

# (Some) biomarkers for early-stage prostate cancer: Blood, urine, and tissue

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Peter T. Scardino, MD

Chair, Department of Surgery

David H. Koch Chair and Head, Prostate Cancer Program

Memorial Sloan Kettering Cancer Center

New York, NY



# Disclosures

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- Scientific Advisory Board, OPKO (4K test)
- Chair, Clinical Trials Oversight Committee, Xtandi (enzalutamide) Phase 3 Trial, Medivation/Astellas
- Advisory Board, Riverside Partners Biomedical Investments



## A Better Prostate-Cancer Test?

Several new prostate-cancer tests aim to reduce needless biopsies and unnecessary treatments by sorting out harmless from aggressive tumors



Cell division of a prostate-cancer cell, captured in a colored scanning electron micrograph (SEM) image. Several new tests performed on blood, urine or tissue samples aim to tell patients not simply if they have prostate cancer, but also whether it is aggressive enough to warrant treating—or whether it can be safely monitored instead.



# Change in diagnostic approach since 2000

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From: Reliance on one feature (e.g., PSA)  
to predict presence of any cancer

To: Use of multiple features incorporated  
into models, tables, or nomograms  
to predict for **high-risk** cancer  
(e.g., Gleason  $\geq 7$ )



# What is your risk of having cancer? (Pre-biopsy features predictive of cancer)

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## Stronger

- Age
- PSA, fPSA
- DRE
- Prostate volume (PSAD)

## New

- *phi*
- 4K score
- urinary PCA3
- urinary TMPRSS2

## Weaker

- Prior negative biopsy
- Family history / genetic profile
- Ethnicity



# Biomarkers in the blood

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- PSA
- Free PSA
- **4K score test (OPKO)**
- ***phi* (Prostate Health Index, Beckman Coulter)**
- CTCs
- cfDNA
- RNA, exosomes, etc.



# New PSA marker panels increase specificity (reduce false positives) and help identify high-grade cancers

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## Standard markers

tPSA = total PSA, the standard measure

%fPSA = ratio of free to total PSA

## New marker panels

**4K panel = tPSA, fPSA, iPSA, hK2\***

*phi* =  $([-2] \text{ proPSA/fPSA} \times \sqrt{\text{tPSA}})^{**}$

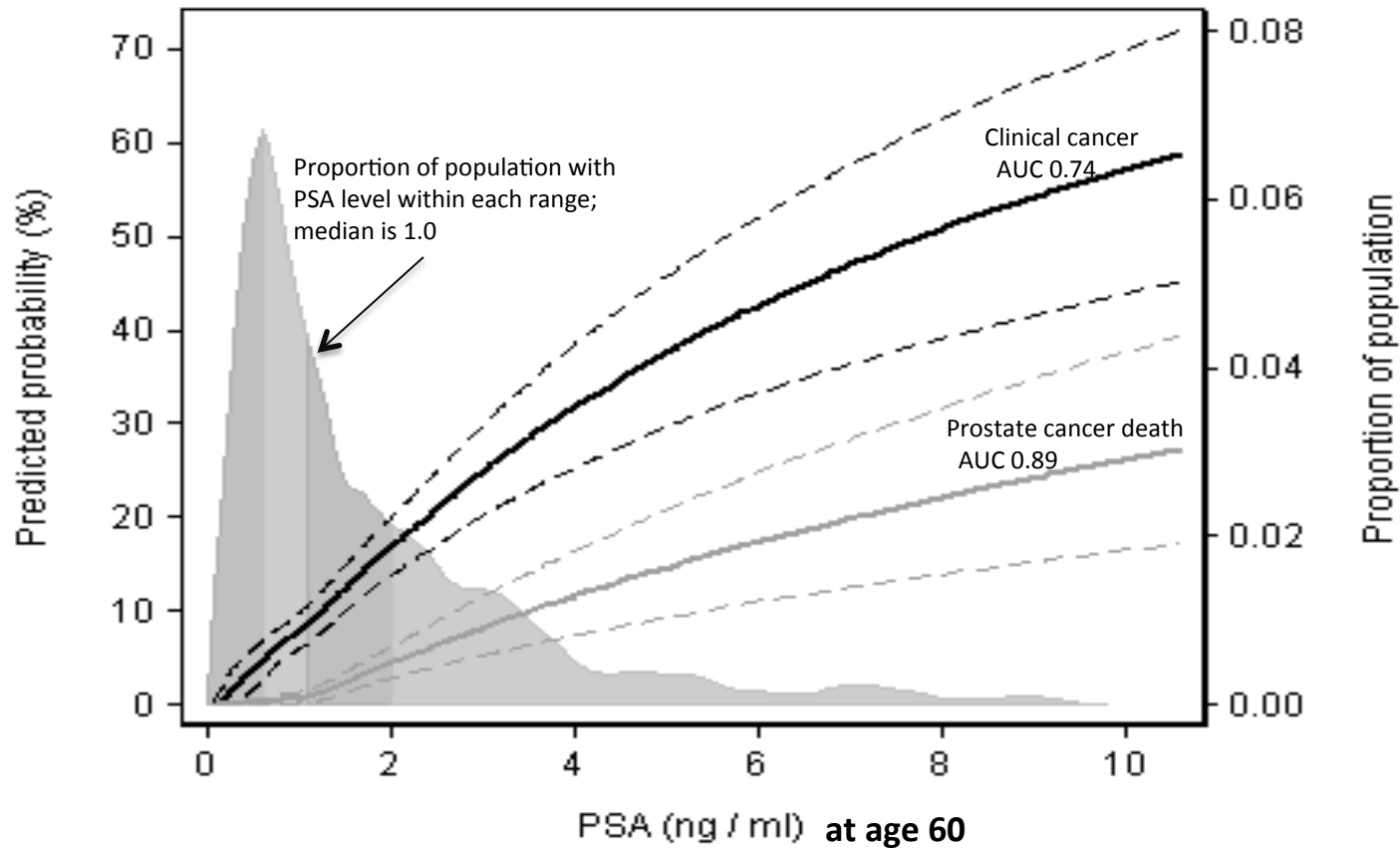
\* 4K Score Test, OPKO Diagnostics, Inc.

\*\* Prostate Health Index, Beckman Coulter, Inc.

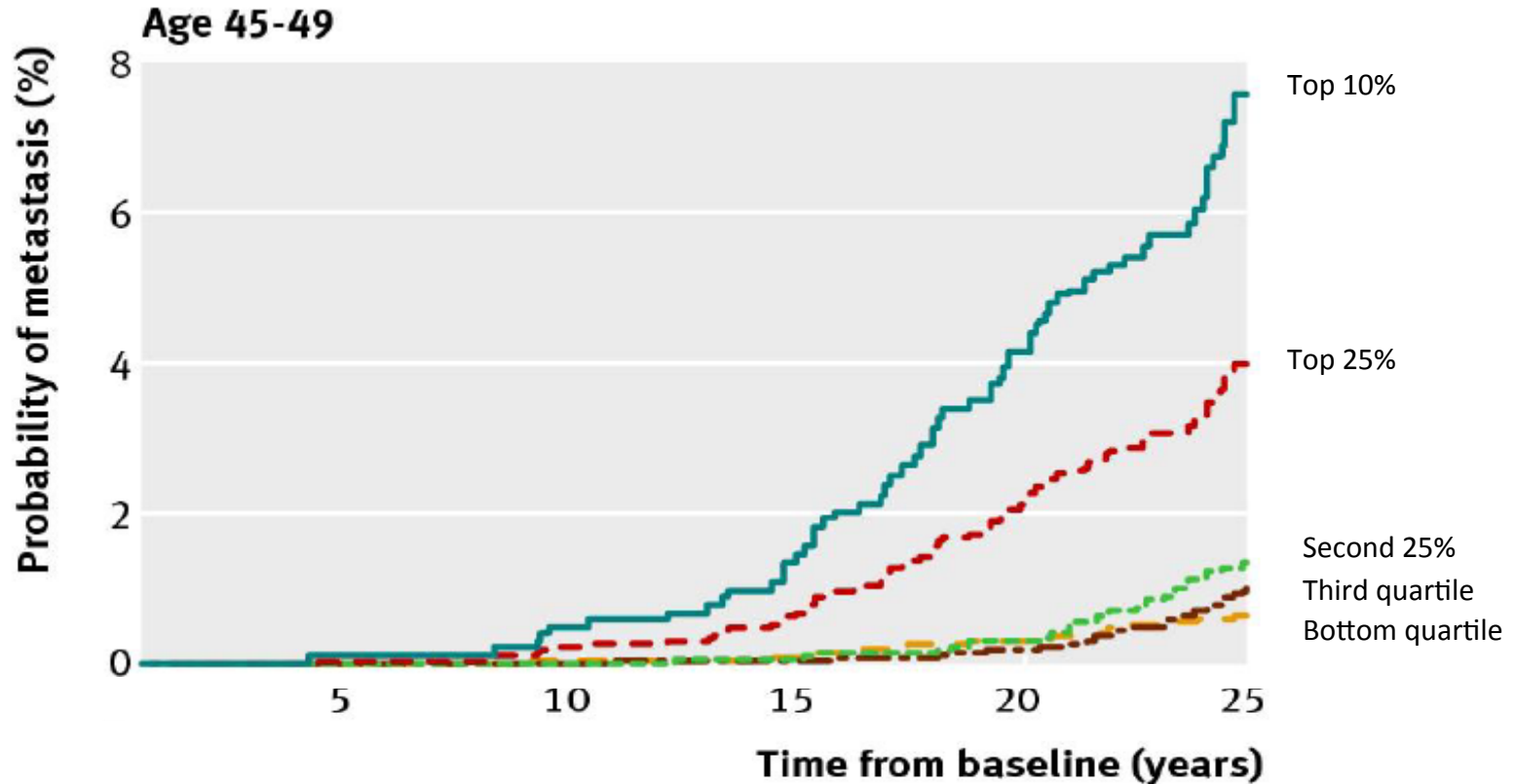


# Probability of eventually developing or dying of prostate cancer by PSA at age 60

Mid-life PSA levels strongly predict long-term risk of prostate cancer morbidity



# PSA at age 45-49 strongly predicts risk of metastasis within 25 years

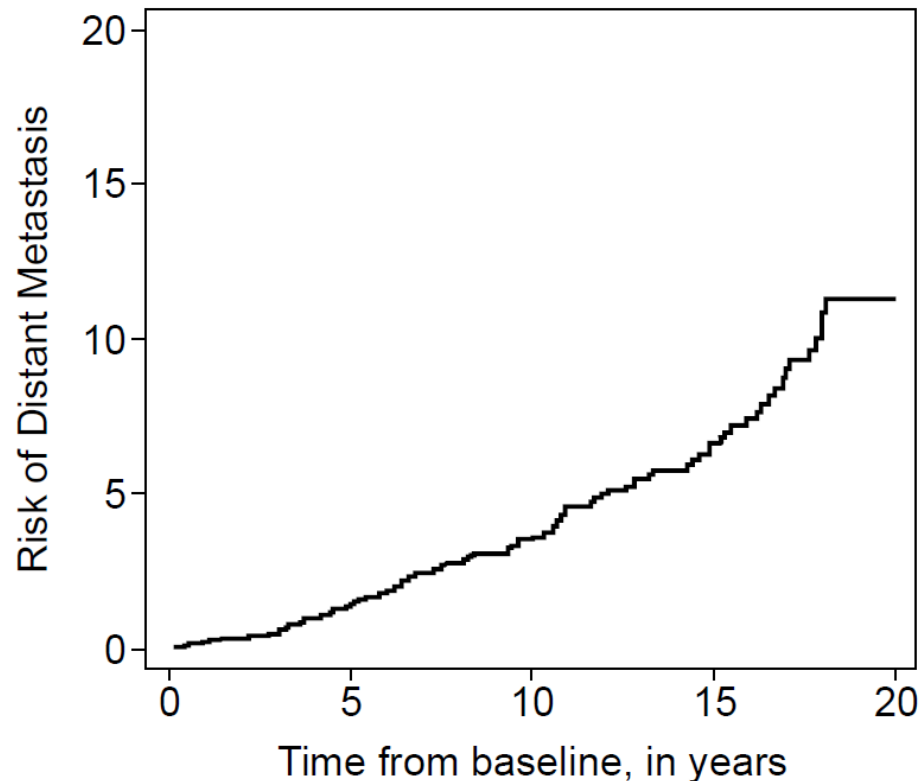


Vickers AJ, Lilja H et al. Strategy for detection of prostate cancer based on relation between prostate-specific antigen at age 40-55 and long-term risk of metastasis: case-control study. *BMJ* 2013;346:2023.



# Risk of developing metastases over 20 years for men with a PSA $\geq 3$ at age 60

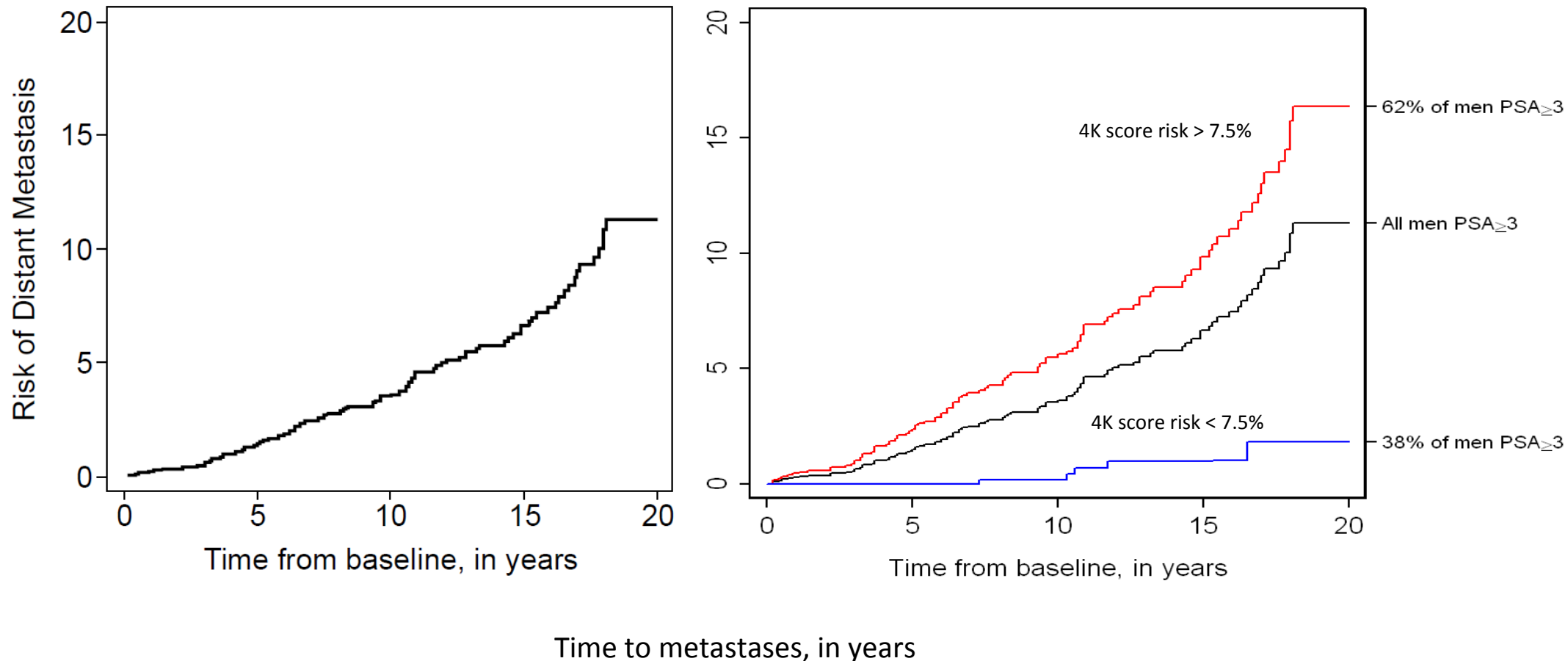
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Time to metastases, in years



# Risk of developing metastases over 20 years for men with a PSA $\geq 3$ at age 60, stratified by 4K score





## Prostate Cancer

## A Multi-institutional Prospective Trial in the USA Confirms that the 4Kscore Accurately Identifies Men with High-grade Prostate Cancer

Dipen J. Parekh<sup>a,\*</sup>, Sanoj Punnen<sup>a</sup>, Daniel D. Sjoberg<sup>b</sup>, Scott W. Asroff<sup>c</sup>, James L. Bailen<sup>d</sup>, James S. Cochran<sup>e</sup>, Raoul Concepcion<sup>f</sup>, Richard D. David<sup>g</sup>, Kenneth B. Deck<sup>h</sup>, Igor Dumbadze<sup>i</sup>, Michael Gambla<sup>j</sup>, Michael S. Grable<sup>k</sup>, Ralph J. Henderson<sup>l</sup>, Lawrence Karsh<sup>m</sup>, Evan B. Krisch<sup>n</sup>, Timothy D. Langford<sup>o</sup>, Daniel W. Lin<sup>p</sup>, Shawn M. McGee<sup>q</sup>, John J. Munoz<sup>r</sup>, Christopher M. Pieczonka<sup>s</sup>, Kimberley Rieger-Christ<sup>t</sup>, Daniel R. Saltzstein<sup>u</sup>, John W. Scott<sup>v</sup>, Neal D. Shore<sup>w</sup>, Paul R. Sieber<sup>x</sup>, Todd M. Waldmann<sup>y</sup>, Fredrick N. Wolk<sup>z</sup>, Stephen M. Zappala<sup>aa</sup>

**Design, setting, and participants:** 1012 men (85 African-American) scheduled for prostate biopsy, regardless of prostate-specific antigen level or clinical findings, at 26 US urology centers

**Results and limitations:** Gleason  $\geq 7$  PCa was found in 231 (23%) of the 1012 patients. The 4K score showed excellent calibration and demonstrated higher discrimination (AUC 0.82) and net benefit compared to a modified Prostate Cancer Prevention Trial Risk Calculator 2.0 model and standard of care (biopsy for all men) according to DCA. **A possible reduction of 30-58% in the number of biopsies was identified with delayed diagnosis in only 1.3-4.7% of Gleason  $\geq 7$  PCa cases, depending on the threshold used for biopsy.**

# 4K score report for patient at intermediate risk

**Interpretation**

**INTERMEDIATE RISK**

There is a **90%** probability that the patient will not have aggressive disease on a prostate biopsy.

**4Kscore Test Results**

4Kscore: **10%**

Low Risk Intermediate Risk High Risk

1% 2% 3% 4% 5% 6% 7.5% 10% 12% 14% 16% 18% 20% 30% 40% 50% 60% 70% 80% >90%

4Kscore Test Result

**Clinical Information**

Digital Rectal Exam (DRE): **Normal**      Prior Biopsy Status: **Yes - Negative**



# Clinical utility of 4K score

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ORIGINAL RESEARCH

## The 4Kscore<sup>®</sup> Test Reduces Prostate Biopsy Rates in Community and Academic Urology Practices

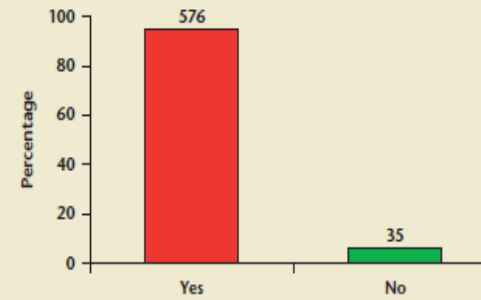
Badrinath Konety, MD,<sup>1</sup> Stephen M. Zappala, MD,<sup>2</sup> Dipen J. Parekh, MD,<sup>3</sup> Danielle Osterhout,<sup>4</sup> Jeffrey Schock, DO,<sup>4</sup> Randy M. Chudler, MD,<sup>4</sup> Gregory M. Oldford, MD,<sup>4</sup> Kenneth M. Kernen, MD,<sup>4</sup> Jason Hafron, MD<sup>4</sup>

Vol. 17 No. 4 • 2015 • Reviews in Urology

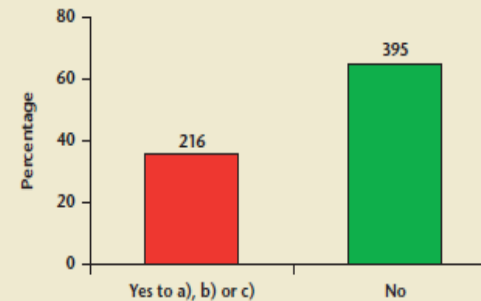


## Patient questionnaire and summary of responses

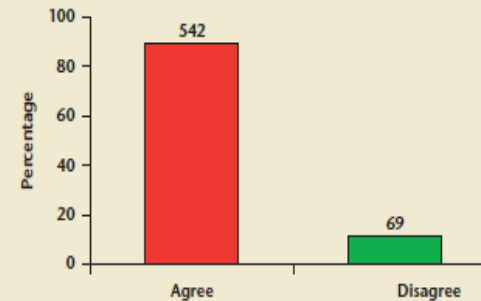
1) Before you ordered the 4Kscore Test, were you considering a prostate biopsy for this patient?



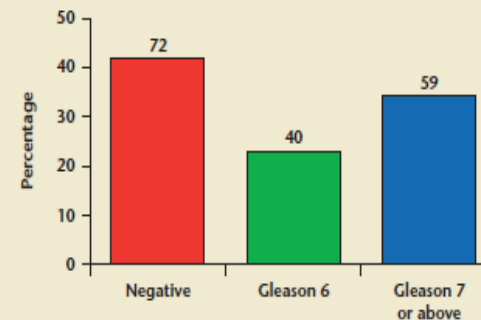
2) After you received the 4Kscore Test results, did the patient either a) have a prostate biopsy performed by you, b) get scheduled for a prostate biopsy, or c) get referred by you to have a prostate biopsy within 90 days of the 4Kscore Test result?



3) Do you feel the 4Kscore Test influenced the decision for the patient to have (or not have) a prostate biopsy?



4) What were the results of the prostate biopsy (if the patient went on to have the biopsy)?



# 4-Kallikrein Test and Kallikrein Markers in Prostate Cancer Screening

Michelle L. McDonald, MD, J. Kellogg Parsons, MD, MHS\* Urol Clin N Am 43 (2016) 39-46

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## 4K score test (OPKO)

- A “reflex” blood test, can be done on same sample as PSA, fPSA
- Improves specificity of PSA (reduces false positives) for detecting high-grade cancers – adds to PSA, fPSA, DRE, age, prior bx
- Algorithm validated in >15,000 patients predicts presence of high-grade cancer (Gleason >7) and risk of mets/death from cancer 10-20 years later
- Reduces biopsies by 40-50% while missing few high-grade cancers
- When to use: in men without cancer, deciding whether to recommend a biopsy
- Works in unscreened men, previously screened, prior biopsy, after clinical evaluation, in AA men, at PSA up from 2 to 25 ng/ml
- May predict adverse pathology in RP specimens and high grade cancer during AS

## Disadvantages

- Not FDA-approved (CLIA Reference Lab)
- Complex assay requires separate blood sample
- Expensive



# New PSA marker panels increase specificity (reduce false positives) and help identify high-grade cancers

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## Standard markers

tPSA = total PSA, the standard measure

%fPSA = ratio of free to total PSA

## New marker panels

4K panel = tPSA, fPSA, iPSA, hK2\*

***phi* = ([-2] proPSA/fPSA x  $\sqrt{tPSA}$ )\*\***

\* 4K Score Test, OPKO Diagnostics, Inc.

\*\* Prostate Health Index, Beckman Coulter, Inc.



# phi Patient Report

Courtesy of Stacy Loeb

<b>Patient</b>	Name: Case Study	Phone #: 804-123-1234	Patient ID#: 10-063-0025	
	Fasting Status: Unknown	Gender: Male	Birthdate: 6/15/1957	Age: 55
	Height: 5 ft. 6 in.	Weight: 173	BMI:	

<b>Specimen</b>	Collection Time: 9:54 am	Specimen ID: 10030400027
	Collection Date: 1/4/2014	Report Type: Complete
	Received Date: 1/5/2014	Report Date: 1/10/2014

<b>Provider</b>	Requesting Provider: Bob Johnson, MD 123 Broad St. Ste 456 Richmond, VA 12345
	Client ID: 11-22222-33-4444444

PSA = 4.4

p2PSA = 41.9

%fPSA = 21

phi = 97

Tumor Markers	Result	Reference Interval	Probability of Cancer		
Total PSA (ng/mL)	<b>4.4</b>	Normal <2.0 and at risk ≥2.0			
free PSA (ng/mL)	0.9	See %free PSA			
p2PSA (pg/mL)	41.9	See phi			
%free PSA	21%	<b>Prostate Cancer Probability by Age</b>			
		%free PSA	<60yr	60-70yr	>70yr
		<7	85%	95%	96%
		7-15	25%	50%	60%
		16-25	11%	27%	35%
<b>Prostate Health Index phi</b>	97	<b>phi (calculated)</b>			
		0-24.9	11.0%		
		25.0-34.9	18.1%		
		35.0-54.9	32.7%		
		>55.0	52.1%		

**52.1%**



# ERSPC Risk Calculator App for *phi* Results

Courtesy of Stacy Loeb

**Risk Calculator**

What is your PSA level, in ng/mL?

5

Clear Done

1	2 ABC	3 DEF
4 GHI	5 JKL	6 MNO
7 PQRS	8 TUV	9 WXYZ
.	0	<X>

**Risk Calculator**

Prostate volume (mL) 40

Outcome of TRUS Normal

Phi available? Yes

How much is your Phi?

56

Clear Done

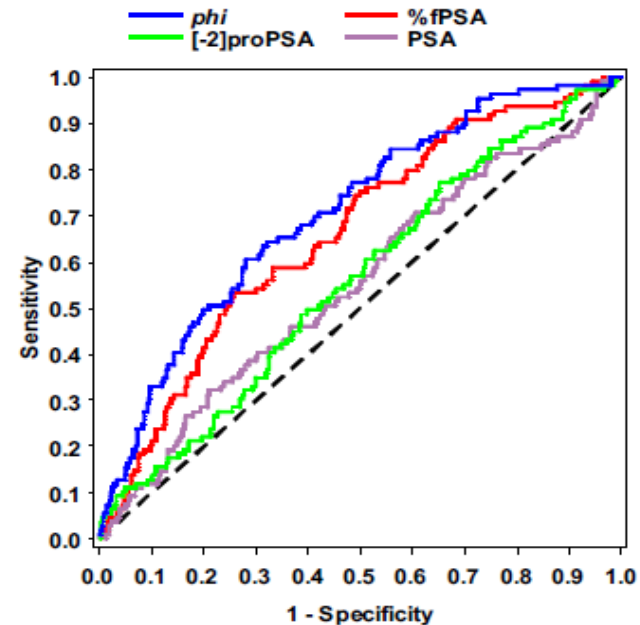
1	2 ABC	3 DEF
4 GHI	5 JKL	6 MNO
7 PQRS	8 TUV	9 WXYZ
.	0	<X>



# [-2] Pro-PSA panel (Prostate Health Index: *phi*)

## Accuracy for detecting high grade (G1 >6) cancers in biopsy (n=658)

To detect high-grade (Gleason 7 or more) cancers, the use of a *phi* cutoff point of 28.6 could potentially **avoid 30% of biopsies** in men with benign or insignificant disease while **missing or delaying the diagnosis of 10% or fewer prostate cancers** with aggressive features (Gleason pattern 4 or more.)



Loeb S et al. A multicenter study of [-2] Pro-PSA combined with PSA and free PSA in 658 men with prostate cancer and PSA scores in the 4.0 to 10.0 ng/mL range. *J Urol* 2014;193:1163-69

	AUC	95% Confidence Interval	P-value
PSA	0.551	0.490 - 0.612	Ref.
[-2]proPSA	0.558	0.499 - 0.601	0.845
%fPSA	0.661	0.607 - 0.716	0.010
<i>phi</i>	0.707	0.655 - 0.729	<0.001
P-value for PSA vs. [-2]proPSA, %fPSA, or <i>phi</i>			



# The Prostate Health Index Its Utility in Prostate Cancer Detection

Abbey Lepor<sup>a</sup>, William J. Catalona, MD<sup>b</sup>,  
Stacy Loeb, MD, MSc<sup>a,c,\*</sup>  
Urol Clin N Am 43 (2016) 1-6

- *phi* is more specific than fPSA and/or PSA
- Higher *phi* scores predict greater risk of high-grade cancer in biopsies and in RP specimens and greater risk of PSA recurrence after RP
- *phi* may help predict progression/reclassification in patients on AS



# Urinary biomarkers

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- PCA3 (Progenesa)
- TMPRSS2-ERG +/- PCA3 (Hologic/Gen-Probe Inc.)
- cfDNA (e.g., GSTP)
- Methylation of GSTP1
- Peptides
- Metabolic products (sarcosine)



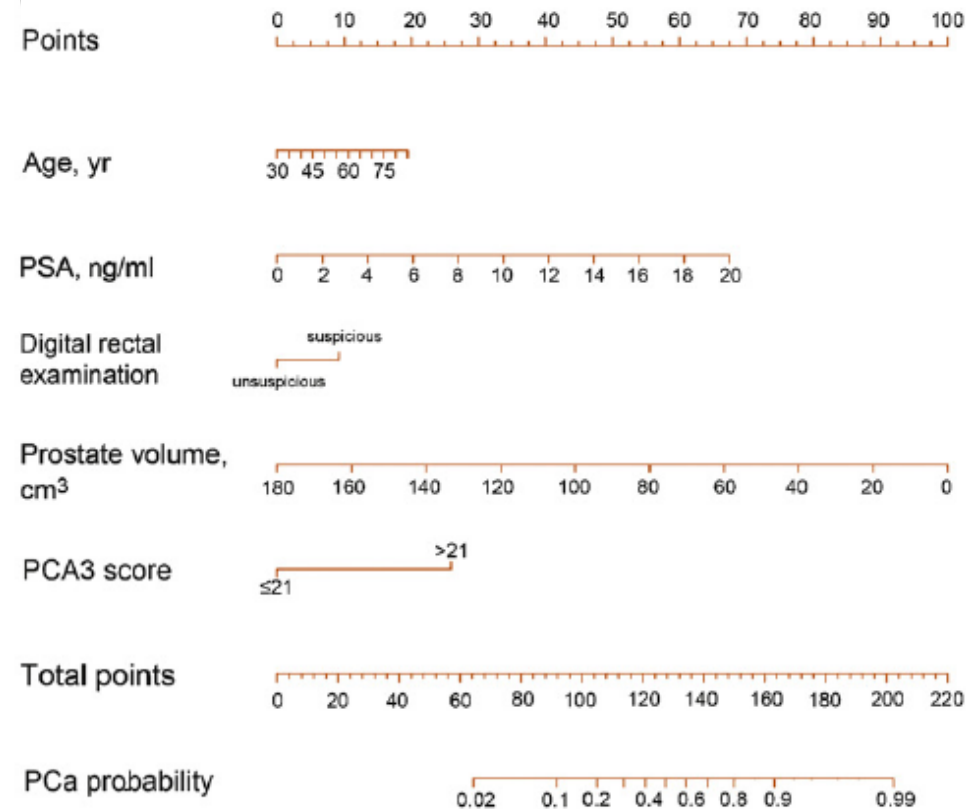


Platinum Priority – Prostate Cancer

Editorial by Michael R. Abner and Stephen J. Freedland on pp. 210–211 of this issue

## Initial Prostate Biopsy: Development and Internal Validation of a Biopsy-specific Nomogram Based on the Prostate Cancer Antigen 3 Assay

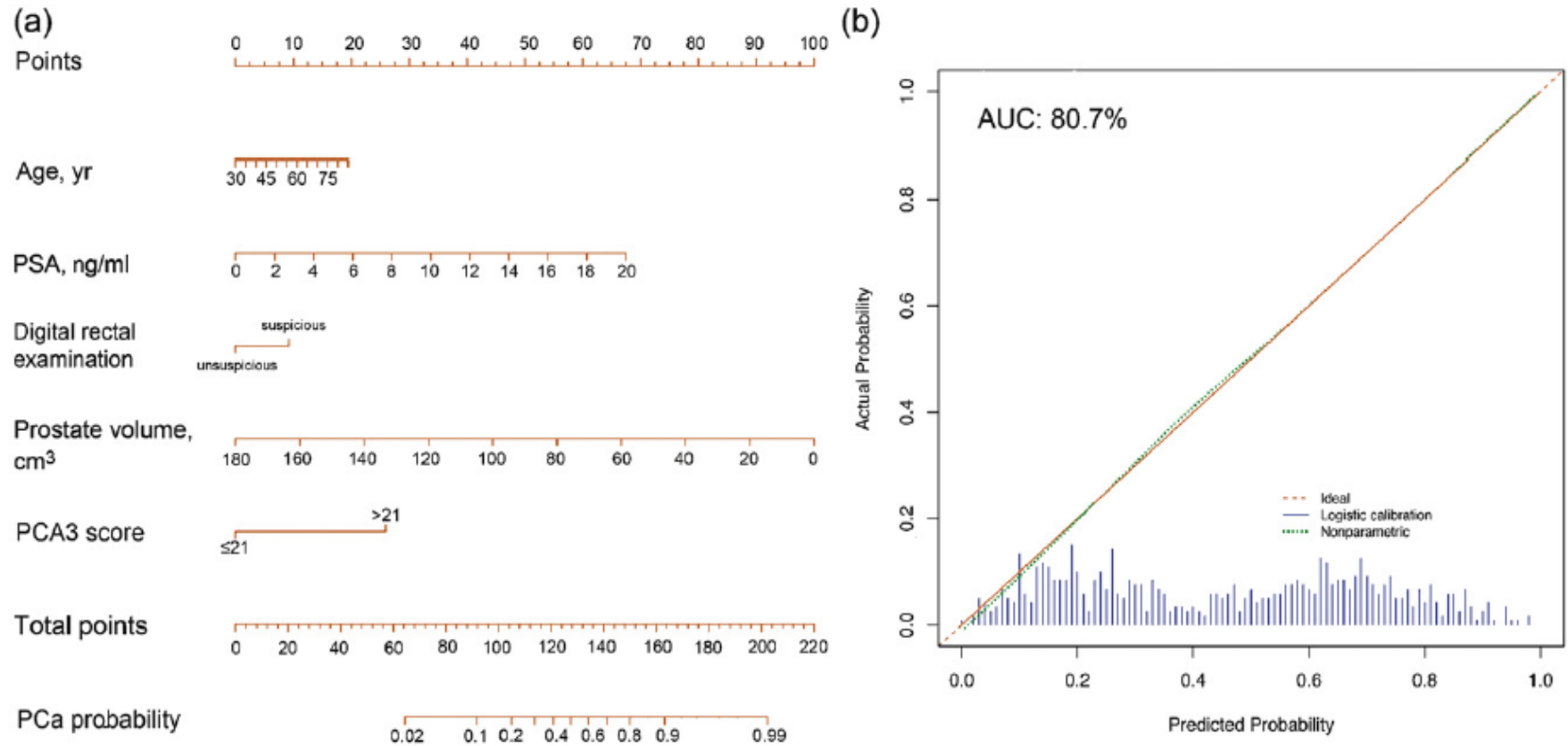
Jens Hansen<sup>a,b,†</sup>, Marco Auprich<sup>a,b,†</sup>, Sascha A. Ahyai<sup>a</sup>, Alexandre de la Taille<sup>c</sup>, Hendrik van Poppel<sup>d</sup>, Michael Marberger<sup>e</sup>, Arnulf Stenzl<sup>f</sup>, Peter F.A. Mulders<sup>g</sup>, Hartwig Huland<sup>b</sup>, Margit Fisch<sup>a</sup>, Clement-Claude Abbou<sup>c</sup>, Jack A. Schalken<sup>g</sup>, Yves Fradet<sup>h</sup>, Leonard S. Marks<sup>i</sup>, William Ellis<sup>j</sup>, Alan W. Partin<sup>k</sup>, Karl Pummer<sup>l</sup>, Markus Graefen<sup>b</sup>, Alexander Haese<sup>b</sup>, Jochen Walz<sup>m</sup>, Alberto Briganti<sup>n</sup>, Shahrokh F. Shariat<sup>o</sup>, Felix K. Chun<sup>a,\*</sup>



**Results:** Any PCa and HGPCa were diagnosed in 46% ( $n=318$ ) and 20% ( $n=137$ ).... The PCA3-based IBX nomograms significantly outperformed the clinical models without PCA3 (all  $p < 0.001$ )... When applying nomogram-derived PCa probability thresholds  $\leq 30\%$ , only a few patients with HGPCa ( $\leq 2\%$ ) will be missed while avoiding up to 55% of unnecessary biopsies.

# PCA3 nomogram

From Hansen J et al. Development and internal validation of a biopsy-specific nomogram based on the prostate cancer antigen 3 assay. *Eur Urol* 2012; 63:201-09



(a) PCA3 assay score predicting PCa on initial biopsy

(b) Local regression nonparametric smoothing plot showing calibration of PCA3-based IBX nomogram



# Urinary PCA3

Tosoian JJ et al. *Urol Clin N Am* 2016;34:17-38

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- Urinary PCA3 (Progenesa) is an ncRNA specific to prostate cancer
- Levels of PCA3 are independent of age, PSA level, and prostate volume
- More specific than PSA and fPSA (fewer false positives)
- At a cutpoint of 21, high negative predictive value (NPV)
  - For any cancer, high-grade cancer
  - Can avoid ~50% of repeat biopsies in men with elevated PSA levels
- Adds to nomogram (age, PSA level, prostate volume)
- When to use: For men with elevated PSA and no known cancer, before initial or repeat biopsy

## Disadvantages

- Requires DRE/prostate massage
- Probably not as accurate as the 4K score or *phi*
- Poorly predicts adverse pathology in RP
- Does not seem useful in AS



# If you have cancer, how aggressive is it? (Tissue biomarkers)

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- Copy Number Alterations (CNA)
- *Prolaris* (Myriad)
- *Oncotype-Dx* (Genomic Health)
- Decipher
- ProMark



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# Molecular Profiles of Prostate Cancer: To Treat or Not to Treat

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Itay A. Sternberg,<sup>1</sup> Ian Vela,<sup>2</sup> and Peter T. Scardino<sup>3</sup>

<sup>1</sup>Department of Urology, Meir Medical Center, Kefar Sava, 4428164, Israel;  
email: sternberg.itay@clalit.org.il

<sup>2</sup>Department of Urology, Princess Alexandra Hospital and Australian Prostate Cancer Research Center, Queensland University of Technology, Brisbane, Queensland, Australia;  
email: ian.vela@qut.edu.au

<sup>3</sup>Department of Surgery and the Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center, New York, New York 10065;  
email: scardinp@mskcc.org

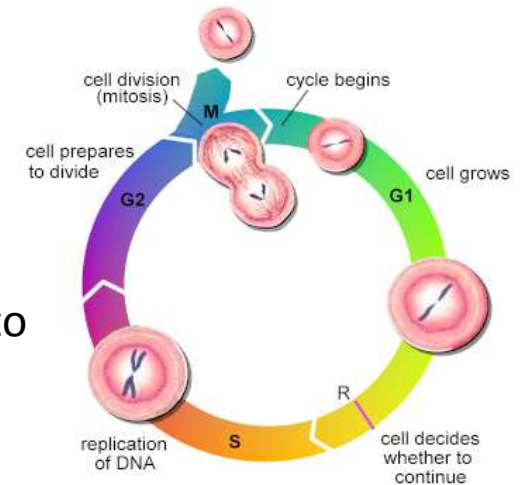
*Annual Review of Medicine* 2016; 67:119-35



# Cell cycle progression (CCP) profile (Myriad Prolaris®)

Cuzick J et al. *Lancet Oncol* 2011;12:245-55

- RNA expression profile of 31 cell cycle progression (CCP) genes and 15 housekeeper genes
- Each 1-unit change in CCP score corresponds roughly to a doubling of risk
- Evaluated in tumor samples from needle biopsy, TURP and RP
- Adds independent prognostic information to Gleason grade and PSA, and to models that include clinical stage, grade, PSA and extent of cancer
- Predicts risk of biochemical recurrence (BCR), metastasis, and death from cancer



Function	Genes
DNA repair/replication	<i>FOXM1, KIAA0101, RRM2, TOP2A, TK1, RAD54L, PTTG1, RAD51C, ORC6</i>
Microtubule function/stability	<i>CDC20, CDCA8, KIF11, NUSAP1, CENPF, ASPM, DLGAP5, PLK1, C18orf24</i>
Cell cycle regulators	<i>CDKN3, CDC2, CDCA3, BUB1B, PBK, DTL</i>
Chromosome structure	<i>ASF1B, MCM10, CENPM</i>
Cytokinesis	<i>KIF20A, PRC1, CEP55</i>



# Prolaris RNA expression profile in paraffin-embedded needle biopsy samples independently predicts death from prostate cancer in a watchful waiting cohort

Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort

J Cuzick<sup>\*,1</sup>, DM Berney<sup>2</sup>, G Fisher<sup>1</sup>, D Mesher<sup>1</sup>, H Møller<sup>3</sup>, JE Reid<sup>4</sup>, M Perry<sup>4</sup>, J Park<sup>4</sup>, A Younus<sup>4</sup>, A Gutin<sup>4</sup>, CS Foster<sup>4</sup>, P Scardino<sup>4</sup>, JS Lanchbury<sup>4</sup> and S Stone<sup>4</sup> on behalf of the Transatlantic Prostate Group

<sup>1</sup>Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary, University of London, Charterhouse Square, London EC1M 6BQ, UK; <sup>2</sup>Department of Molecular Oncology, Barts Cancer Institute, Queen Mary, University of London, London EC1M 6BQ, UK; <sup>3</sup>King's College London, Thames Cancer Registry, London, SE1 3QD, UK; <sup>4</sup>Myriad Genetics, Inc., 320 Wakara Way, Salt Lake City, UT 84108, USA; <sup>5</sup>Department of Cellular Pathology and Molecular Genetics, Liverpool University, Liverpool, L1 3GA, UK; <sup>6</sup>Department of Urology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Block(s) Analyzed: S11-60591\_4\_28

**Prolaris Score: 0.4**

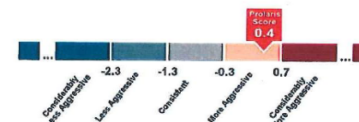
More Aggressive Than Average AUA Low Risk

Interpretation: The Prolaris Score of 0.4 indicates that this cancer is more aggressive than the average cancer in the American Urology Association (AUA) Low Risk category.

10-Year Prostate Cancer-Specific Mortality Risk: 2% (95% CI: 1-8%)

Interpretation: The patient has a 10-year mortality risk of 2% if managed conservatively. Mortality risks could be altered by various therapeutic interventions.

AUA Low Risk\*



The above chart illustrates the AUA Low Risk category, which is composed of patients with varying degrees of cancer aggressiveness. Cancer aggressiveness can be stratified within this category based upon Prolaris Scores, which are indicated below the graph.\*

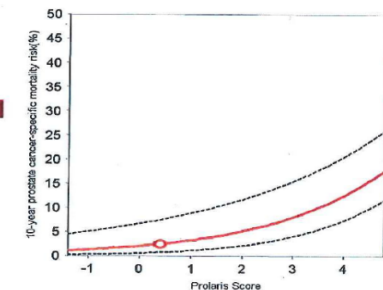
US Distribution Percentile: 94%

(For AUA Low Risk)

Interpretation: 94% of patients in the AUA Low Risk category have a lower Prolaris Score.

CLINICO-PATHOLOGIC FEATURES USED FOR ANALYSIS

PSA Prior to This Biopsy: 3.73  
Clinical T Stage: T1c  
Gleason Score: 3+3=6

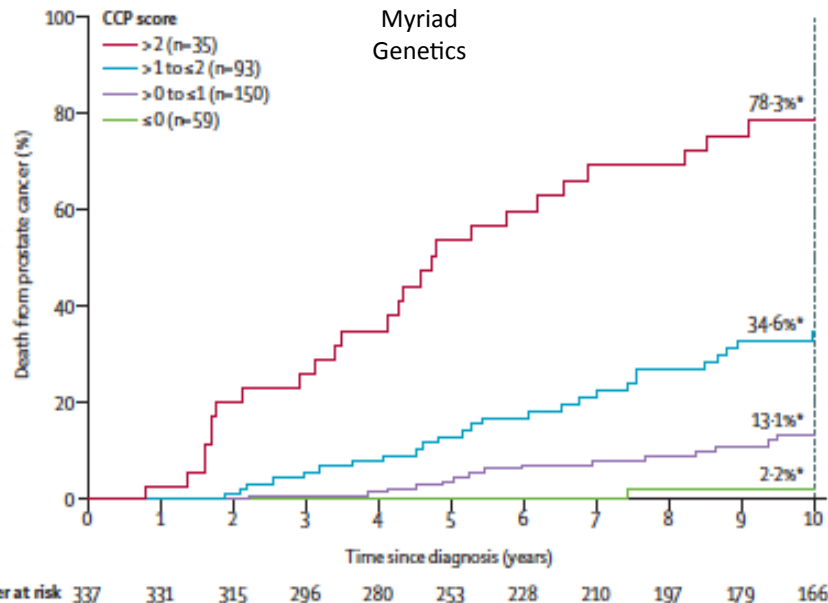


Patients with similar clinico-pathologic features, as defined by their CAPRA score, have the same *a priori* 10-year prostate cancer-specific mortality risk. The addition of the Prolaris Score further differentiates this risk, as illustrated in the above graph, which is specific to this patient's CAPRA score.<sup>24</sup> The orange line depicts the relationship between the Prolaris Score and the mortality risk with the 95% confidence interval indicated by dashed lines and the patient's Prolaris Score indicated by the orange dot.

CLINICO-PATHOLOGIC FEATURES USED FOR ANALYSIS

Patient Age: 57 % Positive Cores: 16% (3/18)  
PSA Prior to This Biopsy: 3.73 Gleason Score: 3+3=6  
Clinical T Stage: T1c

Note: Clinico-pathologic parameters are provided by the healthcare provider and have not been verified by Myriad.



Kaplan–Meier estimates of prostate cancer death according to CCP score

Cuzick et al. *Lancet Oncol* 2011;12:245 and *Br J Cancer* 2012;106:1095



# Overview of clinical validation cohorts

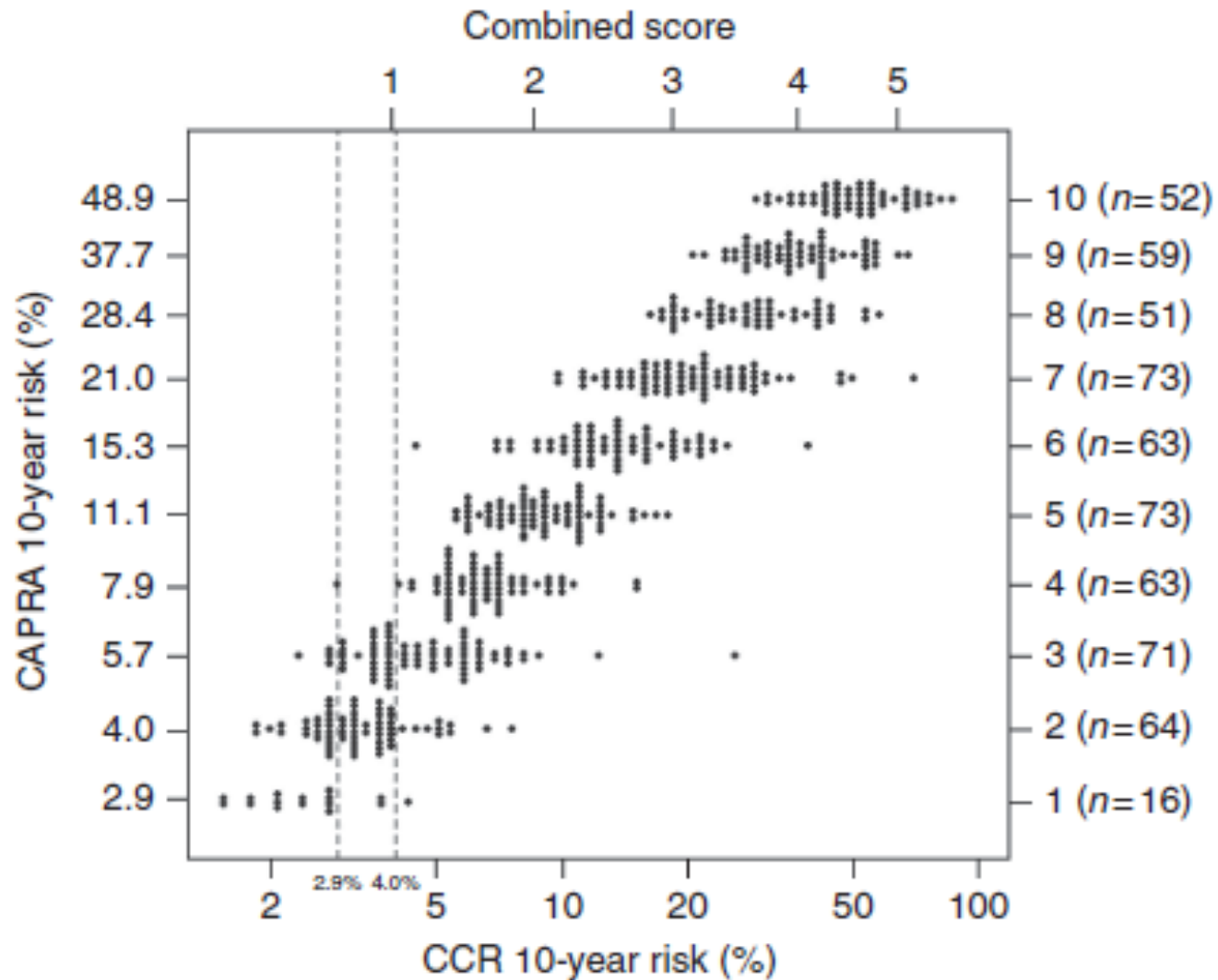
Cohort	N	Primary endpoint	HR [95% CI] */1-unit change in CCP	Correlation with	
				Gleason score	PSA
TURP (WW) <i>Cuzick J, Lancet Oncol 2011</i>	337	Death due to PCa	2.9 [2.4-3.6]	0.57	0.27
Biopsy 1 (WW) <i>Cuzick J, Br J Cancer 2012</i>	349	Death due to PCa	2.0 [1.6-2.5]	0.37	0.14
RP 1 <i>Cuzick J, Lancet Oncol 2011</i>	353	BCR	1.9 [1.5-2.3]	0.22	0.21
RP 2 <i>Cooperberg M, JCO 2013</i>	413	BCR	2.1 [1.6-2.9]	0.18	0.11
RP 3 <i>Bischoff J, J Urol in press 2014</i>	582	BCR	1.5 [1.2-1.8]	not reported	not reported
Germany	283	BCR	2.1 [1.5-2.8]		
North Carolina	176	BCR	1.3 [1.0-1.7]		
Salt Lake City	123	BCR	2.6 [1.4-4.6]		
EBRT <i>Freedland S, Int J RadOncPhys 2013</i>	141	BCR	2.6 [1.4-4.6]	0.23	0.31

\* $P < 0.03$  for all studies



# 10-yr risk of death from prostate cancer based on combined CCR (cell cycle risk) + CAPRA scores

Cuzick J et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. Brit J Ca 2015



# Clinical Utility of Prolaris CCP assay

Change in treatment intensity with use of CCP score across AUA risk categories

Change in selected treatment from pre-test to post-test n (%)				
AUA Risk Group	Non-interventional to non-interventional	Interventional to non-interventional	Interventional to interventional	Non-interventional to interventional
Low (n=83)	47 (57)	18 (22)	13 (16)	5 (6)
Intermediate (n=93)	18 (19)	15 (16)	47 (51)	12 (14)
High (n=29)	1 (3)	4 (14)	18 (62)	6 (21)

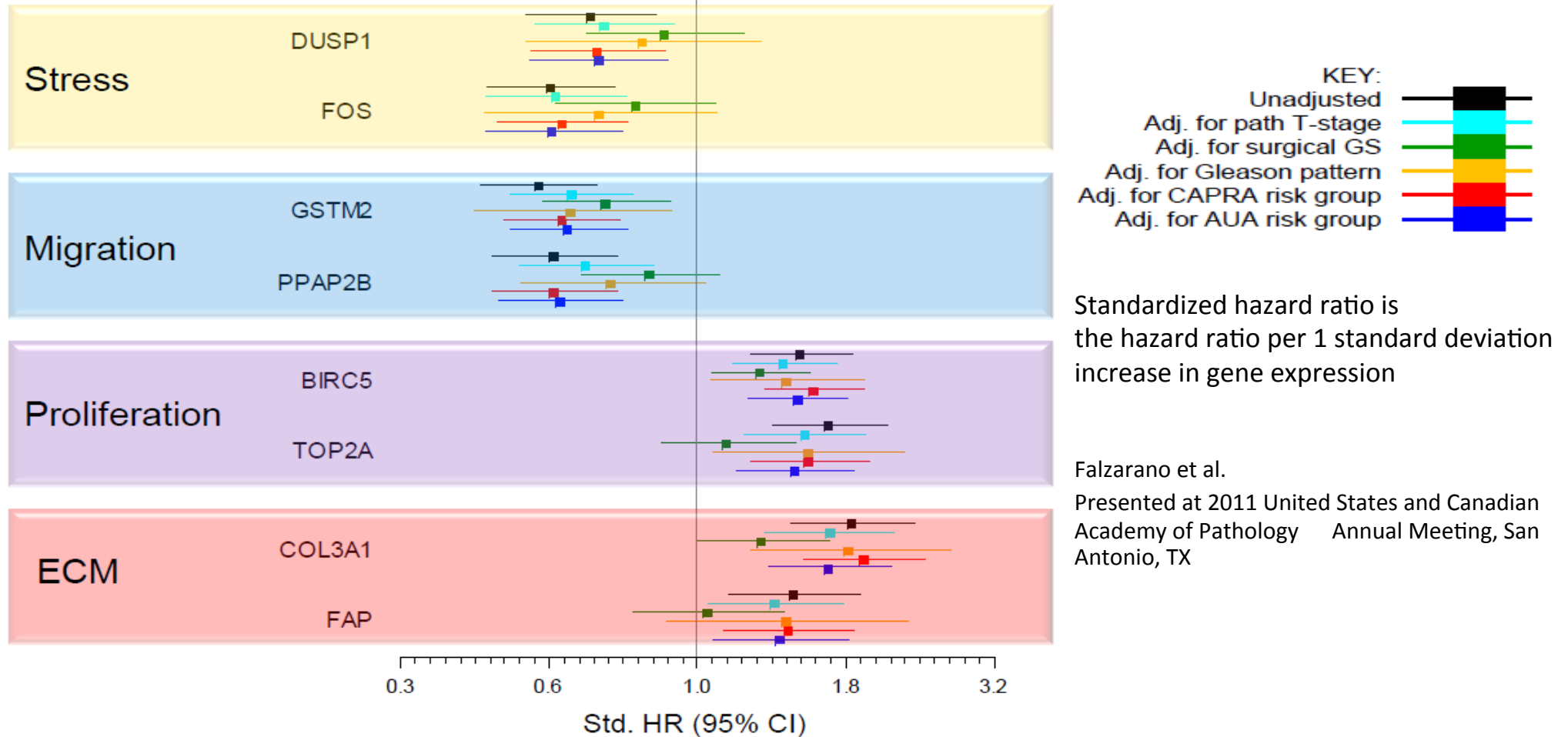
Crawford ED et al. *Curr Med Res Opin* 2014;6:1025

- Of candidates for AS (GI  $\leq$ 3+4, PSA <10, cT  $\leq$ T2b, <25% cores positive), Stone et al. reported no cancer deaths within 10 years in those with a low CCP score.
- Among 1718 samples sent for the commercial assay, 29% qualified for AS by clinical criteria, but 55% qualified when CCP was added to clinical criteria.



# OncotypeDx gene expression profile

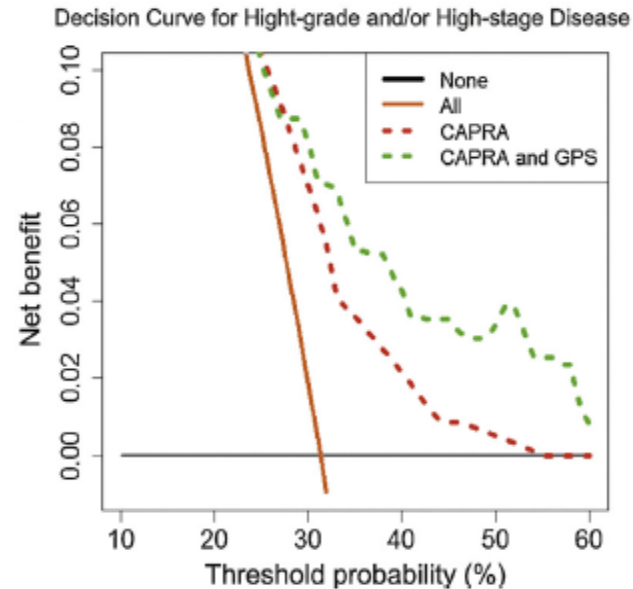
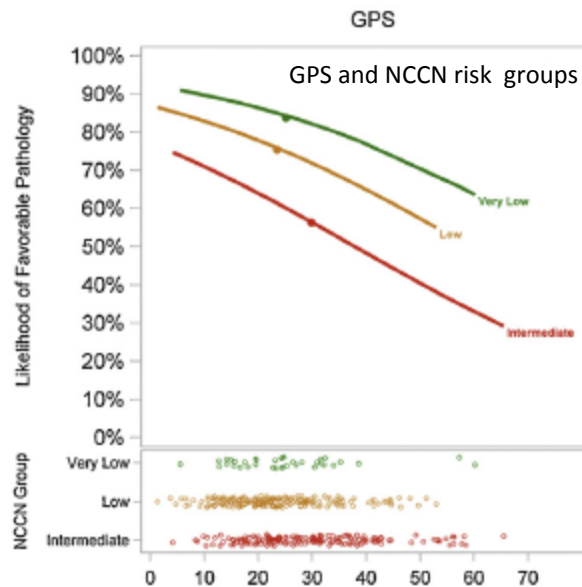
Multiple gene groups add prognostic value beyond clinical and pathologic covariates



## Prostate Cancer

### A 17-gene Assay to Predict Prostate Cancer Aggressiveness in the Context of Gleason Grade Heterogeneity, Tumor Multifocality, and Biopsy Undersampling

Eric A. Klein<sup>a,†,\*</sup>, Matthew R. Cooperberg<sup>b,c,†</sup>, Cristina Magi-Galluzzi<sup>d</sup>, Jeffrey P. Simko<sup>b,e</sup>, Sara M. Falzarano<sup>d</sup>, Tara Maddala<sup>f</sup>, June M. Chan<sup>b,c</sup>, Jianbo Li<sup>f</sup>, Janet E. Cowan<sup>b</sup>, Athanasios C. Tsiatis<sup>f</sup>, Diana B. Cherbavaz<sup>f</sup>, Robert J. Pelham<sup>f</sup>, Imelda Tenggara-Hunter<sup>b</sup>, Frederick L. Baehner<sup>e,f</sup>, Dejan Knezevic<sup>f</sup>, Phillip G. Febbo<sup>f</sup>, Steven Shak<sup>f</sup>, Michael W. Kattan<sup>g</sup>, Mark Lee<sup>f</sup>, Peter R. Carroll<sup>b,\*\*</sup>



# Genomic tests of biopsy samples: how aggressive is the cancer?

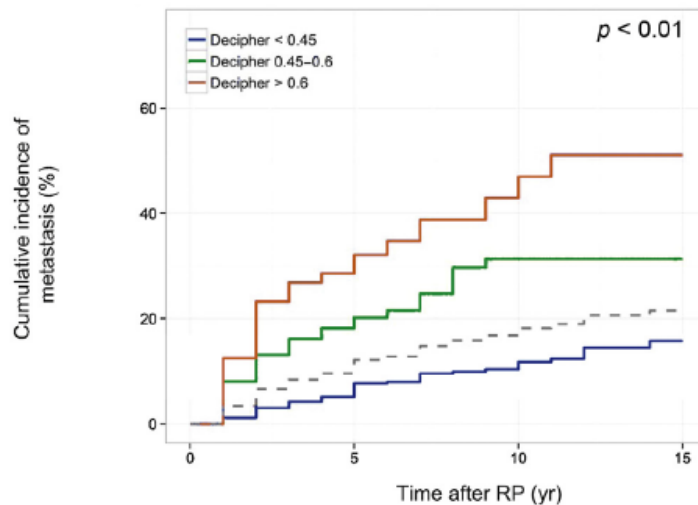
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- Two well studied and technically sound assays are available to assess the biology of prostate cancer in biopsy specimens
- Both assays can be performed successfully in more than 90% of FFPE needle biopsy samples of cancer 0.5 mm or more
- Independent of Gleason grade and PSA, these tests add to predictive models that also include clinical stage and extent of cancer
- *OncotypeDx* focuses on predicting high-risk pathology (EPE, GI >3+4), while *Prolaris* focuses on predicting 10-year risk of death from cancer with no intervention
- **When to use:** For men with biopsy-proven localized cancer, to help determine risk of AS v. immediate therapy, especially when the decision is equivocal



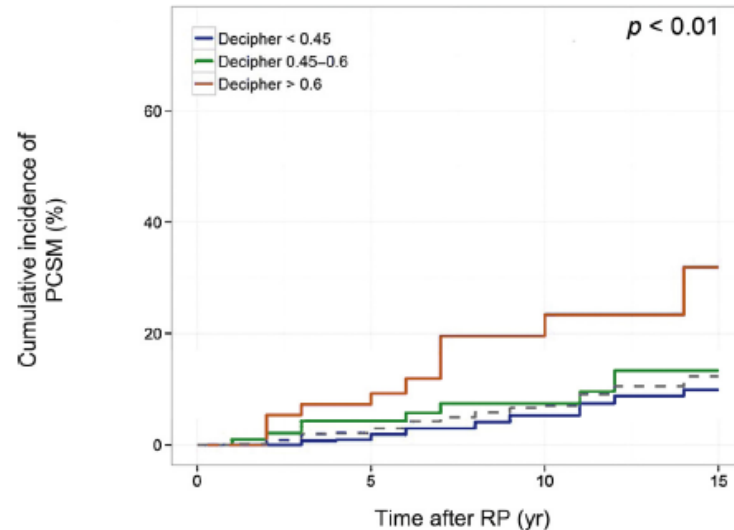
# Decipher GS: Predicting risk of metastases after radical prostatectomy (RP)

Time to metastasis



Decipher > 0.6	56	40	14	6
Decipher 0.45-0.6	99	81	39	12
Decipher < 0.45	427	405	188	51
		Patients at risk		

Time to death from prostate cancer



Decipher > 0.6	56	47	21	8
Decipher 0.45-0.6	98	86	49	14
Decipher < 0.45	427	422	205	58
		Patients at risk		

Cumulative incidence curves over time stratified by Decipher score for metastasis (left) and PCSM (right).

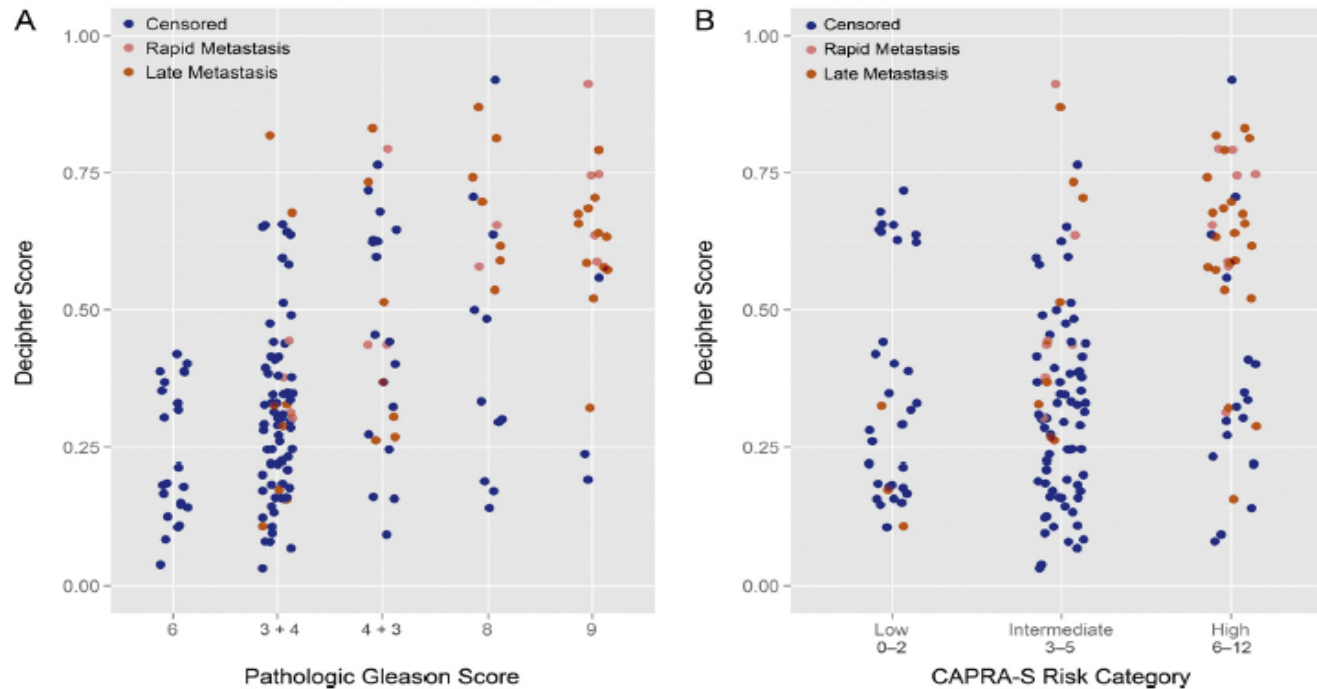




Prostate Cancer

**A Genomic Classifier Improves Prediction of Metastatic Disease Within 5 Years After Surgery in Node-negative High-risk Prostate Cancer Patients Managed by Radical Prostatectomy Without Adjuvant Therapy**

Eric A. Klein<sup>a,\*</sup>, Kasra Yousefi<sup>b</sup>, Zaid Haddad<sup>b</sup>, Voleak Choerung<sup>b</sup>, Christine Buerki<sup>b</sup>, Andrew J. Stephenson<sup>a</sup>, Jianbo Li<sup>c</sup>, Michael W. Kattan<sup>c</sup>, Cristina Magi-Galluzzi<sup>d</sup>, Elai Davicioni<sup>b</sup>



Comparing Decipher with (A) pathologic Gleason score and (B) CAPRA-S score. Men with higher Decipher scores are at higher risk for developing metastases.



## Prostate Cancer

## Tissue-based Genomics Augments Post-prostatectomy Risk Stratification in a Natural History Cohort of Intermediate- and High-Risk Men

Ashley E. Ross<sup>a,b,c</sup>, Michael H. Johnson<sup>a</sup>, Kasra Yousefi<sup>d</sup>, Elai Davicioni<sup>d</sup>, George J. Netto<sup>a,b,c</sup>, Luigi Marchionni<sup>e</sup>, Helen L. Fedor<sup>a</sup>, Stephanie Glavaris<sup>a</sup>, Voleak Choeurng<sup>d</sup>, Christine Buerki<sup>d</sup>, Nicholas Erho<sup>d</sup>, Lucia L. Lam<sup>d</sup>, Elizabeth B. Humphreys<sup>a</sup>, Sheila Faraj<sup>b</sup>, Stephanie M. Bezerra<sup>b</sup>, Misop Han<sup>a</sup>, Alan W. Partin<sup>a</sup>, Bruce J. Trock<sup>a</sup>, Edward M. Schaeffer<sup>a,c,\*</sup>

Cumulative incidence of metastasis (%) 10 yr post-RP for Decipher results within each Eggener nomogram category

Risk model	Decipher <0.45	Decipher 0.45-0.60	Decipher > 0.60
Eggener <2.5%	0	0	25
Eggener 2.5-25%	11	23	37
Eggener >25%	61	61	77

# Biomarker Summary 2016

## How to use in practice

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- Blood tests that supplement PSA (4K score, *phi*) are convenient and clinically efficient, reduce false positive PSAs and the number of unnecessary biopsies, and give prognostic information about the presence and grade of cancer in biopsy specimens. These tests may prove useful in AS and before treatment with RP or XRT.
- Urinary markers (PCA3, TMPRSS2) are inconvenient (require urine sample after prostatic massage) but useful to detect any cancer, and perhaps high-grade cancer, before initial and repeat biopsy, but they show less promise in AS or before RP.
- Tissue biomarkers (*Prolaris*, *OncotypeDx*) in biopsies add significant independent prognostic information to standard clinicopathologic features and are most useful in deciding for AS v. radical therapy, but they have not been compared with MRI and confirmatory biopsy or with blood tests such as 4K score or *phi*.
- None of these biomarkers have established clinical utility in the selection of primary therapy (RP v. XRT), adjuvant XRT or ADT after RP, or salvage therapy for BCR after RP or XRT (XRT, salvage RP, ADT, chemo).

