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CASE REPORT

# Prostate Cancer: Beyond PSA

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## COMMENTARIES

For men 65 years and older, the risk of having prostate cancer (PCa) is 17% and dying of PCa is 3%, higher than the general population. Globally, in 2020, there will be estimated 553 million males older than 65 years, and there will be 94 million new cases with PCa each year. Of these (3%) 2,820,300 will die of PCa. This translates into>5 PCa deaths/sec. In the USA alone, estimated PCa related deaths in 2020will be>3/hr [1-3].

Early diagnosis saves lives. The commonly practiced methods for early diagnosis of PCa are DRE (digital rectal examination) and the serum measurement of PSA (prostate specific antigen).DRE allows physicians to "feel" the prostate size but not to diagnose the PCa unless the PCa nodules are grown on the prostate surface.

Millions of PSA tests are performed each year in the USA and abroad. The major limitation of the PSA test is its non-specificity, in that PSA can be elevated under several non PCa conditions, such as benign prostatic hyperplasia (BPH) or prostatitis. Such a lack of specificity, leads the PSA measurements to over diagnosis and over treatment. In 2012, therefore, the US Preventive Service Task Force (USPSTF) recommended against the routine use of the PSA test [4].

Today, therefore, for the diagnosis of PCa, the pathologic examination of prostatic tissue remains a gold standard. Tissue extraction from a prostate however is a morbid procedure and can lead to a prolonged or excessive bleeding and infection. Furthermore biopsies are known to find benign pathology, without evidence of malignancy, in >66% of the cases [5-7]. More than one million such biopsies are performed annually in the US alone [8]. The annual cost of unnecessary biopsies is estimated to be hundreds of millions of US dollars.

Increased understanding of PCa at the cellular and molecular levels has paved the way to the development of new approaches that can serve as reliable and minimally invasive diagnostic tests. One such a test, approved by the US Food and Drug Administration (FDA) is a PCA3 test. It is a multiplex gene test that targets a PCa molecular signature for which the patient's urine must be collected following prostate massaging performed in a specific manner. Prostate massaging is not a comfortable procedure to most subjects. Furthermore PCa is a heterogeneous disease that requires sequencing of several genes for a reliable diagnosis. The multiplex gene sequencing makes the test over expensive. The complexity of this procedure, in part, have rendered the sensitivity of the test between 62% to 94%, specificity from 37% to 99%, positive predictive value from 42% to 98% and negative predictive value from 36% to 96%. [9]. As a result, the accuracy of the PCA3 test is considered questionable. This together with its high cost, the PCA3 test has remained controversial.

Another PCa test performed commercially by OPKO Laboratory is the 4Kscore test. The test is based upon the measurements of specific Kallikrein markers in blood serum of patients suspected to have PCa. The test determines serum concentration of i) total PSA, ii) free PSA, iii) intact PSA and iv) human Kallikrein (hK2). Although promising, its general clinical acceptance remains undetermined [10].

A new test, known as PHI (the Prostate Health Index), is determined by a formula that combines all 3 forms of PSA (total PSA, free PSA and proPSA (p2PSA)) into a single score. The formula is p2PSA/free PSA multiplied by the square root of PSA. The PHI gives more information on what an elevated PSA level might mean to the patient condition. At 95% confidence level, the clinical sensitivity, and clinical specificity of PHI was 16% as compared to 8.4% for free PSA and 6.5% for PSA [11].

SelectMDx is another test that performs reverse transcription PCR (Rt-PCR) assay on post DRE urine samples. The test measures the mRNA levels of DLX1 and HOXC6 biomarkers of the PCa. These markers are associated with increased probability of high grade (>7) Gleason score. Routine clinical utility of the SelectMDx test is awaited [12].

A biotechnology company ExosomeDx recently announced a ExoDxTM Prostate (IntelliScore) (EPI), a urine based test that allows physicians to assess whether a patient presenting for initial prostate biopsy is at a greater risk for prostate cancer. EPI is intended for use in men 50 years or older with

PSA 2-10 ng/ml serum and scheduled for prostate biopsy.

Exosomes are cell derived 30 to 100 nm diameter vesicles that are present in certain body fluids such as blood or urine. The isolation and detection of exosomes from other vesicle types has proved to be complex [13]. Exosomes contain RNA, lipids and certain proteins that are reflective of the cell type and their tissue of origin. RNA extracted from exomes separated from patient urine is sequenced for identification of prostate cancer. The clinical utility of this approach is yet to be validated.

The development of so many scholarly tests, in one form or another, strongly reflects upon the weaknesses of the PSA determination test that has been in use for more than two decades. However these new assays have not yet met with universal acceptance. There remains therefore an unmet need for a non-invasive, simple, yet reliable and relatively affordable assay that can be used for screening and diagnosis of PCa.

We have recently published what appears to be an assay that might satisfy the current needs [14]. The assay uses only voided urine, does not need DRE and does not require gene sequencing. It targets VPAC1 receptors expressed in high density on shed PCa cells by using a fluorophore that is specific for VPAC1. When observed under a microscope the malignant cells can easily be identified by a characteristic orange/red fluorescence around the cell nucleus, appearing distinctly different than the healthy/normal epithelial cells. The authors have shown >98% accuracy for detecting PCa in (N=141) voided urine of patients with PCa and 100% accuracy (N=10) in finding only epithelial cells in BPH subjects. The authors have validated their hypothesis that all fluoresced cells, had VPAC1 receptors expressed on cell surface and that the cells were malignant by three different well established techniques.

VPAC1 is a genomic biomarker that belongs to a super family of G-protein coupled surface receptors which promote cell survival and cell proliferation. These receptors are expressed in high density on the onset of oncogenesis and a way ahead of the alternations in cell morphology. In principle, the technique provides a simple, yet effective approach to detect PCa early and reliably. The simplicity of the procedure makes the assay a patient friendly and economical.

Once further substantiated the assay can be used for screening for PCa, for detection of PCa in patients with recurrent PCa, monitoring the disease of those on surveillance and to determine effectiveness of therapeutic interventions. The assay also promises to reduce patient morbidity, reduce unnecessary biopsy procedures and to save on healthcare dollars.

Beyond PSA, will there be a better substitute, for screening and diagnosis of PCa? Only the time will tell.

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