PROMISE Registry: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness

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Study Phase	Registry
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Regulatory Sponsor & Data Coordinating Center	Prostate Cancer Clinical Trials Consortium, LLC
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Number of Sites	The PROMISE Registry is a nationwide decentralized study – participants can join from anywhere in the US and do not have to be affiliated with a particular investigator or medical center.

Protocol Synopsis

Rationale	For about 10% of metastatic prostate cancer patients, germline genetic testing can identify inherited mutations that may offer additional options for precision-based treatments unique to these mutations. The proportion of patients in the high-risk localized disease and biochemical recurrent setting is less defined yet important to characterize. Clinical trials using targeted agents in earlier disease states are being developed and identifying patients who carry germline genetic mutations may be a rate-limiting step in advancing research of new treatment strategies. By developing a registry of men with prostate cancer who carry germline genetic mutations, the PROMISE registry will: 1. Provide information on the incidence of pathogenic variants in prostate cancer populations 2. Describe the association of pathogenic variants with disease characteristics and responses to specific treatments, treatment sequences or therapy combinations used for treating prostate cancer 3. Identify how pathogenic variants are associated with overall survival
Study Design	PROMISE is a national, decentralized prospective prostate cancer genetics registry.
Primary Objective	Identify and recruit participants 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.
Secondary Objectives	• Assess the frequency of pathogenic or likely pathogenic germline variants of interest in men with prostate cancer. • Identify and recruit a control group of participants with a variant of uncertain significance (VUS) in their clinical or research results in the following genes: *ATM, ATR, BRCA1, BRCA2, FAM175A, GEN1, HOXB13, MRE11A, PALB2 and XRCC2.* • Collect data on disease characteristics and examine the association between disease characteristics and pathogenic and likely pathogenic germline variants and VUS of interest. • Collect patient-reported outcome (PRO) measures associated with genetic testing in men with prostate cancer using the validated EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30). • Collect longitudinal outcome data on men with pathogenic and likely pathogenic germline variants and VUS of interest, for specific treatments, treatment sequences or therapy combinations used for treating prostate cancer. These outcomes aim to measure clinically significant events and, when possible, will include: **o** radiographic and PSA progression-free survival (PFS) **o** metastasis free survival **o** overall survival **o** time on treatment **o** time to next treatment • Data permitting, compare overall survival of men with pathogenic and likely pathogenic germline variants of interest and men with VUS.
Exploratory Objectives	• Capture family history to assist with the interpretation of germline genetic testing results. • Provide a mechanism to notify men with inherited homologous recombination deficiency pathogenic variants about current and future clinical management and research opportunities. • Provide participants with updated information about new research results, clinical trial opportunities, and treatments approved by the Food and Drug Administration (FDA).
Number of Participants	5,000 participants will be screened to identify 500 with germline genetic mutations who will be enrolled for long-term follow-up. There will be two cohorts: 1. Participants with at least one germline pathogenic/likely pathogenic variant (n=400) 2. Participants with at least one variant of uncertain significance will serve as a control group (n=100)
Participant Selection Criteria	● Males ≥18 years of age with a diagnosis of prostate cancer are eligible for screening (documented via tissue biopsy, PSA > 100ng/dL, and/or clear radiographic evidence of disease & receiving systemic therapy). ● Participants must be a resident of the United States at the time of consent. ● Participants with target pathogenic/likely pathogenic variants or variants of uncertain significance are eligible for long-term follow-up.

Duration of Study	• Participants will be recruited & screened over a five-year period. • All screened participants will have baseline demographic, medical/family history & patient-reported outcomes data. • Eligible participants (those with target germline mutations) will be followed every 6 months to obtain updated health records data and patient-reported outcomes data. Participants will be followed for a minimum of 15 years, or until death or withdrawal of consent.
Statistical Plan	Based on available data, we will conservatively assume an overall 10% prevalence of at least one pathogenic variant in the screened population. We will also assume a 20% prevalence of at least one VUS in the screened population. Based on these rates, we will need to screen approximately 5,000 men over the accrual period to identify 400 with at least one germline pathogenic variant and 100 with at least one VUS (control group). We will examine the screening patterns after one year of accrual to see the distribution of the subpopulations that agree to germline genetic and whose results show at least one pathogenic variant. Outreach efforts may be adjusted to increase screening of various subpopulations.

Study Roadmap