Biomarkers for Prostate Cancer Detection

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Purpose: The limitations of prostate specific antigen as a biomarker for prostate cancer screening, characterized by low sensitivity for acceptable false-positive rates, are well known. New markers that differentiate indolent from aggressive cancers to decrease potential the over treatment of prostate cancer are needed. We reviewed current and potential biomarkers for prostate cancer detection.

Materials and Methods: A literature search was performed to identify established and emerging biomarkers for prostate cancer detection. Recent suggested guidelines by the Early Detection Research Network for phases of biomarker studies were interpreted for use in prostate cancer and the existing status of marker studies were reviewed with respect to these phases of study.

Results: Advances in high throughput bench research, including high dimensional genomic, proteomic and autoantibody signatures, have the potential to improve the operating characteristics of prostate specific antigen but they are undergoing reproducibility and multicenter validation studies. None of the prostate specific antigen derivatives or isoforms, such as prostate specific antigen density, velocity or percent complexed prostate specific antigen, improve operating characteristics enough to likely replace prostate specific antigen. Prostate stem cell antigen, alpha-methyl coenzyme-A racemase, PCA3, early prostate cancer antigen, human kallikrein 2 and hepsin are promising markers that are currently undergoing validation.

Conclusions: The process of discovering novel biomarkers to replace or augment the existing best marker, prostate specific antigen, requires standardized phases of evaluation and validation. Several biomarkers are currently on the cusp of initial validation studies.

Key Words: prostate; prostatic neoplasms; tumor markers, biological; validation studies [publication type]; prostate-specific antigen

The discovery and development of novel biomarkers for prostate cancer detection remain a formidable challenge despite the widespread use of PSA for prostate cancer screening. It took more than a decade to transform the discovery of PSA into its clinical application for prostate cancer detection and treatment, and a similar period to understand that PSA is not an ideal biomarker for prostate cancer detection. In 2004 it was reported that there is no absolute lower value of PSA below which there is a negligible risk of prostate cancer and PSA is not a dichotomous marker, but rather one with values that reflect a continuum of risk for prostate cancer.[1] Biomarker discovery in prostate cancer is a complex challenge because, in addition to the desirability of a yes or no answer for a potentially continuous disease, there is a need for markers that differentiate indolent from aggressive cancers to minimize over treatment. Significant efforts have been initiated in the discovery of new biomarkers in different biospecimens, including serum, urine and prostatic tissue. New high throughput technologies, including genomic microarrays and proteomics, have facilitated high dimensional, rapid biomarker discovery. However, the road from the initial discovery of a biomarker to widespread clinical application is a long one that involves several steps, including accurate methods for marker detection, pilot single institutional studies, and rigorous validation in retrospective and prospectively performed studies. The focus of this review was to evaluate existing and emerging biomarkers for prostate cancer detection, and the current consensus regarding the design of marker studies to facilitate validation in this important field. The Appendix lists select biomarkers and biospecimens.

GENE FUSION/TRANSLOCATION MARKERS

In contrast to hematological malignancies, few translocations have been identified in solid tumors. A recent study using sophisticated bioinformatics technology for data mining (cancer outlier profile analysis) to identify outlier genes showing high expression in a subset of cancers identified a gene fusion (translocation) present in 80% of cancers (23 of 29 prostate cancer tissue samples) and absent from benign prostate tissue.[2] Among the top 10 over expressed genes found were ERG and ETV1, which were fused to the 5′ untranslated regions of TMPRSS2. TMPRSS2 is an androgen responsive membrane anchored serine protease. Cur-

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rently the expression products of this translocation are not characterized and this would be a subject of future interest.

PROTEOMICS

Representing DNA and RNA function, proteins are the ultimate end products for gene expression. They act as the functional molecules that mediate most changes at the cellular level in cancer. There has been a recent uptrend in the application of proteomics, the simultaneous study of multiple proteins on a large scale, to discover novel proteins and patterns of proteins as biomarkers for prostate cancer by high throughput analysis of body fluids, cells and tissues as well as animal models and tumor cell lines.[3] SELDI-TOF and matrix assisted laser desorption/ionization-TOF mass spectrometry are currently the most common techniques.[4] Adam et al reported 83% sensitivity and 97% specificity for prostate cancer discrimination from benign prostatic disease for a panel of 9 terminal nodes from a decision tree algorithm beginning with 63,157 peaks, as measured by SELDI-TOF.[5] Proteomic technology continues to evolve but reproducibility is a concern. An ongoing study by NCI EDRN is evaluating the potential for SELDI to produce biomarkers for prostate cancer in a 3-stage protocol, including the establishment of reproducibility, multi-institutional case control and validation in a prospective trial with complete disease ascertainment.[6]

AUTOANTIBODY SIGNATURES

High throughput proteomic techniques have facilitated the discovery of autoantibodies directed against tumor specific antigens in the serum of patients with cancer. Autoantibodies, which to date have been the cornerstone of diagnosis in autoimmune and infectious diseases, may have a similarly prominent role in prostate cancer detection, risk stratification, prognostication and prediction of the response to therapeutic modalities.

Multiple prostate cancer specific antigens were recently identified via the detection of autoantibodies in the serum of patients with prostate cancer via high throughput phage-peptide microarray analysis.[7] The measurement of serum autoantibodies against a panel of 22 tumor associated peptides detected prostate cancer with 88.2% specificity and 81.6% sensitivity in a case-control study. Compared to PSA, this autoantibody signature had significantly better performance with an AUC of 93% compared to the AUC of PSA of 80% from the same sample. Multiple logistic regression analysis confirmed the independent prognostic value of the panel vs PSA ($p < 0.001$). To appropriately account for over optimism due to the selection of 22 peptides from a much larger set of potential markers a separate data set was used to train the model in 119 cases and 138 controls from the data set used to test the model in 60 cases and 68 controls. This study suggests that these promising operating characteristics of the 22 peptide panel may be maintained in other populations. Future studies establishing the reproducibility of this technology and its validation on more disparate populations are necessary.

Antibodies to other antigens that are over expressed in prostate cancer, such as huntingtin interacting protein-1 and prostasomes, have also been evaluated.[8,9] Improvements in sensitivity and specificity were reported for the markers alone or in combination with other established markers, paving the way for future clinical studies using multiple biomarkers in combination as a panel.[8]

PSA AND PSA ISOFORMS

Serum PSA is the most widely used biomarker for the screening and early detection of prostate cancer. Higher PSA levels are directly associated with the risk of cancer and the risk of high grade disease as well as with tumor stage.[10] There is a nonnegligible risk of prostate cancer at any PSA level, making it difficult to recommended a lower PSA cutoff for a recommendation for more invasive screening.[1,11] Indeed, as a group, in men with PSA below 4.0 ng/ml the risk of cancer is approximately 15% and 15% of these patients have high grade disease.[1] Nonetheless, at lower PSA levels, eg less than 1.0 ng/ml, the risk of high grade disease is quite low. Conversely while PSA levels above 4.0 ng/ml have traditionally been deemed increased, cancer is found on biopsy in only 25% to 30% of the men evaluated. The operating characteristics of all other cutoffs for PSA, in addition to 4.0 ng/ml, are similarly challenging from a clinical standpoint when tradeoffs in sensitivity and specificity are examined.[11]

To improve its operating characteristics several modifications of PSA have been introduced, including the rate of change in PSA with time (PSA velocity), the ratio of PSA to prostate volume (PSA density), age specific PSA ranges and PSA doubling times.[12–15] However, none of these modifications have shown operating characteristics that are markedly superior to those of PSA.[1,16] These modified biomarkers tend to correlate highly with PSA and the few studies that appropriately evaluated their independent diagnostic contribution to PSA, by simultaneously including PSA and the proposed derivative in the same risk model, showed no incremental value above PSA.[16] Since these PSA derivatives are more difficult to measure than PSA, eg PSA density requires transrectal ultrasound, it is unlikely that they will replace PSA for prostate cancer screening.

New PSA assays have also been developed, including percent free (unbound) PSA, percent complexed PSA and PSA isoforms. PSA in serum may be free or complexed, commonly with alpha 2-microglobulin and alpha 1-antichymotrypsin.[17] The amount of unbound PSA, expressed as the free-to-total PSA ratio (percent free PSA), has been used to improve the operating characteristics of PSA, especially in patients with PSA values in the uncertain range between 4 and 10 ng/ml. Free PSA levels below 15% to 25% are associated with an increased risk of prostate cancer but it is estimated that only 30% to 50% of men with free PSA less than 15% have a positive biopsy.[18] Complexed PSA was shown to moderately improve specificity by 6.2% to 7.9% compared to total PSA in the PSA range 2.0 to 10.0 ng/ml in a prospectively performed multicenter clinical trial but the AUC for complexed PSA over all PSA ranges only exceeded that from PSA by 1.5% in the same trial.[19] This value was quite similar to the approximately 70% reported for PSA in PCPT.[16]

Free PSA comprises at least 3 inactive isoforms, including proPSA and BPSA, and assays for these isoforms have been proposed for enhancing PSA accuracy. ProPSA improves the detection of prostate cancer in PSA ranges less than 4 ng/ml and it is more highly associated with aggressive prostate cancers than other PSA forms, such as PSA-

alpha 1-antichymotrypsin and free PSA.[20] BPSA typically represents benign tissue, so that the proPSA-to-BPSA ratio was proposed in an attempt to improve the performance of proPSA. For a proPSA/BPSA cutoff achieving 90% sensitivity, 46% specificity was attained for men with free PSA less than 15%.[21] To date studies of PSA isoforms have produced only minor improvement in operating characteristics along restricted ranges of PSA and they have not yet reached the point of specific recommendations for integrated use in a global screening scheme across all PSA levels. Using complex rules combining total to percent free PSA Etzioni et al also found only modest improvements in accuracy compared to PSA alone.[22] Future studies should explore the added value of these isoforms to current early detection strategies.

PSCA

PSCA is a prostate specific glycoprotein that is expressed on the cell surface. Currently it is possible to detect PSCA protein in prostate cancer tissues by immunohistochemistry and PSCA RNA in blood by reverse transcriptase-PCR.[23] A correlation between increased PSCA expression and prostate cancer risk was observed in several studies[23,24] but further larger validation studies evaluating its operating characteristics are needed to confirm its usefulness for prostate cancer detection.

AMACR

AMACR is an isomerase that is over expressed in virtually all prostate cancers.[25] The detection of AMACR by immunohistochemistry in tissue is commonly used to resolve difficult diagnostic biopsy cases. It is not readily detected in blood, although autoantibodies to AMACR, anti-AMACR, have been detected in measurable quantities in serum. In subjects with intermediate PSA levels (4 to 10 ng/ml) the immune response against AMACR was more sensitive and specific than PSA in distinguishing serum from patients with prostate cancer relative to control subjects with a sensitivity and specificity of 77.8% and 80.6% vs 45.6% and 50%, respectively, and an AUC of 78.9% vs 49.2% ($p < 0.001$).[26] The surprisingly low operating characteristics of PSA in this study, which were well below those in other large-scale studies, were biased because control subjects were selected from men with PSA 4.0 to 10.0 ng/ml. A lesson learned here is the importance of case and control subject selection independent of PSA to properly evaluate the clinical usefulness of AMACR and other markers as an independent or adjunct marker to PSA.

GSTP-1 HYPERMETHYLATION

The GSTP-1 gene belongs to a family of enzymes with a primary role in protecting DNA from free radical damage. Loss of GSTP-1 expression due to promoter hypermethylation is the most frequent somatic genome alteration reported in prostate cancer and in high grade prostate intraepithelial neoplasia.[27] GSTP-1 may prove to be a valuable biomarker since it is highly prostate cancer specific. It can be detected in prostate cancer tissues, urine and seminal fluid/expressed prostatic secretions. However, significant improvements must be made to improve detection rates in urine because the current method of detection with methylation specific PCR has resulted in disappointing NPVs when applied to urine specimens.[28,29] Suggestions for overcoming this problem by performing prostatic massage before voiding have met with mixed results.[30,31] A recent case-control study used quantitative methylation specific PCR tested urine sediment DNA for the aberrant methylation of 9 gene promoters. Promoter hypermethylation of at least 1 gene studied was detected in urine samples from all patients with prostate cancer. Overall methylation found in urine samples matched the methylation status in the primary tumor. A combination of only 4 genes (p16, ARF, MGMT and GSTP-1) allowed the detection of 87% of prostate cancers with 100% specificity.[32]

PCA3

$PCA3^{DD3}$, which is over expressed in 95% of prostate cancers with a median 66-fold up-regulation compared with adjacent normal tissue, is a promising test for prostate cancer detection.[33] This marker is measured in urine after DRE in which repeat pressure is placed on the prostate to allow the shedding of prostate epithelial cells and the presence of the marker is evaluated using reverse transcriptase-PCR. In a group of 443 men undergoing prostate biopsy 66% sensitivity and 89% specificity were achieved and in the subgroup of 94 with PSA less than 4.0 ng/ml 74% sensitivity and 91% specificity were achieved.[34]

EPCA

EPCA is a nuclear matrix protein identified in prostate cancers. Using enzyme-linked immunosorbent assay EPCA was detected in the serum of men with prostate cancer but not in age matched serum from organ donors or men with other cancers.[35] EPCA has promise as a tissue and serum marker for prostate cancer.

HK2

HK2 belongs to the HK family, a group that includes PSA. HK2 and PSA are specifically expressed in the prostate at high levels under androgen regulation. Over expression of HK2 has been reported in prostate cancer tissues in several studies and HK2 has been used in various combinations with free and total PSA to improve specificity and sensitivity for prostate cancer detection as well as for prognosis but with mixed results.[36–38]

HEPSIN

Multiple studies have shown over expression of the gene that expresses the protein hepsin in up to 90% of prostate tumors.[39,40] However, the lack of detection of hepsin in serum or urine currently limits its role as a biomarker. Future studies aimed at better detection methods may facilitate the role of hepsin as a potential biomarker for prostate cancer detection.

GUIDING PRINCIPLES FOR MARKER STUDIES

In 2001 to parallel the established phase I-IV trial guidelines for clinical trials the NCI EDRN identified 5 phases of biomarker development for the early detection of cancer[41]

and recommended guidelines for the performance of studies in each phase. These guidelines were developed to standardize biomarker studies, so that cross-study comparisons and validations could be more easily performed. We briefly interpret the guidelines into recommendations for designing prostate cancer biomarker studies.

Phase I

Phase I encompasses preclinical exploratory studies comparing the molecular characteristics of tumors to nontumors for leads in biomarker identification,[41] including the genomic, proteomic and autoantibody studies discussed. Because such studies often screen a large number of markers and they are more likely to be based on tissue specimens, they are typically underpowered with case and control tissue specimens selected by convenience. The primary end points of these studies include the assessment of biomarker operating characteristics, including AUC, sensitivity and specificity, the establishment of marker ranking and the assessment of multiple marker risk model algorithms. These algorithms, such as those generated by decision trees or artificial intelligence, and power and sample size determinations, may be based on a large number of multiple hypothesis tests of the null hypothesis that the AUC equals 50% or a multiple marker risk model would detect prostate cancer with AUC estimated within a certain accuracy. For designing studies to screen large numbers of markers sample sizes should control for the false discovery rate instead of the family wide error rate based on the popular Bonferroni correction since the latter can be too conservative.[42] Recently Dobbin and Simon provided sample size formulas for developing classifiers following an initial screening of high dimensional markers.[43] They found that sample sizes in the range of 20 to 30 per class may be adequate for building a good predictor in many instances. Additional secondary hypotheses for these studies should include formal assessment of the reproducibility of the technology, when feasible.

Phase I studies are generally case-control studies and tissue from normal controls typically comes from patients with benign conditions, such as benign prostatic hyperplasia. Unfortunately this group of men may not be representative of the population of men without cancer. Nonetheless, it is important to the greatest degree possible to match controls to cases on risk factors for prostate cancer and high grade disease, including age, race (black vs not black), family history of prostate cancer and, if possible, DRE and PSA collected within similar time frames. Even if it is not feasible to match on DRE and PSA, it is important to summarize the differences in these factors between cases and controls, and adjust for them in the analysis to yield the incremental diagnostic value of the new tests, especially in multiple marker evaluations, in which there is a greater chance to declare clinical significance due to chance.

In a recent evaluation of 54 potential new markers from a matched 125 case-125 control study for prostate cancer we found 8 markers associated with prostate cancer risk but none of them retained statistical significance after adjustment for PSA or the estimated PCPT risk score (Parekh et al, unpublished data). Because these previously validated prostate cancer risk factors were measured in each subject, it was possible to adjust the prostate cancer risk estimate by combining all risk factors, including PSA, into a single composite risk for each subject. When possible, we strongly recommend adjusting for the prostate cancer risk using the PCPT risk calculator, rather than adjusting for individual risk factors. It is also possible in a case-control study to use cases as their own controls by extracting normal tissue. Finally, it is desirable to include a wide spectrum of prostate cancers in terms of disease grade as cases for exploratory investigations of biomarker performance to predict tumor grade.

Phase II

Phase II was defined by the EDRN as the clinical assay validation stage and studies in this phase are typically small to moderately sized case-control studies.[41] In this stage a smaller set of markers is moved up from phase I or serum based markers are defined based on the molecular findings in phase I. In the latter case if there are subjects with measurement of the molecular and serum markers available, it is worthwhile to assess their correlation to verify the hypothesized biological pathway. In this phase it is important to establish the reproducibility of the assay across laboratories. As in phase I, in this phase the operating characteristics of the assay are quantified but specific cutoff levels for the marker can be suggested for use in screening in later phases. Therefore, the sample size criterion in this phase is typically driven by ensuring that there exists a cutoff, such that the FPR (FPR = 1 − specificity) is sufficiently low and the TPR (TPR = sensitivity) is sufficiently high. Pepe et al described this in terms of testing the composite null hypothesis H_0, in that TPR $\leq TPR_0$ or FPR $\geq FPR_0$, where FPR_0 is the highest acceptable FPR and TPR_0 is the lowest acceptable TPR for the biomarker to be worth pursuing through future phases.[41]

There is no official consensus in prostate cancer on the required lower limits of TPR and the upper limits of FPR, and the determination is muddled with the current problem of over detection and the inability to differentiate over detected from aggressive cancers at biopsy. Generally it is desirable to require the FPR to decrease below 20% and the TPR to increase above 80%. This is an ambitious task, given that there is no cutoff for the leading biomarker, PSA, that achieves this criterion.[11] In PCPT the PSA cutoff 4.0 ng/ml achieved an FPR of 6.2%, well below the limit of 20%, but a TPR of only 20.5% was attained. The PSA cutoff of 2.5 ng/ml achieved an FPR of 18.9% but only increased the TPR to 40.5%, still approximately half of the desired TPR_0. In the PCPT the only cutoff point and end point definition that came close to satisfying the required limits was 2.5 ng/ml for detecting Gleason grade 8 or greater prostate cancer with an FPR of 24.9% and a TPR of 78.9%.[11] This illustrates the point in case-control selection, which was also made for phase I, that operating characteristics of a marker can vary greatly by disease type and it is important to include a spectrum of disease states in the cases when possible.

Phase III

Phase III was defined by the EDRN as the retrospective longitudinal evaluation of biomarkers.[41] It has been common for evaluating PSA and its derivatives, eg PSA velocity (change in PSA with time) and PSA density (PSA divided by prostate volume) due to the availability of observational

cohorts with these data. Phase III is the first stage in which the preclinical operating characteristics of a proposed biomarker are identified. Typically in these studies a cohort of healthy men is evaluated with regular screening by the marker with correlation to subjects who later have prostate cancer. With sufficient marker measurements at various times before clinical detection the operating characteristics can be quantified at these prediagnostic time points. Sample size calculation is determined by the number of cases with sufficient preclinical measurements of the biomarker available. All such cancer cases in the cohort should be used and all controls or age matched controls should be compared. The type of hypotheses evaluated may be similar to that in phase II.

Because PSA screening increased in the 1980s, many cohorts are dominated by PSA detected cancers, especially in the latter years. Therefore, studies of PSA or its derivatives should include a verification bias adjustment algorithm to account for the potential for PSA based cancers. We and others have outlined verification bias algorithms that are suitable for this purpose.[11,44,45]

Phases IV and V

Phases IV and V involve prospective evaluation of the biomarker based screening test for prostate cancer detection and the impact on decreasing the burden of cancer in the general population (mortality and costs), respectively. Because these phases begin with healthy individuals, they require a long duration and a large number of subjects. PCPT is an example of a prospective evaluation for PSA nested within a chemoprevention trial that afforded the opportunity to assess the operating characteristics of PSA for biopsy detectable prostate cancer in men treated for an extended period with finasteride.[46,47] The ongoing Prostate Lung Colorectal and Ovarian Cancer Screening trial is a phase V evaluation study.[48]

CAVEATS IN BIOMARKER STUDIES

We encourage studies of PSA derivatives, such as percent free-to-total PSA, PSA velocity or PSA doubling time, to assess the independent diagnostic value adjusting for PSA and report the correlation between the marker and PSA. These markers often highly correlate with PSA and they are more difficult to measure. The same guideline applies to studies evaluating new markers. A randomized clinical trial compares a new treatment against the standard of care and a similar study design should be expected for biomarkers. Ideally in the design phase PSA would be measured in all subjects so that, in addition to the end point of evaluating the operating characteristics of the new marker, a comparison to the performance of PSA could be made.

Selecting controls and/or cases based on PSA strongly biases any evaluation of the operating characteristics of PSA and its derivatives as well as comparisons to a new marker. For example, many studies evaluate a new marker at limited PSA ranges, such as the uncertain range between 4.0 and 10.0 ng/ml. These studies do not provide evidence that the new biomarker would outperform PSA when used in practice for all PSA values and any comparison of the operating characteristics of the new marker to those of PSA in these ranges is severely biased. It would be more informative to perform a study that evaluates all ranges of PSA and defines a conditional test based on the new marker for PSA values in the uncertain range. Such combined rules for PSA and percent free PSA were evaluated by Etzioni et al.[22] Such conditional tests can then be compared against PSA across

Candidate Biomarker	Phase I (Discovery and early Refinements)			Phase II	Phase III	
	Discovery	Predictive Analysis	Assay Refinement	Charactizization (Blinded)	Retrospective/ Longitudinal	Comments
Prostate						
GSP1, Methylation[37]	→	→				Promising prevalidation
Proteomics (serum)	→	→	→			Promising prevalidation
Pro-PSA	→	→				Promising NPV
HK2	→	→				Promising NPV
DD3/PCA3[3-39]	→	→				Promising NPV
uPM3	→	→				Promising NPV
N-Methylacyl-CoA Racemase (AMACR)	→					Overexpressed in prostate cancer and detection of autoantibodies against the protein
Hepsin	→					Overexpressed in prostaste cancer

Developmental status of prostate cancer biomarkers

the whole range of values, also using the ROC curve. Indeed, an advantage of the ROC curve is that multiple different tests of single or multiple biomarkers can be compared without regard to units. In such studies in which the new marker is evaluated on a restricted range of PSA, such as values between 4.0 and 10.0 ng/ml, the operating characteristics of PSA in the same restricted subset should not be reported or used for comparison since they are incorrect and do not correspond to the usual definitions. For example, in the mentioned restricted range of PSA between 4 and 10 ng/ml the sensitivity of PSA for all cutoffs less than 4.0 ng/ml is 100% and for all cutoffs greater than 10.0 ng/ml it is 0%. Sensitivity and specificity are biased even for cutoffs between 4 and 10 ng/ml and, hence, the AUC is biased from the usual AUC for PSA. This can be seen in the report by Wang et al.[7]

CURRENT STATUS OF EDRN BIOMARKER STUDIES

The figure shows a partial list of biomarkers at different stages of development. These biomarkers are being examined at various NCI EDRN laboratories (www.cancer.gov/EDRN). EDRN comprises a group of Biomarker Developmental Laboratories, where new biomarkers are developed and characterized or existing biomarkers are refined; Biomarker Reference Laboratories, which serve as a resource for the clinical and laboratory validation of biomarkers, including technological development, standardization of assay methods and refinement; Clinical Epidemiology and Validation Centers, where the early phases of clinical and epidemiological research on the application of biomarkers are performed and supported; and a Data Management and Coordinating Center, and Informatics Center led by investigators at the National Aeronautics and Space Administration Jet Propulsion Laboratory, where theoretical statistical approaches to simultaneous pattern analysis of multiple markers are developed.

CONCLUSIONS

Early detection of prostate cancer with biomarkers of the disease is a current fait accomplish, in that a large fraction of the population at risk in the United States currently undergoes PSA screening. Nonetheless, advances are necessary to decrease unnecessary biopsies in men without cancer and perhaps more importantly to detect those tumors, especially high grade tumors, that are present at PSA levels below traditional cutoff values. There are many methodological and analytical challenges to well designed clinical trials that must be understood when studies are designed and interpreted, and when biomarkers are considered for clinical use.

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APPENDIX

Biomarkers

Biomarker	Blood/Serum	Urine	Expressed Prostatic Secretions/Semen	Tissue
PSA, PSA Isoforms	+			
PSCA	+			+
AMACR	+	+	+	+
GSTP-1 Methylation		+	+	+
PCA3/uPM3		+	+	+
EPCA	+			+
HK2	+			
Autoantibody signatures	+			
Hepsin				+

Candidate biomarkers for prostate cancer detection with biospecimens in which they are commonly detected.

Abbreviations and Acronyms

AMACR	=	alpha-methyl coenzyme-A racemase
AUC	=	area below the ROC curve
BPSA	=	benign PSA
DRE	=	digital rectal examination
EDRN	=	Early Detection and Research Network
EPCA	=	early prostate cancer antigen
FPR	=	false-positive rate
GSTP-1	=	glutathione-S-transferase P1
HK2	=	human kallikrein
NCI	=	National Cancer Institute
NPV	=	negative predictive value
PCPT	=	Prostate Cancer Prevention Trial
PCR	=	polymerase chain reaction
proPSA	=	precursor PSA
PSA	=	prostate specific antigen
PSCA	=	prostate stem cell antigen
SELDI	=	surface enhanced laser desorption ionization
TOF	=	time of flight
TPR	=	positive rate

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