Urinary Biomarkers for Prostate Cancer

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KEYWORDS

• Prostate cancer • Biomarkers • Urine • PCA3 • TMPRSS2:ERG • GSTP1 • Metabolomics • Microbiota

KEY POINTS

- Prostate cancer antigen 3 scores less than 20 seem to reliably rule out the presence of prostate cancer and particularly higher-risk prostate cancer on repeat biopsy; complementary RNA-based markers, such as TMPRSS2:ERG, and DNA-based markers, such as GSTP1, may improve its predictive ability and require additional study.
- In addition to traditional RNA, DNA, and protein-based biomarkers, emerging areas of study include urinary microRNA, long noncoding RNA, metabolomics, exosomes, and microbiota.
- Optimal diagnostic ability is generally obtained when novel biomarkers are added to multivariable models, including clinical factors, such as age, prostate-specific antigen, digital rectal examination, and prostate volume.
- Studies comparing urinary biomarkers with other promising diagnostic tools, such as the Prostate Health Index and multi-parametric MRI, are limited but will be necessary to optimize accurate and efficient disease detection.
- Future biomarker studies should consistently report the rate of biopsy avoidance with marker use, rate of undiagnosed cancers if biopsy omitted, performance associated with specific threshold values, marker utility in multivariable models, and marker utility in diagnosing high-grade cancers.

INTRODUCTION

Significant technological advances in analytical methods and a greater understanding of molecular carcinogenesis has paved the way toward a new era of disease detection.[1–3] Potential biomarkers of human disease range from whole-cell analysis to characterization of cell-free components, such as proteins and nucleic acids.[4] In addition to traditional serum or plasma, urine has been proposed as an easily obtained substrate for prostatic biomarkers.[5] To date, several urinary biomarkers have been identified and considered for use in prostate cancer (PCa), each with varying levels of evidence. In the subsequent review, the authors' primary aim is to assess the evidence basis and potential applications of urinary biomarkers for PCa.

Urine as a Substrate

Before considering the multitude of molecular isolation and quantification techniques, successful urine-based screening largely depends on the (1) the shedding of PCa cells or their components into urine and (2) successful acquisition, processing, and preservation of urine.[6] The technical aspects of such methodologies have been previously reviewed in significant detail.[4,5] Initial questions considering the type (single void vs 24 hour)

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and timing (first catch vs midstream) of specimen collection have come out largely in favor of single-void, first-catch sampling.[4–6] From a clinical perspective, evidence supports collection of urine after prostatic manipulation (eg, digital rectal examination [DRE]) to optimize assay yield, and collection after transrectal ultrasonography (TRUS)–guided biopsy has proven feasible as well.[7,8] The authors have herein considered potential urinary markers of PCa with attention to clinically relevant factors impacting their use.

RNA-BASED MARKERS

Prostate Cancer Antigen 3

From bench to bedside

In 1999, Bussemakers and colleagues[9] first described *Differential Display Code 3* as a potential urinary biomarker for PCa. Based on differential display analysis, the investigators described a messenger RNA that was highly overexpressed in 95% of PCa tissue and absent from benign prostate tissue and other tumor types. Subsequently identified as PCa antigen 3 (PCA3), it was further characterized as a noncoding RNA that was indeed highly specific for PCa.[10,11] Early quantification with quantitative real-time–polymerase chain reaction (qRT-PCR) demonstrated a 34-fold increased expression in malignant prostate tissue and high discriminative value as demonstrated by an area under the receiver operating characteristic curve (AUC) of 0.98 (**Table 1** includes key definitions in the assessment of diagnostic tests).[10] These findings were subsequently replicated by other investigators, and the introduction of a novel urinary assay to detect PCA3 helped lead its transition to the clinical setting.[11,12]

In 2006, a functional platform for clinical use was introduced as the Progensa PCA3 assay.[12] Urine specimens were obtained after attentive DRE (3 strokes to each prostate lobe), and PCA3 was quantified based on transcription-mediated

Table 1
Measures of diagnostic performance

	Meaning	Equation	Practical Use	Threshold[a]
Sn	Ability of a test to correctly identify those who have the disease	$\frac{TP}{TP + FN}$	Emphasize sensitivity when penalty for missing a case is high (eg, disease spreads easily and is fatal but can be successfully treated)	Decrease threshold = test is more sensitive, less specific
Sp	Ability of a test to correctly identify those who do not have the disease	$\frac{TN}{TN + FP}$	Emphasize specificity when consequence (eg, treatment, additional testing) of positive test is significant (eg, invasive, toxic)	Increase threshold = test is more specific, less sensitive
PPV[b]	The proportion of patients who truly *do* have the disease out of all who test positive	$\frac{TP}{TP + FP}$	If a person tests positive, what is the probability that he or she *does* have the disease?	—
NPV[b]	The proportion of patients who truly *do not* have the disease out of all who test negative	$\frac{TN}{TN + FN}$	If a person tests negative, what is the probability that he or she *does not* have the disease?	—
AUC[a]	The probability the test score of a randomly selected diseased subject will be greater than that of a randomly selected nondiseased subject	—	Quantifies the diagnostic performance of a test in terms of sensitivity and specificity independent of a specific threshold value	—

Abbreviations: FN, false negatives; FP, false positives; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; TN, true negatives; TP, true positives.

[a] Assuming higher/increased values are positive test results.

[b] Predictive values (ie, positive predictive value, negative predictive value) are *not* fixed characteristics of a test; they depend on the disease prevalence in the tested population.

Data from Refs.[209–212]