MELVIN AND BREN SIMON
CANCER CENTER
INDIANA UNIVERSITY

The Role of ^{68}Ga-PSMA-11 PET in MRI Fusion Biopsy and Surgery Guidance in Prostate Cancer

INDIANA UNIVERSITY PROTOCOL

IUSCC-0658/ IRB # 1805494415/ NCT03429244

Principal Investigator:
Clinton D. Bahler, MD, MS
Assistant Professor of Urology
Indiana University School of Medicine
535 Barnhill Dr., Ste 150
Indianapolis, IN 46202
Cell: 317.313.5405
Fax: 317.944.0174
cdbahler@iupui.edu

Co-investigators:
Michael Koch, MD
Professor of Urology
mkoch2@IUHealth.org

Mark Tann, MD
Professor of Radiology
matann@iupui.edu

Mark Green, PhD
Professor of Radiology
magreen@iu.edu

Gary Hutchins, PhD
Professor of Radiology, Vice Chair of Research
gdhutchi@iupui.edu

Liang Cheng, MD
Virgil H. Moon Professor of Pathology, Department of Pathology and Laboratory Medicine
lcheng@iu.edu; liang_cheng@yahoo.com

Temel Tirkes, MD
Associate Professor of Radiology and Urology, Director of Genitourinary Radiology
atirkes@iupui.edu

Jason Parker, PhD
Associate Professor, Director of Diagnostic Physics, Dept. of Radiology
parkerjg@iu.edu

Yang Zong, PhD
Assistant Professor of Biostatistics
zangy@iu.edu

Yan Tong, PhD, MS
Biostatistician, Department of Biostatistics
tongy@iu.edu

Justin Sims, MD
Assistant Professor of Clinical Radiology
simsjb@iupui.edu

Support: Indiana University Departments of Urology, Radiology, and Pathology

IND#: 141706

Date of Protocol: January 30, 2020

INVESTIGATOR'S AGREEMENT

By signing below, I confirm that I have read this protocol and agree:

- To assume responsibility for the proper conduct of this study at this site
- To conduct the study according to the procedures described in this protocol and any future amendments
- Not to implement any deviation from, or changes to, the protocol without written approval from the Institutional Review Board (IRB), except where necessary to eliminate immediate hazard to the subject(s)
- That I am aware of all updates and will comply with all applicable regulations and guidelines

Principal investigator's signature | Date

Clinton D. Bahler, MD, MS

Principal investigator's name (print)

Assistant Professor of Urology,
Indiana University School of Medicine

Principal investigator's title (print)

PROTOCOL SYNOPSIS

Primary Objectives:	Define the accuracy of *^{68}Ga-PSMA-11* PET-CT for detecting the location and size of clinically significant prostate cancer lesions in low and intermediate risk disease.
Secondary Objectives:	Evaluate how knowledge of the PSMA-PET might inform treatment planning.
Exploratory Objectives:	Generate pilot data to be validated in larger studies
Study Design:	Prospective, early phase clinical trial, single arm
Test Factor/Exposure:	Intravenous injection of ^{68}Ga-PSMA-11 and detection with PET-CT scanner
Duration of Treatment:	Patients will undergo injection of ^{68}Ga-PSMA-11 PET-CT and pre-treatment MRI scan and followed until biopsy and/or surgical resection.
Enrollment:	Subject accrual is planned for 24 months
Inclusion Criteria:	**1.** ≥ 18 years of age **2.** Must provide written informed consent 3. Presence of low or intermediate risk prostate cancer or at risk of having intermediate risk cancer a. Intermediate risk prostate cancer: i. Grade group **2** = 3 + 4, or ii. Grade group **3** = 4 + 3 b. At Risk of intermediate risk prostate cancer: i. 4K score ≥ 20%, or ii. Select MDx ≥ 20%, or iii. PSA Density ≥ 0.15 iv. Grade group 1= 3+3 **4.** Scheduled for MRI or has recently completed SOC MRI (within 6 months) for further biopsy, surgical removal or focal therapy. **5.** Willing and able to lie still for approximately 50 minutes in an enclosed space for the CT

Exclusion Criteria:	**1.** Participation in another investigational trial involving research exposure to ionizing radiation concurrently or within 30 days. **2.** Does not meet safety criteria for MRI scan (e.g. metal implant that is not allowed). **3.** Significant acute or chronic medical, neurologic, or illness in the subject that, in the judgment of the Principal Investigator, could compromise subject safety, limit the ability to complete the study, and/or compromise the objectives of the study.
Number of Subjects:	36 patients
Number of Sites:	Indiana University Simon Cancer Center, Indiana University Health Hospital, IU Health North, IU Health North medical office building, IU Health Methodist Hospital
Primary Outcome:	Sextant based analyses using prostatectomy whole-mount analysis or biopsy as Gold Standard: **1)** Sensitivity, specificity, Receiver operator curve (ROC) of mpMRI for each Gleason pattern (3, 4, 5) **2)** Sensitivity, specificity, ROC of PSMA PET-CT for each Gleason pattern (3, 4, 5)
Secondary Outcomes:	**1.** Lesion based analysis of accuracy **2.** For 3+4: Sensitivity and specificity of mpMRI based on Gleason %pattern 4 **3.** For 3+4: Sensitivity and specificity of PET-CT based on Gleason %pattern 4 **4.** Sensitivity and specificity for extra-capsular extension (mpMRI vs PET-CT) **5.** Sensitivity and specificity for seminal vesicle invasion (mpMRI vs PET-CT) **6.** Impact of PSMA PET-CT on treatment plan for surgery: **a.** Additional lesions found, additional sextants involved, extra-capsular extension detected, seminal vesicle invasion detected, lymph node invasion detected. **7.** Impact of PSMA PET-CT on treatment plan for biopsy: **a.** Additional lesions found, additional sextants involved

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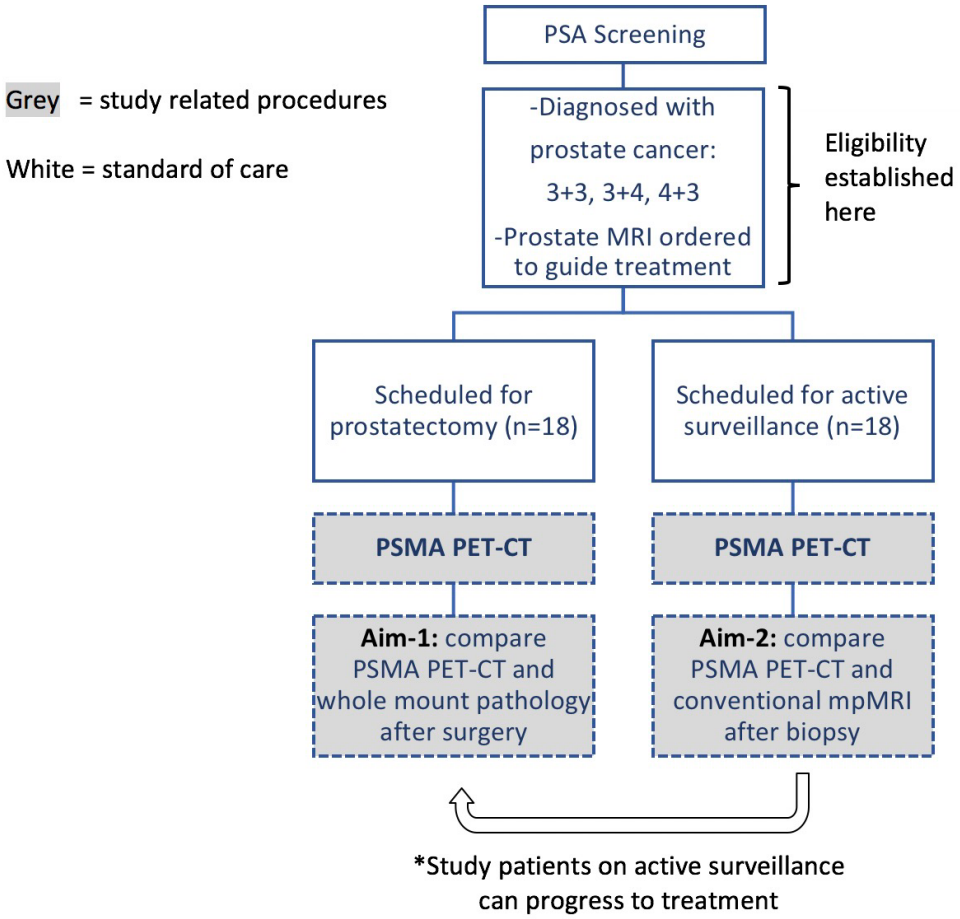
2 SCHEMA



While the total N=36 for this trial, the number of subjects enrolled on each arm (prostatectomy vs. surveillance) is not required to be divided evenly.

3 BACKGROUND

3.1 Background & Preliminary Work

Up to 60% of men in the U.S. unwittingly have Gleason 6 (pure pattern 3: 3+3) prostate cancer by their 80s on autopsy, which argues for active surveillance of this tumor (Zlotta, et al. 2013). Long-term active surveillance cohorts demonstrate low (<5%) 15-year metastasis rates (Musunuru, et al. 2017). However, <50% choose active surveillance when diagnosed on biopsy with Gleason 6 prostate cancer (Womble, et al. 2015). This is due to multiple factors: *(1)* prostate cancer is multi-focal in >80%; *(2)* prostate cancer commonly has mixed grade lesions; and *(3)* conventional imaging modalities (US, MRI) miss significant cancer. There is also disagreement on what follow-up is needed during active surveillance. Molecular imaging agents would bring assurance and peace of mind to hundreds of thousands of men, if they are capable of selectively detecting clinically significant prostate cancer (Gleason patterns 4 and 5). *We expect to determine whether the PSMA-targeted PET agent, ^{68}Ga-PSMA-11, reliably detects significant prostate cancer and what minimum percentage Gleason pattern 4 is required for detection by comparison of PET/MR to whole mount analysis.*

Multiparametric 3-T MRI has shown the ability to locate prostate cancer lesions that are higher grade and increased size. For example, MRI-targeted biopsy increases the detection of clinically significant prostate cancer using fewer cores than template biopsy (Pokorny, et al. 2017, Wysock, et al. 2014), while reducing detection of insignificant Gleason 6. However, recent studies mapping MRI lesions to final whole-mount pathology show limitations. For example, a recent study showed only 80% of index (largest) tumors were seen by MRI and even fewer clinically significant non-index lesions (Le, et al. 2014). Another recent study showed MRI missed a clinically significant lesion in 26% of patients using whole-mount analysis (Borofsky, et al. 2017). Fittingly, Borofsky titled their paper, “What are we missing? False negative cancers at Multiparametric MR imaging of the prostate.” MRI interpretation has also been shown to vary substantially across radiologists, which persisted after correcting for radiologist practice volume (Sonn, et al. 2017). Therefore, the majority of urologists still take ultrasound-based template biopsies at the time of MRI guided biopsy (MRI-ultrasound fusion).

The status quo for pathologic assessment is Gleason Grading, which combines the two dominant Gleason patterns and sometimes lists a tertiary pattern. Gleason grading might be sufficient when treating the whole gland: surgery, radiation, cryotherapy, etc. However, conventional Gleason grading gives insufficient detail when considering active surveillance or focal therapy because the Gleason grade combines all the lesions into a

single score and is not lesion specific. For example, a prostate with three cancer lesions might be reported as Gleason 3 + 4 (90%/10%) on final pathology while the individual lesions are: (1) 3 + 4 + 5 (30%/60%/10%), (2) 3 + 4 (90%/10%), (3) 3 + 3.

Lesion (1) is clinically significant while lesion (3) is not. Lesion (2) is of debatable significance and requires further study. Certainly, the above 3-lesion cancer is different than a single lesion 3+4 cancer despite the same grading. A detailed lesion-specific analysis is required to accurately assess new imaging agents and ultimately to test the paradigm of focal organ-sparing therapy. *The proposed research is innovative, in our opinion, because we perform lesion and intra-lesion specific analyses while testing ^{68}Ga-PSMA-11 with PET-CT. This requires researchers with experience in lesion specific prostate cancer pathology, mpMRI and PET imaging, and focal therapy.* Finally, we feel the study design is innovative because it incorporates PSMA PET-CT imaging into the standard clinical workflow. This enables pilot data using the current standard-of-care as the control; the goal is to facilitate translation of molecular imaging more quickly to clinical care.

Whole mount pathologic analysis of PET imaging in prostate cancer has been reported primarily out of Germany. No prospective trials were found combining PSMA, PET-CT, and whole-mount analysis. Furthermore, studies have focused on high-risk disease rather than low/intermediate risk. For example, a retrospective trial out of Germany (Eiber, et al. 2016) combined ^{68}Ga-PSMA-11 and PET-CT and found improvement in Receiver operator curve (ROC) for PET-CT over MRI (0.73 to 0.88, $p<0.001$). Of the 53 patients, 53% were high risk. The authors concluded prospective studies were warranted for biopsy guidance. Recently, ^{18}F-FACBC (Fluciclovine) was used with PET-CT and compared to MRI for biopsy guidance in a prospective clinical trial (Jambor, et al. 2017). ^{18}F-FACBC had high sensitivity (87%), but low specificity (56%) resulting in a low ROC (0.72). ^{18}F-FACBC is not specific for prostate cancer resulting in replacement with PSMA-based tracers in clinical practice.

The Urology-Radiology-Pathology team at Indiana University has been employing fusion biopsy since 2013 and has performed more than 600 during this time. A recent abstract presented at the annual meeting of the American Urologic Association in 2017 demonstrated 22% of index lesions (largest tumor) were missed by MRI (Bahler, *et al.* 2017), and MRI undersized the index cancer lesion when compared to final pathology (2.2cm *vs*. 1.9cm, $p = 0.03$). A tracer that is both more sensitive and specific is desired leading urologists to continue ultrasound template biopsies with MRI targeted biopsy.

The 68Ga-PSMA-11 (HBED-CC) radiopharmaceutical (Eder, et al. 2014; Eiber, et al. 2015, Afshar-Oromieh, et al. 2015) is structurally based on a class of urea-derived inhibitors of PSMA (Pillai, et al. 2016). The targeting peptide has been modified at its N-terminus to incorporate the HBED-CC chelating agent with an exceptionally high binding affinity (~1039) for the Ga3+ ion (Figure 1 and Table 1). Methods for on-demand

production of 68Ga-PSMA-11 are already established (IND # 131,806), based on our research use of this radiopharmaceutical in imaging patients with recurrent prostate cancer.

Table 1. PSMA Affinities of the PSMA-11 Agent Before, and After, Ga^{3+} Chelation

PSMA Ligand	IC50 (nM)
PSMA-11 HBED-CC	5.7 ± 0.5
Ga-PSMA-11 HBED-CC	6.1 ± 0.8

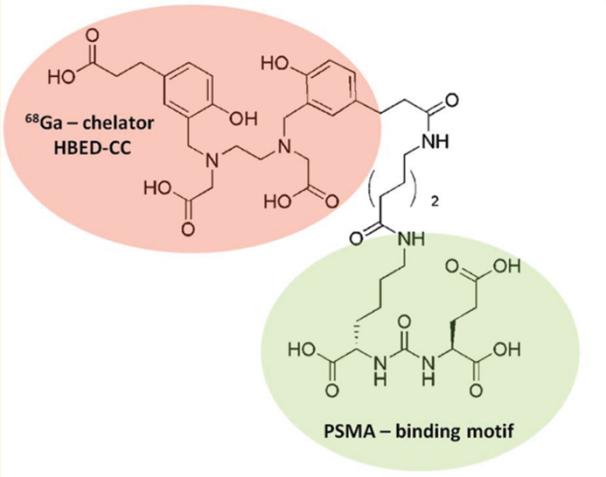


Figure 1. Structure of the PSMA-11 (HBED-CC) conjugate employed in preparation of the 68Ga-PSMA-11 radiopharmaceutical. The PSMA-11 has a molecular weight of 947 g/mol. The radiopharmaceutical synthesis protocol for on-demand production of 68Ga-PSMA-11 employs 10-µg of the PSMA-11 conjugate per batch.

The project investigators have significant experience in PET with ^{68}Ga-PSMA-11. Our initial human experience with ^{68}Ga-PSMA-11 PET was in performing patient imaging for dosimetry assessment, studying ten prostate cancer patients with biochemical recurrence who had been previously clinically imaged with ^{11}C-acetate under an Expanded Access IND (Green, *et al.* 2017). The expected utility of ^{68}Ga-PSMA-11 PET was apparent even in that limited series, with ^{68}Ga detection of sites of metastasis that were not apparent in ^{11}C-acetate imaging (Figure 2). We have subsequently dropped ^{11}C-acetate imaging in prostate cancer patients with biochemical recurrence in favor of ^{68}Ga-PSMA-11 PET, and have performed clinical imaging on over 100 patients under Expanded Access IND 131,806. When evaluating the first 70 ^{68}Ga-PSMA-11 PET scans, we found improved detection ($p<0.05$) over ^{11}C-acetate PET at PSA-values >2 (abstract accepted to America Urologic Association 2018 national meeting).

We have also recently completed a prospective clinical trial evaluating ^{68}Ga-PSMA-11 whole-body PET-CT in 10 patients with biopsy-proven high-risk prostate cancer. The PET-CT was obtained prior to scheduled surgical resection for correlation of imaging

findings with whole-mount pathology. These subjects also received a second ^{68}Ga-PSMA-11 dose intraoperatively to allow *in vitro* high-resolution PET assessment of tracer binding within the resected tissue. All staging ^{68}Ga-PSMA-11 PET/CT scans showed suspicious prostate lesions with median (IQR) of 10.6 SUV (8-14); benign prostate had a median (IQR) of 3.8 SUV (3-5). Four staging ^{68}Ga-PSMA-11 PET-CT scans showed seminal vesicle invasion, and two showed nodal involvement; all were confirmed on final pathology.

Indiana University performed >1,000 robotic prostatectomies over the past four years and >600 MRI-fusion biopsies during the same span. This clinical volume will provide adequate numbers for trial accrual (n=36). There are currently no competing trials for our study population. The investigators (Koch, Bahler) and clinical trial coordinator (Beasley) will identify patients in the Indiana University urology clinic and inclusion/exclusion criteria will be assessed prior to informed consent

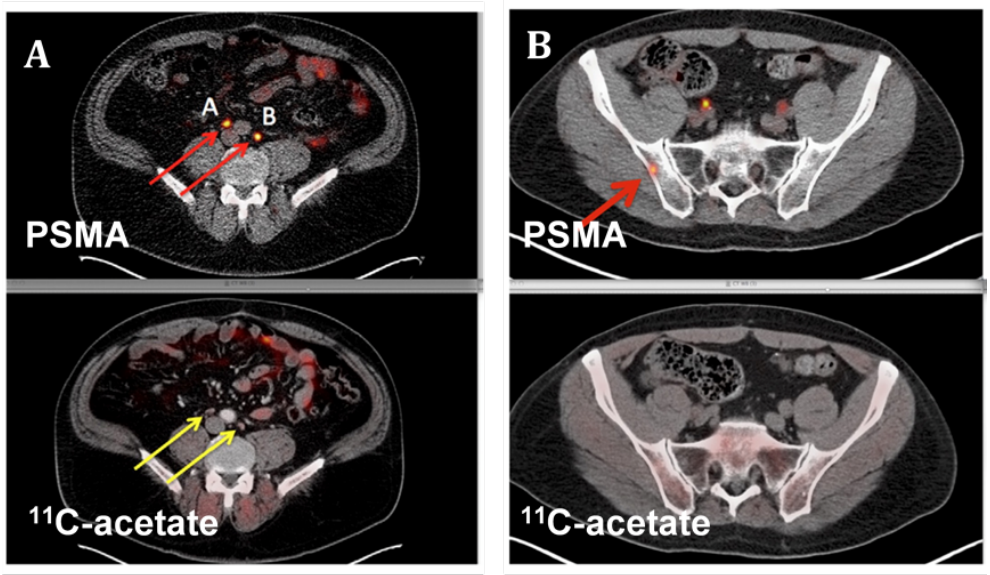


Figure 2: ^{68}Ga-PSMA-11 PET/CT demonstrated avid lymph nodes (A) and bony metastasis (B) not seen with the ^{11}C-acetate PET/CT. The PSA was 1.7 and 11.1, respectively. During the recent clinical trial, a PET-CT scanner was installed at Indiana University allowing us to compare PET-CT to PET-MRI (Figure 3). MRI has far superior soft-tissue contrast compared to the CT, which cannot identify the lesions within the prostate gland by itself, and cannot qualify as a “one-stop-shop” examination. Integrated utilization of PSMA PET and MRI has paramount implications for the improved diagnostic pathway of the prostate cancer. In addition to the better diagnostic potential, there is also a potential for significantly reduced cost of the total diagnostic workup of the prostate cancer using a single examination (i.e., PSMA PET-CT) compared to having a mpMRI, PSMA PET study, and a bone scan. We hypothesize the improved

soft tissue resolution will improve biopsy accuracy and surgical planning when compared to PET-CT.

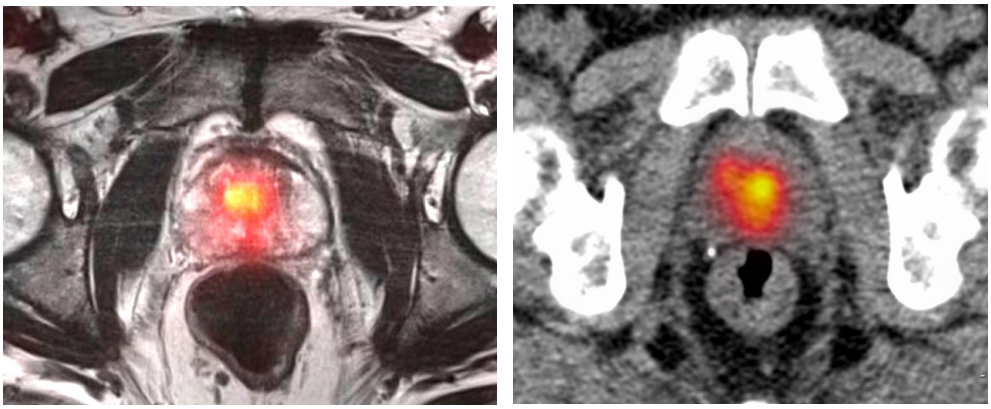


Figure 3: The PET-CT (A) shows much more soft tissue detail within the prostate when compared to the PET-CT (B) on the same patient.

3.2 Rationale

Our long-term goal is to improve cancer outcomes and quality of life for prostate cancer patients by bringing novel imaging agents and systems to the diagnosis and treatment of prostate cancer. The overall objective of this Early Phase Clinical Trial is to begin defining the accuracy of ^{68}*Ga-PSMA-11* for detecting the location and size of clinically significant prostate cancer lesions in low and intermediate risk disease.

The proposed studies will be performed with a state-of-the-art Vision PET-CT system which offers unprecedented spatial resolution and counting sensitivity for a clinical PET system that make it ideal for supporting biopsy and focal therapy decisions. We propose detailed intra-lesion whole-mount pathologic analysis as the gold standard for critically assessing PSMA PET accuracy in patients undergoing surgery, and blinded PSMA PET-CT comparison with standard multi-parametric MRI (mpMRI) for patients having biopsy on active surveillance. This intensive testing of the accuracy and value of PSMA-based tracers requires our unique collaboration of surgeons, radiologists, pathologists, and imaging scientists with decades of experience and innovation.

4 STUDY OBJECTIVES

4.1 Primary

Define the accuracy of ^{68}*Ga-PSMA-11* PET-CT for detecting the location and size of clinically significant prostate cancer lesions in low and intermediate risk disease.

4.2 Secondary

Evaluate how knowledge of the PSMA-PET can inform treatment planning.

4.3 Exploratory

Generate pilot data for future larger clinical trials

5 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

To be considered eligible to participate in this study, a patient must meet all the inclusion criteria listed below:

1. ≥ 18 years of age
2. Must provide written informed consent

3. Presence of low or intermediate risk prostate cancer or at risk of having intermediate risk cancer
    a. Intermediate risk prostate cancer:
        i. Grade group **2** = 3 + 4, or
        ii. Grade group **3** = 4 + 3
    b. At Risk of intermediate risk prostate cancer:
        i. 4K score ≥ 20%, or
        ii. Select MDx ≥ 20%, or
        iii. PSA Density ≥ 0.15
        iv. Grade group 1= 3+3

    Note: Where multiple cancer lesions are present on biopsy, it is allowable to have Gleason 8 or 9 cancer lesions if they are in addition to the intermediate risk cancer as described above.

4. Scheduled for MRI or has recently completed SOC MRI (within 6 months) for further biopsy, surgical removal, or focal therapy.
5. Willing and able to lie still for approximately 50 minutes in an enclosed space for the CT.

5.2 Exclusion Criteria

1. Participation in another investigational trial involving research exposure to ionizing radiation concurrently or within 30 days.
2. Does not meet safety criteria for MRI scan (e.g. metal implant that is not allowed).
3. Significant acute or chronic medical, neurologic, or psychiatric illness in the subject that, in the judgment of the Principal Investigator, could compromise subject safety, limit the subject's ability to complete the study, and/or compromise the objectives of the study.

6 PATIENT REGISTRATION

Patient enrollment will take place over 24 months at a single institution – Indiana University Simon Cancer Center (IUSCC) encompassing Indiana University Hospital (IUH), IU Health North, IU Health North medical office building, IU Health Methodist Hospital. Potential patients will be identified in the Urology clinic, or by physician referrals, mostly likely but not exclusively during pre-operative consultations for biopsy or surgical removal of prostate cancer. All study procedures will take place at IUSCC/IUH/IU-Health Methodist Hospital, with the research imaging performed at the IU Health Goodman Hall outpatient facility. All patients will be registered with the Indiana University (IU) Department of Urology. Regulatory files will be maintained by the Department of Urology. Applicable regulatory documents must be completed and on file

prior to registration of any patients. Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the Eligibility Criteria. Individual patient registration will be done in the REDCap database. The original signed Institutional Review Board (IRB) approved Informed Consent Document and completed eligibility checklist will be stored in the following location: Indiana University Department of Urology, 535 N. Barnhill Dr., Ste 150, Indianapolis, IN, 46202.

7 STUDY PROCEDURES

7.1 Summary

This patient population will have low (**1** = Gleason 3 + 3) or intermediate risk (**2** = 3 + 4; **3** = 4 + 3) prostate cancer, or be at risk of having intermediate disease as evidenced by a 4K score ≥20%, or Select MDx ≥ 20%, or PSA Density ≥ 0.15. Patients will be scheduled for a MRI as part of routine care for either surgical planning or for further biopsy. Following the informed consent process, patients who enroll in the study will receive a ^{68}Ga-PSMA-11 PET study along with their standard of care (SOC) MRI on an PET-CT. If the Vision PET-CT is not available, a standard PET-CT and SOC MRI can be done with co-registration of PET and MRI done using software to generate the equivalent of the PET-CT images. Patients receiving SOC MRI guided biopsy will have the additional PET data factored into their guided biopsy plan. The sensitivity and specificity for lesion characterization will be evaluated, along with the ability of the tracer to inform the treatment planning. Patients receiving surgical removal of the prostate will have a slice-by-slice whole mount analysis to assess the sensitivity and specificity the PSMA PET.

7.2 Study Calendar

	Screening/ Baseline (-180 days)	Biopsy if indicated	Imaging	Surgery if indicated
REQUIRED ASSESSMENTS				
Informed Consent	X			
Inclusion/Exclusion	X			
Medical History[1]	X			
PSMA dose and PET scan			X[2]	
SOC MRI				
SOC MRI-guided biopsy		X		
SOC PET-guided biopsy		X		
SOC Focal Therapy				X
Pathologic assessment of biopsy		X		
SOC prostatectomy				X
Pathologic assessment of whole mount				X

Footnotes:

1. Medical history may be obtained via medical records, as necessary.
2. A second ^{68}Ga-PSMA-11 PET, approximately 6-12 months following initial scan may be requested, if: (1) the subject undergoes HIFU treatment and/or (2) during follow-up, is rescheduled for MRI-fusion biopsy as standard of care.

7.3 Assessments by Visit

7.3.1 Baseline/Screening (within 6 months of scan(s)/biopsy):

- Informed consent: investigators or their designees will discuss with subjects the nature of the study, its requirements, risks, and restrictions to obtain informed consent for participation in the study. Subjects should have sufficient time to review the study information and consent form and to ask any questions necessary to make an informed decision regarding their participation in the study. Written informed consent is to be obtained before any other study-specific procedure.

- Eligibility criteria: make sure patient meets study eligibility criteria.

- Demographics: track sex, race, ethnicity, date of birth, address, etc.

- Medical history: includes past medical history, past surgical history, allergies, any ongoing medical conditions, and including medications noted in patients record at time of screening

7.3.2 Imaging

- Eligibility criteria: ensure subject continues to meet study eligibility (if longer than 60 days since screening)
- Medical history: capture additional medical history since screening (if longer than 60 days since screening)
- Concomitant medications: record medications taken since screening through day of surgery (if longer than 60 days since screening)
- There will be a ≥4week wait period between prior biopsy and protocol related MR imaging to allow for resolution of hematomas.

- ^{68}Ga-PSMA-11 PET-CT and mpMRI:

- Patient receives a ~3-5 mCi dose of ^{68}Ga-PSMA-11. (A physician-sponsored IND has been successfully obtained)
- Patient will undergo research Vision PET-CT and SOC MRI at Goodman Hall (or similar facility) which is anticipated to last approximately 60 minutes. Per our institutional standard of care, patients will receive intravenous iodinated contrast with the PET-CT unless medically contraindicated.
- Imaging Protocol for ^{68}Ga-PSMA-11 PET Data Acquisition (approximate times):

Time (minutes)	Activity
- 60	Patient arrives, and completes consent forms, while radiopharmaceutical synthesis and quality control procedures are completed.
0	Administer ^{68}Ga-PSMA-11, 3-5 mCi (outside the camera).
5-50	Start standard-of-care pelvic MR acquisition with simultaneous collection of ^{68}Ga-PSMA-11 PET.
50-55	Patient can leave camera and depart.

- The PET read will be done by a board certified nuclear medicine specialist (e.g. Mark Tann, MD or similar) and the MRI read will be done by a board certified MR radiologist (e.g. Temel Tirkes, MD or similar). Suspicious lesions will be marked in a blinded fashion.
- AE assessment: AEs will be assessed at the time of ^{68}Ga-PSMA-11 administration and also at the appointment for biopsy (if done) any event not expected is collected including but not limited to: rash and shortness of breath.
- Safety monitoring following radiopharmaceutical administration will consist of visual and verbal monitoring of the patent after injection, and during and at the conclusion of the PET/CT procedure, with any apparent patient abnormalities, reactions or reported effects noted in the study records.
- The nuclear medicine technologists administering the radiopharmaceutical are responsible for immediately reporting any adverse or unexpected events to the principal investigator or clinical

designee, who will report the occurrence of any adverse events to the IRB.

- As in most clinical nuclear medicine procedures, these radiopharmaceuticals are administered at a sub-pharmacologic doses. Adverse events are exceedingly unlikely, as ^{68}Ga-HBED-CC has been clinically employed, extensively and without reported incident, in clinical patient diagnostic imaging studies in prostate cancer patients in Germany and other European countries, as well as in over 100 patients locally.

- If there is a discrepancy between the PSMA and conventional MRI scan, the investigators will discuss the treatment plan with the patient at the investigator's discretion.

- If the patient does not undergo a prostatectomy, no further study procedures will be performed.

- If the Vision PET-CT is not available, a standard PET-CT and mpMRI may be done with software registration of PET and MR images.

- A patient may have a second ^{68}Ga-PSMA-11 PET, approximately 6-12 months following initial scan, if: (1) the patient undergoes HIFU treatment and/or (2) during follow-up, is rescheduled for MRI-fusion biopsy as standard of care.

7.3.3 PET, MRI Biopsy:

- Patients proceeding to surgery following PSMA PET and MRI may forgo biopsy.

- Patients not proceeding to surgery will undergo a SOC MRI-fusion biopsy based on the pre-biopsy scan detailed in 7.3.2. PET findings will be integrated into the planning of the fusion biopsy. See appendix C for details of the fusion biopsy.

- AE assessment: AEs will be assessed at the time of ^{68}Ga-PSMA-11 administration and also at the appointment for biopsy (if done) any event not expected is collected including but not limited to: rash and shortness of breath.

- A sextant-based analysis will be performed. See appendix D for details of sextant analysis.

- A secondary "per lesion" analysis will also be performed.

- How the knowledge of the PSMA-PET informs treatment will be tracked. Examples of informing the decision include PSMA-PET detected additional intraprostatic cancer lesions diagnosed.

7.3.4 Surgery and Pathology

- The standard of care surgical procedure is performed as indicated by the cancer.
- Pathologic assessment: whole mount sections of prostate tissue and routine sections of lymph nodes if applicable will be fixed and analyzed by licensed pathologist per routine care. This typically happens within 2 weeks of prostatectomy.
- Additional study-related pathologic assessment: intraprostatic lesion-based assessment will be done to document the % Gleason pattern 3, 4, and 5 within each lesion.
- A sextant-based analysis will be performed. See appendix D for details of sextant analysis.
- A secondary “per lesion” analysis will also be performed.
- How the knowledge of the PSMA-PET informs treatment will be tracked. Examples of informing the decision include the number and location of ^{68}Ga-PSMA-PET detected: additional intraprostatic cancer lesions diagnosed, extra-prostatic extension, seminal vesicle invasion, and lymph node invasion.
- Genomic studies (e.g. Decipher, mRNA sequencing, or similar) may be done as standard of care for medical management following biopsy or surgery or may be done for determining association of mRNA (e.g. FOLH1 or others) and imaging characteristics.

8 STUDY WITHDRAWAL/DISCONTINUATION

Subjects must be discontinued from the study for the following reasons:

- Withdrawal of consent
- Investigator deems withdrawal necessary at any time if it is determined that it is not in the subjects best interest to continue, or if the subject is found to be noncompliant with study procedures.

If subject discontinues after administration of study drug, he or she will be encouraged to continue on study for safety procedures per protocol. Reason(s) for discontinuing must be clearly documented in the appropriate source documents.

9 STATISTICAL CONSIDERATIONS

9.1 Study Design

Prospective, phase 2 clinical trial, single arm

9.2 Study Population

The enrolled population comprises all patients who meet the eligibility criteria and are registered onto the study.

9.3 Sample Size

Table 1: Sample size calculation:

	sensitivity= 0.80	sensitivity= 0.85	sensitivity= 0.90	sensitivity= 0.95
Error allowed (d)= 7.5%	46	37	27	14
Error allowed (d)= 10%	27	21	15	8

Our sample size is based on the key primary endpoint of sensitivity to detect clinically significant (Gleason >6 and >5mm) cancer overall. In the Table above we summarized the sample size required to achieve a certain degree of accuracy for different sensitivity levels. All the calculations are based on the normal approximation of the binomial distribution. For this pilot, we will also assume the samples within each patient are independent statistically. Each patient has six samples for diagnostic testing (sextants) and the prevalence of cancer per sextant is estimated to be 40% (Eiber et al., 2016). The rows (d) present the marginal maximal error under 95% confidence interval and the columns represent the sensitivity rate. The numbers in Table 1 represent the required number of patients needed for each different combination of marginal error (d) and sensitivity rate. In other words, for a sensitivity of 90% and a marginal error of 7.5%, we

are 95% sure that the sensitivity lies between 82.5% and 97.5% if we enroll 27 patients. Based on Table 1, the maximal sample size is 46 assuming the sensitivity is 80%. Therefore, we decided 36 patients was adequate to ensure that the proposed trial can achieve certain accuracy of the sensitivity across the majority the scenarios considered in Table 1.

9.4 Study Endpoints

9.4.1 Primary

Sextant based analyses using prostatectomy whole-mount analysis or biopsy as Gold Standard (Appendix D):

- Sensitivity, specificity, Receiver operator curve (ROC) of mpMRI overall and for each Gleason pattern (3, 4, 5)
- Sensitivity, specificity, ROC of PSMA PET-CT overall and for each Gleason pattern (3, 4, 5)

9.4.2 Secondary

- Lesion based analysis of accuracy
- For 3+4: Sensitivity and specificity of mpMRI based on Gleason %pattern 4
- For 3+4: Sensitivity and specificity of PET-CT based on Gleason %pattern 4
- Sensitivity and specificity for extra-capsular extension (mpMRI vs PET-CT)
- Sensitivity and specificity for seminal vesicle invasion (mpMRI vs PET-CT)
- Impact of PSMA PET-CT on treatment plan for surgery:
    - Additional lesions found, Additional sextants involved, extra-capsular extension detected, seminal vesicle invasion detected, lymph node invasion detected.
- Impact of PSMA PET-CT on treatment plan for biopsy:
    - Additional lesions found, Additional sextants involved

9.5 Participant Characteristics

Demographic characteristics will be summarized using descriptive statistics.

9.6 Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary and will be summarized in tabular format.

9.7 Analysis of Primary Objective

We will use the generalized estimation equation (GEE) to fit the data and estimate the sensitivity and specificity. We will use the receiver operating characteristic (ROC) curve to represent the values of sensitivity and specificity at different thresholds (PET= SUV, mpMRI=suspicion scores). According to the ROC curve, we will determine the optimal threshold with a minimal sensitivity of 50% by maximizing the Youden index. We will use the McNemar test to compare the sensitivity and specificity values between PET and MRI although data from this pilot study is considered hypothesis generating only due to the small sample size. In addition, we will use the bootstrapping method to detect the significant difference of the area under curve (AUC) with different ROC curves.

9.8 Analysis of Secondary Objectives

The proportion of patients who had cancer detected by both the standard of care imaging (MRI) and the ^{68}Ga-PSMA-11 PET imaging will be calculated, along with exact 95% confidence intervals. A similar approach will be used for other secondary outcomes in Section 9.4.2 to compare the cancer detection of the mpMRI and ^{68}Ga-PSMA-11 detection method to the surgical observations and the clinical tissue histopathology findings.

10 DATA FORMS AND SUBMISSION SCHEDULE

This study will utilize the secure, web-based, Research Electronic Data Capture (REDCap) system for data input. REDCap was developed by Vanderbilt University and is provided by Indiana University through their community license. REDCap is managed by the Indiana University Department of Biostatistics and secured by University Information Technology Services Advanced IT Core. Access to the password protected database will be limited to the investigators of this study, and any data that is distributed will be either de-identified or authorized by written permission from the subject.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines.

11 DATA AND SAFETY MONITORING PLAN

This study will be conducted in accordance with the IU Simon Cancer Center Institutional DSMP for High Risk Trials.

Investigators will conduct continuous review of data and subject safety. Weekly review meetings for high risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). Weekly meeting summaries should include review of data and subject safety by including for each dose level: the number of subjects, significant toxicities as described in the protocol, dose adjustments and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

Data and Safety Monitoring Committee

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study semi-annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the principal investigator will notify the DSMC Chair immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

11.1 IND Annual Reports

For trials with an IND held locally by the IU principal investigator or university, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed by the DSMC at the time of FDA submission.

11.2 Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing/monitoring. Reports will be forwarded to the DSMC for review.

11.3 Data Management/OnCore Reporting Requirements

The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than one week from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

11.4 OnCore Safety Reporting

In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information.

Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

11.5 Study Accrual Oversight

Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year while the PPC coordinator reviews accrual quarterly.

11.6 Protocol Deviation Reporting

Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

12 ADVERSE EVENTS

12.1 Definitions of Adverse Events

12.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0 (Appendix A).

12.1.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death or ANY death occurring within 28 days of last dose of study drug (even if it is not felt to be drug related)
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Hospitalizations that are not considered SAEs are:

  - Hospitalization planned prior to first administration of study drug
  - Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

12.1.3 Unexpected Adverse Event

An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's brochure or package insert.

12.1.4 Determining Attribution to the Investigational Agent(s)

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly **NO**T related
	Unlikely	The AE is **doubtfully related**
Related to investigational agent/intervention	Possible	The AE **may be related**
	Probable	The AE **is likely related**
	Definite	The AE **is clearly related**

12.2 Adverse Event Reporting Requirements:

Adverse events will be recorded for the first study drug administration and also for the prostate biopsy (if indicated) regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

12.2.1 Reporting to the IRB:

Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they:

- unexpected;
- related or possibly related to participation in the research; and
- suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the IU IRB. However, it should be reported at the time of continuing review.

Prompt reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event.

12.2.2 Reporting to the IUSCC Data Safety Monitoring Committee:

Regardless of study sponsorship, the study team must enter all initial and follow-up SAE, expedited, and noncompliance reports into OnCore® for review by the DSMC chair and/or coordinator. Expedited reports may include IRB Prompt Report Forms, AdEERS reports, MedWatch, and additional SAE forms as required by the sponsor. When follow-up information is received, a follow-up report should also be created in OnCore®. This DSMC reporting requirement is in addition to any other regulatory bodies to be notified (i.e. IRB, FDA, pharmaceutical company, etc.). The DSMC chair and/or coordinator will review all SAE, expedited, and noncompliance reports monthly.

13 PATIENT CONSENT AND PEER JUDGEMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate IRB prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

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15 APPENDICES

15.1 Appendix A

NCI Common Toxicity Criteria (Version 4.0)

Due to the size of the latest version of the Common Toxicity Criteria, copies of this appendix are not included with this protocol document.

An electronic copy is available on the CTEP web site,
http://ctep.cancer.gov/reporting/ctc.html

15.2 Appendix B

Performance Status Scales/Scores

ECOG or Zubrod		Karnofsky		Lansky	
Score	Activity	Score	Activity	Score	Activity
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.

4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20 10	Very sick, hospitalization indicated. Death not imminent. Moribund, fatal processes progressing rapidly.	20 10	Often sleeping; play entirely limited to very passive activities. No play; does not get out of bed.

15.3 Appendix C

Fusion Biopsy Procedure

Concurrent acquisition of ^{68}Ga-PSMA-11 PET data will be added to our present standard-of-care prostate mpMRI protocol performed in support of surgery planning or fusion biopsy for patients with prostate cancer. There are commercially available devices which allow performing a biopsy by **fusing** the MR targeted lesion with the real-time trans-rectal ultrasound image and thereby increasing the chance of prostate cancer detection. The fusion biopsy will be performed in the urology clinic, with at least two cores from each regions-of-interest defined by both mpMRI and PET.

15.4 Appendix D

Sextant Based Analysis

The biopsy plans will be re-assessed with full knowledge of all the mpMRI and PET findings, to define whether this combined data change diagnostic confidence and/or alter intended biopsy sites. For the primary outcome, a “sextant” based analysis will be performed as previously described (Eiber et al 2016). The sextants are right-base, right-mid, right-apex, left-base, left-mid, and left-apex. Lesions <5 mm or Gleason 3+3 are generally not considered clinically relevant.

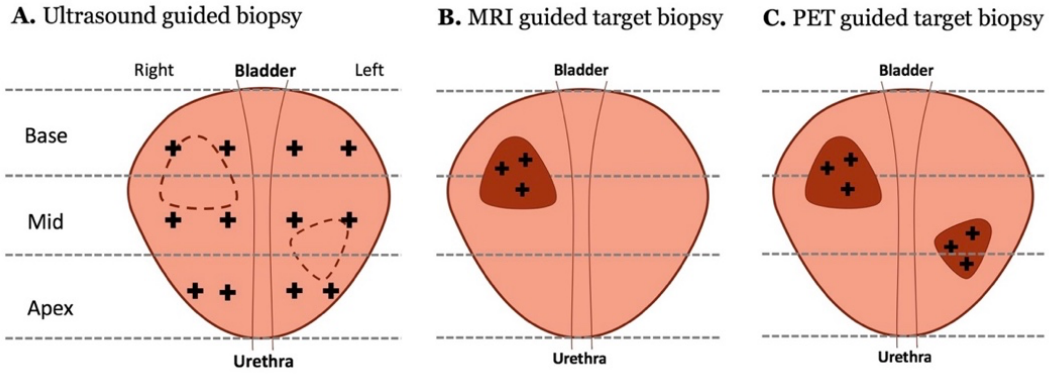

Figure 4. Three different biopsies (A-C) will be performed on each patient during a single session.