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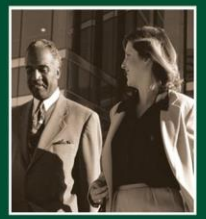

Screening and Risk Stratification of Men for Prostate Cancer *Metastasis and Mortality*

Sanoj Punnen, MD, MAS

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Miami, FL

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Disclosure

- Conflict of interest: None

Prostate Cancer

Goals for Today's Session

- Current prostate cancer screening practices and challenges for early detection of prostate cancer
- The value of PSA as a sensitive predictor of prostate cancer mortality
- PSA ordering practices of primary care physicians
- What is a reasonable approach to prostate cancer screening?
- Validity, safety and effectiveness of an innovative second stage biomarker test as a follow-up test after an abnormal PSA to identify who should (and should not) receive a prostate biopsy

Prostate Cancer 2018

Estimated New Cases

Males				Females		
Prostate	161,360	19%		Breast	252,710	30%
Lung & bronchus	116,990	14%		Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%		Colon & rectum	64,010	8%
Urinary bladder	60,490	7%		Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%		Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%		Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%		Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%		Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%		Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%		Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**		**All Sites**	**852,630**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	84,590	27%		Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%		Breast	40,610	14%
Prostate	26,730	8%		Colon & rectum	23,110	8%
Pancreas	22,300	7%		Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%		Ovary	14,080	5%
Leukemia	14,300	4%		Uterine corpus	10,920	4%
Esophagus	12,720	4%		Leukemia	10,200	4%
Urinary bladder	12,240	4%		Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%		Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%		Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**		**All Sites**	**282,500**	**100%**

FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2017.
Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

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The New England
Journal of Medicine

Volume 317 OCTOBER 8, 1987 Number 15

PROSTATE-SPECIFIC ANTIGEN AS A SERUM MARKER FOR ADENOCARCINOMA OF THE PROSTATE

THOMAS A. STAMEY, M.D., NORMAN YANG, PH.D., ALAN R. HAY, M.D., JOHN E. MCNEAL, M.D., FUAD S. FREIHA, M.D., AND ELISE REDWINE, B.A.

Abstract To compare the clinical usefulness of the serum markers prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), we measured them by radioimmunoassay in 2200 serum samples from 699 patients, 378 of whom had prostatic cancer.

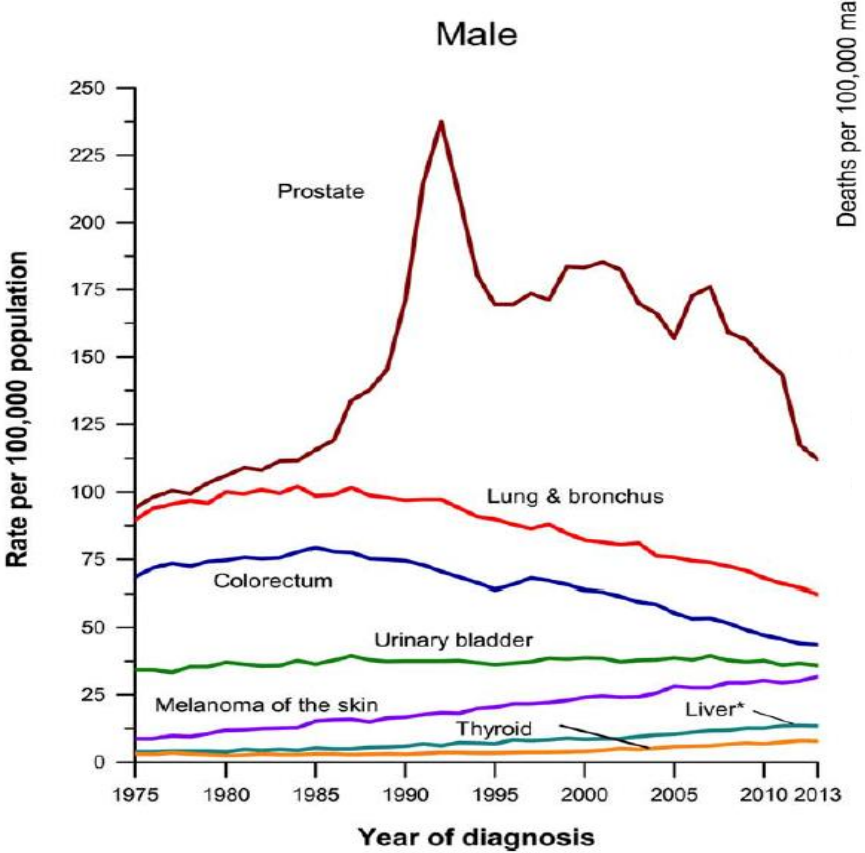
PSA was elevated in 122 of 127 patients with newly diagnosed, untreated prostatic cancer, including 7 of 12 patients with unsuspected early disease and all of 115 with more advanced disease. The PSA level increased with advancing clinical stage and was proportional to the estimated volume of the tumor. The PAP concentration was elevated in only 57 of the patients with cancer and correlated less closely with tumor volume. PSA was increased in 86 percent and PAP in 14 percent of the patients with benign prostatic hyperplasia.

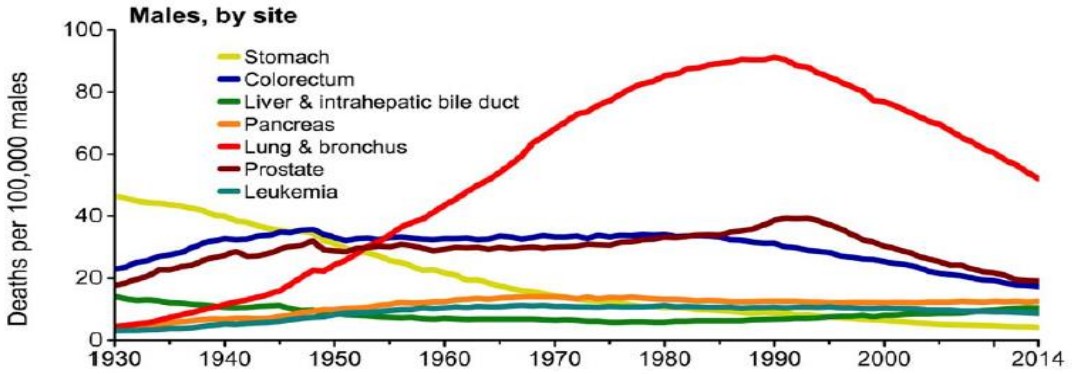
After radical prostatectomy for cancer, PSA routinely fell to undetectable levels, with a half-life of 2.2 days. If initially elevated, PAP fell to normal levels within 24 hours but always remained detectable. In six patients followed postoperatively by means of repeated measurements, PSA — but not PAP — appeared to be useful in detecting residual and early recurrence of tumor and in monitoring responses to radiation therapy.

Prostate massage increased the levels of both PSA and PAP approximately 1.5 to 2 times. Needle biopsy and transurethral resection increased both considerably.

We conclude that PSA is more sensitive than PAP in the detection of prostatic cancer and will probably be more useful in monitoring responses and recurrence after therapy. However, since both PSA and PAP may be elevated in benign prostatic hyperplasia, neither marker is specific. (N Engl J Med 1987; 317:909-16.)

Prostate Cancer Incidence and Mortality





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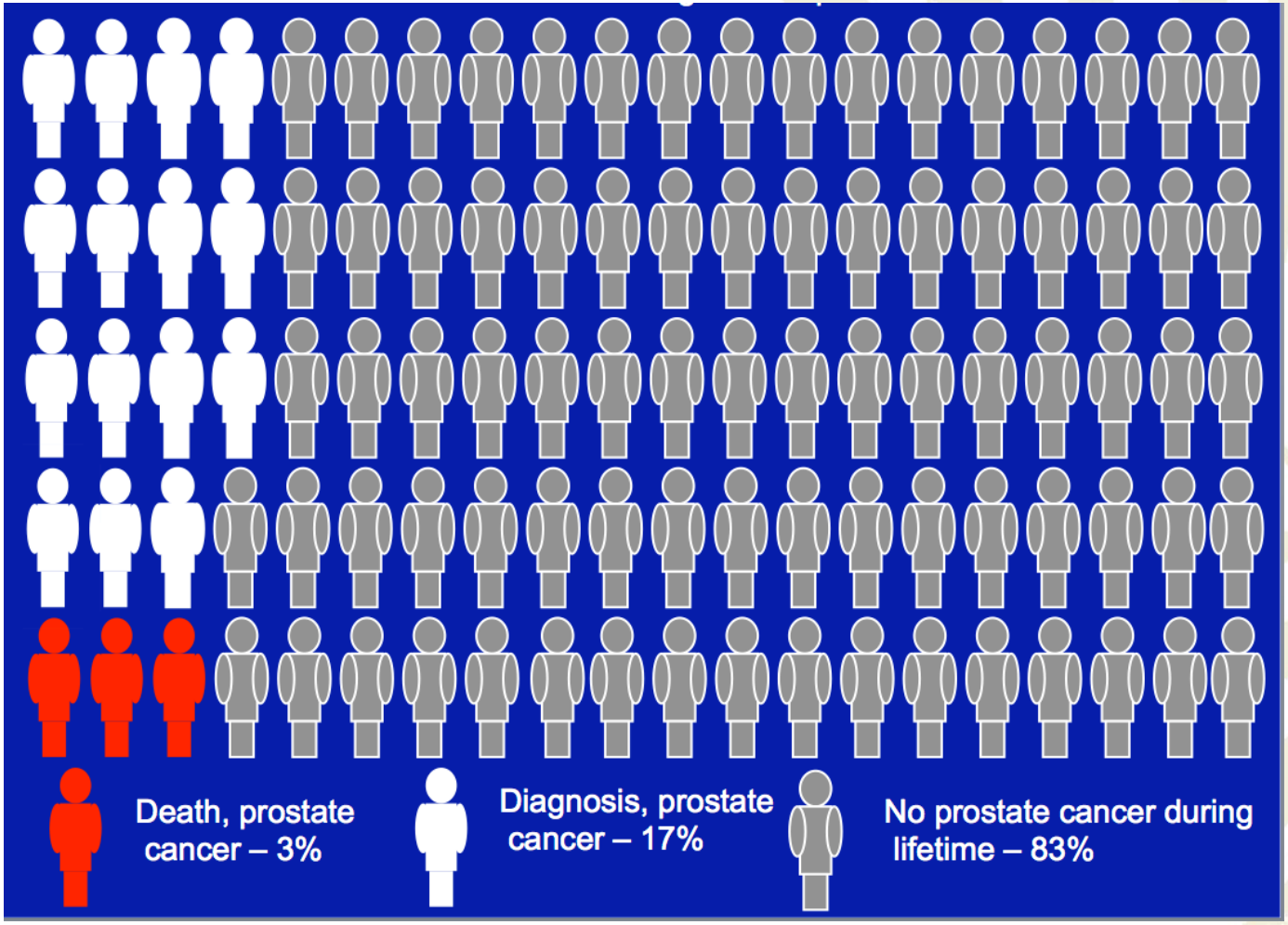
Lifetime Risk of Prostate Cancer Death



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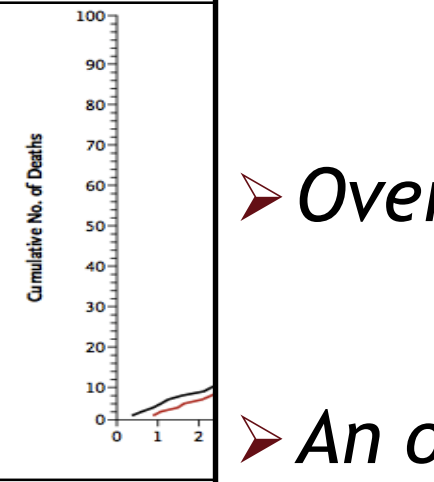
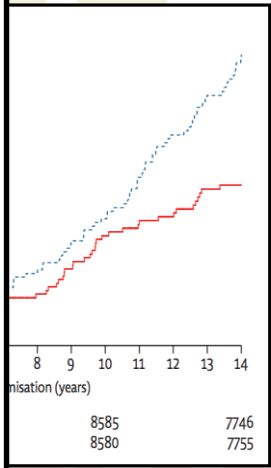
What do we know from randomized trials?

- Screening Works
- *Over-detection is a problem*
- *An overwhelming number of men are exposed to invasive testing and treatment to save one life*





BORG

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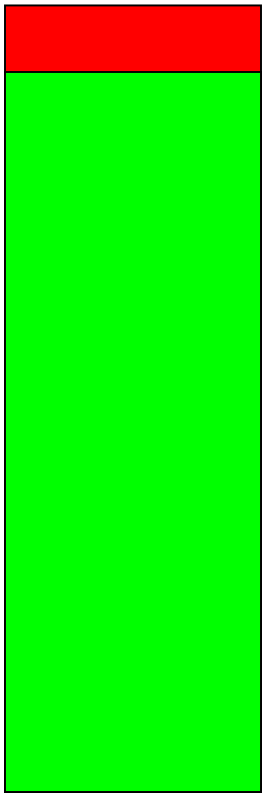
Approaches to Screening: How did we start?



PSA>4.0

PSA<4.0

Your PSA is Elevated.
You need a biopsy.”

“Your PSA is Normal.
No testing is necessary.”

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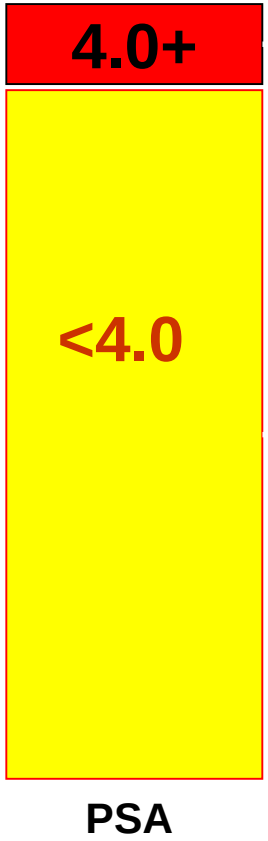
Population Screening with PSA: The Truth!



PSA 4+	7.6%
Positive biopsy	25%
High grade	19%

Screen 10,000 Men

PSA 4+	760
Cancer	190
High grade	36

Normal PSA	92.4%
Positive biopsy	15%
High grade	15%

PSA <4	9240
Cancer	1386
High grade	208

SEER, PCAW, Prostate Cancer Prevention Trial Data

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0022-5347/05/1746-2154/0
THE JOURNAL OF UROLOGY®

Vol. 174, 2154–2157, December 2005
Printed in U.S.A.
DOI: 10.1097/01.ju.0000181213.07447.8f

USE OF 2.6 NG/ML PROSTATE SPECIFIC ANTIGEN PROMPT FOR BIOPSY IN MEN OLDER THAN 60 YEARS

ROBERT B. NADLER,*,† STACY LOEB, KIMBERLY A. ROEHL, JO ANN V. ANTENOR, SCOTT EGGENER AND WILLIAM J. CATALONA‡

From the Department of Urology, Northwestern University, Feinberg School of Medicine (RBN, SL, SE, WJC), Chicago, Illinois, and Departments of Psychiatry (KAR), Neurology (JAVA) and Surgery/Urology (WJC), Washington University, St. Louis, Missouri

ELSEVIER

EDITORIAL
CME ARTICLE

LOWERING PSA CUTOFFS TO ENHANCE DETECTION OF CURABLE PROSTATE CANCER

WILLIAM J. CATALONA, CHRISTIAN G. RAMOS, GUSTAVO F. CARVALHAL, AND YAN YAN

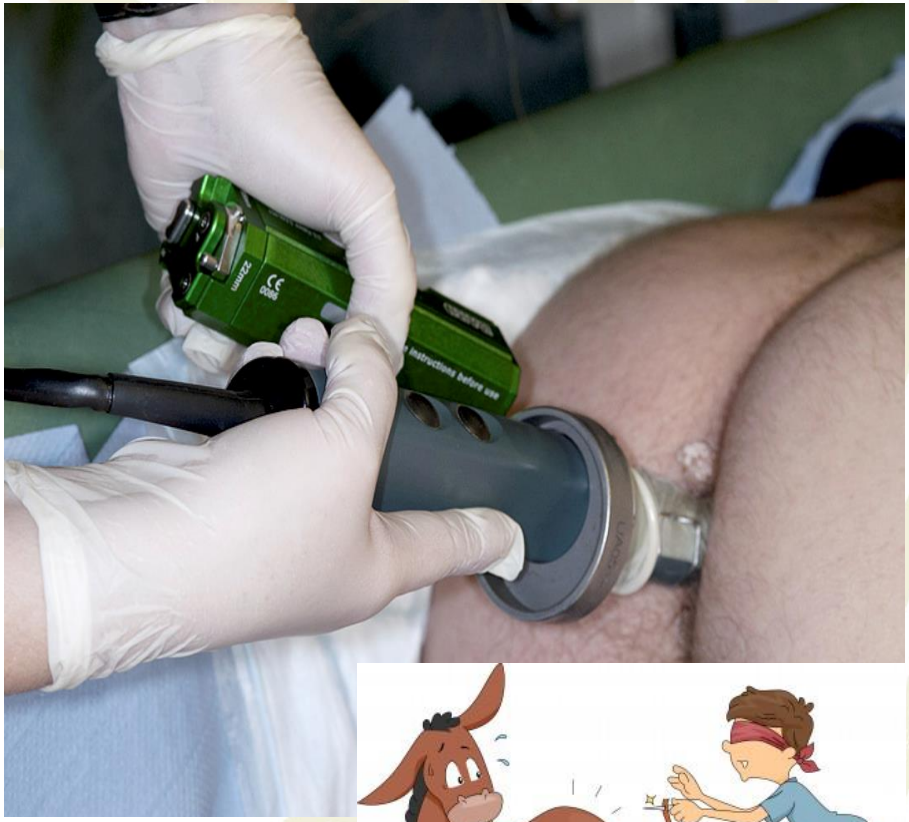
What are the risk of screening?

Prostate Biopsy?

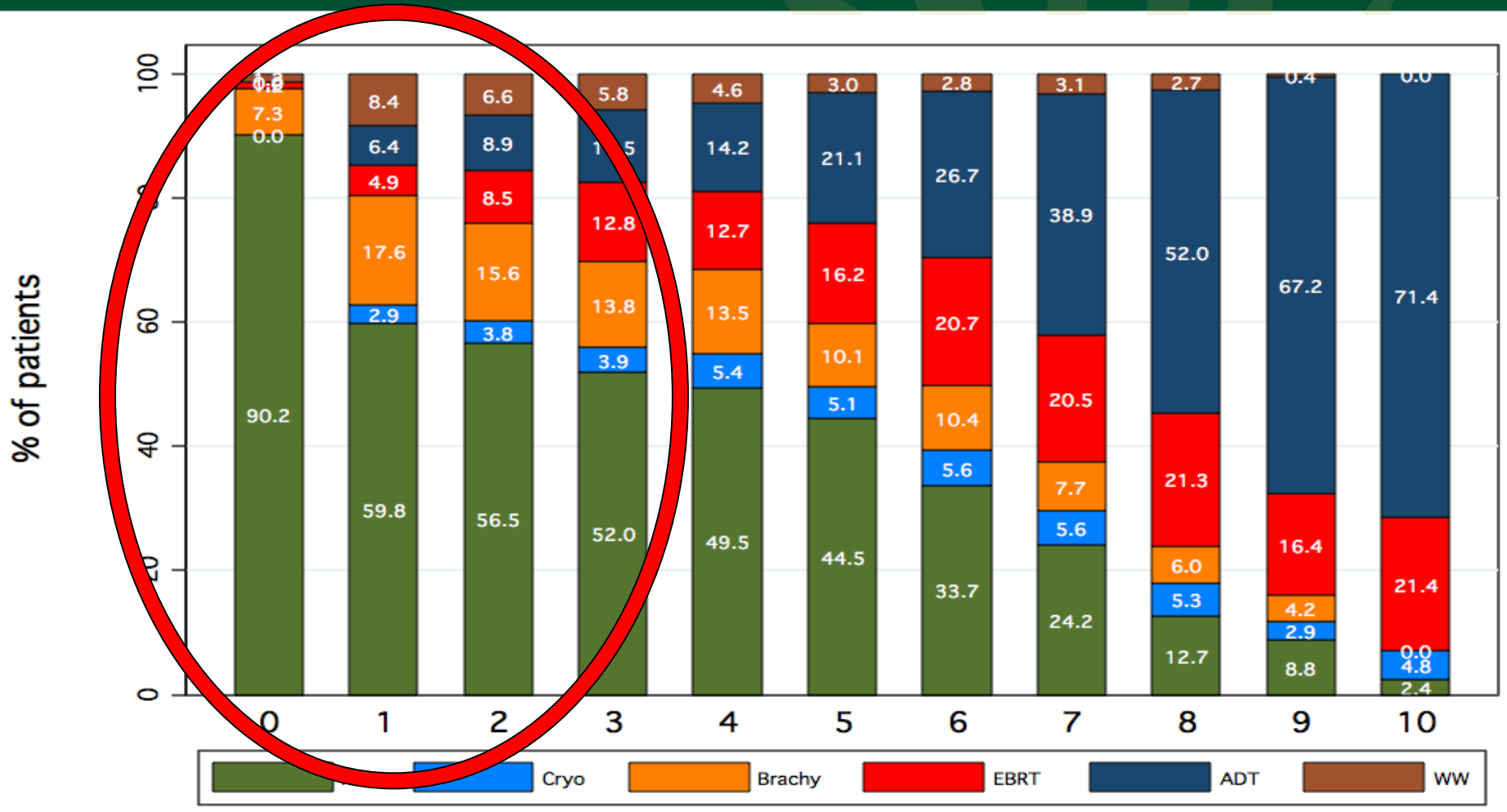
Prostate Biopsy

- Increasing trend of quinolone resistant sepsis
- Urinary Complications
- Costs
- Emotional Stress

- *Up to 75% of biopsies negative for cancer or show low risk – unlikely to affect quantity/ quality of life*



Under and Over Treatment



Cooperberg et al. J Clin Oncol 2010; 28:1117

Quality of Life after Prostate Cancer Treatment

Punnen et al. Eur Urol. 2014

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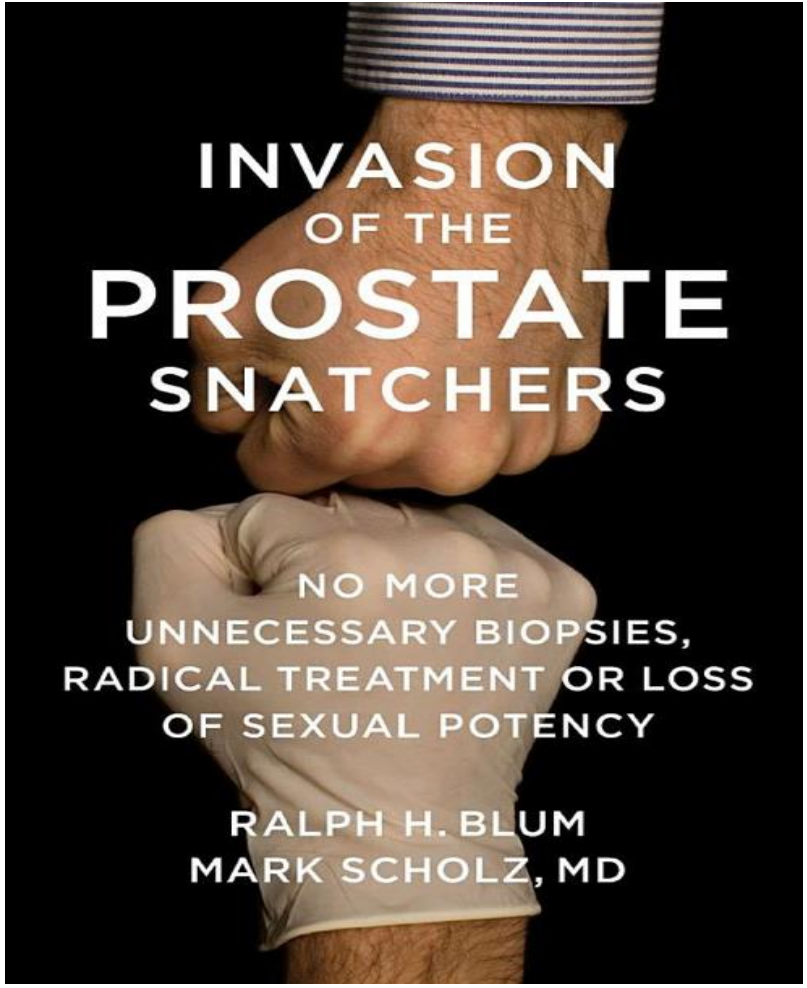
Public Health Impact



- **Patient awareness of overtreatment**
- **Controversy regarding detection and treatment**

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USPSTF 2012

CLINICAL GUIDELINE | Annals of Internal Medicine

Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, PhD, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2008 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for prostate cancer.

Methods: The USPSTF reviewed new evidence on the benefits and harms of prostate-specific antigen (PSA)–based screening for prostate cancer, as well as the benefits and harms of treatment of

Recommendation: The USPSTF recommends against PSA-based screening for prostate cancer (grade D recommendation).

This recommendation applies to men in the general U.S. population, regardless of age. This recommendation does not include the use of the PSA test for surveillance after diagnosis or treatment of prostate cancer; the use of the PSA test for this indication is outside the scope of the USPSTF.

Ann Intern Med. 2012;157:120-134. www.annals.org

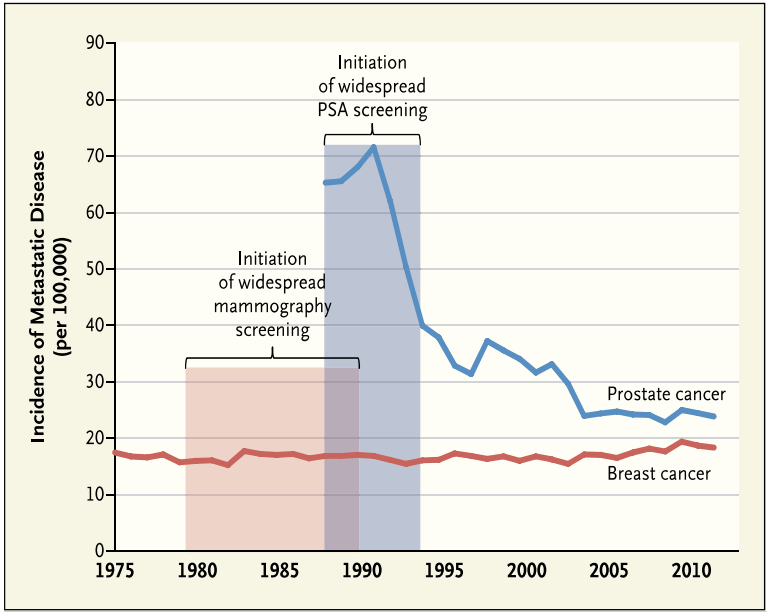
For author affiliation, see end of text.

* For a list of the members of the USPSTF, see **Appendix 1** (available at www.annals.org).

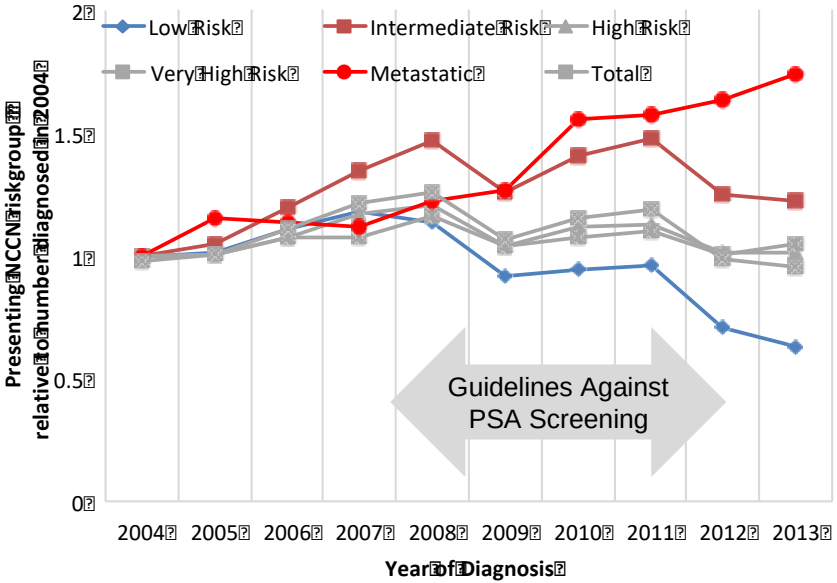
This article was published at www.annals.org on 22 May 2012.

US Preventive Services Task Force. Ann Intern Med 2012

Early Detection & Treatment of Aggressive Prostate Cancer is Essential



Widespread PSA Screening leads to Reduced Diagnoses of Metastatic Disease[1]



In response to over diagnosis and over treatment concerns, guidelines against PSA screening were published: rise in patients presenting with metastatic disease[2]

[1]Welch et al. N Engl J Med. 2016 Feb 11;374(6):596.

[2]Weiner et al. Prostate Cancer Prostatic Dis. 2016 Dec;19(4):395-397.

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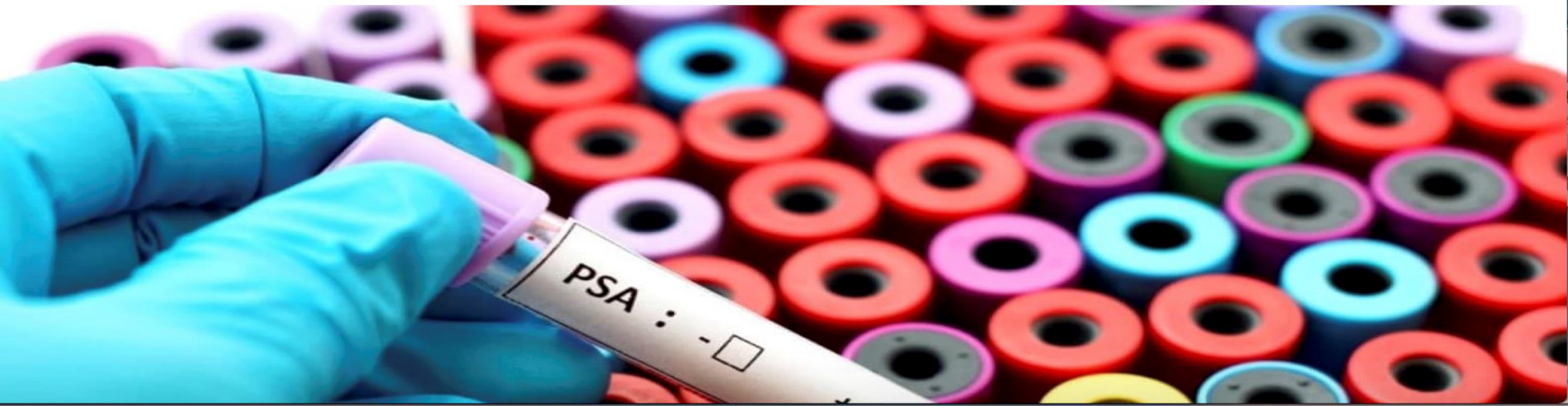
Shared Decision Making

To Your Health

The federal panel that opposed prostate cancer screening just changed its mind

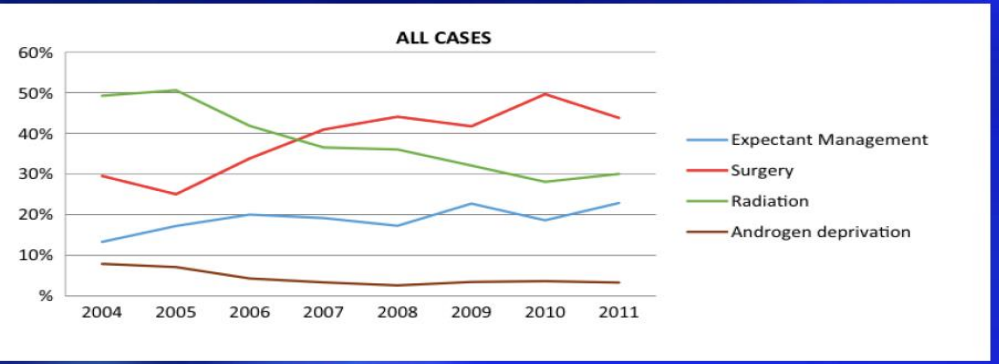
By Laurie McGinley April 11



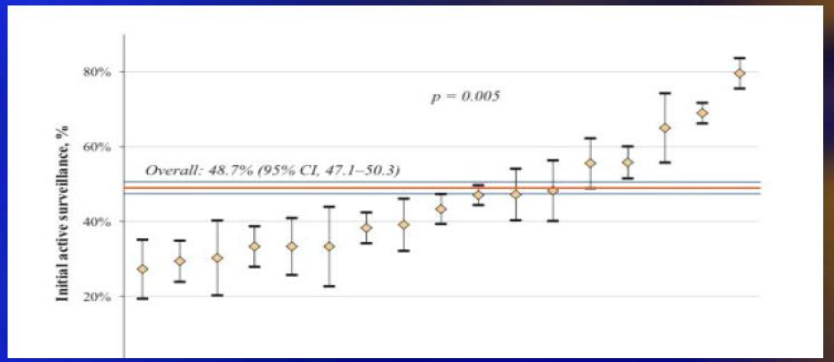
What Should We Do?

- Screen Smarter – Earlier, less often in elderly
- Screen for aggressive disease – minimize further testing in men who are low risk for significant Pca
- Disconnect Diagnosis and Treatment

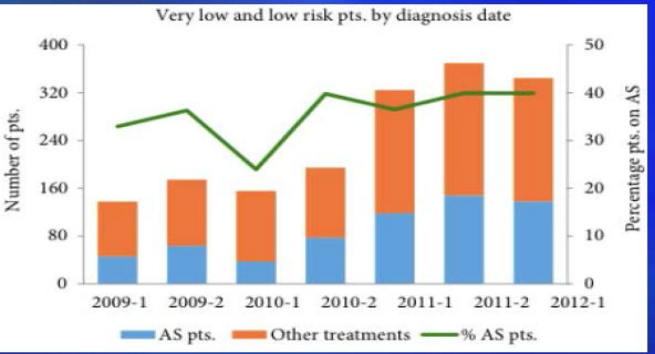
Trends in Active Surveillance: Utilization



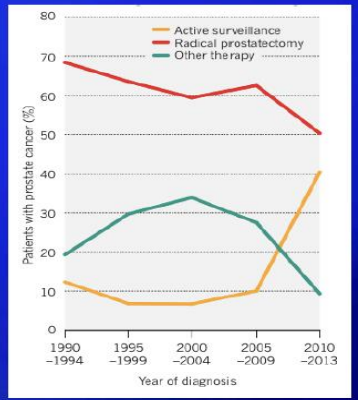
Ingimarsson JP (New Hampshire) Cancer Causes Control. 2015 Jun;26(6):923-9



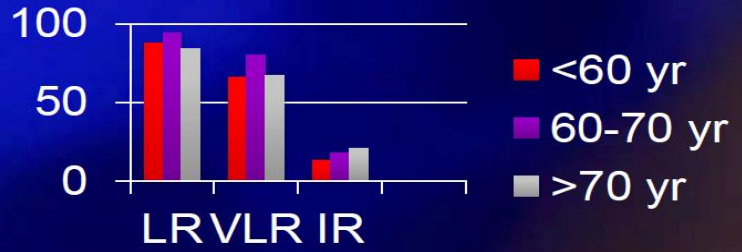
Womble PR (MUSIC): (Michigan) Eur Urol. 2015 Jan;67(1):44-50



Weerakoon M (Australia): BJUI 2015: 115 S5, 50-56



Cooperberg M et al, JAMA. 2015;314(1):80-82 From 7% to 40%



Loeb S (Sweden): AS in 91% VLR and 74% LR, URS 2015

What Should We Do?

- Screen Smarter – Earlier, less often in elderly
- Screen for aggressive disease – minimize further testing in men who are low risk for significant Pca
- Disconnect Diagnosis and Treatment

PSA Screening for Prostate Cancer

- Biomarker PSA is an excellent screening test for prostate cancer - sensitive (93%)*
- But - Poor specificity (24%)*
- Inadequate differentiation between indolent and aggressive prostate cancer
- Leads to over-diagnosis and over-treatment

* At 3 ng/mL cut-off

US Preventive Services Task Force et al. JAMA. 2018 May 8;319(18):1901-1913.

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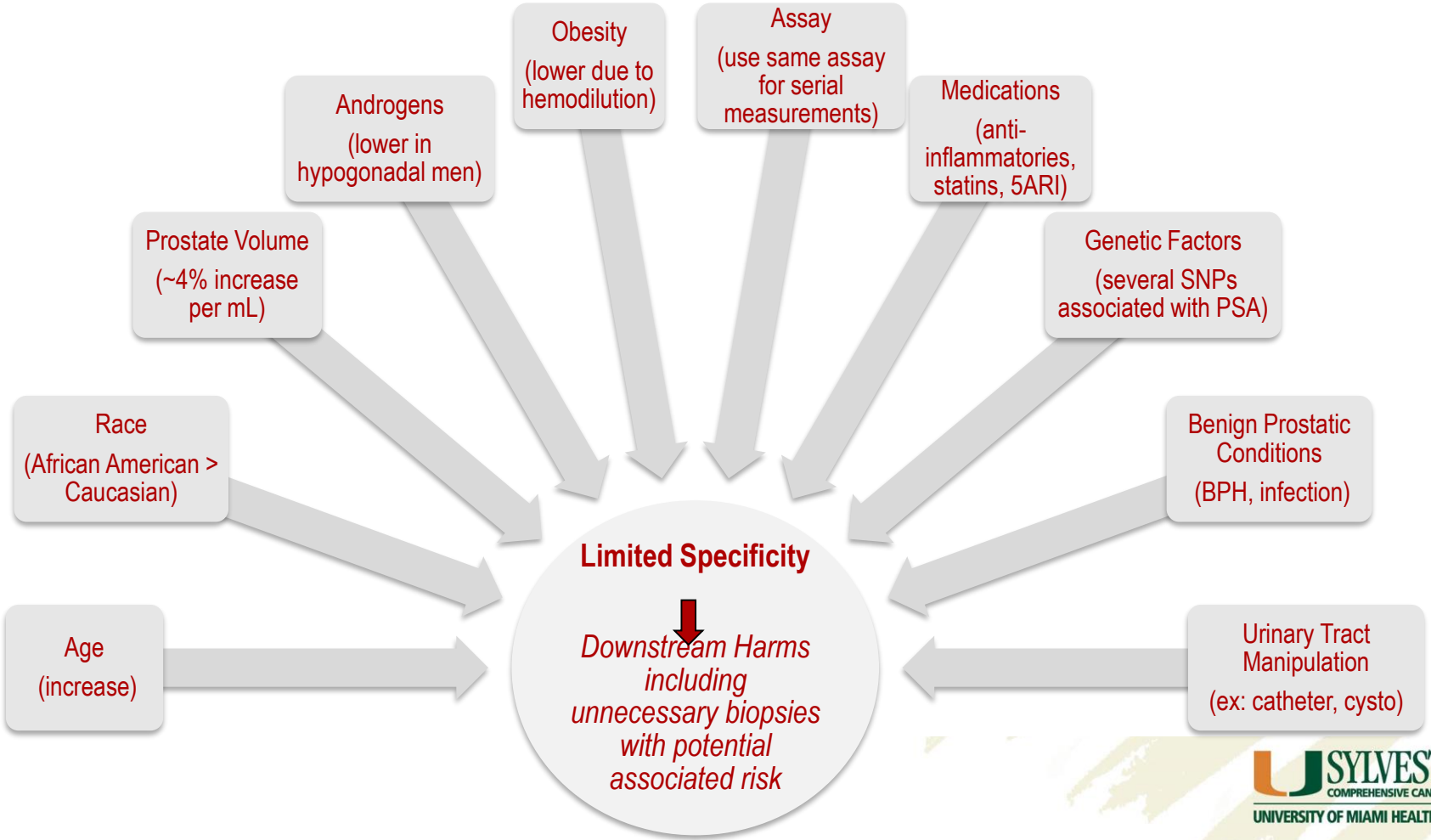
Many Factors Affect PSA Levels



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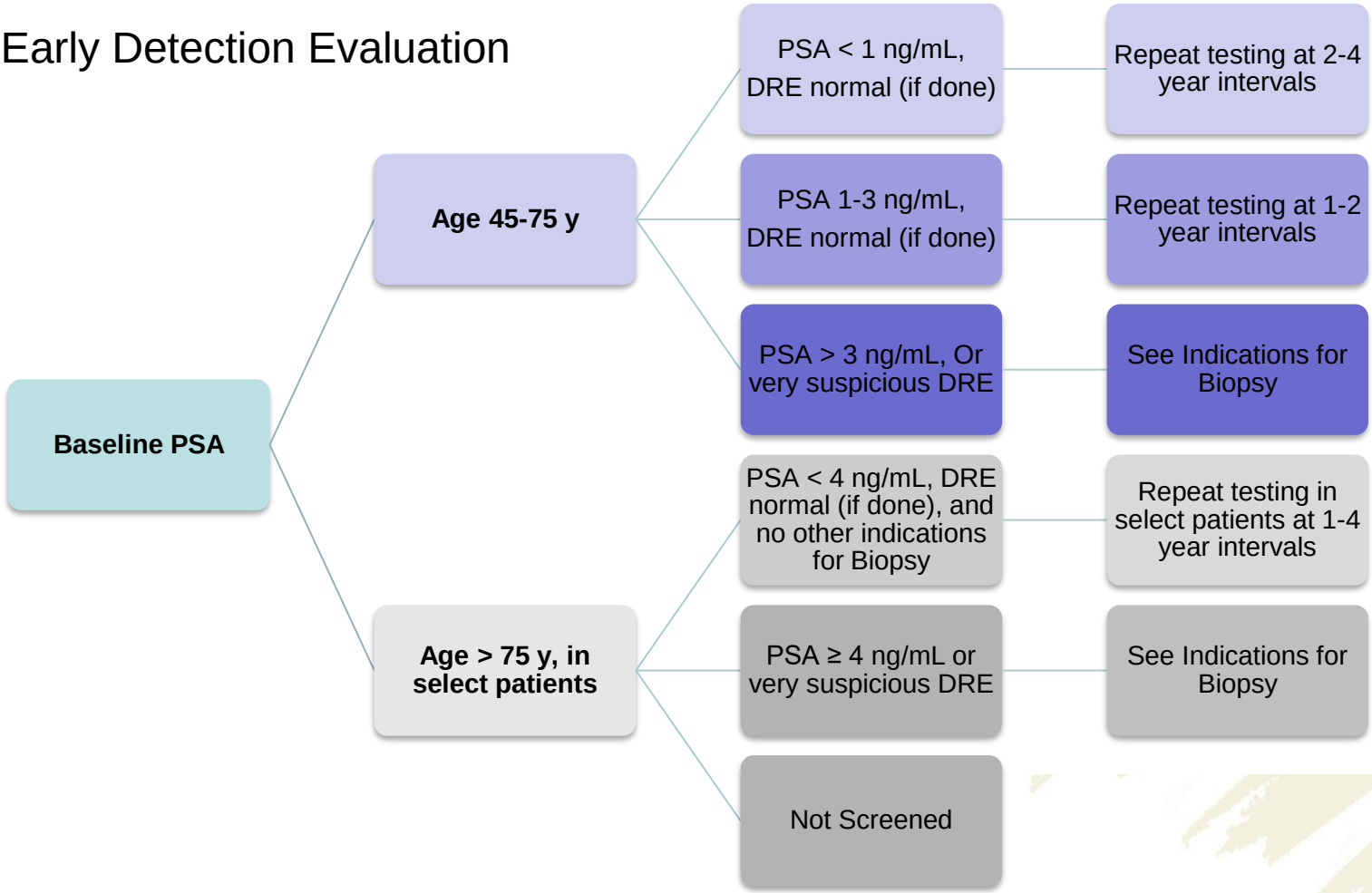
Reasonable Approach Prostate Cancer Early Detection

1. PSA for screening
2. Follow up biomarker test to detect risk of *Aggressive* Prostate Cancer
   - Identify men with a high risk of Aggressive Prostate Cancer who would benefit from further evaluation and treatment
   - Avoid prostate biopsies in men with a low risk of Aggressive Prostate Cancer to avoid unnecessary complications such as sepsis and overtreatment

NCCN Guidelines 2018: Intended Use Population for Prostate Biopsy

Early Detection Evaluation



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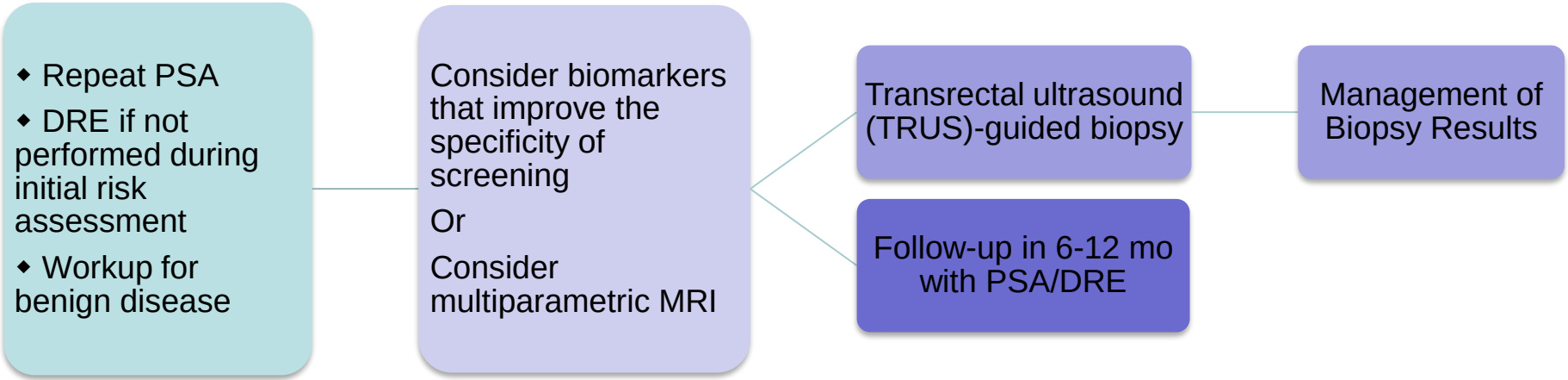
Second Stage Biomarker Consideration Before First or Repeat Biopsy

NCCN 2018 Guidelines: Indications for Biopsy



"…there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define the probability of high-grade cancer. A percent-free PSA <10%, PHI >35, or 4Kscore (which provides an estimate of the probability of high-grade prostate cancer) are potentially informative in patients who have never undergone biopsy or after a negative biopsy;"

Diagnostic Shift: Sensitivity to Specificity

Early Risk Detection of Clinically Significant Prostate Cancer

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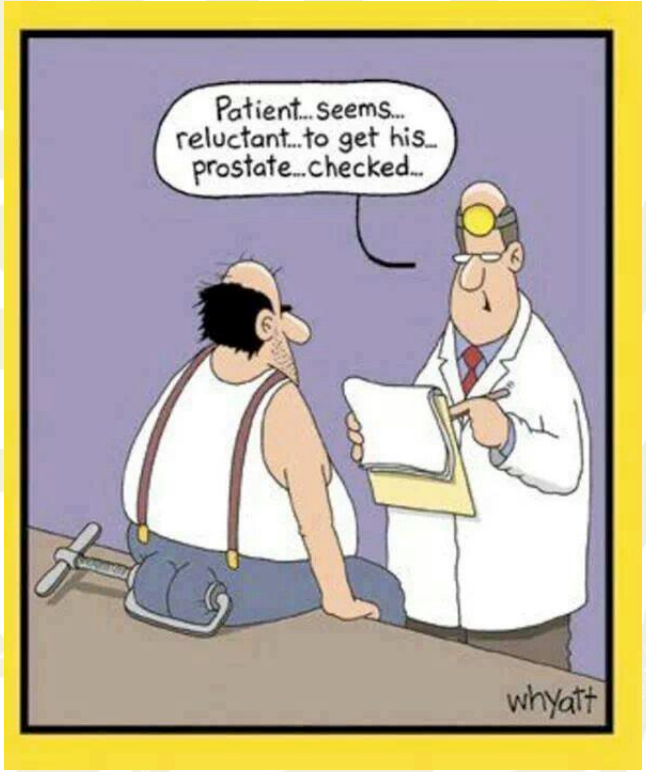
Secondary Biomarker Specificity

- Specific in identifying men at risk of having aggressive prostate cancer
- Improve decision making by developing a personalized treatment plan
- Identify a man at risk for high-grade cancer who would benefit from a prostate biopsy
- Identify men at low risk who may judiciously avoid a prostate biopsy but continue to be followed
- Avoid overtreatment of men with indolent prostate cancer

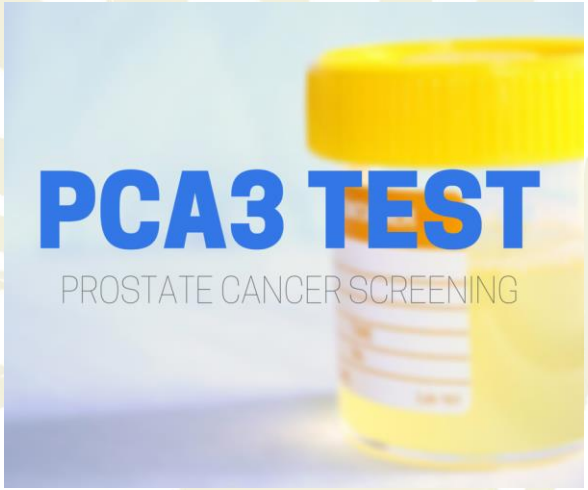


Molecular Markers for Prostate Cancer Detection

4Kscore®

A DIAGNOSTIC BLOOD TEST FOR DETECTING THE RISK OF

AGGRESSIVE PROSTATE CANCER



phi test

prostate health index

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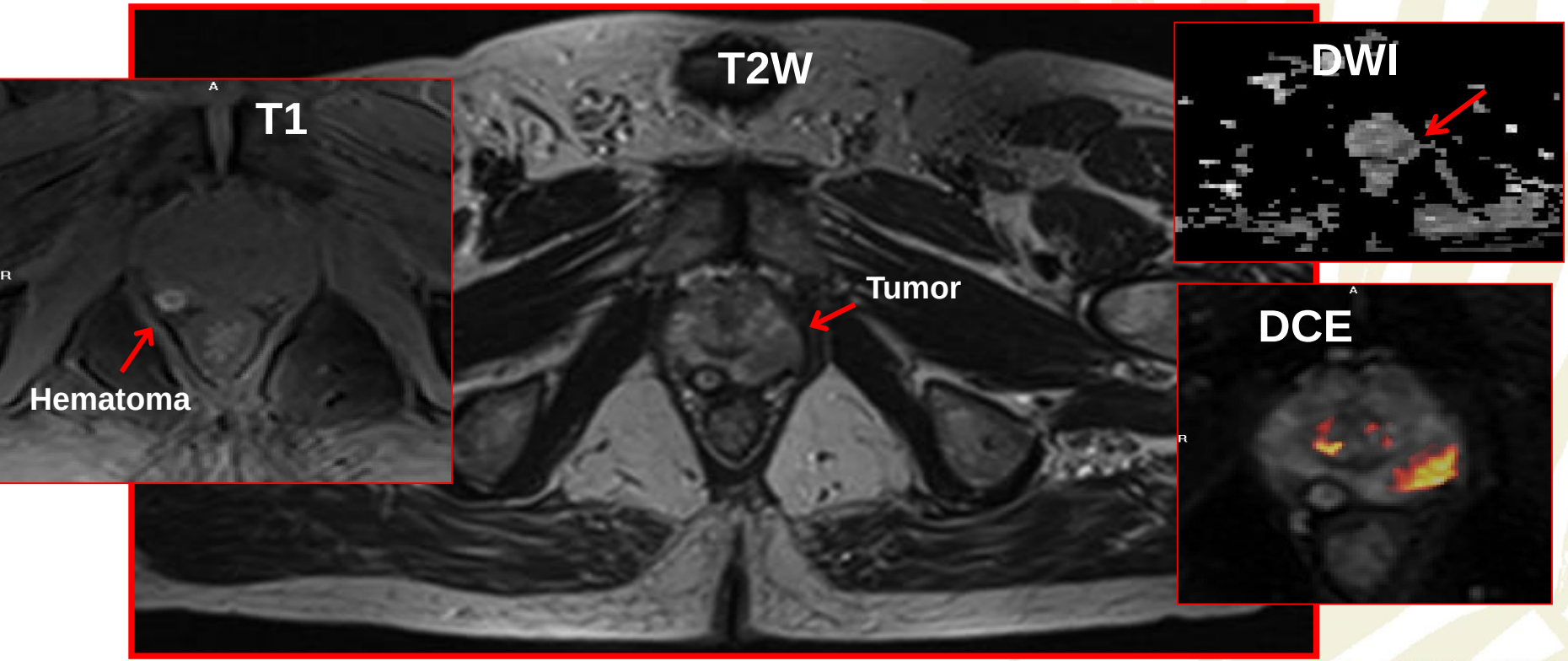
Multi-Parametric MRI of the Prostate



4Kscore Prospective Validation Trials

Initial prospective validation

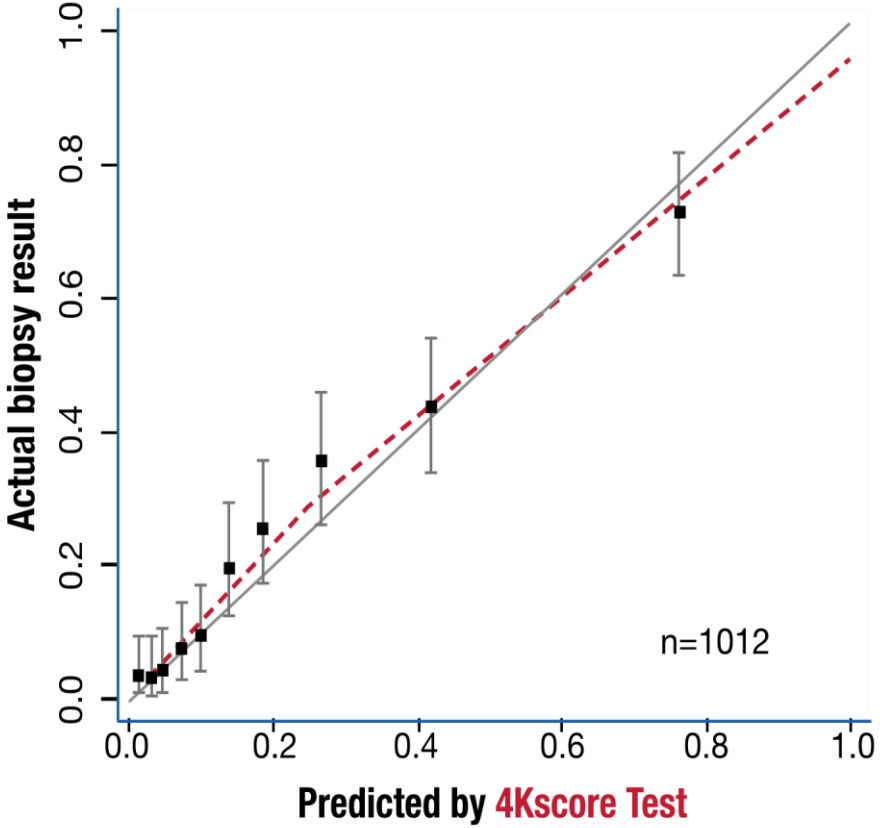
- 1,012 men prospectively enrolled in 26 academic & community practices
- All subjects underwent minimum 10 core prostate biopsy after blood drawn for 4Kscore Blood drawn prior to biopsy
- Outcomes of biopsy and 4Kscore Test were compared

Prospective VA validation

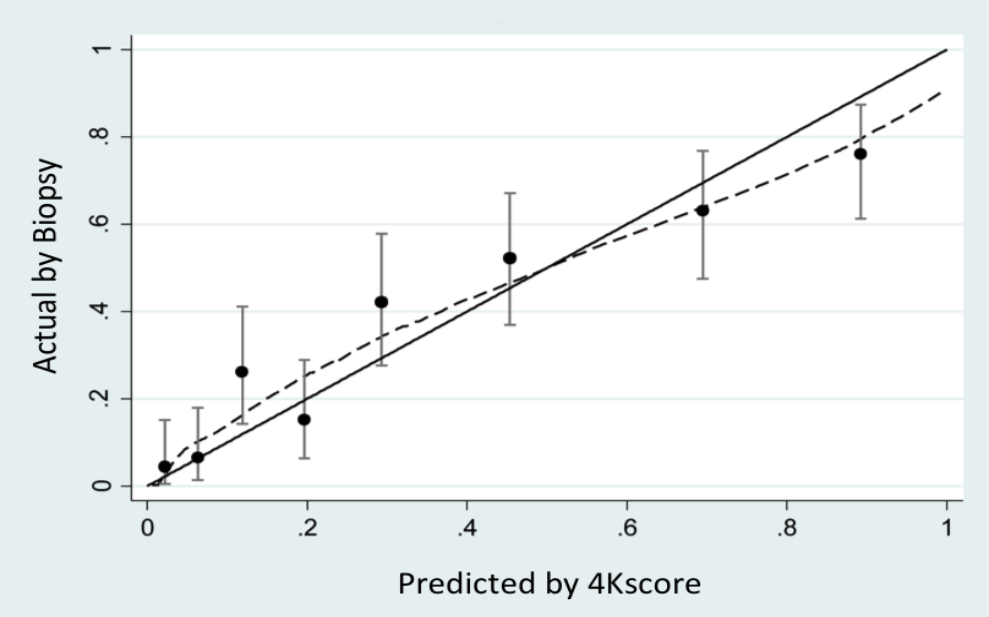
- 8 Veterans Affairs Hospitals
- 56% of the 366 men are African American

4Kscore Prospective Validation Trials

Initial prospective validation



Prospective VA validation



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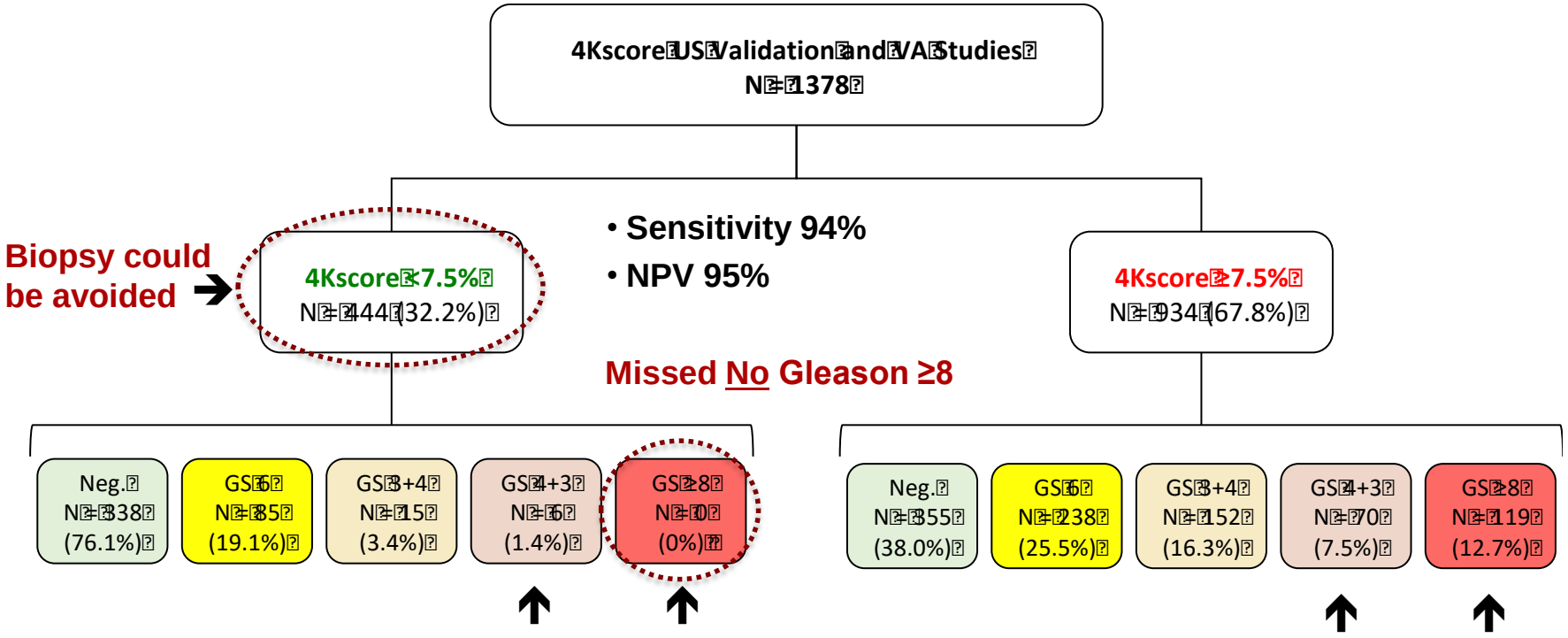
Results of Combined Two Clinical Validation Studies



*(Clinical Performance is illustrated using a 4kscore 7.5% Cut Point)

Data from Parekh et al. Eur Urol 2015 and Punnen et al. J Urol 2018

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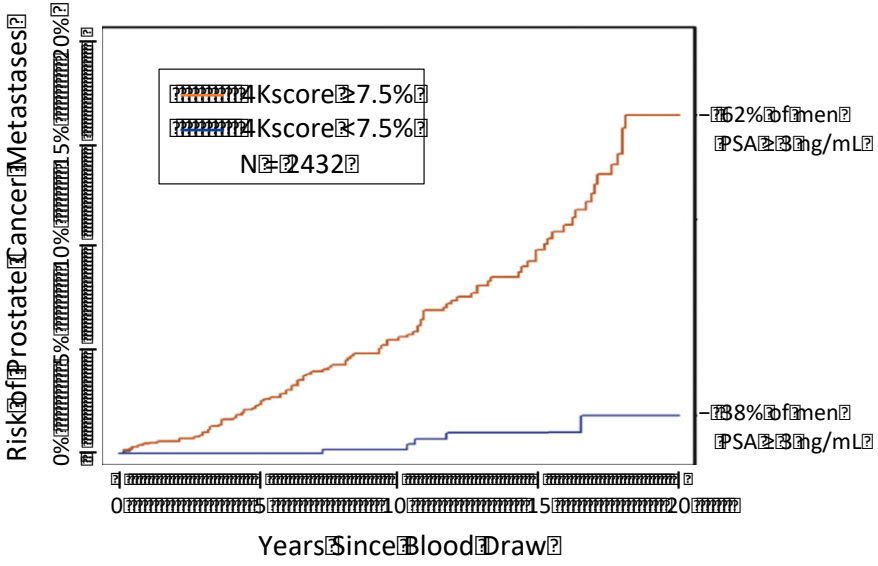
4Kscore Risk Predicts Long-Term Risk of Relevant Endpoints

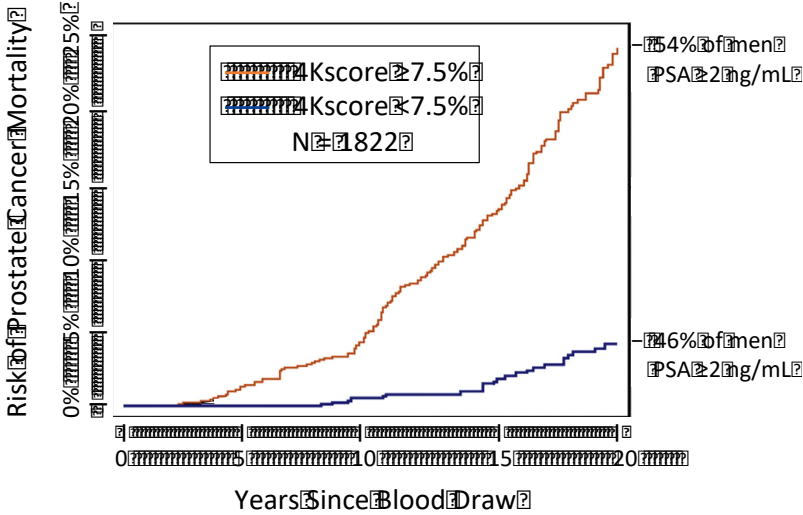
2432 Men Age 60 years old, PSA ≥ 3.0 ng/mL



PSA ≥ 3 ng/mL and 4Kscore < 7.5%:
Safe for 5 to 10 years out with no need for further procedure, except recommended PSA screening in between

4Kscore <7.5%
0.2% Risk 10 years

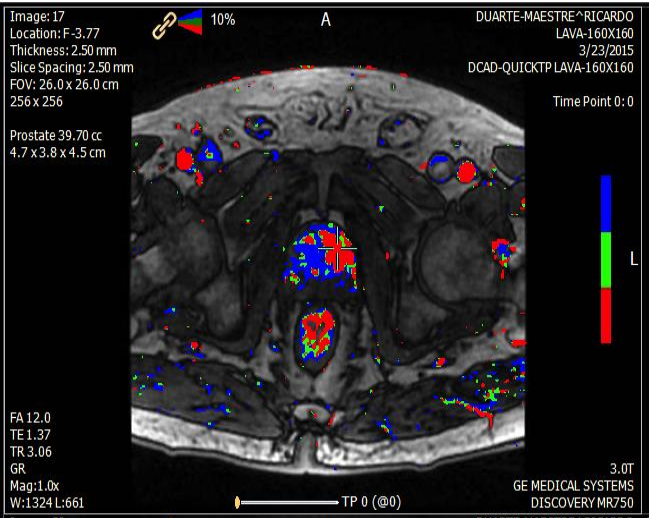
1822 Men Age 60-73 years old, PSA ≥ 2.0 ng/mL

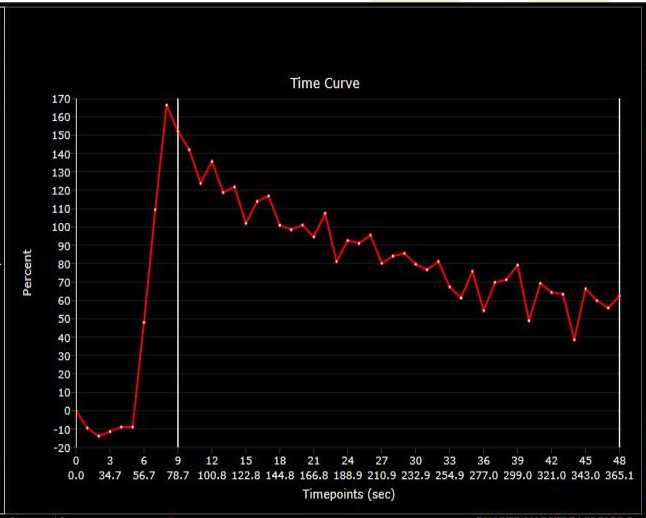


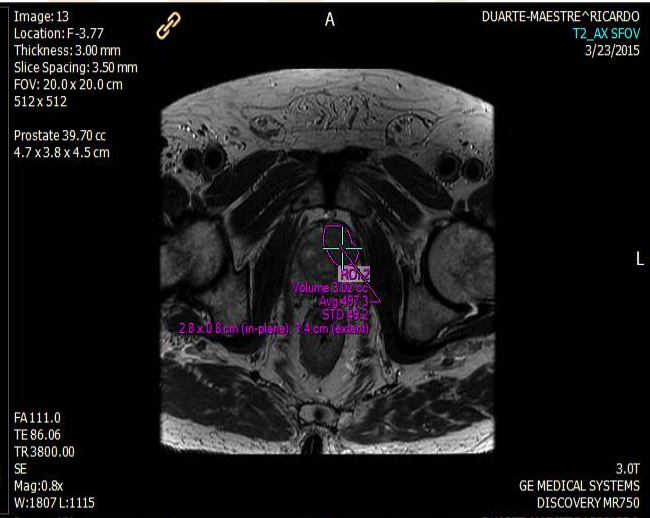
4Kscore <7.5%
0.6% Risk 10 years

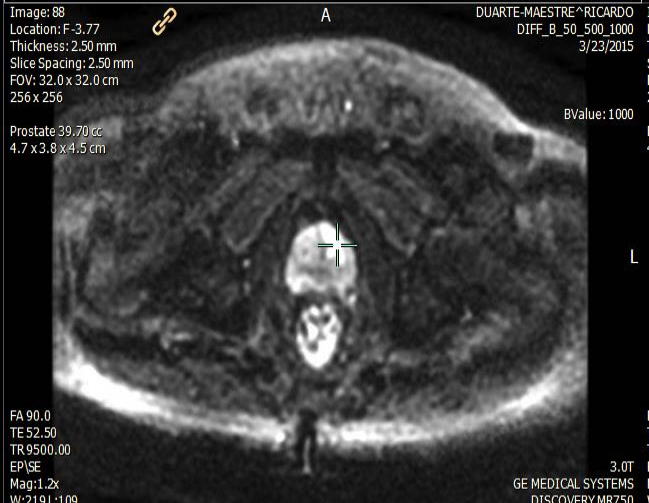
PSA ≥ 2 ng/mL and 4Kscore < 7.5%:
Safe for 5 to 10 years out with no need for further procedure, except recommended PSA screening in between

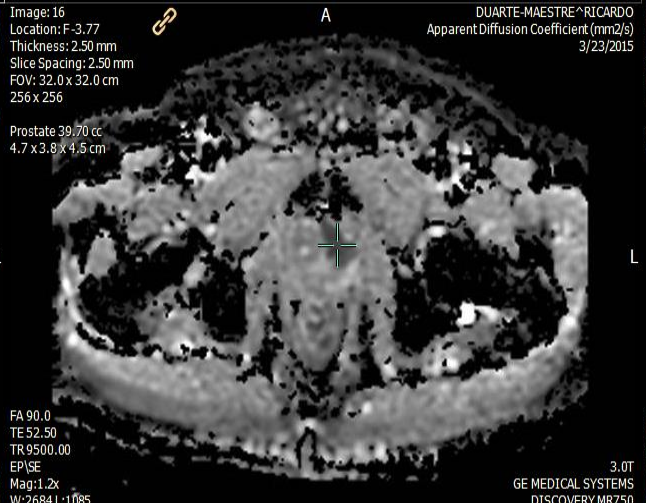
Multi-Parametric MRI for Prostate Cancer Detection

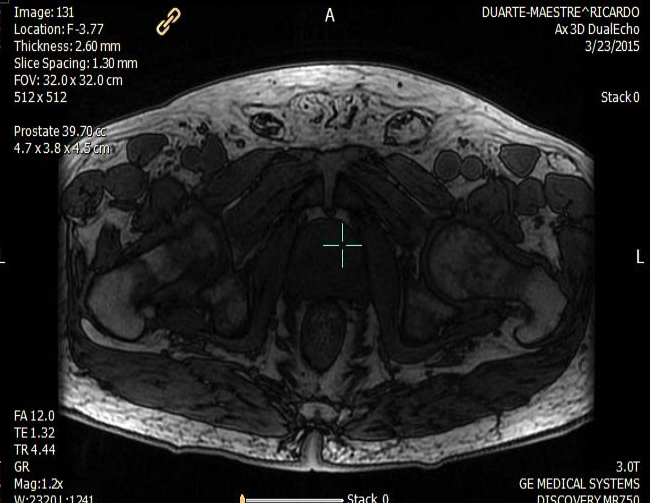




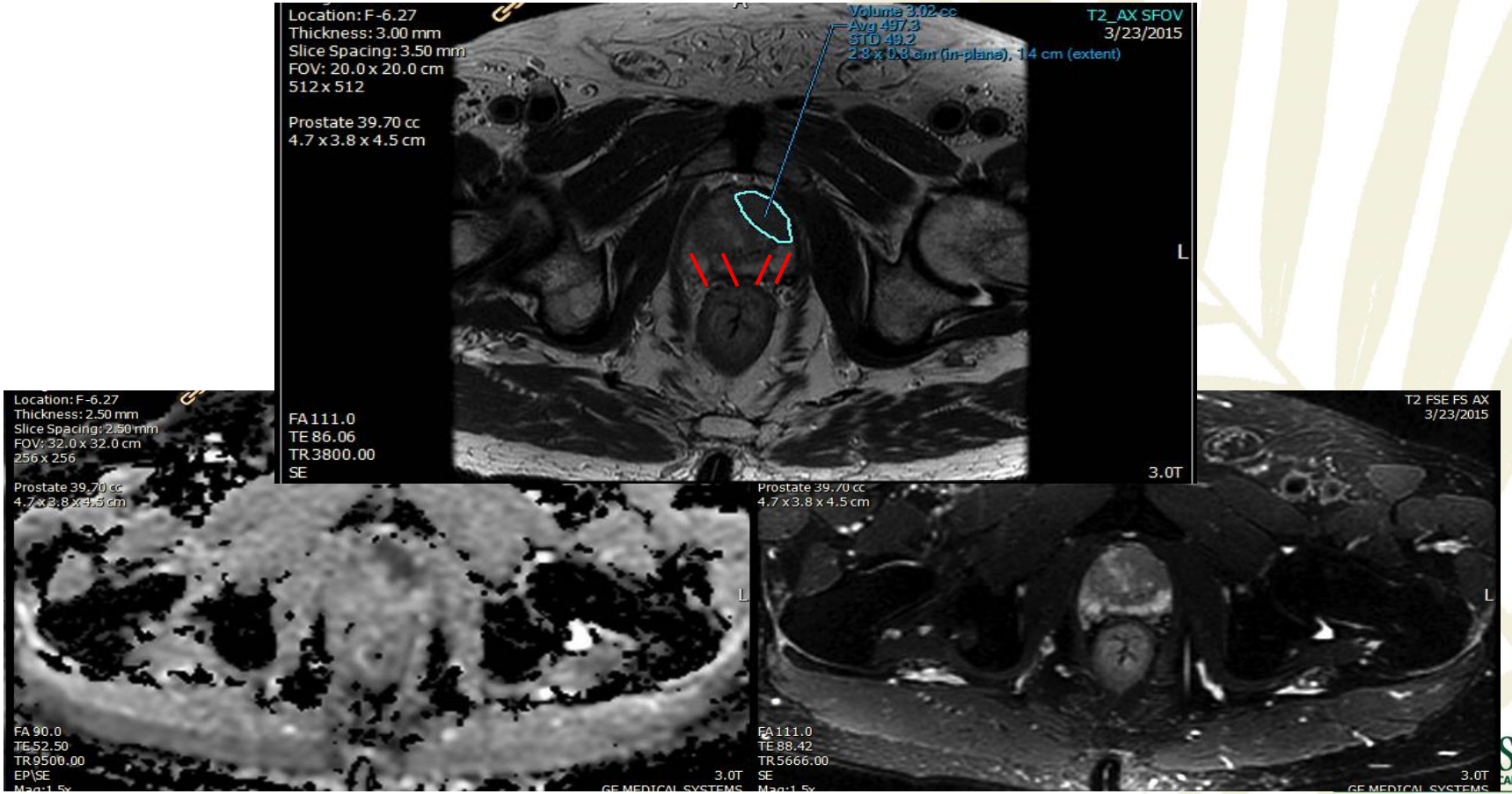








Multi-Parametric MRI for Prostate Cancer Detection



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MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

Outcome	MRI-Targeted Biopsy Group (N=252)	Standard-Biopsy Group (N=248)	Difference†	P Value
Clinically significant cancer¶				
Intention-to-treat analysis — no. (%)	95 (38)	64 (26)	12 (4 to 20)	0.005
Modified intention-to-treat analysis — no./total no. (%)	95/245 (39)	64/235 (27)	12 (3 to 20)	0.007
Per-protocol analysis — no./total no. (%)	92/235 (39)	62/227 (27)	12 (3 to 20)	0.007
Clinically insignificant cancer — no. (%)	23 (9)	55 (22)	−13 (−19 to −7)	<0.001

Kasivisvanathan et al. NEJM 2018

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study

Hashim U Ahmed, Ahmed El-Shater Bosaily*, Louise C Brown*, Rhian Gabe, Richard Kaplan, Mahesh K Parmar, Yolanda Collaco-Moraes, Katie Ward, Richard G Hindley, Alex Freeman, Alex P Kirkham, Robert Oldroyd, Chris Parker, Mark Emberton, and the PROMIS study group†*

575 men underwent mpMRI followed by TPM & TRUS biopsy

- 230 (40%) diagnosed with Gleason ≥4+3
- mpMRI sensitivity 93% & specificity 41%
- 70% with high risk MRI found to have high grade cancer (HGC)

- 11% with low risk MRI found to have HGC
- 21% with indeterminate risk MRI with HGC

Ahmed et al. Lancet 2017

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Prostate Cancer

What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel

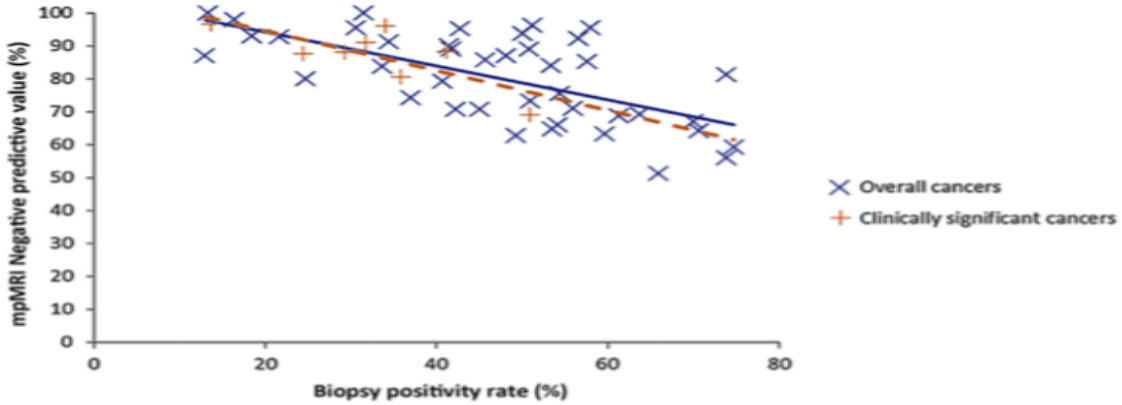


Fig. 3 – Negative predictive value of prebiopsy multiparametric MRI as a function of cancer prevalence (blue crosses: overall prostate cancer; red crosses: clinically significant prostate cancer). The blue line is the correlation line for overall prostate cancer; the red dotted line is the correlation line for clinically significant prostate cancer. mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging.

Biomarkers for Prostate Cancer Detection

- **PRO**
  - Good accuracy for prostate cancer detection
  - Access shouldn’t be an issue
  - Non- Invasive
  - Objective measure of risk

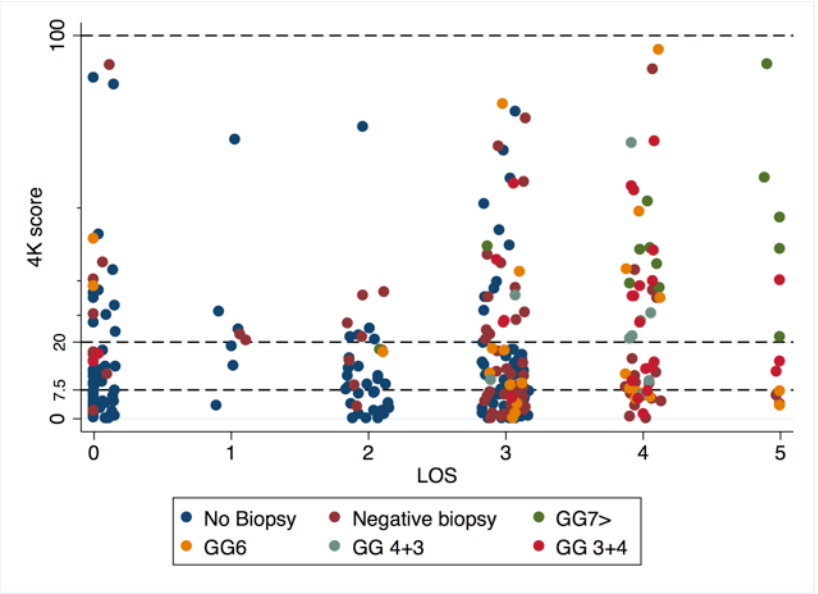
- **Con**
  - Cost
  - Not helpful for targeting
  - Generalizability, cut-offs?

MRI for Prostate Cancer Detection

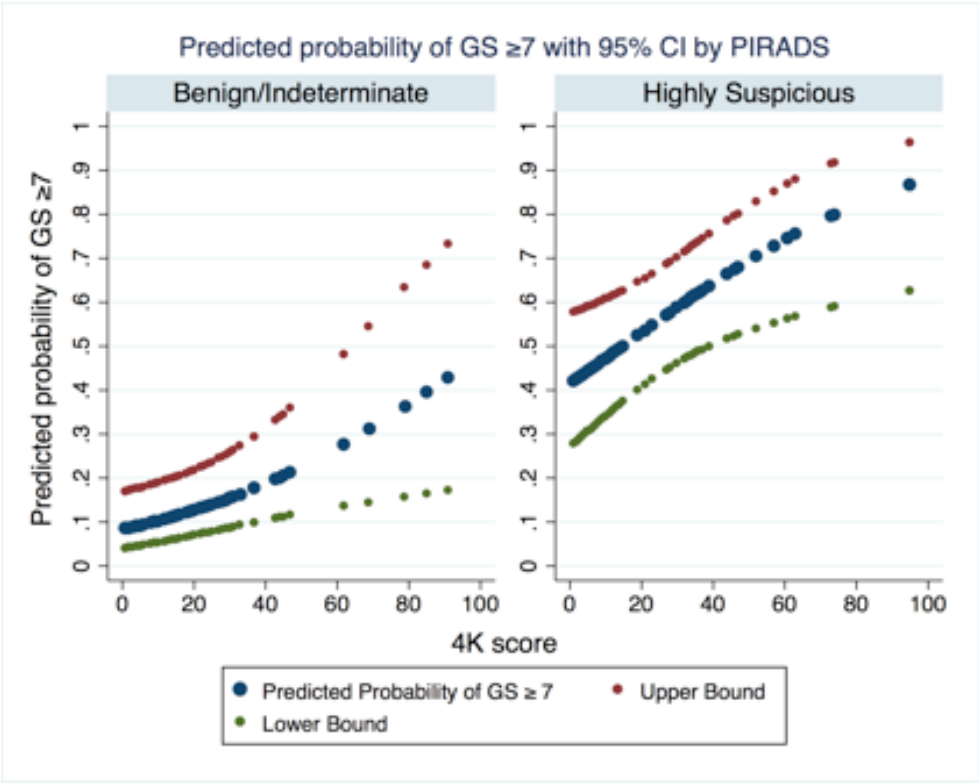
- **PRO**
  - Good accuracy for detecting clinically significant disease
  - Helpful for targeting
  - Appears to trump all other markers when positive

- **Con**
  - 10-25% of significant cancer seen in non-suspicious MRI's
  - Access/Cost
  - Reader variability

MRI and 4Kscore for Significant Prostate Cancer Detection



4Kscore +MRI: AUC - 0.82 (0.73-0.91)
vs MRI alone: AUC - 0.75 (0.65-0.84), p=0.004
vs 4Kscore alone: AUC - 0.70,(0.6-0.8), p=0.02



49 /149 (33%) men had Gleason 7+ cancer

Punnen et al.

Summary:

- **PSA is an excellent screening test for prostate cancer, but it lacks specificity**
- **Need to screen smarter and for aggressive disease, not any prostate cancer**
- **Role of secondary imaging or molecular markers to decide on the need for a biopsy of the prostate**

  (4Kscore, PHI, SelectMDx, PCA3, multi-parametric MRI)
- **Disconnect diagnosis and treatment and apply risk adjusted management**

Clarifying the Prostate Biopsy Decision

PSA SCREENING

BIOPSY CANDIDATES

SECONDARY BIOMARKER

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Appendix

Intended Use Population

Secondary biomarkers are indicated for men considering prostate biopsy and meet the following criteria:

1. Abnormal PSA and/or DRE
2. Prostate biopsy naïve or a prior negative biopsy
3. Age 45-75
4. Age 75 - 80 with a life expectancy >10 years
5. Family history of prostate cancer in at least one affected first-degree relative (father or brother), or known BRCA1, BRCA2 gene mutation