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TITLE: Impact of Germline Genetic Testing for Men with Prostate Cancer on Active Surveillance

PRINCIPAL INVESTIGATOR: Maria I. Carlo

CONTRACTING ORGANIZATION: Sloan Kettering Institute for Cancer Research
New York, NY

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TYPE OF REPORT: Annual

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

# REPORT DOCUMENTATION PAGE

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Impact of Germline Genetic Testing for Men with Prostate Cancer on Active Surveillance

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**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
Maria Carlo, Principal Investigator

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**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

Sloan Kettering Institute for Cancer Research
1275 York Avenue
New York, NY 10065-6007

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U.S. Army Medical Research and Development Command
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**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

Active surveillance (AS) is the standard-of-care treatment for men with low-risk prostate cancer. Although there is an association between the presence of germline pathogenic variants in certain DNA damage repair (DDR) genes an aggressive prostate cancer, whether presence of these mutations also leads to worse clinical outcomes in men on AS has not been systematically sudied. We will conduct a prospective, single arm clinical trial to examine how germline genetic testing in men with prostate cancer on AS affects psychological outcomes and clinical decision making. We will also study the prevalence of germline variants in DDDR genes in this population and compare pathologic outcomes between germline DDR mutation carriers non carriers. We have currently recruited more than half of the planned 600 participants.

**15. SUBJECT TERMS**
Genetic testing, DNA damage repair gene, Prostate cancer, Los-risk Prostate Cancer, Active Surveillance

| 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 |
| Unclassified | Unclassified | Unclassified | Unclassified | 13 | 19b. TELEPHONE NUMBER *(include area code)* |

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1. **INTRODUCTION:**

Active Surveillance (AS) is the standard-of-care treatment for men with low-risk prostate cancer. Between 6% to 14% of men with prostate cancer have germline variants in DNA damage repair (DDR) genes, and presence of some germline variants has been associated with more aggressive disease. However, the association between the presence of germline DDR variants and worse clinical outcomes in men on AS has not been systematically studied. We are conducting a prospective, single-arm clinical trial to examine how germline genetic testing affects men with prostate cancer on AS, both in terms of psychological outcomes and impact on clinical decision-making. The goal is to accrue 600 men who will complete genetic testing and longitudinal questionnaires. Outcomes measured include prevalence of germline DDR variants, association of germline variants and pathologic grade reclassification, acceptability of genetic testing, and impact on clinical decision making for both patients and providers. If germline genetic testing identifies a subset of men at higher risk of lethal prostate cancer, this research will have a considerable impact on how we treat men with localized disease, with the expectation of a sizeable reduction in the morbidity and mortality from prostate cancer.

Although the COVID-19 pandemic significantly affected our original trial design, with many patient visits being cancelled and then shifting to telemedicine, we have made successful modifications to the original protocol to facilitate telemedicine consent and saliva as an alternative to DNA collection. Due to those changes, our rate of accrual has increased in the last year for targeted successful completion of our stated aims.

2. **KEYWORDS:**

- Genetic testing
- DNA damage repair gene
- Prostate cancer
- Low-risk Prostate Cancer
- Active Surveillance

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

1. To describe the prevalence of pathogenic and likely pathogenic (P/LP) germline variants in DNA damage repair (DDR) genes in patients with prostate cancer on active surveillance and to identify risk factors for P/LP variant carriers.
2. To compare pathologic outcomes in patients with prostate cancer on active surveillance with P/LP germline DDR variants versus those without.
3. To evaluate the acceptability and psychological outcomes of genetic testing in men with prostate cancer on active surveillance, and to compare psychological outcomes and clinical decision-making between those with and those without P/LP germline DDR variants.

**STATEMENT OF WORK – 07/18/2019**
**PROPOSED START DATE September 30, 2020**


Site 1: Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10065

PI Maria I. Carlo, MD (MC)
Co-PI Behfar Ehdaie, MD, MPH (BE)
Co-I Jada Hamilton (JH)
Co-I Andrew Vickers, PhD (AV)
Co-I Samson Fine, MD (SF)
Co-I: Kelsey Breen (KB)


**Specific Aims**

1. To describe the prevalence of pathogenic and likely pathogenic (P/LP) germline variants in DNA damage repair (DDR) genes in patients with prostate cancer on active surveillance and to identify risk factors for P/LP variant carriers.
2. To compare pathologic outcomes in patients with prostate cancer on active surveillance with P/LP germline DDR variants versus those without.
3. To evaluate the acceptability and psychological outcomes of genetic testing in men with prostate cancer on active surveillance, and to compare psychological outcomes and clinical decision-making between those with and those without P/LP germline DDR variants.

**Research Site**

| | **Due Date** | **Completion** |
|---|---|---|
| **Major Task 1: Clinical Trial** | | |
| Subtask 1: Prepare Regulatory Documents and Research Protocol for Trial | | |
| Refine eligibility criteria, exclusion criteria, screening protocol | 5/1/2020 | Yes |
| Finalize consent form | 5/1/2020 | Yes |
| IRB protocol submission | 5/1/2020 | Yes |
| Submit amendments, adverse events and protocol deviations as needed | | N/A |
| *Milestone Achieved: Local IRB approval* | 5/1/2020 | Yes (4/21/2020) |
| Subtask 2: Human Research Protection Office (HRPO) Submission | | |
| Review protocol and consent documents | 8/1/2020 | Yes |
| Edits to documents | 9/1/2020 | N/A |
| Resubmission to local IRB | | N/A |
| *Milestone Achieved: HRPO approval* | 9/1/2020 | Yes (8/26/20) |
| Subtask 2: Prepare Trial Infrastructure and Train Research Staff | | |
| Recruitment of two research assistants for study | 9/1/2020 | Yes |
| Coordinate for space allocation for new staff | 9/1/2020 | Yes |
| Training of research assistants | 9/1/2020 | Yes |
| *Milestone Achieved: Research staff trained* | 9/1/2020 | Yes |
| Subtask 3: Initiate Clinical Trial | | |
| Begin subject recruitment | 10/1/2020 | Yes |
| *Milestone Achieved: First participant consented, screened, and enrolled* | 10/1/2020 | Yes (9/18/2020) |
| Subtask 4: Conduct Clinical Trial Goal accrual n=600 | | |

| | | |
|---|---|---|
| Participants consented | | 397/600, 66%<br>In Progress |
| Participants complete genetic testing | | 348/600, 58%<br>In Progress |
| Post-test genetic counseling provided over telephone | | 337/600, 56.2%<br>In Progress |
| Participants complete Assessment Questionnaires 1 and 2 | | 289/600, 48%<br>In Progress |
| Participants complete Assessment Questionnaire 3 and 4 | | 152/600, 25.3%<br>In Progress |
| *Milestone Achieved: Clinical Trial Completed* | 1/1/2025 | No |
| **Major Task 2: Analysis of Genetic Data** | | |
| Subtask1: Determine prevalence of pathogenic genetic variants | | |
| Analysis of genetic testing data from all participants in study | 8/1/2023 | In Progress |
| Subtask 2: Identify risk factors for presence of pathogenic genetic variants | | |
| Clinical annotation | 8/1/2023 | In Progress |
| Statistical analysis of association | 1/1/2024 | |
| *Milestone Achieved: Report findings of prevalence of germline variants and clinical associations* | 4/1/2024 | |
| **Major Task 3: Analysis of Pathological Outcomes** | | |
| Subtask 1: Preliminary analysis of pathologic reclassification | | |
| Determine Gleason score at reclassification for first 300 participants | 1/1/2022 | In Progress |
| Compare rate of grade reclassification in pathogenic germline carriers vs non-carriers | 3/1/2022 | In Progress |
| *Milestone Achieved: Report on rate of grade reclassification for first 300 patients* | 8/1/2022 | In Progress |
| Subtask 2: Full analysis of pathologic reclassification | | |
| Determine Gleason score at reclassification for second 300 participants | 9/1/2024 | |
| Comparison of rate of grade reclassification in pathogenic germline carriers vs non-carriers | 11/1/2024 | |
| *Milestone Achieved: Report on rate of grade reclassification for all patients* | 5/1/2025 | |
| Subtask 3: Compare rate of pathologic progression on prostate biopsy at Year 3 | | |
| Determine Gleason score at prostate biopsy | 8/1/2027 | |
| Comparison of rate of grade reclassification in pathogenic germline carriers vs non-carriers | 11/1/2027 | |
| *Milestone Achieved: Report on rate of grade reclassification at Year 3 biopsy* | 1/1/2028 | |
| Subtask 4: Compare rate of adverse pathologic outcomes in patients on AS who underwent radical prostatectomy | | |
| Determine adverse pathologic features | 6/1/2023 | In Progress |
| Comparison of rate of adverse pathologic features in pathogenic germline carriers vs non-carriers | 10/1/2023 | |
| *Milestone Achieved: Report on rate of grade reclassification in patients who underwent radical prostatectomy* | 10/1/2023 | |

| Major Task 4: Analysis of Acceptability, Psychological Outcomes, and Clinical-Decision Outcomes | | |
|---|---|---|
| Subtask 1: Evaluate data from Assessments 1 through 4 | | |
| Perform analysis on acceptability and psychological outcomes of genetic testing for all participants | 7/1/2024 | |
| Perform analysis on clinical-decision making outcomes after genetic testing for all participants | 7/1/2024 | |
| *Milestone Achieved: Report findings on acceptability, psychological outcomes, and clinical-decision outcomes* | 9/1/2024 | |

- **What was accomplished under these goals?**

Within the past reporting year, we have continued a focus on a hybrid approach to consent, with patients seen remotely and in clinic are being approached by their clinicians and the study team consents accordingly. Although during the COVID pandemic, with a sudden shift to telemedicine, our accrual slowed, we have consented 42% of patients originally projected to consent by 4/1/2022. We have had a fairly high completion rate for assessment questionnaires, with 92%, 73%, 59%, 39% of eligible patients completing assessment 1, 2, 3, and 4, respectively. The team continues to actively recruit patients, provide genetic counseling and administer follow-up assessments.

A major accomplishment in the last year was the addition of primarily Spanish speaking patients to our eligibility. In the past, our study instruments were only available in English. However, we worked with the Memorial Sloan Kettering Patient-Reported Outcomes, Community-Engagement, and Language Core facility to develop translated instruments, and submitted these for evaluation by the IRB. These were approved and our study is now open to our Spanish-speaking patients.

Now that the first 300 patients have been enrolled in the study, we have been actively working with Dr. Samson Fine, pathologist, to review and annotate the prostate biopsy and prostatectomy samples. We have created a secure REDCap database where our study team imported data from the patient's EMR on several clinical features, and Dr. Fine is actively reviewing cases to ensure pathologic annotation is complete. This will allow us to soon complete aims in Major Tasks 3, including preliminary analysis of pathologic reclassification.

Finally, the Principal Investigator (Maria Carlo) and Co-Investigator (Kelsey Breen) published an article on "Clinical Impact of a Rapid Genetic Testing Model for Advanced Prostate Cancer Patients" in *Journal of Urology* regarding the preliminary data that led to the development of the current study.

- **What opportunities for training and professional development has the project provided?**
- Principal Investigator has presented at multiple local and national conferences regarding prostate cancer genetic testing and the schema of our ongoing trial. These include:
    - Invited talk at the NIH Genetics and Genomics of Genitourinary Cancers conference (4/2022)

- Prostate UsToo Patient Group Talk (5/2022)
- Invited talk at Sarah Lawrence College for Genetics Master students on Genitourinary Cancer Genetics (9/2022)
- Genetics Grand Rounds at Case Western University (2/2023)

- Co-Investigator (Breen) contributed to the annual institutional review of the National Comprehensive Cancer Network guidelines of Hereditary Breast/Ovarian cancer, specifically focusing on recommended updates for genetic guidelines for men with prostate cancer
- Principal Investigator, Co-Principal Investigators and clinical research coordinators completed a collaborative project with the Memorial Sloan Kettering "Patient-Reported Outcomes, Community-Engagement, and Language Core" to translate our assessments into Spanish to eventually allow primary Spanish speakers to participate in the clinical trial

- **How were the results disseminated to communities of interest?**

Principal Investigator, Co- Principal Investigators, and Investigator have continued to present at multi-disciplinary MSK meetings and national conferences regarding the design and objectives of our ongoing trial. These include invited academic and patient group lectures, and various working groups including those from the Prostate Cancer Foundation.

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

A main goal of the next reporting period is to continue and near complete accrual of patients. We accrued 146 patients in our last year, and based on this estimate we will accrue an additional 150-200 patients in the next reporting year. We made many modifications in the last year, including adding investigators like nurse practitioners that see patients on active surveillance, who could also mention the study to patients and refer them to review the study with our team.

For the next annual reporting period, we expect to have preliminary analyses for the first 300 participants, including genetic testing results and pathologic outcomes. We have completed a database for collection of the pathologic data and imported data from the Electronic Medical Record. We will compare the rate of grade reclassification in germline carriers vs non-carriers. We will continue the clinical annotation of patients on the study to identify risk factors for presence of pathogenic variants.

4. **IMPACT:**

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

Although still in the preliminary phase, the results of our study may provide much needed evidence to integrate genetic testing and counseling into guidelines for patients with prostate cancer who are candidates for active surveillance. Future pathologic and molecular analysis of tumors from patients with germline DNA

damage repair aberrations can shed light on mechanisms that make these tumors aggressive and thus provide insight for therapeutic targeting that could be broadly applicable to men with prostate cancer.

- **What was the impact on other disciplines?**

Results from this study, including genetic testing acceptability and impact on clinical decision making may be broadly applicable to other cancer patients. Our study results may provide a framework to integrate genetic testing in the upfront care of cancer patients.

- **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**

  Nothing to Report

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

  In the last year, our contracted genetic testing company, raised its test price for academic institutions. We successfully secured philanthropic funds to cover the increased cost and renegotiated the contract to be able to continue genetic testing.

- **Changes that had a significant impact on expenditures**

  Nothing to Report

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

  Nothing to Report

- **Significant changes in use or care of human subjects**

  Nothing to Report

- **Significant changes in use or care of vertebrate animals.**

  Nothing to Report

- **Significant changes in use of biohazards and/or select agents**

  Nothing to Report

6. **PRODUCTS:**

- **Publications, conference papers, and presentations**

  Nothing to Report

- **Journal publications.**

  Nothing to Report

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

  Nothing to Report

- **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?**

**Dr. Maria Carlo**: no change

**Dr. Behfar Ehdaie**: no change

**Dr. Jada Hamilton**: no change

**Kelsey Breen**: assigned Genetic Counselor (returned after leave)

**Brandon Williams**: assigned Clinical Research Coordinator (replaced Jessica Carruthers)

**Gina Yanza**: assigned Clinical Research Coordinator (replaced Ibrahim Shah)

| | |
|---|---|
| Name: | *Maria Carlo, MD* |
| Project Role: | *Principal Investigator* |
| Researcher Identifier (e.g. ORCID ID): | N/A |
| Nearest person month worked: | 1 |
| Contribution to Project: | Oversees all aspects of protocol and award management, including meetings with team, |

| | |
|---|---|
| | oversees accrual of patients and administration of assessments. |
| Funding Support: | |

| | |
|---|---|
| Name: | *Behfar Ehdaie, MD, MPH* |
| Project Role: | *Co-Principal Investigator* |
| Researcher Identifier (e.g. ORCID ID): | N/A |
| Nearest person month worked: | 1 |
| Contribution to Project: | Oversees accrual of patients in prostate cancer active surveillance clinic, coordination within urology service and other aspects of protocol. |
| Funding Support: | |

| | |
|---|---|
| Name: | *Jada Hamilton, PhD, MPH* |
| Project Role: | *Co- Investigator* |
| Researcher Identifier (e.g. ORCID ID): | N/A |
| Nearest person month worked: | 1 |
| Contribution to Project: | Oversees administration and any modifications of study assessments. |
| Funding Support: | |

| | |
|---|---|
| Name: | *Kelsey Breen, MS* |
| Project Role: | *Clinical Genetic Counselor* |
| Researcher Identifier (e.g. ORCID ID): | N/A |
| Nearest person month worked: | 3 |
| Contribution to Project: | Carries out telemedicine genetic counseling with all patients who receive genetic testing though the protocol. |
| Funding Support: | |

| | |
|---|---|
| Name: | *Gina Yanza* |
| Project Role: | *Clinical Research Coordinator* |
| Researcher Identifier (e.g. ORCID ID): | N/A |
| Nearest person month worked: | 3 |
| Contribution to Project: | Ms. Yanza has performed work in administration of study assessments and assisting with data collection. |
| Funding Support: | |

| | |
|---|---|
| Name: | *Brandon Williams* |
| Project Role: | *Clinical Research Coordinator* |
| Researcher Identifier (e.g. ORCID ID): | N/A |
| Nearest person month worked: | 3 |
| Contribution to Project: | Mr. Williams has performed work in preparing documents for protocol submission, overseeing accrual of patients to the protocol, and monitoring the trial per departmental and institutional review board guidelines. |
| Funding Support: | |

| | |
|---|---|
| Name: | *Samson Fine, MD* |
| Project Role: | *Co- Investigator* |
| Researcher Identifier (e.g. ORCID ID): | N/A |
| Nearest person month worked: | 1 |
| Contribution to Project: | Oversees review, re-review and annotation of pathology data for study participants |
| Funding Support: | |

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

- Dr. Hamilton has new support from:
    - National Institute of environmental health Sciences (R01 ES033743-01A1), 1.2 calendar months (2023-2027)
    - National Human Genome Research Institute (R01HG011914), 1.8 calendar months (2023-2026)
- Dr. Ehdaie has new support from:
    - American Cancer Society (DBG-23-1036155-01-CDP), 0.12 calendar months (2023-2025)
    - Prostate Cancer Foundation (22CHAL12), 0.6 calendar months (2023-2025)
    - National Institutes of Health (1R01CA272678-01), 0.6 calendar months (2023-2027) will

- **What other organizations were involved as partners?**
    - **Organization Name:** Invitae
    - **Location of Organization:** San Francisco, CA
    - **Partner's contribution to the project:** performs genetic testing with our custom-designed multiplex panel of 17 genes (BRCA1, BRCA2, TP53, HOXB13, PALB2, CHEK2, NBN, BRIP1, FANCA, MLH1, MSH2, MSH6, PMS2, EPCAM, RAD51C, RAD51D, and ATM)
    - **Financial support;** We pay $350 per patient sample

- **In-kind support:** Invitae will provide all materials (EDTA tubes, mailing kits) for samples to be shipped same day to the company, with a median turnaround of results of approximately 14 day
- **Facilities:** We utilize their CAP and CLIA clinical diagnostic laboratory to perform full-gene sequencing and deletion/duplication analysis using next-generation sequencing technology (NGS)
- **Collaboration:** N/A
- **Personnel exchanges:** N/A
- **Other.**

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS: N/A**
- **QUAD CHARTS: N/A**

9. **APPENDICES: None**