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## Germline Genetic Testing in Advanced Prostate Cancer - Practices and Barriers: Survey Results from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium

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## Abstract

**Background:** Germline genetic testing increasingly identifies advanced prostate cancer (PCa) patients who are candidates for precision therapies. The Prostate Cancer Clinical Trials Consortium (PCCTC) established the Germline Genetics Working Group to provide guidance and resources to expand effective use of germline genetic testing.

**Methods:** A 14-item questionnaire was emailed to academic oncologists at 43 PCCTC sites to collect information on germline genetic testing patterns, including patients considered, choice of assays, barriers slowing adoption, and actions to overcome barriers.

**Results:** 26 genitourinary oncologists from 19 institutions responded. Under 40% reported referring patients to a genetics department, while the remainder take personal responsibility for genetic testing and counseling; 62% consider testing all metastatic PCa patients, while 11% consider testing all patients with high-risk local disease; and 27% use multi-gene comprehensive pan-cancer panels while 54% use smaller or targeted cancer gene panels. Barriers to widespread use are (1) delayed or limited access to genetic counseling, (2) no insurance coverage, (3) lack of effective workflows, (4) insufficient educational materials, and (5) time and space constraints in busy clinics. The primary limitation was the <50% response from PCCTC sites and no coverage of non-academic cancer treatment facilities.

**Conclusion:** Joint efforts by urologists, oncologists, genetics counselors, insurers, and cancer centers can accelerate implementation of integrated germline genetic services for personalized treatment and clinical trial eligibility for PCa patients.

## MICRO ABSTRACT

Over 10% of patients with advanced prostate cancer carry inherited genetic mutations that may amplify their response to targeted therapies, but barriers, including a shortage of genetic counselors, limit patient access to testing that would enable targeted therapy. This study of practices in nineteen U.S. comprehensive cancer centers found that a shortage of genetic counselors and 4 other barriers limit adoption of this important advance. The paper also catalogues germline genetic testing practices and illuminates initiatives that may expand testing availability.

## Keywords

prostate cancer; survey; BRCA; Lynch; clinical trials; genetic testing; germline; somatic; metastatic; DNA repair; PARP inhibitors; pembrolizumab

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## INTRODUCTION

A significant number of prostate cancer (PCa) cases have a heritable component. Germline DNA damage repair (DDR) defects are present in over 10% of patients who develop metastatic PCa (mPCa), with *BRCA2* found in more than 5% and *BRCA1*, *ATM*, and *CHEK2* each found in 1%-2%. Prevalence of germline mutations in DDR genes in men with mPCa exceeded the observed 5% prevalence in men with localized PCa and 3% prevalence in men without a known cancer diagnosis.<sup>1, 2</sup> In recent years, the treatment landscape for mPCa has been refined by the discovery of DDR deficiency as predictive biomarkers for response to targeted therapies. For example, the presence of homologous recombination deficiency may predict response to poly (ADP-ribose) polymerase (PARP) inhibitors as well as to other DNA-damaging chemotherapy agents (platinum chemotherapy).<sup>3-6</sup> Similarly, the presence of germline mutations in mismatch repair genes (MMR) may identify candidates for treatment with immune checkpoint inhibitors.<sup>7-10</sup> Thus, it has become progressively important to assess practice patterns and needs regarding germline genetic testing and counseling for men with PCa. Urologists are increasingly ordering germline testing for their PCa patients in light of recent evidence that *BRCA1/2* and *ATM* mutation status is associated with grade reclassification or PCa patients undergoing active surveillance.<sup>11</sup> Urology involvement in germline genetic testing will grow as the area evolves to include high risk localized and earlier disease states.<sup>12-14</sup>

The Germline Genetics Working Group (GGWG) of the Prostate Cancer Clinical Trials Consortium (PCCTC) was established in June 2017 in response to the need to better inform and advise clinicians of the increasing evidence that germline alterations in DDR genes may identify additional options for prostate cancer therapy. The objectives of the GGWG are to work together with clinicians and researchers around topical challenges of treatment selection and eligibility for trials of investigational therapeutics, and to enable more streamlined and effective use of germline genetic testing in PCa patients in the face of a rapidly evolving genetics-informed therapeutic landscape.

In June 2018, the GGWG produced a White Paper that presented a framework to address unique challenges and therapeutic opportunities regarding germline testing for precision therapy in patients with advanced PCa and identified areas of future research.<sup>15</sup> The White Paper recommended that clinicians: (1) consider expanding germline genetic testing beyond cancer risk assessment to inform treatment selection and eligibility for clinical trials, (2) work with genetic counselors to ensure pre-test informed decision-making through education or counseling and post-testing counseling and, (3) where appropriate, ensure mechanisms for offering cascade germline genetic testing to family members. However, barriers and challenges to broader implementation of these recommendations require attention.

To elucidate practice patterns and challenges in germline genetic testing of PCa patients in oncology, the GGWG surveyed medical oncologists from institutions that are members of the PCCTC. Here, we report survey data from responding oncologists from nineteen PCCTC cancer centers identifying commonalities and differences in practice patterns. The survey results were used to support recommendations for addressing barriers to germline testing for men with PCa and are placed in the context of current NCCN guidelines for genetic testing of PCa patients.

## MATERIALS AND METHODS

### Survey.

A 14-question survey was developed by the GGWG to capture the practice patterns and needs of oncologists at PCCTC institutions. The survey was refined after pilot testing and then distributed to oncologists at their institutions using RedCap, a web-based survey tool, with an email (12/20/17) asking members to complete the survey and to ask other investigators at their institutions to respond. A reminder email was sent on 1/16/18 to GGWG members who had not completed the survey. PCCTC principal investigators were reminded of the survey during two sequential monthly conference calls that took place between the two email-based survey distributions (12/21/17 and 1/8/18).

The survey questions offered multiple choice answer selections on personal practices around genetics services, on patient characteristics oncologists consider for germline testing (metastatic disease, advanced stage, family history), on cascade genetic testing processes, and on gene panels. The remainder were free-form questions asking for clarifications of answers to the multiple-choice questions and also asking participants to describe their approaches to integrating germline testing with therapeutic clinical trials and to cascade testing. The full survey may be found in the Supplementary Materials.

### Analysis:

Data were gathered in the RedCap package and exported to a comma separated value file. Data were imported into Excel, where they were summarized, tabulated, and graphed.

## RESULTS

Between 12/20/2017 and 4/3/2018, representatives of the 43 PCCTC participating and affiliate sites received the germline genetic testing current practice survey and an email encouraging redistribution to institutional colleagues, and twenty-six PCa oncologists from nineteen sites (44%) completed the survey (Table 1)

### Personal Practices of PCa Oncologists regarding Genetics Services for PCa Patients

Whereas 38% (10/26) of participating oncologists reported that they refer patients to a separate department for genetic testing and counseling, more than half reported taking personal responsibility for some or all genetic education and testing of their patients. Fifteen percent (4/26) reported personally performing pre-test counseling, ordering germline testing, and performing post-test counseling. Those who reported using a combination of approaches

generally referred to genetic counselors for post-test counseling. Variation in practice appears to depend on factors such as (1) patient's insurance coverage for genetic testing and counseling, (2) availability of testing and counseling resources within the oncology group, (3) testing and counseling resources in a separate genetics department, and (4) wait times for referrals.

### Patients Considered for Germline Genetic Testing

**Metastatic PCa**—All twenty-six participating oncologists reported considering *some* mPCa patients for germline genetic testing: 62% reported considering *all* mPCa patients; 27% considered testing mPCa patients with a family history and/or who were eligible for clinical trials; and 12% considered testing only for patients with a family history for germline genetic testing (Fig. 1A).

**High-risk Localized PCa Patients and Non-metastatic PCa**—More than half of the participating oncologists (54%) considered germline genetic testing for some PCa patients with high-risk localized or non-metastatic disease (HRL/nmPCa), while twelve (46%) did not consider germline testing for these patients. Three (12%) reported testing *all* HRL/nmPCa patients; 3 (12%) reported considering testing only for patients with a family history for germline genetic testing; and 8 (31%) reported considering testing only those with a family history of cancer (Fig. 1B).

### Operational Barriers Faced by Oncologists Considering Germline Genetic Testing for PCa Patients

Based on participant responses and free text comments, five barriers in streamlining genetic testing were identified: access to genetic counselors, insurance coverage and cost, clinic workflow, time and space availability, and access to resources for provider and patient education. Fig. 1C shows the role of those operational barriers and the flow of considerations on whether to conduct germline genetic testing reported by responding oncologists, while Fig. 1D shows how referral decisions are made on the basis of those results.

### Reported Germline Testing Approaches

Participating oncologists reported their approaches for germline cancer predisposition testing. Twenty-seven percent (7/26) reported using only “comprehensive pan-cancer panels,” while 54% (14/26) listed only “expanded cancer panels (e.g., Lynch and *BRCA1/2* and hereditary breast and ovarian cancer genes),” and 4 others reported using more than one type of panel. One participant did not answer this question (Table 2).

### Resources for Patients and Family Members Regarding Genetic Testing

The GGWG aggregated a list of websites that it has found valuable for educating patients and their families about germline genetic testing for PCa (Table 3). Two participants reported they are developing local resources (a video and an information sheet for patients).

## DISCUSSION

The relevance of germline genetic testing in PCa is emerging today as it did in breast cancer three decades ago, although in PCa it is accompanied by concurrent therapeutic relevance. These rapid and exciting changes have resulted in challenges illustrated by the 2018 PCCTC GGWG survey of medical PCa oncologists at academic institutions in the PCCTC consortium, around their practices in germline genetic testing of PCa patients. The survey identified common themes across nineteen institutions as well as substantial variation in those practices. Five barriers to obtaining genetic testing were identified: lack of timely access to genetic counselors, lack of insurance coverage or high patient out-of-pocket costs, lack of integrated clinic workflow, time and space constraints, and insufficient resources for provider and patient education. Our survey found that more than half of oncologists reported taking part or full responsibility for germline genetic testing and education/counseling, despite the fact that most oncologists are not trained in genetic counseling.<sup>16</sup> Nearly 40% of the participating oncologists reported that among mPCa patients, they considered germline genetic testing mainly for those patients with a family history of cancer and those who were eligible for a clinical trial with genetic eligibility criteria, rather than all mPCa patients. Germline testing results are increasingly important for consideration of clinical trial eligibility. PCCTC sites reported ten therapeutic trials for PCa patients with relevance to germline mutations and four trials testing new models of genetics delivery in prostate cancer (Table 4). Similarly, a little more than half of respondents reported considering germline genetic testing for patients with high-risk localized PCa and non-metastatic PCa. These responses may reflect a period of limited resources and substantial logistical barriers and the need for triaging and prioritization of genetic counseling and testing until barriers can be better addressed.

At the time the survey was distributed, the National Comprehensive Cancer Network (NCCN) guidelines did not include recommendations for germline testing for most PCa patients. Based on recent data of germline mutations in men with PCa, before all GGWG survey responses were returned, NCCN Prostate Guidelines (Version 4.2018) were expanded to recommend consideration of germline genetic testing for most metastatic and high-risk localized PCa patients.<sup>17</sup> Thus, the survey captured change in action.

The current guidelines recommend consideration of germline testing for all patients with high-risk and very high-risk local disease, regional disease, and metastatic disease. Further, with more sensitive techniques for early identification of metastatic disease such as PSMA, fluciclovine,<sup>18</sup> and choline,<sup>19, 20</sup> more patients may be classified as metastatic than in the past, further increasing the numbers of patients to be considered for germline genetic testing. This expansion of patient populations to be considered for genetic testing, together with the barriers reflected in our findings, highlight the need for dedicated education and training for radiation oncologists, urologists and medical oncologists. In the localized disease setting with risk levels that are very low, low, favorable intermediate, and unfavorable intermediate, the NCCN Prostate guidelines suggest consideration for germline testing based on a strong family history of prostate cancer and/or other primary cancers, or for patients with a relative with a known familial cancer risk syndrome.

The current NCCN Prostate guidelines also suggest that patients whose tumor testing is positive for MSI-high or deficient-MMR (indicating potential use of pembrolizumab in treatment for mCRPC), also be referred for genetic counseling to assess for the possibility of Lynch syndrome. Finally, the current NCCN guidelines recommend that physicians consider testing tumors of patients with mCRPC for germline and somatic mutations in *BRCA1*, *BRCA2*, *ATM*, *PALB2*, and *FANCA*.

Approximately half of survey participants indicated that they would refer patients for genetic counseling and dedicated confirmatory germline testing if a tumor mutation was potentially germline in nature (thus with family counseling implications<sup>21</sup>) consistent with the recommendation in the GGWG White Paper<sup>15</sup>. As tumor sequencing for targeted treatment opportunities increase in PCa, the likelihood of identifying mutations that are potentially germline may increase, raising the need for distinct workflows to address this specific clinical scenario.

Several respondents noted that patient willingness to undergo germline genetic testing could be affected by concerns about genetic discrimination for life, disability, and long-term care insurance. The Genetic Information Nondiscrimination Act (GINA) of 2008<sup>22</sup> provides protection from genetic discrimination in health insurance and employment in most employment scenarios, but does not cover life insurance, long-term care, disability insurance, Indian Health Service, federal employees enrolled in the Federal Employee Health Benefits Plan, and other specific VA or U.S. military plans. Given these gaps in protection by the GINA law and potential changes over time, patients approached about germline testing need to consider these issues and their own financial situations prior to proceeding with germline testing. Thus, providers and patients can benefit from educational and practice-ready resources to help address the need to discuss genetic discrimination laws.

There are some limitations to consider in our results. Urologists were not surveyed, as metastatic disease has been a key driver of genetic testing up to the present time. However, since guidelines for testing is expanding to earlier stage disease, including urologists in future surveys will add important information. Our analysis does not account for institutional limitations that may have informed physician decisions regarding whom to test. In addition, there were site-specific differences in clinical trial availability with germline genetic eligibility criteria, including in the non-metastatic PCa setting which would have influenced consideration of genetic testing for that group. Another limitation is the response rate (oncologists from only nineteen of forty-three PCCTC sites responded), and the composition of respondents being largely oncologists with specific focus on prostate cancer in academic centers. Nevertheless, we feel that the general concepts around the clinical need for better integration of germline genetic testing in prostate cancer care and the current barriers to implementation will be broadly applicable across oncology practice settings.

## CONCLUSION

The NCCN and other professional organizations advocate informed decision-making for patients in the pre-test setting.<sup>23–27</sup> Research to improve delivery of pre-test education and optimization of informed decision-making is key to streamlining genetic testing for men

with PCa. In the post-test setting, discussion with a genetic counselor is important for patients with germline mutations, variants of uncertain significance, and with no mutations but with a family history of cancer to ensure understanding of results and appropriate follow up with regards to additional cancer screening and cascade testing recommendations. Physicians ordering genetic testing need to be well-versed in cancer risk guidelines for screening, genetic results interpretation, GINA laws, and population-level cancer screening guidelines. While referral to a genetic counselor is preferred when possible, there is a recognized shortage of genetic counselors that is predicted to worsen,<sup>28, 29</sup> suggesting a role for subspecialty oncologists with training in genetics as well as for genetics training for oncology providers who perform aspects of genetic counseling themselves.<sup>30</sup> Registries that include germline data, family history, treatments, and outcomes such as those being developed in the GEM, GENTLeMEN, and ProGEN trials, along with systems to address barriers to genetic testing, will help inform future guidelines and facilitate integrated genetic testing and counseling services into busy clinical practices.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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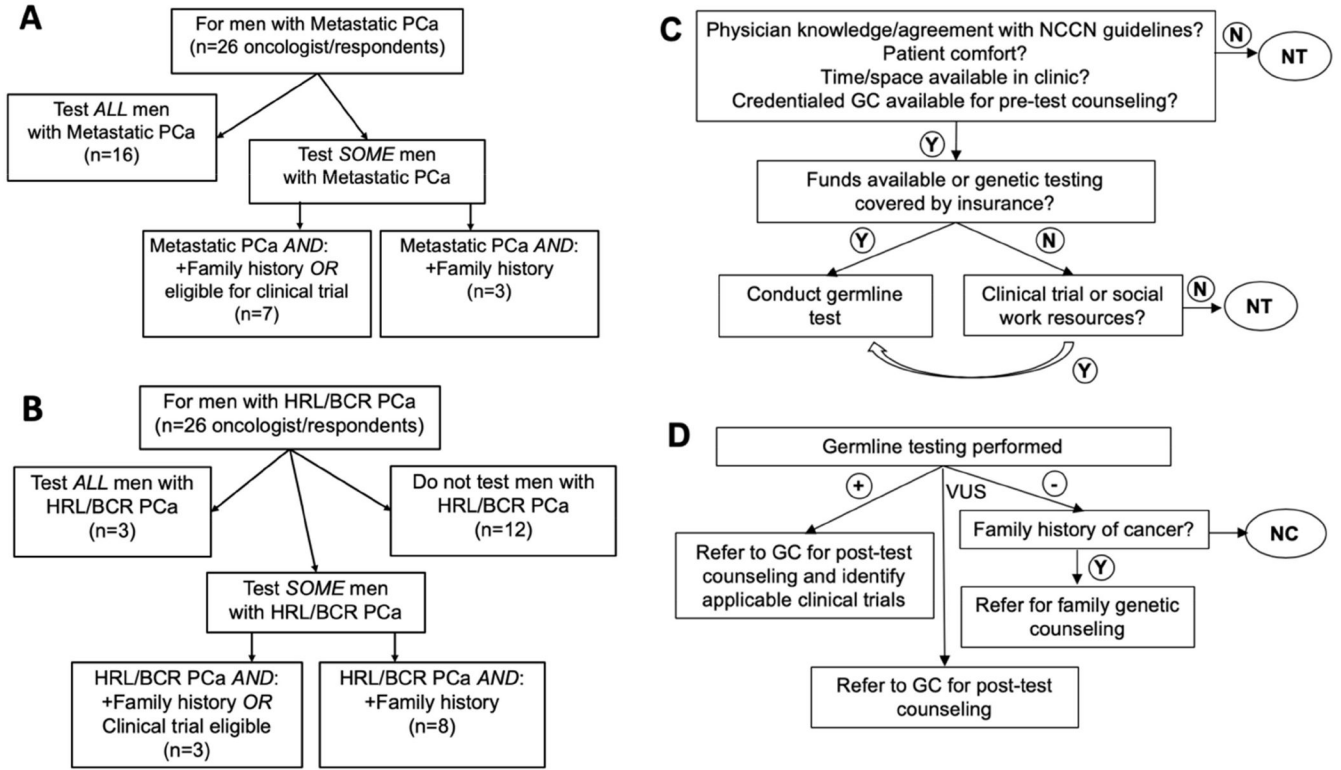


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**CLINICAL PRACTICE POINTS**

In the context of an evolving therapeutic landscape for men with mPCa and expanding NCCN guidelines for germline testing for patients with earlier stage disease, oncologists and urologists will increasingly need to consider incorporating genetic education, counseling, and germline testing for men with PCa. Providing guideline-concordant care now requires that practices and institutions prioritize including germline genetic testing as part of optimal care delivery. Physicians, mid-level providers, genetic counselors, practice managers, and other team members must work in a concerted manner to overcome these barriers in practice- and resource-specific ways to this evolving care model.



**Figure 1: Provider Considerations of Germline Testing Among Men with Prostate Cancer**  
 Note: Panel A: Men with mPCa considered for germline testing; Panel B: Men with high-risk localized and biochemically recurrent PCa considered for germline testing; Panel C: Factors affecting decision to test; Panel D: Factors affecting decisions on results.  
 Abbreviations: +, positive results; -, negative results; BCR, biochemically recurrent; GC, genetic counselor; HRL, high risk localized; N, no; NC, no post-test genetic counseling; NT, no germline genetic testing; PCa, prostate cancer; VUS, variant of uncertain significance; Y, yes.

**Table 1:**

## Cancer Centers Providing Germline Genetic Testing Survey Responses

<b>Cancer Center</b>	<b>Responses</b>
Fred Hutchinson Cancer Research Institute	3
Johns Hopkins Sidney Kimmel Comprehensive Cancer Center	3
Lurie Comprehensive Cancer Center	2
Rush University Medical Center	2
Weill Cornell Medical College	2
Beth Israel Deaconess Cancer Center	1
Carbone Cancer Center	1
Dana-Farber Cancer Institute	1
Duke Comprehensive Cancer Center	1
Jonsson Comprehensive Cancer Center	1
Lineberger Comprehensive Cancer Center	1
Masonic Cancer Center	1
Memorial Sloan Kettering Cancer Center	1
Moores Cancer Center	1
Oregon Health and Science University Knight Cancer Institute	1
Sidney Kimmel Cancer Center at Thomas Jefferson University	1
University of Chicago Medicine Comprehensive Cancer Center	1
Wayne State Karmanos Cancer Institute	1
Yale Cancer Center	1

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**Table 2.**

**Approaches to Germline Cancer Predisposition Testing**

	Respondent																									
	11	6	10	17	21	1	22	18	20	16	19	13	2	8	12	3	15	7	24	5	25	26	23	4	9	
General approach to germline cancer predisposition testing*																										
Comprehensive, pan-cancer panel	•	•	•	•	•	•	•	•																		
Expanded cancer panel (e.g., Lynch and BRCA1/2 and hereditary breast and ovarian cancer genes)	•								•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Limited prostate-cancer-specific panel																										
Specific individual genes (e.g., BRCA1, BRCA2)																										
Clinical-trial focused panel	•																									

\* Sites that listed multiple approaches (e.g., comprehensive and limited) explained that lack of insurance or limited patient capacity to pay sometimes causes them to select a more limited panel.

**Table 3:** Web Resources for Educating PCa Patients and Families about Germline Genetic Testing

Source	URL	Content
Color	<a href="https://www.color.com/learn/can-cancer-be-inherited">https://www.color.com/learn/can-cancer-be-inherited</a>	Patient-friendly discussion and data about cancer due to inherited (germline) genetic mutations
Dana Farber	<a href="https://www.dana-farber.org/cancer-genetics-and-prevention/videos/">https://www.dana-farber.org/cancer-genetics-and-prevention/videos/</a>	Videos explaining topics in cancer genetics and testing
Invitae	<a href="https://www.invitae.com/en/patients/genetic-diagnosis/">https://www.invitae.com/en/patients/genetic-diagnosis/</a>	Brief descriptions of genetic testing
Memorial Sloan Kettering	<a href="https://www.mskcc.org/cancer-care/risk-assessment-screening/hereditary-genetics/genetic-counseling/inherited-risk-prostate">https://www.mskcc.org/cancer-care/risk-assessment-screening/hereditary-genetics/genetic-counseling/inherited-risk-prostate</a>	Very brief discussion of inherited risk of PCa
National Society of Genetic Counselors	<a href="https://www.nsgc.org/">https://www.nsgc.org/</a>	Comprehensive guidance for patients, including help finding counselors
Prostate Cancer Foundation	<a href="https://www.pcf.org/news/genetic-screening-guidelines-for-prostate-cancer/">https://www.pcf.org/news/genetic-screening-guidelines-for-prostate-cancer/</a>	High-level overview of genetics-related knowledge helpful to patients with PCa and their families
	<a href="https://www.pcf.org/patient-resources/family-cancer-risk/genetic-testing-prostate-cancer/">https://www.pcf.org/patient-resources/family-cancer-risk/genetic-testing-prostate-cancer/</a>	Recommendation to speak with physician about whether patients need genetic testing, with five more detailed sub-pages
Sidney Kimmel Cancer Center of Thomas Jefferson University	<a href="https://prostatogenetics.jeffersonhealth.org/">https://prostatogenetics.jeffersonhealth.org/</a>	Prostate-cancer-focused and patient-friendly, web-based resource explaining genetic counseling, genetic testing, family history, genes, and cancer risks

**Table 4.**

## Therapeutic and Delivery Model Clinical Trials in PCa with Relevance for Germline Genetic Eligibility Criteria

Phase	Title	Disease State	Abbreviated Title	<a href="https://clinicaltrials.gov">Clinicaltrials.gov</a>
<b>Therapeutic Trials</b>				
III	Study of Olaparib versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer	mCRPC	PROFOUND	
III	A Study of Rucaparib versus Physician's Choice of Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer and Homologous Recombination Gene Deficiency	mCRPC	TRITON3	
II	A Phase 2 Efficacy and Safety Study of Niraparib in Men with Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies	mCRPC	GALAHAD	
II	A Multicenter, Open-Label Phase 2 Study of Rucaparib in Patients with Metastatic Castration-Resistant Prostate Cancer Associated with Homologous Recombination Deficiency	mCRPC	TRITON2	
II	Response Rate Study of Talazoparib in Men with DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer Who Previously Received Taxane-Based Chemotherapy and Progressed on at Least 1 Novel Hormonal Agent (Enzalutamide and/or Abiraterone Acetate/ Prednisone)	mCRPC		
II	Olaparib in Men with High-Risk Biochemically-Recurrent Prostate Cancer Following Radical Prostatectomy, with Integrated Biomarker Analysis	BCR		
II	Abiraterone/Prednisone, Olaparib, or Abiraterone/Prednisone + Olaparib in Patients with Metastatic Castration-Resistant Prostate Cancer with DNA Repair Defects	mCRPC	BRCAaway	
Pilot	Docetaxel and Carboplatin in Treating Patients with Metastatic, Hormone-Resistant Prostate Cancer Containing Inactivated Genes in the BRCA 1/2 Pathway	mCRPC	ABCD	
II	Docetaxel and Carboplatin for Patients with mCRPC and DNA-Repair Deficiencies	mCRPC	V-ABCD	
II	Trial of Rucaparib in Patients with Metastatic Hormone-Sensitive Prostate Cancer Harboring Germline DNA Repair Gene Mutations	mHSPC	TRIUMPH	
<b>Delivery Model Trials</b>				
N/A	Evaluating an Alternative Clinical Genetics Cancer Care Delivery Model: A Pilot Study of Patient Outcomes: Evaluating greater oncologist participation in genetic testing	PCa		
-				
N/A	Genetic Evaluation of Men: Registry of PCa patients with increased risk with family history and biospecimen bank	PCa	GEM Registry	
-				
N/A	Genetic Counseling Processes and Outcomes Among Males with Prostate Cancer: Testing pre-genetic-test video versus traditional pre-test counseling	PCa	ProGen	
-				
N/A	Genetic Testing for Men with Metastatic Prostate Cancer: Assess germline homologous recombination variants and family history, and identify men who might benefit from research and treatment options	mPCa	GENTleMEN	

Abbreviations: PCa, prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; mPCa, metastatic prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; BCR, biochemical recurrence