement of federal support (yes).

  Khani F, Wobker SE, Hicks JL, Robinson BD, Barbieri CE, De Marzo AM, Epstein JI, **Pritchard CC**, Lotan TL. Intraductal carcinoma of the prostate in the absence of high-grade

invasive carcinoma represents a molecularly distinct type of in situ carcinoma enriched with oncogenic driver mutations. *J Pathol*; 2019; PMID:30993692; published; acknowledgement of federal support (yes).

Abida W, Cyrta J, Heller G, Prandi D, Armenia J, Coleman I, Cieslik M, Benelli M, Robinson D, Van Allen EM, Sboner A, Fedrizzi T, Mosquera JM, Robinson BD, DeSarkar N, Kunju LP, Tomlins S, Wu YM, Nava Rodrigues D, Loda M, Gopalan A, Reuter VE, **Pritchard CC, Mateo J,** Bianchini D, Miranda S, Carreira S, Rescigno P, Filipenko J, Vinson J, Montgomery RB, Beltran H, Heath EI, Scher HI, Kantoff PW, Taplin ME, Schultz N, deBono JS, Demichelis F, Nelson PS, Rubin MA, Chinnaiyan AM, Sawyers CL. Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci; 116: 2019; 11428-11436; published; acknowledgement of federal support (yes).

Antje Neeb*, Nicolas Herranz*, **Sara Arce-Gallego***, Susana Miranda, Lorenzo Buroni, Wei Yuan,, **Alejandro Athie**, Teresa Casals, Juliet Carmichael, Daniel Nava Rodrigues, Bora Gurel, Pasquale Rescigno, Jan Rekowski, Jon Welti, Ruth Riisnaes, Veronica Gil, Jian Ning, Verena Wagner, Irene Casanova-Salas, **Sarai Cordoba**, Natalia Castro, Maria Dolores Fenor de la Maza, George Seed, Khobe Chandran, Ana Ferreira, Ines Figueiredo, Claudia Bertan, Diletta Bianchini, Caterina Aversa, Alec Paschalis, Macarena Gonzalez, Rafael Morales-Barrera, Cristina Suarez, Joan Carles Amanda Swain, Adam Sharp, Jesus Gil, **Violeta Serra**, Christopher Lord, Suzanne Carreira, **Joaquin Mateo**, and Johann S de Bono. Advanced prostate cancer with ATM loss: PARP and ATR inhibitors. European Urology, 2020 (in press) Acknowledgement of federal support (yes).

Rebeca Lozano, **Elena Castro**, Isabel M. Aragón, Ylenia Cendón, Carlo Cattrini, Pedro P. López-Casas, **David Olmos.** Genetic aberrations in DNA repair pathways: a cornerstone of precision oncology in prostate cancer. Bristih Journal of Cancer 2020 [Epub ahead of Print] doi: https://doi.org/10.1038/s41416-020-01114-x
Acknowledgement of federal support (yes).

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).*

BOOK CHAPTER (in press): Germline and Somatic Defects in DNA Repair Pathways in Prostate Cancer. Book Title: Prostate Cancer - Cellular and Genetic Mechanisms of Disease Development and Progression. Authors: Sara Arce, Alejandro Athie, **Colin C. Pritchard, Joaquin Mateo**

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.*

- **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.

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

-
  terms and conditions of an award.

- **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.*

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".

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*

Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

SITE 3 (VHIO)

Name: Joaquin Mateo
Project Role: Principal Investigator
Nearest person month worked: 12
Contribution to Project: Dr. Mateo is the PI of this award. Work in Aim 2 Patient Recruitment and Sample Acqusition.
FUNDING SUPPORT: Prostate Cancer Foundation, European Commission H2020 Programm, FERO Foundation and this award.

Name: Alejandro Athie
Project Role: Postdoctoral Researcher
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 6
Contribution to Project: Optimization of NGS protocols and bionformatic analysis for Aim 2.
Funding support: this award.

Name: Sara Arce
Project Role: Laboratory Technician
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 2
Contribution to Project: Task 5

Name: Sarai Cordoba
Project Role: Laboratory Technician
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 3,4
Contribution to Project: Task 5

Name: Violeta Serra
Project Role: Collaborator
Nearest person month worked: 2
Contribution to Project: Dr Serra collaborates with Dr Mateo in development of Task 5.
FUNDING SUPPORT: Spanish Ministry of Science, Asociacion Española contra el Cancer

Name: Raquel Perez-Lopez
Project Role: Collaborator
Nearest person month worked: 3
Contribution to Project: Dr Perez-Lopez oversees patient evaluation for pursuing biopsies and has participated in set up of Aim 3.

FUNDING SUPPORT: Prostate Cancer Foundation, CRIS Foundation, FERO Foundation

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.

SUPPORT
Mateo, Joaquin

Current Funding
Title: Perfiles moleculares de cáncer de próstata asociados a defectos de la reparación del ADN para el desarrollo de estrategias de medicina personalizada
Time Commitments: 1 calendar months
Supporting Agency: Instituto Salud Carlos III
Contracting/Grants Officer: Andrés de Kelety Alcaide
Performance Period: 01/1/2019 – 12/31/2021
Level of funding:
Project Goals: 1) To optimize the detection of actionable mutations in biopsies from metastatic castration-resistant prostate cancer in the clinical setting. 2) To study the impact of ATM and TP53 loss in preclinical models of prostate cancer
Specific Aims:
Overlap: N/A

Title: Co-targeting androgen receptor signalling and DNA damage repair for precision therapy
Time Commitments: 3 calendar months
Supporting Agency: European Commission, H2020 Programme
Contracting/Grants Officer: Andrés de Kelety Alcaide
Performance Period: 05/1/2019 – 07/31/2021
Level of funding:
Project Goals: To study the impact of co-targeting AR and PARP in preclinical models of prostate cancer; To study the transcriptomic profile of biopsies collected after AR inhibition.
Specific Aims:
Overlap: N/A

Title: Optimizing liquid biopsy in prostate cancer
Time Commitments: 1 calendar months
Supporting Agency: FERO Foundation
Contracting/Grants Officer: Ruben Ventura
Performance Period: 09/1/2019 – 08/31/2021
Level of funding:
Project Goals: To develop multi-omic approaches to interrogating prostate cancer molecular features based on liquid biopsies.
Specific Aims:
Overlap: N/A

Title: Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN)
Effort: 0.30 calendar
Supporting Agency: Movember (via PCCTC, LLC)
Contracting/Grants Officer: Casey Sisco,
Performance Period: 08/18/17 – 07/31/22
Level of Funding:
Project Goals: The major goal of this study is to create an international, population-based, prospective registry of at least 5,000 men with advanced prostate cancer.
Overlap: None

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

- *Nothing to report*

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.*

9. APPENDICES: