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Commentary

Collaboration is Key to Advancing Precision Medicine in Prostate Cancer Treatment

By Heather Cheng, MD, PhD, and Channing Paller, MD



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Commentary Overview

- Prostate cancer kills more American men than any type of cancer except lung cancer.
- An estimated 7 percent of men with early-stage prostate cancer have germline mutations; 12-17 percent of men with metastatic prostate cancer also have inherited variants.
- The PROMISE Registry aims to expand biomarker-informed treatment guidelines and clinical trials for prostate cancer.
- Key findings from the study will be shared across the prostate cancer research, clinical, and patient communities.

In the fight against prostate cancer, patients' DNA may be our most powerful tool. Understanding the genes of prostate cancer patients at all stages of the disease is the next step in our collective mission to improve outcomes for patients fighting this pervasive cancer. A collaborative, focused effort to advance precision medicine by collecting and democratizing important new data is needed to hasten discovery and transform the prostate cancer treatment paradigm.

Most individuals will not die from prostate cancer. Early disease is often curable. Yet **approximately 35,000 men** each year will succumb to the disease. Prostate cancer kills more American men than any type of cancer except lung cancer due to its high incidence. An estimated 7 percent of men with early-stage disease have germline mutations; **12-17 percent of men with metastatic prostate cancer** also have inherited variants.

In the current era of big data in biomedical research and clinical care, we encourage America's

cancer institutions, oncologists, urologists, and prostate cancer patients to join us in our effort to better understand the role germline DNA plays in the treatment and outcomes of the second most common cancer in the United States. The potential for extraordinary clinical impact is tremendous.

Leveraging biomedical data to compare treatments and aggregate data from distinct patient populations can help us identify patterns in diagnosis and therapies to treat breast, colorectal, and lung cancers. Now we are bringing that same approach to prostate cancer.

The effect of precision medicine on patient outcomes across prostate cancer disease states has become increasingly evident with early clinical trials. For example, a [clinical trial looking at Olaparib](#) showed that nearly 30 percent of men with advanced prostate cancer responded to the drug. Olaparib, like Rucaparib, has received approval for the treatment of metastatic castration-resistant prostate cancer (mCRPC) harboring alterations in homologous recombination repair genes. These two recent approvals by the U.S. Food and Drug Administration (FDA) have opened a new avenue of treatment for some men with prostate cancer: an expanded role for targeted therapies.

PROMISE Registry to Provide Data

Currently, the [National Comprehensive Cancer Network \(NCCN\) Prostate Cancer Guidelines](#) recommend germline genetic testing for patients with metastatic disease, high-risk localized disease, and node-positive disease. However, less is known about biochemically recurrent, low-risk localized, and active surveillance populations. Due to a paucity of data, there are not yet biomarker-informed treatment guidelines and clinical trials for these prostate cancer disease states. We hope to change this with the [PROMISE Registry](#) (clinical trial ID NCT04995198) – Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness.

There is much more we need to discover – particularly among the group of men with rare germline variants whose outcomes are all too often bleak. We want to gain a broader real-world understanding of the prevalence of potentially targetable DNA damage repair alterations as well as the efficacy of therapies such as abiraterone, PARPoly (ADP-ribose) polymerase (PARP) inhibitors, and the combination of abiraterone with Olaparib. Furthermore, for mutations in genes such as ataxia telangiectasia mutated (ATM)—which increasing evidence suggests does not predict response to PARP inhibitors—we need new strategies to direct these patients to other therapies and clinical trials looking at new targeted options, such as ATR (ataxia-telangiectasia and Rad3 related protein) inhibitors.

That is why we are building a coalition of oncologists, urologists, radiation oncologists, researchers, and patients across cancer centers and institutions nationwide to establish the first genetic database of prostate cancer patients who have rare germline variants associated with more aggressive disease. In addition to the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University and University of Washington and Fred Hutchinson Cancer Center, partner sites currently include the Cleveland Clinic, Dana-Farber Cancer Institute, Duke Cancer Institute, Memorial Sloan Kettering Cancer Center, and The University of Chicago Medical Center. This list continues to grow.

Using a home-based, medical-grade saliva assay, we aim to screen 5,000 prostate cancer patients at no cost to identify and enroll 500 patients with germline variants that are known and likely pathogenic variants, or variants of unknown significance in selected DNA damage repair genes (ATM, ATR, BRCA1, BRCA2, BRIP1, CHEK2, FAM175A, GEN1, HOXB13, MRE11A, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, TP53, and XRCC2).

We plan to collect data on disease characteristics and examine the association between disease characteristics and pathogenic and likely pathogenic germline variants and variants of uncertain significance (VUS). We will gather patient reported outcomes (PRO) associated with genetic testing in subjects with prostate cancer using the validated European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-C30). Over the course of 15 years, we will amass longitudinal outcome data on subjects with pathogenic and likely pathogenic germline variants and VUS of interest, for specific treatments, treatment sequences, or therapy combinations used for treating prostate cancer. And we will compare overall survival in subjects with pathogenic and likely pathogenic germline variants of interest and subjects with VUS.

In addition to creating a community for these patients and their physicians, we will share knowledge through newsletters and webinars. Patients with pathogenic variants will be able to gain support from a genetic counselor to offer germline testing to their family members, also known as cascade testing. Finally, patients with known pathogenic variants will be updated about novel FDA-approved targeted therapies as well as clinical trial options associated with their germline variant.

A Call for Collaboration

As we analyze genetic information from patient partners around the country, we will build the foundation for a better future of prostate cancer knowledge and treatment. We will share key findings from our study widely across the prostate cancer research, clinical, and patient communities to help accelerate advancements in knowledge and treatment.

We call on colleagues at other cancer research institutions to join us. Only through open collaboration and urgency can we increase scientific discovery and facilitate use of precision medicine to treating prostate cancer patients. Together, we can save lives now and for generations to come.

It is time to advance precision medicine in prostate cancer treatment and shape the future of prostate cancer care.

About the Authors

Heather Cheng, MD, PhD, is a medical oncologist at the University of Washington. Dr. Cheng focuses on improving the care of patients with prostate and bladder cancers. An expert in prostate cancer genetics, she is studying ways to use genetics to guide the care of prostate cancer patients and their family members who may also be at high risk for the disease.

Channing Paller, MD, is a medical oncologist and associate professor of oncology and urology at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center and an expert on biomarkers that enable patient-centered treatment strategies. Her research focuses on developing improved, targeted treatments to extend survival and improve quality of life for prostate cancer patients.

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