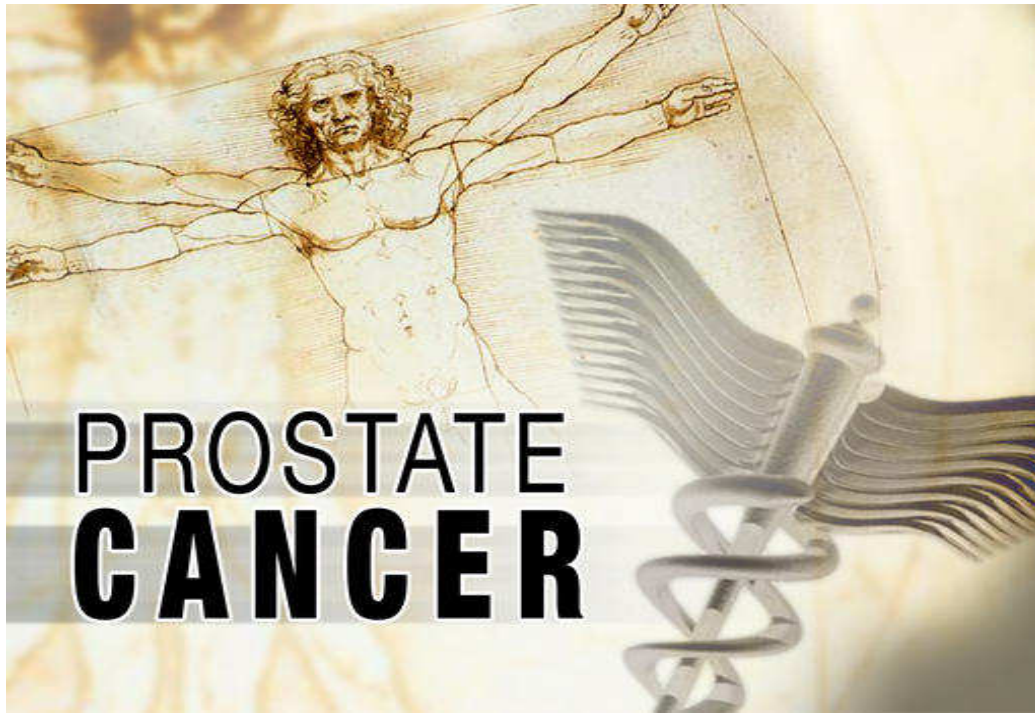


Biomarkers and Early Detection: A Way Forward and Local Therapies for CaP



E. DAVID CRAWFORD, M.D

Professor of Surgery/Urology/Radiation Oncology
University of Colorado



School of Medicine

UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Greetings from Colorado



Disclosures Consultant: MDxHealth, Myriad and Genomic Health,
Speaker: Ferring, Bayer, and Myriad

This is a urine based test to detect aggressive cases of prostate cancer

- 1. PCA3
- 2. 4 K Score
- 3. SelectMDx
- 4. phi

What percent of men have a PSA of < 1.5ng/ml in a screening population ?

- 1. < 50%
- 2. < 30%
- 3. > 70%
- 4. > 80%

Prostate Cancer Clinical Needs

1. Screening: Primary Care Physicians (PCPs) need a simple message
2. Early Detection: Identify patients with clinically significant PCa earlier

Beyond PSA: Prostate Cancer Challenges

- PSA Screening
 - Poor specificity
 - Too many negative prostate biopsies
 - Over detection/treatment of insignificant Disease
- False Negative Biopsies
- Incorrect Risk Stratification for treatment decision making
- Over-treatment of tumors with prolonged natural history >>>> life expectancy of patient

Prostate Cancer Marker (PCM)

Tissue

Blood

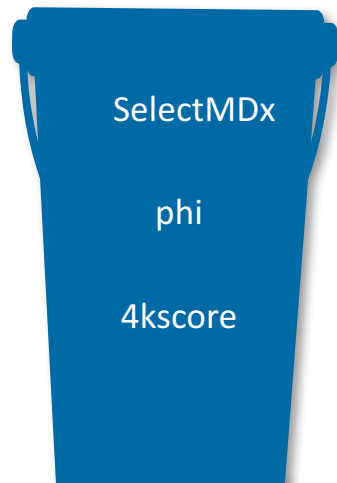
Urine

What is a PCM?

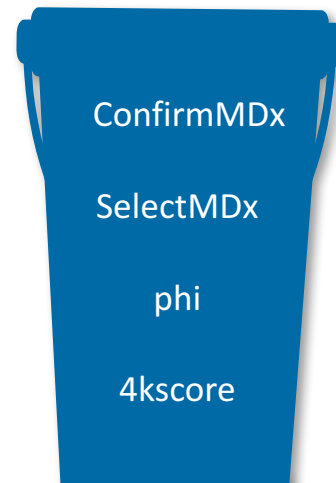
A molecule that can be found in blood, tissue or body fluids that is a sign of a normal or abnormal process

PCM Buckets

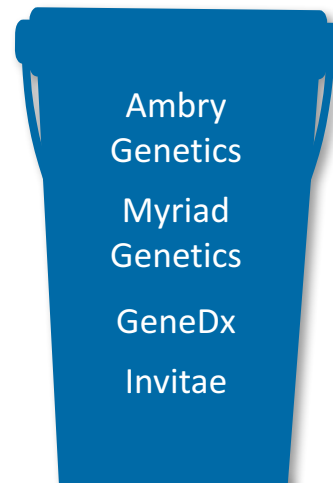
**Initial Biopsy:
Identify
Significant PCa**



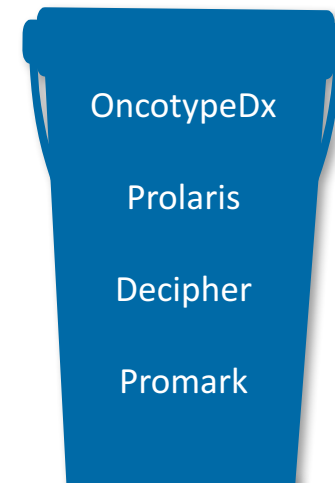
**Negative Biopsy:
Whom to
Rebiopsy**



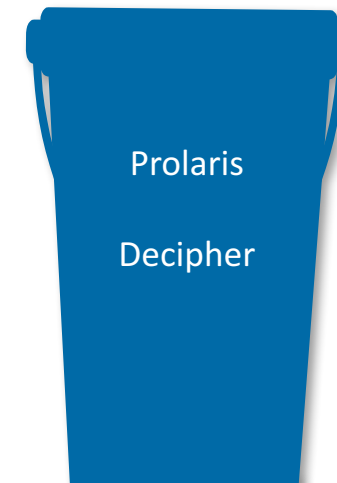
**Whom to offer
Genetic Testing:**



**Who to offer
Interventional
Therapy vs Active
Surveillance**



**Whom to treat
or not treat post-
prostatectomy:**



Fox Hunt

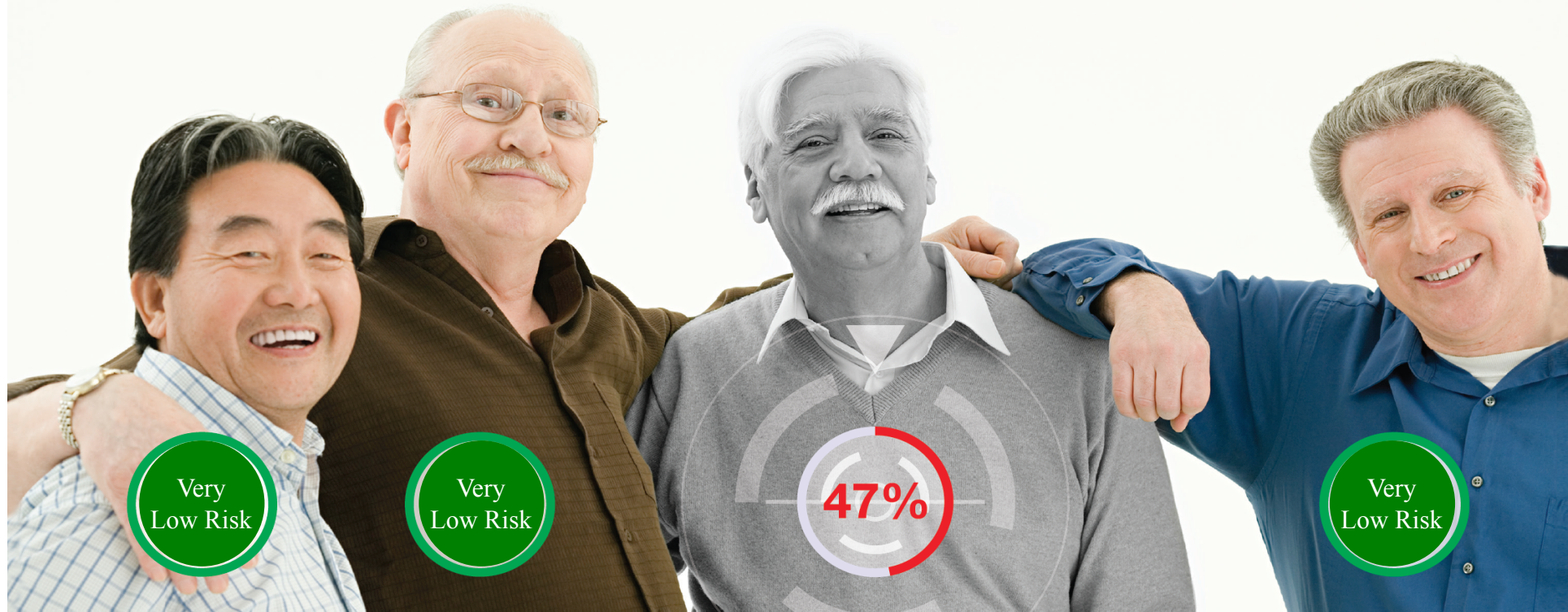
Whom to Bx, ReBx, and to Treat



Fox Hunt



Which of these men is harboring aggressive, potentially lethal, prostate cancer?



Relative Risk of a Bank Robber



(5-7%)



(2-3%)



(40-55%)



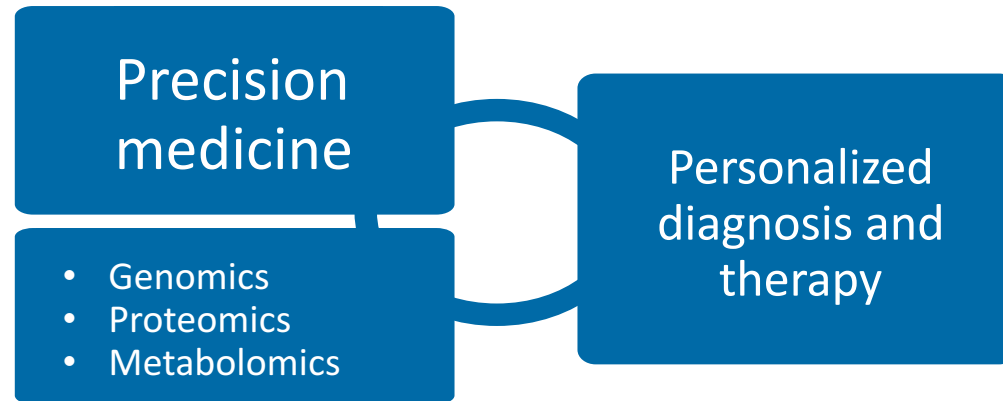
(10-25)

2 variables = 9 - 40%

4 variables = 75 - 95%

Biomarker Tests for Molecularly Targeted Therapies-

The Key to Unlocking Precision Medicine



New England Journal of Medicine 375;1, July 7, 2016

Message from USPSTF

and Other Organizations Following the Lead

PSA screening is a “D”
recommendation

- Do Not Order
- Shared Decision Making

**Supported by AAFP and other
organizations**



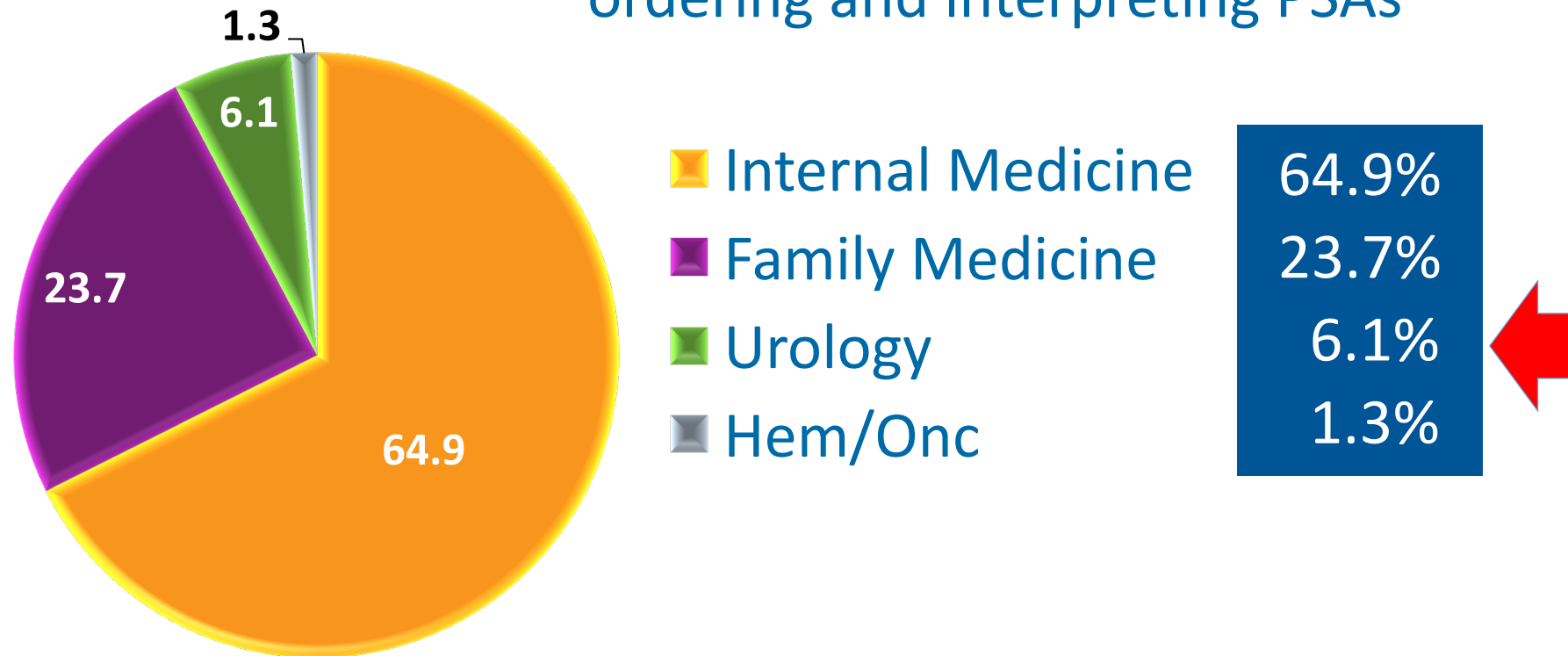
Beyond PSA...

- Using PSA *alone* to guide prostate biopsy decisions should for the most part **END**
- Tools are needed to provide better risk assessment to detect clinically meaningful cancers
 - Reduce unnecessary biopsies
 - Reduce over-detection of indolent disease

**What Percent of all of the PSA's
ordered in the US are by Urologists?**

What Percent of all of the PSA's ordered in the US are by Urologists?

We need to educate those who are ordering and interpreting PSAs



Ways Forward With PCPs: Don't Confuse them

- Educate those who order PSAs: **PCPs There**
Confused

- 1.5
- 2.5
- 4
- Velocity

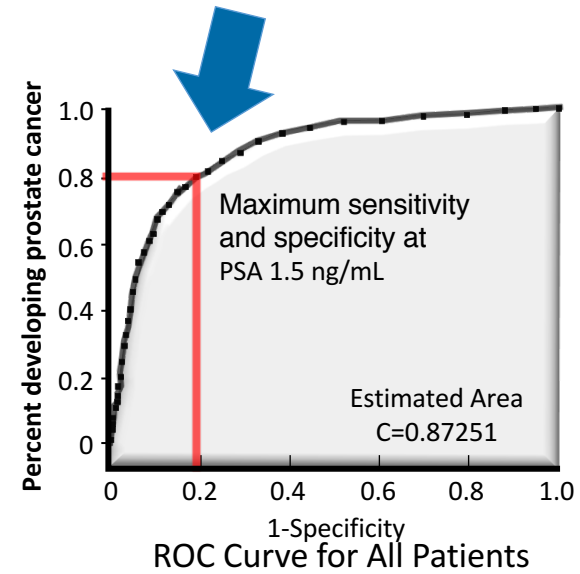
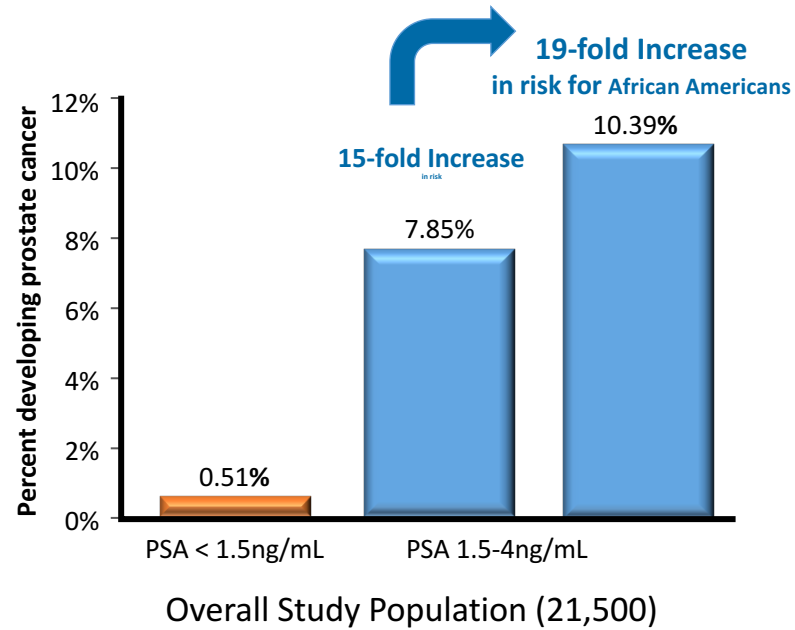
- Density
- Age Specific
- % Free PSA
- Complex PSA

- Phi
- PCA3
- SelectMDx
- 4kscore

HELP!

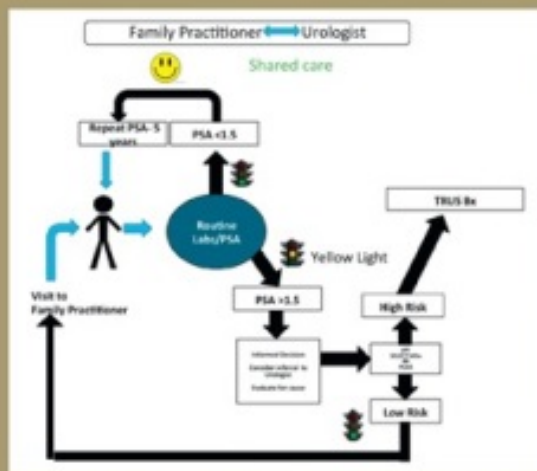
- Define a PSA level with little risk
- Who/when to refer to urologist?

5-year Diagnosis Rates Based on Initial PSA Level



UROLOGY

SPECIAL ISSUE ON UROLOGIC ONCOLOGY



Using PSA Levels of 1.5 ng/ml as the Cutoff for Prostate Cancer Screening in Primary Care

IN THIS ISSUE

Management of Penile Cancer

Gregory J. Diorio, Andrew R. Leone, and Philippe E. Spiess
Page 15

The Future of Enhanced Recovery for Radical Cystectomy: Current Evidence, Barriers to Adoption, and the Next Steps

Bernard J. Danna, Erika L. Wood, Janet E. Back Kikreja, and Jay B. Shah
Page 62

Endovascular Removal of Intracardiac Thrombus Prior to Radical Nephrectomy and Inferior Vena Cava Thrombectomy

Drew A. Palmer, John E. Humphrey, Ariel Fredrick, Thomas C. Piemonte, and John A. Libertino
Page 85

Practical Guidance on the Role of Corticosteroids in the Treatment of Metastatic Castration-resistant Prostate Cancer

Maria De Santis and Fred Saad
Page 156

Early Stage Prostate Cancer

An Approach Using PSA Levels of 1.5 ng/mL as the Cutoff for Prostate Cancer Screening in Primary Care



**E. David Crawford, Matt T. Rosenberg, Alan W. Partin, Matthew R. Cooperberg,
Michael Maccini, Stacy Loeb, Curtis A. Pettaway, Neal D. Shore, Paul Arangua,
John Hoenemeyer, Mike Leveridge, Michael Leapman, Peter Pinto, Ian M. Thompson, Jr,
Peter Carroll, James Eastham, Leonard Gomella, and Eric A. Klein**

Top Manuscript 2016



Channels ▾


★ FEATURED

Published in *Urology*

(/explore/channel/urology/sp3)

Expert Opinion / Commentary · November 08, 2016

2016 Top Stories in Urology: Prostate Cancer Screening

Written by  Alan W Partin MD, PhD

(/author/alan-partin/80)

An approach using PSA levels of 1.5ng/mL as the cutoff for prostate cancer screening in primary care

This paper, recently published in *Urology* and highlighted as the “Story of the Week” in *PracticeUpdate Urology*, addresses a major—until now—unanswered question in medicine related to early detection of prostate cancer.¹ The discussion and recommendations made by this esteemed group of authors and the comments provided by Dr. Laurence Klotz outline the potential impact of this manuscript not only urologists but for general practitioners as well
(<http://www.practiceupdate.com/c/45333/48/3>
(<http://www.practiceupdate.com/c/45333/48/3>)).

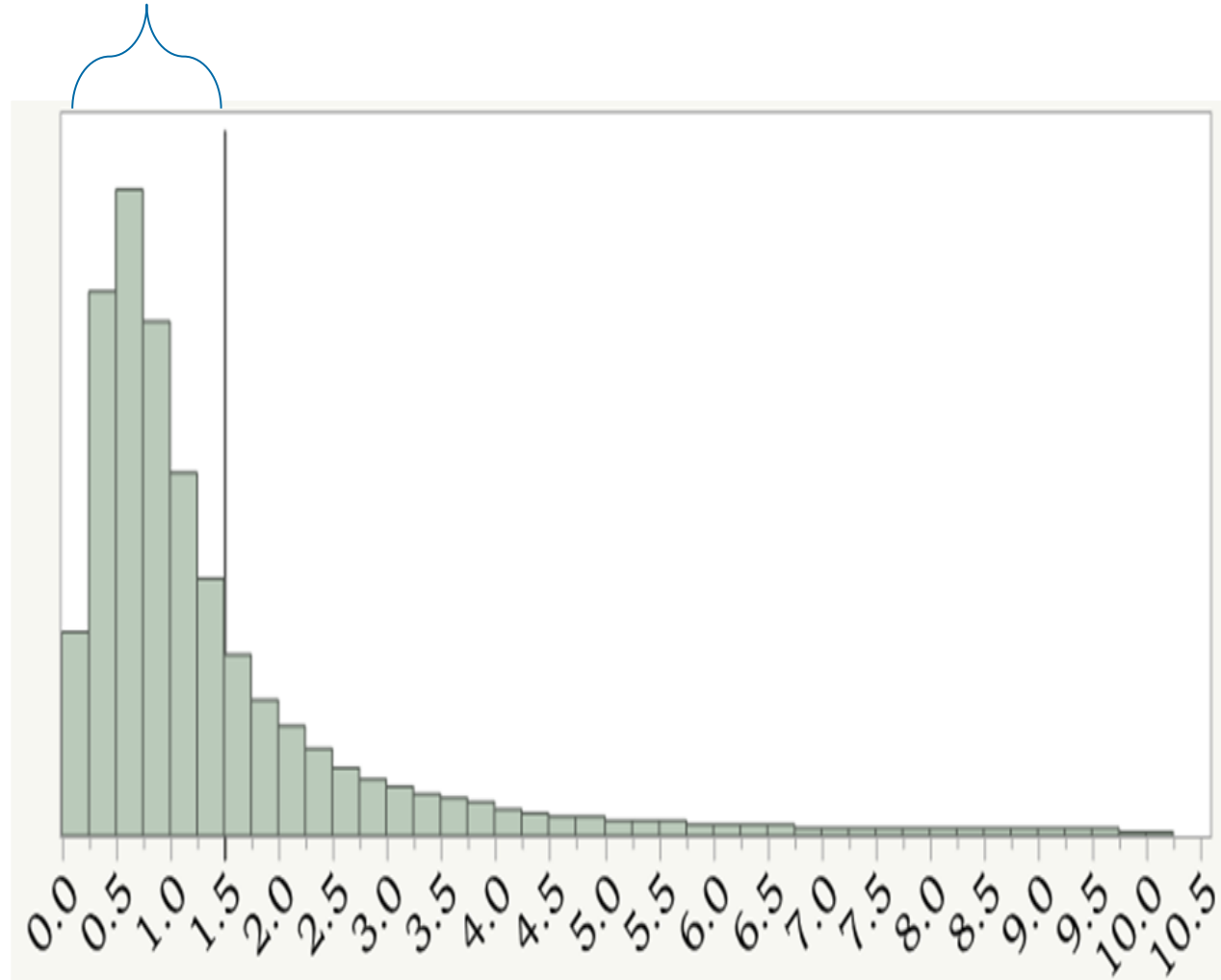


Search PracticeUpdate



Result Distribution

73% PSA < 1.5 ng/ml



Early Detection a Way Forward

Vital signs and many tests routinely performed by PCPs before informed decision

- Informed decision when tests are abnormal
- Why not PSA?
- 73% of men require no discussion

PSA treated like other lab tests:

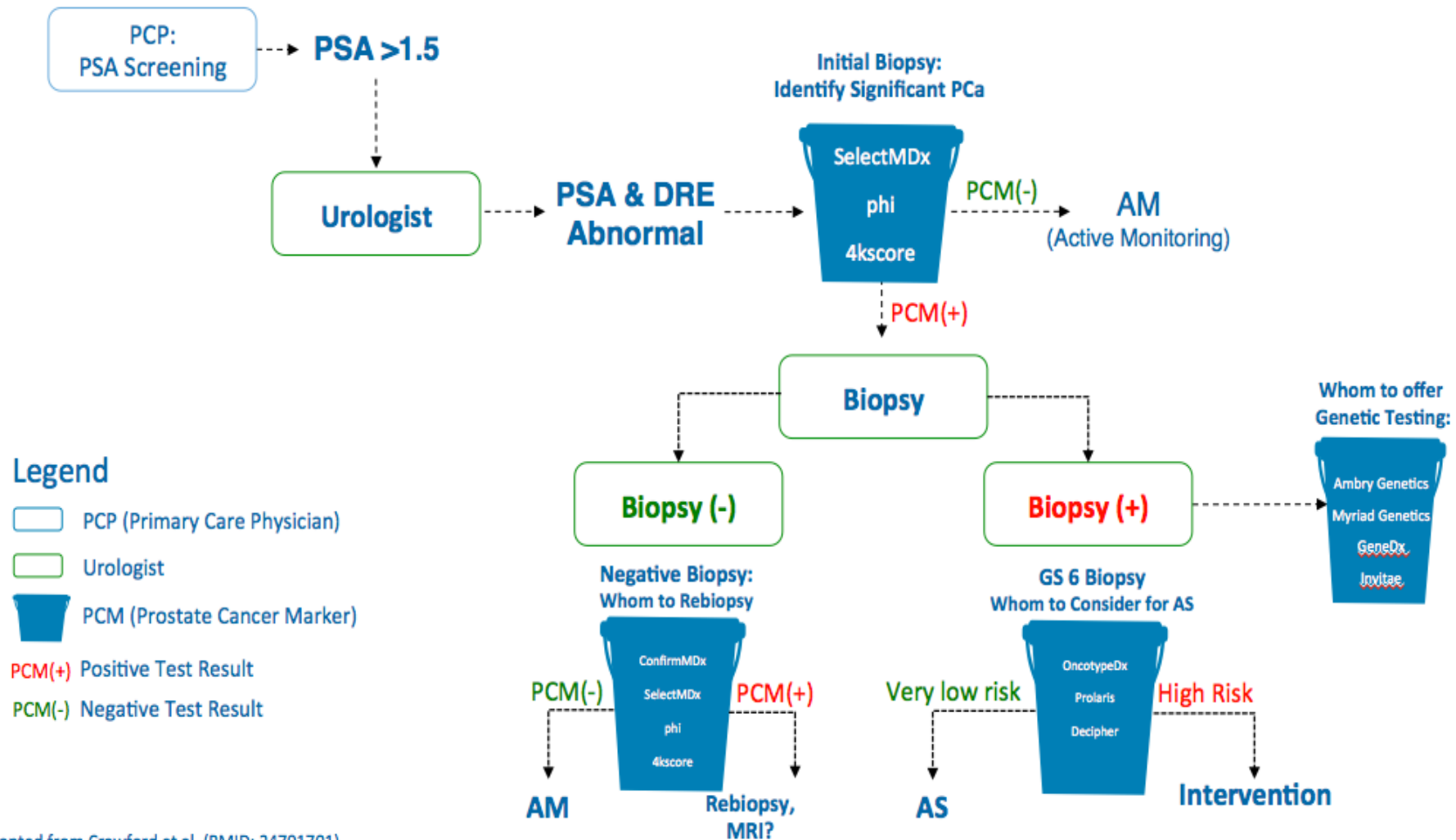
- lipids
- electrolytes
- weight
- BP-routine

Men's health broader issue

> 1.5 ng/ml surrogate for BPH, Prostatitis, Prostate Cancer

Prostate Cancer Evaluation Algorithm

PCMs (Prostate Cancer Markers)



PSA Screening

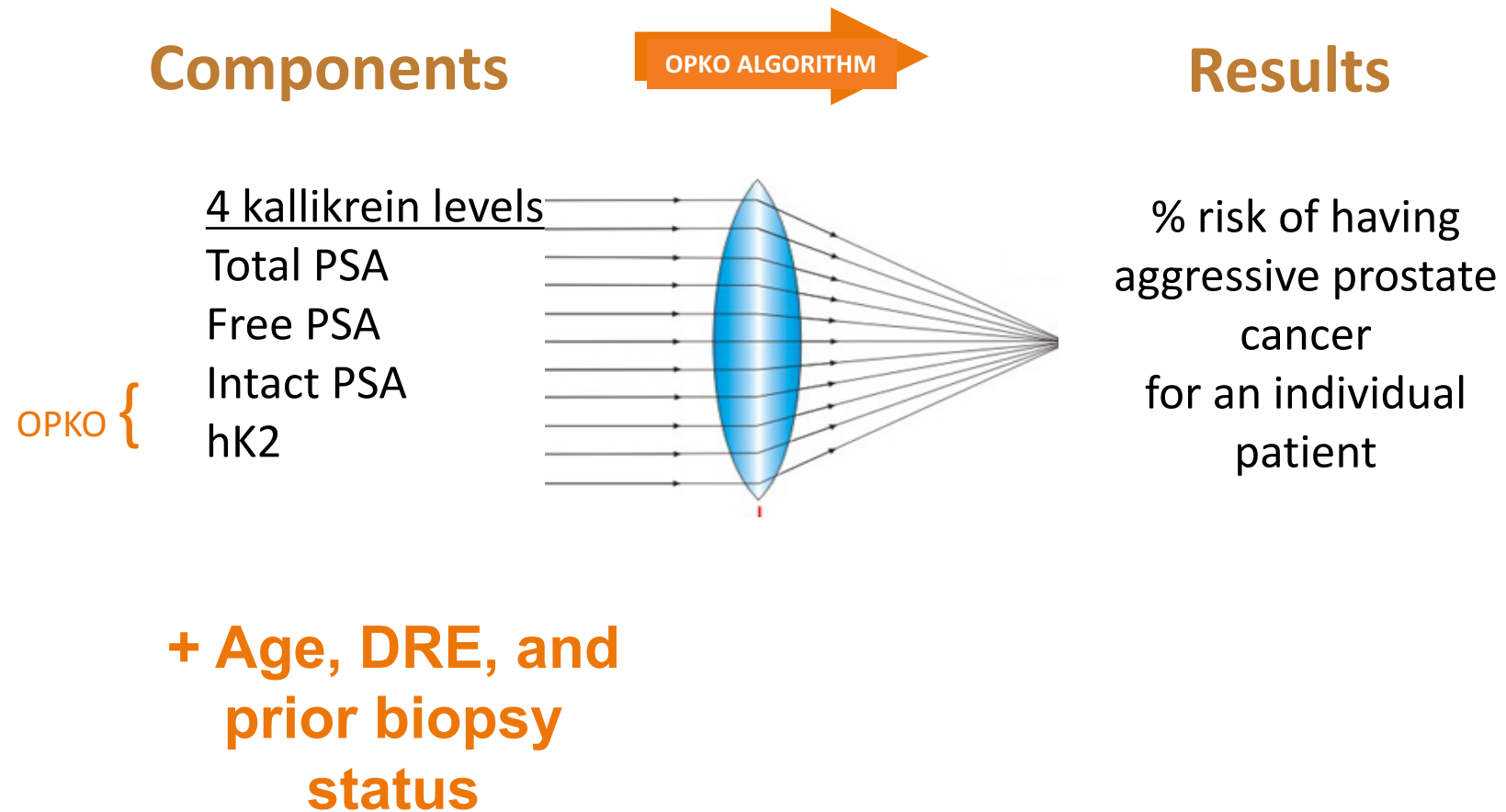
Improve Patient Selection for Biopsy

~20 million
PSA tests each year

~5 million men
with elevated PSA result

Diagnose < 180,000 and most
40% are candidates for AS

4Kscore™ Test

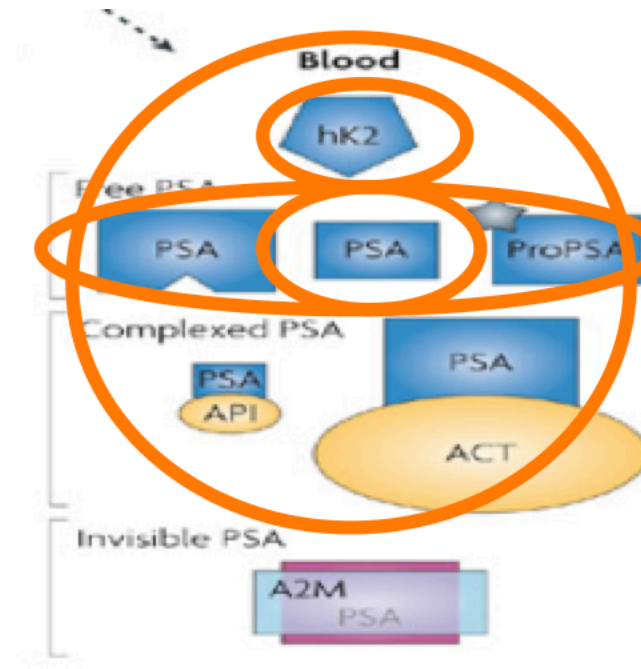


4Kscore[®]

Prostate Bx for aggressive PCa

- **4Kscore[®] Prostate Cancer Test**
- Based on the following panel of kallikrein markers:
 - Total PSA
 - Free PSA
 - Intact PSA
 - Human Kallikrein 2 (HK2)

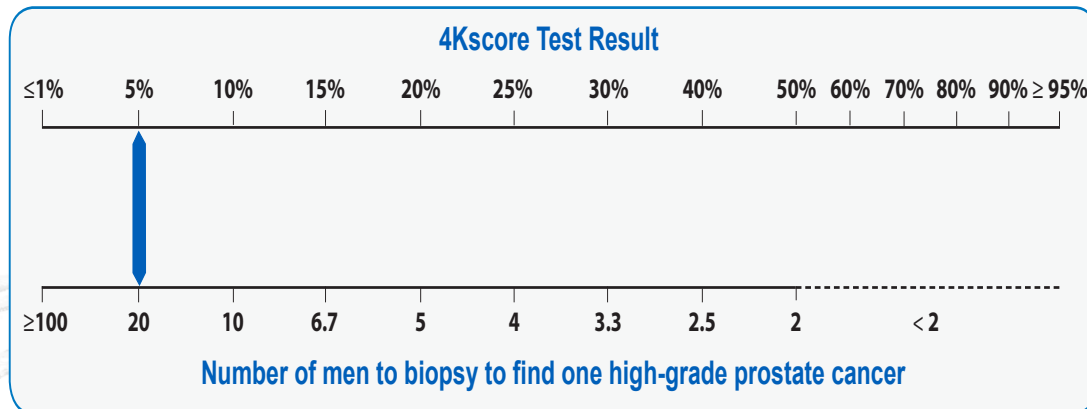
**+ Age, DRE,
and prior
biopsy status**



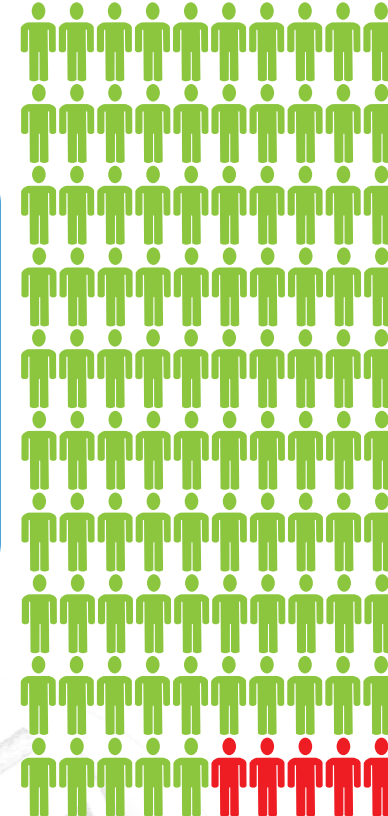
4Kscore[®] test: Reports individual % risk of aggressive prostate cancer if prostate biopsy was performed


The patient's **4Kscore Test** result is **5%**


At a **4Kscore Test** result of 5%, about **1 in 20** men biopsied would have high-grade prostate cancer.



4Kscore = Positive Predictive Value



 = 95% chance that the biopsy does not find a high-grade prostate cancer.

 = 5% chance that the biopsy finds a high-grade prostate cancer.



4Kscore FINAL REPORT

DOCTOR
SAMPLE DOCTOR
123 Main St
Anytown, USA 12345
Acct #: (1234)
P: (123)456-7890

PATIENT
SAMPLE PATIENT
DOB: 04/30/1938 Age: 76 Y
Sex: M
Address: 123 Main Street
Anytown, USA 12345
P: (123)456-7890

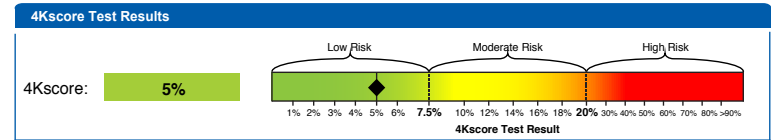
SAMPLE
Specimen ID: 123456789
Date Of Report: 04/19/2015
Date Collected: 04/18/2015
Time Collected: 08:00
Date Received: 04/18/2015
Time Received:

Interpretation

LOW RISK

There is a **95%** probability that the patient will not have aggressive disease on a prostate biopsy.

For a patient aged 60 years or older with a total PSA \geq 3 ng/mL and a 4Kscore $<$ 7.5%, the probability of not developing distant metastases within the next 10 years is **99.8%**.



Clinical Information

Digital Rectal Exam (DRE): Prior Biopsy Status:

Test Information

The 4Kscore result is the prediction of the individual's risk of aggressive prostate cancer of Gleason score 7 or higher if a prostate biopsy is performed.

The 4Kscore is calculated from the results of four immunoassays: Total PSA, Free PSA, Intact PSA, and Human Kallikrein-2 (hK2), plus patient age, reported DRE result, and history of prior negative biopsy.

Based on the 4Kscore US validation study, prostate biopsy should be considered in most men with a 4Kscore of 7.5% or higher. However, patient management should be based on clinical judgment and shared decision-making about undergoing biopsy.

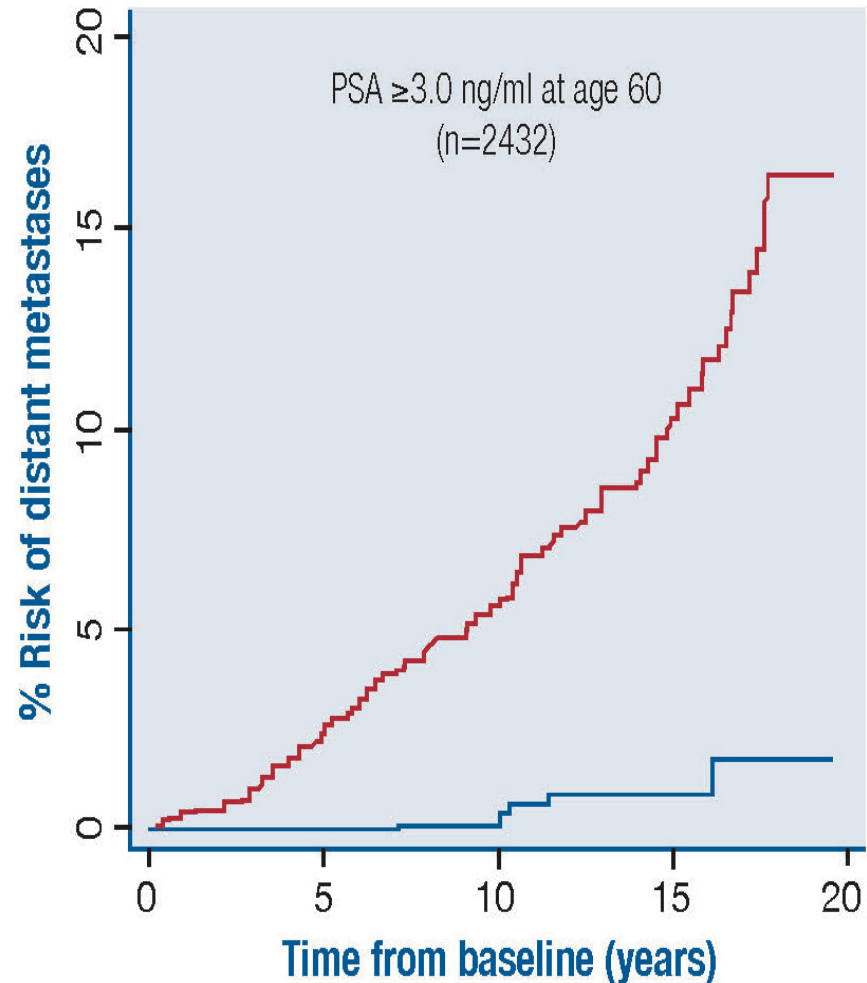
In a landmark study by Stattin et al. 12,542 men were followed for up to 20 years in Västerbotten, Sweden to determine the risk of prostate cancer metastases. Men who had a suspicious PSA and a 4Kscore of 7.5% or less had a low risk (<1%) of having metastatic prostate cancer within 20 years.

References:

1. Parekh, DJ, Punnen S, Sjoberg DD, et al. Eur Urol. 2015 Sep;68(3):464-70.
2. Gupta A, Roobol J, Savage CJ, et al. Br J Cancer. 2010 Aug;103(5):708-14.
3. Stattin P, Vickers AJ, Sjoberg DD, et al. Eur Urol. 2015 Aug;68(2):207-13.

Note: This test was evaluated and its performance characteristics determined by BioReference Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. BioReference Laboratories is certified under the Clinical Laboratory Improvement Act of 1988 (CLIA) as qualified to perform high complexity clinical testing.

The 4Kscore™ Test predicts the probability of distant metastases within 20 years



4Kscore™ Test
Biomarkers > 7.5%

4Kscore Test Biomarkers
> 7.5% (N = 922, 38%)

5 year = 2.4%
10 year = 5.6%
15 year = 9.9%
20 year = 16.4%

4Kscore™ Test
Biomarkers
 \leq 7.5%

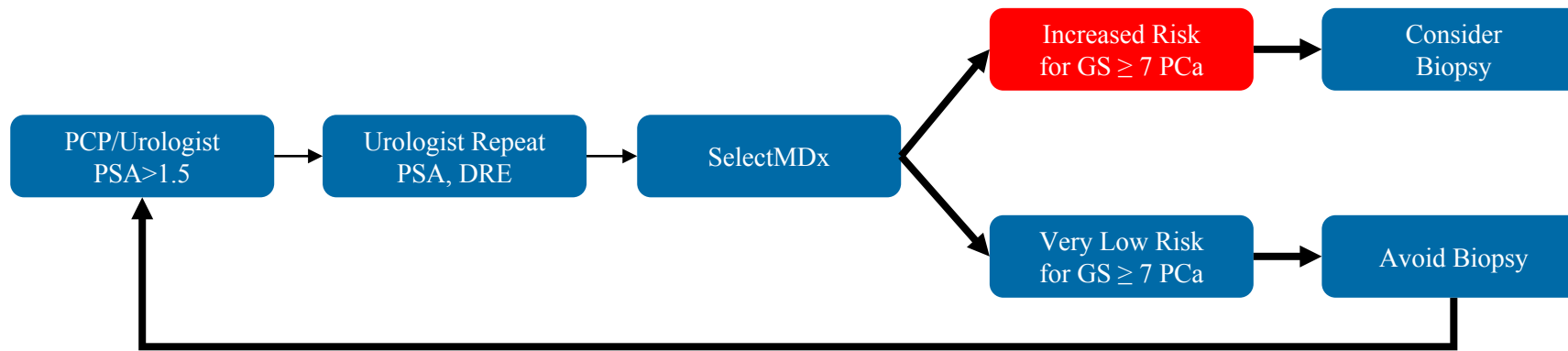
4Kscore Test Biomarkers
 \leq 7.5% (N = 1510, 62%)

5 year = 0%
10 year = 0.2%
15 year = 1.0%
20 year = 1.8%

SelectMDx for Prostate Cancer: *

Risk Stratification for Clinically Significant PCa

➔ For patients being considered for prostate biopsy



➔ * 2 genes associated with aggressive CaP- Urine Assay

Very Low Risk
99.6% NPV for GS ≥ 8
98% NPV for GS ≥ 7

SelectMDx Clinical Validation of a Risk Profile for the Detection of High Grade Cancer

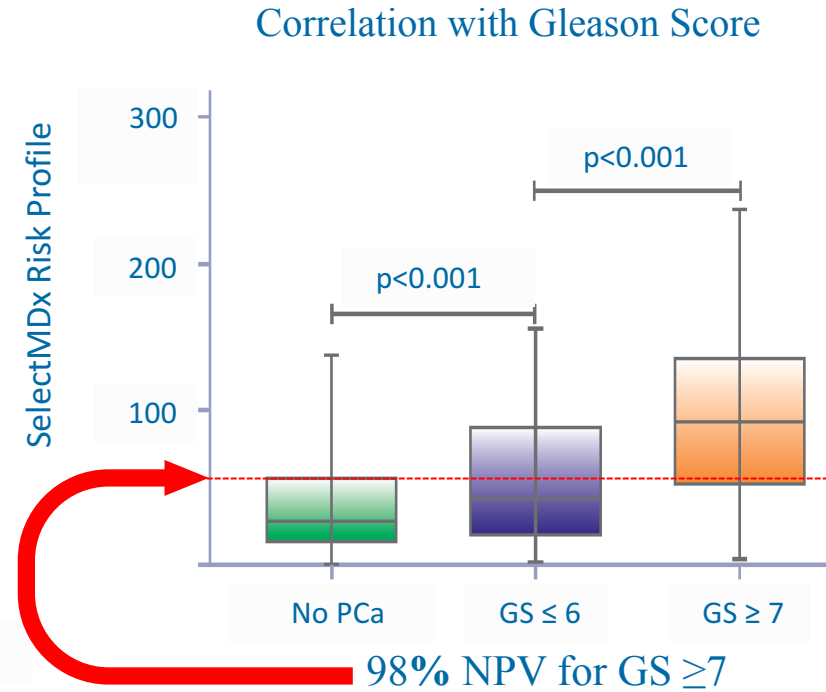
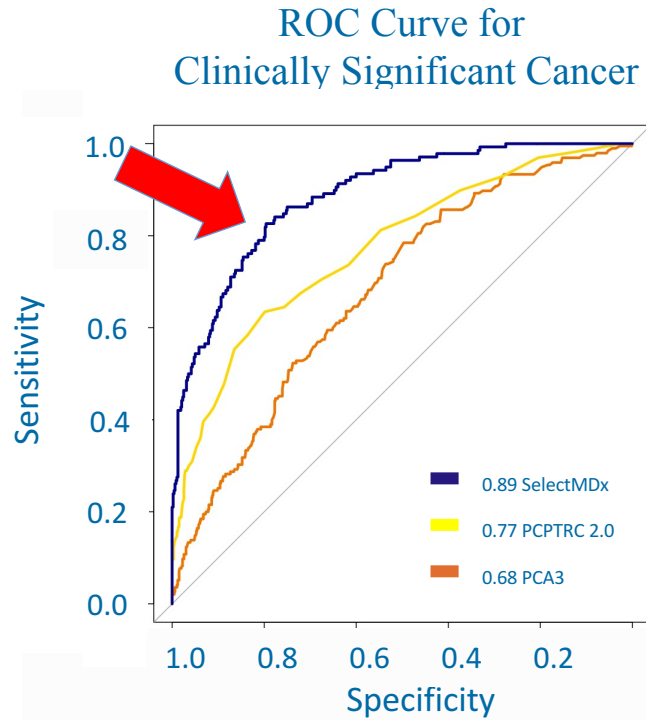
SelectMDx for Prostate Cancer:

- Strongest predictor of high-grade disease compared to traditional clinical risk factors
- 98% NPV for GS ≥ 7 cancer
- 99% NPV for GS ≥ 8 cancer



European Urology 2016

SelectMDx Outperforms PCA3 & PCPT Risk Calculator for Detection of High Grade Cancer



Sample Patient Report

Identification of Men for Prostate Bx:

High Risk

- Increased risk for aggressive cancer
- Men who may benefit from biopsy

Very Low Risk

- 98% NPV for aggressive cancer
- May avoid biopsy
- Return to routine screening

Risk for CS PCa

SAMPLE
Patient Report

SelectMDx
for Prostate Cancer

PATIENT

Patient Name: David Sample
Date of Birth: 12/27/1962
MRN/PatientID: 897821
Prostate Volume: 30cc
Family History: None
PSA: 9 ng/ml DRE: Normal

SPECIMEN

SpecimenID: 72398
Collection Date: 11/05/2015
Received Date: 11/07/2015
Report Date: 11/09/2015
Specimen Type: Urine
MDxH Accession#: SL-91322

ACCOUNT

Physician: Randolph Smith, MD
Account: Urology Associates
Address: 15279 Alton Parkway
Suite 100
City/State/Zip: Irvine CA 92618

Patient Result:

The SelectMDx test result for this patient indicates a 57% likelihood of detecting prostate cancer, with a 50% probability for Gleason score ≥ 7 , when performing a standard 12-core TRUS guided biopsy.

57% Likelihood of prostate cancer upon biopsy

50% Likelihood of detecting Gleason score ≥ 7

Test Description:

SelectMDx for Prostate Cancer is a reverse-transcription PCR (RT-PCR) assay performed on urine specimens collected immediately following DRE from patients who are being considered for prostate biopsy. The test measures the urinary mRNA levels of the *DLX1* and *HOXC6* biomarkers to aid in patient selection for prostate biopsy. Higher levels of *DLX1* and *HOXC6* mRNA are associated with an increased probability for Gleason score ≥ 7 (GS ≥ 7) prostate cancer. A logistic regression model combining *DLX1* and *HOXC6* mRNA levels with established clinical risk factors, including PSA, prostate volume, DRE, family history and age, is used to estimate the likelihood of detecting GS ≥ 7 prostate cancer upon biopsy, with an area under the curve (AUC) of 0.88 (95% CI: 0.85-0.91), in addition to the likelihood of no cancer or GS ≤ 6 disease. Performance is based on the presence of all relevant data elements; if all data are not available, or 5 α -reductase inhibitors (5-ARIs) have been administered to decrease serum PSA values, results should be interpreted with caution and AUC of the test may vary.

Comments:

References:

1) Van Neste et al. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. *European Urology* 2016. <http://dx.doi.org/10.1016/j.eururo.2016.04.012>.
2) Leyten et al. Identification of a Candidate Gene Panel for the Early Diagnosis of Prostate Cancer. *Clin Cancer Res* 2015. Jul 1;21(13):3061-70.
3) Hmeid et al. The role of HOXC6 in prostate cancer development. *The Prostate* 2015. Dec;75(18):1868-76.

Disclaimer:
MDxHealth is regulated under the Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists as an accredited laboratory to perform high complexity clinical testing. The SelectMDx for Prostate Cancer test was developed and its performance characteristics determined by MDxHealth. The test is intended for use as an aid to clinicians for patient management decisions about the need for a prostate biopsy on men with critical factors suggesting an increased risk for prostate cancer. Use outside of this indication has not been validated by MDxHealth. Test results should be interpreted in conjunction with other laboratory and clinical data available to the clinician and relevant guidelines on the decision for biopsy.
MDxHealth is certified by ISO 9001:2008 Quality Management System. This test was performed by MDxHealth Inc., 15279 Alton Parkway, Suite 100, Irvine, California 92618, CLIA 0520203898; CAP B015389.
General information about SelectMDx for Prostate Cancer can be found at www.mdhealth.com. If you have any questions regarding this report, please contact MDxHealth Client Services at 866-259-5644 or clientservices@mdhealth.com.

Jess Sevala
Jess Sevala, Jr., MD, Laboratory Director

MDxHealth Inc.

15279 Alton Parkway | Suite 100 | Irvine, CA 92618 | Toll Free: 866.259.5644 | P: 949.812.6979 | F: 949.788.0014 | E: clientservices@mdhealth.com | www.mdhealth.com
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Very Low Risk

SAMPLE
Patient Report

SelectMDx
for Prostate Cancer

PATIENT

Patient Name: David Sample
Date of Birth: 12/27/1962
MRN/PatientID: 897821
Prostate Volume: 30cc
Family History: None
PSA: 9 ng/ml DRE: Normal

SPECIMEN

SpecimenID: 72398
Collection Date: 11/05/2015
Received Date: 11/07/2015
Report Date: 11/09/2015
Specimen Type: Urine
MDxH Accession#: SL-91322

ACCOUNT

Physician: Randolph Smith, MD
Account: Urology Associates
Address: 15279 Alton Parkway
Suite 100
City/State/Zip: Irvine CA 92618

Patient Result: Very Low Risk

The SelectMDx test result for this patient indicates a very low risk for the detection of Gleason score ≥ 7 prostate cancer upon biopsy with a negative predictive value of 98%, and a negative predictive value of 99% for Gleason score ≥ 8 prostate cancer.

Test Description:

SelectMDx for Prostate Cancer is a reverse-transcription PCR (RT-PCR) assay performed on urine specimens collected immediately following DRE from patients who are being considered for prostate biopsy. The test measures the urinary mRNA levels of the *DLX1* and *HOXC6* biomarkers to aid in patient selection for prostate biopsy. Higher levels of *DLX1* and *HOXC6* mRNA are associated with an increased probability for Gleason score ≥ 7 (GS ≥ 7) prostate cancer. A logistic regression model combining *DLX1* and *HOXC6* mRNA levels with established clinical risk factors, including PSA, prostate volume, DRE, family history and age, is used to estimate the likelihood of detecting GS ≥ 7 prostate cancer upon biopsy, with an area under the curve (AUC) of 0.88 (95% CI: 0.85-0.91), in addition to the likelihood of no cancer or GS ≤ 6 disease. Performance is based on the presence of all relevant data elements; if all data are not available, or 5 α -reductase inhibitors (5-ARIs) have been administered to decrease serum PSA values, results should be interpreted with caution and AUC of the test may vary.

Comments:

References:

1) Van Neste et al. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. *European Urology* 2016. <http://dx.doi.org/10.1016/j.eururo.2016.04.012>.
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3) Hmeid et al. The role of HOXC6 in prostate cancer development. *The Prostate* 2015. Dec;75(18):1868-76.





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Jess Sevala, Jr., MD, Laboratory Director

MDxHealth Inc.

15279 Alton Parkway | Suite 100 | Irvine, CA 92618 | Toll Free: 866.259.5644 | P: 949.812.6979 | F: 949.788.0014 | E: clientservices@mdhealth.com | www.mdhealth.com
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Tests in Bucket of who to biopsy

Assay Characteristics				
Company	Beckman Coulter	Opko	Hologic	MDxHealth
Specimen	Blood	Blood	Urine	Urine
Methodology	Immuno assay	Immuno assay	qPCR	qPCR
	3 Protein biomarkers	4 kallikriens biomarkers	mRNA test, 1 biomarker	2 mRNA Biomarkers
	tPSA and fPSA, proPSA	PSA, fPSA, Intact PSA, HK-2	PCA3	DLX1, HOXC6
Regulatory	FDA/CE	LDT/CLIA/CE	FDA/CE	LDT/CLIA/CE
List price (\$)	\$499	\$1,900	\$500	\$500
Assay Performance (AUC)	AUC 0.73	AUC 0.82	AUC 0.68	AUC 0.89
Comments	Requires Phlebotomist	Requires Phlebotomist & Centrifuge	Urine Sample - In Office Procedure	Urine Sample - In Office Procedure

1) PCEC 2015, 2) Curr Opin Oncol. 2014 May ; 26(3): 259–264

The Goal in 2017

Goal 6
Active Surveillance



What PCM helps us identify patient harboring
high risk cancers?

Patient/Physician Website

www.pcmakers.com



PCMs
Prostate Cancer Markers

Guiding you through the newest state
of the art prostate cancer diagnostic
and prognostic tests

Surgery, XRT, Cryo, WW

- No RCT
- Discuss the pros and cons of surgery

Treatment of Prostate Cancer

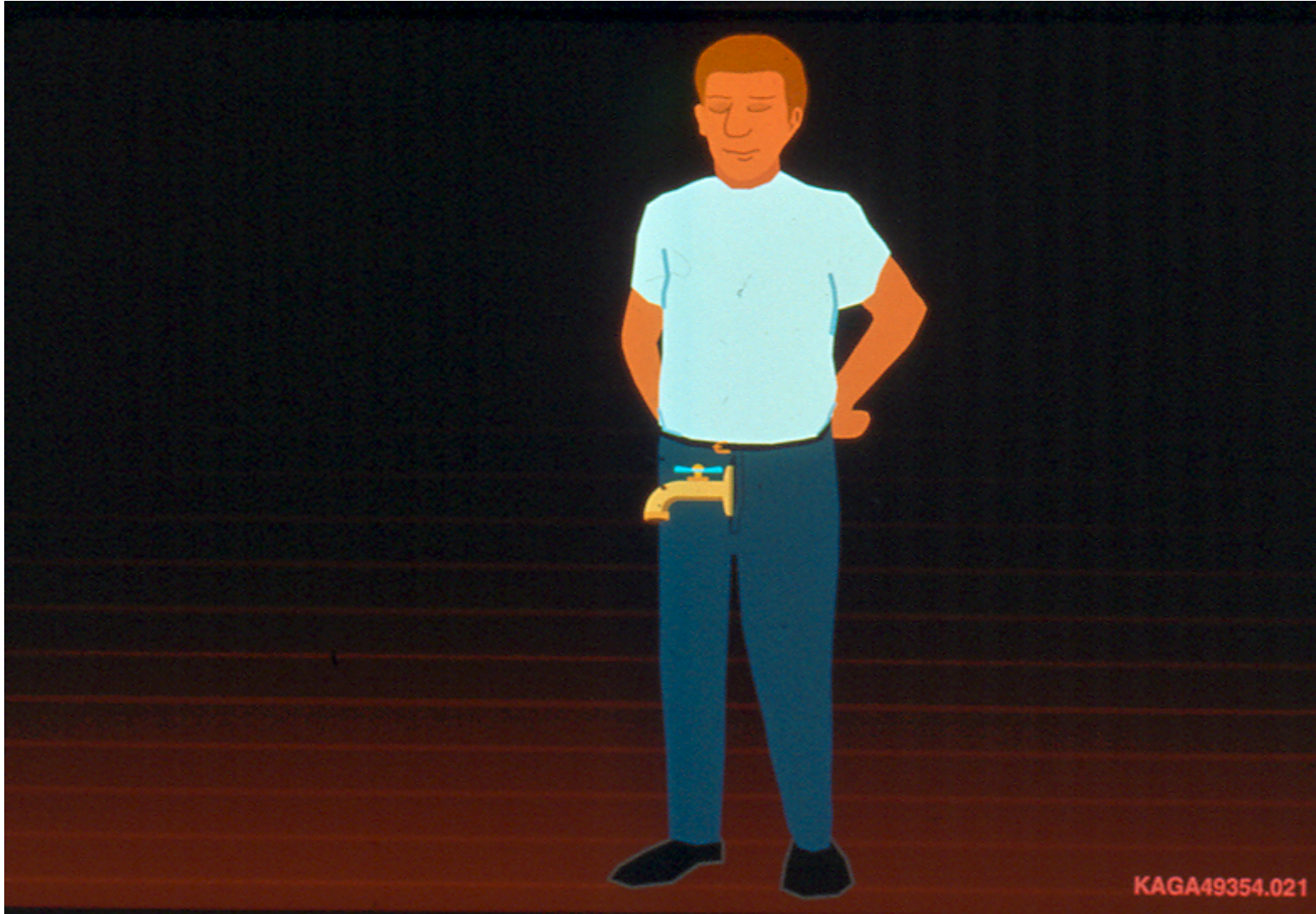
Patients Influenced by:

- Physician(s)
- Family
- Friends
- Media
- Newspapers
- Support Groups
- Side Effects

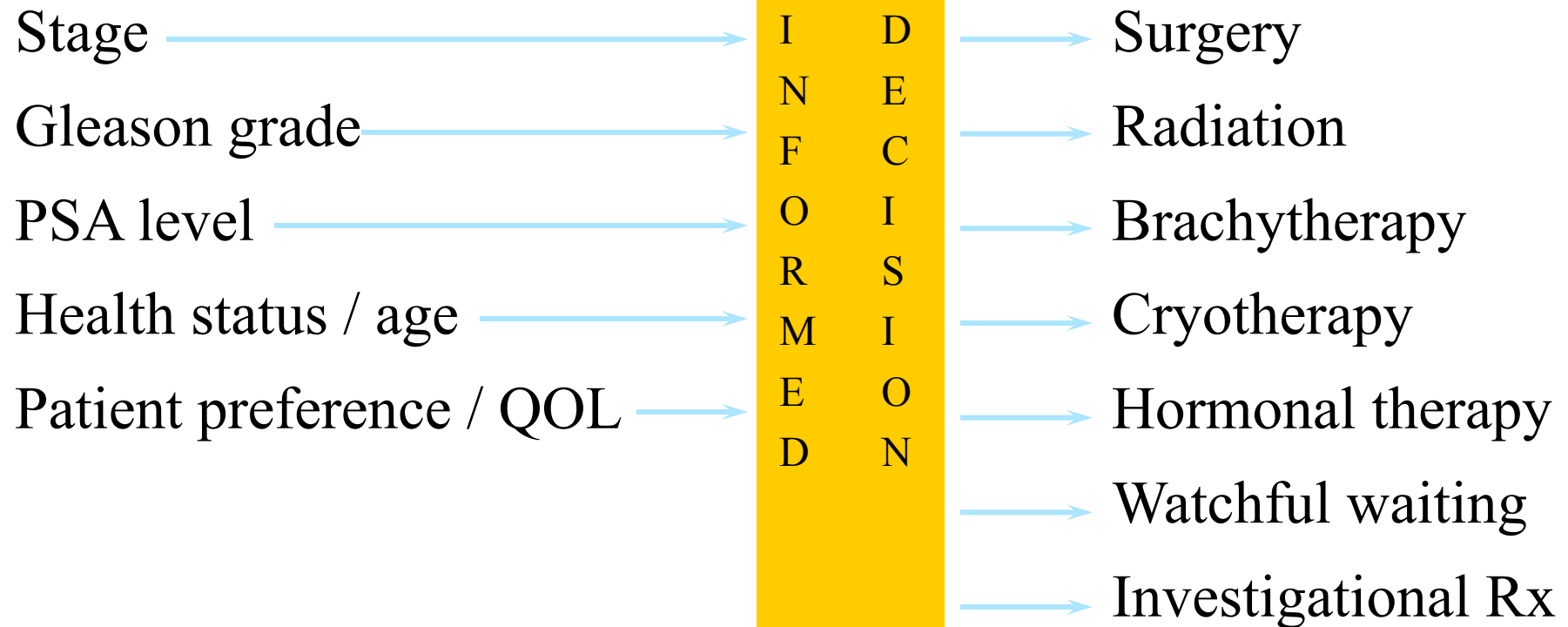
Intent of Therapy

- Curative
- Prevention
- Delay Progression
- Palliative





Getting the Correct Match



Advantages of Prostatectomy

“Gold Standard”

Staging

Local Control-very important!

Complications

Survival

Willet Whitmore, MSKCC 1963-1986

- Is treatment sufficient for those in whom it is necessary, and necessary for those in whom it is sufficient?

The transition in oncology:

20th century 'seek and destroy'

21st century 'target and control'

A. Von Eschenbach

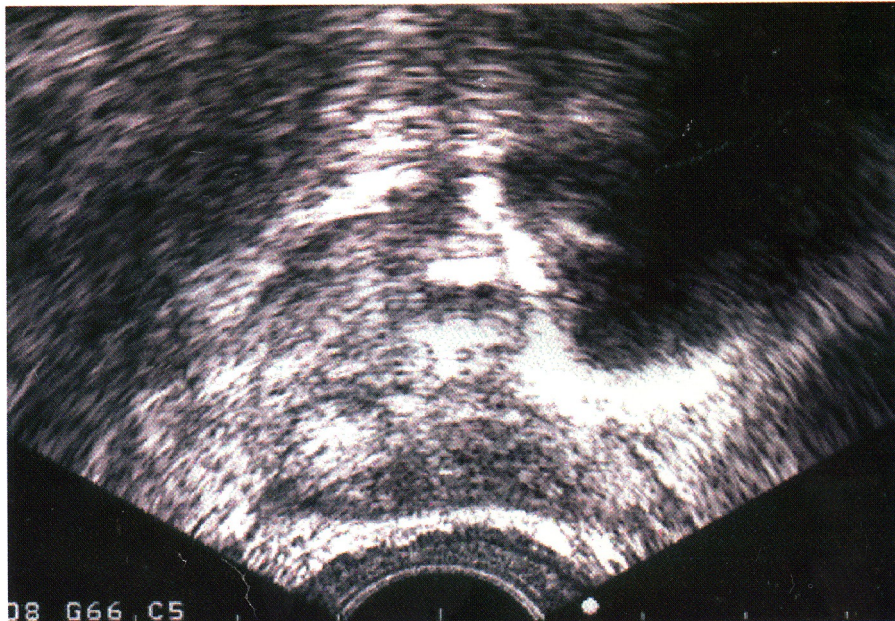
Director, NCI

Renal & Urology News

WORLD REVIEW FOR UROLOGISTS & NEPHROLOGISTS

And Now, the Male Lumpectomy

Focal cryoablation targets only the prostate tumor itself and not the entire gland



FREEZING IS occurring in the anterior portion of the left side of a patient's prostate gland.

BY JOHN SCHIESZER

NEW ORLEANS—New data suggest that a “male lumpectomy,” in which only the tumor region of the prostate is destroyed, appears

plications, without compromising cancer control.

If long-term studies confirm the findings, the new approach could change the treatment paradigm of

of the Society of Interventional Radiology.

“It is a totally new way of thinking for urologists,” said lead investigator Gary Onik, MD, an interventional radiologist at Florida Hospital/Celebration Health in Celebration, Fla. “Treating only the tumor instead of the whole prostate gland is a major and profound departure from the current thinking about prostate cancer. Focal cryoablation changes the whole picture in terms of complications, and the cancer control is as good as for any other treatment. Focal cryoablation appears to preserve urinary and sexual function superiorly to any other treatment yet available.”

Cryoablation of the whole prostate gland has been approved by Medicare for more than five years as a primary treatment for prostate cancer. Recent data show that cryoablation has a 10-year disease-specific survival rate of over 98%. Cryoablation also is

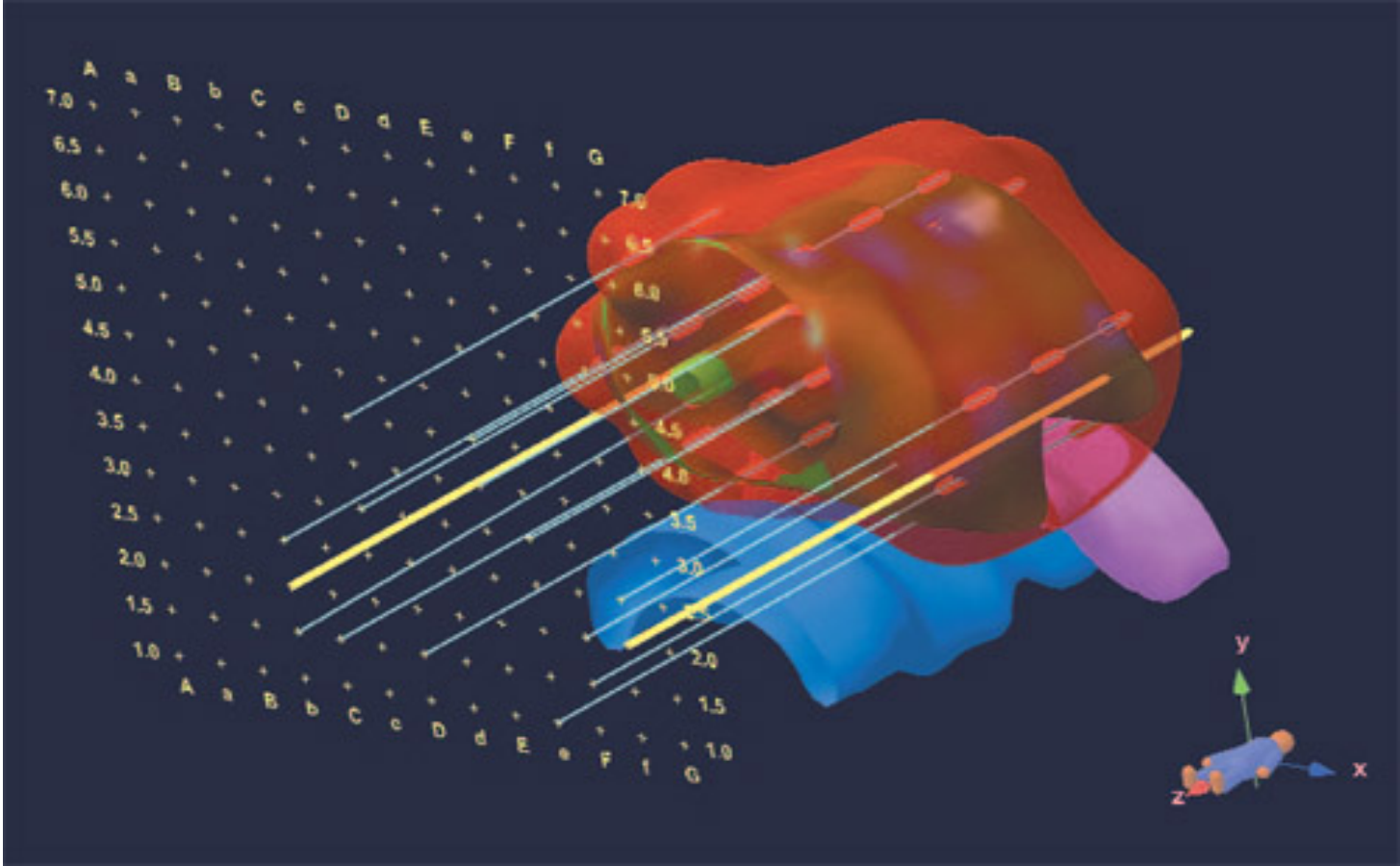
PVD Predicts Worse Dialysis Outcomes

WASHINGTON, DC—Moderate to severe peripheral vascular disease (PVD) in dialysis patients with elevated albumin levels predicts an increased mortality risk, researchers reported here at the National Kidney Foundation Clinical Meetings.

Out of a cohort of 922 dialysis patients, 25% had a diagnosis of PVD. After a median follow-up of 2.8 years, the crude mortality was 45.2% among subjects with PVD, compared with 29.8% in patients without PVD.

The presence of PVD was associated with a 23% elevated death risk for the study group as a whole, after adjusting for confounders. PVD increased the death risk by 48% among patients with a serum albumin level greater than 3.5 g/dL, but did not affect the risk among subjects with lower albumin levels, according to a team led by Bernard

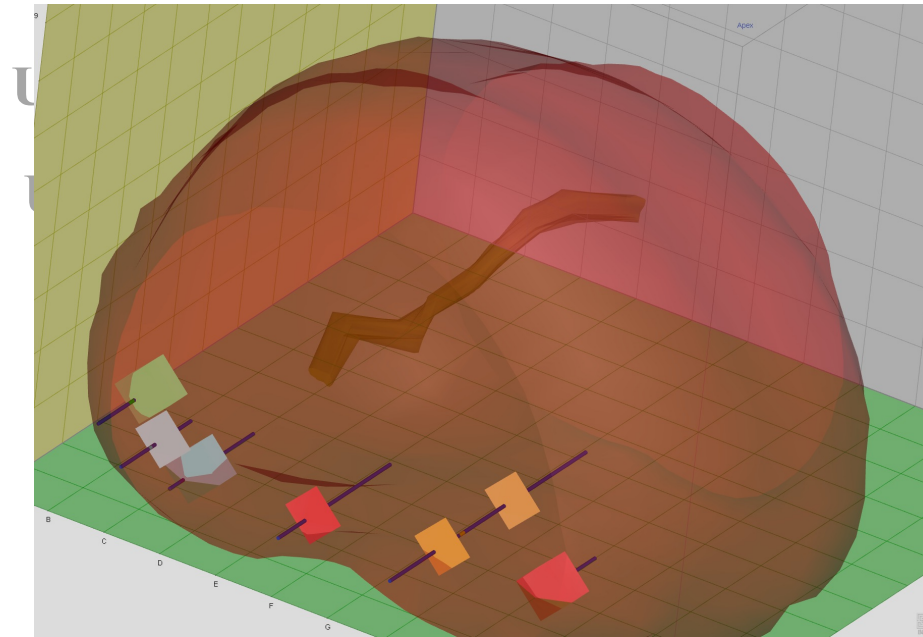
Transperineal Mapping Prostate Biopsy





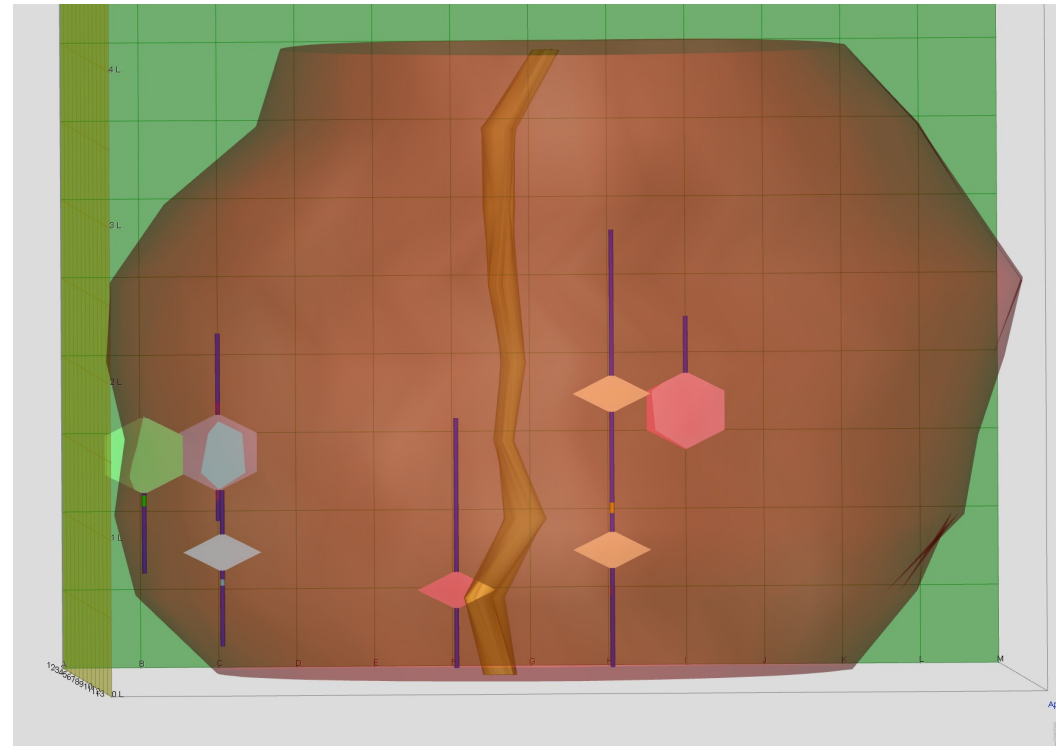
Top, Side, Front (tilted) Views of Capsule

(Somewhat transparent)



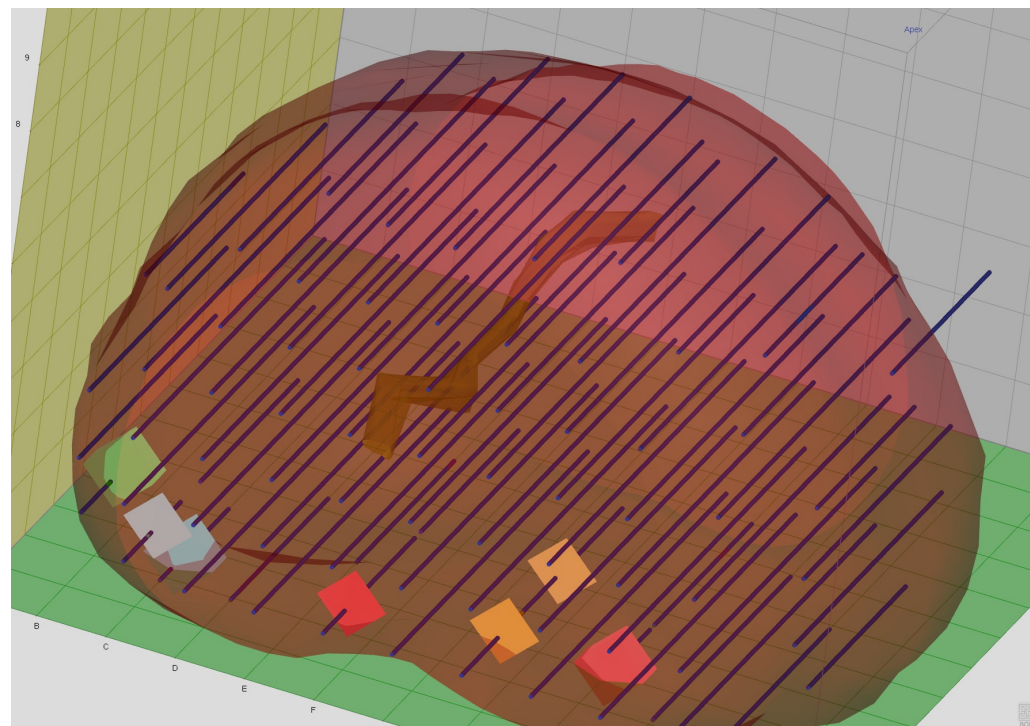
Patient GE
MRN

Top View of Prostate



Patient GE
MRN

Capsule & Biopsy Probes/Volumes



Patient GE
MRN