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

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

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> Active surveillance (AS) is now 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 genes and aggressive prostate cancer, whether presence of these mutations also lead to worse clinical outcomes in men on AS has not been systematically studied. We will conduct 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. We will also study the prevalence of germline pathogenic or likely pathogenic variants in DDR genes in this population and compare pathologic outcomes between germline DDR mutation carriers vs non-carriers. We will recruit 600 participants over 3 years. The specific aims include: (1): to describe the prevalence of pathogenic and likely pathogenic germline variants in DNA damage repair 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 germline variants versus those without; and (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.					
<b>15. SUBJECT TERMS</b> Genetic testing, DNA damage repair gene, Prostate cancer, Low-risk Prostate Cancer, Active Surveillance					
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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.

## 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.

	<b>Due Date Per SOW</b>	<b>Completion</b>
<b>Major Task 1: Clinical Trial</b>		
<b>Subtask 1: Prepare Regulatory Documents and Research Protocol for Trial</b>		
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
<i>Milestone Achieved: Local IRB approval</i>	5/1/2020	Yes (4/21/2020)
<b>Subtask 2: Human Research Protection Office (HRPO) Submission</b>		
Review protocol and consent documents	8/1/2020	Yes
Edits to documents	9/1/2020	N/A
Resubmission to local IRB		N/A
<i>Milestone Achieved: HRPO approval</i>	9/1/2020	Yes (8/26/20)
<b>Subtask 2: Prepare Trial Infrastructure and Train Research Staff</b>		
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
Protocol Principal Investigator changed to Dr. Maria Carlo*		03/16/21
<i>Milestone Achieved: Research staff trained</i>	9/1/2020	Yes
<b>Subtask 3: Initiate Clinical Trial</b>		
Begin subject recruitment	10/1/2020	Yes
<i>Milestone Achieved: First participant consented, screened, and enrolled</i>	10/1/2020	Yes (9/18/2020)
<b>Subtask 4: Conduct Clinical Trial</b>		Goal accrual n=600
Participants complete genetic testing		58/600, 9.6%
Post-test Genetic counseling provided over telephone		57/600, 9.5%
Participants complete Assessment Questionnaires 1 and 2		50/600, 8.3%
Participants complete Assessment Questionnaire 3 and 4		0%
<i>Milestone Achieved: Clinical Trial Completed</i>	1/1/2025	No

. \*Added goal since original SOW submission

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

Within the past reporting year, the study’s regulatory documents and research protocol were approved by MSK’s IRB and DOD’s HRPO. The team onboarded and fully trained clinical research coordinators, who have assisted with screening and consenting patients and administering assessments. The study workflow has adjusted to changes in clinic due to COVID-19, which heavily relies on telehealth. Both patients seen remotely and in clinic are being approached by their clinicians and the study team consents accordingly.

We exceeded our goal of 75 patients accrued, consenting 77 patients prior to 4/1/2021. While bloodwork needs further coordination following remote consents due to COVID-19, 58 patients have received their genetic test results and had their counseling session. The team continues to actively recruit patients, provide genetic counseling and administer follow-up assessments.

Amendment 13 was approved by local IRB and DOD on 03/16/21. Following the amendment, Dr. Maria Carlo is now the Principal Investigator of the protocol. In addition, we have converted our educational brochure to an infographic, which is easier to send remotely for patients.

<b>Study Milestones</b>	<b># of patients completed</b>
Consented Patients	77
Genetic testing completed	58
Assessment One	74
Assessment Two	51
Assessment Three	0
Assessment Four	0

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

- Principal Investigator presented at the GU Cancer Symposium 2021 on the Genomics of Prostate Cancer

- Co-Principal Investigator and clinical research coordinator attended a MSK sponsored seminar on monitoring and evaluating patient participation and hesitancy with research, specifically within marginalized communities

- Clinical research coordinator attended MSK sponsored seminars on community-based approaches to educating diverse patient populations on genetic testing

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

Principal Investigator and Co- Principal Investigator presented at MSK's Radiation Oncology service research meeting to introduce the study. This was used as an opportunity to engage radiation oncologists about MSK's Active Surveillance protocol and discuss how they view the utility of germline mutations in decision making for patient's treatment plan.

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

The study team will continue screening and consenting patients to achieve our accrual goal of 600 early-stage prostate patients. We will continue to follow up with participants to ensure they receive genetic testing, have their counseling session and complete their assessments.

During the next reporting period, the research team will begin to build a database for clinical annotation with Dr. Ehdai's Active Surveillance expertise. The team will work to accrue a cohort of 60 patients who were previously on Active Surveillance and are now post-radical prostatectomy. This will give the team access to retrospective data on disease progression in early-stage patients. The team will begin pathology assessments with the guidance of Dr. Samson Fine for this cohort.

#### 4. **IMPACT:**

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

Although still in the initial phases, 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 DDR 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**

Due to the unanticipated COVID-19 pandemic, which significantly affected New York City early on, we had to rapidly change our planned patient consenting procedures from in-person to virtual. We developed a streamlined e-consent process in which patients have the opportunity to watch educational video, review the study consent documents, discuss study with consenting professional and consent through through our institutional e-consent platform.

Due to a technology issue between MSK and DOD's email servers, the PI-change approval notice was not received by our team until April 19. This resulted in an 8 week pause on consenting patients. The study team will work to consent patients referred during this time remotely.

- **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?**

Name: Maria Carlo  
Project Role: Principal Investigator  
Researcher Identifier (e.g. ORCID ID): 0000-0002-4786-7408  
Nearest person month worked: 1  
Contribution to Project: Dr. Carlo has worked in guiding protocol through local IRB approval, HRPO submission process, and coordination infrastructure and research assistant training to initiate patient accrual in collaboration with Dr. Behfar Ehdaie and rest of study team.

Name: Behfar Ehdaie  
Project Role: Co-Principal Investigator  
Researcher Identifier (e.g. ORCID ID): 0000-0003-2949-0632  
Nearest person month worked: 1  
Contribution to Project: Dr. Ehdaie has worked in overseeing the overall progress of the study, recruiting patients from active surveillance clinic, and ensuring that all study activities progress in a timely manner.

Name: Jada Hamilton  
Project Role: Co-Investigator  
Researcher Identifier (e.g. ORCID ID): 0000-0001-8377-4666  
Nearest person month worked: 1  
Contribution to Project: Dr. Hamilton has performed work in guiding protocol workflow to ensure continued accrual during COVID pandemic.

Name: Megha Ranganathan  
Project Role: Clinical Genetic Counselor  
Researcher Identifier (e.g. ORCID ID): N/A  
Nearest person month worked: 1  
Contribution to Project: Ms. Ranganathan has monitored all genetic testing results from Invitae and performed genetic counseling with all patients enrolled in the study during Q4.

Name: Jessica Carruthers  
Project Role: Clinical Research Coordinator  
Researcher Identifier (e.g. ORCID ID): N/A  
Nearest person month worked: 3  
Contribution to Project: Ms. Carruthers 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.

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

Name:	<i>Kelsey Breen, MS</i>
Project Role:	<i>Clinical Genetic Counselor</i>
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 through the protocol.
Funding Support:	

Name:	<i>Ibrahim Shah</i>
Project Role:	<i>Clinical Research Coordinator</i>
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	3
Contribution to Project:	Mr. Shah has performed work in administration of study assessments and assisting with data collection.
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?**
- In the last year, Dr. Hamilton has new support from MSK Department of Medicine (expects 0.60 CM) and from NIH/NCI in the form of 4 different grants (expects 3.6 CM, 0.60 CM, 0.60 CM and 0.24 CM). The following grants have now closed: NIH/NCI (1.20 CM) and The Breast Cancer Research Foundation (1.20 CM).
- **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 \$250 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:**
  - **QUAD CHARTS:**
- 9. APPENDICES:**