Urine Biomarkers for Prostate Cancer Detection

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Acknowledgement of Support

Funding

US National Institutes of Health (NCI CA111891; CA165202)
US Department of Defense (PC040569)
US North Carolina Biotechnology Center (MRG-1101)
US Golfers Against Cancer Foundation

Patents

US 7,445,906 (Prostate Cancer)
US 8,058,020 (Lung Cancer)
US 8,932,824 (Esophageal Cancer)
PCT/CN2012/000708 (ZCL278)
US #20140051081 (Prostate Cancer-pending)

Urine Biomarkers for Prostate Cancer Detection

- Significances of cancer biomarkers

- Biomarker sources

- Potential urine biomarkers for prostate cancer detection

- Challenges and opportunities

Cancer Biomarker Applications as An Industry

Biomarker Market

- **An active world market**
  20 billion

- **International conferences**

- **Publications**
PubMed: 264,855
4,700 (2015)
27,180 (Prostate)
761 (Urine)

- **Merger and acquisition**

Biomarkers improve and save life

- ***EGFR mutations and Iressa (Gefitinib)***
- ***Prostate specific antigen (PSA)***

Precision and personalized medicine on the horizon

- ***NGS and genome diagnosis***
- ***Omics in all categories***
- ***Point-of-care technologies (POCT) and mobile technologies***

Enriched Biomarker Sources

Tissues

- ❑ *Pathology meets molecular biology*
- ❑ *Pathology meets immunology*

MDxHealth Test: DNA hyper-methylation

1. *GSTP1-DNA detoxification*
2. *APC-apoptosis*
3. *RASSF1-cell cycle regulation*

Cells and their presence in body fluids

- ❑ *Circulating tumor cells (CTCs)*
- ❑ *Cell debris and/or exosomes (prostasomes)*

Fluids (serum and urine)

- ❑ *Nucleic acids*
- ❑ *Proteins*
- ❑ *Metabolic products*

Hologic Gen-Probe Test:

1. *Progensa PCA3 assay*

Urine Biomarker Characteristics

- Simple and non-invasive
- Cost effective
- Early detection and screening
- Variable and unstable

Urine biomarkers are attractive because they may offer a simple, non-invasive approach for early detection of prostate cancer and can allow broader population access to the screening. However, their reliability is subject to changes by diet, behavior, ways of collection and storage.



Lu et al., 2012. Cancer Biomarkers

Urine Biomarkers for Prostate Cancer Detection

Prostate cancer biomarkers in commercial applications

- ***PSA: Paradoxes (USPSTF)***
- ***PCA3: Paradoxes (FDA approval and market acceptance)***
- ***MDxHealth Test: (Epigenetics)***

Urine biomarkers under development

- ***Non-coding RNA (miRNA; TMPRSS2:ERG; SchLAP1; TTTY15-USP9Y)***
- ***Engrailed 2 (EN2)***
- ***δ-Catenin/NPRAP/Neurojungin***
- ***Minichromosome maintenance 5 protein***
- ***Anterior gradient 2 (ARG2)***
- ***Sarcosine***
- ***PSMA***

PCA3

Urine sediments following DRE or post-biopsy

1. *Urine collection following DRE with push.*
2. *First void urine following biopsy*

Brown et al., 2014. Urology (2000 patient tests)

Acceptable sensitivity and specificity

1. *Sensitivity: 0.62 (0.59-0.65). CI: 95%*
2. *Specificity: 0.75 (0.73-0.76). CI: 95%*
3. *AUC: 0.75 (0.71-0.78). CI: 95%*

Xue et al., 2014. J Cancer Res Ther (Meta analysis of 13 trials)

Obstacles in clinical applications

1. *Market acceptance*
2. *Medical insurance reimbursement*

Moul J, 2014 Urology (Editorial comments)

PROGENSA® PCA3 Assay - FDA



TMPRSS2:ERG Fusion

MLabs
Expertise Delivered Personally

Mi-Prostate Score (MiPS)

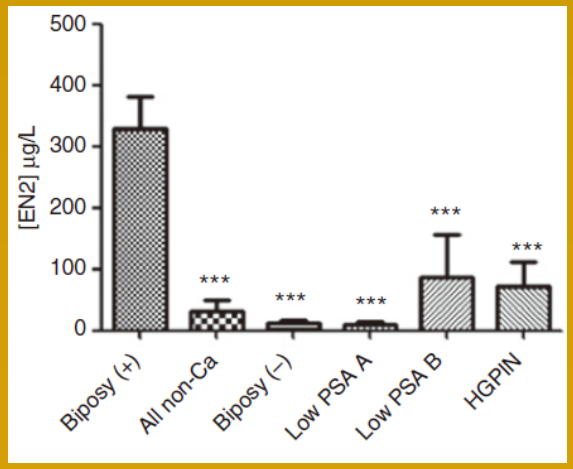
-TMPRSS2:ERG, PCA3 and PSA-

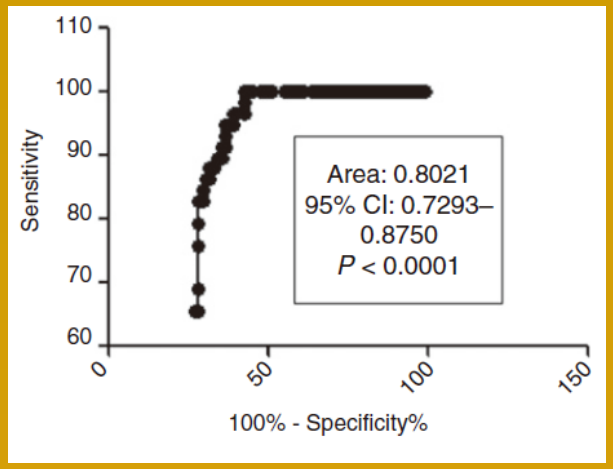


From the three groups based upon the levels of TMPRSS2:ERG and PCA3 in their urine: low, intermediate and high levels, cancer was diagnosed in each of the groups respectively: 21%, 43%, and 69%. **High-grade prostate cancer, defined as a Gleason score greater than 6, also occurred at different frequencies in the three groups** with 7%, 20%, and 40% diagnosed in each group respectively

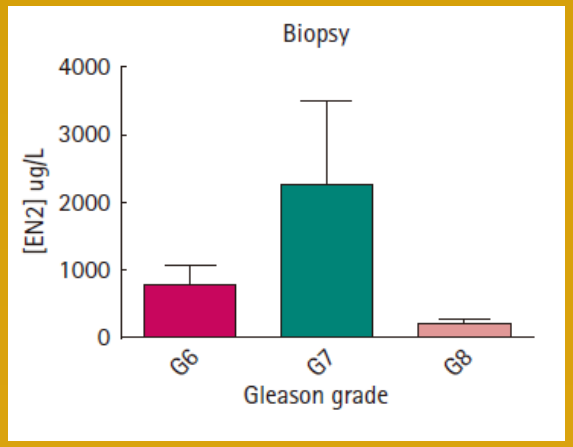
Engrailed 2 (EN2)

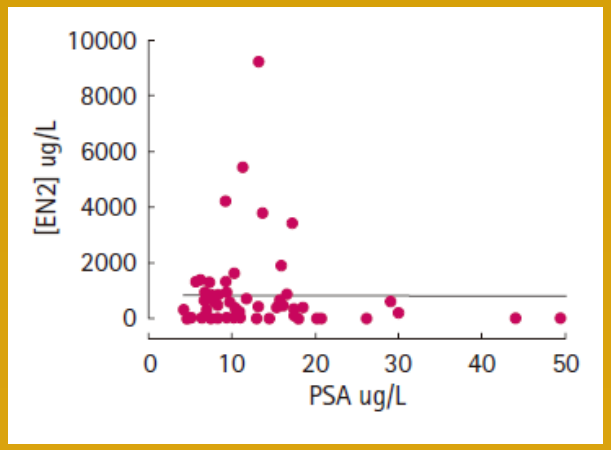
A Hox family protein overexpressed in PCa urine





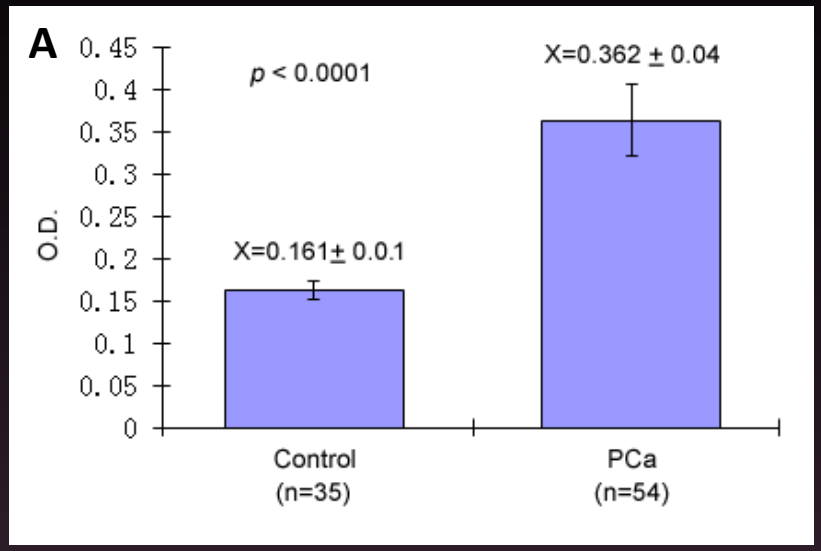
Morgan et al., 2011. Clin Can Res

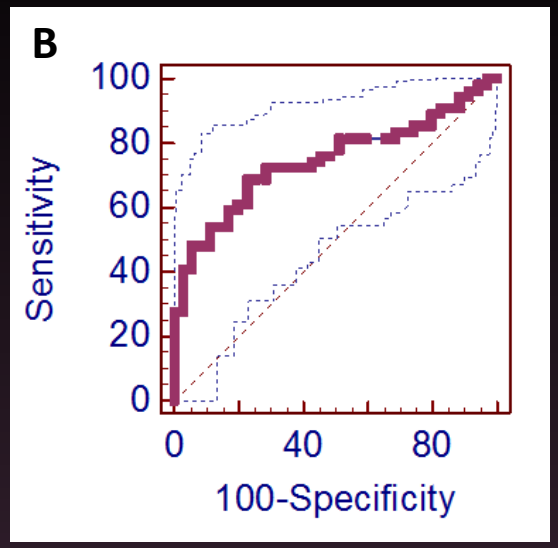




Pandha et al., 2012. BJUI

δ-Catenin/NPRAP/Neurojungin





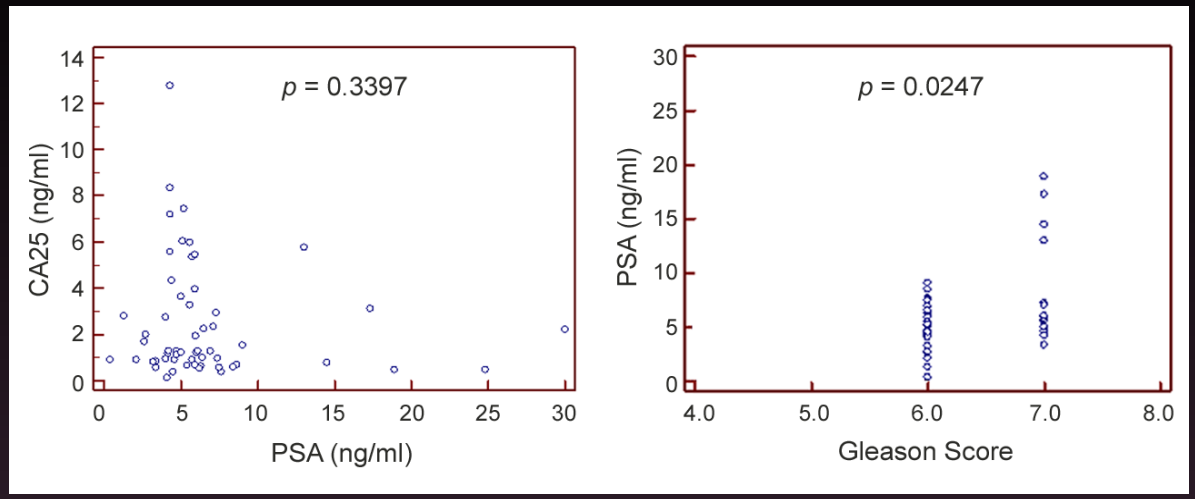
Sensitivity: 68.52%
Specificity: 77.14%

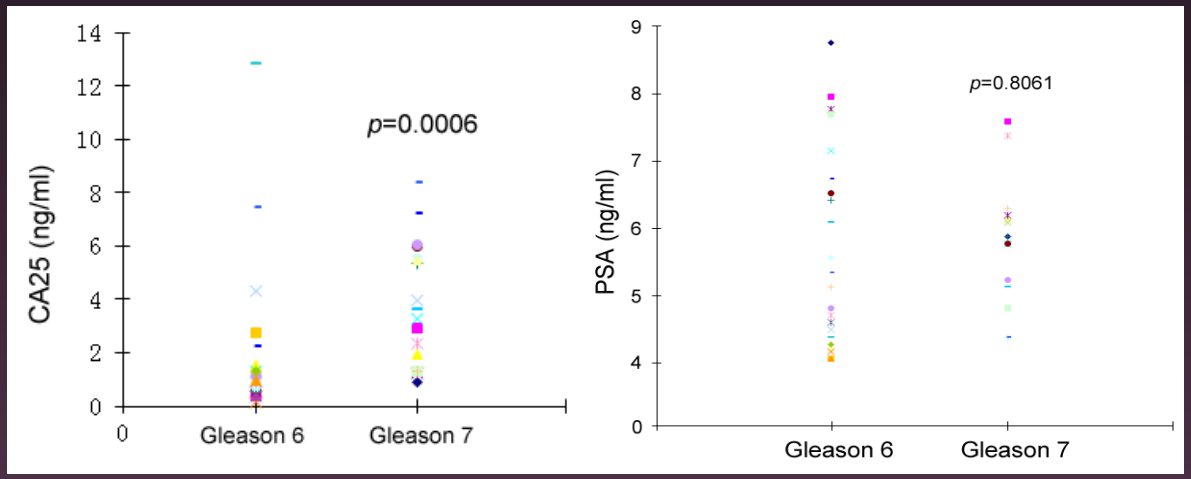
ROC curve		
Variable	Control/PCa	
Sample size		89
Positive group :	diag = 1 PCa	54
Negative group :	diag = 0 Control	35
Area under the ROC curve (AUC)		0.744
Standard Error a		0.0519
95% CI		0.640 to 0.830
Significance level P (Area=0.5)		<0.0001

a DeLong et al., 1988
b Binomial exact

ECU-UNC Epidemiology Study
(Unpublished)

Comparison betweeb δ-Catenin and PSA





ECU-UNC Epidemiology Study

(Unpublished)

δ-Catenin/NPRAP/Neurojungin

Detection of PCa Using CA25 Based ELISA

Study	CA25 (ng/ml) Cut-off	Sensitivity	Specificity	AUC
China (n=46)	> 0.92	69.44	70.00	0.70
China + NCBC (n=142)	> 1.18	54.17	69.57	0.60
Gleason 7 Corrected (n=58)	>1.18	81.82	70.00	0.80

ECU-UNC Epidemiology Study: PCa Case Analysis

(Unpublished)

Urine Biomarkers for Monitoring PCa Recurrence

- Biochemical recurrence: ***PSA (0.2~0.4 ng/ml)***

- Urine biomarkers

- ***DNA methylation in urine***

RASSF1, GSTP1 and RARB genes were methylated in the urine of 60% of patients with prostate cancer. RASSF1 was methylated in 45% of prostate cancer urine samples.

In a univariate model RASSF1 methylation and the total number of methylated genes were predictive of time to biochemical recurrence. On multivariate analysis RASSF1 methylation together with pathological stage was the most significant predictor of biochemical recurrence in patients with Gleason score 6 tumors when analyzed in tissue and urine.

Daniunaite et al., J. Urol 2014

- ***Protein levels independent of DNA/RNA alterations***

YB-1 and MTA-1 protein levels predict prostate cancer recurrence. High protein levels of YB-1 and MTA1 are associated with a 3-fold increased risk for requiring future hormone therapy or radiation therapy.

Ruggero et al. Oncotarget, 2015

The Rise of Theragnostics

Advanced Accelerator Applications (AAA):

Lutathera, a theragnostic somatostatin analogue, emits two types of radiation---gamma radiation used to make SPECT images and beta radiation, energetic electrons that destroy the DNA of tumor cells.

FDA Fast Track Designation for Lutathera for the treatment of midgut neuroendocrine tumors.

Molecular theragnostics targeting urine components?

- ❑ **Prostate-Specific Membrane Antigen (PMSA)**
- **- Radiopharmaceutics;**
- **- Vaccine therapy**

Challenges and Opportunities

- ***Improved sensitivity/specificity (Differential priority)***
- ***New categories of biomarkers***
- ***Diversified platforms (Hospital, third party, Theranos, retail consumer)***
- ***Clinical laboratory and market acceptance (Commercialization and medical reimbursement)***
- ***Accessibility and portability (internet and mobile technology)***
- ***Global health strategy***



Omics to big data and big health





POCT and global accessibility


Thank YOU!