Memorandum of Understanding
Between the National Cancer Institute and the Canary Foundation

WHEREAS the National Cancer Institute (NCI), a component of the National Institutes of Health and an agency of the United States Government, is interested in identifying and validating biomarkers for cancer detection and diagnosis; and

WHEREAS the Early Detection Research Network (EDRN) is a program within the NCI with a goal of establishing validated cancer biomarkers that are ready for large-scale clinical testing. EDRN activities are guided by the EDRN Steering Committee, a group comprised of the principal investigators funded by EDRN cooperative agreements and NCI staff. Many EDRN members contribute to organ-site specific cancer research and have been organized into EDRN Collaborative Groups such as the EDRN Genitourinary Collaborative Group. An Executive Committee of the EDRN Steering Committee is comprised of chairs of the Collaborative Groups, the NCI EDRN program director, and the EDRN Steering Committee chair and co-chair; and

WHEREAS the NCI has multiple ongoing studies related to the early detection of prostate cancer that are coordinated by NCI's EDRN, with support from the Data Management and Coordinating Center (DMCC) component of the EDRN. The DMCC provides statistical and informatics support to EDRN and has developed an infrastructure for conducting collaborative validation studies with the ability to capture, archive, and manage information from multiple study sites. In order to establish consistency across institutions collecting data, a set of standard terms and associated values (Common Data Elements) must be established as well as an appropriate biospecimen tracking system and a protocol oversight program for biomarker discovery and validation protocols; and

WHEREAS the Canary Foundation, a non-profit corporation located at 333 W. Santa Clara St., No.1, in San Jose, CA, is committed to funding research in identifying and validating early detection biomarkers of cancer; and

WHEREAS the Canary Foundation has initiated a collaboration of a number of institutions with the purpose of identifying biomarkers that predict prostate cancer which has a high likelihood of progressing while on a program of active surveillance. Towards this purpose, the Canary Foundation has identified a group of institutions that will follow the Canary Prostate Active Surveillance Protocol (Attachment A) to accrue patients to an active surveillance study (Canary Study) while collecting biologic samples as well as clinical information and tracking patients for ultimate disease progression and/or institution of active treatment; and

WHEREAS current methods of prostate cancer detection and categorization are suboptimal and lead to overdiagnosis by identifying tumors that may be present in the general population and will not progress to life-threatening disease. Overdiagnosis of prostate cancer can lead to unnecessary treatment and procedures with harmful side-

effects. The ideal biomarker not only detects tumor early, but also detects those tumors that pose a risk to the patient; and

WHEREAS the biomarkers identified by the Canary Study may be useful in conjunction with early detection programs for prostate cancer as they may be used either as 1) a part of early detection with the purpose of identifying prostate cancers or 2) a secondary screening after prostate cancer diagnosis to identify high-risk tumors that may optimally be managed with active treatment; and

WHEREAS improved prognostic markers for prostate cancer would benefit the public at large, and studies to detect such markers require large groups of patients and multiple centers. There is currently no large-scale repository of biologic materials, linked with high-quality clinical data that provides pre-diagnosis biologics followed by long-term outcomes for prostate cancer. Such a repository requires a significant investment of both funding and resources; and

WHEREAS the Canary Foundation is making a significant investment to generate such a large-scale repository of biological specimens linked with high-quality clinical data via the Canary Study. In addition, the Canary Foundation is committed to providing the specimens/data to the most qualified researchers for biomarker studies and is, therefore, an ideal partner for the NCI EDRN; and

WHEREAS the value of this large-scale repository to the public health cannot be fully realized without a system for 1) managing the specimens and data and 2) providing access to the specimens and data to investigators with scientifically meritorious biomarker discovery/validation proposals. The NCI EDRN has infrastructure that can provide such systems; and

WHEREAS the NCI and the Canary Foundation have reached the conclusion that a partnership for the purpose of identification of biomarkers of high-risk prostate cancer within the context of the proposed Canary Study is in the best interests of the public health. The partnership is critical to maximizing the potential benefits of the specimens and data collected and generated under the Canary Study and to advancing the search for improved prognostic markers of prostate cancer; and

WHEREAS the benefits to the public health include 1) reducing overdiagnosis of non-life threatening prostate cancer, 2) eliminating unnecessary treatments and procedures in men with non-life threatening prostate cancer tumors which will improve the quality of life for these men as well as their family members, and 3) advancing research towards personalized medicine – since not every prostate cancer tumor needs to be treated, research to identify and validate prognostic biomarkers for aggressive prostate cancer are key to improving an individual's treatment; and

WHEREAS the benefits to the NCI include 1) the establishment of a well-annoted repository of serial specimens from a unique patient population (men newly diagnosed with prostate cancer) which will be accessible to NCI and other investigators for research

aimed at discovery and/or validation of prostate cancer biomarkers, 2) the identification of predictive biomarkers for prostate cancer aggressiveness – an important step towards reducing prostate cancer overdiagnosis, and 3) promoting NCI's mission to support programs with the goal of improving the diagnosis and treatment of cancer; and

WHEREAS the benefits to the Canary Foundation include 1) access to and use of EDRN's extensive infrastructure for managing biospecimens and data collected from biomarker discovery/validation studies and 2) partnering with the EDRN, a group with connections to many leading biomarker researchers and practical experience in reviewing biomarker discover/validation research proposals;

NOW, THEREFORE, the parties agree to combine their resources and efforts to identify biomarkers of high-risk prostate cancer. In order to accomplish the goals of this Agreement, the parties agree as follows:

A. NCI Responsibilities

1. The NCI will provide supplementary funding to the DMCC to modify pre-existing NCI-funded, DMCC-designed software based on the particular parameters of the Canary Study. These modifications will be conducted by the EDRN DMCC and will involve establishing disease-specific Common Data Elements, an appropriate biospecimen tracking system, and a protocol oversight program for the Canary Study.

2. The NCI will provide the Canary Foundation with technical advice regarding Canary's protocol oversight program including data transmission, data expectation, accrual, and data entry for the Canary Study. The NCI will 1) provide training on using a web-based data management system, and 2) develop, with investigators involved in the Canary Study, the Manual of Operations (MOP) and train staff at Canary Foundation-funded institutions on using the MOP. The NCI will provide technical assistance to the Canary Foundation to establish a database for the retrospective specimens already collected at the Canary Study sites that meet the study inclusion criteria.

3. The NCI will seek the input of the members of the EDRN Genitourinary Collaborative Group and the DMCC, in order to provide input to the Canary Foundation protocol committee regarding opportunities for new prognostic biomarkers for prostate cancer.

4. The NCI EDRN, with input from investigators involved in the Canary Study, will provide statistical support on the study design and data analysis for the Canary Study and the subsequent biomarker discovery and validation studies using the Canary Study specimens and data.

B. Canary Foundation Responsibilities

1. The Canary Foundation will provide funding to participating institutions in the Canary Study and will ensure that its grantees are responsible for conduct of the Canary Study.

2. The Canary Foundation will be responsible for establishing 1) a protocol oversight program including data transmission, data expectation, accrual, and data entry for the Canary Study and 2) a database for the retrospective specimens already collected at the Canary Study sites that meet the study inclusion criteria.

3. The Canary Foundation will solicit input on the Canary Study protocol from members of the EDRN Genitourinary Collaborative Group as well as the DMCC.

4. The Canary Foundation will include two EDRN-supported investigators on the Canary Foundation protocol committee.

5. The Canary Foundation, through the Canary Study, will generate a large-scale repository of biological specimens linked with high-quality clinical data that provides pre-diagnosis biologics followed by long-term outcomes. The biological specimens will physically reside at the individual Canary Foundation-funded institutions where they were collected. The clinical data will be stored in a DMCC-maintained Canary Study database that is accessible to the Canary Foundation-funded investigators and the NCI EDRN. Any investigator, including Canary Foundation-funded investigators and EDRN investigators, may submit proposals for biomarkers to be studied using the Canary Study biological specimens and accompanying clinical data. Proposals will be evaluated based upon scientific merit using a formal and consistent process of review that includes statistical significance of biomarkers from discovery to analytical validation to clinical validation to post-marketing surveillance. A biomarker evaluation group (BEG), comprised of one representative from each of the five Canary Foundation-funded sites and two representatives from the EDRN, will review the proposals and will determine those biomarkers that are most promising for evaluation using the biological specimens in combination with clinical data and outcomes for the purpose of the diagnosis of high-risk prostate cancer.

6. On a biannual basis, the Canary Foundation will prepare a report on the status of the collaboration and the Canary Study. This report will be presented to the NCI EDRN Steering Committee and may be presented by an EDRN or a Canary Foundation member.

C. Mutual Responsibilities

The NCI and the Canary Foundation will coordinate regular conference calls to discuss the progress of the activities under this Agreement.

D. General Provisions

Duration: This Agreement becomes effective when signed by each party and shall remain in full force and effect for three (3) years, unless modified or terminated.

Modification/Termination: This Agreement may be amended by written agreement of the parties. Either party may terminate this Agreement by providing thirty (30) days written notice to the other party. The Canary Foundation's obligations under section B.4 and B.5 shall survive termination.

Notices: All notices relating to the activities described in this Agreement should be delivered by hand or sent by pre-paid courier or registered mail to the following contacts:

For NCI:
Sudhir Srivastava, Ph.D., MPH
Chief, Cancer Biomarkers Research Group
Division of Cancer Prevention
National Cancer Institute
6130 Executive Boulevard, Suite 3142
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For Canary Foundation:
Pete Nelson, M.D.
333 W. Santa Clara St., No.1
San Jose, CA 95154

On behalf of Canary Foundation

Don Listwin Date
Founder, Canary Foundation

On behalf of NCI

John E. Niederhuber, M.D. Date
Director, National Cancer Institute

Canary Foundation signed 5/6/08 NCI signed 4/22/08

Signature dates added by Lisa D. Finkelstein; NCI Technology Transfer Specialist

CANARY PROSTATE
ACTIVE SURVEILLANCE PROTOCOL

FINAL PROTOCOL
11.09.07

INVESTIGATORS:

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1. TREATMENT SCHEMA

This is a multi-center, prospective active surveillance study with selective intervention in patients with previously untreated, clinically localized, favorable risk prostate cancer at diagnosis. Candidates are assessed based on an extended core biopsy, transrectal ultrasound, serum PSA (including PSA kinetics, if available), DRE and assessment of cancer grade and extent.

Active surveillance is defined as serial PSA measurements and prostate examination with routine prostate biopsy and therapeutic intervention considered at the time one or more of the following:

- Biochemical progression
- Grade or volume progression
- Clinical progression

This protocol is not designed as a formal clinical trial with randomization of different treatments, although the following measures will be obtained:

- Serum and tissue specimen banking for biomarker studies
- Rates of radical intervention
- Clinical recurrence/progression
- Disease specific survival
- Overall survival

2. OBJECTIVES

Primary Objective

- To discover and confirm biomarkers that predict aggressive disease as defined by pre-specified histological, PSA, clinical criteria, or outcomes based on these variables.

Secondary Objectives

- To determine the proportion of patients on active surveillance who progress based on the above criteria.
- To determine the clinical predictors of disease progression.
- To measure the recurrence-free, disease-specific, and overall survival of men on active surveillance for clinically localized prostate cancer.

3. BACKGROUND INFORMATION AND RATIONALE

Treatment options for newly diagnosed, clinically localized prostate cancer include radical treatment utilizing radiation/surgery or surveillance with or without delayed intervention. Studies have suggested comparable 10-year survival rates in men followed by surveillance compared to prostatectomy or radiation, with a consistent demonstration

that a subset of patients with favorable tumor characteristics will experience long-term survival regardless of initial treatment modality.

For these favorable risk prostate cancer patients, the active surveillance approach appears to be appropriate for the majority, although there is a major concern that a small but important subset of patients with biologically aggressive, but potentially curable, disease would be denied the benefits of early radical therapy. Recent results from multiple groups have reported on this active surveillance strategy for those with favorable tumor characteristics based on Gleason score, T stage and PSA values.[1-7] These strategies involve selective, delayed intervention based on disease progression as defined by several clinical factors, including rapid PSA doubling time, clinical progression (local and/or distant) or increase in Gleason score on repeat biopsy. Entry criteria and definitions of progression varied between these reports, and reported estimated progression-free survival rates were approximately 65-70% at five years. Overall survival rates exceeded 80%, and disease-specific survival was 98-100% with limited follow-up. Additionally, various nomograms have been constructed to predict the probability of indolent disease based on clinical and pathologic parameters.[8,9] These studies as a whole demonstrate that an active surveillance strategy employing selective delayed intervention for men with good risk prostate cancer is feasible and is associated with low rates of prostate cancer death.

4. STUDY POPULATION

This study will recruit patients with previously untreated, early stage prostate cancer. Staging will be according to AJCC 6th edition.

4.1. Inclusion Criteria

Patients must fulfill all of the following criteria to be eligible:

1. Histologically confirmed adenocarcinoma of the prostate.
2. Clinically localized prostate cancer: T1-2, N0, M0.
3. No previous treatment for prostate cancer (including hormonal therapy, radiation therapy, surgery, or chemotherapy).
4. Suitable candidate for radical prostatectomy or radiotherapy.
5. ECOG Performance Status 0 or 1.
6. Patient has elected Active Surveillance as preferred management plan for prostate cancer.
7. Patient consent has been obtained according to local Institutional Review Board for acquisition of research specimens.
8. Patient is able and willing to complete study questionnaires.
9. Patient is accessible and compliant for follow-up.

4.2. Exclusion Criteria

Patients who fulfill any of the following criteria are not eligible:

1. Unwillingness to refrain from hormonal agents as an initial therapy
2. Unwillingness or inability to undergo serial prostate biopsy

3. History of other malignancies, except: adequately treated non-melanoma skin cancer or adequately treated superficial bladder cancer or other solid tumors curatively treated with no evidence of disease for > 5 years

5. EVALUATION DURING ACTIVE SURVEILLANCE

Patients will be evaluated by serial DRE, serum PSA, prostate biopsies, and imaging (as appropriate).

DRE/PSA evaluation
Assessment by digital rectal examination and serum PSA will be performed every 4 months from time of study entry. When possible, PSA measurements will be obtained from the same local clinical laboratory to minimize inter-assay variability.

Prostate Biopsy
Patients will undergo repeat prostate biopsy with the following schedule:

1. At study entry if initial diagnostic biopsy was <10 cores.
2. At 6-12 months from study entry
3. At two years from study entry, then every 2 years.
4. At any time "for cause" as determined by local physician.

The rationale for this schema: a.) to ensure that initial diagnostic biopsy adequately sampled the prostate; b.) to avoid false negative diagnosis of high grade cancer; and c.) to capture "early" histologic progression.

Follow-up for relocated patients
If a patient who is currently on the study relocates, and if one of the participating institutions is present at the new location, then the patient will be offered the opportunity to re-enroll at the receiving institution. If this is not the case, and if the patient opts not to return for the protocol follow-up at the original institution, the schedule of follow-up will be provided to the patient who will have the opportunity to seek a new medical provider at his new location. Patients will have the opportunity to request that all clinical information regarding their prostate cancer be sent to the original enrolling institution to maintain follow-up.

Appendix I and II give the evaluation schedule and timeline.

6. PROGRESSION DEFINITIONS ON ACTIVE SURVEILLANCE

Progression on active surveillance will be defined when patients fulfill one or more of the following criteria. These definitions of disease progression are the most sensitive collection of measures for progression but are not necessarily specific for disease progression. For this reason, while active treatment for prostate cancer will be offered to the subject if any of these elements are met, the patient may opt to remain on active surveillance. Should the patient do so, a new PSA/TNM/Grade status will be assigned

and further progression events will be determined using these same criteria. Additionally, all investigators will be blinded to biomarker status.

Biochemical Progression

PSA doubling time < 2 years, based on at least 3 separate measurements over a minimum of 6 months as assessed by the local investigator.

Histologic/Grade Progression

Any increase in tumor grade

Clinical Progression

Local – stepwise increase in tumor stage by DRE or other local staging study.

Regional or Distant Metastasis – as defined by radiology/cytology/histology at sites remote from prostate

6.1. OTHER REASONS FOR RADICAL INTERVENTION OR OFF STUDY STATUS

Patient Choice

Patients who do not meet the criteria for biochemical, histologic/grade, or clinical progression, but who are uncomfortable remaining on surveillance, will be free to elect definitive therapy at any time.

Clinical Judgment

A clinical decision to proceed with radical intervention based on reasons other than the pre specified protocol criteria, such as patient compliance.

7. STATISTICAL CONSIDERATIONS: SAMPLE SIZE AND STUDY POWER

The primary objective of this repository is to discover and validate biomarkers predicting aggressive disease, with emphasis on validation. The sample size and power is based on validation of a biomarker after its initial discovery. Since this cohort of men has already elected AS, a desirable biomarker should have high specificity so that clinicians will minimize the proportion of those men advised for more aggressive treatment, while still identifying the subset of men with high risk for progression. Therefore, we evaluate the sensitivity of a biomarker predicting aggressive disease at 95% specificity. We assume the threshold for 95% specificity needs to be estimated from this study, i.e., there is no pre-fixed threshold. This is more realistic because estimating the threshold usually requires a large study. The proportion of disease progression at 3 and 5 years from diagnosis is estimated at 25% and 33%. We want 90% power to confirm a sensitivity better than 10% (unacceptable) if the true sensitivity is 30% or better, at 95% specificity. Point estimate of sensitivity, specificity, and threshold and their 95% confidence intervals will be calculated. The sample size also depends on the slope of Receiver Operating Characteristic (ROC) curve at 95% specificity, usually quite steep when specificity is near 100%. We used 4 as the slope parameter for power analysis.

Based on above assumptions, for a cohort with at least 3 years follow up, this study requires 100 men with disease progression and 300 men without progression, totally n=400. For a cohort with at least 5 years follow up, this study requires 125 men with progression and 250 men without progression, total n=375. Therefore, the total needed person-years follow up should be 375*5=1,875.

The estimated number of patients elected for AS is about 350 in five sites combined. Given a conventional 25% recruitment rate, we expect 100 patients per year accrual. With 25% loss of follow-up, we estimate that each year's 100 recruited men will finally contribute 375 person-years by the end of 5 years. It should be noted that we need full 5 years follow up to ensure that the men who had not progressed are indeed non-progressors, not false negatives. By the same reason, men after 5-years follow up will contribute little to the total person-years follow up because their risk of progression is felt to be low. Therefore, the study needs continuing 5 years recruitment and subsequent 5-years follow up with minimum 100 recruitment per year and a minimum 75% follow up rate.

8. MEASURES: (methods in Operations Manual)

Prostate Tissue Collection

The collection of prostate biopsy tissue is an important and mandatory part of this trial. Tissue will be collected in two methods: formalin-fixed, paraffin-embedded (FFPE) blocks and fresh frozen tissue. All tissue will be banked as part of the tumor bank at each individual institution. One of the objectives will be to create tissue microarrays, and thus we can optimize the amount of tissue available to investigators and permit the preservation of the tumor block submitted. Creation of tissue microarrays may necessitate temporary transfer of tissue to one central institution. If, at any time, the submitting hospital requires the block to be returned, it will be returned by courier on request. The tissue may be used by researchers now or in the future to better understand the nature of prostate cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of entry to the trial. Diagnostic pathology reports should be supplied as part of the supporting documentation required for this trial. Patients on whom tissue is collected will be aware of this retrieval and will have given their consent.

<u>Tissue collection methods:</u>

Transrectal ultrasound and prostate biopsy will conform to each established local institutional protocol. Use of local anesthesia is recommended. Prostate volume, presence of lesions, and digital rectal examination findings are required at each biopsy. Diagnostic biopsy schemes should incorporate at least 10-core regimens. Extra cores for research purposes will be acquired only after diagnostic cores are obtained.

a. Formalin-fixed, paraffin-embedded (FFPE):
FFPE tissue from each biopsy will be collected as part of the standard diagnostic biopsy cores. All tissue blocks will be acquired from the local pathology department after final pathologic diagnosis is completed.

b. Fresh Frozen:
(optional, but strongly encouraged, at each serial biopsy)
For research purposes, 2-6 extra cores will be immediately snap frozen in polyethylene glycol tissue freezing media or directly snap frozen in liquid nitrogen, then stored at -70°C. Attempts will be made to sample both cancer and normal for fresh frozen tissue acquisition. At the University of Washington, our experience with this protocol shows that approximately 80% of patients undergoing diagnostic prostate biopsy agree to donate the extra biopsy cores for research purposes.

Blood collection
Participants will have blood drawn at study entry, at each biopsy, and at time of intervention (off protocol). At each time-point, 15ml of blood in an EDTA lavender top tube (plasma) and 15ml of blood into a pre-chilled heparin green top tube (serum) will be collected. Immediately after collection, both tubes will be spun in a refrigerated centrifuge. Plasma and serum will be separated into 500 ul aliquots in 1.5ml cryovials, immediately stored at –80ºC. At study entry, a yellow top tube will be drawn for immortalization of white blood cells.

Urine
A mid-stream, clean catch urine will be obtained at study entry, time of each biopsy, and annually. Additionally, expressed prostatic secretions after DRE will be collected at study entry, time of each prostate biopsy, and annually.

Radical prostatectomy tissue (when applicable):
If the participant undergoes radical prostatectomy upon progression, prostate tissue will be acquired. Both FFPE and fresh frozen tissue is required for tissue banking, and both malignant and benign tissue will be sampled with both methods of tissue preservation.

9. INFORMED CONSENT

Informed Consent Document
The IRB of each institution must approve the consent form for the study timeline and acquisition of research specimens. The consent will also specify that at each visit, patients will be reminded that active treatment remains an alternate option to active surveillance. Physicians will also inform patients of new developments in the treatment of prostate cancer and provide consultation with regards to treatment options for clinically localized prostate cancer.

Changes to the consent form in the course of the study will also require IRB approval. It is essential that the consent form contain a clear statement, which gives permission for:

1) tissue and information to be sent to and 2) source medical records to be reviewed by other collaborating institutions

Consent Process/Patient Eligibility
Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Each patient will be provided with a full explanation of the study before consent is requested.

10. REFERENCES:

1. Warlick CA, Allaf ME, Carter HB: Expectant treatment with curative intent in the prostate-specific antigen era: triggers for definitive therapy. Urol Oncol 24:51-7, 2006
2. Carter HB, Walsh PC, Landis P, et al: Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. J Urol 167:1231-4, 2002
3. Hardie C, Parker C, Norman A, et al: Early outcomes of active surveillance for localized prostate cancer. BJU Int 95:956-60, 2005
4. Klotz L: Active surveillance with selective delayed intervention for favorable risk prostate cancer. Urol Oncol 24:46-50, 2006
5. Meng MV, Elkin EP, Harlan SR, et al: Predictors of treatment after initial surveillance in men with prostate cancer: results from CaPSURE. J Urol 170:2279-83, 2003
6. Patel MI, DeConcini DT, Lopez-Corona E, et al: An analysis of men with clinically localized prostate cancer who deferred definitive therapy. J Urol 171:1520-4, 2004
7. Roemeling S, Roobol MJ, de Vries SH, et al: Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. Eur Urol 51:1244-50; discussion 1251, 2007
8. Kattan MW, Eastham JA, Wheeler TM, et al: Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumors. J Urol 170:1792-7, 2003
9. Steyerberg EW, Roobol MJ, Kattan MW, et al: Prediction of indolent prostate cancer: validation and updating of a prognostic nomogram. J Urol 177:107-12; discussion 112, 2007

APPENDIX I - PATIENT EVALUATION FLOW SHEET

Investigations		Timing from entry
History and Physical Examination	History Performance Status Digital Rectal Exam	q 4 mos
Biochemistry	Serum PSA	q 4 mos
Radiology	As clinically indicated	-
Other investigations	TRUS-guided biopsy	at entry if < 10 core diagnostic bx, at 6-12 months, at 2 years, then q 2 years
	Urine/EPS	at entry, at each biopsy, and q 1 yr

APPENDIX II – PATIENT EVALUATION TIMELINE

Measure	Entry	4	8	12	16	20	24	28	32	36	//	Tx
DRE/PSA	x	x	x	x	x	x	x	x	x	x		
Blood	x	x	x	x	x	x	x	x	x	x		x
Tissue/Bx	x*			x¥			x					x
DNA	x											
Urine	x			x			x			x		x
EPS	x			x			x			x		x

*** if less than 10-core diagnostic biopsy**
¥ biopsy performed at 6-12 months from entry