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Streamlined Genetic Testing in Prostate Cancer

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1.0 Study Summary

Study Title	Streamlined Genetic Testing In Prostate Cancer
Study Design	Pilot Randomized Controlled Trial
Primary Objective	To evaluate the impact and efficacy of a streamlined genetic education and testing intervention for men with prostate cancer.
Secondary Objective(s)	
Research Intervention(s)/ Investigational Agent(s)	Streamlined genetic education and testing intervention.
IND/IDE #	n/a
Study Population	Eligible participants are men who are currently being followed at MGUH or MWHC for metastatic prostate cancer or Gleason 7+ prostate cancer with Ashkenazi Jewish ancestry or Gleason 7+ with a family history of breast, ovarian, pancreatic or prostate cancer.
Sample Size	120
Study Duration for individual participants	Three-months.
Study Specific Abbreviations/ Definitions	MGUH: Medstar Georgetown University Hospital; MWHC: Medstar Washington Hospital Center; PV: Pathogenic Variant; VUS: Variant of Uncertain Significance; ST: Streamlined Testing; UC: Usual Care; EMR: Electronic Medical Record; SRBSR: Subject Recruitment and Biospecimen Shared Resource

2.0 Objectives*

Genetic testing is established as part of clinical care for women with breast and ovarian cancer. Clear guidelines have led to increasing genetic testing participation among eligible women. Identifying pathogenic variants (PVs) in cancer susceptibility genes has important treatment, management and risk reduction implications for breast and ovarian cancer patients and their family members. Men are just as likely as women to carry a PV in a cancer risk gene and men with prostate cancer are at particularly high risk for carrying a PV. NCCN guidelines recommend germline genetic testing in all men with metastatic prostate cancer or with Gleason 7+ prostate cancer and Ashkenazi Jewish ancestry or a family history of prostate, breast, ovarian or pancreatic cancer. These guidelines are likely to expand given recent studies suggesting that 17% of prostate cancer patients may harbor a cancer susceptibility PV and that current referral criteria miss many of these patients. Prostate cancer patients with a PV in *BRCA1* or *BRCA2* (*BRCA*) have more aggressive prostate cancers, are at risk for other primary cancers (e.g., male breast and pancreatic) and their family members are at risk for a variety of cancers. Thus, genetic testing of prostate cancer patients has implications for treatment, management, and risk reduction for the patient and his family members.

Despite these benefits and existing referral guidelines, few men with prostate cancer are tested. This reflects low genetic counseling referral and participation, since men who attend genetic counseling get tested at the same high rate as women. Low participation in genetic counseling is likely due to men's underestimation of the personal health relevance of testing and lack of physician genetic counseling referral. Thus, the requirement to obtain individual genetic counseling prior to genetic testing may be a barrier to the receipt of guideline consistent genetic testing. In fact, recent evidence suggests that traditional comprehensive, patient-centered, educationally focused pre-test genetic counseling often does not match the needs of patients. Further, as genetic referral guidelines continue to expand, demand for genetic counseling will outstrip delivery capacity. Thus, alternative approaches that raise awareness and facilitate access to genetic testing are needed to maximize our ability to extend the benefits of testing to prostate cancer patients and their family members while at the same time accommodating increased demand and conserving scarce genetic counseling resources.

In the proposed pilot, we will develop and test a proactive and streamlined pre-test genetic education (ST) print intervention designed to speed, simplify and target genetic testing delivery for prostate cancer patients. Participants randomized to ST will have the option to proceed directly to genetic testing bypassing traditional pre-test genetic counseling. In contrast, usual care (UC) participants will be informed that they meet guidelines for genetic counseling referral and will be provided with contact information to schedule a standard telephone pre-test genetic counseling session. All participants with a PV or variant of uncertain significance (VUS) will be scheduled for a telephone genetic counseling disclosure session. ST participants who are found not to carry a PV or VUS will have this result disclosed via clinical letter while disclosure for all UC participants will be per standard clinical care by the genetic counselor by phone. By proactively identifying eligible patients, providing streamlined information and facilitating genetic testing, the ST intervention will increase awareness, facilitate informed testing decisions, remove the barrier of pre-test genetic counseling and improve genetic testing delivery capacity.

We will enroll eligible prostate patients who were diagnosed between 2010 and 2019 and are being followed within radiation and medical oncology clinics at the MedStar Georgetown University Hospital (MGUH) and MedStar Washington Hospital Center (MWHC). In this initial pilot, we will not focus on newly diagnosed patients but instead will focus on patients who are being followed for a number of reasons: 1) Substantial numbers of patients who are currently being followed have now become candidates for genetic testing based on updated guidelines and 2) This will allow us to maximize our potential sample size within the one year framework of this grant, allowing us to obtain preliminary efficacy data in preparation for a planned multisite R01 study of newly diagnosed patients with high risk localized or metastatic disease. By providing information particularly salient to prostate cancer patients, reducing barriers to genetic testing and proactively facilitating genetic testing delivery, we expect that our proactive and streamlined approach will yield increased uptake of genetic testing. Our specific aims are:

1: **Evaluate the impact of ST vs. UC on genetic testing uptake.** *H1.1:* Patients randomized to ST will be more likely to complete genetic testing compared to UC. *H1.2:* Participants randomized to ST will make better informed genetic testing decisions (characterized by high knowledge, risk comprehension and concordance with attitudes) compared to UC. *H1.3*: Few patients in the ST arm will opt for traditional genetic counseling prior to testing.

2: **Evaluate patient satisfaction and psychosocial outcomes in ST vs. UC.** *H2.1:* Compared to UC, those randomized to ST will be more satisfied with their genetic testing decision and will have less decisional regret.

3: **Evaluate the impact of ST vs. UC on uptake of cascade testing in unaffected family members.** In exploratory analyses designed to provide effect size estimates, we will compare the arms on rates of genetic testing in relatives of patients found to carry a PV.

3.0 Background*

Germline Genetic Testing in Prostate Cancer. Up to 17% of men with prostate cancer have an inherited PV in a cancer gene. For many of these men, this knowledge may impact their medical management. Prostate cancer patients with *BRCA* PV develop higher risk disease than non-carriers. Prostate cancer patients with a *BRCA* PV with localized disease have more frequent nodal involvement, higher Gleason scores, more T3/T4 disease and lower cause specific overall survival at 5 years. Men with metastatic castration-resistant prostate cancer have significantly shorter cause specific overall survival in *BRCA2* carriers vs. non-carriers. The use of single agent PARP inhibitors in patients with *BRCA* PVs and metastatic castration-resistant prostate cancer was associated with high rates of response, leading the FDA to grant breakthrough therapy designation for olaparib and rucaparib in patients with *BRCA* positive metastatic castration resistant prostate cancer. NCCN guidelines suggest germline testing in patients with castration resistant metastatic prostate cancer to guide the early use of platinum chemotherapy as well as for eligibility for clinical trials using PARP inhibitors. In addition, prostate cancer patients with localized Gleason Grade 7+ prostate cancer are recommended to consider genetic testing if they have a family history of breast, ovarian, pancreatic or prostate cancer or are of Ashkenazi Jewish ancestry, regardless of family history . All prostate cancer patients with a *BRCA* PV are at increased risk for second malignancy (e.g., pancreatic cancer, male breast cancer, melanoma). The identification of a PV in a prostate cancer patient also has important

implications for his male and female family members who can use test results to guide their cancer risk reduction and management decisions. *Thus, the identification of a PV in a prostate cancer patient may often have treatment and risk management implications for the patient and his unaffected family members.*

Awareness and Access to Genetic Testing. Despite clear benefits and established guidelines, few men with prostate cancer get genetic testing. Men underestimate the personal relevance of *BRCA* mutations and have poorer knowledge and awareness of testing. Although physicians are less likely to refer men for genetic counseling than women and genetic education materials are generally not targeted to men, evidence indicates that when provided with adequate information men have increased uptake rates. Finally, emerging evidence also suggests that the requirement for traditional in-person genetic counseling may be a barrier to genetic testing among men. While men and women have comparable rates of genetic testing uptake *after* genetic counseling, men are much less likely to participate in genetic counseling. *Thus, our intervention is designed to increase appropriate uptake of genetic testing by proactively providing relevant genetic information emphasizing the personal and family relevance of testing to prostate cancer survivors while reducing barriers to genetic testing.*

These goals align with recent changes in genetic service delivery. Given rapidly increasing demand for genetic services, genetic counseling capacity has emerged as a rate limiting factor. *This lack of capacity will become more significant as genetic testing expands in cancer and beyond - prompting consideration of alternative delivery approaches that improve access and efficiency.* While studies have generally indicated that traditional genetic counseling results in positive participant outcomes, recent research suggest that the quantity, relevance and complexity of the information provided in genetic counseling does not always match patient needs. This is particularly true in the cancer setting where the issues covered in traditional genetic counseling may not be of primary concern. Further, most patients who meet clinical referral criteria will not be found to carry a PV. Thus, requiring comprehensive pre-test genetic counseling may not meet the needs of patients and survivors, is inefficient and may serve as a barrier to testing.

Given the unsustainability of the entrenched genetic counseling model, alternative strategies must be considered. We are at the forefront of developing practice changing alternatives to traditional genetic service delivery. We were the first to document the impact of rapid presurgical genetic testing for newly diagnosed breast cancer patients and that access to genetic counseling can be safely and effectively expanded via telephone delivery. Both of these approaches are now part of standard care. More recently, we and others have focused on streamlining content and delivery to more effectively address access and demand while removing barriers that patients find overwhelming or irrelevant. An approach labeled 'direct testing' or 'post-test only', provides patients with brief print information prior to testing. This approach has been used in studies of population-based testing and in newly diagnosed breast, ovarian and colorectal cancer patients. A recent single-arm trial of a brief pre-test summary letter for newly diagnosed breast cancer patients yielded high patient satisfaction and only 2% of participants contacted the study genetic counselor with questions. *Although these studies provide promising preliminary data, it is important to note the lack of RCTs and the focus on populations with high rates of testing. We propose an RCT designed to: 1) proactively deliver genetic education to increase awareness and knowledge among patients who underutilize testing; 2) eliminate*

the pre-test genetic counseling requirement for patients who wish to proceed directly to testing; and 3) direct scarce genetic counseling resources to patients who receive a PV result – the patients most vulnerable to adverse outcomes. This pilot will provide preliminary data supporting a planned R01 for a multisite RCT of ST vs UC in newly diagnosed prostate patients.

4.0 Study Endpoints*

4.1 Primary and secondary endpoints:

1. Genetic test uptake

2. Receipt of pre-test genetic counseling

3. Psychosocial outcomes (Satisfaction, distress, decision regret)

4. Use of cascade testing among unaffected family members of mutation carriers

5.0 Study Intervention/Investigational Agent

The streamlined testing (ST) intervention includes: proactive identification and contact of patients eligible for genetic services, streamlined pre-test genetic education, facilitated delivery of genetic testing, targeted genetic counseling disclosure for patients with a PV or variant of uncertain clinical significance (VUS) and a clinical disclosure letter for patients who do not carry a PV. We have developed a range of media for cancer risk communication, including print, electronic and in-person education. The ST print materials will include the following topics: 1) Introduction and explanation of genetic testing guidelines for prostate cancer patients; 2) Explanation of panel testing and potential genetic testing outcomes (positive, negative, uncertain variant); 3) Personal implications of a PV (cancer risks associated with a positive genetic testing result; treatment/management, risk management for second cancers); 4) Implications for family members; 5) Legislation to protect against genetic discrimination; 6) Process of genetic testing: DNA collection (saliva kit), costs, and insurance coverage; 7) Options for and logistics of genetic counseling: pre-test counseling is optional unless required by insurance; post-test genetic counseling for all positives (no charge for telephone genetic counseling). Drawing on our prior work, the ST materials will include text, images, illustrations and graphics. We expect that the material will take 10-15 minutes to review. *Participants randomized to the usual care (UC) arm will be sent a letter from their physician indicating that they meet eligibility criteria for genetic counseling and recommending that they schedule genetic counseling. UC participants can receive free telephone genetic counseling through the study.*

6.0 Procedures Involved*

6.1-6.4 The objective is to develop and pilot a novel streamlined approach to deliver genetic education and testing to the rapidly increasing number of prostate cancer patients who meet guidelines for genetic referral. Our streamlined genetic testing approach is designed to facilitate genetic education and testing for men with prostate cancer. The intervention will incorporate proactively delivered print educational materials in lieu of pre-test genetic counseling. The materials will increase awareness, expand access, provide

balanced information to foster informed genetic testing decisions and reduce barriers to facilitate the delivery of genetic testing. All men who are found to carry a PV or variant of uncertain significance (VUS) in a cancer risk gene will have an individual telephone genetic counseling disclosure session with a board-certified genetic counselor. We will recruit 120 prostate cancer survivors who meet clinical referral criteria. After a baseline survey, we will randomize participants to: ST vs. UC. Participants will complete a follow-up survey at 2-3-months post-randomization. Our primary outcome is genetic testing uptake.

Eligibility and Accrual. Men eligible for this study are currently being followed at MGUH or MWHC for either:

Metastatic prostate cancer;

Gleason 7+ prostate cancer.

We will exclude patients who have had, or are already scheduled for genetic counseling or testing for *BRCA1* or *BRCA2* mutations. We will also exclude men who cannot participate in English and provide meaningful consent. We will recruit participants from medical and radiation oncology clinics at MGUH and MWHC. These clinics currently follow well over 1000 eligible patients.

Gender and Minorities. Participants will be adult men. Given the racial/ethnic breakdown of the clinics we are recruiting from. We expect that at least 30% of participants will be members of racial/ethnic minority groups.

Recruitment. Working with our clinical collaborators and the Survey, Recruitment and Biospecimen Collection Shared Resource (SRBSR) will obtain contact information of potentially eligible patients from clinical databases and/or the EMR. We will mail an introductory letter describing the study (from the study MPIs and the patient's physician), opt-out postcard/phone number, informed consent document and a print version of the baseline survey to all potentially eligible participants. We will also email electronic versions of these materials for patients who prefer to complete them online. Two-weeks following this mailing, an SRBSR research assistant (RA) will call patients who have neither opted out nor completed the baseline survey. For men who have not returned the consent document, we will use an IRB-approved verbal consent for completing the baseline survey and request return of the written consent prior to randomization. Following completion of print or electronic consent and the baseline survey, the RA will randomize participants. Men randomized to ST will be sent a priority mail packet with detailed genetic testing educational material. Men randomized to UC will be mailed a letter informing them that they meet guidelines for genetic counseling and provided with contact information to schedule a genetic counseling appointment with a LCCC genetic counselor.

Randomization. Following completion of the baseline survey and consent document, an RA will randomize participants via computer-generated random numbers in blocks of 8 and a ratio of 1:1. Participants will be notified of their random assignment via letter and email.

Assessments. We will administer baseline (T0) and 2- to 3-month (T1) follow-up telephone/electronic surveys. Genetic testing uptake will be assessed via clinical records and basic clinical and demographic information abstracted from the EMR. See Table 1 for assessment instruments and schedule of administration.

Table 1. Measures

Variables	Measures	T0	T1
Covariates/Background Variables	Demographics, clinical variables, family history (EMR/survey)	X	
Health Literacy	Brief Health Literacy Screening Tool	X	
Genetic Test Uptake	Study Records		X
Knowledge/Risk Comprehension	Genetic Knowledge Scale and Perceived Mutation Risk.	X	X
Attitudes	Adapted version of the Multimodal Measure of Informed Choice (MMIC), Fatalism, Medical Mistrust Index	X	
Decision Regret	Decisional-Regret Scale.		X
Decision Satisfaction	Satisfaction with Decision Scale.		X
Distress	Cancer distress: PROMIS Anxiety and Depression; Genetic testing distress MICRA.	X	X
Quality of Life/Functional Status	PROMIS Physical Function and Social Function Short Forms	X	X
Cascade Testing	Number of relatives who have proceeded with genetic testing.		X

Streamlined Testing (ST) Intervention. Men randomized to ST will be sent a priority mail packet with the ST print education materials and information on how to proceed with genetic testing. ST participants will have the option of proceeding directly to genetic testing or scheduling a telephone genetic counseling session. The content of the ST intervention is described in section 5.0 above.

Usual Care (UC). After completion of the baseline survey, UC participants will be sent a letter from their physician indicating that they meet eligibility criteria for genetic testing, recommending that they schedule genetic counseling and providing a contact telephone number to schedule their session. Patients may opt for free telephone genetic counseling.

Genetic Testing. Participants who choose to pursue genetic testing will be offered a standard clinical multigene panel of at least 40 genes, including *BRCA* and genes associated with potential differential diagnoses (e.g., Lynch syndrome). All testing will be performed by Invitae, a CLIA certified clinical lab not affiliated with the GLCCC. Invitae offers genetic testing free of charge to eligible prostate cancer patients (all study participants will be eligible for free genetic testing through Invitae). Prior to proceeding with genetic testing, participants will be required to sign and return a clinical genetic testing consent form, after which we will mail them an at-home DNA kit for saliva collection which will be returned directly to Invitae (shipping costs are pre-paid).

7.0 Data and Specimen Banking*

7.1 All information will be retained for five years after the completion of the study. Only the PI, research staff and data managers will have access to this information.

All paper documents will be securely stored in the participant's research file, which will be kept in a locked cabinet in research team offices within secure buildings. In all data sets, including those with genetic testing and counseling information, we will use ID numbers only. A separate data set linking names with ID numbers will be accessible only through password protected and secure data programs and available only to trained study staff.

7.2 What data will be stored:

Hospital/physician medical records
Lab, pathology and/or radiology results
Interviews/questionnaires

7.3 This data will not be shared.

8.0 Sharing of Results with Subjects*

8.1 Upon receipt of a positive genetic test result or a variant of uncertain clinical significance, participants in either arm will be contacted by a board-certified genetic counselor to schedule a telephone disclosure session. This session will follow standard clinical protocols for the delivery of genetic test results. Participants in the ST arm who receive a negative result will be notified by mail only, but may choose to schedule a free telephone genetic counseling session if they wish. They and their referring physician will receive a copy of the test report along with a standard clinical letter prepared by a board-certified genetic counselor.

9.0 Study Timelines*

9.1 Participants will remain in the study for 3 months after randomization.

We expect participant enrollment to be completed within three-months.

The anticipated study completion date is 9/1/20.

10.0 Inclusion and Exclusion Criteria*

10.1 Screening for Eligibility: The Survey, Recruitment and Biospecimen Collection Shared Resource (SRBSR) will work with our clinical collaborators to obtain a list of potentially eligible patients from the clinical databases and the EMR. To each potentially eligible patient, we will mail an introductory letter (from the study Principal Investigators and the patient's physician), opt-out postcard/phone number, informed consent document and baseline survey (we will also email electronic versions of these materials). Two-weeks following this mailing, we will call all patients who have not opted out or completed the baseline survey. At the start of this telephone call we will confirm study eligibility.

10.2 Inclusion Criteria:

- Men who are being followed at MGUH or MWHC for metastatic prostate cancer or Gleason 7+ prostate cancer.

Exclusion Criteria:

- Above age 80.
- Previous cancer genetic counseling or currently scheduled for cancer genetic counseling related to the *BRCA1* or *BRCA2* genes.
- Have had or are scheduled for germline cancer genetic testing of the *BRCA1* or *BRCA2* genes.
- Cannot participate in English
- Are not capable of providing informed consent

10.3 We will exclude adults unable to provide meaningful informed consent, individuals under the age of 18 and prisoners. Since the study focuses on prostate cancer survivors, women are ineligible.

11.0 Vulnerable Populations*

11.1 This research does not involve individuals from vulnerable populations.

12.0 Local Number of Subjects

12.1 120 subjects will be recruited locally.

13.0 Recruitment Methods

13.1 Working with our clinical collaborators, the Survey, Recruitment and Biospecimen Collection Shared Resource (SRBSR) will obtain contact information of potentially eligible patients from the clinical databases and the EMR. We will mail an introductory letter (from the study MPIs and the patient's physician), opt-out postcard/phone number, informed consent document and baseline survey (we will also email electronic versions of these materials) to all potentially eligible patients. Participants who do not wish to be contacted further for the study or are ineligible for the study will be able to easily opt out using an enclosed postcard, toll-free telephone line or electronic mail address. Patients who have questions about the study can also contact the study team via the toll-free telephone line.

Two-weeks following the initial study mailing, we will call patients who have not completed the baseline survey or opted out. After confirming eligibility, explaining the study and answering any questions, an SRBSR RA will administer an IRB-approved verbal consent for the baseline survey. A verbal consent will allow us to complete the minimal risk baseline survey in a timely fashion. Participants will then be required to complete the print or electronic informed consent document prior to randomization. We have successfully used this approach in multiple previous trials. After providing informed consent, participants will complete the 10-minute baseline survey over the telephone (participants will have the option to complete the survey electronically).

13.2 Subject Source: Participants will be prostate cancer patients/survivors who are currently being followed by one of our physician co-investigators (i.e., have had an appointment in July 2017 or later).

13.3 Method to identify subjects: Prostate cancer patients who are currently being followed by one of our physician co-investigators will be identified via clinical databases or through the EMR. We will generate a list of patients who potentially meet our eligibility criteria. Each of these patients will be mailed a packet of study information and will have eligibility confirmed via an eligibility screener or contact by the SRBSR.

13.4 Participants will be identified by their treating physician who will query the clinical records for patients who meet the study eligibility criteria.

13.5 Recruitment Materials: Study staff will mail a packet to potentially eligible patients. This mailing will include: an introductory letter describing the study, information about how to opt out of the study or to speak to a study team member with any questions, an informed consent document and a print version of the baseline survey. For patients with email addresses available, we will also send these materials electronically.

13.6 Participants will receive an incentive of $20 upon completion of the baseline survey and another $20 incentive upon completion of the follow-up survey.

14.0 Withdrawal of Subjects*

14.1 A participant may be withdrawn from the study without their consent in order to maintain the integrity of the data (e.g., participant is not following procedures or is deliberately providing false information).

14.2 If a participant is withdrawn from the study without their consent, we will take the following steps: a) We will inform he participant in writing of the decision including an explanation for the decision; b) We will notify the IRB of our decision to withdraw the participant.

14.3 If subjects withdraw, their information will be kept and labeled as withdrawn. These withdrawn subjects will not be contacted further. If a subject chooses to withdraw from the study, we will continue to utilize all data collected up to the point of subject withdrawal. It states in the informed consent document that subjects are free to withdraw at any point during the study. Some subjects may decide to withdraw because they no longer wish, or have time, to do the follow-up interviews. From our previous genetic counseling studies, approximately 15% of participants withdraw prior to completion of the study. The majority of those who withdraw usually do so because they no longer want to complete study assessments. We will track withdrawals and report them in study findings. There are no biomedical safety implications from this type of partial withdraw.

15.0 Risks to Subjects*

15.1 Risks associated with participating in this study fall into three categories. First is the risk associated with completing the study surveys. There is a low risk of adverse psychological reactions to the study surveys. Asking men with prostate cancer to reflect on their/their family's cancer risks, their cancer screening behaviors, and their reactions to genetic testing could generate anxiety for some

individuals. However, because these individuals agreed to study participation, these are likely topics that they are willing to discuss. It is possible that persons likely to be overly concerned or harmed by the experience of discussing cancer risk will choose not to participate, although our prior data show that we have recruited participants reporting a broad continuum of cancer worry and risk perception with no adverse consequences. Thus, we consider this to be a minimal risk to patients.

Second, there may be modest risks associated with participation in genetic education or genetic counseling. Participants may experience mild psychological distress regarding their risk for carrying a PV in a cancer risk gene and the potential increase in risk for cancer in the participant and his family members.

Our plan for addressing adverse psychological reactions is comprehensive and is modeled on our current approach within the clinical cancer genetics program at LCCC (Dr. Isaacs, Medical Director; Ms. Peshkin Genetic Counseling Director). First, any participants who report high levels of distress during a study contact or on a study survey instrument will be referred for follow-up psychological assessment to a mental health provider. Second, all participants who undergo genetic testing and receive a PV or VUS result will have an individual genetic counseling disclosure session with a board-certified genetic counselor. As part of this session, the counselor will assess participant distress and coping difficulties. Specific follow-up referrals will be made for participants exhibiting psychosocial difficulties. Because attention to psychological issues has been a longstanding component of comprehensive genetic counseling, it is anticipated that psychological injury will be infrequent. In fact, quite to the contrary, considerable research documents beneficial psychosocial effects of counseling. Even for patients who receive positive test results, there is little evidence to suggest adverse psychological effects.

There may also be risks for ST participants who proceed directly to genetic testing without an individual genetic counseling session. However, we believe that the risk to these participants is low for several reasons. A) In community practice approximately 50% of individuals who receive cancer genetic testing do so without any pre-test genetic education or counseling; B) All participants who are randomized to ST will have the option to request individual telephone genetic counseling free of charge through the study; C) All individuals who proceed to genetic testing and are found to carry a PV or VUS result will receive their test results in the context of a standard genetic counseling disclosure session with a board-certified genetic counselor; D) The population in the current study all meet guidelines for genetic referral. There are insufficient counseling resources to retrospectively contact and counsel all prostate cancer survivors who meet criteria for genetic testing. Thus, from a clinical perspective, it is critical to develop effective and efficient genetic education approaches to foster informed genetic testing decisions. Finally, the personal health implications of a positive genetic test result in men are much less pronounced and immediate than in women. Thus, the risk of adverse psychosocial outcomes (already low in women who undergo testing) is quite low.

For all patients who choose to proceed with genetic testing, there may be additional risks. Although participants will neither be encouraged nor discouraged from undergoing testing as part of this study, for those who choose to pursue testing, additional potential risks include insurance and employment discrimination and the small possibility of incorrect or inaccurate test results. The ST materials contain information about laws protecting against genetic discrimination, and the standard clinical laboratory consent form outlines the small possibility of incorrect or inaccurate test results.

Finally, in addition to psychosocial risks that may be associated with genetic counseling, there may also be risks related to confidentiality and loss of privacy should an unauthorized third-party learn that the participant received genetic counseling and testing.

16.0 Potential Benefits to Subjects*

16.1 The potential benefit of this study to the participants is an increased knowledge of genetic testing for cancer susceptibility and a better understanding of the implications for treatment, screening, and risk reduction in men who carry a PV and their family members.

17.0 Data Management* and Confidentiality

17.1 Data Analysis: We will characterize participants by comparing them to decliners on key demographic and clinical variables derived from the EMR. After performing univariate analysis on dependent variables, we will apply any needed normalizing or variance stabilizing transformations. We will follow Consort guidelines for Intent-to-Treat analyses (ITT). We will compare groups at baseline with $\chi 2$ and t-tests and will include covariates that are associated with group ($p < 0.10$) in our final models.

Aim 1: Evaluate the impact of Proactive Streamlined Education and Testing (ST) vs. Usual Care (UC) on genetic testing. Analysis: H1.1: Patients randomized to ST will be more likely to complete genetic testing compared to UC. We will use logistic regression to test this hypothesis. After entering significant covariates, we will add intervention arm to test the overall intervention effect. H1.2: Participants randomized to ST will make better informed genetic testing decisions (characterized by high knowledge, risk comprehension and positive attitudes) compared to UC. Using multiple regression, we will enter control/confounding variables and intervention to test the impact of group on our informed decision making outcomes (knowledge, testing attitudes, risk comprehension). H1.3: Few patients in the ST arm will opt for traditional genetic counseling prior to testing. We will conduct descriptive analyses describing the proportion of ST participants who opt for genetic counseling vs. proceed directly to testing vs. opt against testing.

Aim 2: Evaluate patient satisfaction and psychosocial outcomes in ST vs. UC. Analysis: H2.1: Compared to UC, those randomized to ST will be more satisfied with their genetic testing decision and will have less decisional regret. After identifying baseline confounders of each outcome, we will generate linear regression models in which we enter: 1) confounders; 2) genetic test result (dummy

coded to generate comparisons of carriers vs. non-carriers and non-carriers vs. untested); 3) group assignment. In the event that we have an insufficient number of PV carriers for these analyses, we will categorize test result into two levels (tested vs. untested) and evaluate results among PV carriers more descriptively. Results of Aim 2 analyses will be primarily focused on generating effect size estimates for our planned trial of newly diagnosed prostate cancer patients.

Aim 3: Evaluate the impact of ST vs. UC on uptake of cascade testing in unaffected family members. In exploratory analyses designed to provide effect size estimates for our planned R01, we will use t-test to compare the ST to UC on the number of relatives of PV carriers who undergo cascade genetic testing.

Power: Power estimates are for 2-tailed tests (α=.05). The study is powered based on our primary outcome of patient genetic testing uptake. We expect no attrition since data will be abstracted from clinic records. With no relevant studies on which to base our effect sizes for this pilot study, Table 2 displays the necessary sample size (per group) to obtain 80% power for a range of potential clinically significant effects on test uptake (40%-50% for ST; 10%-20% for UC). Based on this analysis, we will enroll 120 participants in order to attain 80% power to detect a clinically meaningful difference between 20% in UC and 45% in ST. For our secondary outcomes, a sample size of 120 and 10% attrition at 3-months (n=108 in final sample) will provide > 80% power to detect medium sized effects of d=.54 SDs on our secondary outcomes (e.g., decisional conflict, patient satisfaction). This effect size is well within the range that we have seen in previous studies and represents an effect that is generally considered to be clinically significant.

Table 2. Sample Size Calculation

	ST Uptake		
UC Uptake	.40	.45	.50
10%	39	25	20
15%	49	36	27
20%	81	54	39

17.2 Data Security: Our plan for maintaining confidentiality is as follows:

The protection of privacy of participants in studies related to genetic risk information is of the utmost importance. Our plan to maintain confidentiality is as follows: 1) We will minimize communication that involves names or other identifying information. Where this is unavoidable, communications will be made via express mail, on a study dedicated fax machine, or via HIPAA compliant, access protected and SSL encrypted REDCap data capture system. 2) Clinical information such as personal and family cancer history and genetic testing results will not be communicated together with names in any written materials for study-related communication or data storage. However, as part of standard clinical practice, participants who opt for testing will receive a genetic testing report generated by the lab that will contain their name and other identifying information. This report will also be sent to the participant's treating physician as per standard clinical practice. Similarly, the genetic counselors' summary letters will contain participants' names, test results, and other identifying information. 3) All paper documents will be securely stored in the participant's research file, which will be kept in a locked cabinet in research team offices within secure buildings. 4) Information obtained during or as a result of this study will not be released without

the written consent of the participating individual. 5) In all data sets, including those with genetic counseling and testing info, we will use ID numbers only. A separate data set linking names with ID numbers will be accessible only though password protected and secure data programs and available only to trained staff.

17.3 Quality assurance reviews will be conducted throughout the course of the study to ensure data quality and protocol adherence.

17.4 Data Handling: Personal information will only be used to contact potential study participants. This information will not be stored with the survey data. Only a code number will be used to identify study-related data. A matching list will be created as a cross-reference for contact information and data.

Matching lists of names and code numbers will be kept in locked storage facilities in the PI's office and/or laboratory space. All data will be similarly stored in locked facilities. All computer files containing participant data will be accessed only through password protected security systems and are stored on a secure and private server used by the Cancer Prevention and Control Program at LCCC. Further, procedures for ensuring data integrity and security will be reviewed at regular intervals through team meetings between the PI and other members of the study team. Ethical issues and topics related to the responsible conduct of research will be also be discussed routinely with the overall study team, including the potential for adverse events, data safety and data management, handling misconduct, etc.

Only the PI, research staff and data managers will have access to this information. Transfer of information will occur via the HIPAA compliant and fully secure REDCap system and through the HIPAA compliant and fully secure Georgetown Box system.

Protected Health Information (PHI) that will be collected includes: lab results, interviews/questionnaires, data previously collected for research purposes under another approved GU or MedStar IRB study, and from a database.

All study-related data will be stored in the secure REDCap system and within Georgetown Box. Only study investigators will have access to this information. All access to study-related data will be via password protected and encrypted access. Data from this study will be stored for seven years after the final publication from the study. During this time, the PI will be responsible for approving access to the study data. Any computer used to access the study-related data will have active and up to date software in place to protect against malware, all operating systems and software updates and patches will be applied regularly and two factor authentication will be in place for all systems accessing research data

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

This research does not involve more than minimal risk to subjects.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 To protect privacy interest of participants, we first contact potentially eligible patients by mail. This contact includes multiple options to easily opt out of further contact: a stamped and addressed opt-out card; a toll-free telephone number to opt out of the study and an e-mail address for opting out of the study. We will wait two weeks before contacting men who have not opted out/indicated their ineligibility.

19.2 Participants will be assured of the confidentiality of their data and that their data will be carefully protected and safeguarded. Only a code number will be used to identify study-related data. Participants will be told that during the survey, they may decline to answer any questions that do not wish to answer and can leave the study at any time and for any reason.

19.3 The research team will have access to study data on password protected servers or by password protected web interfaces. Access to data will be strictly controlled.

20.0 Compensation for Research-Related Injury

20.1 The risk of injury in this study is minimal.

21.0 Economic Burden to Subjects

21.1 Participation in this study will not result in any additional costs for the subjects.

22.0 Consent Process

22.1 We will follow the SOP: Informed Consent for Research. Consent will be obtained in one of two ways:

1) Print Informed Consent Document. This document will be sent to all participants. This document will be reviewed by participants and any questions that they have will be addressed during a telephone call with the study RA. Those who wish to complete the written consent can return it directly to the study team in a postage paid return envelope.
2) Electronic Consent. Participants who prefer to complete an electronic consent process can complete an electronic consent form immediately prior to the baseline study survey. This form is comparable to the print consent form - but adapted for electronic administration.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception): Not Applicable

Subjects who are not yet adults (infants, children, teenagers): N/A

Cognitively Impaired Adults: N/A

Adults Unable to Consent: N/A

23.0 Process to Document Consent in Writing

23.1 We will follow "SOP: Written Documentation of Consent (HRP-091)." We will obtain print or electronic consent from all participants prior to randomization. The written consent document will be sent to all participants. Those who wish to complete the written consent can return it directly to the study team in a postage paid return envelope. Participants who prefer to complete the consent form electronically can complete an electronic version of the consent form online prior to the baseline survey.

23.2 We are requesting a waiver of written consent so that participants who choose to complete the baseline study survey by telephone can complete the survey following an IRB-approved verbal consent process. Participants who we contact by telephone (who have not completed a print or electronic informed consent document), will complete an IRB-approved verbal consent process. Verbal consent will pertain only to the completion of baseline study survey. All study participants will be required to complete the print or electronic informed consent document prior to randomization. We believe this approach is justified for several reasons. First, the data collected during the baseline survey are limited to behavioral, psychosocial, attitudinal and demographic information. This survey represents minimal risk to participants. Second, with the increasing difficulty of reaching study participants by telephone, it becomes extremely important to be able to complete the baseline survey when we get a chance – rather than wait for the return of the consent documents. This process allows us to complete the minimal risk baseline survey while still requiring full informed consent prior to randomization and the delivery of the intervention. Finally, completing the survey does not in any way represent a commitment to participate in genetic counseling or testing. Participants can decline further study participation at any time.

Participants will be required to sign a clinical consent form from the testing laboratory (Invitae). This form outlines the potential benefits, limitations, and risks of genetic testing.

24.0 Setting

24.1 All study participants will be patients of our collaborating medical and radiation oncologists at MGUH and MWHC. Participants who are potentially eligible for the study (i.e., meet clinical genetic referral criteria) will be identified via EMR query and then contacted by the study team. All research procedures will be conducted remotely (survey completion, delivery of print genetic education and telephone genetic counseling).

25.0 Resources Available

25.1 Recruiting Feasibility: Men eligible for this study are currently being followed at MGUH or MWHC for metastatic prostate cancer or Gleason 7+ prostate cancer with a family history of breast, ovarian, pancreatic or prostate cancer or Ashkenazi Jewish ancestry. We will exclude patients who have had or are scheduled for, genetic counseling or testing. We will also exclude men who cannot participate in English and provide meaningful consent. We will recruit participants from medical and radiation oncology clinics at MGUH and MWHC (see letters of

support in attached protocol). These clinics currently follow well over 1000 eligible patients. Although we routinely attain 70% case participation, we can attain our required sample size (n=120) with much lower rates of participation.

Time: The project will be conducted over the next year with data analysis and manuscript preparation continuing for 1 years after the completion of participant follow-up.

Facilities: Participants will be contacted via mail, telephone and electronically. The study staff will initiate these contacts from the Cancer Prevention and Control office suite and from the offices of SRBSR in MGUH. Each member of the study staff has a private or semi-private office with private telephone and private secured workstations. Each office is locked and accessible only by the study staff member and the PI or Project Director. All DNA will be collected using standard DNA saliva kits used by the study participants in the privacy of their home. DNA will be shipped by mail to the designated commercial genetic testing company for preparation and sequencing in a secure and CLIA-approved facility as is standard for all clinical genetic testing samples.

Medical and Psychological Resources: This is a low-risk study. However, all participants will have access to a board-certified genetic counselor. All of these counselors are trained and experienced at recognizing signs of psychological distress. All positive genetic test results will be delivered by a board-certified genetic counselor who will assess psychological reactions to genetic test results and make referrals for additional services as needed. All negative or VUS results will be delivered via mailed clinical letter and will include contact information for the assigned genetic counselor in case the participant wishes to schedule a session.

Training: All persons involved in this research study are trained on the protocol prior to their involvement in the study. All study personnel complete standard Georgetown University Human Subjects Training through the CITI program. All staff are supervised directly by the PI and participate in weekly study meetings. Further, procedures for ensuring data integrity and security will be reviewed at regular intervals throughout the study. Ethical issues and topics related to the responsible conduct of research will also be discussed routinely with the overall study team, including the potential for adverse events, data safety and data management, handling misconduct, etc.

26.0 Multi-Site Research*

26.1 This is not a multisite study.