EH21-338: Observational and Prospective Study on the Performance of Inherited Risk Assessment for Predicting Prostate Cancer from Prostate Biopsy (GenBx)

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1. Background

Inherited genetic changes, including rare pathogenic mutations (RPMs) in several major genes and single nucleotide polymorphisms (SNPs)-based genetic risk scores (GRS), have been consistently associated with prostate cancer (PCa) risk.[1-8] In addition, GRS values and RPMs are associated with earlier age of diagnosis.[2,9] Furthermore, a recent study found men with higher GRS values are found to have more tumor lesions in the prostate, suggesting a genetic basis for multifocal disease.[10]

These consistent findings suggest inherited risk assessment may have clinical utility in improving personalized PCa care. Specifically, inherited risk assessment has potential to improve prediction of detecting PCa from diagnostic prostate biopsy, a major clinical challenge considering PCa is only detected in <40% patients, especially in those with moderately elevated PSA levels.[11] This clinical utility has been demonstrated in retrospective analyses of two clinical trials and several biopsy cohorts.[12-14] For example, the PCa detection rate was 15%, 25% and 40% in men with low-GRS (<0.5), intermediate-GRS (0.5-1.5), and high-GRS (>1.5) in the REDUCE clinical trial.[12]

However, the issue is that GRS has not been incorporated routinely into clinical practice. In addition, it has not been incorporated into modern day clinical practice utilizing other modalities to improve PCa detection (e.g. prostate health index (PHI), multiparametric MRI, transperineal biopsies).

The primary goal of this trial is to demonstrate the performance of inherited risk assessment for predicting PCa from prostate biopsy. The prospective aspect of the trial is necessary for guideline committees to review evidence and make decisions in their recommendations.

2. Specific Aims

The study has the following aims:

1. The primary aim is to compare detection rate of PCa from diagnostic prostate biopsy in patients with different inherited risks as measured by GRS and RPMs: high-risk (RPMs+ and/or GRS ≥1.5), low-risk (no RPMs and GRS <1.5), and intermediate-risk (remaining subjects).
2. The secondary aim is to perform the above analysis and stratified by the purpose of diagnostic biopsy (initial and repeat biopsy), race, and other variables such as PSA, Prostate Health Index (PHI) and multiparametric MRI results.

3. Rationale

The objective of this observational prospective study is to assess the utility of both RPMs and GRS to identify patients who are more likely to have positive prostate biopsies (i.e., PCa) by looking at their inherited risk for PCa. The study aims to recruit 1000 multi-racial subjects from patients scheduled to undergo a prostate biopsy to detect PCa. Results from this trial will provide a critical piece of evidence for guideline committees to consider the adoption of genetic testing results in the decision making for prostate biopsies for the purpose of detecting PCa.

4. Design

This is a multi-site study with three locations: NorthShore University HealthSystem, Northwestern Memorial Hospital, and Johns Hopkins Hospital. All eligible patients who fit the inclusion

criteria below will be approached for recruitment (consecutive sampling) to obtain a more representative sample group. NorthShore will serve as the main/coordinating site for this study.

The study is divided into two main parts: 1) the observational clinical part, and 2) the genetic part. The clinical part consists of collecting data from standard clinical care practices. The procedures outlined for this part of the study are designed not to interfere with physicians' clinical practices, but rather to collect data regarding predictors and outcomes of prostate biopsy. As such, basic demographic and clinical data (i.e., BMI, PSA, PHI, and MRI) will be collected in order to understand how the addition of inherited risk assessment (i.e., genetic testing) can improve the decision-making process surrounding prostate biopsies for detecting PCa. Study sites participating in this research will assign study-specific research IDs to devoid of identifiers to each participant.

The genetic part consists of germline genetic testing for RPMs and GRS. Biopsy outcomes and clinical variables will be collected from EPIC using patient identifiers. To minimize bias, genetic samples will be assigned a study-specific research ID devoid of identifiers at the time of participant recruitment. Research staff involved in one part of the study will be blinded to the analyses performed for the other part. After all genetic and biopsy results have been collected and analyzed separately, a designated honest broker at NorthShore will reconcile results of participants' genetic analysis with biopsy results using their assigned research IDs.

All enrolled participants will go through both parts of the study. Study procedures are discussed in detail in section 5. Treatment of protected health information is discussed in detail in section 6.

4.1 Population

A total of 1,000 patients (based on power calculations) undergoing prostate biopsies to detect PCa from both study sites will be enrolled, 334 of which will be recruited from NorthShore. Participants will be recruited based on the given criteria:

Inclusion Criteria:

- Male
- 40 to 69 years old
- Self-identify as Caucasian, African American, East Asian, Latino
- Undergoing prostate biopsy for detection of PCa at NorthShore or Johns Hopkins
- PSA between 2.5-10 ng/mL

Exclusion Criteria:

- Previous diagnosis of PCa
- Previous results for germline testing of RPMs/GRS
- Self-identify as more than one race or of mixed racial descent
- Self-identify as any other race outside of the four mentioned in the inclusion criteria
- PSA outside the range of inclusion criterion
- Cannot give informed consent for various reasons (i.e. disability, sedated/unconscious, etc.)

4.2 Power calculation

Based on estimates from our published study,[8] 21%, 56%, and 23% of men are expected to be classified as high-risk, intermediate-risk and low risk-group, respectively. Furthermore, based on another published study,[11] the PCa detection rate from biopsy among high-risk, intermediate-risk and low risk-group are estimated at 40%, 25%, and 15%, respectively. With these estimates, 900 men are needed in order to detect significant different PCa detection rates among the 3 inherited risk groups at $P<0.05$ (Table below). Based on the power calculation and 10% attrition rate (based on our experience), a total of 1,000 subjects will be recruited for this trial.

Power Analysis

Inherited Risk Group	Estimated Effect Size			Estimated Power		
	Proportion	PCa Rate	Effect Size (OR)	N	Subgroup	Overall
High Risk (RPMs+ and/or GRS ≥1.5)	21%	40%	3.78 (H)	189	H vs. L = 0.99	0.84
Intermediate Risk (all others)	56%	25%	1.89 (I)	504	H vs. I = 0.94	
Low Risk (RPMs- and GRS <1.5)	23%	15%	Ref (L)	207	I vs. L = 0.80	
Total Sample needed				**900**		

5. Procedures

5.1 Subject Identification

Participants will be identified from the pool of patients receiving prostate biopsy for diagnosing PCa at NorthShore and Johns Hopkins. Patients must meet the inclusion criteria to be eligible for the study. Per the consecutive sampling requirement, all eligible patients will be approached for recruitment into the study. Patients who have of any of the qualities mentioned in the exclusion criteria will be disqualified from enrollment into the study.

5.2 a Recruitment Procedures

Eligible patients will be approached by research staff for recruitment. Telephone and in-person visits will be used to present the study to patients. During these interactions research staff will explain the contents of the consent form focusing on the purpose of the study, study procedures, study duration, participant's rights and responsibilities, potential risks/benefits to participants and how their protected health information will be used. Participants will be given the opportunity to ask questions about the study and will be provided with as much time as needed to review and to reach a voluntary decision on participation.

5.2 b Consenting Procedures

REDCap, Secure email, postal mail will be use to provide the consent to subjects who are not approached in-person but during the telephone call and have agreed to participate or would like to review the consent form before making a decision.

5.3 DNA Sample Collection

Participants will be asked to provide DNA samples via saliva. A saliva sample collection kit will be distributed in-person to each participant by research staff. Research staff will instruct and assist participants during sample collection. Only one sample per participant will be used in this study. Saliva samples will be assigned a study-specific ID devoid of identifiers to blind downstream genetics research staff involved in DNA analysis. Saliva samples collected at NorthShore will be stored at the Genotyping Core Facility lab at the Research Institute under lock and key at the supervision of Dr. S. Lilly Zheng.

Saliva samples collected from other sites will be delivered to NorthShore and will undergo the same treatment/process as NorthShore's samples.

5.4 DNA Analysis

Participants' DNA will be extracted from saliva samples. Germline DNA will be sequenced to detect RPMs in 11 guideline-recommended (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13, MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2* and *RAD51D*) and other candidate genes (i.e., *KLK3*) as well as calculate race-specific GRS for PCa. The performance of high-inherited risk, defined as positive for RPMs and/or GRS ≥1.5, in predicting PCa will be estimated by C-statistic and positive predictive value (PPV). Race-specific GRS will be calculated based on a model previously developed by Dr. Jianfeng Xu and colleagues at NorthShore.

5.5 Biopsy Results Collection

The procedures outlined in this section of this observational study will not interfere with physicians' standard practice for PCa care. Participants' biopsy results will be collected from standard prostate biopsies for PCa detection. The biopsy procedure itself is not altered in any way as part of the study, but rather is performed as part of standard clinical care for participants. The investigators are only interested in collecting data regarding demographic/clinic predictors and biopsy results. No special study accommodations will be made for how the biopsy procedure is performed. Urologists and clinical staff will follow their respective guidelines and clinical practices for performing prostate biopsies. Details regarding the storage and treatment of protected health information is described later (section 6).

Biopsy results data from other sites will be sent to NorthShore to perform study-specific analyses.

5.6 Demographic and Clinical Data Collection

Demographic and clinical data will be collected by accessing participants' electronic health records on EPIC. Research staff will extract data such as age, race/ethnicity, body mass index (BMI), PSA, Prostate Health Index (PHI), and MRI results. This information will be used to study participants' outcomes with biopsy and genetic testing. Details regarding the storage and treatment of participants' health information is described later (section 6).

Demographic and clinical data from other sites will be sent to NorthShore to perform study-specific analyses.

5.7 Results Analysis and Interpretation

Once DNA analysis has been performed on all samples and all relevant data has been extracted from EPIC for all participants, a designated honest broker will reconcile participants' genetic, biopsy, and demographic/clinical information from all study sites. Study-specific IDs from genetic samples and participants' relevant data will be matched using a key document that only the honest broker can access. Additional statistical analysis will be conducted on the combined results, and any significant findings will be included in a scientific manuscript drafted for a peer-reviewed academic journal.

5.8 Reporting Genetic Testing Results

Genetic testing for this study is performed using a non-clinical-grade, research only panel. Therefore, no genetic results will be returned to participants directly. Once all analyses of combined results are completed, if any participant is found to have a significant genetic result that affects their risk for prostate cancer or (in the case of incidental findings) other diseases/disorders, the honest broker may approach the participant's physician and inform them of their need to recommend said participant for additional genetic testing via a clinical-grade panel. This will be done to ensure the health and well-being of the study participant affected.

6. Security and Confidentiality

6.1 Data Collection and Storage

Participants' data regarding demographics and biopsy results will be extracted from electronic health records on EPIC. Data collected will include health information such as:

1. Age
2. Self-reported race/ethnicity
3. Body mass index (BMI)
4. PSA
5. Prostate Health Index (PHI)
6. MRI results
7. Pathology report on prostate biopsy

Research IDs will be used to protect participants' identity and privacy throughout each step of the study. Research IDs are assigned to each participant by research staff in the study site where the recruitment took place. Information linking participants to their research ID will be logged in a "key" spreadsheet stored locally in each of the study site's institutional firewall. The sole purpose of the "key" is to allow each study site to keep track of the subjects they recruit after their data has been anonymized. Each study site will be responsible for the security and maintenance of their "key". NorthShore will not receive "keys" nor participants' personal information from other study sites; only clinical information linked to the anonymous research IDs will be collected.

All protected health information from NorthShore participants collected for this study will be stored in the organizations' firewall-protected server. Participants' protected health information received from other sites for the purposes of carrying out the study's aims will likewise be secured using the same standards. Data generated by this study will be stored within the organizations' servers or on password-protected computers within secured NorthShore facilities (i.e. the Research Institute). NorthShore's HIT will be notified of this study's use and treatment of protected health information as well the transfer of data between study sites via the submission of Data Governance forms.

6.2 Research Staff Training

All research staff involved in this study will receive training in the use and handling of protected health information before receiving authorization to be a part of the study. Research staff involved in recruitment and data analysis will comply with NorthShore policy regarding the appropriate collection, storage, analysis, and reporting of participants' protected health information. Research staff in wet labs will also receive the appropriate training regarding the handling, processing, and storage of biological samples.

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