AWARD NUMBER:
W81XWH-18-1-0756

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

PRINCIPAL INVESTIGATOR:
Colin Pritchard

CONTRACTING ORGANIZATION:
University of Washington, Seattle, WA

REPORT DATE:
October 2022

TYPE OF REPORT:
Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2022	Annual	30Sept2021-29Sep2022

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER
W81XWH-18-1-0756

5b. GRANT NUMBER
PC170510

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Pritchard, Colin

E-Mail: cpritch@uw.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Washington
4333 Brooklyn Ave NE
Box 359472
Seattle, WA 98195-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

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

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

10. SPONSOR/MONITOR'S ACRONYM(S)

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

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Metastatic castration-resistant prostate cancer (mCRPC) is an incurable disease despite several agents being approved over the last decade. Understanding the inter-patient genomic heterogeneity in this disease is critical to advance to personalized cancer care based on predictive biomarkers. We and others have identified enrichment of homologous recombination (HR) mediated DNA repair defects in mCRPC, accounting for 20-25% cases, with inheritable defects in almost half of these cases. Ongoing clinical trials are studying the role of PARP inhibitors in this subpopulation. Particularly, BRCA2 mutations are known to be an independent poor prognostic factor for relapse in localized disease. Here, we propose to elucidate the prognostic and predictive impact of these mutations with regards to outcome from standard-of-care treatments for mCRPC, and to develop and clinically qualify functional tests to stratify mCRPC patients based on DNA repair damage proficiency, to improve the care of men with advanced prostate cancer.

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

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	46	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

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?

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	80%
Library preparation for targeted NGS	3 to 20	85%
Sequencing of all samples from the PROREPAIR-B study	3 to 20	85%
Variant calling, bioinformatics analysis	3 to 20	85%

	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	85%
Statistical analysis: correlation of genomic biomarkers with previously annotated clinical outcome data	22	35%
Milestone 1.3 – Data analysis and interpretation, Manuscript Preparation	24	35%
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	100%
Milestone 2.1 – Sample acquisition completed	23	100%
Major Task 3: Whole-exome sequencing studies		
DNA extraction from tumor and germline DNA	6 to 24	100%
Whole exome sequencing studies	12 to 26	100%
Variant calling, bioinformatics analysis	12 to 28	80%
Sequencing data analysis board: identification of putative relevant calls for patient care and relatives' risk of cancer	6 to 30	50%
Major Task 4: Expression profiling studies		
RNA extraction from frozen core of biopsies	6-24	100%

RNA-seq studies	9 to 26	100%
Bioinformatics analysis	12 to 28	70%
Major Task 5: Immunofluorescence studies		
Sample preparation	8 to 30	100%
Immunofluorescence studies	10 to 30	100%
Milestone 5.1 – Integrated analysis of sequencing and IF data	32	65%
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		100%
Milestone 6.1 – First patient enrolled in the clinical trial	12	100%
Major Task 7: Clinical Trial conduction		
Patient recruitment	12 to 30	80%
Continuous data monitoring	12-36	50%
Trial-related biopsy acquisition	12 to 30	80%
Milestone 7.1 Recruitment completed for cohort 1	26	80%
Milestone 7.2 Recruitment completed for cohort 2, stage 1	22	80%
Recruitment for cohort 2, stage 2 (depending on results from stage 1)	23-30	20%

Milestone 7.3 Recruitment completed for cohort 2, stage 2	30	20%
Major Task 7: Biomarker studies in trials samples		
Preparation of trial related biopsies for NGS studies	12 to 30	50%
Targeted sequencing in trial-related biopsies	12 to 30	10%
Variant calling, bioinformatics analysis	12 to 30	0%
Immunofluorescence studies	12 to 30	90%
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?

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.

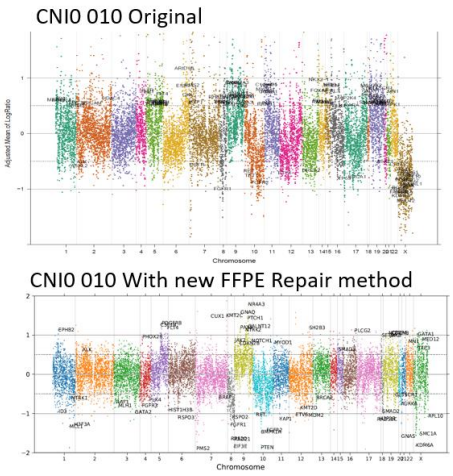
Major Task 1: Targeted NGS on all study samples

In year 4 the Pritchard site (site 1) received a shipment of 127 plasma samples corresponding to 36 patients from the Olmos site (site 2) to identify frozen plasma samples for cell-free DNA testing. These samples were highly successful, with >95% have adequate tumor content and sequencing quality from plasma for testing.

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. In year 1-3 a major focus was optimizing methods to allow clinical sequencing of very low input and low-quality DNA samples from the CNIO site. Major activities included review

of an FFPE DNA repair step to improve DNA quality for sequencing (**Figure**), revision of the pooled hybridization capture protocol to include maximum input quantity in NGS, while reducing the control sample input (to avoid sinking DNA sequence), and exploration of low-input single-stranded NGS library prep protocol. In Year 3 we completed experiments using a new FFPE DNA repair protocol on low quality samples.

Figure: Effect of FFPE DNA repair on UW-OncoPlex sequencing results. Example copy number plots of CNIO sample 010 run on the UW-OncoPlex v6 panel without (top, original) or with (bottom) FFPE DNA repair. Quality metrics were improved with the FFPE DNA repair step, including copy number quality



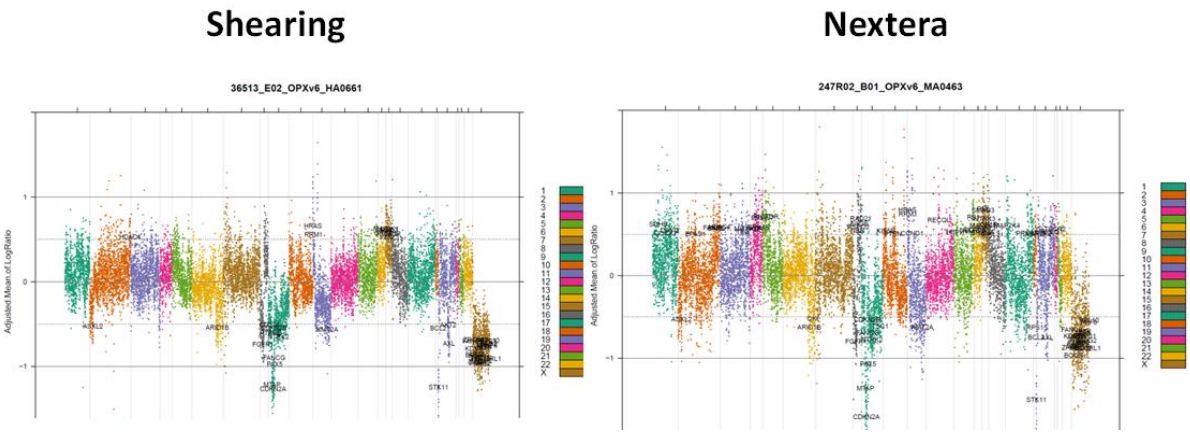


Figure: Comparison of copy number calling between the standard shearing and low input Nextera UW-OncoPlex sequencing. We observed high qualitative and quantitative concordance between the standard shearing-based library prep and Nextera low input library preparation for the UW-OncoPlex assay.

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.

Finally, as a third approach, we focused on 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. 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) worked to complement the results with shallow whole genome sequencing (WGS) to 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. 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. 2021, DOD support acknowledged).

We implemented a technical improvement to the UW-OncoPlex panel that included the additional of a validated Homologous Recombination DNA repair (HRD) signature analysis using global burden of LOH, in the UW-OncoPlex version 7 panel update that went live at the end of Year 3 Q3 (**Figure**).

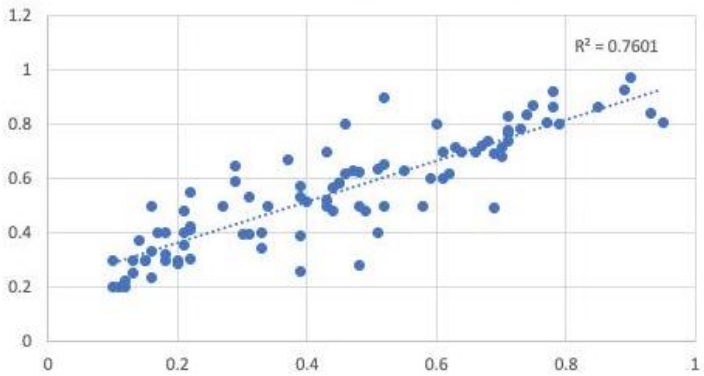


Figure: Comparison of HRD analysis by UW-OncoPlex (X-axis) compared to a commercial lab approach (Y-axis)

Major activities in Year 4: we decided to start the alternative plan to sequence the plasma circulating DNA from those patients which lack adequate tumor tissue, or in which extracted DNA did not yield the minimum quantity or quality for NGS analysis or quality. At site 1 we have identified those cases in which we have available plasma samples for processing and DNA extraction. A total of five batches of samples have been sent from CNIO to the UW site and UW-OncoPlex sequencing and 133 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 13 had *BRCA2* mutations, 8 had *ATM* mutations, 1 had an *NBN* mutation, 2 had *CHEK2* mutations, 3 had *MUTYH* mutations, 2 had a FANCA mutation, 2 had *CDK12* mutation, 1 had *BRIP1* mutation, 1 had *MLH1* mutation (MSI-high), 2 had MSI-high without underlying MMR gene mutation detected, 1 had *MRE11A* 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	DRD Mutation?	Interpretation
OLM_01.006	198R01_A01_OPXv5_NB0187	**BRCA2**	1. Very low quality limits the study. 2. POSITIVE for BRCA2 copy loss, cannot determine if 1 or 2 copies. Possible MYC amplification.
OLM_01.039	198R07_G01_OPXv5_NB0187	**BRCA2**	1. POSITIVE for a pathogenic mutation in BRCA2 (c.6650_6654del); cannot tell if germline or somatic. 2. Low quality limits the study.
OLM_02.033	198R12_D02_OPXv5_NB0187	**MLH1, MSI-high**	1. Low quality limits the study. 2. Favor MSI-high due to MLH1 loss, high total mutation burden.
OLM_03.035	198R16_H02_OPXv5_NB0187	**ATM**	1. POSITIVE for a pathogenic ATM mutation with associated LOH (p.R521*), CHD1 focal homozygous copy loss, possible MYC amplificatio
OLM_03.047	198R17_A03_OPXv5_NB0187	**ATM?**	1. POSITIVE for a pathogenic TP53 mutation, ATM VUS in the FAT domain (p.I2401T), and PTEN copy loss. 2. Low quality limits the study.
CNIOUW 005	272R03_C01_OPXv6_NA0414	**BRCA2**	1. POSITIVE for BRCA2 focal deletion (favor bi-allelic) and FOXA1 mutation 2. Low sample quality limits the study, false negative results
CNIOUW 008	272R06_F01_OPXv6_NA0414	**NBN**	1. Very low sample quality limits the study, false negative results are certain. 2. POSITIVE for a pathogenic mutation in NBN (p.R43*)
CNIOUW 009	272R07_G01_OPXv6_NA0414	**MUTYH (carrier)**	1. Very low sample quality limits the study, false negative results are very likely. 2. POSITIVE for a pathogenic mutation in MUTYH (p.G3
CNIOUW 010	272R08_H01_OPXv6_NA0414	**MSI/MMRd**	1. MSI-high likely (limited analysis due to low sample quality). 2. POSITIVE for TP53 mutation with LOH and ATM VUS (p.I2401T, germlin
CNIOUW 012	272R10_B02_OPXv6_NA0414	**ATM**	1. POSITIVE for a pathogenic ATM mutation (p.R531*) with LOH (bi-allelic), CHD1 homozygous copy loss (bi-allelic), possible MYC amplifi
CNIOUW 018	275R06_F01_OPXv6_NB0350	**BRCA2**	1. POSITIVE for BRCA2 exon 1-24 deletion + LOH (bi-allelic) and possible MYC amplification. 2. Low sample quality limits the study, false
CNIOUW 028	276R04_D01_OPXv6_NB0352	**ATM**	1. POSITIVE for two pathogenic ATM mutations (bi-allelic). 2. Low quality limits the study.
CNIOUW 032	276R08_H01_OPXv6_NB0352	**BRCA2**	1. POSITIVE for a pathogenic BRCA2 mutation (c.3264dup), with possible BRCA2 copy loss, BRCA2-RB1 co-deletion cannot be excluded. 2.
CNIOUW 033	277R01_A01_OPXv6_NB0354	**MUTYH**	1. Very low sample quality limits the study, false negative results are very likely. 2. POSITIVE for a pathogenic mutation in MUTYH (p.G3
CNIOUW 034	277R02_B01_OPXv6_NB0354	**CHEK2?**	1. POSITIVE for SPOP p.F102C mutation, KDM6A mutation, MYC amplification, BRCA2-RB1 co-deletion (single copy), and CHEK2 VUS. 2. V
CNIOUW 039	277R07_G01_OPXv6_NB0354	**FANCC**	1. Low sample quality limits the study, false negative results are very likely. 2. POSITIVE for a pathogenic mutation in FANCC (c.455dup,
OLM,02.009	281R01_A01_OPXv6_NB0365	**CHEK2**	1. Low sample quality limits the study, false negative results are very likely. 2. POSITIVE for a pathogenic mutation in CHEK2 (exon 11-12
OLM,03.012	281R08_H01_OPXv6_NB0365	**ATM**	1. POSITIVE for ATM exon 25-63 del mutation with LOH (bi-allelic), CHD1 homozygous copy loss, SPOP p.F102I mutation, and additional a
OLM,02.007	281R11_C02_OPXv6_NB0365	**BRCA2?**	1. POSITIVE for TP53 mutation, BRCA2 single copy loss, possible MYC amplification, and additional alterations. 2. Low quality limits the
OLM,03.065	286R23_G03_OPXv6_NB0365	**CDK12**	1. POSITIVE for CDK12 bi-allelic pathogenic mutation with associated focal tandem duplication signature including MYC amplification fa
OLM,FIVO.012	286R25_A04_OPXv6_NB0365	**BRCA2**	1. POSITIVE for a pathogenic BRCA2 mutation (cannot determine if mono-allelic or bi-allelic), and additional alterations. 2. Low quality
OLM,FIVO.009	286R32_H04_OPXv6_NB0365	**MUTYH (carrier)**	1. POSITIVE for germline heterozygous MUTYH mutation (p.Y179C carrier), TP53 mutation, BRCA2 single copy loss, and additional alterati
OLM,FIVO.228	286R37_E05_OPXv6_NB0365	**FANCA**	1. POSITIVE for FANCA pathogenic mutation (cannot tell if mono-allelic or bi-allelic), TP53 mutation, and additional alterations. 2. Low
PROS02043	396R01_A01_OPXv7_ND0563	**BRCA2**	POSITIVE for bi-allelic BRCA2 mutations (1. p.S1630* which is favored germline and 2. exon 1-10 deletion which is the suspected somatic
PROS02025	396R02_B01_OPXv7_ND0563	**BRCA2, PALB2 (sucblonal)**	POSITIVE for bi-allelic BRCA2 mutation (focal homozygous deletion), subclonal PALB2 mutation, CTNNB1 activating mutation, AR exon 5
PROS05003	396R05_E01_OPXv7_ND0563	**ATM (favor CHIP)**	POSITIVE for AR amplification, SPOP mutation with CHD1 focal copy loss, ATM mutation (cannot exclude CHIP), MYC copy gain, and addit
PROS03086	396R12_D02_OPXv7_ND0563	**FANCA**	1. POSITIVE for AKT1 p.E17K, FANCA mutation, TP53 mutation (bi-allelic), BCORL1 mutation and additional alterations. 2. Low tumor co
PROS05002	396R14_F02_OPXv7_ND0563	**ATM**	1. POSITIVE for a likely pathogenic ATM variant p.L1046P with LOH in tumor (favor germline), SPOP mutation with CHD1 focal copy loss, A
PROS03058	396R16_H02_OPXv7_ND0563	**BRIP1 (subclonal)**	1. POSITIVE for MED12 hotspot mutation, AR resistance mutation, PTEN mutation with LOH (favor bi-allelic), TP53 mutation (cannot excl
PROS02051	396R17_A03_OPXv7_ND0563	**CDK12**	1. POSITIVE for CDK12 mutation (favor bi-allelic) associated with many focal amplifications consistent with the CDK12 tandem duplicatic
PROS02053	396R20_D03_OPXv7_ND0563	**BRCA2**	1. POSITIVE for a pathogenic somatic BRCA2 mutation with associated LOH due to copy loss, TP53 mutation (bi-allelic), TMPRSS2-ERG fus
PROS03036	396R22_F03_OPXv7_ND0563	**BRCA2**	1. POSITIVE for a pathogenic BRCA2 mutation with associated LOH (bi-allelic), TP53 mutation (bi-allelic), KDM6A mutation, KMT2A (MLL)
PROS02067	396R24_H03_OPXv7_ND0563	**ATM (VUS)**	1. POSITIVE for ATM p.I2401T VUS with associated LOH, TP53 mutation (bi-allelic), PTEN and RB1 focal copy loss (cannot determine if mo
PROS02033	396R26_B04_OPXv7_NA0630	**MSI-high**	1. POSITIVE for MSI-high and HIGH tumor mutation burden (42/Mb), SPOP mutation, APC mutation, and numerous additional alterations
PROS02031	396R27_C04_OPXv7_NA0630	**BRCA2**	1. POSITIVE for a pathogenic BRCA2 mutation with associated LOH (bi-allelic, favor germline), APC mutation with LOH (bi-allelic), multip
PROS02055	396R34_B05_OPXv7_NA0630	**BRCA2**	1. POSITIVE BRCA2 and RB1 copy loss, cannot tell if mono- or bi-allelic, TMPRSS2-ERG fusion, MYC amplification, and additional alteratio
PROS02083	396R36_D05_OPXv7_NA0630	**MRE11A**	1. POSITIVE for MRE11A p.R605* (pathogenic, with associated LOH, bi-allelic, favor germline), AR amplification, AR resistance mutation,

We have requested a 1-year NCE to the agency for completing this work. Following completion of these additional optimization experiments Site 1 will plan to complete sequencing of samples from CNIO during the additional year to complete this task.

In addition, a *JAMA Oncology* study led by the Pritchard Group with regard to cell-free DNA sequencing in prostate cancer acknowledged support from this award was featured in many news media outlets.

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.

In this reporting period we applied the validated HRD assay to 49 prostate cancer paired samples, which included both tumor tissue and cell-free DNA (**Figure**). LOH scores were highest overall in tumor with bi-allelic mutations in *CHEK2*, *BRCA1*, and *BRCA2*.

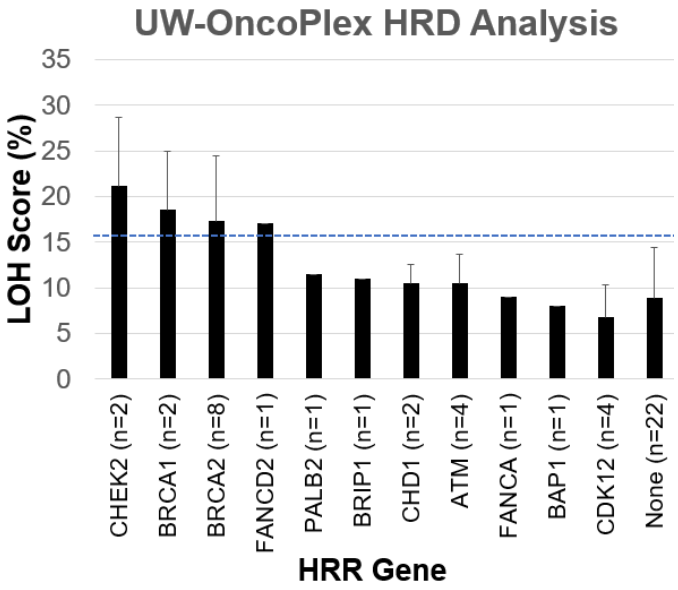


Figure: UW-OncoPlex HRD Analysis in Prostate Cancer by Gene. Mean LOH scores are depicted by gene, error bars are standard deviation. The dashed line indicates the threshold for calling a sample HRD mutation signature positive by this approach.

In summary, major activities to date included review of an FFPE DNA repair step to improve DNA quality for sequencing, revision of the pooled hybridization capture protocol to include maximum input quantity in NGS, while reducing the control sample input (to avoid sinking DNA sequence), exploration of low-input single-stranded NGS library prep protocol, preparation for cell-free plasma DNA testing, and improvement of the UW-OncoPlex panel by the addition of HRD mutation signature analysis.

Summary of progress on milestones related to Aim 1 in Year 4

Milestone 1.1 Shipment of samples From CNIO laboratory to UW laboratory (batches) (Month 3-15): In summary, four 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), 12 additional patients with alterations limited to *BRCA2* (*gene* deletions) has been identified at site 2 using alternative approaches as described above.

Milestone 1.3 – Data analysis and interpretation, Manuscript Preparation (24 months; Site 1, 2 and 3):
Two initial communications related to aim 1 have 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 was accepted for publication in the European Journal of Cancer in 2021:

- **Title:** Association between BRCA2 alterations and intraductal and cribriform histologies in prostate cancer
- **Authors:** R. Lozano, D.C. Salles, S. Sandhu, I.M. Aragón, H. Thorne, F. López-Campos, J. Rubio-Briones, A.M. Gutierrez-Pecharroman, L. Maldonado, T. di Domenico, A. Sanz, J.D. Prieto, I. García, M.I. Pacheco, T. Garcés, C. Llacer, N. Romero-Laorden, F. Zambrana, P.P. López-Casas, D. Lorente, J. Mateo, C.C. Pritchard, E.S. Antonarakis, D. Olmos, T.L. Lotan, E. Castro
DOI: https://doi.org/10.1016/j.ejca.2021.01.027

DOD funding was acknowledged as part of the submitted manuscript.

A manuscript related to Abstract 2 has been submitted with DoD funding acknowledged.

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.

During Year 3 we had several virtual meetings, 1 regular bi-monthly meeting between site 2 and site 3 to improve coordination for aims 2 and 3, and 2 meetings with teams from site 1, site 2 and site 3 in June and September 2021.

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 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. Biopsies from twenty-three cases with metastatic disease that underwent biopsy of their metastatic disease has been identified at site 2, patient has been consented to use remnant tissue under the DoD protocol and samples will be shipped to Site 3 during the first semester of Y4.

For Site 3 (VHIO), the research protocol for acquisition and analysis of patient biopsies was approved by the local ethics board. As of Dec 2023, 196 patients have been consented for consideration of biopsies. After discussion of suitability with interventional radiology, 91 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 141 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 all acquired biopsies, 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. As of Feb 2022, we have completed and analyzed whole-exome sequencing for 68 fresh biopsies included in this study, and there are 20 more cases with libraries prepared but waiting to be sequenced at the time of this report.

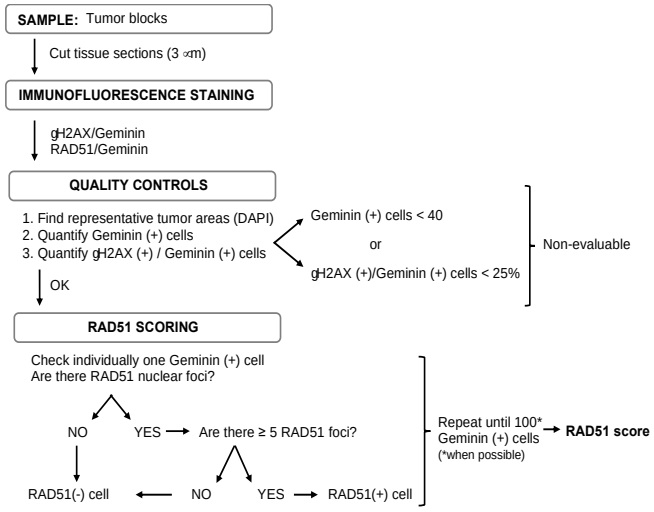
Major Task 4: Expression profiling studies

RNA extraction from the frozen blocks of the metastatic biopsies was started in Sept 2020. Unfortunately, this represented 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. During the rest of year 2 and the most of year 3 the work site 2 for this task was delayed to due to staffing (see section 5 Changes and problems during the project at site 2).

During Year 4 we have completed this task. We extracted RNA and prepared RNA libraries for all acquired biopsies in the study. As of Feb 2022, we have successfully completed RNAseq 94/113 samples with RNA extracted. This total of 94 cases with analysis completed completed as of Dec 2022 include 64 fresh biopsies as well as 30 primary biopsies of mHNPC patients.

Major Task 5: Immunofluorescence studies

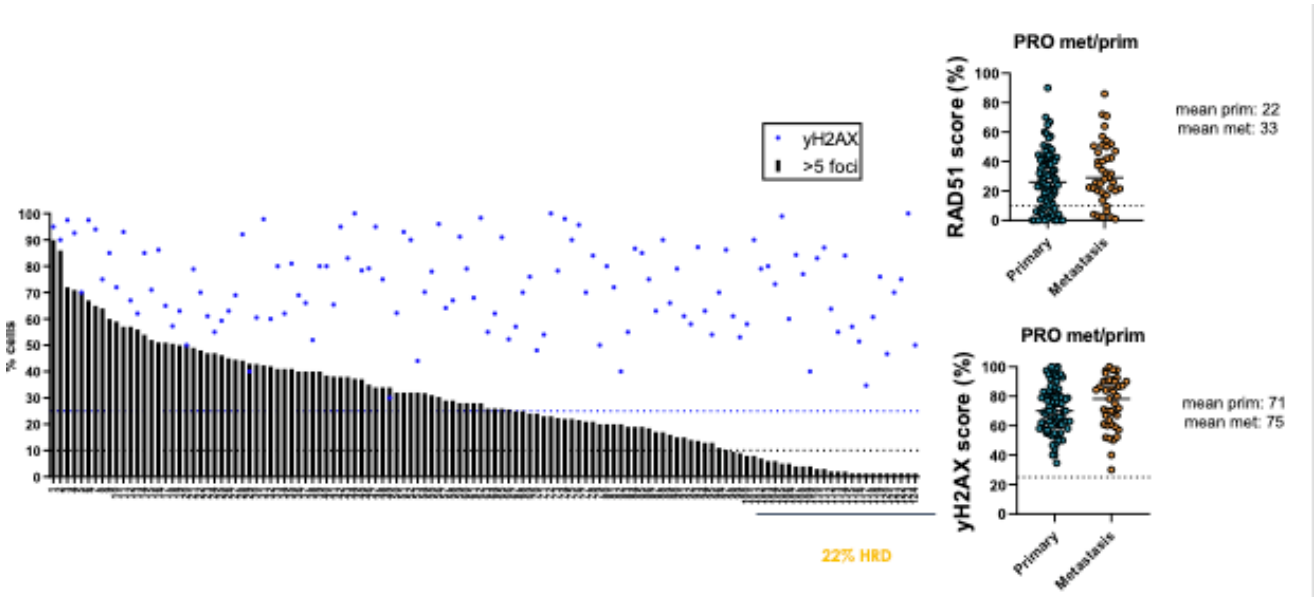
As planned, we have re-optimized now an IF-based test initially developed in breast cancer patient-derived xenoimplant models and then validated in breast cancer biopsies (Cruz et al, Ann Onc 2018; Castroviejo-Bermejo et al, EMBO Med 2019). We are using FFPE slides from prostate cancer primary and metastatic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



We evaluated baseline HRR function based on detection of RAD51 and γH2AX foci in geminin-positive tumor cells by immunofluorescence (IF). All samples were scored by two trained readers blinded to genomic and clinical data. Samples were considered HRR deficient (HRD) when RAD51 scores were low, pre-defined as <10% tumor cells presenting ≥5 RAD51 foci/cell.

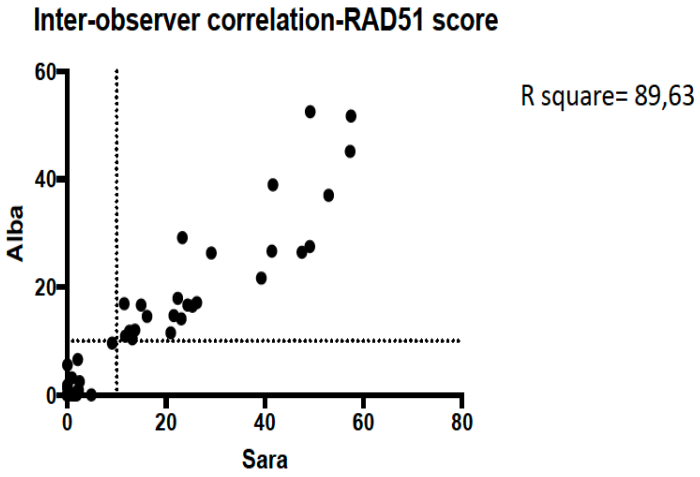
We have now completed the RAD51 IF studies in 193 cases (in all cases we have either WES or targeted sequencing data). Of 193 cases, 131 were evaluable for RAD51 foci assessment whereas 62 (32%) were non-evaluable. Reasons for technical failure included: low tumor content or insufficient number of germline-positive cells for RAD51 evaluation, as per the QC criteria described in the figure above. The success rate has decreased in Year 4 probably due to the addition of a few archival prostatectomy samples. We have observed that differences in paraffin embedding procedures between surgical specimens and core biopsies, probably related to the time from sample acquisition to fixation, impact the quality of fluorescence. We have decided, as a side project (not funded by this grant), to pursue RAD51 assessment by IF and by IHC in a cohort of 25 cases with patient-matched diagnostic biopsy and prostatectomy specimen. We anticipate results will be available by Q2 2023.

For the project in this award, 22% of the evaluable samples presented HR deficiency as per the RAD51 test criteria. A figure showing the distribution of gHA2X (blue dots) and RAD51 (black columns) across the study cohort can be found below. We did not observe differences based on primary vs metastatic origin of the biopsy.



Also during the time of this award, we managed to test the assay in a further cohort of samples from metastatic prostate cancer patients enriched for DNA repair gene mutations. In particular, primary or metastatic biopsies from 52 men with metastatic prostate cancer who participated in the phase II TOPARP clinical trial of olaparib (results published in Mateo et al, Lancet Onc 2020) were made available to us. The methodology for the gHA2X and RAD51 evaluation is the same as in the previous cohort. The association of the RAD51 score, response to olaparib and survival (radiographic progression-free survival, rPFS, and overall survival, OS) was analyzed by Chi-Square and log-rank tests. Results were summarized in the Year 3 report and have now been published in Carreira et al, Cancer Discovery 2021.

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 continuous 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 expedite the development of the assay, we have now employed a pathologist (Dr Sara Simonetti) 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: completed
Milestone 5.1 – Integrated analysis of sequencing and IF data (*month 32*): 50%
Milestone 5.2 – Data analysis and interpretation, Manuscript (month 34): To be pursued during the requested additional Year.

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

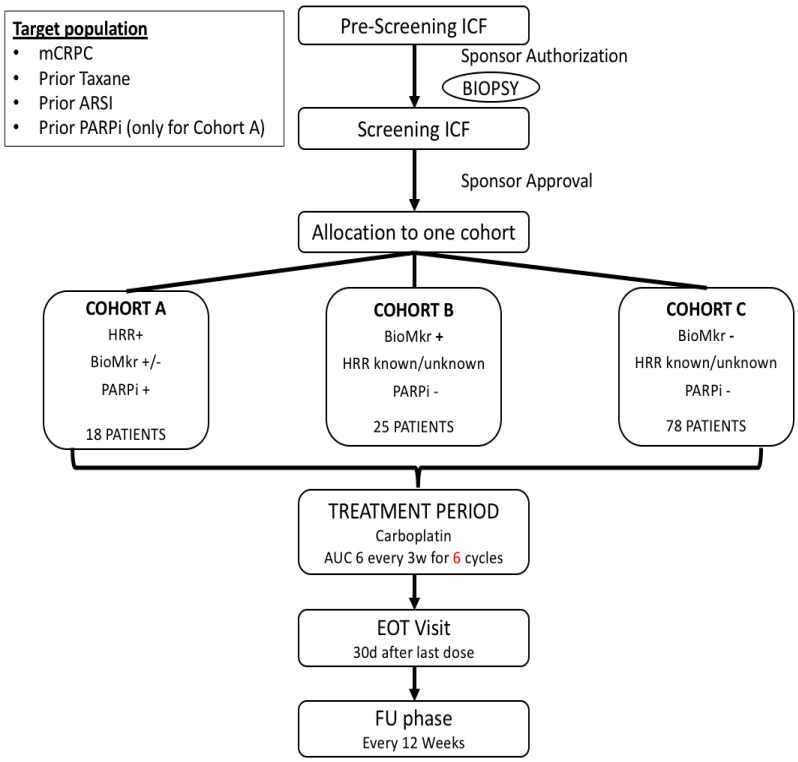
In year 1, we completed the trial protocol which was initially submitted to site 2 reference IRB (CEI Provincial de Malaga) and the AEMPS (Spanish regulatory agency) and initial review and proposed amendments were received by October 2020. The protocol was submitted to the HRPO before regulatory submission, but final feedback from HRPO was received in January 2020. These feedbacks 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.

The first patient on trial started screening in March and was enrolled in study. However, initiation of some sites was delayed due to an unexpected sick leave of the study trial manager. By September 2021 all sites except 1 (H.U. La Princesa) were initiated (see site status list below in the next major task)

Major Task 7: Clinical Trial conduction

By end of October 2021, 28 patients have entered pre-screening, 24 patients have been screened and 20 patients have been successfully enrolled and received at least 1 dose of Carboplatin in the study. Two these 20 patients were enrolled in Cohort A (post-PARPi), 4 in Cohort B and 14 in Cohort C (see trial design below).



The summary of the clinical trial status is as follows:

1. 10 sites have consented and/or enrolled at least 1 patient

Trial site / Hospital	**Consented**	**Screening Failure**	**Enrolled**

Hospital Universitario 12 de Octubre, Madrid	20	6	14
Hospital Universitario Virgen de la Victoria de Málaga	9	2	7
Hospital Universitario Vall D'Hebron, Barcelona	6	1	5
Instituto Valenciano de Oncología, Valencia	6	1	5
Hospital Provincial de Castellón, Castellón	7	2	5
Instituto Catalan de Oncología, L'Hospitalet	6	3	3
Hospital Clínico San Carlos, Madrid	5	0	5
Centro Oncológico de Galicia, La Coruña	3	1	2
Hospital del Mar, Barcelona	2	0	2
Instituto Oncológico de Donostia – Onkologicoa, San Sebastian	3	1	2
Instituto Catalan de Oncología, L'Hospitalet	1	0	1

2. 2 sites have not consented any patient by end of Year 4
    - Hospital Universitario de Santiago, Santiago de Compostela
    - Hospital Universitario Puerta del Hierro, Madrid

By end of Year 4 we achieved 80% enrolment. As described in prior reports, we were not able to fulfil the anticipated plans described in the quarterly reports during year 3 and Y4Q1. CNIO as institutional recipient rejected to transfer sponsorship to another sponsor and rejected to support anew NCE request to complete the trial recruitment. In this context and despite improving trial recruitment, the trial management and monitoring were behind schedule. Site 2 PI, David Olmos, anticipated in prior reports the need to hire an external CRO in order to complete it adequately. After several meetings between CNIO managing director and Site 2, David Olmos (site 2 PI) and Imas12 (David Olmos new institution), an agreement was reached to complete the grant work:

a) David Olmos as PI accepted the following demands from CNIO

1- The trial should finalize enrolment by the end of 2022 and David Olmos as PI undertake the necessary protocol changes to complete such deadline
2- There will not be additional sites and sites that have not recruited patients will be closed
3- No additional NCE of the grant will be supported institutionally for site 2 (CNIO).

b) CNIO agreed to support David Olmos to execute the remaining work in his grant, especially supporting subcontracting of external services where CNIO cannot offer support at the present:

1- allow the hiring of an external CRO to support trial monitoring and to execute trial activities fees invoicing and payments from sites to CNBIO and *vice versa*
2- allow the hiring of support (external services) for managing the trial human samples collection, processing and biobanking
3- Support all changes and expenses related to trial insurance, trial electronic clinical data forms, document translations and fees in order to comply with regulatory demands in Spain and EU as well as with HRPO

Following this agreement, a public tender process was initiated by CNIO, in which EXPERIOR/ClinScience (www.experior.es) a Spanish CRO which previously supported the

pharmacovigilance of Biochip trial) was selected to perform this task. In addition, IBIMA research Institute (www.ibima.eu) was contracted to support trial samples management (collection, shipments, processing and biobanking). An intensive monitoring plan and sample management plan was designed, and was initiated by the end of Year 4 Q3 in order to complete the pending trial work by the end of Q4.

To fulfil the requirement of CNIO to complete the trial recruitment by the end of September 2022, David Olmos organised a "Biochip Trial" virtual meeting with all trial sites PI on May 13th, 2022. Three conclusions were obtained from this meeting:

- First, it was not feasible to reach the initially required sample size in less than a year, since the % of patients entering cohort C (Biomarker negative: HRR deficient) was between 15-20% of all recruitment, and we initially estimated 25-30%.
- Second, a feasible sample size would be below 80 patients, up to 25-26 additional patients between May 15th and September 30th.
- Third, sites needed more support from the sponsor or if that would not be possible, then from a CRO.

Next we decided to amend the study design from 3 different cohorts, each with an independent sample size calculation based on probability of success for each biomarker status/cohort, to a single-stage Phase II design in which the biomarkers of response would be analysed as secondary endpoints, leaving the possibility in the future to add an adaptative design to validate the "winner" biomarker but not as part of this grant. On this basis, we submitted for initial review to the Spanish regulatory agency and the reference ethics committee the following sample size amendment:

"*Up to 90 patients will need to be screened to enroll up to 70 patients with a minimum of 64 eligible for the efficacy analyses. As carboplatin is commonly used off-label palliative treatment for mCRPC who fail other standard treatment options and the overall response-rate and symptomatic benefit has been established we elected a one-stage phase 2 design to test our hypothesis. A multi-stage designs, rather than the proposed single-stage designs, would only be preferable in a situation in which early termination is desirable if a new proposed treatment or combination is ineffective 51; but not in a setting like this trial where we wish to identify populations in which a known treatment option may be more effective using biomarkers.*

To minimize the sample size for this study allowing a minimum number of patients enough to explore potential biomarkers of carboplatin sensitivity based on HRR deficiency proposed to use the A'Hern Tables for single- stage phase 2 trials 51 which is based on the binomial exact distribution and therefore are preferable to those models based on the normal distribution, such as Flemming and others, which could rise more anomalous results.
To calculate the sample size of the study we fixed a significant-level (α or error type I) of 0.05 and a power (1-β or error type II) of 0.90. In addition, we considered a threshold 15% for the null hypothesis (p0), whilst the probability of success or alternative hypothesis (p1) was adjusted to 30%.

With this, we will require to see 15 responses out of 64 patients enrolled. In addition, we have estimated an 8% over-recruitment (up to 70 patients) to allow the final efficacy analysis population is similar to the a priori calculated sample size"

To preserve the initial scientific aims, the original primary trial endpoint:
"*To estimate the efficacy of single agent carboplatin, as measured by response rate, in three different cohorts of patients with progressive metastatic CRPC*" namely: biomarker negative, biomarker positive/Unknown and post-PARPi

We proposed the following aims:

- Primary aim: "*To estimate the efficacy of single agent carboplatin, as measured by response rate, in patients with progressive metastatic CRPC independently of DNA repair gene status*"
- New secondary aims: "*To estimate the efficacy of single agent carboplatin, as measured by response rate in CRPC patients accordingly to its DNA repair status defined by the γ-histone-2AX–RAD51 immunofluorescent assay or the prior use of PARPi*"

Finally, we are subcontracting the performance of RNAseq to derive signatures associated to response in the clinical trial with GENYO (www.genyo.es). Initially in the scientific plan we proposed to derive transcriptomic signatures from biopsies using RNAseq or arrays.

Major Task 8: Biomarker studies in trials samples

Prospective allocation of patients to the different study cohorts is based on the RAD51-IF assay performed at Site 3 (VHIO).

As of Dec 2022, Site 3 has received 91 tumor samples from 72 individual patients who consented for trial participation as part of their prescreening or screening procedures. For some patients, more than one sample was tested due to 1) the trial biopsy block received was deemed not evaluable and a second block was sent; or 2) some trial sites sent to the central lab the archival biopsy and the fresh biopsy in parallel. For those cases, the result on the fresh sample was prioritized for trial enrolment.

Of 91 samples, 57 were prostate biopsies, 13 were bone metastasis biopsies, 11 were lymph node biopsies and 5 were liver biopsies. The remaining 5 samples were labelled as "other". 10 samples were returned after pathology review, so the RAD51 test was performed in 81 samples. The breakdown of results were as follows:

- 28 samples not evaluable (34%)
- 12/52 evaluable samples were HR Deficient as per RAD51 test criteria (23%)
- 41/52 evaluable samples HR proficient as per RAD51 test criteria (77%)

Additionally samples from biopsies and plasma have been gathered to preform NGS analysis with the UW-OncoPlex assay, they are being submitted to site 1 to complete analyses, as described above.

Finally, exploratory RNAseq analysis is undergoing in a small subset of tumor samples from the first 10 clinical trial patients enrolled. These analyses are performed in collaboration with GENYO-GFranada University (Spain), as a potential future new partner/subawardee. As explained during aim 2 achievements narrative, Site 2 was hampered to continue this work onsite by reasons largely explain in section 5.

- ***Summary of progress on milestones related to Aim 3 in Year 4***

Milestone 6.1 – First patient enrolled in the clinical trial (12 m): completed
Milestone 7.1 Recruitment completed for cohort A (n=18) – (48): not completed
Milestone 7.2 Recruitment completed for cohort B (n=25) – (46): not completed
Milestone 7.3 Recruitment completed for cohort C (n=78) – (48): not completed
Milestone 8.1 – Integrated analysis of clinical and biomarker data (48): not completed
Milestone 8.2 – Data analysis and interpretation, Manuscript Preparation (48+6): planned for additional year

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 continued training to learn how to analyze UW-OncoPlex data. A molecular genetic pathology fellow, Regina Kwon MD has been trained on UW-OncoPlex prostate cancer variant interpretation and leading the molecular tumor board. Colin Pritchard, site 1 PI was awarded the C2 Catalyst for Precision Medicine Award from Scientific American.

- **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 3, her fellowship was evaluated and renewed for an additional year. During the 4th quarter of Year 3 Q3, Daniel Alameda joined site 2 team with an EU funded post-doctoral researcher fellowship. He will support them with bioinformatics and genomics work in aims 1 and aims 2 from Hospital 12 de Octubre, the new site that Dr. Olmos will be joining as PI by the end of 2022

- **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. Sara Arce remains involved in the project by acting as 2nd reader for all the

RAD51 IF assays. Dr Daniel Aguilar has joined the team as bionformatician dedicated to this project, starting May 2021. Dr Sara Simonetti, MD PhD, Pathologist, has joined the project as senior researcher (part-time dedicated to this project), to provide support in evaluating challenging cases from the pathology-immunofluorescence perspective.

How were the results disseminated to communities of interest?

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

- **Site 2 (CNIO):** This project has been discussed with other projects at a virtual Patient Engagement Event held 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.

- **Site 3 (VHIO):** J Mateo has participated in virtual Dissemination Events organized by the FERO Foundation directed at employees of Mango and CocaCola Europe, talking about prostate cancer in general and this project in particular. Also, Sara Arce, PhD student in this proposal, participated in an event annually organized by VHIO for primary and secondary schools in Barcelona, where she presented her group to undergraduate students.

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

Site 1 (UW): For Aim 1, we anticipate completing UW-OncoPlex testing for PROREPAIR-B samples with the available and adequate DNA is available. For Aim 3, we anticipate beginning to receive samples for targeted sequencing from Site 3. As we progress toward the characterization of 100% of cases in aim 1 and aim 3, we will shift our focus to data analysis and manuscript preparation.

Site 2 (CNIO): The team at site 2 moved during Y4Q1 from CNIO to a new institution, and once this is complete we probably would need to ask to transfer the grant to the new institution. From our new institution (Hospital 12 de Octubre), we plan to send to site 1 the samples required to complete the analysis in aim 1 (between Q1 and Q3). At our new institution, we anticipate access to extra resources (including pathology and technicians' hours) to accelerate sample review and sample shipment. We will also finish the collection of additional samples for aim 2 to support the work led in aim 2 at site 3, and finally we will focus our greatest effort in advancing the clinical trial in aim 3 by transferring the sponsorship to CRIS foundation, enrolling new sites and contacting a professional CRO to overcome potential limitations at CNIO.

Site 3 (VHIO): All wet-lab procedures for Aim 2 have been completed. During this final year we are pursuing final bioinformatics analysis and result interpretation tasks. Our involvement in Aim 3 with regards to pre-screening samples for RAD51 test has been completed as of Dec 2022, although we have requested additional tumor blocks for some of the non-evaluable patients.

4. IMPACT:

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

There has been significant interest in our results demonstrating 1) the clinical utility of functional RAD51 foci assays to predict homologous recombination DNA repair deficiency, 2) our work on the PROREPAIR study as it relates to novel insights into the predictive value of *BRCA2 a*nd other homologous recombination DNA repair genes in prostate cancer, and 3) our work with UW-OncoPlex assay has garnered attention through highlighting the issue of false positives among HRD genes in cell-free plasma DNA testing in prostate cancer due to clonal hematopoiesis interference.

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.

Site 1 PI Dr. Colin Pritchard received a prestigious award from Scientific American, the 'C2 Catalyst for Precision Medicine Award', in recognition for his leadership in molecular diagnostics – particularly in the area of DNA repair gene assays and dissemination into the community.

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

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 activities 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 publicly 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

As outlined above, we developed additional protocols and alternative strategies for use with low input DNA quantity as many of the PROREPAIR-B samples have limited DNA. In parallel, we prioritized

sequencing of samples from patients with high input DNA. As third option, in the no cost extension year we will now prioritize ctDNA from plasma samples when available.

Due to the COVID pandemic, the recruitment of patients and biopsy acquisition was severely restricted during 2020. After having been awarded a no-cost extension, recruitment was accelerated again in Q3-Q4 2021.
An additional problem came to the number of samples were the fresh-frozen core of the biopsy had insufficient tumor content for RNAseq analysis. At site 3, we have been working to optimize RNAseq from FFPE material testing different reagents kits and optimizing the bioinformatics pipeline, and are now capable to include both FFPE or fresh-frozen blocks in this study, which will allow us to increase the number of evaluable samples.

In addition, and as described above and in prior reports the activation of the Clinical Trial embedded in Aim 3 has delayed due to the Covid-19 pandemic in addition to recent changes in the legal frame for conducting clinical trials which difficult role as sponsor of CNIO.

Finally, in year 3 the institution of site 2 (CNIO) decided to deprioritize in investment in prostate cancer research, and therefore site 2 PI (David Olmos) and his team has been invited to move to a new institution by September 2021. Site 2 (CNIO) scientific management also experienced significant challenges in supporting the tasks in this grant in year 3, especially the clinical trial embedded in aim 3, which was exacerbated by the crisis provoked by COVID-19 pandemic in Spain. Due to the increasing difficulties to continue the grant of CNIO (site 2), the Site 2 PI and the prostate research team have proposed to change the site 2 sponsor to a third party "CRIS Cancer Research Foundation" a non-for-profit cancer research-oriented NGO. As part of the planned amendment to complete the sponsor transfer, we will add new trial sites in order to achieve the study enrollment trial in a shorter timeframe.

With regard to Dr. David Olmos as PI for site 2 and his team moving institutions, negotiations with the new institution "Research Institute Hospital 12 de Octubre (i+12)" in Madrid has advanced positively and the team is aiming to move to this new institution by December 2021. The CDMRP grant officer has been informed and the possibility to transfer the grant to this new institution has been proposed.

Changes that had a significant impact on expenditures

None

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

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:

De Sarkar N, Patton RD, Doebley AL, Hanratty B, Adil M, Kreitzman AJ, Sarthy JF, Ko M, Brahma S, Meers MP, Janssens DH, Ang LS, Coleman IM, Bose A, Dumpit RF, Lucas JM, Nunez TA, Nguyen HM, McClure HM, Pritchard CC, Schweizer MT, Morrissey C, Choudhury AD, Baca SC, Berchuck JE, Freedman ML, Ahmad K, Haffner MC, Montgomery RB, Corey E, Henikoff S, Nelson PS, Ha G. Nucleosome patterns in circulating tumor DNA reveal transcriptional regulation of advanced prostate cancer phenotypes. Cancer Discov.; 2022: CD-22-0692; acknowledgement of federal support (yes). Patel RA, Coleman I, Roudier MP, Konnick EQ, Hanratty B, Dumpit R, Lucas JM, Ang LS, Low JY, Tretiakova MS, Ha G, Lee JK, True LD, De Marzo AM, Nelson PS, Morrissey C, Pritchard CC, Haffner MC. Comprehensive assessment of anaplastic lymphoma kinase in localized and metastatic prostate cancer reveals targetable alterations. Cancer Res. Commun.; 2: 2022; 277-285; acknowledgement of federal support (yes).

Brady L, Newcomb LF, Zhu K, Zheng Y, Boyer H, Sarkar N, McKenney JK, Brooks JD, Carroll PR, Dash A, Ellis WJ, Filson CP, Gleave ME, Liss MA, Martin F, Morgan TM, Thompson IM, Wagner AA, Pritchard CC, Lin DW, Nelson PS. Germline mutations in penetrant cancer predisposition genes are rare in men with prostate cancer selecting active

surveillance. Cancer Med.; 11: 2022; 4332-4340; acknowledgement of federal support (yes).

Maxwell KN, Cheng HH, Powers J, Gulati R, Ledet EM, Morrison C, Le A, Hausler R, Stopfer J, Hyman S, Kohlmann W, Naumer A, Vagher J, Greenberg SE, Naylor L, Laurino M, Konnick EQ, Shirts BH, AlDubayan SH, Van Allen EM, Nguyen B, Vijai J, Abida W, Carlo MI, Dubard-Gault M, Lee DJ, Maese LD, Mandelker D, Montgomery B, Morris MJ, Nicolosi P, Nussbaum RL, Schwartz LE, Stadler Z, Garber JE, Offit K, Schiffman JD, Nelson PS, Sartor O, Walsh MF, and Pritchard CC. Inherited *TP53* Variants and Risk of Prostate Cancer. Eur Urol. 81:2022; 243-250; acknowledgement of federal support (yes).

De Sarkar N, Dasgupta S, Chatterjee P, Coleman I, Ha G, Ang LS, Kohlbrenner EA, Frank SB, Nunez TA, Salipante SJ, Corey E, Morrissey C, Van Allen E, Schweizer MT, Haffner MC, Patel R, Hanratty B, Lucas JM, Dumpit RF, Pritchard CC, Montgomery RB, Nelson PS. Genomic attributes of homology-directed DNA repair deficiency in metastatic prostate cancer. JCI Insight; 6:2021; 23:e152789; acknowledgement of federal support (yes).

Zurita AJ, Graf RP, Villacampa G, Raskina K, Sokol E, Jin D, Antonarakis ES, Li G, Huang RSP, Casanova-Salas I, Vivancos A, Carles J, Ross JS, Schrock AB, Oxnard GR, Mateo J. 2022. Genomic biomarkers and genome-wide loss-of-heterozygosity scores in metastatic prostate cancer following progression on androgen-targeting therapies JCO Precis. Oncol.; 6: 2022; pp.e2200195-e2200195; acknowledgement of federal support (yes).

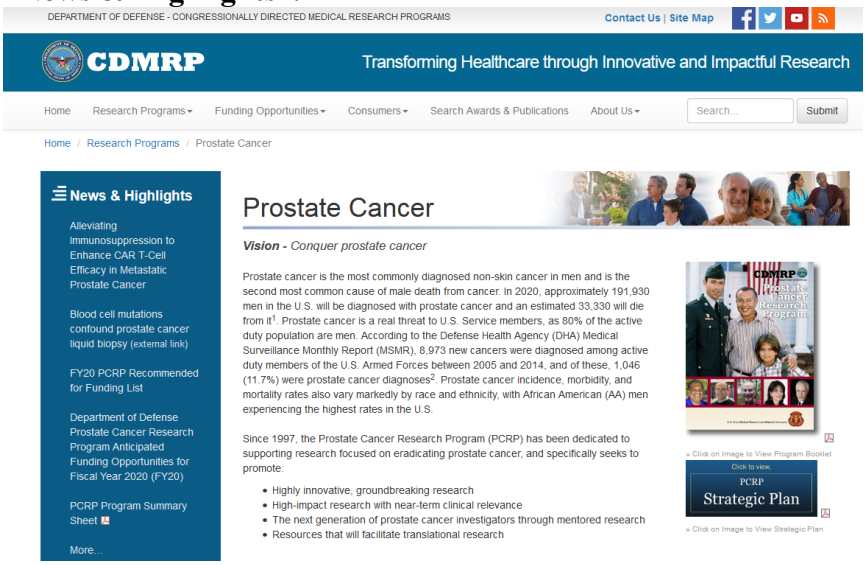
Pellegrino B, Herencia-Ropero A, Llop-Guevara A, Pedretti F, Moles-Fernández A, Viaplana C, Villacampa G, Guzmán M, Rodríguez O, Grueso J, Jiménez J, Arenas EJ, Degasperi A, Dias JML, Forment JV, O'Connor MJ, Déas O, Cairo S, Zhou Y, Musolino A, Caldas C, Nik-Zainal S, Clarke RB, Nuciforo P, Díez O, Serres-Créixams X, Peg V, Espinosa-Bravo M, Macarulla T, Oaknin A, Mateo J, Arribas J, Dienstmann R, Bellet M, Oliveira M, Saura C, Gutiérrez-Enríquez S, Balmaña J, Serra V. 2022. Preclinical in vivo validation of the {RAD51} test for identification of homologous recombination-deficient tumors and patient stratification. Cancer Res.; 82: 2022; 1646-1657; acknowledgement of federal support (yes).

Carreira S, Porta N, Arce-Gallego S, Seed G, Llop-Guevara A, Bianchini D, Rescigno P, Paschalis A, Bertan C, Baker C, Goodall J, Miranda S, Riisnaes R, Figueiredo I, Ferreira A, Pereira R, Crespo M, Gurel B, Nava Rodrigues D, Pettitt SJ, Yuan W, Serra V, Rekowski J, Lord CJ, Hall E, Mateo J, de Bono JS. Biomarkers Associating with PARP Inhibitor Benefit in Prostate Cancer in the TOPARP-B Trial. Cancer Discov.; 11: 2021; 2812-2827; acknowledgement of federal support (yes).

Schweizer MT, Sivakumar S, Tukachinsky H, Coleman I, De Sarkar N, Yu EY, Konnick EQ, Nelson PS, Pritchard CC, Montgomery B. Concordance of DNA Repair Gene Mutations in Paired Primary Prostate Cancer Samples and Metastatic Tissue or Cell-Free DNA; JAMA Oncology; 7: 2021; 1-5; acknowledgement of federal support (yes).

Rebeca Lozano, Daniela C. Salles, Shahneen Sandhu, Isabel M. Aragón, Heather Thorne, Fernando López-Campos, José Rubio-Briones, Ana M. Gutierrez-Pecharroman, Tomas di Domenico, Alejandro Sanz1, Juan Daniel Prieto, Isabel García, María I. Pacheco, Teresa Garcés, Casilda Llacer, Nuria Romero-Laorden, Francisco Zambrana, Pedro P. López-Casas, David Lorente, Joaquin Mateo, Colin C. Pritchard, Emmanuel S. Antonarakis, David Olmos, Tamara L. Lotan, Elena Castro. Association between BRCA2 alterations and intraductal and cribriform histologies in prostate cancer; European Journal of Cancer; 147: 2021; 74-83; acknowledgement of federal support (yes).

Jensen K, Konnick EQ, Schweizer MT, Sokolova AO, Grivas P, Cheng HH, Klemfuss NM, Beightol M, Yu EY, Nelson PS, Montgomery B, and Pritchard CC. Clonal Hematopoiesis in DNA Repair Genes Substantially Interferes with Prostate Cancer Plasma Cell-free DNA Testing. JAMA Oncology; 7:2021:107-110; published; acknowledgement of federal support (yes). **This study is currently featured on the CDMRP PCPR website homepage under "News & Highlights".**



Michael T. Schweizer, Smruthy Sivakumar, Hanna Tukachinsky, Ilsa Coleman, Navonil De Sarkar, Eric Q. Konnick, Peter S. Nelson, **Colin C. Pritchard**, R. Bruce Montgomery. Concordance of DNA Damage Repair (DDR) Gene Mutations in Paired Primary and Metastatic Prostate Cancer Samples. (2021). American Society for Clinical Oncology (ASCO) annual meeting.

Dines JN, Shirts BH, Slavin TP, Walsh T, King MC, Fowler DM, and Pritchard CC. Systematic misclassification of missense variants in BRCA1 and BRCA2 "coldspots". Genet Med; 22: 2020; 825-830; published; acknowledgement of federal support (yes).

Nyquist MD, Corella A, Coleman I, De Sarkar N, Kaipainen A, Ha G, Gulati R, Ang L, Chatterjee P, Lucas J, Pritchard C, Risbridger G, Isaacs J, Montgomery B, Morrissey C, Corey E, Nelson PS. Combined TP53 and RB1 Loss Promotes Prostate Cancer Resistance to a Spectrum of Therapeutics and Confers Vulnerability to Replication Stress. Cell Rep; 31; 107669; published; acknowledgement of federal support (yes).

Graham LS, Montgomery B, Cheng HH, Yu EY, Nelson PS, Pritchard C, Erickson S, Alva A, Schweizer MT. Mismatch repair deficiency in metastatic prostate cancer: Response to PD-1 blockade and standard therapies. PLoS One; 15; 2020 5:e0233260; published; acknowledgement of federal support (yes).

Chatterjee P, Schweizer MT, Lucas JM, Coleman I, Nyquist MD, Frank SB, Tharakan R, Mostaghel E, Luo J, Pritchard CC, Lam HM, Corey E, Antonarakis ES, Denmeade SR, Nelson PS. Supraphysiological androgens suppress prostate cancer growth through androgen receptor-mediated DNA damage. Clin Invest; 10; 2019; 4245-4260. published; acknowledgement of federal support (yes).

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).

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).

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).

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

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.

Nothing to report

- **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?

SITE 1 (UW)

Name:	Pritchard, Colin
Project Role:	Initiating PI
Research Identifier:	cpritch (eRA Commons)
Nearest person month worked:	3.20 calendar months
Contribution to Project:	Colin Pritchard coordinates UW-OncoPlex sequencing and focuses on interpreting the sequencing data for this project. He is guiding experiments and participating in manuscript preparation and review.

Name:	Cheng, Heather
Project Role:	Co-Investigator
Research Identifier:	hhcheng (eRA Commons)
Nearest person month worked:	0.36 calendar months
Contribution to Project:	Heather Cheng reviews sequencing data at molecular tumor boards to identify relevant findings for patient care and relatives' risk of cancer.

Name:	Salipante, Stephen
Project Role:	Co-Investigator
Research Identifier:	stevesal (eRA Commons)
Nearest person month worked:	0.32 Calendar Months
Contribution to Project:	Stephen Salipante directed the development and implementation of the data analysis pipeline, assists with UW-OncoPlex data interpretation, and in guiding and preparation of manuscripts.

Name:	Beightol, Mallory
Project Role:	Research Tech
Research Identifier:	N/A
Nearest person month worked:	6.50 Calendar Months
Contribution to Project:	Mallory Beightol is responsible for preparing genomic libraries and UW-OncoPlex sequencing for this project.

Name:	Reichel, Jonathan
Project Role:	Bioinformaticist
Research Identifier:	N/A
Nearest person month worked:	0.60 Calendar Months
Contribution to Project:	Jonathan Reichel is responsible for UW-OncoPlex bioinformatics pipeline development and data analysis.

Name:	Hassan, Sajida
Project Role:	TBD
Research Identifier:	N/A

Nearest person month worked: 0.25 Calendar Months
Contribution to Project: Please include bio/role for Sajida

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

OTHER SUPPORT (*all Other Support awards and grants listed and included are as of October 2022*)

PRITCHARD, COLIN

Current Funding
Title: Pacific NW Prostate Cancer SPORE (66-5269; 68-6188)
Time Commitments: 0.36 Calendar Months
Supporting Agency: Fred Hutch
Address: 1100 Fairview Ave N, Seattle WA 98109
Contracting/Grants Officer: Mackenzie Krouse
Performance Period: 9/1/2020 – 8/31/2023
Level of funding:
Project Goals: The University of Washington (PI: Dr. R. Bruce Montgomery, MD; Co-Investigator: Colin C. Pritchard, MD, PhD) will design and conduct the clinical trials described in this proposal that include platinum-based chemotherapy and the maintenance therapy with PARP inhibitors. Drs. Montgomery and Pritchard will work closely with Dr. Nelson to facilitate the molecular assays from biospecimens acquired on the clinical studies and will work closely with Biospecimen Core B for sample collection and Clinical Core D for trial management.
Specific Aims:

1) Conduct Phase 2 clinical trials of FDA-approved genotoxic therapeutics and PARPi in patients with mCRPC to determine response rates, identify resistance mechanisms, and establish associations between those specific genomic defects predicted to result in HRD and the depth and duration of clinical responses.
2) Systematically assess tumor responses to rational combinations of genetic and pharmacological targeting DNA repair pathways using Patient Derived Xenograft (PDX) models with inherent or engineered HRD aberrations.

3) Develop minimally-invasive biomarkers involving the capture and analysis of circulating tumor DNA capable of distinguishing patients for therapeutics targeting DNA repair pathways.
Overlap: None

Title: Bringing OncoPlex Tumor Genomic Data to the BBI Community (68-3861)
Time Commitments: 0.12 Calendar Months
Supporting Agency: Brotman Baty Institute
Address: University District Magnuson Health Sciences Building H-564, 1959 NE Pacific St, Seattle, WA 98195
Contracting/Grants Officer: Nola Klemfuss
Performance Period: 02/01/2021 – 01/31/2023
Level of funding:
Project Goals: The proposed plan the University of Washington Medical Center (UWMC) in partnership with the Seattle Cancer Care Alliance (SCCA) routinely performs a clinical next-generation sequencing assay called UW-OncoPlex for the molecular profiling of tumors from SCCA patients, with over 10,000 patient samples tested since 2011. This in-system tumor genomic data is very valuable for translational and clinical research, but there are currently not effective methods for sharing it broadly with Brotman-Baty Institute members and the larger community. Improved access to OncoPlex data for BBI members will advance precision medicine by accelerating research on tumor genome alterations and their role in cancer risk and response to therapy.
Overlap: None

Title: Northwest Genomics Center for All of Us (61-8385)
Time Commitments: 0.60 calendar
Supporting Agency: National Institutes of Health; 1 OT2 OD 002748-01
Address: 9000 Rockville Pike, Bethesda, Maryland 20892
Contracting/Grants Officer: Irene Haas (grissomi@mail.nih.gov)
Performance period: 9/25/18 – 8/31/2023
Level of funding:
Project Goals: The goal of the proposal is to establish a Genome Center for the All of Us Research Program. The NWGC for All of Us will provide whole genome sequencing, genotyping and clinical validation of variants in the ACMG 59 genes.
Specific Aims: To advance the goals and objectives of the All of Us Research Program we will produce and interpret variants from genotyping arrays for up to 100,000 samples in year 1 and up to 200,000 samples in years 2 - 5. We will also produce and interpret variants on more than 10,000 samples by WGS in year 1; up to 100,000 samples in year 2; and up to 200,000 samples in years 3-5 using the Illumina NovaSeq platform. To accomplish this, we will:
1- Work with the All of Us program, the DRC, the Biobank, and other groups to deliver an efficient and effective process for evaluating and completing high-throughput genotyping and WGS, call variants, and interpret the impact of variants in the ACMG 59 genes and other genes as indicated by the program in a CLIA-certified environment.
2- Interact directly with the Biobank to carefully develop the logistics and methods for preparing and receiving samples.
3- Track all samples and data transfers for all samples at every stage of the process (from project initiation to data delivery using our secure, completely interactive, and integrated laboratory information management system (LIMS)) and provide reports to the program, the DRC, and other

groups as required.
4- Provide genotype and WGS data of the highest quality, in formats required by the program such as IDAT files for genotyping and CRAMs and VCFs for WGS.
5- Provide a team of specialized personnel and staff versed in the workflow of a well-established high throughput CLIA-certified genome center. These include individuals specifically trained in DNA sample receipt, quality control, and large-scale bioinformatics analysis and variant interpretation.
6- Assist as needed with additional data interpretation (beyond the ACMG genes), with publications (i.e., materials and methods), and other activities as required for the program.
7- Provide secure backup of raw sequence data from the samples and all metadata associated with the project (i.e., sample tracking, storage, and QC information).
Overlap: None

Title: Project 1: Molecular Predictors of Prostate Cancer Progression and Mortality (66-5269; 63-0945)
Time Commitments: 0.36 calendar
Supporting Agency: Fred Hutchinson Cancer Center through NIH
Address: 1100 Fairview Ave N, Seattle, WA 98109
Contracting/Grants Officer: Mackenzie Krouse
Performance period: 09/18/2018 – 08/31/2023
Level of funding:
Project Goals: Prostate cancer (PCa) is the most common solid tumor in men and is a major cause of cancer-related morbidity and mortality. Prostate-specific antigen (PSA) testing is controversial, and current consideration of high risk men is inadequate. Also, clinicopathological criteria are insufficient to differentiate indolent vs aggressive disease. The recent discovery of high prevalence of high to moderate penetrance germline cancer risk mutations in metastatic PCa will lead to increased testing and cascade testing of unaffected male relatives, thus identifying men at high risk for developing aggressive PCa. Preliminary evidence suggests the need for refined cancer screening in this high risk group. The overall intent of this population sciences research is to find men at high genetic risk for aggressive prostate cancer and to conduct an early Pca detection study and incorporate novel PCa biomarkers.
The proposed plan builds on our prior SPORE work, taking advantage of our experience to prospectively recruit a population-based PCa cohort with germline mutations (index cases) and their male first degree relatives (high risk cohort) with the goal of conducting a PCa early detection study that will incorporate germline DNA sequencing to characterize risk, novel PCa biomarkers, clinical and PCa-specific outcomes data. Univariate, stratified, and multivariate analyses will be completed to evaluate sensitivity and specificity of new biomarkers. The Cox proportional hazards model will be used to calculate hazard ratios, 95% CIs, and p-values to examine the association of individual and combinations of germline genetic biomarkers and with PCa outcomes. The overall goal is to identify and validate prognostic genetic-epigenetic biomarkers and begin to translate these findings into better patient management by investigating novel screening and detection approaches for men at high risk for aggressive PCa.
Specific Aims:
1) To ascertain and recruit men at high genetic risk for developing aggressive prostate cancer.
2) To test new approaches to early detection of prostate cancer in men with high genetic risk for aggressive prostate cancer.
3) To identify and evaluate new prostate cancer biomarkers in men with high genetic risk for

aggressive prostate cancer.
Overlap: None

Changes/Ended
Title: Clinical qualification of DNA repair defects as biomarkers in metastatic prostate cancer using integrated genomics and tissue-based functional assays (61-7639)
Time Commitments: 3.6 calendar
Supporting Agency: Department of Defense US Army; W81XWH-18-1-0756
Address: 820 Chandler ST, Fort Detrick, MD 21702-5000
Contracting/Grants Officer: Elena Howell (elena.g.howell.civ@mail.mil)
Performance period: 9/30/2018 – 9/29/2022 (pending NCE request to 9/30/2023)
Level of funding:
Project Goals: The major goals we propose will provide physicians tools to develop more effective treatment strategies for men with mCRPC, by assessing DNA repair defects as predictive biomarkers of patient outcome to standard therapies. In the near term, developing and validating functional biomarkers of HR functionality would facilitate implementation of personalized treatment-decisions in mCRPC into clinical practice in the community and also provide valuable information to address mechanisms of drug resistances to PARP inhibitors and DNA damaging chemotherapy in this subclass of the disease. Eventually these data could be relevant for men with localized disease too, and help personalizing treatment to prevent progression to lethal disease.
Specific Aims: 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 Ra-223, in samples from a prospective study.
Aim 2: To optimize tissue-based tests of HR functionality samples for CRPC samples, and study the correlation with genomic aberrations in HR genes.
Aim 3: To clinically qualify this HR functional test in a clinical trial of carboplatin in CRPC.
Overlap: N/A

CHENG, HEATHER H.

CURRENT

Title: A ph I/II trial of concurrent chemohormonal therapy using enzalutamide (MDV-3100) and cabazitaxel in patients with metastatic castration resistant prostate cancer
Effort: 0.60 calendar
Supporting Agency: PCCTC, LLC (Medivation and Sanofi)
Contracting/Grants Officer: Casey Sisco, siscoc@mskcc.org, (646) 888-0404
Performance Period: 07/14/16 to 11/30/22
Level of Funding:
Project Goals: The major goal of this project is to test the safety and efficacy of combination treatment with enzalutamide (MDV3100) and cabazitaxel chemotherapy of prostate cancer.
Specific Aims: To determine safe dosing level. To collect correlative biospecimens to understand the biological effects of the treatment and to evaluate for potential prognostic biomarkers.
Overlap: None

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, siscoc@mskcc.org, (646) 888-0412
Performance Period: 08/18/17 – 01/31/2029
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

Title: A phase 1b study of enzalutamide plus CC-115 in men with castration-resistant prostate cancer
Effort: 0.60 calendar
Supporting Agency: PCCTC, LLC (Celgene)
Contracting/Grants Officer: Casey Sisco, siscoc@mskcc.org, (646) 888-0404
Performance Period: 10/01/17 to 12/31/22
Level of Funding:
Project Goals: The major goal of this study is to determine the safety, pharmacokinetics, and the Maximum Tolerated Dose and/or Recommended Phase 2 Dose of the combination of CC-115 plus enzalutamide.
Overlap: Dr. Cheng will be the site PI for this study, which will provide the biospecimens used in Aim 4 of the Movember-PCF proposal to develop a predictive biomarker. Dr. Cheng's effort on the CC-115 trial will be paid for by the Movember-PCF grant, and remaining costs for running the CC-115 trial will be paid on the PCCTC budget.

Title: PLATI-PARP: A phase 2 study of induction docetaxel and carboplatin followed by maintenance rucaparib in treatment of patients with metastatic castration resistant prostate cancer with homologous recombination DNA repair deficiency
Effort: 0.60 calendar
Supporting Agency: Clovis Oncology, Inc
Contracting/Grants Officer: Vivian Chen, vchen@clovisoncology.com, (310) 803-0334
Performance Period: 07/26/2018 to 02/28/2023
Level of Funding:
Project Goals: The major goal of this trial is to determine radiographic progression free survival with 4 cycles of docetaxel with carboplatin followed by maintenance rucaparib in the treatment of patients with metastatic castration resistant prostate cancer with homologous recombination DNA repair deficiency.
Overlap: None

Title: Pacific Northwest (PNW) Prostate Cancer Sponsored Program of Research Excellence (SPORE) Project 1: Molecular Predictors of Prostate Cancer Progression and Mortality (Pritchard)
Effort: 1.20 calendar
Supporting Agency: NIH/NCI
Contracting/Grants Officer: Samantha Farrell, farrellsa@mail.nih.gov
Performance Period: 09/01/18 to 08/31/23

Level of Funding:
Specific Aims: The proposed study will ascertain and recruit germline cancer risk mutation carriers from: 1) population- and clinic-based incident cases of metastatic PC to find index cases with germline cancer risk mutations; 2) to conduct a PC early detection study incorporating novel biomarkers for unaffected, male germline mutation carriers (including first degree relatives of those with metastatic PC who are mutation carriers); and 3) to understand the cascade genetic testing process what will facilitate an innovative recruitment strategy for recruiting men at highest genetic risk of aggressive prostate cancer.
Overlap: None

Title: ACT PROMISE (Cheng)
Effort: .42 calendar
Supporting Agency: DOD PROSTATE CANCER CLINICAL TRIALS CONSORTIUM
Contracting/Grants Officer: ADVANCING CANCER TREATMENT
Performance Period: 06/19/2020 to 06/30/2023
Level of Funding:
Project Goals: The major goal of this study, in collaboration with Dr. Channing Paller, is to design, implement, recruit patients and identify prostate cancer patients who carry germline pathogenic variants, assessing frequency, family history, outcomes, longitudinal treatment response, treatment sequences and therapy combinations.
Specific Aims: 1) Identify and recruit subjects to a prospective registry of men with localized, biochemically recurrent, and metastatic prostate cancer with a germline pathogenic or likely pathogenic variant in one of the following cancer risk genes of interest — *ATM, BRCA1, BRCA2, BRIP1, CHEK2, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, and TP53* — using public education programs, outreach, and no-cost germline cancer risk testing. 2) Identify and recruit subjects with a variant of uncertain significance (VUS) in one of the cancer risk genes of interest. 3) Capture family history to assist with the interpretation of germline genetic testing results

Title: Technology-Enhanced Acceleration of Germline Evaluation for Therapy - The TARGET Study
Effort: 0.6 calendar
Supporting Agency: Prostate Cancer Foundation
Contracting/Grants Officer: Brigid Czyszczon, Brigid.Czyszczon@jefferson.edu
Performance Period: 08/06/20 – 12/31/22
Level of Funding:
Specific Aims: The proposed study will 1) evaluate understanding of providers around genetic testing in prostate cancer patients and uncover barriers to identifying patients who meet the NCCN guidelines for genetic testing. 2) develop a mobile app to assist providers in educating patients and identifying candidates for genetic testing. 3) devise a randomized clinical trial comparing mobile-assisted app to traditional, in-person genetic counseling for men with metastatic prostate cancer in different practice settings.
Overlap: None

Title: Enhanced Genetic Awareness and Genetic Evaluation for Men Through Technology - The ENGAGEMENT Study
Effort: 0.60 calendar

Supporting Agency: DOD W81XWH2010310
Contracting/Grants Officer: Jennifer Shankle, jennifer.e.shankle.civ@mail.mil
Performance Period: 09/30/2020-09/29/2023
Level of Funding:
Specific Aims: The project will 1) Develop and implement a web-based virtual PCA genetics board across academic, community, and VA settings. Perceived usefulness, acceptability, self-efficacy for genetically-based recommendations, and genetics knowledge from dynamic case-based learning will be assessed. 2) Establish a web-based, national, patient-driven registry for any male who has undergone PCA genetic testing to assess men's experience with the genetic evaluation process and inform patient centered genetics practice and resource development. 3) Utilize digital media to share updated information on genetic testing and precision management of PCA through a public-facing podcast series.
Overlap: None

Title: CO-338-063 (Triton 3)
Effort: 0.60 calendar
Supporting Agency: Clovis Oncology
Contracting/Grants Officer: Ben Shoemaker; bshoemaker@clovisoncology.com
Performance Period: 8/21/2018 – 4/30/2023
Level of Funding:
Project Goals: The major goal of this study is to assess the efficacy of rucaparib versus physician's choice of treatment based on radiographic progression free survival (rPFS) in mCRPC patients with HRD who progressed on prior AR-directed therapy and have not yet received chemotherapy in the castration-resistant setting.
Overlap: None

Title: Long-read DNA-sequencing and targeted RNA-Seq to identify previously undetectable classes of mutations in families with lethal prostate cancer. (Walsh)
Effort: 0.60 calendar
Supporting Agency: US Department of Defense (DOD)
Contracting/Grants Officer:
Performance Period: 06/01/2021 – 05/31/2024
Level of Funding:
Project Goals: We intend our approach to improve genetic testing for inherited predisposition to prostate cancer, particularly in families with a severe history of the disease but no genetic diagnosis. We will Inform all patients with positive test results and integrate new genetic information into their care following NCCN guidelines for mutation carriers and offer genetic testing to their family members. As such, our proposal specifically addresses the overarching challenge of reducing lethal prostate cancer in high risk populations.
Overlap: None

Title: 67652000PCR3002
Effort: 0.60 calendar
Supporting Agency: Janssen Research & Development, LLC
Contracting/Grants Officer: Sean Murphy: smurph41@its.jnj.com
Performance Period: 8/16/2021 – 1/31/2026

Level of Funding:
Project Goals: The major goal of this study is to assess the primary endpoint, rPFS, and defined as the time from the date of the randomization to the date of radiographic progression, or death.
Overlap: None

Title: A Phase 1, open label study evaluating the safety, pharmacokinetics and clinical effects of intravenously administered PT-112 injecting in patients with advanced solid tumors and subsequent expansion cohorts
Effort: 0.60 calendar
Supporting Agency: Phosplatin Therapeutics LLC
Contracting/Grants Officer:
Performance Period: 9/28/21 – 7/31/2026
Level of Funding:
Project Goals: Define the recommended dose level for PT-112, administered on Days 1 and 15 of each 28-day cycle, for pivotal studies based on the risk/benefit ratio of 360 mg/m2 (Arm 1) and 250 mg/m2 (Arm 2) dose levels.
Overlap: None

PENDING

Title: Expanding National Clinical Trials Network (NCTN) Opportunities for Prostate Cancer (R50)
Effort: 3.0 calendar
Supporting Agency: TBD
Contracting/Grants Officer:
Performance Period: 7/1/2023 - 6/30/2028
Level of Funding:
Project Goals: The goal of this R50 project award is to support continued PI leadership in the scientific
development and implementation of NCI-sponsored clinical trials conducted through the NCI clinical trials networks as well as continued productivity and research excellence in the implementation of NCI-funded clinical trials through salary support and associated cancer research career continuity and autonomy.
Overlap: None

Stephen Salipante

Active
Title: Development of inexpensive point-of-care testing strategies for the detection of Treponema pallidum by RT-LAMP and organism-specific aptamers (62-7685)
Effort: 0.60 calendar months
Supporting Agency: Centers for Disease Control & Prevention
Performance Period: 9/30/2022 – 8/29/2025
Level of Funding:

Project Goals: Here, we propose to develop two methodologically distinct but complementary *T. pallidum* assays to meet multiple clinical needs. This proposal will ready both assays for pre-market authorization studies in advance of FDA filings. Moreover, the proposal encompasses assay development and clinical validation (Burd EM, 2010) in our hospital laboratories, that are licensed to perform and report patient results from laboratory developed tests (LDT), enabling their immediate integration into patient care.
Overlap: None
Role: Co-Investigator

Title: Efficient, cost-effective, and ultrasensitive sequencing of somatic mutations (62-6962)
Effort: 0.96 calendar months
Supporting Agency: National Institutes of Health
Performance Period: 8/8/2022 – 7/31/2025
Level of Funding:
Project Goals: Our goal is to make ultrasensitive, error corrected sequencing so inexpensive and straightforward that it will be used as standard operating procedure for NGS clinical oncology assays and cancer research studies.
Overlap: None
Role: PI

Title: PROMISE-OB-18 (66-0031; 68-4440)
Effort: 0.36 calendar months
Supporting Agency: Cystic Fibrosis Foundation
Performance Period: 06/01/2021 – 05/31/2023
Level of Funding:
Project Goals: This is a prospective, multi-center observational study. The study is designed to measure the clinical effectiveness of triple combination modulator therapy (TCT) in people with one or more copies of the F508del mutation, study the effects of TCT across a number of CF disease manifestations, and collect specimens for future research. Subjects in the study will have one "before TCT" visit within 30 days before initiation of the therapy and five "after TCT" visits over a 24-month follow-up period. Most participating sites will be divided into sub-study groups; each sub-study group will have specific non-optional procedures conducted in addition to the "Core" procedures. Finally, there are four optional procedures (pH pill, transient elastography, chest CT, and nasal cell procurement) that will be offered to subjects at certain sites. The duration of participation for each subject is 25 months.
Overlap: None
Role: Co-Investigator

Title: Defining the intrinsic cystic fibrosis respiratory phageome (63-1099)
Effort: 0.12 calendar months
Supporting Agency: Cystic Fibrosis Foundation
Performance Period: 11/01/2021 – 10/31/2022
Level of Funding:
Project Goals: We propose to define both the phageomes and microbiota in longitudinal sputum samples from people with CF during periods of stability, exacerbations, and antibiotic treatment. We hypothesize that changes in CF sputum bacterial microbiota during clinical change or treatment will

be accompanied by corresponding changes in sputum phageomes within subjects. The results of this study will establish reliable methods for sampling and defining the CF sputum phageome and will have important implications for the predicted durability and efficacy of phage therapy for CF infections.
Overlap: None
Role: Co-Investigator

Title: Cystic fibrosis microbiological outcomes advancement core (63-7035; 63-5154)
Effort: 0.12 calendar months
Supporting Agency: Cystic Fibrosis Foundation
Performance Period: 4/1/2021 – 3/31/2023
Level of Funding:
Project Goals: This application is for support for a new research core specifically dedicated to non-standard microbiological tests for infections due to the disease cystic fibrosis. Specifically, this core will provide clinical isolates of bacteria to interested researchers, as well as performing tests for microbiological outcomes of novel CF therapies that are not performed by standard CF clinical laboratories.

Overlap: None

Role: Co-Investigator

Title: Combined Methylation and Mutation to Predict Response to PARP Inhibitors (62-1023)
Effort: 0.396 Calendar Months
Supporting Agency: National Institutes of Health
Performance Period: 5/1/2020 – 3/31/2025
Level of Funding:
Project Goals: The overall goal of the current proposal is to develop and validate a combined mutation and methylation assay as a clinical predictor of PARP inhibitor response. We will develop and refine a quantitative methylation assay, then test whether combining methylation and mutation analyses can predict PARP inhibitor sensitivity in patients with BRCA wildtype cancers using clinical samples from 4 large randomized controlled trials in ovarian and breast cancer.

Overlap: None
Role: Co-Investigator

Title: Understanding Staphylococcus aureus host-bacterium interactions that drive chronic infection in CF patients (66-2477)
Effort: 0.72 calendar months
Supporting Agency: Vertex Pharmaceuticals Inc
Contracting/Grants Officer: Emily Matusiak
Performance Period: 2/5/2020 – 2/4/2023
Level of Funding:
Project Goals: The major goals we propose are we hypothesize that polygenic mutations arising in S. aureus during CF infections can increase bacterial tropism for host airway cells and produce phenotypes that promote persistent infection. We will test this hypothesis and identify genes involved using a novel, cross disciplinary approach combining methods from evolutionary biology, population genetics, genomic sequencing, and genome editing.

Specific Aims:
Aim 1: Identify spontaneous mutations in S. aureus that promote increased persistence phenotypes in CF. (Years 1-2)
Aim 2: Define variants associated with persistence phenotypes in S. aureus isolates from chronic CF infection. (Years 1-2)
Aim 3: Determine the function of mutations associated with persistence phenotypes in S. aureus using high throughput genome editing techniques. (Years 2-3)
Overlap: None
Role: PI

Title: Microbial Cell-Free DNA sequencing to Diagnose Respiratory Infection (66-4185; 63-0222)
Effort: 0.60 Calendar Months
Supporting Agency: Cystic Fibrosis Foundation
Performance Period: 08/01/2021 – 07/31/2023
Level of Funding:
Project Goals: Diagnosis of respiratory infection in people with cystic fibrosis (CF) has remained a persistent challenge by conventional techniques using in vitro microbiological culture of patient sputum, which is variably sensitive, specific, and informative. Moreover, with the rise of highly effective CFTR modulator therapies, CF patients are increasingly unable to generate sputum for diagnostic purposes. There is consequently an increasing need for alternative methods to diagnose respiratory infection in the CF patient population. This proposal will define robust methodology for identifying cfDNA from the circulation of CF patients, and will provide foundational data for establishing microbial cfDNA as a biomarker of infection and/or exacerbation in CF patients. Collectively, these efforts have great potential to enhance CF patient care through improved diagnosis of respiratory pathogens, enabling improved therapeutic interventions and patient outcomes.
Overlap: None
Role: PI

Title: A Prospective Study to Evaluate Effects of Corrected CFTR Function BEGIN (63-4915)
Effort: 0.48 Calendar Months
Supporting Agency: Cystic Fibrosis Foundation
Performance Period: 01/01/2020 – 12/31/2026
Level of Funding:
Project Goals: Cystic fibrosis (CF) is a result of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR dysfunction leads to disease in multiple organ systems, including the lungs, pancreas, liver, intestines, and blood. A triple-combination therapy for restoring CFTR function was approved in the US (elexacaftor/tezacaftor/ivacaftor [ETI]) for people with CF and one copy of the F508del mutation 12 years of age and older and is soon expected to be available to younger people with CF.
A Prospective Study to Evaluate Effects of Corrected CFTR Function (BEGIN) is designed to measure the direct and indirect effects of ETI by collecting and analyzing clinical research outcomes and biomarkers on infants and toddlers with CF both before and after they begin this treatment, focusing on the earliest stages of disease. The primary objective of Part A is to describe and define the natural history of growth, gastrointestinal health, and pulmonary function in infants and young children with CF without CFTR modulators, while Part B will describe changes in growth, gastrointestinal health, and pulmonary function in this age group following initiation of CFTR

modulators.
Measures selected for analysis in this study include those for endocrine function, bone and body composition, gastrointestinal and respiratory symptoms, microbiology and inflammation, liver and pancreatic function, and sweat chloride. Blood, urine and stool will be collected to enable future research in this modulator-naive and exposed population. BEGIN will also provide a platform for a detailed imaging ancillary study.
Overlap: None

Title: Field Study to Understand Progression of Chronic Airway Infection (62-6655; 62-0010)
Effort: 0.60 Calendar Months
Supporting Agency: National Institute of Health
Performance Period: 8/1/2019 – 7/31/2023
Level of Funding:
Project Goals: This proposal investigates the contribution of genetic variation that evolves in Pseudomonas aeruginosa strains that infect cystic fibrosis (CF) patients to lung function decline in CF. This work will provide proof of principle for a new idea to explain disease variability that could have implications for many chronic infections.
Overlap: None

Title: UW RDP - Center for Basic and Translational Research in Cystic Fibrosis Respiratory Disease (66-5763; 63-1421)
Effort: 0.48 Calendar Months
Supporting Agency: Cystic Fibrosis Foundation
Performance Period: 10/1/2020 – 09/30/2023
Level of Funding:
Project Goals: This proposal will focus on providing instrumentation, computational infrastructure, technical and analytic expertise, and guidance to broadly enable and enhance the use of genomic analysis for research of bacteria important in CF airway infections. The Aims of the Core are to: 1) Provide sequencing and computational resources that advance research on important CF pathogens, with a focus on organisms under intense study at our center, 2) Provide sequencing and computational resources to facilitate understanding of airway microbial communities, and 3) Develop novel technologies for the genome-scale analysis of CF infections.
Overlap: None

Title: P30 Cystic Fibrosis Research Translation Center (66-0146; 68-4390)
Effort: 0.96 Calendar Months
Supporting Agency: Seattle Children's Hospital through NIH
Contracting/Grants Officer: Donna Crist
Performance Period: 6/1/2021 – 5/31/2023
Level of Funding:
Project Goals: The goals of the Genomics Core are to provide instrumentation, computational infrastructure, technical and analytic expertise, and guidance in order to broadly enable and to enhance the use of genomic analysis in Cystic Fibrosis (CF) research. Among other areas of research focus, the Genomics Core will support studies of microbial communities in the CF gut, will advance research on pathogens associated with CF disease states, and will develop novel technologies for the genome-scale analysis of CF microbiology.

Overlap: None

Changes/Ended

Title: Clinical qualification of DNA repair defects as biomarkers in metastatic prostate cancer using integrated genomics and tissue-based functional assays (61-7639)
Effort: 0.60 Calendar Months
Supporting Agency: National Institute of Health
Performance Period: 9/30/2018 – 9/29/2022 (Pending NCE Request through 9/29/2023)
Level of Funding:
Project Goals: The major goals we propose will provide physicians tools to develop more effective treatment strategies for men with mCRPC, by assessing DNA repair defects as predictive biomarkers of patient outcome to standard therapies. In the near term, developing and validating functional biomarkers of HR functionality would facilitate implementation of personalized treatment-decisions in mCRPC into clinical practice in the community and also provide valuable information to address mechanisms of drug resistances to PARP inhibitors and DNA damaging chemotherapy in this subclass of the disease. Eventually these data could be relevant for men with localized disease too, and help personalizing treatment to prevent progression to lethal disease.
Overlap: None
Role: PI

Title: Development and Implementation of a Tumor Type-Specific LOH Assay for the Clinical Determination of Homology Directed Repair Deficiency (68-3860)
Effort: 0.60 Calendar Months
Supporting Agency: Brotman Baty Institute
Contracting/Grants Officer: Nola Klemfuss
Performance Period: 2/1/2021 – 7/15/2022
Level of Funding:
Project Goals: In this proposal we will develop approaches for quantitating LOH using NGS assays, determine sensitive and specific LOH scores for the tumor type-specific HRD classification, and integrate this assay into the UW-OncoPlex pipeline for the routine clinical assessment of HRD from tumor biopsies.
Overlap: None
Role: Co-Investigator

Title: Contribution of altered lipid metabolism to resistance to cell envelope-targeting antimicrobials in MRSA (61-6832)
Effort: 0.60 Calendar Months
Supporting Agency: National Institute of Health
Contracting/Grants Officer:
Performance Period: 8/15/2018 – 8/15/2022
Level of Funding:
Project Goals: The major goals we propose to comprehensively interrogate the mechanisms of resistance and cross-resistance to GP, LP, and LGP antimicrobials in MRSA by integrated lipidomics, genomics, and transcriptomics.
Overlap: None
Role: Co-Investigator

What other organizations were involved as partners?

Two other organizations are involved in this Impact Award:

Organization Name: Vall D'Hebron Institute of Oncology (VHIO)
Award # W81XWH-18-1-0758
PC170510P1
PI: Joaquin Mateo
Location of Organization: Barcelona, Spain

Organization Name: Centro Nacional Investigaciones Oncologicas (CNIO)
Award # W81XWH-18-1-0770
PC170510P2
PI: David Olmos
Location of Organization: Madrid, Spain

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

See attached

9. APPENDICES:

None