Prostate Cancer Detection Using a Quantitative Screening MRI Protocol

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LIST OF ABBREVIATIONS

PCa	Prostate cancer
MRI	Magnetic resonance imaging
mpMRI	Multiparametric MRI
TRUS	Transrectal ultrasound
PSA	Prostate specific antigen
DRE	Digital rectal examination
AS	Active surveillance
GS	Gleason score
DWI	Diffusion weighted imaging
ADC	Apparent diffusion coefficient
DDC	Distributed diffusion coefficient
SEM	Stretched exponential model
FROC	Fractional order calculus
CEST	Chemical exchange saturation transfer
ROC	Receiver operating curve
AUC	Area under the receiver operating curve
SOC	Standard of care
H&E	Hematoxylin and Eosin
PBCG	Prostate Biopsy Collaborative Group
IPSS	International Prostate Symptom Score
SHIM	Sexual Health Inventory for Men
DICOM	Digital Imaging and Communications in Medicine
PI	Primary Investigator
IRB	Institutional Review Board
AIC	Advanced Imaging Center

1.0 Project Summary/Abstract

Currently men with elevated prostate specific antigen (PSA) or abnormal digital rectal examination (DRE) undergo systematic sampling of the prostate with transrectal ultrasound (TRUS)-guided needle biopsies. PSA and DRE have low specificity for prostate cancer (PCa), and TRUS biopsies have an approximately 30% false negative rate. Whether a quantitative detection specfic magnetic resonance imaging (MRI) protocol improves PCa detection in biopsy naïve men is not adequately studied.

This pilot study aims to test a novel detection specific MRI protocol which uses image collection and post-processing to assist the radiologist find areas of the prostate with increased suspicion for clinically significant cancer. Men with an MRI negative for cancer will undergo standard of care TRUS biopsies, and men with suspicious MRI lesions (as defined by our preliminary data) will undergo biopsies of these lesions in addition to systematic TRUS biopsies. We will compare the yield of significant PCa between systematic sampling and MRI determined areas of the prostate.

2.0 Background/Scientific Rationale

While there is concern for over-treatment of prostate cancer (PCa) it remains the 2nd leading cause of cancer death in U.S. men (1). This paradox is due in part to the accuracy limitations of current detection methods of serum prostate specific antigen (PSA) and digital rectal examination (DRE) screening, and the inability of current clinical information to discriminate indolent from aggressive tumors. Clinical patient characteristics including age, race, family history of PCa, DRE, and prior negative prostate biopsy history have been combined into a predictive calculator to guid biopsy decisions(2). Men found to have adequate suspicion for PCa require a tissue diagnosis. Standard PCa detection relies on 12-core transrectal ultrasound (TRUS) guided biopsy that samples anatomic zones of the prostate gland. Approximately 35% of men undergoing immediate radical prostatectomy (RP) for low grade PCa on standard biopsy will be found to have higher grade tumors in the pathologic specimen(3). Furthermore, between 30-38% of men with clinical suspicion for PCa and a negative standard biopsy will be diagnosed with PCa on re-biopsy(4). Finally, TRUS biopsy is an invasive procedure with a rate of sepsis as high as 2%, and this risk is proportional to the number of biopsy cores sampled(5). With a more precise method for early detection of the most aggressive tumors, men with indolent PCa could be spared treatment with its associated cost and morbidities and instead be managed conservatively with active surveillance (AS), while those with potentially lethal disease could be expediently referred for radiation or surgery with curative intent.

Improved PCa detection may be particularly important for African American (AA) men, who are almost twice as likely to die from PCa as white men(1). A recent study of men with very low risk PCa based on clinical information who underwent immediate RP found that AA men were more likely to have adverse RP pathology and anteriorly located tumors not reached with standard TRUS prostate biopsies(6). In addition, two series of men selected for AS based on standard clinical information reported that AA men progressed to treatment faster than white men(7, 8). These data have questioned the safety of managing AA men with AS without more accurate risk stratification tools such as imaging. At UIC, over 60% of PCa cases diagnosed are in AA men.

Standard TRUS imaging does not provide enough resolution to localize most PCa, much less provide information about its aggressiveness. One promising approach to improve PCa detection and risk stratification is through advanced imaging such as magnetic resonance imaging (MRI). In this setting an ideal imaging study would differentiate aggressive PCa from indolent PCa and benign processes such as hyperplasia (BPH) or inflammation as well as localize the aggressive PCa to reduce biopsy sampling error. Currently in the US, prostate mpMRI is approved for : 1) men with continued suspicion for PCa but negative TRUS biopsy or 2) for staging of known high risk PCa for treatment planning. The images from the mpMRI can be used for

targeted biopsies using TRUS/mpMRI imaging fusion to improve PCa detection(9). As such, there is interest in using mpMRI as a confirmatory test in men with elevated PSA and prior to the first biopsy to improve biopsy accuracy and potentially obviate the need for unnecessary “random” biopsies. A landmark study conducted in Europe, the PRECISION trial, recently reported that TRUS/mpMRI fusion biopsies in biopsy naive men with suspected PCa resulted in an increase in the absolute detection of clinically significant PCa of 12% in men randomized to mpMRI, despite 28% of the men in this group avoiding biopsy due to a negative study(10). These data are certainly compelling, but have yet to be replicated in a US population, and particularly in a high-risk group such as AA men. The implications in the US are significant as approximately 1 million TRUS biopsies are performed annually for known or suspected PCa(11).

While MRI protocols are variable and evolving, the current recommended standard is combining T2-weighted anatomical imaging (T2WI) with two functional MRI techniques, typically diffusion-weighted images (DWI) and dynamic contrast enhanced images (DCE), together to create a multi-parameter MRI (mpMRI) study. A radiologist reviews the imaging and assigns a semi-qualitative suspicion of high grade PCa on a 1-5 Likert scale. This score, called the prostate imaging reporting and data system (PI-RADS), is an attempt to standardize mpMRI assessment and guide clinical management(12). ThePI-RADS has several limitations including modest inter-rater reliability(13, 14), and a false positive rate of as high as 88% of the PI-RADS 3 (indeterminate) scores (figure 1). Currently the same prostate MRI protocols are used for PCa detection in men with prior negative TRUS biopsies, staging of known PCa, and for suspected PCa local recurrence after treatment. As such, the protocol contains several imaging sequences such as T1 weighted imaging to detect hemorrhage related to biopsy and DCE which is of limited value for PCa detection which add to the study time and cost(15). In addition, the fields of view of prostate MRI protocols are designed to show surrounding structures such as the pelvic lymph nodes for staging purposes which aren’t applicable to the primary PCa detection setting. These larger fields of view come at the expense of longer study times, and lower imaging detail in the prostate.

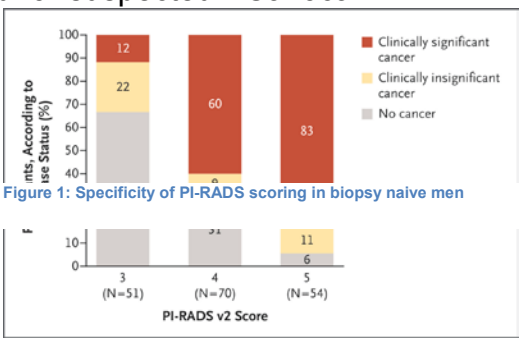

Figure 1: Specificity of PI-RADS scoring in biopsy naive men

Finally, current prostate MRI protocols are designed for qualitative assessment and PI-RADS scoring. A detection specific protocol can be designed so that quantitative parameters can be measured as an adjunct to PI-RADS scoring. We hypothesize that quantitative tools for image assessment could benefit radiologists to further characterize indeterminate MRI studies, and to facilitate comparisons across patients, centers, and populations.

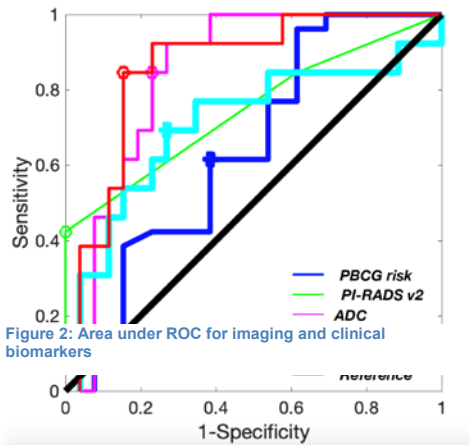

Figure 2: Area under ROC for imaging and clinical biomarkers

Our study explores 2 ways to improve mpMRI for PCa detection: 1) Developing an imaging protocol specifically designed for biopsy naïve men with suspected PCa and 2) improving utility of the collected images with quantitative image analysis tools as an adjunct to PI-RADS. DWI characterizes the Brownian movement of water molecules in tissues. Conventional DWI fits a line to data acquired using two strengths (b-values) of the magnetic diffusion gradient, the slope of which is the apparent diffusion coefficient (ADC) which can be used as a quantitative parameter. When compared to RP histology, ADC has a moderate inverse correlation with PCa grade(ref ADC and grade). With conventional DWI the calculation of ADC assumes a gaussian distribution of water molecule diffusion and tissue homogeneity which may oversimplify water motion in organs with complex tissue structures. A technique that more accurately determines water diffusion through tissues may better discriminate cancer grade. As such, we have tested stretched exponential (SEM) and kurtosis models of DWI with high b-values to determine the grade of PCa in 31 men undergoing biopsy targeted to MRI lesions identified using standard PI-RADS scoring. We found accuracy as measured by area under the receiver operator curve (AUC) that is significantly improved over PI-RADS, the PBCG model, and modestly improved over conventional ADC (Figure 2). Therefore, we propose to prospectively use quantitative DWI as a biomarker to determine regions of the prostate suspicious for high grade PCa in biopsy naïve men.

3.0 Objectives/Aims

This study aims to determine whether a detection specific MRI protocol with quantitative image analysis can improve high grade PCa detection in men with clinical suspicion and no prior biopsy.

Aim 1: Design a PCa detection specific MRI protocol which will facilitate quantitative image analysis and reduce study time by ~50%

Current prostate mpMRI protocols include image sequences and fields of view outside of the prostate gland and its immediate surrounding that are not useful for PCa detection. We will create a detection specific MRI protocol featuring: smaller fields of view zoomed to the prostate, T2 weighted imaging at multiple echo times, chemical exchange saturation transfer imaging (CEST), and DWI at higher b values (up to 4000) that will allow for quantitative prediction of high grade PCa. The exact imaging acquisition parameters can be found in Appendix 3. We expect this MRI protocol to

reduce study (acquisition) time from approximately 45 minutes to 27 minutes, which will potentially lower cost and improve tolerance of the procedure. Significantly, we will omit DCE which will reduce the imaging time, and the risks associated with intravenous contrast including systemic fibrosis, and patient discomfort.

Aim 2: Determine the accuracy of the novel MRI protocol for detection of high grade PCa

50 men with clinical suspicion of PCa (elevated PSA and/or abnormal DRE) will be enrolled into a prospective protocol and will undergo detection protocol MRI described in Aim 1. Quantitative image analyses will be performed to generate SEM maps of DWI. Areas of suspicion for high grade PCa (GS ≥7) will be targeted for biopsy. Men with MRI with no areas of suspicion for high grade PCa will undergo standard of care 12 core TRUS biopsy. The primary endpoint will be the rate of detection of high grade PCa on the per patient and per biopsy core basis. Men with biopsy pathology negative for PCa will undergo standard of care (SOC) continued monitoring.

4.0 Eligibility

Men with suspected PCa (elevated PSA and/or abnormal DRE) and no prior prostate biopsy will be identified in the UI Health Urology ambulatory clinics by the clinical research coordinator and study investigators.

4.1 Inclusion Criteria

- *Adult men between 18 and 80 years of age*
- *Suspected PCa as defined by elevated PSA ≥4 ng/mL and ≤20 ng/mL and/or abnormal DRE as determined by a physician*
- *Abililty to provide informed consent*

4.2 Exclusion Criteria

- *Prior prostate biopsy*
- *Prior diagnosis of PCa*
- *MRI incompatible implanted medical devices or foreign bodies*
- *Rectal anatomy incompatible with TRUS biopsy*
- *Life expectancy <10 years as determined by the treating urologist*

4.3 Excluded or Vulnerable Populations

- *No vulnerable populations such as minors or incarcerated persons will be included in the study.*

5.0 Subject Enrollment

The study investigators and clinical research coordinator will screen the scheduled encounters at the Urology clinics at UI Health for potentially eligible subjects meeting the inclusion criteria. No advertising materials will be used. No data will be collected from men screened but not enrolled. The clinical research coordinator will discuss the study risks and benefits and obtain informed consent separate from the study investigators to minimize coercion.

5.0 Study Design and Procedures

This will be a single arm prospective clinical trial. Men with clinical suspicion for PCa but no prior prostate biopsy will be enrolled from the UI Health Urology clinics. All eligible men will be screened and enrolled by the clinical research coordinator. Enrolled men will undergo detection protocol MRI at the UIC Advanced Imaging Center (AIC) prior to diagnostic biopsy. The image acquisition parameters are listed in the Appendix 3. The MRI will be processed by the study team and evaluated for areas suspicious for high grade PCa by a board certified clinical radiologist (Dr. Xie). Subjects with MRI with no suspicious areas for high grade PCa will undergo SOC 12 core TRUS biopsy. Subjects with MRI suspicious for high grade PCa will have 2-4 biopsies guided toward each suspicious lesion using MRI/TRUS fusion biopsies (maximum of 12 cores). All biopsies will undergo SOC histologic processing and interpretation in pathology. Biopsy results will be communicated to the patients by the Urologist performing the biopsy and all additional management will be SOC. This visit will signify the end of the study. See the study schema in Figure 4.

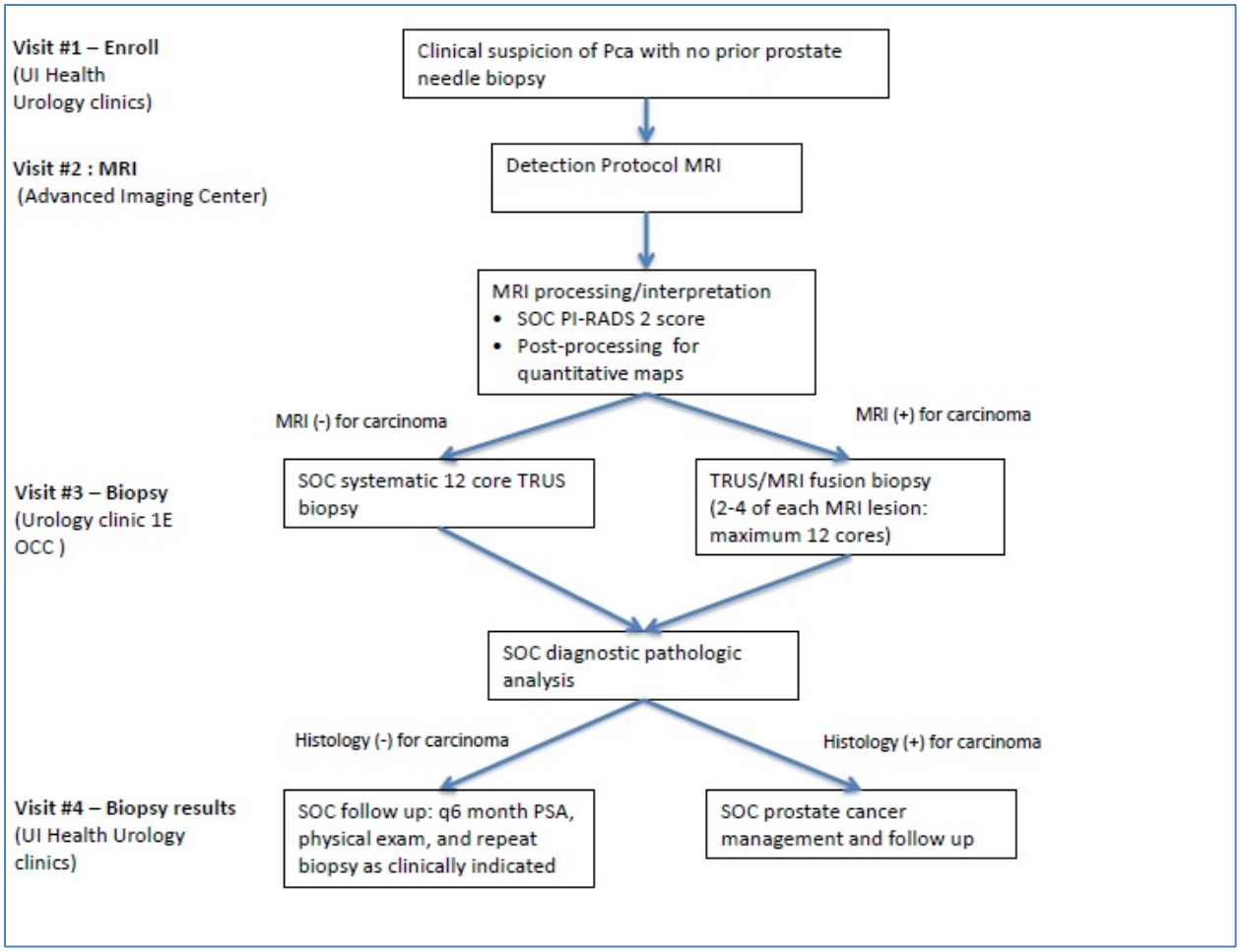

Figure 4: Study schema

The primary outcome will be the rate of detection of high grade PCa on a per-patient and per biopsy core basis. The detection rate will be compared between patients with and without evidence of high grade PCa (GS ≥7) based on the detection protocol MRI. Secondarily we will analyze the accuracy of the individual MRI parameters including: T2 imaging, ADC, the SEM parameters (DDC and α), the FROC parameters (μ, Δ, β), the Kurtosis model parameters (D, K), and PI-RADS score.

7.0 Expected Risks/Benefits

The study intervention is the detection protocol MRI and all other aspects of the study are standard of care. The detection protocol MRI is a minimal risk procedure as it does not require intravenous contrast and does not expose the subject to ionizing radiation. Also, in contrast to the aforementioned PRECISION study, patients not found to have suspicion of PCa on the detection protocol MRI will undergo the SOC 12 core TRUS

prostate biopsy thereby resulting in no additional risk of a missed or delayed PCa diagnosis.

The risks of the study are therefore mild anxiety due to the MRI examination itself, and violation of patient privacy due mishandling of protected health information.
Anxiety related to the MRI study, if mild, may be treated with an oral anxiolytic by the primary investigator (Dr. Abern) or the patient's primary care physician as is SOC. Severe anxiety precluding MRI without intravenous sedation or general anesthesia will be a reason to exclude a patient from the study. If this severe anxiety is discovered during the MRI, the study and the patient's involvement in the research will be terminated. Health information will be secure in REDCap, principal investigator will allow access to key research personnel only.

The benefits of the study may include: improved detection rate of high grade PCa and lower complication rates compared to standard TRUS 12 core biopsy, If the detection protocol MRI has high negative predictive value, it is possible in the future that unnecessary prostate biopsies could be avoided in men with a negative study, thereby reducing the discomfort and infectious complications of the procedure.

8.0 Data Collection and Management Procedures

To meet the study goals, clinical, imaging, and pathologic data will be collected prospectively. The co-investigators and other key personnel will have access to the identified data while the subject is on study. A REDCap database will be used to record all of the baseline and clinical data for each subject including: age (continuous in years), self reported race (white, black, Hispanic, other), family history of prostate cancer (positive or negative), serum PSA (continuous, in ng/mL), International Prostate Symptoms Score (IPSS: continuous), Sexual Health Inventory for Men score (SHIM: continuous). All source MRI images from the scanner as well as post-processed images will be collected in Digital Imaging and Communications in Medicine (DICOM) format. Image data will be stored on a password protected server and physically transported from the scanner to the post-processing workstation and to the radiologist workstation using an encrypted flash drive. Data from interpretation of the MRI images to be stored in REDCap will include: PI-RADS score (ordinal), number of lesions (ordinal), and the lesion mean, median, minimum and maximum for each quantitative MRI parameter if applicable. In addition, if applicable each lesion will be outlined on the T2 weighted image series by the radiologist for use at the time of biopsy. At the time of biopsy the prostate volume (continuous, cubic centimeters), type of biopsy (standard or targeted), and number of biopsy cores obtained (ordinal) will be entered in REDCap. Pathology data to be collected and stored in REDCap includes: presence of any carcinoma (Boolean), number of biopsy cores involved with carcinoma (ordinal), location of positive biopsy cores (ordinal lesion number), and maximum GS of biopsies (categorical:

6,7,8,9, or 10). At the biopsy results visit, biopsy complications will be recorded in REDCap: hematuria persisting greater than 72 hours (boolean), urinary retention (boolean), infectious complication (boolean), All data will be de-identified for each subject after study visit #4 when the biopsy results are known. We anticipate approximately 1 year to meet the enrollment goals. At this time, a 3 month period for data analysis of the primary outcome is anticipated. After this time, the de-identifed data will be stored by the primary investigator (Dr. Abern) for potential use for secondary retrospective studies under separate IRB approval. See Appendix 4 for the data flow diagram.

9.0 Data Analysis

The data analysis will be performed on de-identified data by the primary investigator, Dr. Abern, who has extensive experience in the statistical analysis of PCa outcomes and biomarkers. Dr. Gann, a co-investigator who is a world expert in PCa biomarker study design and analysis, will provide analytical support and oversight. Statistical methods are outlined in section 12 below.

10.0 Quality Control and Quality Assurance

The quality of the MRI images will be assessed qualitatively by the scanner technician in the Advanced Imaging Center at the time of data acquisition. In addition, the source and processed images will be assessed for acceptable quality by the study radiologist (Dr. Xie). It is possible that a patient would need to undergo a repeat MRI if the data are not adequate for assessment for PCa. All pathologic analysis is subject to the UIC Department of Pathology clinical quality assurance procedures as is the current clinical SOC.

11.0 Data and Safety Monitoring

Privacy of protected health information will be maintained by minimizing identifiable patient data and maintaining this information in a secure database for use only by study investigators. All identifiers needed for the research will be kept in the secure REDCap server. Only de-identified data will be retrieved from the server in order to perform data analyses

12.0 Statistical Considerations

As this is a single arm pilot study, no power analysis is necessary. Based on the PRECISION study, we expect a high grade PCa detection rate of approximately 30% or in 17/50 subjects (10). The primary outcome will be the comparison of the rate of high grade PCa detection based on the 2 possible MRI outcomes: men undergoing standard

12 core TRUS biopsy (detection protocol MRI negative) versus men undergoing MRI targeted biopsy (detection protocol MRI positive for lesions). This will be analysed for statistical difference using the chi-square test. Each MRI quantitative parameter will be evaluated on a per lesion basis as a predictor of high grade PCa using ROC logistic regression and will be reported as AUC with 95% confidence intervals (CI). The Youden's Index and 90% fixed sensitivity thresholds of each quanititative parameter will be reported. Combinations of MRI quantitative and clinical parameters will be combined into multinomial logistic regression models for which AUC with 95% CI will be reported. The AUC of the multi-parametric models will be compared iteratively for statistical differences using the likelihood ratio test.

13.0 Regulatory Requirements

13.1 Informed Consent

Informed consent will be obtained by the clinical research coordinator, Ruben Sauer Calvo, in the Urology ambulatory clinics at UI Health. He is an experienced coordinator currently in this role for several other PCa studies at UI Health. He is a native Spanish speaker and will therefore be able to enroll Spanish speaking subjects using the translated consent form. Completed consent documents will be stored in a locked file cabinet in the coordinator's office in the Urology administrative office in Clinical Sciences North Suite 515.

13.2 Subject Confidentiality

As this research is not funded by the NIH, a certificate of confidentiality is not required. That said, every effort will be taken to protect the confidentiality of the research subjects. The study investigators, as well as the other key personnel including graduate students performing the image post processing will have access to the data. The MRI and clinical data will maintain identifiers which is necessary to allow for MRI/TRUS fusion biopsy. After the biopsy result is reported, approximately 1 week after the biopsy procedure, the MRI DICOM data and REDCap clinical data will be de-identified. No data analysis will take place until the accrual target is met and the data has all been de-identified.

13.3 Unanticipated Problems

Any unanticipated problems or protocol deviations will be reported to the IRB and the Cancer Protocol Review Committee within 5 business days using OVCR Form 0257. The form will be prepared by the coordinator or co-investigator that discovered the problem and will be reviewed and approved by the PI.

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APPENDICES

Appendix 1: International Prostate Symptom Score questionnaire

International Prostate Symptom Score (I-PSS)

Patient Name: _____ **Date of birth:** _____ **Date completed** _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

Appendix 2: Sexual Health Inventory for Men questionnaire

1. How do you rate your confidence that you could get and keep an erection?		Very Low	Low	Moderate	High	Very High
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No Sexual Activity	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did Not Attempt Intercourse	Extremely Difficult	Very Difficult	Difficult	Slightly Difficult	Not Difficult
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5

Appendix 3: Detection protocol MRI imaging acquisition parameters

Hardware:
3 Tesla GE Discovery MR750 (GE Healthcare, Chicago, IL)
Coil: 32-channel pelvic/cardiac phased-array

Acquisition parameters:

Imaging plane: axial
Slice thickness: 3mm
Number of slices: 10-15 (depending on prostate size)
Field of view: 15cm x 15cm using FOCUS
Matrix size: 256x192

DWI
b values: 0, 50, 100, 400, 700, 1000, 1300, 1600, 2000, 3000, 4000 s/mm2
Averages:
- b 0-1000: 1
- b 1300-2000: 2
- b 3000: 4
- b 4000: 8

Directions: 3 (x,y,z)
TR/TE = 1538 ms/69.8 ms,
Acquisition time ~3.5 minutes

T2 Mapping
TR: 1900 ms
TE: 14, 28, 41, 55, 69, 83, 97, 110 ms
Acquisition time ~ 5.6 minutes

CEST
Frequency selective saturation pulse at various amplitudes B1 (100 Hz), durations (2 s)
Saturation frequencies: −5 to 5 ppm with 0.25 ppm step size, ±20, and ±100 ppm
Acquisition time ~ 18 min

Appendix 4: Data flow