A Pilot Study to Improve Germline Testing in At-Risk Patients with Prostate Cancer

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Observational Study Protocol

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IMPRINT: A Pilot Study to Improve Germline Testing in At-Risk Patients with Prostate Cancer

A quality improvement initiative to improve rates of germline testing among men with prostate cancer through the use of an in-clinic educational session.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
HRR	Homologous Recombination Repair
mCRPC	Metastatic Castrate Resistant Prostate Cancer
NCCN	National Comprehensive Cancer Network
PARP	Poly-ADP Ribose Polymerase
UCSD	University of California San Diego

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PROTOCOL SYNOPSIS

This is a pilot study to improve germline genetic testing for patients with aggressive prostate cancer as recommended by the updated guidelines by the National Cancer Comprehensive Network (NCCN) in 2018. Implementation of germline testing in men with prostate cancer has been low, in part due to the lack of resources to educate patients on germline testing including a growing national shortage of genetics counselors. Given limited genetic counseling services and a growing number of patients who qualify for germline testing, there has been interest in developing models to educate patients on germline testing in the clinic. In this study, consented patients will undergo a low-risk intervention of an educational session with a trained staff member on germline testing in prostate cancer and if agreeable, subsequent germline cancer genetic testing via a commercial lab test.

Background/Rationale: Germline testing is recommended for patients with high risk localized, locally advanced, and metastatic prostate cancer. Despite this recommendation, implementation of germline testing in prostate cancer has been suboptimal. This is due in part to a large number of patients who are eligible for testing and a national shortage of genetic counsellors. Given this, there is a need for novel strategies to engage oncology clinicians in germline testing and integrate germline testing into the clinic. Improving the rates of germline testing is vitally needed as pathogenic germline alterations can have therapeutic significance for a patient's prostate cancer and can have implications for family members in terms of their own cancer risk.

Objectives and Hypotheses: The primary objectives of this study are to both assess the feasibility of a patient educational program to improve germline genetic testing for eligible patients with prostate cancer and to assess the effectiveness of a patient educational program with regards to increasing germline genetic testing rate among adult prostate cancer patients who are recommended to receive germline testing per guidelines.

We hypothesize that the intervention will be feasible with successful recruitment of our target sample size. We additionally hypothesize that the rates of germline testing among patients recruited to the study will be higher than rates of testing among patients not enrolled in the study.

Methods:

Study design: This is a prospective single arm quality improvement initiative for the use of a standardized educational intervention on germline testing in prostate cancer to improve the rates of germline genetic testing among patients recommended for testing. Patients who consent to the study will undergo a one-on-one in-person education session regarding the rationale and the benefits/risks of germline testing. Following the educational session, if a patient wishes to proceed with testing, they will sign the standard consent to proceed with germline testing via a commercial assay.

Data Source(s): Patients with prostate cancer treated in the UCSD Genitourinary oncology clinics.
Study Population: Men with prostate cancer who meet the criteria for germline testing.
Exposure(s): Consented patients will undergo an in-clinic educational session on germline testing in prostate cancer with a trained educator.
Outcome(s): Assess the proportion of patients enrolled in the study who underwent germline testing to the proportion of patients who did not enroll in the study. Assess the effect of a patient educational program on increasing germline genetic testing rate among adult prostate cancer patients who are recommended to receive germline testing per NCCN guidelines. .
Sample Size Estimations: Target accrual is 50 patients in 12 months.
Statistical Analysis: For the primary endpoints of feasibility of implementing an educational intervention, this will be assessed by the accrual rate over 12 months. For the endpoint of efficacy of the intervention in improving rates of germline testing, the proportion of patients who undergo germline testing in this study will be compared to the proportion of patients who undergo germline testing who were eligible, but not enrolled into this study during the study time period.

AMENDMENT HISTORY

Date	Section of study protocol	Amendment or update	Reason
		N/A	

MILESTONES

Milestone	Planned date
Finalize survey instruments	July 2021
Finalize Redcap database along with CRFs	August 2021
Hiring of clinical research coordinator	August 2021
Completion of video	September 2021
Training of research coordinator	August- September 2021
Start of accrual	October 2021
6-month assessment of accrual	April 2022
Database lock	October 2022 (or sooner if 50 patients are accrued)
Analysis	November 2022
ASCO Abstract	January 2023
First Manuscript	March 2023

1. BACKGROUND AND RATIONALE

1.1 Background

Prostate cancer is the most common cancer in men in the United States with a lifetime risk of 16% and the second leading cause of cancer-related death in men in the United States. While patients with localized prostate adenocarcinoma have 5-year survivals that approach 100% per the Surveillance, Epidemiology, and End Results (SEER) Program database, outcomes are much more dismal in the metastatic setting with an estimated 5-year survival of 30% (1). Given this, there has been considerable effort to further understand the pathogenesis and genetic underpinnings of locally advanced and metastatic prostate cancer.

While the average age of diagnosis of prostate cancer is 66 years old (1), there is increasing evidence for inherited genetic susceptibility to prostate cancer, particularly in patients with advanced prostate cancer. The most common germline mutations seen are those in the DNA repair pathway, and more specifically, the homologous recombination repair pathway, including BRCA1/2 which can predispose to not only prostate cancer, but breast, ovarian, pancreatic, and skin cancers. In addition to the known incidence of mutations in *BRCA1* and *BRCA2*, germline mutations have been noted in other DNA repair genes including *ATM, CHEK2, PALB,* and others. Prostate cancer has been also been previously reported in patients with Lynch syndrome, another inherited genetic syndrome due to mutations in either *MLH1, MSH2, EPCAM, MSH6,* and *PMS2.*

A large multi-institutional study evaluated the prevalence of germline DNA repair gene mutations in 692 men with metastatic prostate cancer unselected for age and family history from eight centers, results of which are shown in Table 1 (2). Germline DNA was isolated and used for multiplex sequencing assays to assess 20 DNA repair genes. The study demonstrated that 84 germline DNA repair gene mutations were identified in 11.8% of men in 16 genes. In men with Gleason 8-10 prostate cancer, the prevalence of germline DNA repair gene mutations is 6%. Mutations were found most frequently in the following genes: BRCA2 (37 men, 5.3%), ATM (11 men 1.6%), CHEK2 (10 men 1.9%) and BRCA1 (6 men 0.9%).

Table 1. Pathogenic Germline DNA Repair Aberrations in Prostate Cancer.

	Germline Mutations in DNA Repair Genes	
Metastatic Prostate Cancer	n=84/692	11.8%
Localized Prostate Cancer	n=23/499	4.6%
Gleason 6	n=2/45	4%
Gleason 7	n=9/249	4%
Gleason 8-10	n=12/205	6%
NCCN Low-Intermediate Risk	n=4/162	2%
NCCN High-risk	n=19/337	6%
No Cancer Diagnosis	n=1433/53,105	2.7%

NCCN=National Comprehensive Cancer Network.

Given this data, the most recent iteration of the NCCN guidelines for prostate cancer, published in April 2019, notes "Germline genetic testing is recommended for all men with high-risk, very-high-risk, regional, or metastatic prostate cancer." Additionally, it is recommended that patients with localized low or intermediate risk prostate cancer with a positive family history or presence of intraductal histology are recommended to undergo germline testing (3). In addition to the NCCN recommendations, there have been other published recommendations. At the Philadelphia Prostate Cancer Conference, an expert panel convened to develop guidelines for germline testing which is shown in Table 2 (4). With regards to germline testing in localized prostate cancer, a collaboration between AUA, ASTRO, and SUO recommended consideration of genetic counseling for patients with high-risk localized prostate cancer and a strong family history of breast, ovarian, pancreatic, or other GI tumors (5). It is important to note that there are discrepancies among these guidelines and the NCCN guidelines are primarily utilized by payers, including Medicare, to determine coverage for testing.

Table 2: Guidelines on Germline Testing in Prostate Cancer

Organization	**Source**	**Guidelines**
National Comprehensive Cancer Network	Prostate Cancer, Version 4.2019	All men with high-risk localized, very-high-risk localized, locally advanced, or metastatic prostate cancer. • Family history criteria and consideration to prompt genetic testing: A strong family history of prostate cancer consists of: brother or father OR • Multiple family members who were diagnosed with prostate cancer (but not clinically localized Grade Group 1) at less than 60 years of age or who died from prostate cancer • Ashkenazi Jewish ancestry • ≥3 cancers on same side of family, especially diagnoses ≤50 years of age: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer • Genetic testing in the absence of family history or clinical features (eg, high- or very-high-risk prostate cancer, intraductal histology) may be of low yield. The patient should be counseled to inform clinicians of any update to family history.

Expert Panel	Philadelphia Consensus Meeting Publication, 2017	Men meeting any one of the following suggested criteria should undergo genetic counseling and genetic testing: • All men with prostate cancer from families meeting established testing or syndromic criteria for the following: ○ Hereditary breast and ovarian cancer syndrome (HBOC) (Consensus: 93%) ○ Hereditary prostate cancer (HPC) (Consensus: 95%) ○ Lynch syndrome (LS) (Consensus: 88%) • Men with prostate cancer with two or more close blood relatives on the same side of the family with a cancer in the following syndromes: • Post-consensus discussion included consideration of age cutoff for this criterion. A specific age cutoff will require additional data, and age at diagnosis is important to inquire in the genetic counseling session with patients. o HBOC (Consensus: 93%) o HPC (Consensus: 86%) o LS (Consensus: 86%) • All men with metastatic castrate-resistant prostate cancer should consider genetic testing (Consensus: 67%). Post-consensus discussion also included consideration of testing men with metastatic, hormone-sensitive prostate cancer to identify germline mutations to inform potential future treatment options and cascade testing in families. • Men with tumor sequencing showing mutations in cancer-risk genes should be recommended for germline testing, particularly after factoring in additional personal and family history (Consensus: 77%).
American Urological Society	Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline, 2017	• The Panel recommends that clinicians take detailed family history of cancers and give consideration to patient referral for genetic screening and counseling for men with localized high-risk prostate cancer, particularly in the setting of family history of first-degree relatives with cancers of breast, ovary, pancreas, other gastrointestinal cancers, and lymphoma.

Given that prostate cancer is the most common cancer among men, the recommendation to test such a large population of patients has placed significant demands on health systems and clinical workflows. There is increased demand for trained genetics professionals to provide quality counseling and testing services. Genetic counselors are trained in assessing family history for genetic risk, ordering

appropriate genetic testing and interpreting the results, discussing appropriate cancer screening recommendations, and helping families adapt to genetic testing results. Unfortunately, access to these services is often limited, with the majority of the small workforce of genetic counselors and clinical geneticists often centered in urban and academic areas (6). In 2016, The Genetic Counselor Workforce Working Group estimated a 72% growth in the workforce between 2017-2026, with the demand for genetic counselors not expected to meet population equilibrium until 2024-2030 (7). This limited access may necessitate other healthcare clinicians, such as oncologists, primary care physicians, or urologists, taking on some of the responsibilities of genetic testing. With expanded clinician education which utilizes the expertise and guidance of genetic counselors, healthcare clinicians can deliver quality genetic counseling education with the support from the geneticists for questions or more complicated cases. Taken together, this highlights a critical need for expanding genetic services and developing novel approaches to care outside of the historic delivery model (10).

While germline testing in prostate cancer offers patients further information regarding their genetic risk of malignancy, it also has therapeutic implications. As discussed previously the most commonly detected germline mutations include *BRCA1, BRCA2, PALB2, CHEK2, ATM, RAD51,* which compromise the DNA repair or homologous repair pathway. This pathway is involved in the repair of double stranded DNA breaks and maintenance of genomic stability (2). In cells with deficiency in homologous recombination repair, inhibition of PARP results in cell death via synthetic lethality. In a phase 2 trial of olaparib, a PARP inhibitor, in patients with metastatic CRPC with homologous repair mutations, 88% (n=14/16) of patients demonstrated a response to olaparib (6). Based on these data, the FDA granted “breakthrough therapy” designation status to the PARP inhibitor olaparib in metastatic CRPC in 2016. PROfound, a phase III trial examining olaparib compared to standard of care enzalutamide or abiraterone in mCRPC patients with homologous recombination repair alterations. In the PROfound trial, the radiographic progression-free survival with olaparib was 7.39 months compared to 3.55 months in patients treated with either abiraterone or enzalutamide (HR 0.34, 95% CI 0.25, 0.47, $p<0.0001$). Based on the results of this study, the FDA recently granted approval for olaparib in the treatment of mCRPC that has progressed on abiraterone or enzalutamide harboring a somatic or germline alteration in an HRR gene.

1.2 Rationale

Given the prevalence of germline mutations in 10-12% of patients with advanced prostate cancer and the diagnostic and therapeutic implications of germline testing, improving the frequency of testing is greatly needed. Here, we propose a pilot study to improve germline testing among patients with prostate cancer via implementation of an in-clinic educational intervention on germline testing with a trained staff member. We will start by assessing baseline knowledge and attitudes on germline testing in prostate cancer among oncologists and urologists. An educational session will be provided for all oncologists and urologists to review germline testing guidelines. We will then screen clinics for patients with prostate cancer who meet criteria for germline testing per NCCN guidelines and offer them the opportunity to meet with the trained educator to review germline testing. Following this standardized educational session, patient’s will be given the opportunity to consent for a commercially available germline genetic testing platform.

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objective(s) & Hypotheses

Objectives

(1) To assess the feasibility of a patient educational program to improve germline genetic testing for eligible patients with prostate cancer.
(2) To assess the effectiveness of a patient educational program with regards to increasing germline genetic testing rate among adult prostate cancer patients who are recommended to receive germline testing per NCCN guidelines.

Hypotheses

(1) We hypothesize intervention will be feasible with successful recruitment of our target sample size.
(2) We hypothesize that the rates of germline testing among patients recruited to the study will be higher than rates of testing among patients not enrolled in the study.

2.2 Secondary Objective(s) & Hypotheses

Objectives

(1) To assess patients' baseline knowledge of germline testing and the change in knowledge of germline testing with the educational intervention.
(2) To assess a patient's baseline attitudes towards germline testing and assess the impact of an education interventional on patient perceptions of germline testing.
(3) To assess the impact of germline testing results on prostate cancer management.
(4) To assess prevalence of pathogenic germline mutations in patient population.

Hypotheses

(1) We hypothesize that the educational intervention will lead to an improvement in knowledge of germline testing.
(2) We hypothesize that the educational intervention will lead to a more favorable attitude towards germline testing among patients enrolled in the study.
(3) We hypothesize that the educational intervention will result in greater prescribing of targeted therapies given detection of germline alterations in the HRR pathway.
(4) We hypothesize that the educational session will improve patient's perception and familiarity with germline testing.

2.3 Exploratory Objective(s) & Hypotheses

Objectives

(1) To describe the demographic and clinical characteristics among all patients who received germline testing and subsequently, stratify by presence of germline mutations in cancer susceptibility genes.

Hypotheses

(1) We hypothesize that patients with pathogenic germline alteration have more aggressive disease patterns in both the localized and advanced settings.

3. METHODOLOGY

3.1 Study Design – General Aspects

We will then screen genitourinary oncology clinics at UC San Diego Health System to identify patients who are eligible for germline testing. After approval from their treating physician, we will approach patients in the clinic and introduce the educational intervention, which will consist of a one-on-one in-person educational sessions reviewing the rationale and the risks and benefits of germline testing. A virtual educational session was added due to the COVID-19 pandemic and will ideally occur over the Epic video chat platform, Doximity video chat, but can also occur via telephone for patients who are unable to use video chat.

The educational intervention will occur with a clinical research coordinator who will be trained to educate on germline testing in prostate cancer. At the start of the session, the patient will be given a short questionnaire (Appendix A) to assess their understanding about germline and genetic testing, along with a Family History questionnaire (Appendix B). Following this, the session will then include a one-on-one review of an educational handout on germline testing in prostate cancer (Appendix E). The handout will provide a concise, yet comprehensive review of germline testing including:

1. Overview of genetic germline testing
2. Rationale for germline testing in prostate cancer
3. Implications of germline testing in terms of patient's clinical care
4. Implications to family
5. Overview of results including discussion of pathogenic germline mutation and variants of unknown significance
6. Discussion of benefits and risks of testing

Session Overview	
Time (approximately)	**Objective**
1-5 minutes	Introduction
10 minutes	Pre-intervention survey
5 minutes	Video
10 minutes	Review of brochure
5 minutes	Time for patient to ask questions
10 minutes	Post-intervention survey

The patient will then have an opportunity to ask questions. If a patient wishes to proceed with testing, they will sign the standard consent to proceed with germline testing and the patient's clinician will be notified of intent to proceed with germline testing. Patients can elect to decline testing, defer testing to a later time, or request referral to genetic counseling to discuss the testing. We will track patterns of patient decision making following the educational intervention. Upon a patient deciding to pursue testing, testing will consist of a prostate cancer germline panel with a commercially available blood or saliva-based assay. Following the educational intervention, the patient will be asked to complete a short patient education and satisfaction questionnaire (Appendix D). Upon receipt of the results, the coordinator will alert the patient's clinician, who will then share the results with the patient either in clinic or by phone. If the results show a

pathogenic germline mutation, the patient will be referred to see the UCSD cancer medical genetics clinic for consultation with a genetics counselor. Additionally, the patient can elect to see a genetics counselor independent of the test results once the test results are reviewed. If a patient pursues genetic testing, following receipt of results, the patient's clinicians will be asked to complete a short survey on to assess how the results of germline testing affected the patient's current and future management (appendix D). There will be capacity for patients to complete questionnaires electronically. Additionally, to systematically understand the scope of questions asked by patients which will provide opportunity to optimize the educational intervension, we will record the educational sessions.

3.1.1 Data Source(s)

This is a single center study of prostate cancer patients treated in the UC San Diego genitourinary oncology clinics. Data will be captured in secure RedCap database. Data to be captured including demographics, clinical characteristics, disease characteristics and results of study questionnaires.

3.2 Study Population

The target population for this study is patients older than 18, with prostate cancer who meet the NCCN criteria for germline testing and who have not undergone prior germline testing.

Subjects will include those patients seen at a facility in the UCSD Health System. Genitourinary oncology clinics will be screened 1 week in advanced for eligible patients. Recruitment procedures will also involve the review of subject records by designated study personnel (e.g., investigators and/or study coordinators) in order to identify potentially eligible subjects. Since Protected Health Information (PHI) will be accessed via the hospital's medical record database and scheduling system (e.g., EPIC/IDX) *prior* to contacting the potential subject about the research study, we have been granted a *partial* waiver of HIPAA authorization for access to PHI for purposes of prescreening only.

For patients who are eligible for the trial, the investigator will approach the subject and offer participation in the trial. Standard HIPAA authorization to collect research data from the subject's medical record will be obtained at the time of informed consent. Given the COVID-19 pandemic, we are conducting sessions both in clinic and virtually. This will primarily occur via video chat or telephone. Given that this is a low-risk intervention of an educational session, we believe that virtual consenting is also appropriate here given the current pandemic.

For patients who decline the intervention or have not been approached at the time of analysis, these patients will be considered a separate cohort for comparison to the intervention cohort.

3.3 Inclusion Criteria

1. Men, age greater than or equal to 18 years of age.
2. Diagnosis of prostate cancer of any histology.
3. Must meet NCCN guidelines for germline testing (see table below for specific definition of risk groups).
    a. Men with very low, low or intermediate risk prostate per NCCN guidelines with a positive family history or intraductal histology OR

- Family history here is considered significant if the patient has a first degree relative with prostate cancer or more than one first/second degree relative with prostate cancer.
- ≥3 cancers on same side of family, especially diagnoses ≤50 years of age: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer

b. Men with high-risk, very-high risk (see Table 3 for NCCN definitions of risk groups), lymph node positive, or metastatic prostate cancer independent of family history of histology.

NCCN definitions of risk groups in localized prostate cancer

Risk group	Clinical/pathologic features			Imaging[h,i]	Germline testing
Very low[f]	• T1c AND • Grade Group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] AND • PSA density <0.15 ng/mL/g			Not indicated	Recommended if family history positive or intraductal histology See PROS-1
Low[f]	• T1-T2a AND • Grade Group 1 AND • PSA <10 ng/mL			Not indicated	Recommended if family history positive or intraductal histology See PROS-1
Intermediate[f]	Has no high- or very-high-risk features and has one or more intermediate risk factors (IRF): • T2b-T2c • Grade Group 2 or 3 • PSA 10–20 ng/mL	Favorable intermediate	• 1 IRF and • Grade Group 1 or 2 and • <50% biopsy cores positive[g]	• Bone imaging[j]: not recommended for staging • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1
		Unfavorable intermediate	• 2 or 3 IRFs and/or • Grade Group 3 and/or • ≥50% biopsy cores positive[g]	• Bone imaging[j]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1
High	• T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			• Bone imaging[j]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended[c,k]
Very high	• T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Grade Group 4 or 5			• Bone imaging[j]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended[c,k]

3.4 Exclusion Criteria

Patients are excluded from the study if they:

1. Have had prior germline testing.
2. Have somatic genetic testing that is positive for a possible germline variant.

3.5 Participant Follow-up

Patients will be followed for 24 months following the educational session. We will capture deferred decisions to pursue germline testing during the 24-month follow up period. Data on oncologic outcomes, prostate cancer management, and cancer surveillance will be obtained from the medical record.

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposures

4.1.1 Definition of Primary Exposure

The primary exposure to be tested is an educational session including video on germline testing and review of brochure on germline testing in men with prostate cancer. See attachment.

4.1.2 Definition of Comparison Exposure

The comparison group will include individuals with prostate cancer who meet criteria for germline testing however were not approached about participating in the intervention or were approached and declined participating in the educational intervention. In this context, germline testing education will be at the discretion of the treating medical team.

4.2 Outcomes

Primary Endpoints

1. The proportion of patients who undergo germline testing among those who are enrolled to the study compared to the proportion of patients who undergo germline testing who were eligible, but not enrolled into this study during the study time period
2. Feasibility of implementing an educational intervention for men with prostate cancer at risk of having a hereditary cancer syndrome. This will be assessed by:
    - Accrual rate by month.
    - Proportion of patients who consent to educational intervention among those who are approached (stratified by whether consent was performed in-person or virtually).

Secondary Endpoints

1. Patient understanding of germline testing before and after the education intervention based on questionnaire responses.
2. Patient-reported opinions on germline testing before and after intervention, and patient-reported satisfaction after educational intervention based on questionnaire responses.
3. Physician responses regarding how the germline testing result changed patient management.
4. Prevalence of pathogenic germline mutations among study patients who undergo germline testing.

Exploratory Endpoints

1. Clinical factors (patient and family history, disease characteristics, and outcomes) that are associated with the presence of a germline mutation in a cancer susceptibility gene.

4.3 Other Variables and Covariates

We will capture the following additional demographic, clinical, and disease variables:

- Demographic data: Age, Marital Status, Race, Ethnicity, Employment Status, Clinician, Primary Language, Country of Birth, Education Level.
- Previous medical history: Comorbidities, Smoking History, and Family History of Malignancies.
- Disease characteristics: Date of Diagnosis, Site of Disease, Site(s) of Metastasis, if applicable, Histology/Grade/Pathologic Parameters, PSA, Stage, Somatic Molecular Profile, Date of Collection of Tissue Analyzed, Type of Tissue Analyzed.
- Treatment data: Date of Surgery, Date of Radiation, Dose of Radiation, Systemic Therapy.
- Treatment outcomes data: Toxicity, Dose Reduction, Reason for Dose Reduction, Response, Progression, Survival.

4.4 Statistical Analysis Plan

4.5 Statistical Methods – General Aspects

4.5.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. descriptive statistics, hazard ratios, incidence rates, test/retest reliability)

Primary Endpoints

With regards to the primary endpoint, at the completion of the study, the proportion of patients who complete germline testing among all who are enrolled to the study will be computed. A sample size of 50 patients produces a two-sided 95% confidence interval on the proportion with a width ranging from 0.27 to 0.29 when the observed proportion ranging from 0.3 to 0.7. For proportions, 95% confidence intervals will be calculated using the exact method.

We will also compute the proportion of patients who completed germline testing for all eligible prostate cancer patients evaluated in clinic but not enrolled into this study during the study period. Characteristics between these two groups will be compared using Fisher's Exacts or Wilcoxon Rank Sum tests. The proportion of patients who underwent germline testing in the intervention vs non-intervention cohorts will be compared using Fisher's exact test.

4.5.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

Secondary endpoints including germline mutation frequency, patient understanding of germline testing, and medical management from germline testing will be described using descriptive statistics such as bar graphs, box plots, percentages, means and standard deviations, etc.

4.5.3 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

- Associations between clinical factors and pathogenic germline alterations will be evaluated using Odds Ratio.
- Impact of germline testing on prostate cancer and cancer surveillance management will be qualitatively described.

4.6 Bias

4.6.1 Methods to Minimize Bias

We aim to reduce bias through several methods including systemically screening medical oncology and urology clinics to identify eligible patients. The research coordinator will have a rotating schedule of clinics to screen to ensure systematic non-bias selection of eligible patients. Additionally, the intervention will be offered in multiple media modalities including in-person, video, and telephone to accommodate patient preferences. The intervention and video will be available in English and Spanish to further limit selection bias. Furthermore, there is capacity to perform the intervention in the clinic coinciding with the patients clinic appointment or at a separate time that is feasible for the patient.

4.6.2 Adjustment for Multiple Comparisons

Not applicable.

4.6.3 Strengths and Limitations

The primary strength of the study is the novel approach to integration of germline testing education into the clinic. The study will assess the feasibility of an in clinic educational model led by a clinical research coordinator. This will also assess the feasibility of how other clinicians outside of genetics can provide some degree of genetic counselling that could be applicable to medical assistants, nurses, and advanced practice providers.

A key limitation of this study include bias with regards to recruitment, which we hope to mitigate by offering the study to all eligible patients in all GU oncology clinics, offering the session in English and Spanish, and offering a virtual option.

4.7 Interim Analyses (Optional)

N/A

4.8 Sample Size and Power Calculations

With regards to the primary endpoint, at the completion of the study, the proportion of patients who complete germline testing among all who are enrolled to the study will be computed. A sample size of 50 patients produces a two-sided 95% confidence interval on the proportion with a width ranging from 0.27 to 0.29 when the observed proportion ranging from 0.3 to 0.7.

5. STUDY CONDUCT AND REGULATORY DETAILS

5.1 Study Conduct

5.1.1 Study Flow Chart and Plan

Scheduled of Assessments			
	Pre- Study	Intervention	Follow Up
Family History Questionnaire		X	
Pre-Intervention Patient Questionnaire		X	
Educational Session		X	
Post Intervention Patient Questionnaire		X	
Germline Results Review			X
Clinician Questionnaire			X

5.1.2 Procedures

Recruitment:
Pre-screening procedures will involve the review of subject records by designated study personnel in order to identify potentially eligible subjects. Protected health information (PHI): Patient Name, Medical Record Number, Date of Birth, date and time of upcoming appointments, medications, and disease status, will be accessed via the hospital's medical record database and scheduling system prior to contacting the potential subject about the research study. The Slicer Dicer Epic functionality may also be utilized to identify eligible patients in addition to systematic review of clinician schedules. A partial waiver of HIPAA authorization for access to PHI for purposes of pre-screening is being requested. This study meets the following requirements for this request per 45 CFR 164. 512(i)(2)(ii):

1. The use or disclosure of PHI involves no more than minimal risk to the privacy of individuals as the only risk is loss of confidentiality and all reasonable measures to protect confidentiality will be carried out.

2. Granting of the waiver will not adversely affect privacy rights and welfare of the individuals whose records will be used as the only risk is loss of confidentiality and all reasonable measures to protect confidentiality will be carried out.
3. The pre-screening could not practicably be conducted without a waiver because we need to search project the EPIC electronic database to identify eligible subjects.
4. The project could not practicably be conducted without use of PHI because demographic and clinic information are needed in order to identify eligible subjects.
5. The privacy risks are low relative to the anticipated benefits of research. The privacy risks are minimal since all reasonable efforts to protect confidentiality will be performed and there is the potential to gain scientific knowledge that will benefit future genitourinary cancer patients.
6. An adequate plan to protect identifiers from improper use and disclosure is included in this research proposal.
7. An adequate plan to destroy the identifiers at the earliest opportunity is included in the research proposal.
8. The PHI will not be re-used or disclosed for other purposes.

A partial waiver of informed consent is being requested for pre-screening. The reasons underlying this request include the following per 45 CFR 46.116:

1. The (pre-screening) research involves no more than minimal risk to the subjects as the only risk is loss of confidentiality and all reasonable measures to protect confidentiality will be carried out;
2. The waiver will not adversely affect the rights and welfare of the subjects used as the only risk is loss of confidentiality and all reasonable measures to protect confidentiality will be carried out;
3. The (pre-screening) research could not practicably be carried out without the as the research staff needs to search the EPIC electronic database to identify eligible subjects; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Informed Consent:

Individuals who fulfill the eligibility criteria will be offered participation in this study. The patient's treating physician will authorize the investigator or study coordinator to meet with the patient. Consent may occur in-person, via video chat, or via telephone. Study candidates will be asked to provide written consent, using an IRB-approved informed consent form. The investigator or study coordinator will describe the study to potential participants. The investigator or study coordinator will provide potential participants with a blank informed consent form. The individual will be given ample time to read this consent form at the same visit or may take it with them to read at another time. The study candidate will be given the opportunity to ask and receive answers to all questions they may have about the study, its risks and benefits, and the consent form itself before signing the consent form. As this research is subject to HIPAA Privacy Rule provisions, study candidates will also be requested to sign a separate HIPAA authorization form specific to the research study for the use of PHI. The consent process will be appropriately documented.

Survey Administration:

All surveys will be available as secure links sent to the participant's provided email through REDCap. The patients can also opt to complete the surveys by phone with the research assistant or on paper.

Family History Questionnaire: The Family History Questionnaire (FHQ) is the standard method of self-reported data collection for patients at in the Genitourinary Program at UCSD. This has been modeled from Family History Questionnaires utilized within our Cancer Genetics Program at UCSD and others across the country but modeled for men with prostate cancer.

Pre-Intervention Patient Questionnaire: The pre-intervention patient questionnaire is a brief 16-item investigator-developed knowledge and attitude scale applicable to this population. It was developed through an expert panel to determine if participants are able to recall key core components about multi-gene panel testing and capture attitudes about genetic testing. This survey is estimated to take 10 minutes to complete.

Post-Intervention Patient Questionnaire: The post-intervention patient questionnaire is a brief 24-item investigator-developed knowledge and attitude scale applicable to this population. It includes the same 14 knowledge and attitude items from the pre-intervention survey to assess impact of the educational intervention. It was developed through an expert panel to determine if participants are able to recall key core components about multi-gene panel testing and capture attitudes about genetic testing. There is also a 10-item scale to capture satisfaction with educational intervention. This survey is estimated to take 10 minutes to complete.

Post-Results Clinician Questionnaire: The post-result clinician questionnaire is a brief 6-item investigator-developed scale to assess whether the genetic testing results altered clinical practice for any given patient including change in disease monitoring, change in recommended treatment, referral to genetic counseling and other parameters. This survey is estimated to take 5 minutes to complete.

Intervention Administration:
The educational intervention including video and brochure review will be administered by a study team member in a consult or exam room on a password-protected tablet or on a computer when performed in person. For remote visits, a study team member will provide the participant with either an electronic or paper copy of the brochure for review and will share the educational video electronically via video functionality of EPIC or Doximity with the patient. For patients who prefer a telephone intervention, the video will still be made audible but not visible to the patient for review. The participant may choose to proceed or decline genetic testing after the educational intervention. If the participant has any questions regarding the study, the study team member may answer them. If the participant has any concerns or questions about genetic testing, the study team member will refer them to the educational materials provided, their clinician, or connect them to the Principal Investigator.

Withdrawal of Participation:
A participant is free to withdraw from the study at any time for any reason without prejudice to his future medical care by the physician or at the institution. If the participant decides that he does not want to continue to be a part of this study, he will contact PI Dr. Rana McKay or the study coordinator. Their previously data will be destroyed if requested by the participant. In some cases, it may be impossible to stop future if the resulting data have already been analyzed and/or shared.

5.1.3 Quality Control

Monitoring
Before the first subject is recruited into the study, the local Marketing Company, MEOR Delivery Director, MEOR Operations Lead or CRO Representative will:

- Establish the adequacy of the facilities and the investigator's capability to appropriately select the sample
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regards to protocol compliance, and the responsibilities of AstraZeneca or its representatives. This will be documented in an Observational Study Primary Agreement between AstraZeneca/delegate and the investigator.

During the study the local MC representative or delegate can implement different activities to assure compliance with AZ standards of quality. These activities could include but are not limited to:

Contacts with the sites to:

- Provide information and support to the investigator(s)
- Confirm that the research team is complying with the protocol and that data are being accurately recorded in the case report forms (CRFs)
- Ensure that the subject informed consent forms are signed and stored at the investigator's site
- Ensure that the CRFs are completed properly and with adequate quality.

Monitoring activities for:

- Checking of ICFs
- Checking that subjects exist in medical records

The extent and nature of monitoring will be decided during the study planning based on design, complexity, number of subjects, number of sites, etc. Observational Research Center (multi country) /Marketing Company (MC) will give some recommendations that could be locally adapted.
Different signals (eg, high rejection rate in a site) should be used as potential identification of low protocol compliance by investigators.
If these or any other signal occurs or if the local coordinator is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

Training of Study Site Personnel
The Principal Investigator will ensure that appropriate training relevant to the Observational Study is given to investigational staff, and that any new information relevant to the performance of this Observational Study is forwarded to the staff involved.

5.2 Protection of Human Subjects

The Observational Study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs, GPP and the applicable legislation on Non-Interventional Studies and/or Observational Studies.

The Investigator will perform the Observational Study in accordance with the regulations and guidelines governing medical practice and ethics in the country of the Observational Study and in accordance with currently acceptable techniques and know-how.

The final protocol of the Observational Study, including the final version of the Subject Informed Consent Form, must be approved or given a favourable opinion in writing by the Ethics Committee/Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
The Ethics Committee/IRB/IEC must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations.

5.2.1 Subject Informed Consent (Primary Data Collection Only)

The Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the Observational Study. Subjects must also be notified that they are free to discontinue from the Observational Study at any time. The subjects should be given the opportunity to ask questions and allowed time to consider the information provided.
The signed and dated subject informed consent must be obtained before any specific procedure for the Observational Study is performed, including:

- Interview with the investigator
- Fulfil the questionnaires
- CRFs completion.

The Investigator must store the original, signed Subject Informed Consent Form. A copy of the signed Subject Informed Consent Form must be given to the subject.

5.2.2 Confidentiality of Study/Subject Data (Primary Data Collection Only)

The Subject Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their personal data by the Investigator and by those persons who need that information for the purposes of the Observational Study.
The Subject Informed Consent Form will explain that Observational Study data will be stored in a computer database, maintaining confidentiality in accordance with the local law for Data Protection.

The Subject Informed Consent Form will also explain that for quality check purposes, a monitor of AZ or a monitor of company representing AZ, will require direct access to the signed subject informed consent forms. In case source data verification will be planned as quality check, the Subject Informed Consent Form will explain that for data verification purposes, monitor of AZ or a monitor of company representing AZ may require direct access to source documents that are part of the hospital or practice records relevant to the Observational Study.

5.3 Collection and Reporting of Adverse Events/Adverse Drug Reactions

5.3.1 Management of Adverse Risk

a. Psychologic side-effects

Potential side effects include psychological distress due to issues raised regarding the potential presence of a hereditary cancer syndrome. It is possible that participants may experience anxiety as a result of the questionnaire process. Experience from our previous questionnaire protocols as well as clinical testing programs at the UCSD suggests that individuals do adjust to both information and the experience of participation in a predisposition testing program. There is variation in the degree to which participants rely on project staff for assistance. The program staff will be available throughout the program to respond to clinical questions and concerns that arise. Participants will also be offered the opportunity to receive psychological support from the center psychologist or social worker.

b. Privacy

There have been reports about the possibility of identifying an individual from his or her genetic information along with factors such as age and place of residence, even after the name has been removed. We believe that the chance of this happening in this study is very small but not zero, and will take measures to minimize such occurrences. Confidentiality will be assured by the coding of the questionnaires with a unique study ID assigned to each participant and family member. Files will be kept in password protected computer databases accessible to only study staff. The listing of participant names and numbers will be kept in a separate locked file within the Clinical Trials Office. It will be recommended to participants that they inform their physician of their test results.

c. Insurance Discrimination

The study itself is testing and educational intervention and genetic testing will be performed as standard of care should a participant decide to pursue genetic testing. The Genetic Information Nondiscrimination Act of 2008 (GINA) protects Americans from being treated unfairly because of differences in their DNA that may affect their health, and may prevent discrimination by health insurers and employers based on genetic information. GINA is intended to ease concerns about discrimination that might keep some people from getting genetic tests that could benefit their health, and enable people to take part in research studies such as this without fear that their DNA information might be used against them by health insurers or their workplace. This protection does not extend to disability or life insurance. A current or prior cancer diagnosis is likely to be the most significant factor affecting life insurance, or rates and eligibility for other forms of insurance. Genetic testing information is unlikely to change this risk.

5.3.2 Definition of Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
The term AE is used to include both serious and non-serious AEs.

5.3.3 Definition of Serious Adverse Events (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death

- Is life-threatening (life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe)

- Requires in-patient hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability or incapacity

- Is a congenital abnormality/birth defect

- Is an important medical event that may jeopardise the subject or may require intervention to prevent one of the outcomes listed above. Medical and scientific judgement should be exercised in deciding whether other situations should be considered an SAE.

Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Sections 6.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets one of the criteria shown in Section 6.3.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE if it satisfies one of the criteria shown in Section 6.3.2.

5.3.4 Reporting of Adverse Events

For studies with a primary data source
The Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of:

- All AEs with a fatal outcome
- All serious ADRs

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other serious ADRs.

For all collected AEs, where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information within the same timeframe as the original report.

All collected adverse events will be summarized in the final study report.

LIST OF REFERENCES

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6. APPENDICES

Appendix A: Patient Survey on Germline Testing in Prostate Cancer

Participant Name: _____

Participant Study ID: _____

Date: _____

The purpose of this section is to understand what you know generally about inherited cancer risk (genetic risk that occurs within a family). By understanding what you may or may not know about inherited cancer risk it may help us to improve our educational sessions.

Below we have listed some general questions about genetics and multi-gene panel testing (a genetic test that evaluates more than one gene). These questions are not specific to you or your risk but rather common questions about genetic risk.

Section A:
Please answer these questions as True or False.

		True	**False**
1.	Genes are made from pieces of DNA		
2.	A mutation is a change in DNA sequence		
3.	Cancer is caused by a combination of inheritance, environmental exposure, and lifestyle factors		
4.	Most people who develop cancer do so because they have inherited risk for cancer that they were born with.		
5.	All of the gene mutations that could increase risk for cancer have been discovered.		

Section B
Please answer these questions with agree, disagree, of if you are unsure, "I don't know".

		Agree	**Disagree**	**I don't know**
1.	My doctor has talked to me about genetic testing for my prostate cancer prior to enrolling in this study.			
2.	Some men with prostate cancer were born with genetic mutations which contributed to their development of cancer.			

3.	Knowing about inherited risk (passed down within a family) can affect choices about cancer treatments (for example, medications or surgery).			
4.	People with an inherited risk for cancer (and their at- risk relatives) are more likely to develop more than one type of cancer.			
5.	The blood relatives (for example, sister, father, or child) of a person with a mutation in a cancer risk gene might share the same gene mutation.			
6.	A person with an inherited risk for cancer may have distant relatives (for example, cousins) who also have increased cancer risk.			
7.	All children of a person with inherited cancer risk will also have inherited cancer risk.			

Section C

The following questions are about the extent of your interest in genetic testing for your cancer.

1. How interested are you in undergoing genetic testing to determine if you were born with any genetic mutations which predisposed you to developing prostate cancer?
   A. Very interested
   B. Interested
   C. Neutral
   D. Not interested
   E. Not at all interested

2. Of the following listed factors, which would **<u>most</u>** influence you in a decision to pursue germline DNA testing in the care of your cancer? (***Rank answers in orders of preference from 1 to 5***, **1= best describes, 5= least describes**)

	Rank (1 = best, 5= least)
Potential to guide treatment selection	
Potential to predict disease outcome	
Potential to learn more about my cancer risk	
Potential to learn more about the cancer risk of my family	
Trust in my physician and their recommendation for genetic testing	
Other (*please specify; not required)* _____	

3. Of the following listed factors, which would **most** influence you in a decision to **not** pursue genetic DNA testing in the care of your cancer? (***Rank answers in orders of preference from 1 to 5***, **1= best describes, 5= least describes**)

	Rank (1 = best, 5= worst)
Potential of DNA test results to be of no clinical value	
Potential of DNA test results to lead to health, life or disability insurance discrimination	
Concerns about the privacy and confidentiality of DNA test results	
Concerns about the impact a positive result would have on my family and relatives.	
Other (*please specify; not required)* _____	

4. At the start of this educational session, my current decision on pursuing genetic testing is:

A) I want to proceed with germline testing done today.

B) I do not want to proceed with germline testing today.

C) I am unsure at this time.

Appendix B: *Family History Questionnaire*

Patient Name:
Medical Record #

Family History Questionnaire

Part 1: Personal history information

Have you had any genetic testing of your **tumor** tissue? Yes ☐ No ☐ Not sure ☐
(examples: Foundation, Guardant, Tempus, or Caris testing)

Heath history/ancestry:

Ancestry (e.g. Swedish, Japanese, English)
Mother's side:
Father's side:
Any Ashkenazi Jewish Ancestry? Yes ☐No☐ What side of the family?

Ever had a colonoscopy? Yes ☐No ☐ If yes, any history of colon polyps?

Other health issues you'd like to share

Have you had genetic counseling because of your family history of cancer before? Yes ☐ No ☐ Not sure ☐

If so, where was the genetics consultation done? UCSD ☐ Elsewhere:

Genetic Testing History

Have <u>you</u> ever had genetic testing for cancer risk before? Yes ☐No ☐ Not Sure ☐

If yes, please describe (what test, what year completed if known)

What were the results?
☐A mutation was found in the
_____gene
(Important: Please bring copies of results)
☐No mutations were found
☐My results were "uncertain" in the
_____ gene
☐I'm not sure

Please describe any other genetic testing findings or issues: -

Have any of your relatives had cancer genetic testing? Yes ☐ No ☐ Not Sure ☐

If yes, please describe which relative(s) and their results, if know (**Important: If possible, please bring copies of reports**)

Part 2. Your children:

How many children (living and deceased)? _____

Please list your sons and daughters on the rows below (if you need more rows, please use the back of this form):

Relative	Ever diagnosed with cancer?	Check if deceased	Current age/ Age at death	Cancer Type	Age at diagnosis
Son ☐ Daughter ☐	Y ☐N ☐	☐			
Son ☐ Daughter ☐	Y ☐N ☐	☐			
Son ☐ Daughter ☐	Y ☐N ☐	☐			

Son ☐ Daughter ☐	Y ☐N ☐	☐			
Son ☐ Daughter ☐	Y ☐N ☐	☐			
Son ☐ Daughter ☐	Y ☐N ☐	☐			

Part 3. Your brothers and sisters:

How many brothers and sisters (living and deceased)? _____

Please list your brothers and sisters on the rows below (if you need more rows, please use the back of this form)

Relative	Ever diagnosed with cancer?	Check if deceased	Current age/ Age at death	Cancer Type	Age at diagnosis
Brother ☐ Sister ☐	Y ☐N ☐	☐			
Brother ☐ Sister ☐	Y ☐N ☐	☐			
Brother ☐ Sister ☐	Y ☐N ☐	☐			
Brother ☐ Sister ☐	Y ☐N ☐	☐			
Brother ☐ Sister ☐	Y ☐N ☐	☐			
Brother ☐ Sister ☐	Y ☐N ☐	☐			
Brother ☐ Sister ☐	Y ☐N ☐	☐			

Part 4. Your mother's side of the family:

Relative	Ever diagnosed with cancer?	Check if deceased	Current age or Age at death	Cancer Type	Age at diagnosis

Mother	Y ☐N ☐	☐			
Maternal grandmother	Y ☐N ☐	☐			
Maternal Grandfather	Y ☐N ☐	☐			

How many aunts and uncles (living and deceased) on your **mother's** side?_____

Please list **all** of you your aunts and uncles (**mother's side**) on the rows below (if you need more rows, please use the back of this form):

Relative	**Ever diagnosed with cancer?**	**Check if deceased**	**Current age/ Age at death**	**Cancer Type**	**Age at diagnosis**
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			

Part 5. Your father's side of the family:

Relative	**Ever diagnosed with cancer?**	**Check if deceased**	**Current age or Age at death**	**Cancer Type**	**Age at diagnosis**
Father	Y ☐N ☐	☐			

Paternal grandmother	Y ☐N ☐	☐			
Paternal Grandfather	Y ☐N ☐	☐			

How many aunts and uncles (living and deceased) on your **father's** side? _____
Please list your aunts and uncles (**father's side**) on the rows below (if you need more rows, please use the back of this form):

Relative	Ever diagnosed with cancer?	Check if deceased	Current age/ Age at death	Cancer Type	Age at diagnosis
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			
Aunt ☐ Uncle ☐	Y ☐N ☐	☐			

Appendix C: Patient Post-Education Patient Survey

Participant Name: _____
Participant Study ID: _____
Date: _____
Thank you again for taking part in our educational intervention. Before the session is over, we hope to get your feedback on the session so that we can continue to improve on our education of patients on germline testing.

Section A:
Please answer these questions as True or False.

		True	**False**
1.	Genes are made from pieces of DNA		
2.	A mutation is a change in DNA sequence		
3.	Cancer is caused by a combination of inheritance, environmental exposure, and lifestyle factors		
4.	Most people who develop cancer do so because they have inherited risk for cancer that they were born with.		
5.	All of the gene mutations that could increase risk for cancer have been discovered.		

Section B
Please answer these questions with agree, disagree, of if you are unsure, "I don't know".

		Agree	**Disagree**	**I don't know**
1.	Some men with prostate cancer were born with genetic mutations which contributed to their development of cancer.			
2.	Knowing about inherited risk (passed down within a family) can affect choices about cancer treatments (for example, medications or surgery).			
3.	People with an inherited risk for cancer (and their at- risk relatives) are more likely to develop more than one type of cancer.			
4.	The blood relatives (for example, sister, father, or child) of a person with a mutation in a cancer risk gene might share the same gene mutation.			
5.	A person with an inherited risk for cancer may have distant relatives (for example, cousins) who also have increased cancer risk.			

6.	All children of a person with inherited cancer risk will also have inherited cancer risk.			

Section C

The following questions are about the extent of your interest in genetic testing for your cancer.

1. How interested are you in undergoing genetic testing to determine if you were born with any genetic mutations which predisposed you to developing prostate cancer?

F. Very interested
G. Interested
H. Neutral
I. Not interested
J. Not at all interested

2. Of the following listed factors, which would **most** influence you in a decision to pursue germline DNA testing in the care of your cancer? (***Rank answers in orders of preference from 1 to 5***, **1= best describes, 5= least describes**)

	Rank (1 = best, 5= least)
Potential to guide treatment selection	
Potential to predict disease outcome	
Potential to learn more about my cancer risk	
Potential to learn more about the cancer risk of my family	
Trust in my physician and their recommendation for genetic testing	
Other (*please specify; not required)* _____	

3. Of the following listed factors, which would **most** influence you in a decision to **not** pursue genetic DNA testing in the care of your cancer? (***Rank answers in orders of preference from 1 to 5***, **1= best describes, 5= least describes**)

	Rank (1 = best, 5= worst)
Potential of DNA test results to be of no clinical value	
Potential of DNA test results to lead to health, life or disability insurance discrimination	

Concerns about the privacy and confidentiality of DNA test results	
Concerns about the impact a positive result would have on my family and relatives.	
Other (*please specify; not required)*	

Section D

For each statement, please select if you 'Disagree Strongly', 'Disagree', 'Neither Agree or Disagree', 'Agree' or 'Agree Strongly'.

		Disagree strongly	Disagree	Neither Agree or Disagree	Agree	Agree Strongly
1.	The information presented in this session was **informative**.					
2.	The information presented in the session was **confusing** or **difficult to understand.**					
3.	The information presented in the session was **distressing.**					
4.	The information presented in the session was **useful.**					
5.	The information presented in the session **answered all of my questions and concerns.**					
6.	The session was the **right length of time.**					
1.	The pamphlet was helpful in explaining the concept of genetic testing.					

2. For question #6, if you answered **disagree to disagree strongly**, please tell us whether your education session was:

   A) Too long
   B) Too short

3. For question #7, if you answered **disagree to disagree strongly**, please tell us whether the pamphlet was:

A) Too basic
B) Too advanced
C) Other (*please specify):* _____

4. At the end of this educational session, my decision on pursuing genetic testing is:

A) I want to proceed with germline testing done today.

B) I do not want to proceed with germline testing today.

C) I would like to see a genetic counsellor to discuss this further.

D) I am unsure and will decide at a later date.

If you have any other comments about the educational intervention, please feel free to share below:

_____

_____

_____

_____

_____

Appendix D: Post Results Clinician Questionnaire

Clinician Name: _____ Date: _____

Patient/Patient Study ID: _____

1. Did you find the germline test result helpful in the management of this patient?
    A) Yes
    B) No
    C) Unsure

2. Did the results of germline testing change your management of this patient currently?
    A) Yes
    B) No
    C) Unsure

3. Will the results of the testing change your management of this patient in the future?
    A) Yes
    B) No
    C) Unsure

4. Did the results of this testing change your perception of the patient's prognosis?
    A) Yes
    B) No
    C) Unsure

5. Did the results of this testing lead to further diagnostic testing or referrals?
    A) Yes
    B) No
    C) Unsure

6. If you have any additional feedback about the results or educational intervention with regards to this patient's case, please feel free to share:

Appendix E: List of genes tested with commercial germline assays

Ambry Panel

1. ATM
2. BRCA1
3. BRCA2
4. CHEK2
5. EPCAM
6. HOXB13
7. MLH1
8. MSH2
9. MSH6
10. NBN
11. PALB2
12. PMS2
13. RAD51D
14. TP53

Invitae Panel

1. ATM
2. BRCA1
3. BRCA2
4. BRIP1
5. CHEK2
6. EPCAM
7. FANCA
8. GEN1
9. HOXB13
10. MLH1
11. MSH2
12. MSH6
13. NBN
14. PALB2
15. PMS2
16. RAD51C
17. RAD51D
18. TP53

ATTACHMENTS

See attached file of educational brochure brochure.

7. SIGNATURES

Authoring Instructions

- *The following signature pages for an Observational Study protocol may be required and further details on who is required to sign can be found in the SOP 8-P102-CV-C Design, Execution, and Reporting of AstraZeneca Sponsored Observational Studies :*
  - *Global Medical Affairs Lead or Global Clinical Lead/Delegate for global studies*
  - *MC Medical Director/Delegate for local studies*
  - *Global Epidemiologist /Local Study Leader*
  - *Optional signature from Biostatistician or Delivery Director*
  - *Always print the names and addresses.*

ASTRAZENECA SIGNATURE(S)

<<Study Description>>

<<This Observational Study Protocol >> <<has/have>> been subjected to an internal AstraZeneca review>>
I agree to the terms of this Study protocol.

AstraZeneca representative

<<Name, title>>	Date (Day Month Year)
<<Email address and telephone number>>	

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