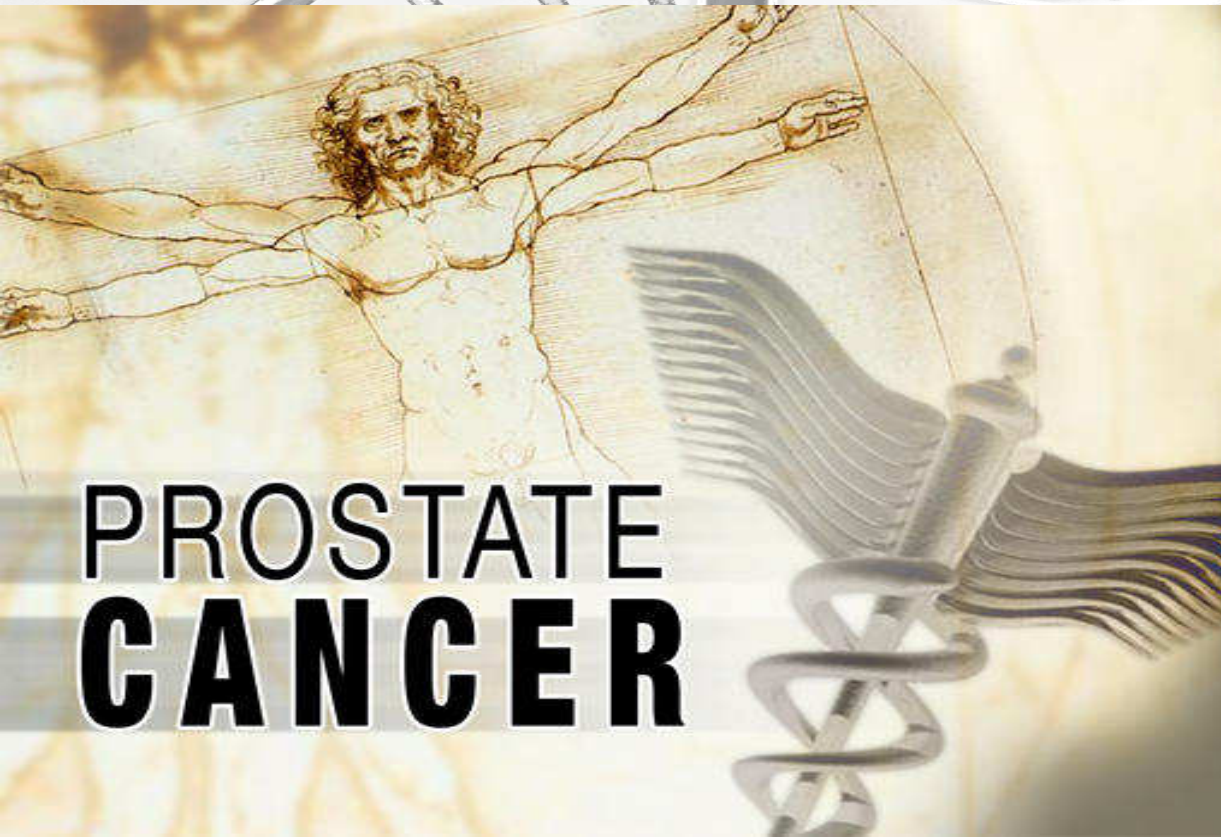


What are currently the best decision markers for biopsy and re-biopsy of the prostate?



**PROSTATE  
CANCER**

E. David Crawford, M.D.



Professor of Surgery/  
Urology/Radiation  
Oncology

University of Colorado

# 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

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- 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**

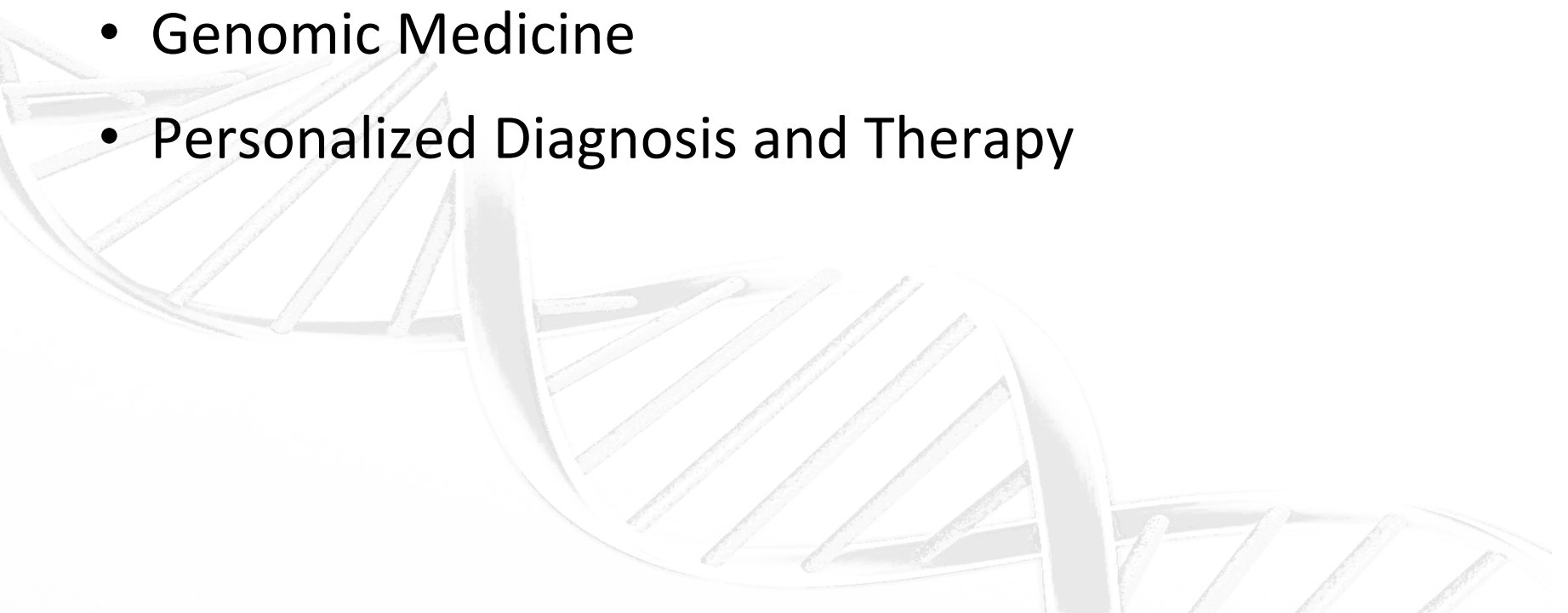
**the answer: Yes**



# Time for Change

## Not one fits all

- Precision medicine
- Selection Medicine
- Stratifying medicine
- Genomic Medicine
- Personalized Diagnosis and Therapy



# PCMs

Tissue

Blood

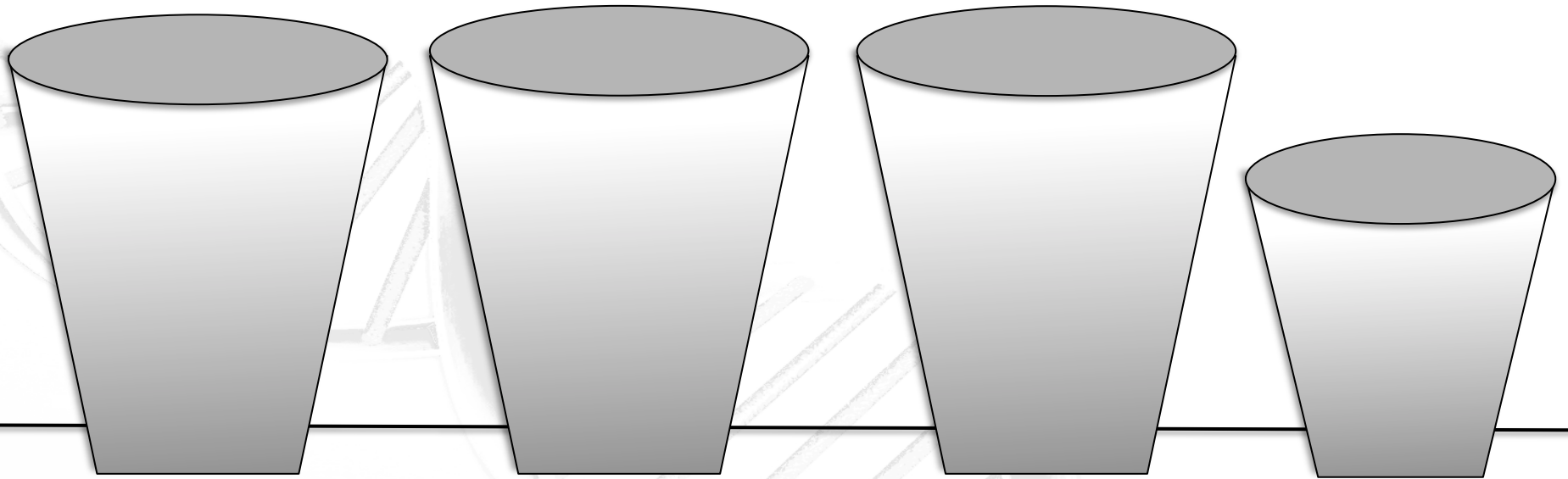
Urine

## **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

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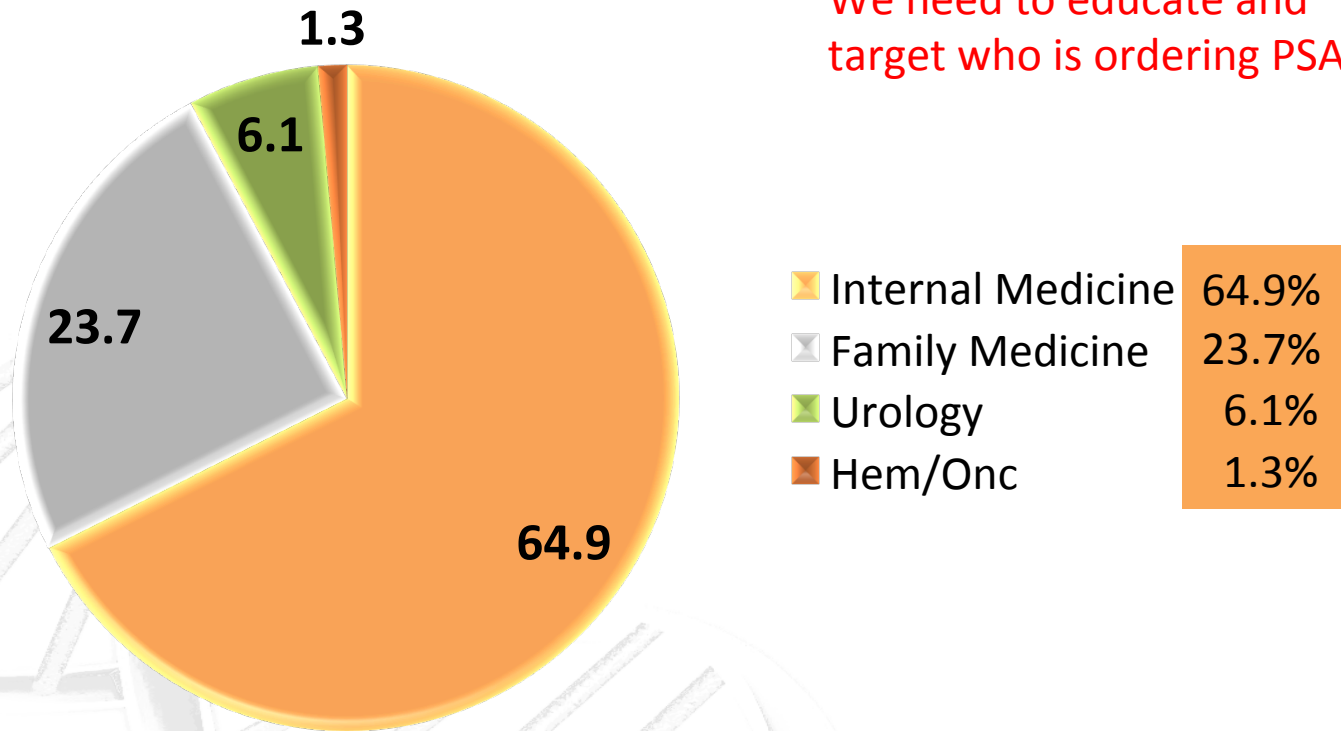
# Ways Forward

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- 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





# 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?



## Prostate-specific antigen 1.5–4.0 ng/mL: a diagnostic challenge and danger zone

E. David Crawford, Judd W. Moul\*, Kyle O. Rove, Curtis A. Pettaway<sup>+</sup>,  
Lois E. Lamerato<sup>+</sup> and Alexa Hughes

*University of Colorado, Anschutz Medical Campus, Aurora, CO, \*Division of Urologic Surgery, Duke University Medical Center, Durham, NC, <sup>+</sup>MD Anderson Cancer Center, University of Texas, Houston, TX, and <sup>+</sup>Josephine Ford Cancer Center, Henry Ford Medical Center, Detroit, MI, USA*

Accepted for publication 20 January 2011

## BJU Best Clinical Paper


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**Uroscan**  
**BJUI awards three 'Best Paper' prizes**

 The Bob Krane Prize, awarded for the best clinical paper goes to E. David Crawford, MD. His paper points to a PSA threshold of 1.5 ng/mL as a potential danger zone when it comes to predicting an increased risk for prostate cancer over a 4-year period.

 The John Blandy Prize is awarded to the best paper published by a resident. Guillaume Ploussard was given the prize for five papers that were published during 2011 alone.

 The Coffey Prize rewards the best research paper. This year's winner, Tarek A Bismar, MD, sheds light on the importance of ERG gene rearrangements and PTEN genomic deletions in the development and progression of prostate cancer.

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# 5-year Diagnosis Rates Based on Initial PSA Level

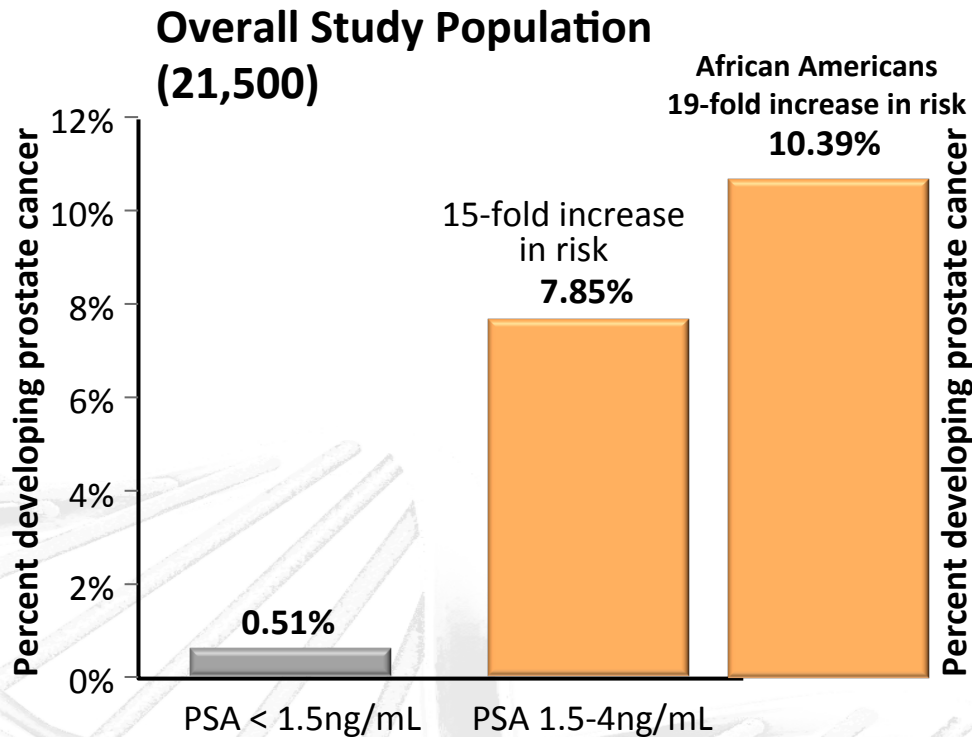
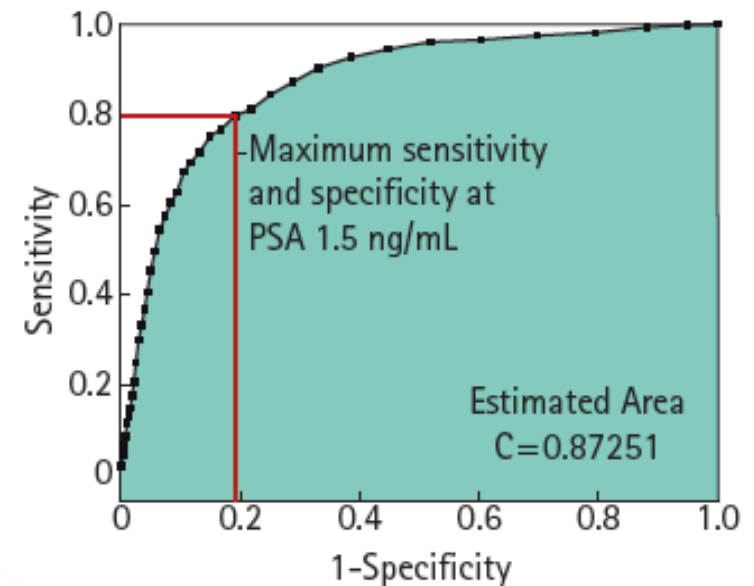


FIG. 2. Receiver operating characteristic curve for all patients.



A first PSA test threshold of 1.5 - 4.0 ng/mL, represents the  
Early-Warning PSA Zone  
Patients with PSA  $\geq 1.5$  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  $> 1.5\text{ng/ml}$  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**

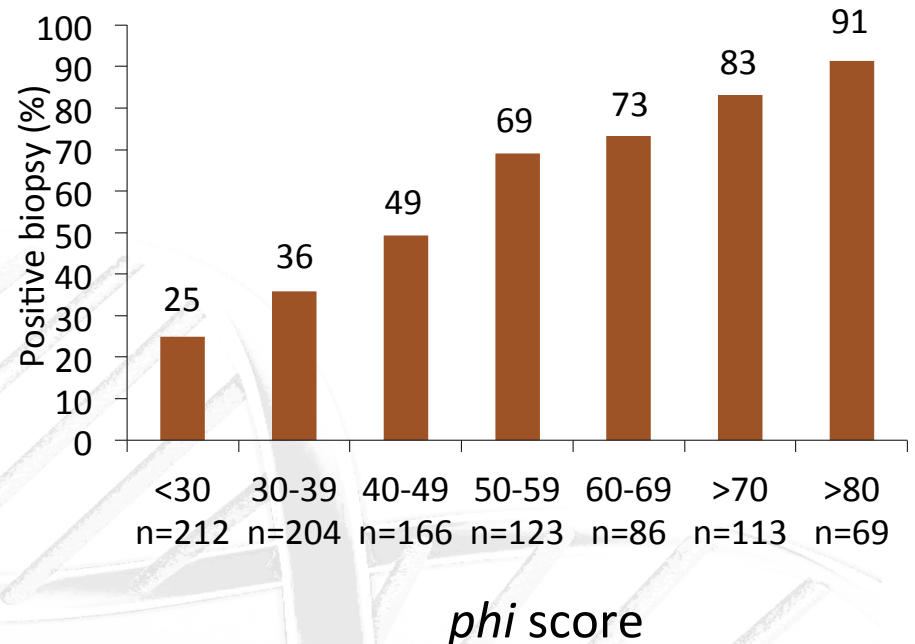
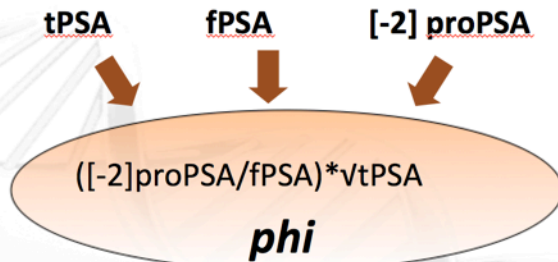


# PSA Performance

## PSA Isoforms

- Beckman Coulter *phi*
- For men with tPSA between 2–10 ng/mL and non suspicious DRE for PCa

- Beckman Coulter *phi*
- For men with tPSA between 2–10 ng/mL and non suspicious DRE for PCa



# PSA

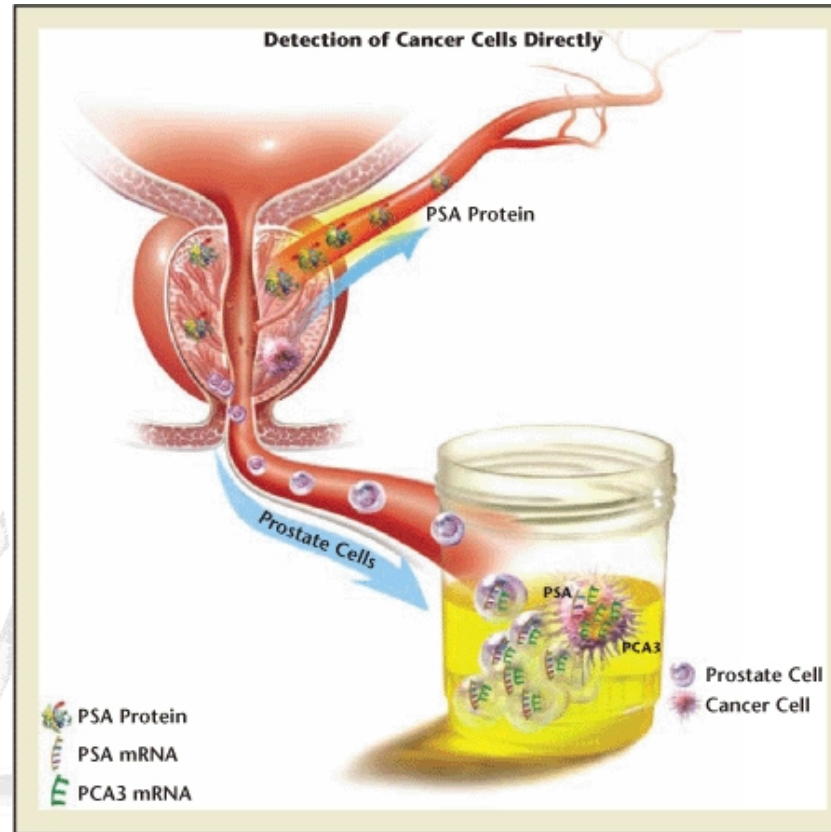
# PCA3 score

prostate tumor  
↓  
marker release  
from tumor

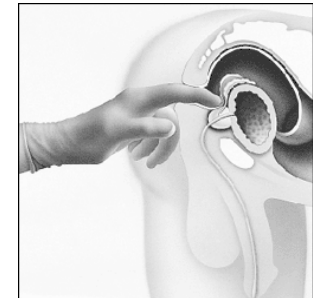


blood sample

↓  
Measure PSA protein  
in serum



DRE



cell shedding ↓

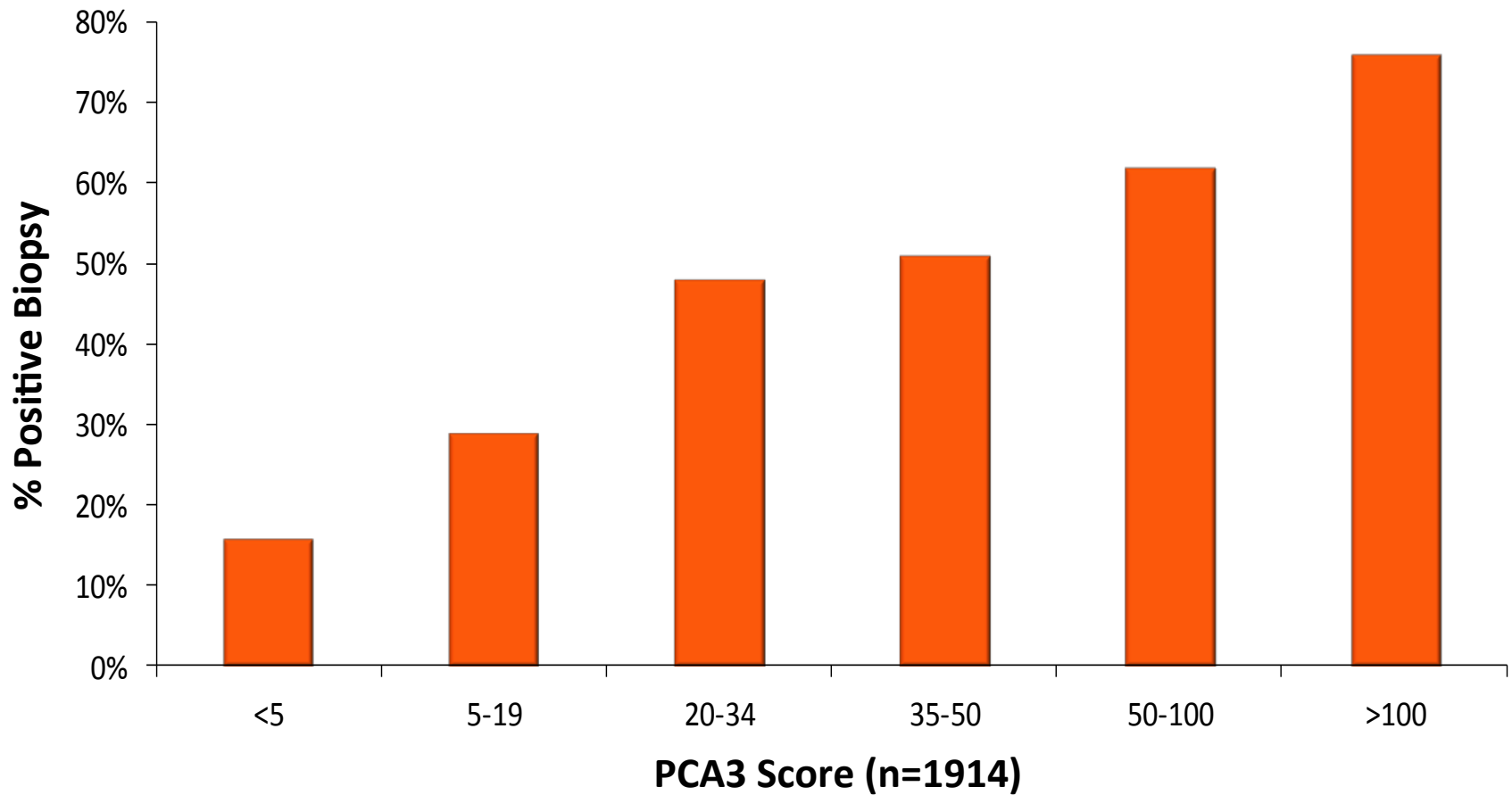


urine sample

↓  
Measure PCA3 and PSA  
mRNA from cells

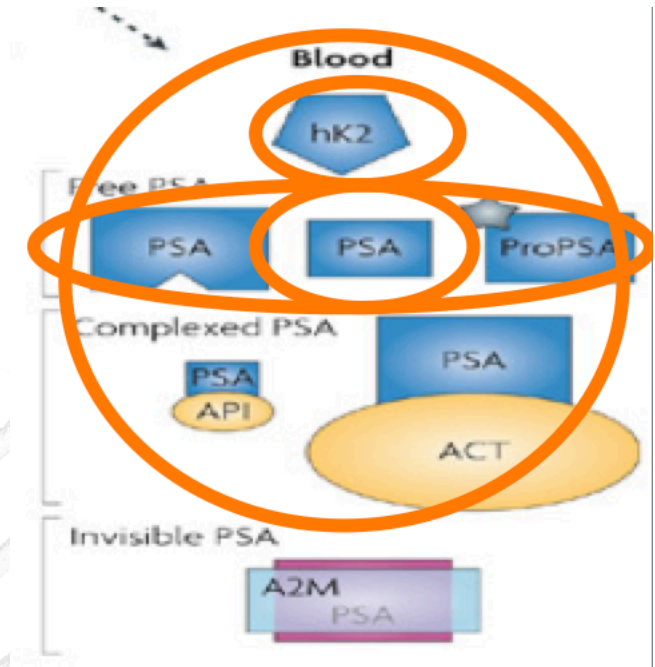
$$\text{PCA3 Score} = \text{PCA3/PSA mRNA} \times 10^{-3}$$

# 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)



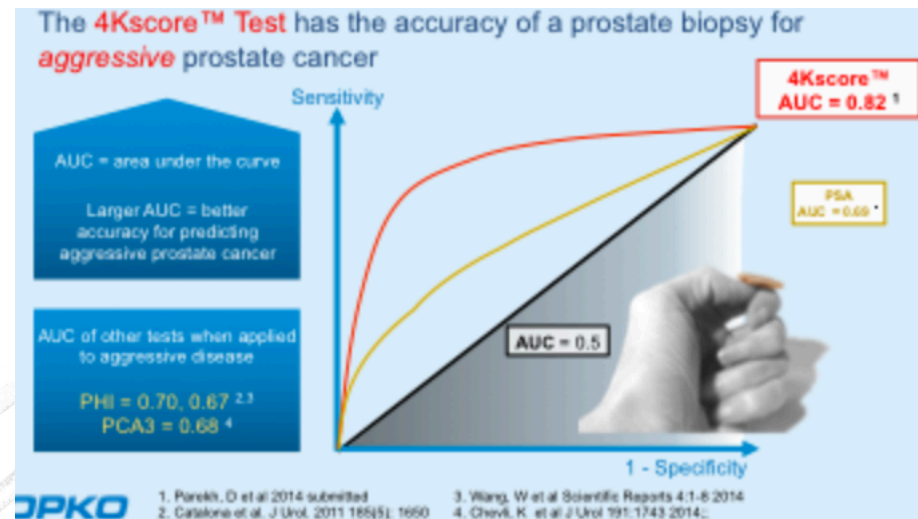
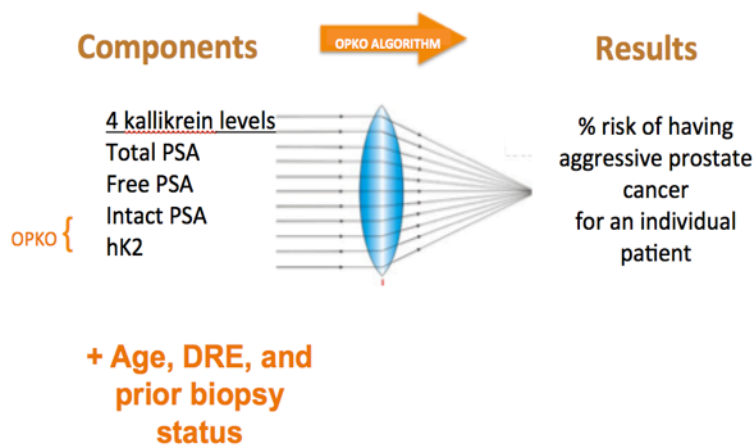


# 4K Score

## Finding a significant cancer

### 4 Kallikreins

### Outperforms PSA



# 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

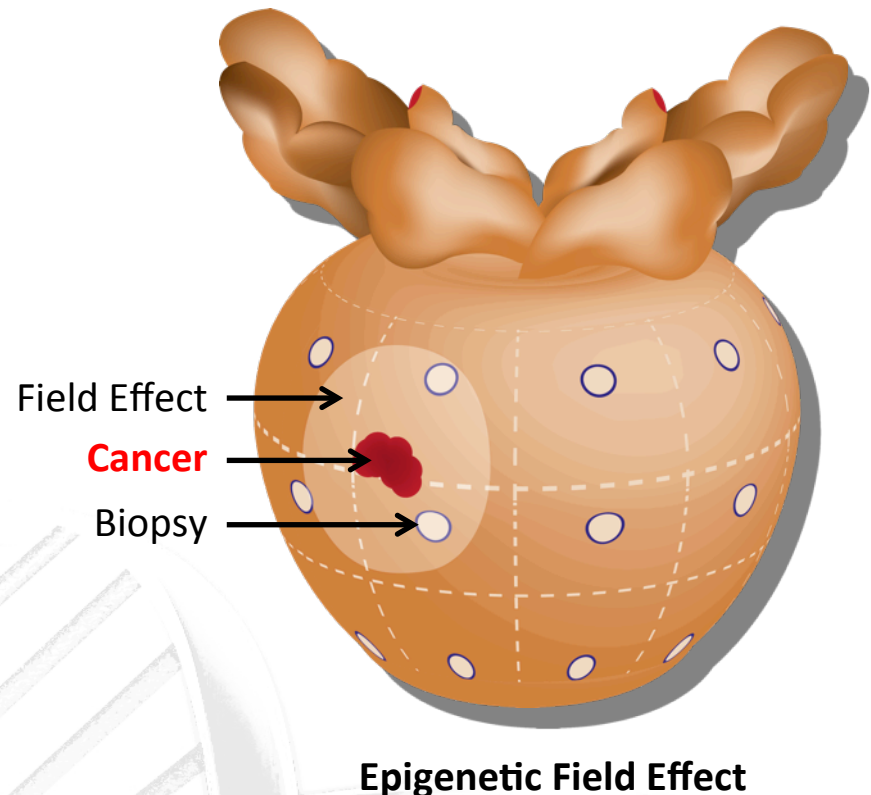
- Anxiety
- Repeat Biopsies
- Infections
- Miss Cancers
- Who to rebiopsy
- ConfirmMDX and PCA3

# 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



# Addressing False-Negative Biopsy Concerns

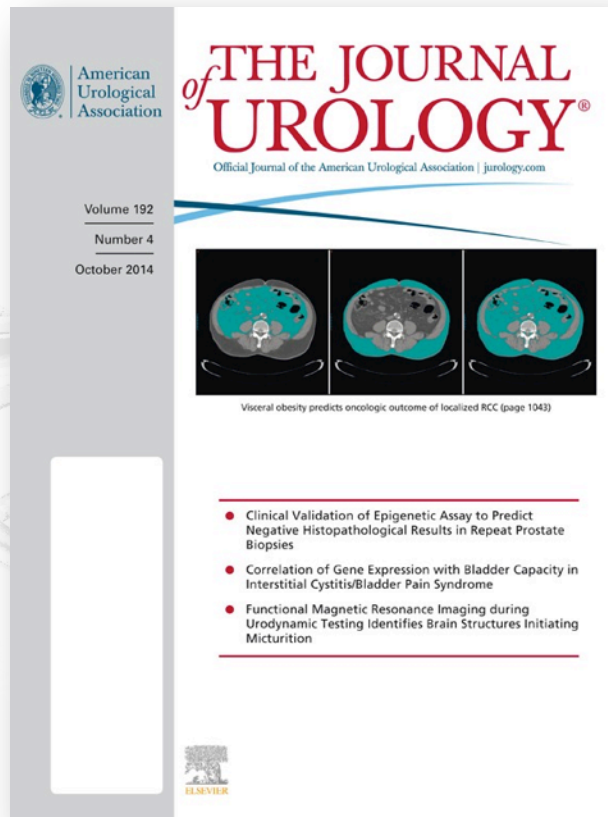
ConfirmMDx provides **actionable information** to improve patient risk stratification and decisions on repeat biopsy:

- **RULE OUT** prostate-cancer-free men from undergoing unnecessary repeat biopsies
- **RULE IN** those who require repeat biopsies and potential treatment

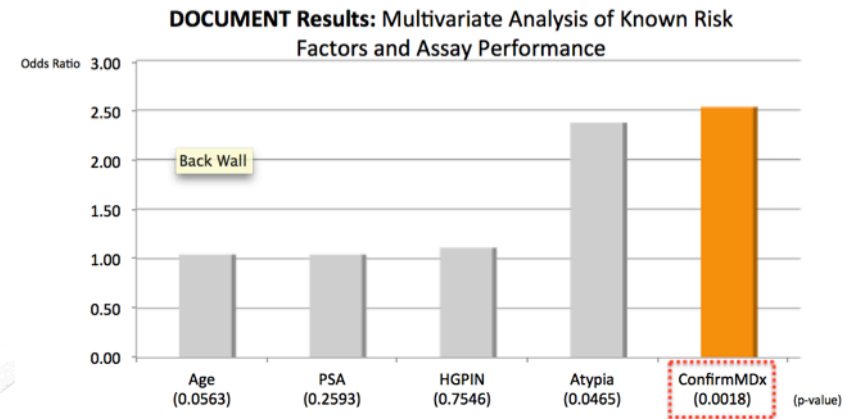


# ConfirmMDx provides actionable information to improve patient risk stratification and decisions on repeat biopsy

## Pivotal Trial: Second Validation Study



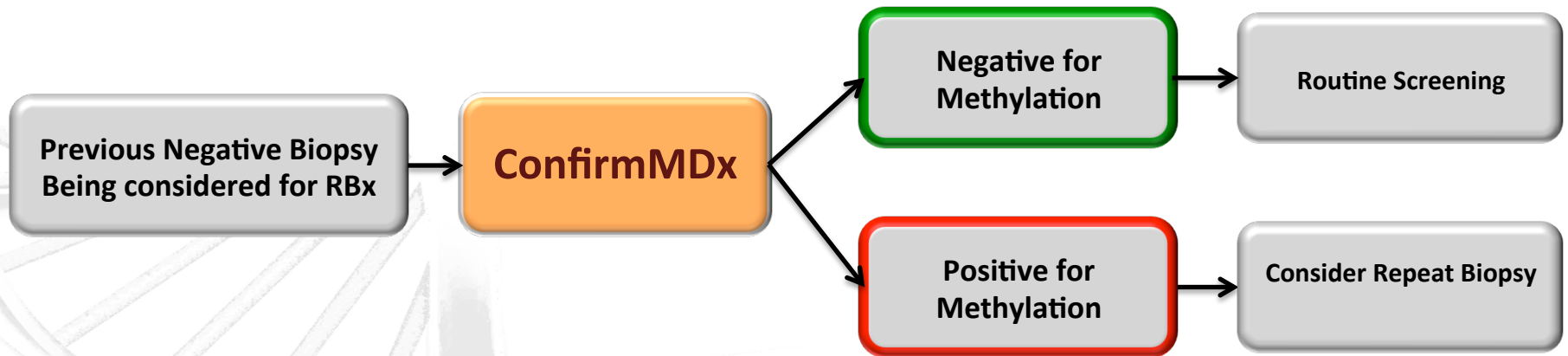
## Document Clinical Trial



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

Urologist



PSA 5 years

PSA <1.5

Routine Lab/PSA

PSA >1.5

Refer to Urologist

PHI, PCA3,4K

Low Risk

High Risk

Consider Tx

GS  $\geq$ 4+3

GS 6 or 3+4

TRUS Bx

ConfirmMDx

MP MRI

Genomic Markers

Active Surveillance

Consider Tx

High Risk

Low Risk

