YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2013-1)

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://www.yale.edu/hrpp/forms-templates/biomedical.html Submit the original application and one (1) copy of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.	**HIC OFFICE USE ONLY**	

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Prostate Cancer Screening in Men with Germline BRCA2 mutations			
Principal Investigator: Preston C. Sprenkle		**Yale Academic Appointment:** **Assistant Professor**	
Department: Urology			
Campus Address: Department of Urology, Fitkin Memorial Pavilion Suite 315b, PO Box 208058			
Campus Phone: 203-785-2815	**Fax:** 203-785-4043	**Pager:** 475-201-5778	**E-mail:** preston.sprenkle@yale.edu
Protocol Correspondent Name & Address (*if different than PI*): Cayce Nawaf			
Campus Phone: 203-785-2815	**Fax:** 203-785-4043	**E-mail:** cayce.nawaf@yale.edu	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :**	**E-mail:**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☐ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI

❑ Yes ■ No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

❑ Yes ■ No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as con-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form:
http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale University PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☐ YCCI/Hospital Research Unit (HRU)

☒ Yale Cancer Center/Smilow
☒ Yale-New Haven Hospital
☒ Cancer Data Repository/Tumor Registry
☐ Specify Other Yale Location:

☐ YCCI/Keck Laboratories
☐ Yale-New Haven Hospital—Saint Raphael Campus

b. External Location[s]:

☐ APT Foundation, Inc.
☐ Connecticut Mental Health Center
☐ Clinical Neuroscience Research Unit (CNRU)
☐ Other Locations, Specify:

☐ Haskins Laboratories
☐ John B. Pierce Laboratory, Inc.
☐ Veterans Affairs Hospital, West Haven
☐ International Research Site
(Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

   Ongoing

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study
   ☐ Multi-Center Study
   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐
   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☒ **N/A**
   ☐ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

- ☒ Clinical Research: Patient-Oriented
- ☒ Clinical Research: Epidemiologic and Behavioral
- ☐ Translational Research #1 ("Bench-to-Bedside")
- ☐ Translational Research #2 ("Bedside-to-Community")
- ☐ Clinical Research: Outcomes and Health Services
- ☐ Interdisciplinary Research
- ☐ Community-Based Research

5. Is this study a clinical trial? Yes ☐ No ☒

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☐

Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)? Yes ☐ No☐

7. Will this study have a billable service? A Billable Service is defined as a service or procedure that will be ordered, performed or result in charging in EPIC for individuals who are enrolled in a clinical research study, regardless if the charge is intended to be paid by the subject/their insurance or the research study.

Yes ☒ No☐

If you answered "yes", this study will need to be set up in OnCore Support
http://medicine.yale.edu/ymg/systems/ppm/index.aspx

8. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes XX No ___ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*
a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? - Yes
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? - No

c. Will a novel approach using existing equipment be applied? - No

If you answered "no" to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Sprenkle		Internal	☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☒ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☒ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:
			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To:

Name:
Company:
Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

	Name	**Affiliation: Yale/Other Institution (Identify)**	**Net ID**
Principal Investigator	Preston C. Sprenkle	Yale University, Dept of Urology	PS577
Co-Investigator(s)	Brian Shuch	Yale University, Dept of Urology	bms53
	Kamyar Ghabili Amirkhiz	Yale University, Dept of Urology	Kga25
	Jamil Syed	Yale Urology	Js3569
Study Personnel	Marta Boeke	Yale University, Dept of Urology	Mb273
	Cayce Nawaf	Yale, Department of Urology	Cbn8

NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV:
PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

__Preston C. Sprenkle___ _____

PI Name (PRINT) and Signature Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☒ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☒ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____

Chair Name (PRINT) and Signature Date

_____

Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____

YNHH HSPA Name (PRINT) and Signature Date

For HIC Use Only

_____ _____

Date Approved **Human Investigation Committee Signature**

This protocol is valid through _____

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
   Specific Aims:
   1.Determine the incidence of prostate cancer in men with the BRCa2 gene mutation as an independent indicator for prostate cancer screening.
2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Prostate cancer remains the most commonly diagnosed malignancy among men with an estimated 230,000 incident cases annually in the U.S. Emphasis has been placed on overtreatment, but prostate cancer remains the most lethal malignancy for men. Genetic factors, like a family history of prostate cancer, are associated with a higher risk of developing the disease, but a connection with more aggressive disease is controversial. Recently, the BRCA mutation, commonly known for its role in breast and ovarian cancer, has been identified as risk factor for prostate cancer in men that may also confer a risk of developing more aggressive prostate cancer at a younger age. While several retrospective studies of men with prostate cancer suggest that BRCA2 mutation carriers are at significantly higher risk of developing prostate cancer at an earlier age and more advanced stage, [1-4] prospective data is lacking. Concern about whether this mutation confers more advanced disease and worse survival may contribute to significant anxiety in some men. A man in England with a BRCA2 mutation, for example, was so worried about his possible risk of prostate cancer that he had a

prophylactic surgical removal of his prostate[5]. This example clearly illustrates the key knowledge gaps that exist about the actual risk of prostate cancer among BRCA2 mutation carriers.

We have established a multidisciplinary group of radiation oncologists, urologists, geneticists and engineers that is uniquely positioned to address this knowledge gap about the importance of the BRCA mutation and risk of prostate cancer. Our group has developed the Yale School of Medicine Fusion Prostate Biopsy Program. This program uses cutting-edge multiparametric magnetic resonance imaging (MRI) to identify previously invisible lesions in the prostate. The office-based Artemis platform (Eigen, Grass Valley CA) then "fuses" these images with 3D ultrasound to achieve more precise and accurate prostate biopsies, allowing for better clinical staging with a single biopsy. The Yale Fusion Prostate Biopsy Program has dramatically improved prostate cancer detection to more than 60%, almost twice that of the current standard of care. Through the Yale Cancer Center Genetic Counseling program, which provides genetic counseling and testing to people at increased risk for hereditary cancer, we have an established cohort of families with known genetic mutations including BRCA2.

Our study, by combining the Fusion Prostate Biopsy Program and the Genetic Counseling program to perform highly sensitive prostate biopsies in a population of BRCA2 mutation carriers, is a novel approach to accurately determine the risk of prostate cancer, adverse pathologic features and abnormal MRI findings among BRCA2 mutation carriers. While it is beyond the scope of this pilot grant, we believe that early identification of men with higher risk disease should allow for more rapid treatment and a higher likelihood of cure. We hypothesize that the BRCA-2 mutation is associated with a higher risk of prostate cancer incidence, worse grade, and abnormal MRI findings compared to patients without this mutation. To address these important questions, our specific aims are:

1. To prospectively determine the incidence of prostate cancer in BRCA2 mutation carriers.

2. To investigate different characteristics of MRI-detected prostate lesions.

3. To compare pathologic and clinical findings to clinically matched controls using the same sensitive MRI-based biopsy technique.
4.

Localized prostate cancer is treatable and often curable while metastatic disease is not, hence prostate cancer screening is performed to identify patients at an earlier stage. Early detection of prostate cancer in this group of younger men at high-risk population may allow for identification while at a lower stage and grade, potentially increasing the number of patients able to receive treatment with curative intent.

All previous studies in the literature have evaluated the incidence of BRCA2 mutation carriers in a population of patients already diagnosed with prostate cancer. The incidence of prostate cancer in men with a BRCA2 mutation, however, has not been previously described.

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

This is a cohort screening study to prospectively identify the incidence of prostate cancer in a population of BRCA2 carriers. All men identified to have a BRCA2 mutation as part of the Yale Cancer Genetic Counseling Program will be approached and offered participation in the study via our program newsletter, BRCA listserv, Facebook page and a targeted mailing. We will also contact all female BRCA2 carriers and ask them to invite their male relatives known to carry BRCA2 mutations into this study through the same means. For patients who test positive for a BRCA2 mutation after this study has opened, we will discuss this study with them at result disclosure and include it as part of their summary letter.

Potential participants will meet with a urologic oncologist to discuss the risks and benefits of prostate cancer screening including individual risks and benefits of PSA testing, prostate examination, pelvic MRI, prostate biopsy, and a prostate cancer diagnosis..

Standard of care screening at the Yale Cancer Center for men with a normal prostate cancer risk consists of a PSA test and prostate physical examination beginning at age 50 years and if either is abnormal an MRI of the prostate followed by Fusion-targeted biopsy of the prostate is performed (Figures 1 and 2). Men with genetic risk factors such as African American or Caribbean heritage, a positive family history of prostate cancer, or a BRCA2 mutation, are counseled about their increased risk of prostate cancer and that prostate cancer screening (PSA and prostate exam then MRI and prostate biopsy if indicated) should begin at age 40yr but is available to them at any age.

Study participants will be identified because of their BRCA2 mutation that places them at increased risk for developing prostate cancer. Because this is a pre-selected high-risk population, and our goal is to establish the incidence of cancer and association of risk factors with developing disease, all men ≥30 years of age, able to give informed consent, and with at least a 5-10 year life expectancy will have PSA testing, prostate examination, Pelvic MRI, and Artemis fusion prostate biopsy (Figures 1 and 2).

Men identified to have prostate cancer will be treated according to current standards of care. Treatment for prostate cancer at the Yale Cancer Center is largely based on clinical risk; options include, but are not limited to, active surveillance for appropriate men with low risk disease, treatment with curative intent for men with localized intermediate and high risk prostate cancer, and systemic therapy for men with metastatic disease.

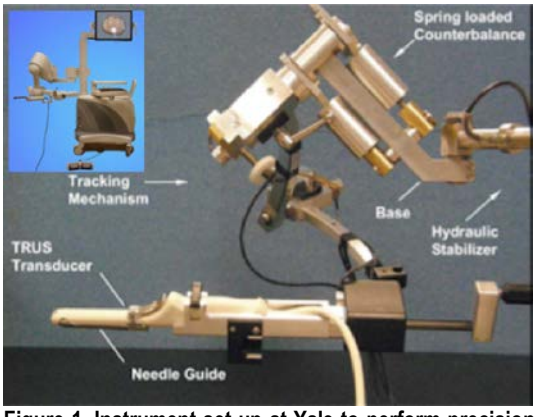


Figure 1. Instrument set up at Yale to perform precision imaging-guided biopsy. The prototype device of Artemis 3D biopsy tracking system. Instrument set up at Yale from Eigen (510K approved).

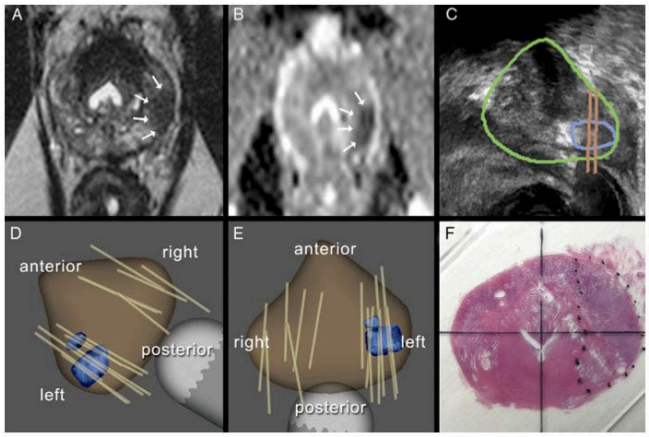
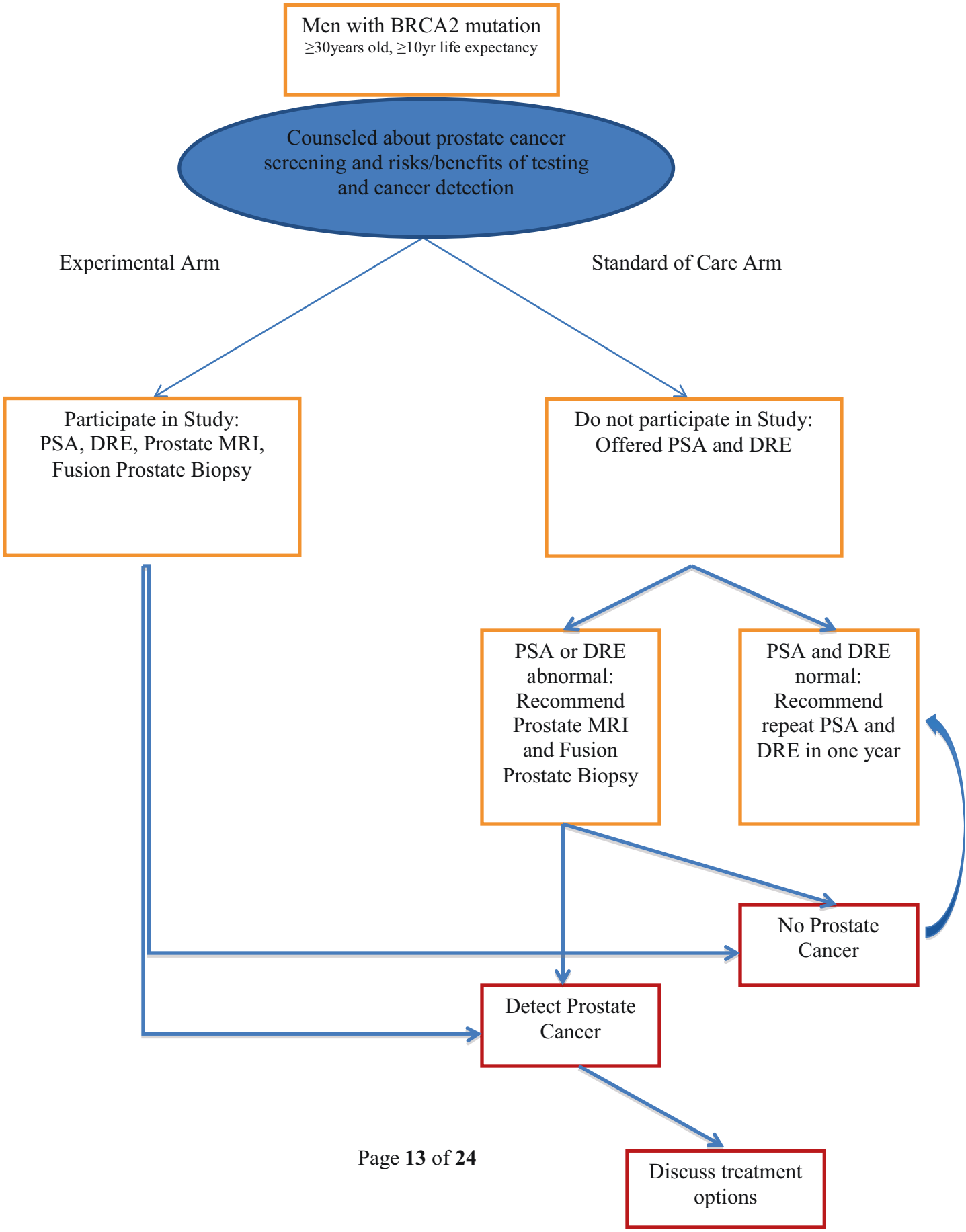


Figure 2. Precision image-guided biopsy. A+B) Identification of suspicious regions in two MRI sequences C) overlay of MR contoured region on realtime US view D+E) two planes of view of the 3D model generated by US and MR segmentation F) matching whole mount histology slide following prostatectomy.

Typical clinical workflow for an Artemis MR-US fusion biopsy includes a pre-procedure MRI followed by a 12-core transrectal-ultrasound (TRUS) guided biopsy (Figure 1,2). The ultrasound transducer is fixed with a needle guide, and the biopsy needle is then guided to specific regions in the prostate gland for systematic sampling of the gland. If any areas suspicious for cancer (labeled regions of interest (ROIs)) are identified in the MRI, they are outlined using specialized software, and the target is visible on the Artemis device. Targeted biopsies will be taken from each ROI to rule out cancer in these suspicious areas.


Men with BRCA2 mutation
≥30years old, ≥10yr life expectancy
Counseled about prostate cancer screening and risks/benefits of testing and cancer detection
Experimental Arm
Standard of Care Arm
Participate in Study: PSA, DRE, Prostate MRI, Fusion Prostate Biopsy
Do not participate in Study: Offered PSA and DRE
PSA or DRE abnormal: Recommend Prostate MRI and Fusion Prostate Biopsy
PSA and DRE normal: Recommend repeat PSA and DRE in one year
No Prostate Cancer
Detect Prostate Cancer
Discuss treatment options

4. Genetic Testing N/A ☒

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

   Men ≥30 years of age with known BRCA2 mutation and able to give informed consent.

6. **Subject classification:** Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?
   All men ≥30 years of age with at least a ten-year life expectancy, a known BRCA2 mutation, ability to have an MRI, and able to give informed consent will be approached to participate in the study. If a man has received or is currently receiving treatment for prostate cancer he will be excluded from the study.

8. How will **eligibility** be determined, and by whom?
   Yale genetic counselors will determine initial eligibility from the BRCA2 registry to confirm the presence of a BRCA2 mutation. Trained physicians will determine clinical eligibility based on medical history.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.
   Risks of prostate biopsy include: infection, rectal bleeding, blood in urine or semen, prostatitis, urosepsis, urinary retention, and potential difficulty with urination.
   Magnetic resonance (MR) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of various parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines.

Patients will be watched closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you have them.

There are some risks with an MR study for certain people. If someone has a pacemaker or some metal objects inside their body, they may not be in this study because the strong magnets in the MR scanner might harm them. Another risk is a metallic object flying through the air toward the magnet and hitting the participant. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. Nothing metal can be brought into the magnet room at any time. Also, once the participant is in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.
Risks will be minimized using standard of care methods to limit prostate biopsy-related patient discomfort and the risk of infection through administration of local anesthetic and peri-procedure antibiotics, respectively.
FDA guidelines for MRI safety are strictly adhered to.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
a. What is the investigator's assessment of the overall risk level for subjects participating in this study?
    - Moderate risk: participants will be offered the standard of care fusion targeted prostate biopsy that is performed at Yale and offered to other patients at risk for prostate cancer. Some participants, however, would not have received a biopsy if not participating in the study.

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB or the Yale Cancer Center Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed moderate for the following reasons: (choose those that apply)

1. We do not view the risks associated with the prostate biopsy as minimal given the alternative is no biopsy.
2. Given the now established safety and validity of the current biopsy procedure in our prior work, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator Preston Sprenkle according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. is life-threatening OR
2. results in in-patient hospitalization or prolongation of existing hospitalization OR
3. results in persistent or significant disability or incapacity OR

4. results in death OR
5. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, OR
6. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting Reportable Adverse Events and other unanticipated problems involving risks to subjects or others to the IRB

The principal investigator will report the following types of events to the IRB: a) adverse events that are serious or life-threatening AND unanticipated (or anticipated but occurring with a greater frequency than expected) AND possibly, probably or definitely related to the drug/device/intervention; and b) other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website.

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

X All Co-Investigators listed on the protocol.

X Yale Cancer Center Data and Safety Monitoring Committee (DSMC)

☐ National Institutes of Health

☐ Food and Drug Administration (Physician-Sponsored IND #_____)

☐ Medical Research Foundation (Grant_____)

The principal investigator Preston Sprenkle will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and

severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A

12. **Statistical Considerations:** Describe the statistical analyses that support the study design. This is a screening study to establish the incidence of prostate cancer in a high-risk population since it is not currently known. There is an estimated 4.6-23 fold increased risk of prostate cancer, especially in men < 58 years of age with a BRCA2 mutation. Typically, prostate cancer detection in normal risk men correlates directly with age and ranges between 0.01 and 6.5% for men in their 30s-60s (CDC website). Given these parameters, we plan initial evaluation of 100 men.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

N/A

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. targeted for enrollment at Yale for this protocol__100

b. If this is a multi-site study, give the total number of subjects targeted across all sites___

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

- ☐ Flyers
- ☐ Posters
- ☒ Letter
- ☐ Medical Record Review
- ☒ Departmental/Center Newsletters
- ☒ YCCI Recruitment database
- ☐ Other (describe):
- ☒ Internet/Web Postings
- ☒ Mass E-mail Solicitation
- ☒ Departmental/Center Website
- ☒ Departmental/Center Research Boards
- ☐ Web-Based Clinical Trial Registries
- ☐ Clinicaltrials.gov Registry (do not send materials to HIC)
- ☐ Radio
- ☐ Telephone
- ☐ Television
- ☐ Newspaper

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

i. Potential subjects will be identified through the Yale Cancer Genetic Counseling Program.

ii. For patients who test positive for a BRCA2 mutation after this study has opened, we will discuss this study with them at result disclosure and include it as part of their summary letter

b. Describe how potential subjects are contacted.

i. Potential subjects with a known BRCA2 mutation will be approached and offered participation in the study via our program newsletter, BRCA listserv, Facebook page and a targeted mailing. We will also contact all female BRCA2 carriers and ask them to invite their male relatives known to carry BRCA2 mutations into this study through the same means.
ii. For patients who test positive for a BRCA2 mutation after this study has opened, we will discuss this study with them at result disclosure and include it as part of their summary letter

c. Who is recruiting potential subjects?
i. Trained genetic counselors will be recruiting possible subjects.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☐ Yes ☒ No

b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:

☐ Names

☐ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☐ Telephone numbers

☐ Fax numbers

☐ E-mail addresses

☐ Social Security numbers

☐ Medical record numbers

☐ Health plan beneficiary numbers

☐ Account numbers

☐ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers, including license plate numbers

☐ Device identifiers and serial numbers

☐ Web Universal Resource Locators (URLs)

☐ Internet Protocol (IP) address numbers

☐ Biometric identifiers, including finger and voice prints

☐ Full face photographic images and any comparable images

☐ Any other unique identifying numbers, characteristics, or codes

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects
☒ Yes, some of the subjects
☐ No

If yes, describe the nature of this relationship.
Dr. Sprenkle could potentially see some of these patients while they are undergoing their standard of care prostate cancer treatment.

6. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one: For entire study: _____ For recruitment purposes only: _____

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   ☒ Compound Consent and Authorization form
   ☐ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.
   Preston Sprenkle

9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
Prior to screening for prostate cancer patients will have an office visit as part of standard clinical care to discuss the risks and benefits of prostate cancer screening. During this visit, if they are interested in being screened for prostate cancer and meet eligibility criteria the study will be described and if patients are interested in participating they will be provided a study information sheet and asked to sign consent. Only patients that can provide written informed consent will be enrolled in this study, and if there is any doubt subjects will not be enrolled. Information sheets will also be available to patients as part of the Yale Cancer Genetic Counseling Program.

10. E**valuation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

    Preston Sprenkle, after explaining the research plan orally, and after providing time for subjects to review written information from an informational flyer, will ask open-ended questions to gauge subject comprehension and capacity to provide informed consent. Questions will include: "Can you tell me what happens if you agree to take part in this study?" and "What should you do if you no longer want to take part in the study?"

11. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

    An adult consent form will be provided, and is attached.

12. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

13. **Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study.** If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.
    - ☒ **Not Requesting a consent waiver**
    - ☐ **Requesting a waiver of signed consent**
    - ☐ **Requesting a full waiver of consent**

    A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)
    ☐ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

☐ **Requesting a waiver of signed consent for the <u>Entire Study</u> (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. **<u>Full waiver</u>** <u>of consent:</u> (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for <u>Recruitment/Screening</u> only**
a. Does the research activity pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the <u>Entire Study</u> (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?
b. Subject Name, date of birth, and Medical Record number as well as clinical imaging, pathologic and staging information will be collected.

c. How will the research data be collected, recorded and stored?
All research data will be collected as part of the medical record and stored in a secure ITS managed database (FMS Med). Only co-investigators will be able to collect, record and access this workstation, and no collaborators on this study will have access to PHI.

d.
c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☐ Laptop Computer ☐ Desktop Computer ☐ Other
d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?
The data will be stored on and ITS managed secure database in the medical school, accessible only by co-investigators
Do all portable devices contain encryption software? ☐ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.
All identifies will be secured in an encrypted database.
f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data) .
PHI will be accessible by co-investigators only, collaborators will not have access
g. If appropriate, has a Certificate of Confidentiality been obtained? N/A
h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -

incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported. N/A

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)
Prostate cancer could potentially be discovered at an earlier and more localized stage allowing for greater chance of cure with treatment.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research? There is no current alternative. Patients may request to be screened for prostate cancer with standard of care management

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation. – no payment for participation

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects. - No cost to participate, all research will be performed as part of standard prostate cancer screening.

4. **In Case of Injury:**
If a patient is injured while on study, he should seek treatment and contact the study doctor as soon as he is able. Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If the patient is injured as a result of participation in this study, treatment will be provided. He or his insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.