What are currently the best decision markers for biopsy and re-biopsy of the prostate?

E. David Crawford, M.D.
Greetings from Colorado

Disclosures: Consultant: MDX Health, Myriad and Genomic Health
What are currently the best decision markers for biopsy and re-biopsy of the prostate?

• **Answer:** Markers which help determine which men have a cancer that would benefit from treatment.

• **Outline:**
  - Defining the Challenge
  - Prostate Cancer Markers (PCMs)
  - Working with Family Practice Physicians
  - Implementing Change
Message from USPSTF
And other organizations following the lead

• PSA screening is a “D” recommendation
• Physicians should not order PSA screening unless they are prepared to engage in shared decision making that enables an informed choice by patients

• What to do?

Prostate Cancer: Current Needs

• **Refine PSA**

• Increase the probability of an initial **positive biopsy**

• Reduce the number of **unnecessary repeat** biopsies by better distinguishing benign from malignant disease

• **Stratify** low risk from higher risk tumors

• Will **PCMs** (Prostate Cancer Markers) improve the answer: Yes
Time for Change
Not one fits all

• Precision medicine
• Selection Medicine
• Stratifying medicine
• Genomic Medicine
• Personalized Diagnosis and Therapy
What is a biomarker?
A molecule that can be found in blood, tissue or body fluids that is a sign of a normal or abnormal process.
PCM Buckets
Ways Forward

• Educate those who order PSAs—Family Doctors
• Define a PSA level with little risk
• Identify those who need further evaluation by a Urologist
Who is Ordering PSA Tests in United States?

We need to educate and target who is ordering PSAs

- Internal Medicine: 64.9%
- Family Medicine: 23.7%
- Urology: 6.1%
- Hem/Onc: 1.3%

Ways Forward

• PSA Levels
  • Improving the Performance of the test and find cancers that need to be treated
  • Eliminate needless repeat biopsies, but don’t miss a threatening cancer
Defining PSA Levels and Improving Performance

Patients and Methods:
- 350,000 HMO-Henry Ford System
- Men in system 1997-2008
- Initial PSA between 1-5ng/ml
- Minimum 5 years follow-up
- No 5 ARIs

Results:
- Mean age 55
- Mean PSA 1.0
- African American 29%
- Detected Cancer: 2%
- 21,502 men eligible
What is the Appropriate PSA Level?

 BJU Best Clinical Paper

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Accepted for publication 20 January 2011

African Americans 19-fold increase in risk 10.89%

A first PSA test threshold of 1.5 - 4.0 ng/mL, represents the Early-Warning PSA Zone
Patients with PSA ≥1.5 ng/mL have an increased risk of developing PC
Early Detection
A Way Forward

- PSA treated like other lab tests, lipids, electrolytes, weight, and BP - Routine
- Informed decision when tests are abnormal
- 70% of men require no discussion-based on our screening data on 150,000 men.
- Men’s Health broader issue > 1.5ng/ml surrogate for BPH, Prostatitis, Prostate cancer.
Early Detection
A Way Forward

- PSA Levels > 1.5 ng/ml - Evaluate
- Improving the Performance of the test and find cancers that need to be treated
PSA Performance

PSA Isoforms

- Beckman Coulter $\phi$
- For men with $t$PSA between 2–10 ng/mL and non suspicious DRE for PCa

![Diagram showing PSA isoforms and phi score]
PSA

marker release from tumor

prostate tumor

blood sample

Measure PSA protein in serum

DRE

cell shedding

urine sample

Measure PCA3 and PSA mRNA from cells

PCA3 Score = PCA3/PSA mRNA x10^-3

Percent of Men with Positive Biopsy by PCA3 Score
First Biopsy

PSA PERFORMANCE  4Kscore

- 4Kscore™ Prostate Cancer Test
- Prostate cancer test
- Based on the following panel of kallikrein markers:
  - Total PSA
  - Free PSA
  - Intact PSA
  - Human Kallikrein 2 (HK2)
4K Score
Finding a significant cancer

4 Kallikreins
Outperforms PSA

Components
- 4 kallikrein levels
- Total PSA
- Free PSA
- Intact PSA
- hK2

Results
- % risk of having aggressive prostate cancer for an individual patient

The 4Kscore™ Test has the accuracy of a prostate biopsy for aggressive prostate cancer:

- Sensitivity
- Specificity
- AUC = area under the curve
- Larger AUC = better accuracy for predicting aggressive prostate cancer

AUC of other tests when applied to aggressive disease:
- pH6 = 0.70, 0.67
- PCA3 = 0.68

References:
1. Paeckin, O et al. 2014 submitted

OPKO
Ways Forward

• PSA Levels -1.5ng/ml

• Improving the Performance of the test and find cancers that need to be treated-PHI, PCA3, 4 K

• Eliminate needless repeat biopsies, but don’t miss a threatening cancer
TRUS Biopsies

- Anxiety
- Repeat Biopsies
- Infections
- Miss Cancers
- Who to rebiopsy
- ConfirmMDX and PCA3
Improve Biopsy Outcomes
Epigenetic Field Effect

ConfirmMDx detects an **epigenetic field** effect associated with the presence of cancer at the DNA level

- **Field effect** around a cancer lesion can be present despite normal appearance under the microscope
- **Absence of methylation** changes helps rule out malignancy
- **Presence of methylation** changes indicates increased risk for malignancy
  - **GSTP1** – DNA detoxification
  - **APC** – apoptosis
  - **RASSF1** – cell cycle regulation

Henrique R, et al., Epigenetic Heterogeneity of High-Grade Prostatic Intraepithelial Neoplasia: Clues for Clonal Progression in Prostate Carcinogenesis, Mol Cancer Res 2006 4 1 8
Addressing False-Negative Biopsy Concerns

ConfirmMDx provides actionable information to improve patient risk stratification and decisions on repeat biopsy:

- **RULE OUT** prostate-cancer-free men from undergoing unnecessary repeat biopsies

- **RULE IN** those who require repeat biopsies and potential treatment
ConfirmMDx provides actionable information to improve patient risk stratification and decisions on repeat biopsy.

Pivotal Trial: Second Validation Study

Document Clinical Trial

- Clinical Validation of Epigenetic Assay to Predict Negative Histopathological Results in Repeat Prostate Biopsies
- Correlation of Gene Expression with Bladder Capacity in Intestinal Cystitis/Badder Pain Syndrome
- Functional Magnetic Resonance Imaging during Gradianyent Testing Identifies Brain Structures Initiating Micturition

**DOCUMENT Results: Multivariate Analysis of Known Risk Factors and Assay Performance**

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</table>

Partin et al.; Clinical Validation of an Epigenetic Assay to Predict Negative Histopathological Results in Repeat Prostate Biopsies, *Journal of Urology* 2014; doi.org/10.1016/j.juro.2014.04.013
Where ConfirmMDx Fits

**Patient Profile:** Men considered for repeat prostate biopsy.

- Assay performed on residual tissue from previous negative biopsy
- Does not require repeat patient visit
Family Practitioner

- PSA 5 years
  - PSA <1.5
    - Routine Lab/PSA
      - PSA >1.5
        - Refer to Urologist
        - High Risk
          - PHI, PCA3,4K
            - Low Risk
        - High Risk
          - PHI, PCA3,4K
            - Low Risk
          - Consider Tx
            - GS 6 or 3+4
              - GS 6 or 3+4
                - Consider Tx
                - PHI, PCA3,4K
                  - Low Risk
                  - PHI, PCA3,4K
                    - Low Risk
                    - Consider Tx
                      - GS ≥4+3
                          - GS ≥4+3
                            - ConfirmMD
                              - Active Surveillance
                                    - Genomic Markers
                                          - Consider Tx
                                            - High Risk
                                              - HSUS Bx
                                                - ConfirmMD
                                                  - MP MRI
                                                    - Low Risk