Biomarkers: PSA, 4K, or PHI

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Disclosures

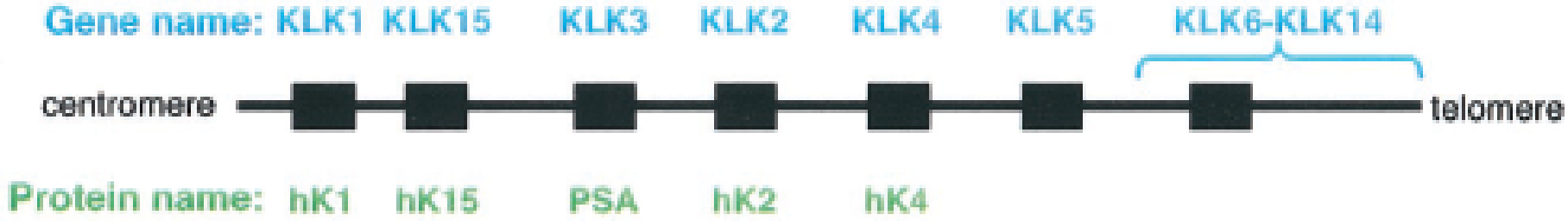
- 3DBiopsy LLC
  - President, CEO and Owner

PSA Assays

- PSA-FDA approved
- PHI-FDA approved
- 4KScore-CLIA approved

Biology of Prostate-Specific Antigen

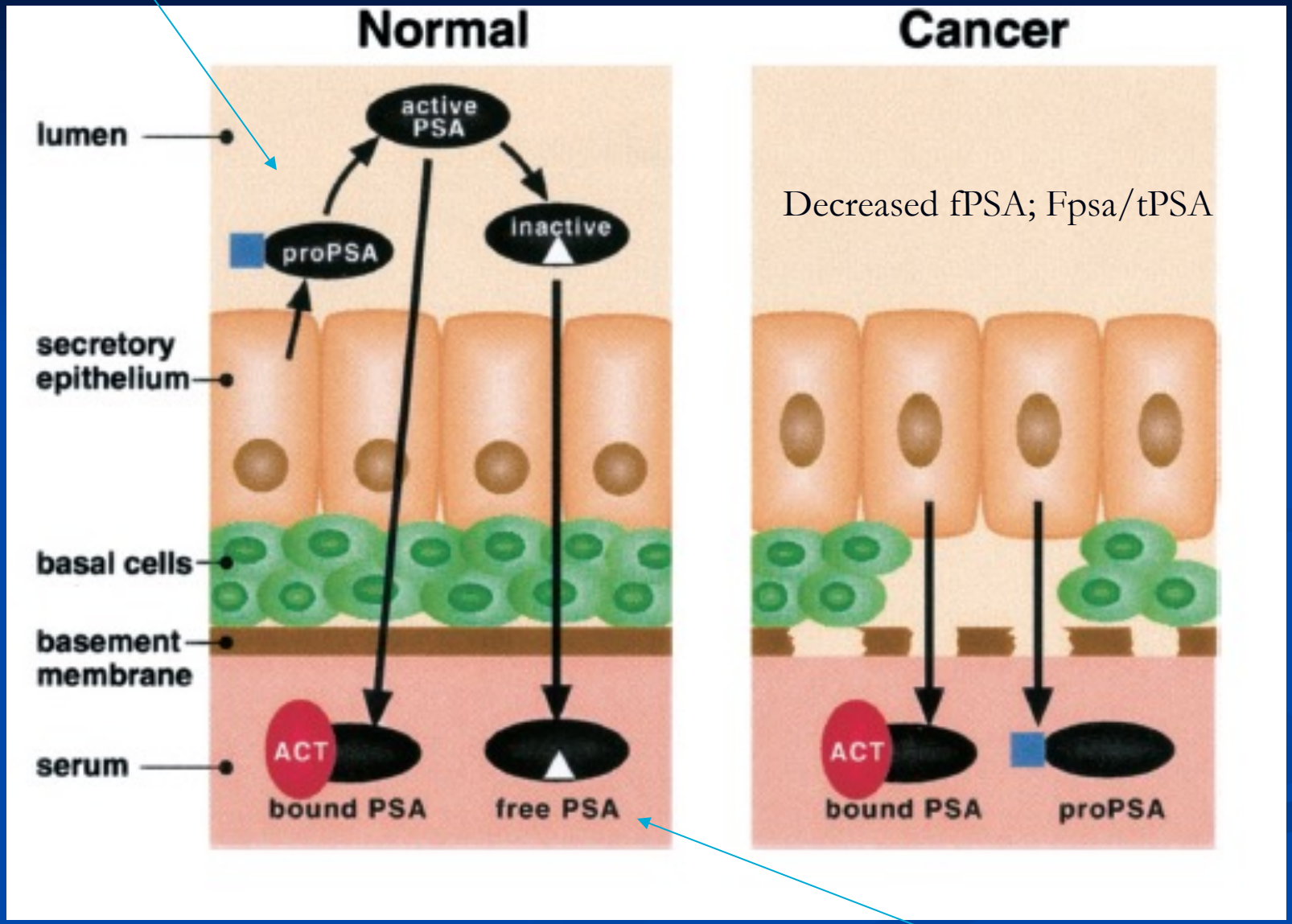
Steven P. Balk, Yoo-Joung Ko, and Glenn J. Bubley



Androgen regulated serine protease
Produced in ductal and acinar epithelium
Cleaves semenogelin I&II (mediate gel formation)
15 tissue kallikreins
hK2 and hK4 also produced in prostate and androgen regulated

J Clin Oncol 21:383-391. © 2003

hK2 cleaves propeptide



70-90% PSA in blood bound to alpha 1 antichymotrypsin

Includes proPSA

SCREENING FOR PROSTATE CANCER BY DIGITAL RECTAL EXAMINATION AND PROSTATE-SPECIFIC ANTIGEN

RESULTS OF PROSTATE CANCER AWARENESS WEEK, 1989–1992

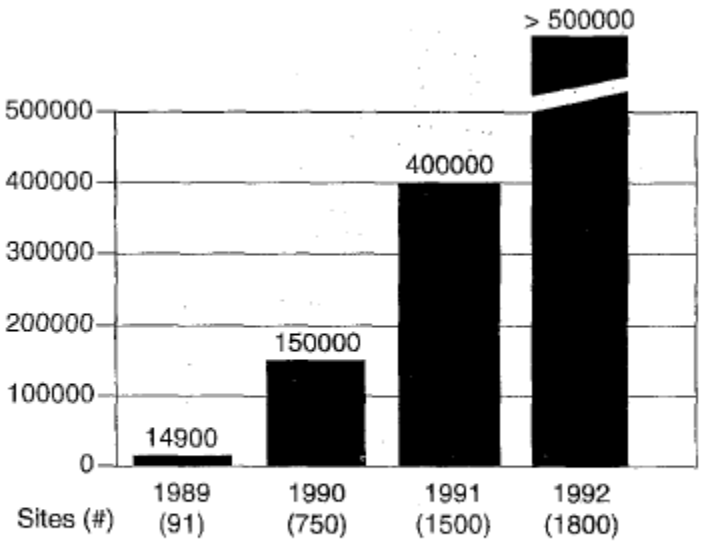


FIGURE 1. Number of participants per year during prostate cancer awareness week. In 1992 there were > 500,000 participants.

NELSON N. STONE, M.D.
EDWARD P. DeANTONI, Ph.D.
E. DAVID CRAWFORD, M.D.
THE PROSTATE CANCER EDUCATION COUNCIL*

UROLOGY SYMPOSIUM / *December 1994* / *Volume 44,*

TABLE II. *Percentage with an abnormal digital rectal examination or prostate-specific antigen and biopsy rate*

	1989	1990	1991	1992	Total
Positive DRE	16.4% (1698/10,327)*	12.2% (10,416/85,698)	13.9% (10,727/77,235)	12.9% (6817/52,790)	13.1% (29,658/226,046)
Positive PSA	10.4% (183/1768)	24.2% (2309/9545)	17.6% (10,159/57,686)	8.6% (3982/46,224)	14.4% (16,633/115,223)
Biopsy rate	11.8% (200/1698)	38.7% (4035/10,416)	10.3% (1108/10,727)	37.5% (1873/6817)	24.3% (7216/29,658)
Positive biopsy rate	21% (42/200)	20% (805/4035)	28.6% (317/1108)	21.9% (465/2119)	22.6% (1629/7216)
Positive biopsy, positive DRE	16.3% (27/166)	20% (769/3844)	29.2% (215/317)	29.1% (300/1030)	24.5% (1311/5357)
Positive biopsy, positive PSA	47.9% (34/71)	77% (288/693)	36.8% (255/692)	41.5% (314/756)	49.3% (891/2212)

*Number of participants positive/number of participants tested.

Prostate Cancer Prevalence

4.8% 18.6% 6.5% 3.5% Total 7.1%

Message from USPSTF
And Other Organizations Following the Lead

PSA screening is **a "D"** recommendation

- Physicians should not order PSA screening unless they are prepared to engage in **shared decision making** that enables an informed choice by patients

Supported by AAFP

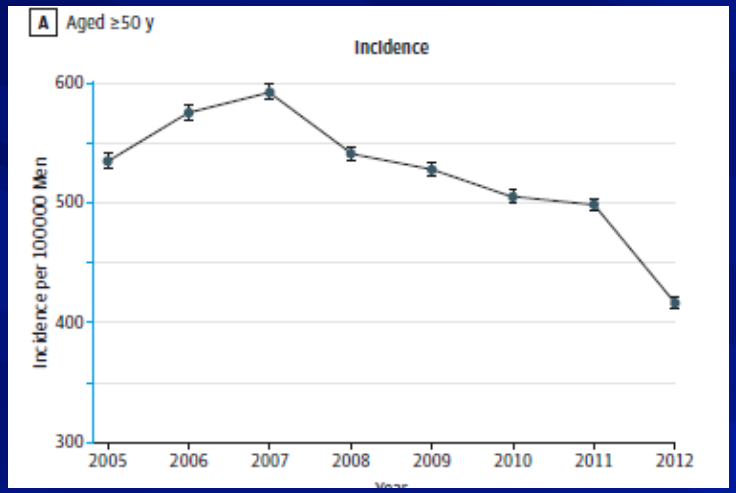
- AAFP recommends against performing PSA-based screening for prostate cancer in asymptomatic men

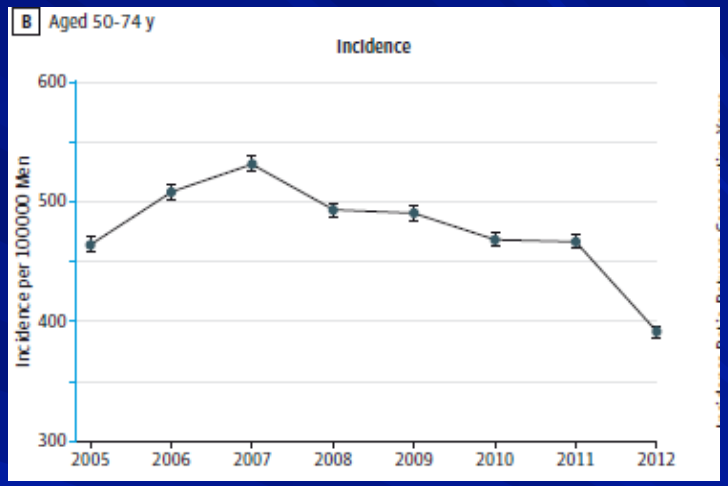
What to do ?

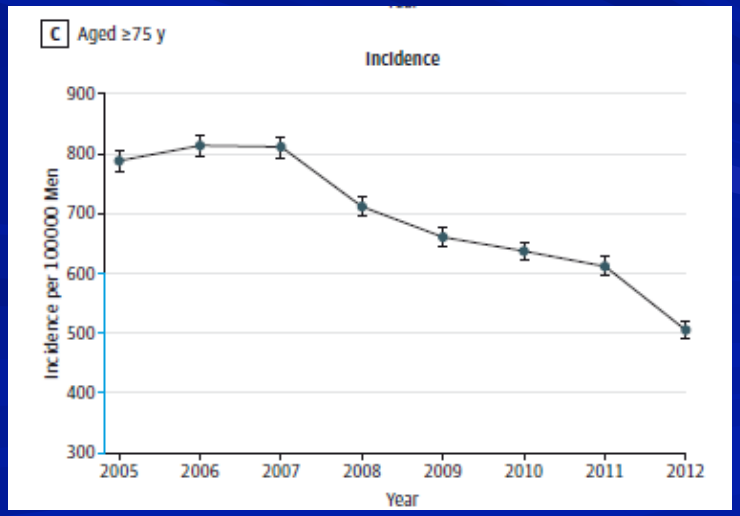
Moyer VA, et al. *Ann Intern Med.* 2012 Jul 17;157(2):120–34.
AAFP, USPSTF Issue Final Recommendation Against Routine PSA-based Screening for Prostate Cancer

Prostate Cancer Incidence and PSA Testing Patterns in Relation to USPSTF Screening Recommendations

Ahmedin Jemal, DVM, PhD; Stacey A. Fedewa, MPH; Jiemin Ma, PhD; Rebecca Siegel, MPH; Chun Chieh Lin, PhD; Otis Brawley, MD; Elizabeth M. Ward, PhD







JAMA. 2015;314(19):2054-2061.

Table. Adjusted Screening Rate and Rate Ratios of PSA Testing in the Past Year for Screening Reasons Among Men 50 Years and Older[a]

	National Health Interview Survey Year			
	2005	2008	2010	2013
No. of men				
≥50 y	4580	3476	4157	6172
50-74 y	3854	2900	3540	5221
≥75 y	726	576	617	951
No. of men with PSA test in past year				
≥50 y	1633	1345	1457	1771
50-74 y	1332	1079	1220	1464
≥75 y	301	266	237	307
Adjusted screening rate (99% CI)[b]				
≥50 y	36.9 (34.5-39.1)	40.6 (37.9-43.3)	37.8 (35.3-40.2)	30.8 (29.0-32.7)
50-74 y	35.8 (33.4-38.3)	39.1 (36.2-42.0)	36.8 (34.3-39.4)	29.9 (28.0-32.0)
≥75 y	42.6 (37.6-47.9)	50.1 (43.7-56.4)	43.1 (37.1-49.2)	36.3 (31.1-41.9)
Adjusted SRR (99% CI)[c]				
≥50 y		1.10 (1.01-1.21)	0.93 (0.84-1.02)	0.82 (0.75-0.89)
50-74 y		1.09 (0.99-1.21)	0.94 (0.85-1.05)	0.81 (0.74-0.89)
≥75 y		1.18 (0.99-1.40)	0.86 (0.71-1.04)	0.84 (0.68-1.05)

Impact of Prostate-specific Antigen (PSA) Screening Trials and Revised PSA Screening Guidelines on Rates of Prostate Biopsy and Postbiopsy Complications

Boris Gershman [a], *Holly K. Van Houten* [b], *Jeph Herrin* [c,d], *Daniel M. Moreira* [a], *Simon P. Kim* [e], *Nilay D. Shah* [b,f], *R. Jeffrey Karnes* [d,*]

Fig. 1 – Interrupted time series analysis of monthly rates of prostate biopsy and 30-d complications (January 2005 to September 2014) among men aged ≥40 yr (n = 5 279 315).
AUA = American Urological Association; ERSPC = European Randomized Study of Screening for Prostate Cancer; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; USPSTF = US Preventive Services Task Force.

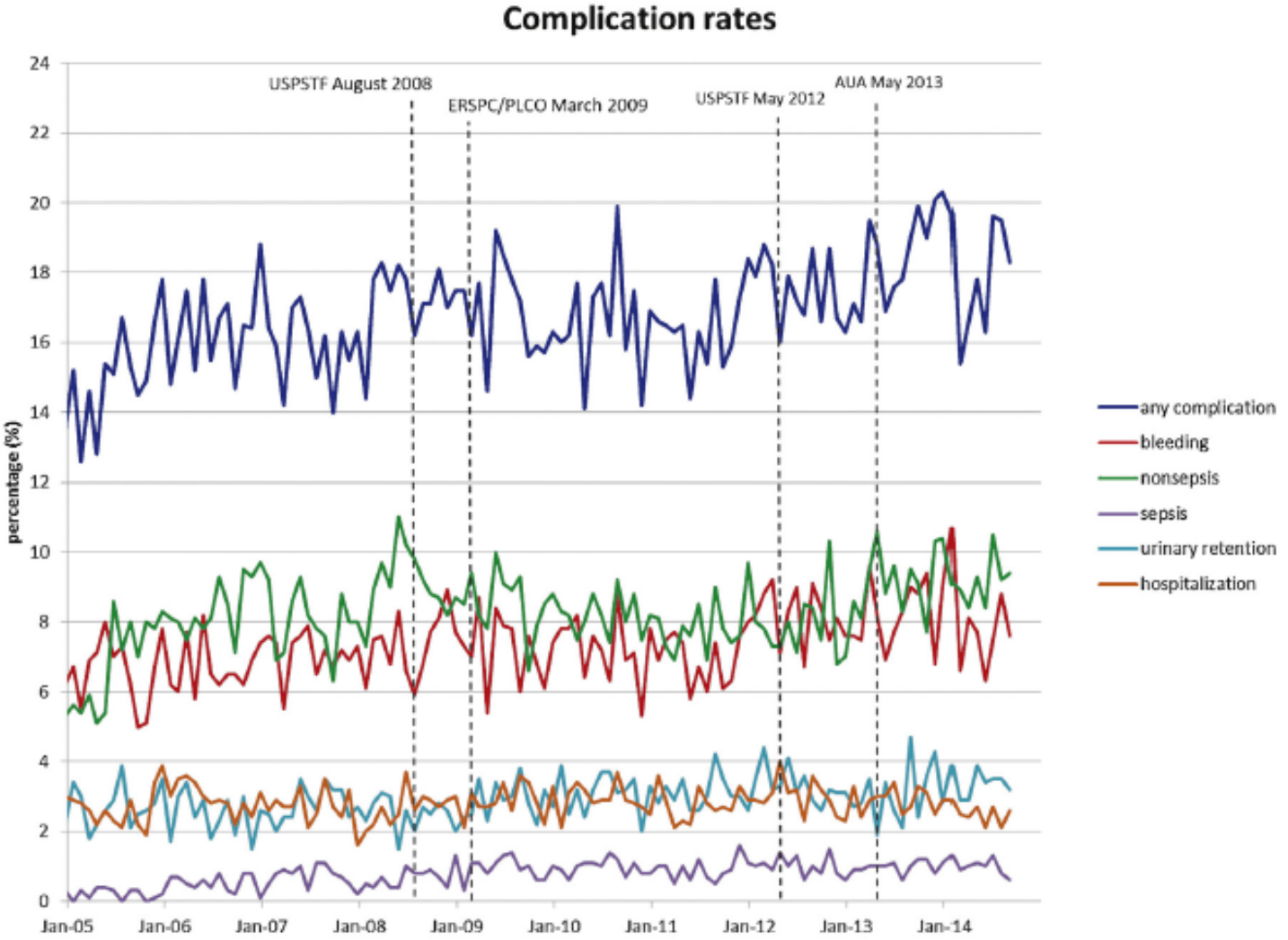


Fig. 2 – Interrupted time series analysis of monthly rates of 30-d postbiopsy complications (January 2005 to September 2014) among men aged ≥40 yr undergoing biopsy (*n* = 104 584).

AUA = American Urological Association; ERSPC = European Randomized Study of Screening for Prostate Cancer; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; USPSTF = US Preventive Services Task Force.

Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level ≤4.0 ng per Milliliter

Ian M. Thompson, M.D., Donna K. Pauler, Ph.D., Phyllis J. Goodman, M.S., Catherine M. Tangen, Dr.P.H., M. Scott Lucia, M.D., Howard L. Parnes, M.D., Lori M. Minasian, M.D., Leslie G. Ford, M.D., Scott M. Lippman, M.D., E. David Crawford, M.D., John J. Crowley, Ph.D., and Charles A. Coltman, Jr., M.D.

Table 2. Relationship of the Prostate-Specific Antigen (PSA) Level to the Prevalence of Prostate Cancer and High-Grade Disease.*

PSA Level	No. of Men (N=2950)	Men with Prostate Cancer (N=449)	Men with High-Grade Prostate Cancer (N=67)	Sensitivity	Specificity
		no. of men (%)	*no./total no. (%)*		
≤0.5 ng/ml	486	32 (6.6)	4/32 (12.5)	1.0	0.0
0.6–1.0 ng/ml	791	80 (10.1)	8/80 (10.0)	0.93	0.02
1.1–2.0 ng/ml	998	170 (17.0)	20/170 (11.8)	0.75	0.33
2.1–3.0 ng/ml	482	115 (23.9)	22/115 (19.1)	0.37	0.73
3.1–4.0 ng/ml	193	52 (26.9)	13/52 (25.0)	0.12	0.92

* High-grade disease was defined by a Gleason score of 7 or greater. The population was restricted to men with a PSA level of 4.0 ng per milliliter or less throughout the study. Therefore, the definitions of sensitivity and specificity are restricted to cutoff values of less than 4.0 ng per milliliter (the cutoff values are equal to the lower value of the ranges in the PSA column [0.0, 0.6, 1.1, 2.1, and 3.1 ng/ml]). Sensitivity was defined as the proportion of men with cancer who had a PSA value above the cutoff among all men with cancer who had a PSA value of 4.0 ng per milliliter or less. Specificity was defined in a like manner.

N Engl J Med 2004;350:2239-46.

Part of the challenge is that we rely on TRUS biopsy to make a diagnosis of prostate cancer-this method gives incorrect information 50% of the time. Can this be solved by alternate forms of detection:

1.mpMRI

2.TPMB

The Prostate Health Index & [-2]proPSA

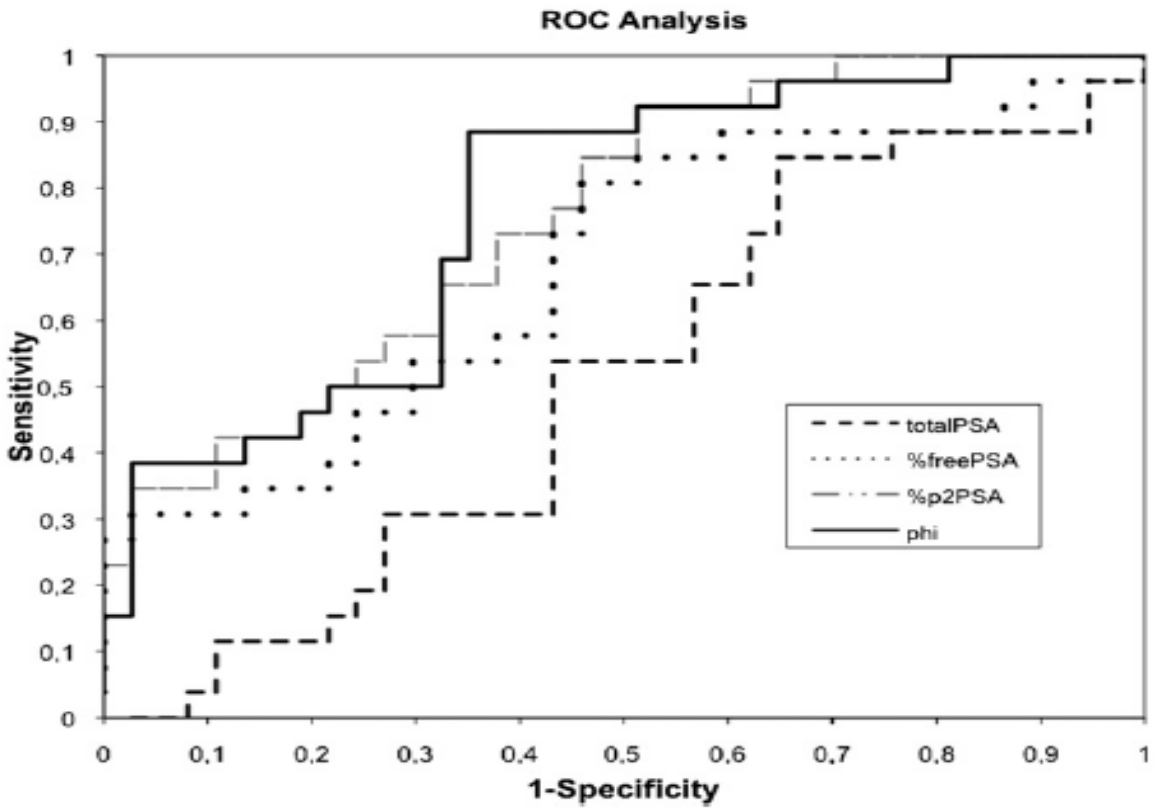
- The Prostate Health Index (*phi*) from Beckman Coulter is made up of three immunoassays:
  - Total PSA
  - Free PSA
  - p2PSA (measures [-2]proPSA)
- *phi* is a calculation from the results of these three immunoassays which gives a "*phi* score" (probability of cancer)

[-2]Proenzyme Prostate Specific Antigen is More Accurate Than Total and Free Prostate Specific Antigen in Differentiating Prostate Cancer From Benign Disease in a Prospective Prostate Cancer Screening Study

Brian V. Le, Christopher R. Griffin, Stacy Loeb, Gustavo F. Carvalhal, Donghui Kan, Nikola A. Baumann and William J. Catalona*,†

- 2,034 men undergoing prostate cancer screening
  - tPSA
  - fPSA/tPSA (%fPSA)
  - p2PSA
  - p2PSA/fPSA (%p2PSA)
  - Beckman Coulter prostate health index or phi®:
    - (p2PSA/fPSA) X √tPSA
  - biopsy with a prostate specific antigen of 2.5 to 10 ng/ml and non-suspicious digital rectal examination

Vol. 183, 1355-1359, April 2010
THE JOURNAL OF UROLOGY®



ROC curve comparing PSA, %fPSA, %p2PSA and phi for prostate cancer detection on prostate biopsy at total PSA 2.5 to 10 ng/ml.

Table 2. *Performance characteristics at a set sensitivity of 88.5%*

	Specificity (%)	Pos Predictive Value (%)	Neg Predictive Value (%)
Total PSA	24.3	45.1	75
%fPSA	40.5	51.1	83.3
%p2PSA	48.6	54.8	85.7
phi	64.9	53.9	88.9

Serum Index Test %[-2]proPSA and Prostate Health Index are More Accurate than Prostate Specific Antigen and %fPSA in Predicting a Positive Repeat Prostate Biopsy

Massimo Lazzeri,* Alberto Briganti, Vincenzo Scattoni, Giovanni Lughezzani, Alessandro Larcher, Giulio Maria Gadda, Giuliana Lista, Andrea Cestari, Nicolòmaria Buffi, Vittorio Bini, Massimo Freschi, Patrizio Rigatti, Francesco Montorsi and Giorgio Guazzoni

- 1 or 2 previous negative prostate biopsies
- diagnostic accuracy of %p2PSA and PHI
- 71 of 222 (31.9%) positive biopsy
  - Pos vs Neg Biopsy (mean values)
    - tPSA 7.2 vs 7.8 ng/ml (NS)
    - p2PSA 17.8 vs 15.1 pg/ml (NS)
    - fPSA 0.9 vs 1.2 ng/ml (0.025)
    - %fPSA 0.14 vs 0.16 (0.014)
    - %2PSA 1.9 vs 1.4 (<.001)
    - PHI 51.6 vs 37.0 (<.001)

Vol. 188, 1137-1143, October 2012
THE JOURNAL OF UROLOGY®

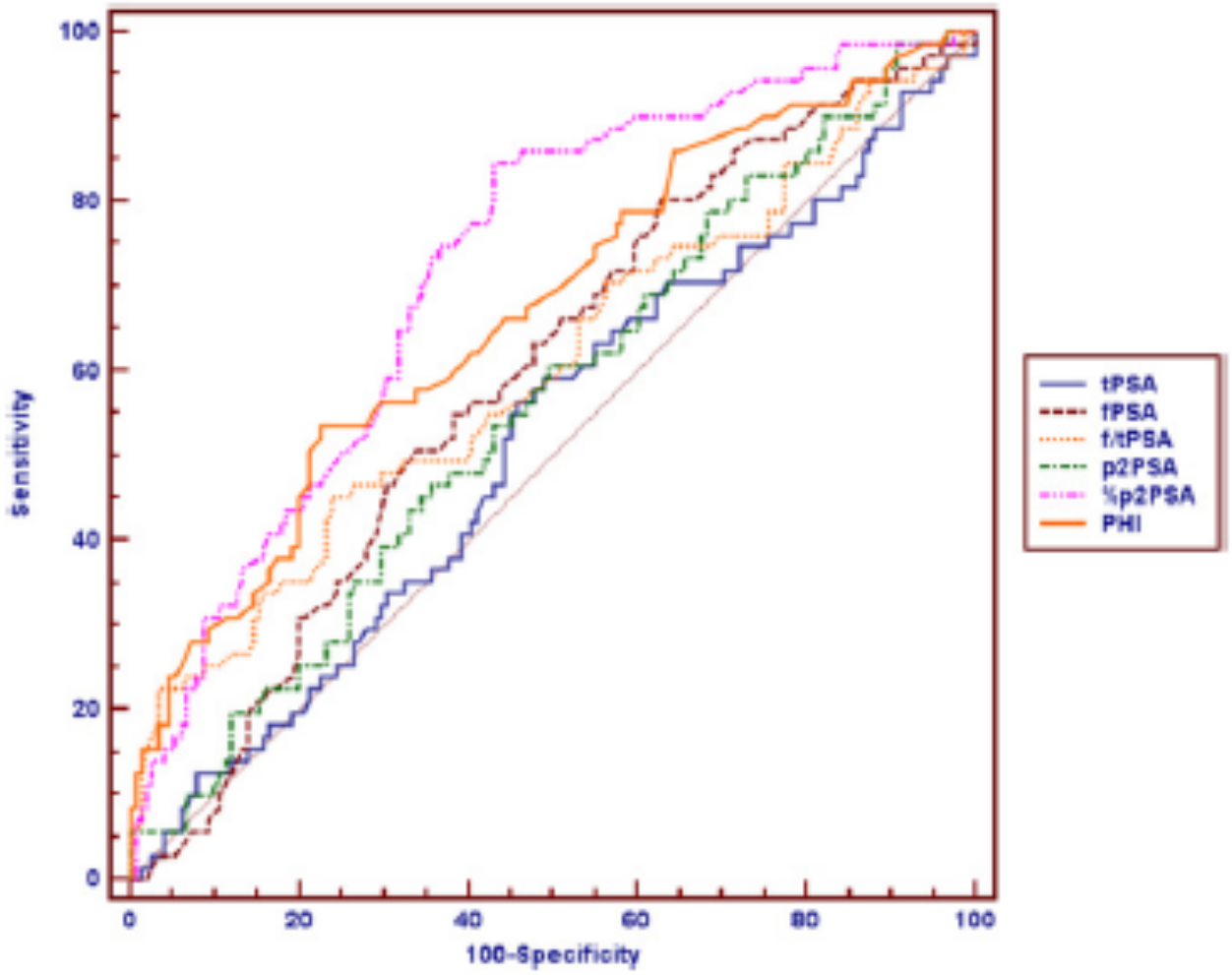


Figure 2. Predictive accuracy, quantified as area under receiving operating characteristics curve, for single biomarkers.

Development and Internal Validation of a Prostate Health Index Based Nomogram for Predicting Prostate Cancer at Extended Biopsy

Giovanni Lughezzani,*,† Massimo Lazzeri,† Alessandro Larcher, Giuliana Lista, Vincenzo Scattoni, Andrea Cestari, Nicoló Maria Buffi, Vittorio Bini and Giorgio Guazzoni

- 729 patients prostate biopsy for suspicious digital rectal examination and/or increased PSA
  - saturation scheme consisting of at least 18 biopsy cores
- tPSA, %fPSA/tPSA, 2proPSA and PHI
- Prostate cancer in 280 of 729 patients (38.4%)

Vol. 188, 1144-1150, October 2012
THE JOURNAL OF UROLOGY®

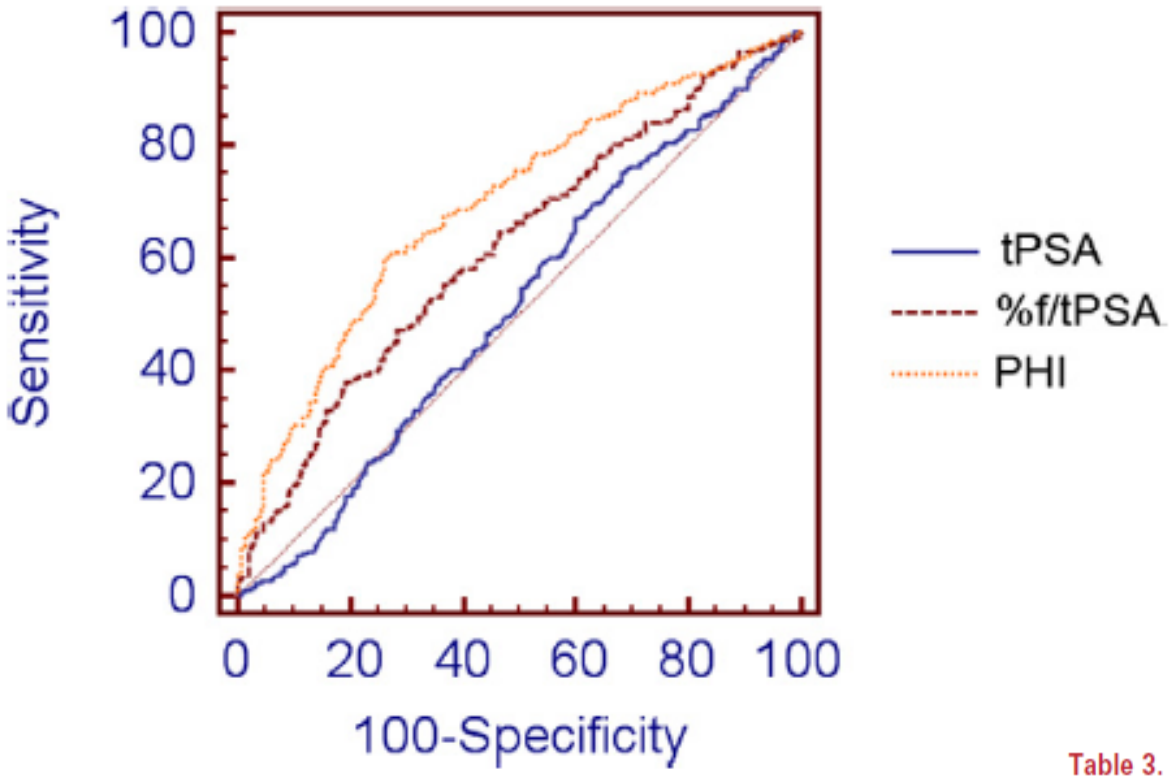


Figure 1. ROC AUC shows accuracy of total PSA, percen
and PHI for predicting PCa at biopsy.

Table 3. *Specificity at 90% sensitivity of variables predicting PCa at biopsy*

Predictors	% Specificity at 90% Sensitivity (95% CI)
tPSA	9.3 (6.8–12.4)
% fPSA	17.8 (14.4–21.7)
p2PSA	15.6 (12.4–19.3)
PHI	27.0 (22.1–30.4)
Base multivariable model:*	33.8 (29.1–38.8)
+ tPSA	34.6 (29.9–39.6)
+ % fPSA	35.1 (30.4–40.1)
+ p2PSA	35.6 (30.9–40.7)
+ PHI	41.6 (36.6–46.7)

* Including age, prostate volume, DRE and biopsy history.

4K Score

- Available March 2014
- total prostate-specific antigen [tPSA], free PSA [fPSA], intact PSA, and hK2)
- Low risk < 7.5%
- Intermediate risk 7.5% - 19.9%
- High risk ≥ 20%

A Four-kallikrein Panel Predicts High-grade Cancer on Biopsy: Independent Validation in a Community Cohort

Katharina Braun[a], **Daniel D. Sjoberg**[b], **Andrew Vickers**[b], **Hans Lilja**[c,d,e,*], and **Anders Bjartell**[e]

Discrimination of total prostate-specific antigen

	High-grade cancer	Any-grade cancer
Age and PSA*	0.719 (0.672–0.767)	0.632 (0.590–0.674)
Age, four-kallikrein panel	0.777 (0.736–0.819)	0.683 (0.644–0.722)
Age, PSA, DRE*	0.736 (0.689–0.782)	0.638 (0.597–0.679)
Age, four-kallikrein panel, and DRE	0.784 (0.742–0.826)	0.690 (0.652–0.729)

AUC = area under the curve; DRE = digital rectal examination; PSA = prostate-specific antigen.

Eur Urol. 2016 March ; 69(3): 505–511

Comparison between the four-kallikrein panel and Prostate Health Index (PHI) for predicting prostate cancer

Tobias Nordström, M.D.[a,b,*], Andrew Vickers, Ph. D.[c], Melissa Assel, Ph. D.[c], Hans Lilja, M.D. Ph.D.[d,e,f] [Professor], Henrik Grönberg, M.D.[b] [Professor], and Martin Eklund, Ph. D.[b,g]

Performance of models predicting prostate cancer when applied to a cohort of 897 men of which 707 were not previously biopsied (455 controls and 442 prostate cancer cases of which 221 with high-grade cancer).

	All cancer			High-grade cancer		
Model	AUC	CI (95%)	p (vs base)	AUC	CI (95%)	p (vs base)
Base model	62.8	(59.2–66.4)	-	68.4	(64.3–72.5)	-
4K-panel*	74.9	(7.17–78.1)	<0.0001	78.5	(75.1–82.0)	<0.0001
PHI	77.5	(74.5–80.5)	<0.0001	79.0	(75.5–82.5)	<0.0001
AUC comparison: PHI vs 4K-panel			0.22			0.81

Eur Urol. 2015 July ; 68(1): 139–146.

Does PSA Velocity Predict Prostate Cancer in Pre-Screened Populations?

Fritz H. Schröder [a,*], Monique J. Roobol [a], Theo H. van der Kwast [b], Ries Kranse [c], Chris H. Bangma [a]

Table 1 – Prostate cancer detection in 588 men four years after a negative screen (PSA <4.0 ng/ml, no biopsy)

PSA/PSAV	No PC 1	PC (*n*) 2	Total (*n*) 3	PPV (2:3)
PSA ≥.0	421	167	588	28.4
PSAV >0.25	392	158	550	28.7
PSAV >0.50	278	109	387	28.2
PSAV >0.75	154	49	203	24.1
PSAV >1.00	76	34	110	30.9

Comparison of PSA progression to PSA ≥4.0 ng/mL and 3 PSAV cut-offs. All men were biopsied at the second screening.

Table 3 – PSAV and prostate cancer aggressiveness (167 cancers) four year re-screening

	Men (*n*)	PC (*n*)	Indolent N (%)	Aggressive N (%)
PSA ≥4.0	588	167	78 (46.7)	89 (53.3)
PSAV >0.25	550	158	71 (44.9)	87 (55.1)
PSAV >0.50	387	109	44 (40.4)	65 (59.6)
PSAV >0.75	203	49	17 (34.7)	32 (65.3)
PSAV >1.00	110	34	12 (35.3)	22 (64.7)

Aggressive: ≥T2b or pT2b, biopsy Gleason ≥7; Indolent: <T2b or pT2b, biopsy Gleason <7.

EUROPEAN UROLOGY 49 (2006) 460–465

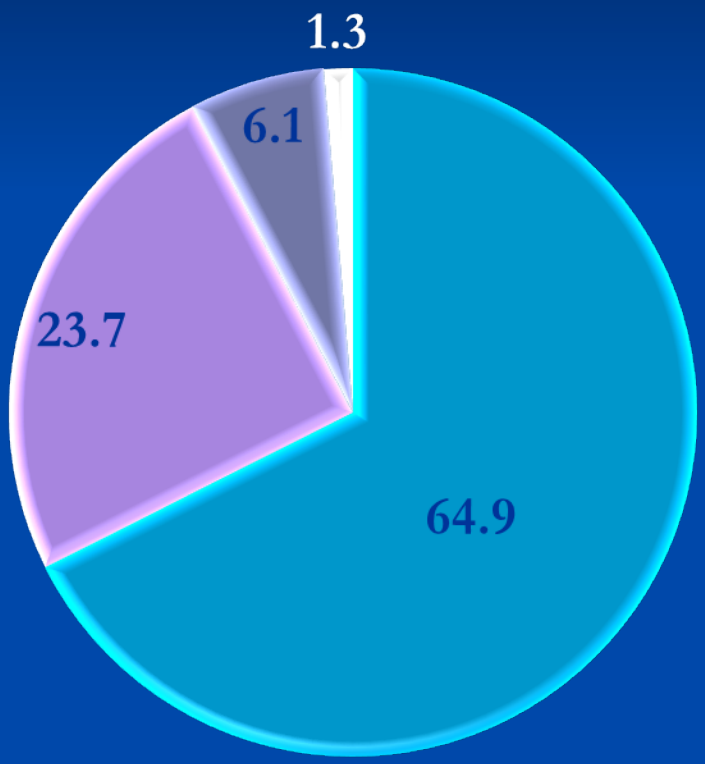
Prostate Cancer Detection Challenges

1) Improve the interpretation **of PSA, thus allow Primary Care Physicians to enhance referral efficiency for Urology evaluation**
2) A test which will decrease unnecessary **negative re-biopsies and enhance detection**
3) A **test** to enhance risk stratification of newly diagnosed PCa patients–who are best suited for surveillance vs interventional therapy

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

- 1. 6%
- 2. 25%
- 3. between 40-60%
- 4. around 70%

Who is Ordering PSA Tests in United States?



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

Aslani A, et al. *J Urol.* 2013;do:10.1016/j.juro.2013.12.010

Ways Forward

- Educate those who order PSAs – **PCPs**
- Define a **PSA level with little risk** (age, family history, prostate gland volume, symptoms, DRE)
- Identify those who need further evaluation by a Urologist

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

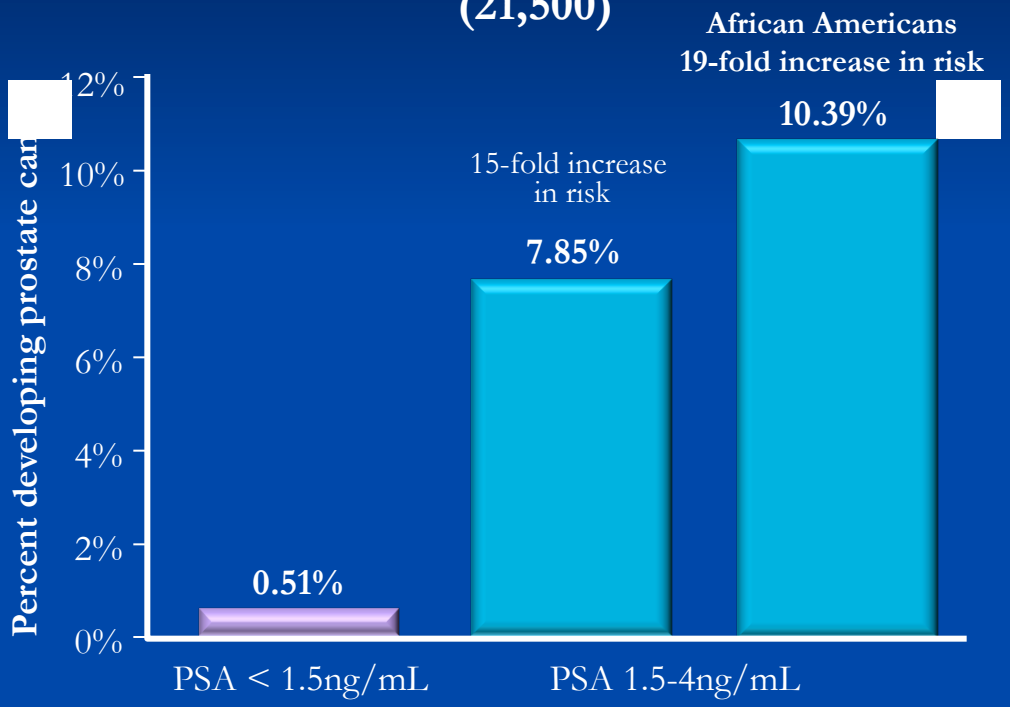
Results:

Mean age -55 years Mean PSA 1.0
African American 29%
Detected Cancer: 2%

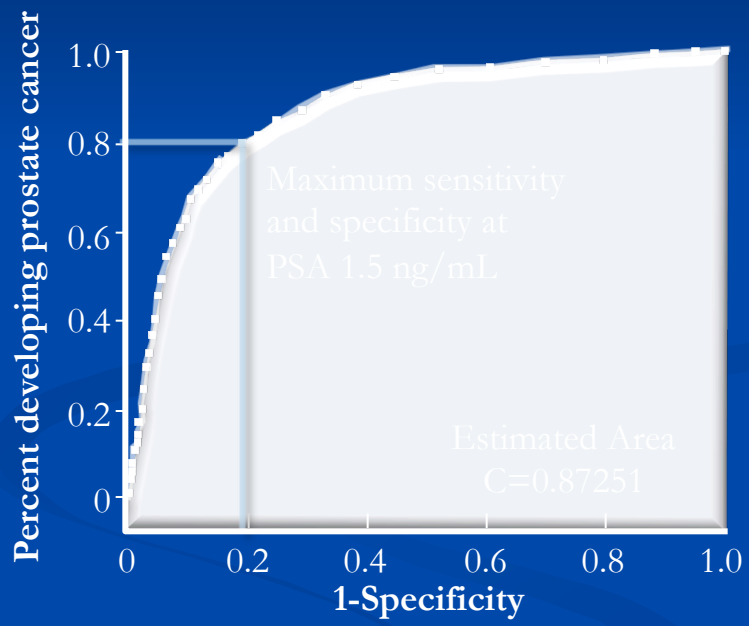
21,502 men eligible

5-year Diagnosis Rates Based on Initial PSA Level

Overall Study Population (21,500)



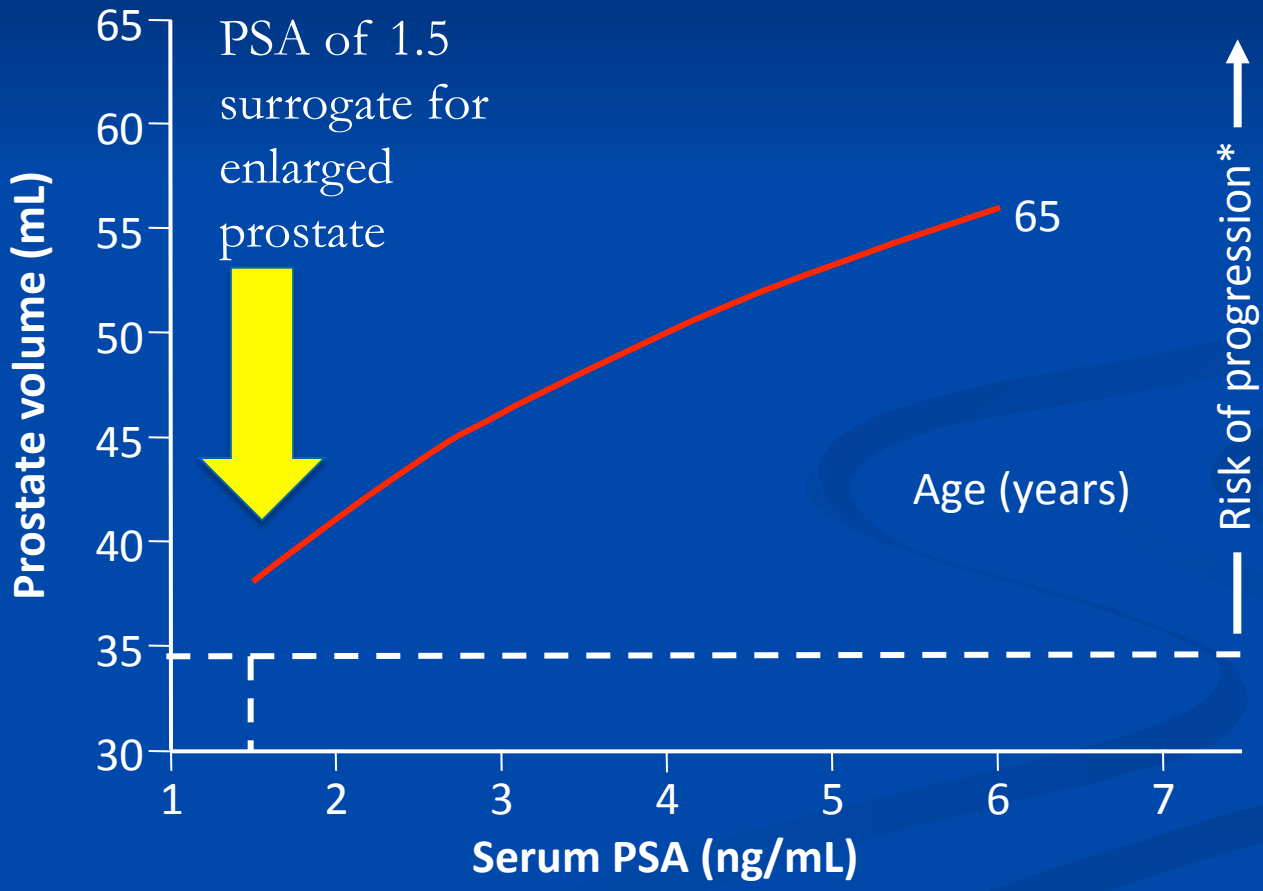
Receiver Operating Characteristic Curve for All Patients



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

Crawford ED, et al. *BJU Int.* 2011;108(11):1743-9

Serum PSA ≥1.5ng/mL
Predicting Enlargement & Risk of Progression



Adapted from Roehrborn CG et al. *Urology*. 1999;53:581–589.
*Crawford ED et al. *J Urol*. 2006;175:1422–1427.

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

Table 1. PSA measurements of less than 1.5 ng/mL (provided with permission of Charles T. Todd Jr., BioReference Laboratories, Inc.)

Age Group	No. of Men With PSA < 1.5 ng/mL	% of Men by Age Group with PSA < 1.5 ng/mL	Total No. of Results
41-45	36,121	89.6	40,306
46-50	54,616	84.1	64,920
51-55	69,853	76.8	90,949
56-60	59,195	67.2	88,034
61-65	45,386	58.1	78,072
66-70	34,931	51.6	67,675
71-75	23,742	48.3	49,185
76-80	16,255	47.1	34,506
81-85	9572	46.4	20,616
86-90	4562	44.9	10,154
91-96	1266	40.1	3154
Grand total	355,499	64.9	547,571

PSA, prostate-specific antigen.

PSA values from reference lab

UROLOGY 96, 2016

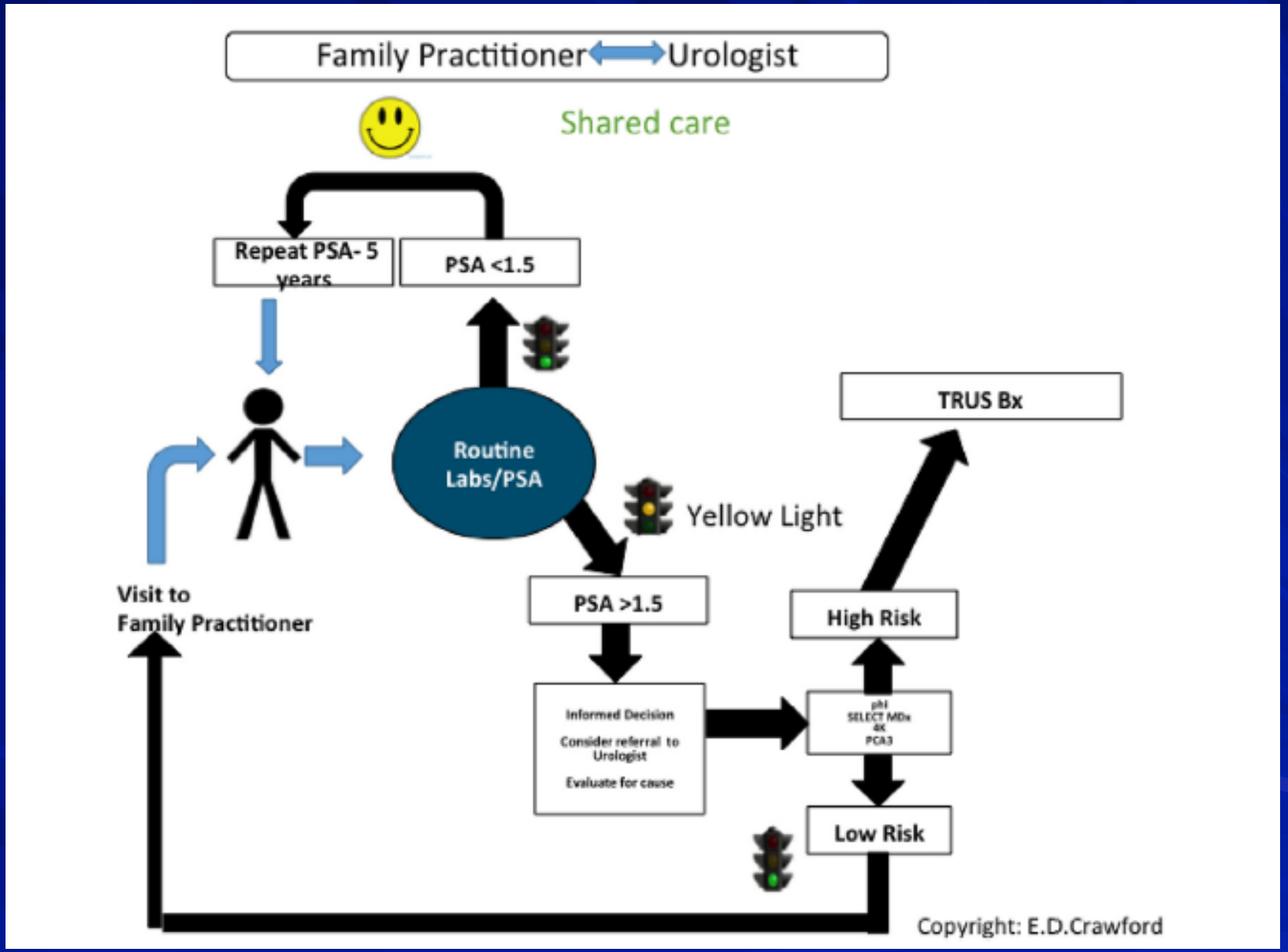

Family Practitioner ⟷ Urologist
Shared care
Repeat PSA- 5 years
PSA <1.5
Routine Labs/PSA
Yellow Light
TRUS Bx
Visit to Family Practitioner
PSA >1.5
High Risk
Informed Decision
Consider referral to Urologist
Evaluate for cause
phi
SELECT MDx
4K
PCA3
Low Risk
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Table 2. Molecular tests to identify Gleason sum equal to or greater than 7

Assay	PHI	4KScore	PCA3	SelectMDx
Company	Beckman Coulter	Opko	Hologic	MDxHealth
Specimen	Blood	Serum	*Urine	*Urine
Methodology	Immunoassay, 3 protein biomarkers: tPSA and fPSA, proPSA	Immunoassay, 4 kallikreins biomarkers,: PSA, fPSA, intact PSA, HK-2	qPCR, mRNA test, 1 biomarker: PCA3	qPCR, 2 mRNA biomarkers: DLX1, HOXC6
Regulatory	FDA/CE	LDT/CLIA/CE	FD/CE	LDT/CLIA/CE
List Price ($)	499	1900	500	500
Assay Performance	AUC 0.73	AUC 0.82	AUC 0.68	AUC 0.89

* After digital rectal examination.
Secondary molecular tests that may be used to refine the specificity of screening to detect high-risk prostate cancer.

Obesity-Related Plasma Hemodilution and PSA Concentration Among Men With Prostate Cancer

Table 2. Plasma Volume, PSA Concentration, and PSA Mass by BMI Category

		BMI Category[a]				*P* for Trend
	Study Cohort	<25.0	25.0-29.9	30.0-34.9	≥35.0	
Plasma volume, mean (SD), L	SEARCH	3.16 (0.22)	3.40 (0.23)	3.67 (0.23)	3.87 (0.28)	<.001
	Duke	3.18 (0.22)	3.40 (0.23)	3.61 (0.25)	3.87 (0.34)	<.001
	Johns Hopkins	3.22 (0.20)	3.44 (0.21)	3.66 (0.22)	3.88 (0.28)	<.001
Adjusted PSA concentration, mean (SE), ng/mL[b]	SEARCH	7.82 (0.25)	7.17 (0.18)	7.17 (0.27)	6.15 (0.34)	.001
	Duke	6.64 (0.23)	6.67 (0.15)	5.93 (0.21)	5.27 (0.33)	<.001
	Johns Hopkins	5.90 (0.07)	5.86 (0.05)	5.72 (0.10)	5.27 (0.24)	.02
Mean adjusted PSA mass, mean (SE), μg[b]	SEARCH	24.72 (0.77)	23.92 (0.57)	26.17 (0.90)	23.68 (1.29)	.76
	Duke	21.15 (0.70)	22.63 (0.51)	21.25 (0.74)	20.50 (1.25)	.50
	Johns Hopkins	19.02 (0.22)	20.13 (0.17)	20.84 (0.35)	20.30 (0.91)	<.001

Abbreviations: BMI, body mass index; PSA, prostate-specific antigen; SEARCH, Shared Equal Access Research Cancer Hospital.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Mean PSA concentration and mean PSA mass were adjusted for age, race, year of surgery, SEARCH site, prostate specimen weight, pathological Gleason sum, extracapsular extension, positive surgical margins, and seminal vesicle invasion.

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New PSA normal values adjusted by age, benign prostatic hyperplasia and body weight: development of a simplified online calculator

Stone NN and Crawford ED

- Health screening to 14,859 men during 2011-13 Prostate Cancer Awareness Weeks
- Responses from a questionnaire about age, race, fat intake (FI-low, medium, high), history of BPH, diabetes (AODM), amount exercised (Ex-less or more than 2x/week), weight (Wt-normal-1, overweight under 20 lbs-2 and > 20 lbs-3) were analyze

Results

- The mean and median PSAs were 2.72 and 1.10 ng/ml.
- 7.3% and 1.6% has a PSA > 4.0 and > 10.0
- For men with PSA < 10
- (91.1%) the mean and median PSA was 1.60 and 1.08, respectively.

Age Group (years)	N	Mean (ng/ml)	Std. Deviation	Mean + 2SD (ng/ml)	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
<40	152	.93082	.896789	2.73	.78710	1.07453	.150	7.050
≥40-50	1276	.94207	.876914	2.70	.89391	.99023	.010	8.230
≥50-60	3397	1.28198	1.254534	3.79	1.23978	1.32418	.000	9.390
≥60-70	4448	1.72118	1.520681	4.76	1.67648	1.76588	.010	9.950
≥70-80	2357	2.06156	1.744124	5.55	1.99111	2.13200	.010	9.730
≥80	490	2.43102	1.985377	6.40	2.25479	2.60725	.020	10.000
Total	12120	1.60104	1.511690	4.62	1.57412	1.62795	.000	10.000
P<0.001								

Race	N	Mean	Std. Deviation	Mean+2SD	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Caucasian	8997	1.63672	1.520780	4.68	1.60529	1.66814	.000	10.040
African American	2210	1.50842	1.511331	4.53	1.44538	1.57146	.010	10.000
Hispanic	639	1.42364	1.389955	4.20	1.31567	1.53162	.010	10.070
Asian	321	1.82614	1.847051	5.52	1.62331	2.02896	.200	9.410
Native American	56	1.14250	.910782	2.97	.89859	1.38641	.180	5.200
Native Alaskan	6	1.54333	1.463184	4.47	.00782	3.07885	.150	3.690
Hawaiian	15	2.81267	2.881828	8.57	1.21676	4.40857	.160	8.200
Other	95	1.73718	1.640285	5.02	1.40304	2.07132	.070	9.400
Total	12339	1.60754	1.525250	4.66	1.58063	1.63446	.000	10.070
P<0.001								

Fat in Diet	N	Mean	Std. Deviation	Mean+2SD	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Low	2897	1.73170	1.614810	4.96	1.67288	1.79053	.010	10.000
Median	8668	1.59206	1.515538	4.63	1.56015	1.62397	.000	10.040
High	742	1.37448	1.364535	4.10	1.27614	1.47282	.040	10.070
Total	12307	1.61182	1.533127	4.67	1.58473	1.63890	.000	10.070
P<0.001								

Exercise	N	Mean	Std. Deviation	Mean+2SD	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
≤1x/week	4577	1.50623	1.459080	4.43	1.46395	1.54851	.000	10.040
≥2x/week	7498	1.67295	1.568794	4.81	1.63744	1.70847	.010	10.070
Total	12075	1.60976	1.530213	4.67	1.58246	1.63705	.000	10.070
P<0.001								

Overweight	N	Mean	Std. Deviation	Mean+2SD	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
No	5701	1.71719	1.611901	4.94	1.67534	1.75904	.000	10.040
<20lbs	3593	1.59682	1.513129	4.62	1.54733	1.64631	.010	10.070
>20lbs	2825	1.42930	1.381232	4.19	1.37834	1.48026	.010	10.000
Total	12119	1.61439	1.535726	4.69	1.58705	1.64174	.000	10.070
P<0.001								

Prostatitis	N	Mean	Std. Deviation	Meam+2SD	95% Confidence Interval for Mean		Minimum	Maximum	Between-Component Variance
					Lower Bound	Upper Bound			
No	11768	1.59453	1.519006	4.63	1.56708	1.62197	.000	10.070	
Yes	687	1.87953	1.713228	5.30	1.75119	2.00787	.040	10.020	
Total	12455	1.61025	1.531668	4.66	1.58334	1.63715	.000	10.070	
P<0.001									

BPH	N	Mean	Std. Deviation	Mean+2SD	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
No	9496	1.42574	1.341095	4.11	1.39877	1.45272	.000	10.070
Yes	2959	2.20236	1.908969	6.02	2.13354	2.27117	.010	10.040
Total	12455	1.61025	1.531668	4.67	1.58334	1.63715	.000	10.070
P<0.001								

Model	Hazard Rate	P Value	95.0% Confidence Interval for B	
			Lower Bound	Upper Bound
Age	.216	.000	.029	.034
Race	.038	.000	.032	.088
Fat in Diet	-.014	.138	-.094	.013
Exercise Frequency	.006	.523	-.038	.075
Overweight	-.050	.000	-.130	-.061
Prostate infection	.004	.625	-.086	.143
BPH	.165	.000	.522	.650

- These analysis were used to create an online calculator that includes age, race, presence of BPH, and 3 weight categories (http://centerforprostatecancer.org/calculators/psacalculator/startScreen.html).
- The calculator gives PSA with 95%CI. As an example, a 55 y/o white male without BPH and normal weight should have a PSA of 1.28 ng/ml (1.0-1.56), a 65 y/o black male with BPH and 20 lbs overweight should have a PSA of 1.89 ng/ml and a 72 y/o white male, normal weight with BPH should have a PSA of 2.46 ng/ml (2.09-2.83).
- An updated population based analysis of screening PSA values demonstrate 9% of the population at increased risk for prostate cancer because of an elevated PSA. BPH increases mean PSA by an average of 39.8% (range 31.5-52.3) while overweight by more than 20 lbs decrease it by 17%. The online calculator could improve patient selection for further evaluation.

Conclusions

- A simple cut off for PSA of 4.0 ng/ml is not ideal to discriminate between those with or without risk for prostate cancer
- Both PHI and 4Kscore add marginal benefit when deciding to re-biopsy an at-risk patient-AUC 80%
- The message to PCPs for men with PSA> 1.5 is valuable and can reduce screening frequency
- The lifestyle/demographic approach using weight status, BPH presence, age and race warrants investigation to further refine who to biopsy