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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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14. ABSTRACT

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;

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

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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TABLE OF CONTENTS

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.

With the COVID-19 pandemic shifting most of the active surveillance visits to telemedicine, we have made modifications to the original protocol to facilitate telemedicine consent and saliva as an alternative to DNA collection. Although telemedicine and the fewer than expected visits during the pandemic did slow our accrual, we are still on track for 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		251/600, 42% In Progress
Participants complete genetic testing		198/600, 33% In Progress
Post-test genetic counseling provided over telephone		193/600, 32.2% In Progress
Participants complete Assessment Questionnaires 1 and 2		156/600, 26% In Progress
Participants complete Assessment Questionnaire 3 and 4		34/600, 5.7% 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	
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. We also have amended our protocol to allow for saliva as a form of collection of DNA, where kits are sent to patients to their home.

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 89%, 82%, 78%, 58% 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.

Amendment 15 was approved by local IRB. Following the amendment, we can also obtain DNA through saliva, facilitating participation of patients in more remote locations or who prefer telemedicine and cannot routinely do blood draws. Since this recently approved amendment, four patients have elected to send their sample through saliva.

- **What opportunities for training and professional development has the project provided?**
- Principal Investigator presented at the American Urologic Association seminar on Global Advancements in Prostate Cancer
- Principal Investigator, Co-Principal Investigators and clinical research coordinators have met with the Memorial Sloan Kettering “Patient-Reported Outcomes, Community-Engagement, and Language Core” to discuss feasibility of translating our assessments into Spanish to eventually allow primary Spanish speakers to participate in the clinical trial. Through this process we have learned about the process of translating and validating instruments in other languages.
- Genetic counselor applied for a companion grant through the American Board of Genetic Counseling titled: Acceptance and clinical impact of a streamlined model of cancer genetic counseling in Spanish-speaking patients with prostate cancer

- Genetic counselor attended a hereditary cancer symposium for health care providers at MD Anderson on 4/01/22 which included a lecture on integrating universal germline genetic testing for men with prostate cancer into clinical practice by utilizing a mainstreaming model.

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

Principal Investigator and Co- Principal Investigator have continued to present at multi-disciplinary MSK meetings on updates on accrual. We are planning to submit a preliminary report on progress to date for the Genitourinary Cancer Symposium 2023 Annual Conference.

- **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 accrual of patients. We estimate we will accrue 150-250 additional patients given our past accrual, with some limitations given COVID and shift to telemedicine, making both consent and DNA sample collection a lengthier period. We have implemented various strategies to remind clinicians about this study, and continue to re-evaluate more effective methods, such as integrating the office administrative staff in facilitating reminders of study to clinicians. We will continue to follow up with participants to ensure they receive genetic testing, have their counseling session and complete their assessments.

For the next annual reporting period, we expect to have several preliminary analyses for the first 300 participants. First, we will determine of the pathological outcomes in patients on active surveillance who have at least two pathologic samples. For this, we are implementing a database for collection of the pathologic data. We will do a data query for Gleason score of each biopsy sample. We will compare the rate of grade reclassification in germline carriers vs non-carriers. Second, we will continue the clinical annotation of patients on the study to identify risk factors for presence of pathogenic variants. For these analyses, we will involve our statistical co-Investigators, Dr Andrew Vickers and staff, as well as our pathology co-Investigator, Dr Samson Fine.

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 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**

  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 though our institutional e-consent platform. In the last reporting year, this process has been further streamlined using institutional resources. We have also amended our protocol to allow for saliva as another method of DNA collection. This has facilitated timely sample collection in patients who do not have upcoming appointments in our center within the next few months and for patients who reside farther away.

- **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)

Ibrahim Shah: assigned Clinical Research Coordinator (replaced Hannah Ovadia)

Name:	*Maria Carlo, MD*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	0000-0002-4786-7408
Nearest person month worked:	2.4
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):	0000-0003-2949-0632
Nearest person month worked:	2.4
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):	0000-0001-8377-4666
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:	*Ibrahim Shah*
Project Role:	*Clinical Research Coordinator*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	12
Contribution to Project:	Performs work in administration of study assessments and assisting with data collection.
Funding Support:	

Name:	*Jessica Carruthers*
Project Role:	*Clinical Research Coordinator*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month	9

worked:	
Contribution to Project:	Coordinate's physician and patient appointments, facilitates study accrual, and assists integrating genetic testing process.
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:	Coordinate's physician and patient appointments, facilitates study accrual, and assists integrating genetic testing process.
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 supplemental support from National Institute of Health on MSK's Cancer Center Support Grant - P30 (no specified effort).
- Dr. Carlo has new support from National Institutes of Health (NIH) R01CA255323 as sub-award Principal Investigator (0.6 calendar months).
- Dr. Ehdaie has new support from Patient Centered Outcomes Research Institute (2.4 calendar months).

- **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:**