In Support of PSA Screening

"*The Great Debate*"

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Criteria of a Screening Program

- The Disorder
- The Test
- The Treatment
- The Screening Program

Criteria of a Screening Program

- **The Disorder -Prostate Cancer**
- The Test
- The Treatment
- The Screening Program

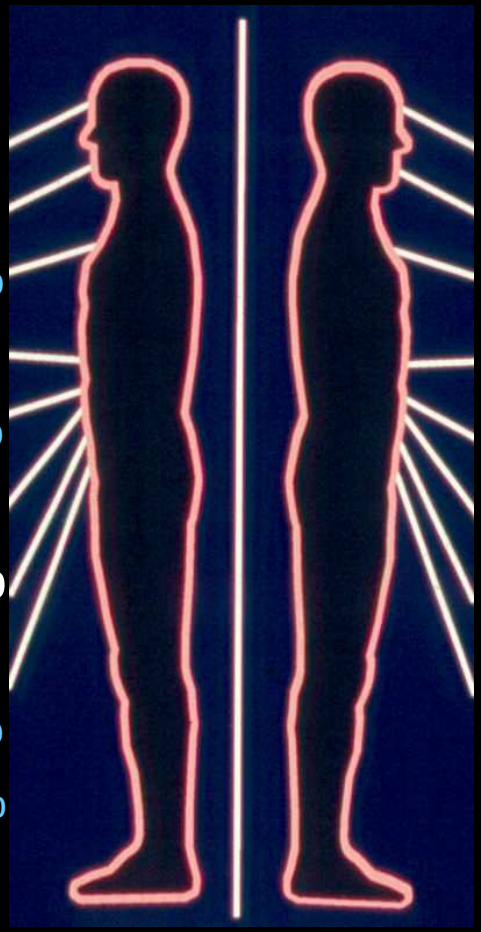
PROSTATE CANCER

Highest in Incidence and Second in Cause of Death from Cancer in American Males

Incidence

Melanoma of Skin	5%
Oral Cavity & Pharynx	3%
Lung & Bronchus	14%
Pancreas	2%
Colon & Rectum	11%
Kidney	3%
Prostate	**30%**
Urinary Bladder	7%
Leukemia	3%
Non-Hodgkin's Lymphoma	4%
All Sites	637,500

189,000 New Cases



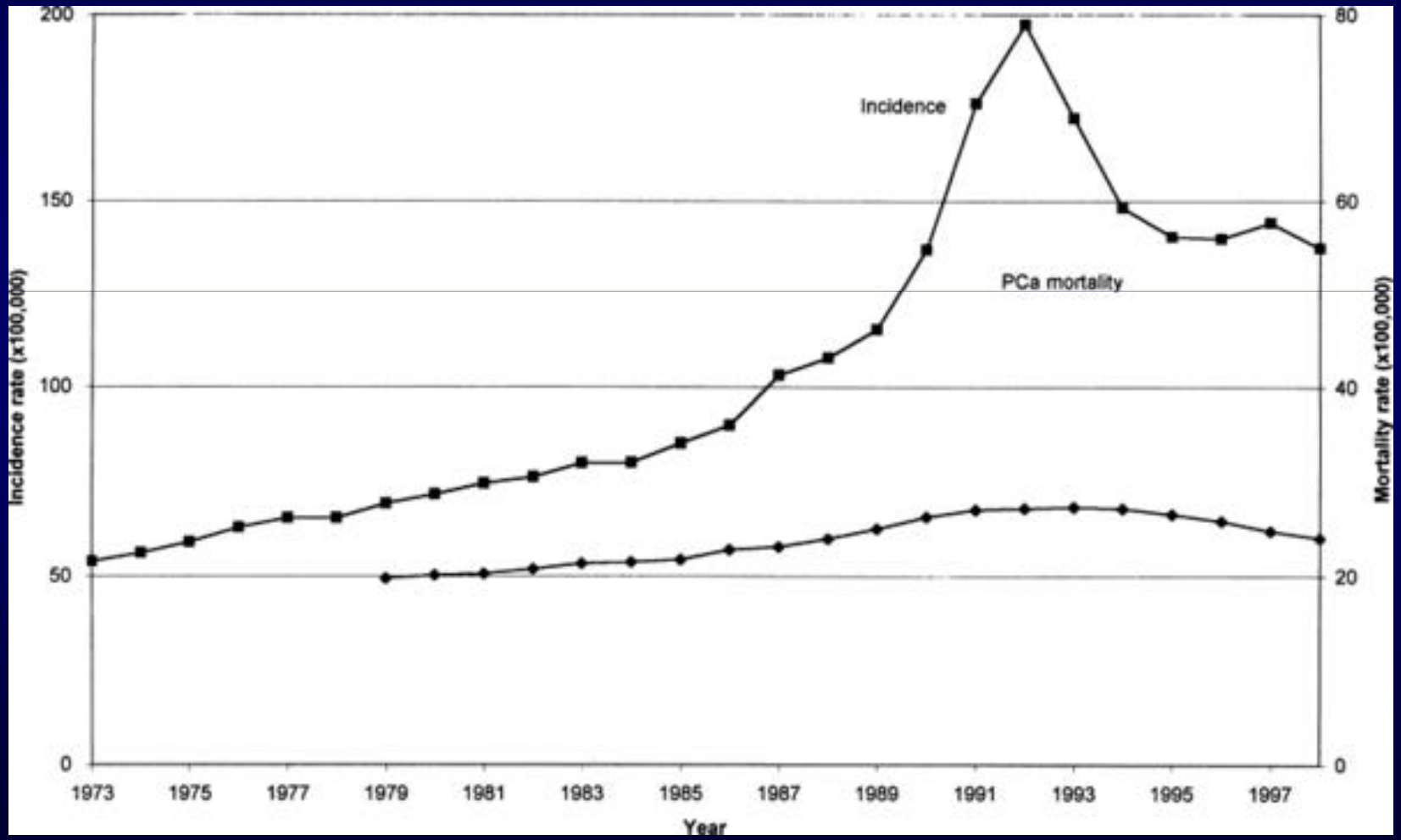
2002 Estimates

Cause of Death

3%	Esophagus
31%	Lung & Bronchus
5%	Pancreas
3%	Kidney
3%	Liver
10%	Colon & Rectum
11%	**Prostate**
3%	Urinary Bladder
4%	Leukemia
5%	Non-Hodgkin's Lymphoma
288,200	All Sites

30,200 Death

U.S. Incidence and Mortality of Prostate Cancer



Surveillance, Epidemiology and End Results (SEER) Data

Criteria of a Screening Test

The Disorder

"Prostate Cancer"

- Natural history understood:

  -To die of prostate cancer or die with prostate cancer?

  -Conservative Treatment:

  a.) Gleason 2-4: 4-7% chance of death
  b.) Gleason 6: 18-30% chance of death
  c.) Gleason 8-10: 60-80% chance of death**

Frankel et al. Lancet, 361: 1122, March 2003
****Albertsen et al., JAMA, 280: 975, 1998**

Lifetime Risk of Developing or Dying of Prostate Cancer for a 50-Year-Old Man in the United States

Lifetime Risk of	Risk	Risk Ratio	Proportional Risk
Developing histologic cancer	42 %	11.7	100
Developing clinical cancer	16 %	4	38
Dying of prostate cancer	3.6 %	1	8.6

Modified from Scardino PT. Urol Clin N Am 1989 and Hum Path 1992; and from CA Cancer J Clin Jan-Feb, 2000.

Criteria of a Screening Program

- The Disorder
- **The Test**
- The Treatment
- The Screening Program

Criteria of a Screening Test

The Test

- Simple, safe and precise
- Distribution in target population should be known
- Appropriate cut-offs and age defined ranges
- Test should be acceptable to the population

  Diagnostic tests performed when a positive test is found should be agreed upon

Criteria of a Screening Test

The Test

"DRE and PSA"

TABLE II. *Ratio between the biopsies taken and the carcinomas detected (the Bx/PC) for each of the screening modalities, or the four possible combinations*

	No. biopsies	No. PC	Bx/PC
TRUS alone	53	2	26.5
DRE alone	29	3	9.7
PSA alone	126	22	5.7
TRUS + DRE	48	7	6.9
TRUS + PSA	11	4	2.8
DRE + PSA	11	6	1.8
TRUS + DRE + PSA	30	23	1.3
Total	308	67	4.6

KEY: Bx = biopsy; DRE = digital rectal examination; PC = prostate cancer; TRUS = transrectal ultrasonography.

Bangma et al., Urology, 46(6): 773, 1995

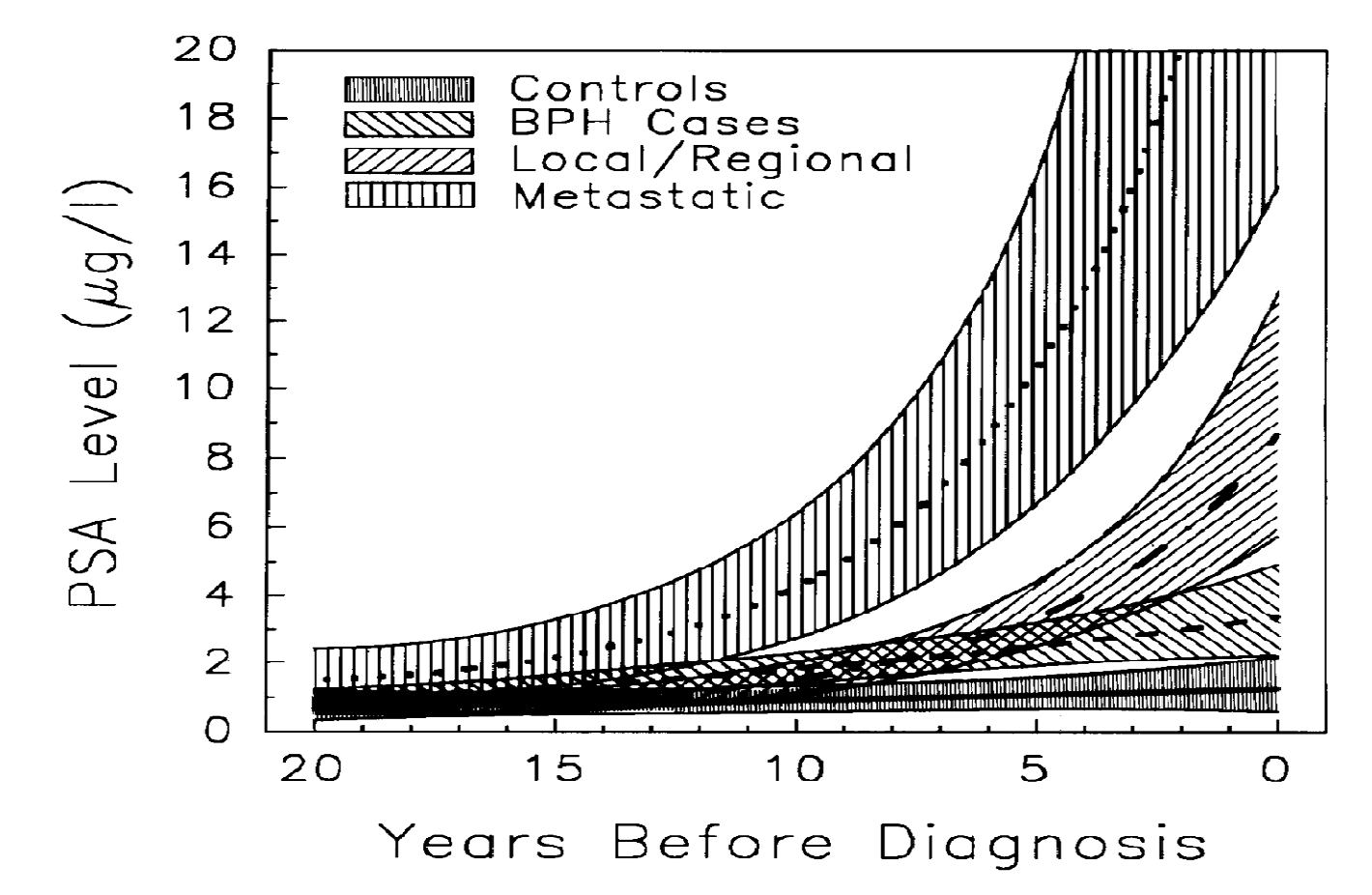
Rate of Detection of Prostate Cancer by Needle Biopsy

Positive Predictive Value of DRE and PSA (n=6630)

	PSA (ng/ml)			
	0-2	2-4	4-10	>10
DRE-	1%	15%	25%	>50%
DRE+	5%	20%	45%	>75%

Modified from Catalona et al: J Urol 1994: 151:1283.

Serum PSA Levels Rise Prior to the Development of Significant Cancer



From Carter HB et al. JAMA 267:2215,1992

Criteria of a Screening Test

The Test

"DRE and PSA"

AUA Best Practice Policy

- PSA detects more tumors than does DRE and it detects them earlier
- Most Sensitive method uses both DRE and PSA

PSA Best Practice Policy, Oncology, 14(2), Feb. 2000

Sensitivity/Specificity of PSA

- Sensitivity: 67.5-80%

  (20-30% tumors will be missed if PSA<4.0 ng/ml used)

  Ways to Improve Sensitivity:

  a.) age-adjusted PSA
  b.) PSA velocity

- Specificity: 60-70% (if PSA>4.0 ng/ml)

  (only ¼ prostate biopsies reveal CaP)

  Ways to Improve Specificity:

  a.) Age adjustment
  b.) Free-to-total PSA
  c.) PSA density

Improvements on PSA

- **Age-adjusted PSA**
- **Free-to-Total PSA (14-28%)**
- **PSA Velocity (>0.75ng/ml/yr)**

Age	PSA Cutoff (ng/ml)
<40-50	2.5
50-60	3.5
60-70	4.5
>70	6.5

Criteria of a Screening Program

- The Disorder
- The Test
- **The Treatment**
- The Screening Program

Criteria of a Screening Test
"The Treatment"

- Watchful Waiting
- Hormonal Deprivation Therapy
- Radiation Therapy
- Radical Prostatectomy

Criteria of a Screening Program

- The Disorder
- The Test
- **The Treatment**
- The Screening Program

Policies of Prostate Cancer Screening

Group	Policy Statement	Recommendations
AUA	**Screen annually at age 50**	**Take personal decision after consultation**
ACS	**Screen annually at age 50**	**Provide risk and benefit information**
AMA	Mass screening is premature	Allow “well informed” decision
ACP	Routine PSA is “inappropriate”	Counsel patient
EU	Introduction as policy is premature	Provide risk and benefit, await randomized trials

Evidence for the Effectiveness of Screening

- PSA screening initiated in 1989
- A **decrease** in prostate cancer mortality has been demonstrated in the U.S. by 4.4%/year from 1994-97
- Total decrease in mortality of 17.6%

Controversies in Screening

- Decline in mortality since 1989 is too rapid given the indolent natural history of prostate cancer
- Improvements in locally advanced disease could explain decline in mortality
- Decline in mortality has been seen in countries where screening is not prevalent

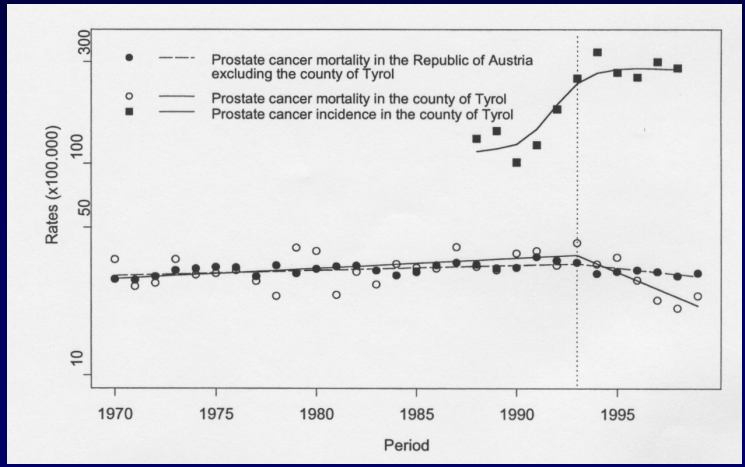
Quebec City Screening Study

- November 1988-Decmeber 1996
- 46,193 men randomized
  screening vs. non-screening
- Screening Group: 8,137 were screened
- Relative risk of dying of CaP was 3.7 times higher in the control group
- 69% reduction in mortality with screening

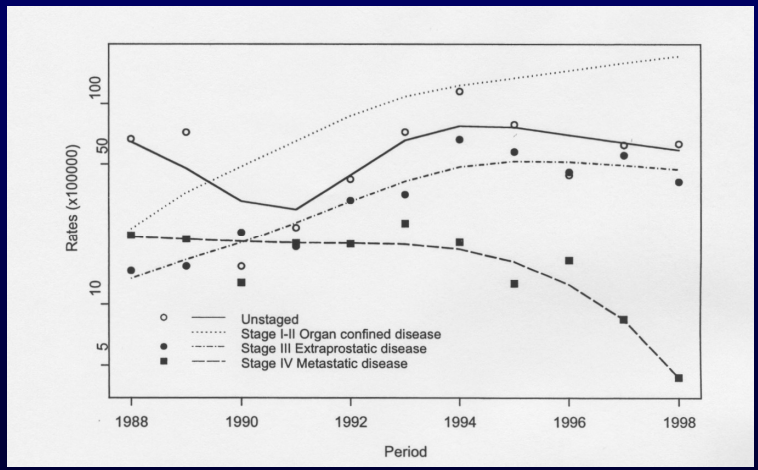
Labrie et al., Prostate, 38(2): 83-91, 1999

Tyrol Prostate Cancer Screening Group

- 1993-1998, PSA screening offered to 65,123 men in Tyrol, Austria



Mortality Rates



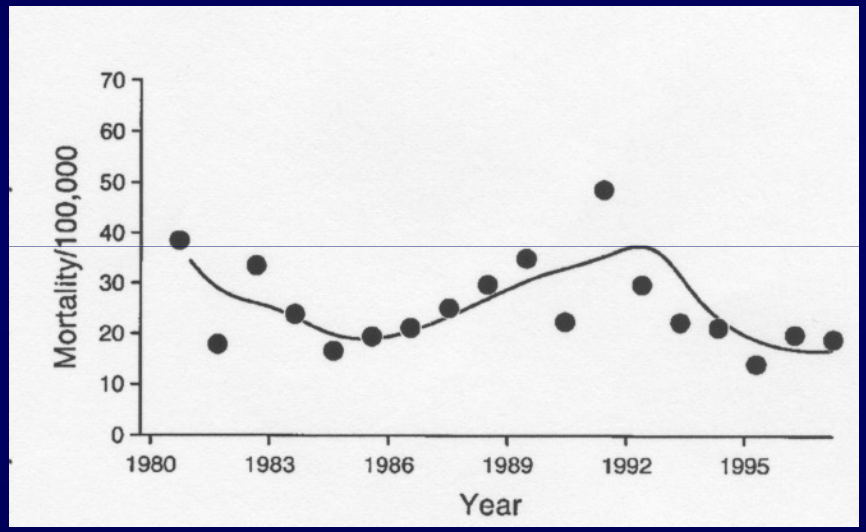
Incidence by Stage

Bartsch et al., Urology, 58(3): 417-24, 2001

Olmstead County Screening Trial

- Retrospective analysis of death record between 1980-1997

- Decline in mortality of 22% between the earliest and most recent time periods



Trends in Prostate Cancer Mortality

Roberts et al., J Urol, 161: 529, 1999

Cost Effectiveness of PSA Screening

Intervention	Cost Per Quality-Adjusted Life-Year Gained
Liver Transplantation	$237,000
Screening Mammography (age <50)	$232,000
Worst Case – CaP Screening	**$145,000**
CABG-2 vessels (angina)	$106,600
Captopril for HTN	$82,600
HCTZ for HTN	$23,500
Best Case- CaP Screening	**$8,700**
Stop Smoking-MD Message	$1,300

Thompson et al., Oncology, 9: 141-5, 1995

Breast Cancer vs. Prostate Cancer

	PROSTATE CA	Breast cancer
New Cases/Yr.	184,500	180,300
Deaths/Yr.	39,200	43,900
Deaths/Cases	21%	24%
Lifetime risk of Developing	17%	14%
Mets at Diagnosis	9%	6%
Mortality Rate Trend (22 yr.)	+ 17%	- 3%
5 Yr. Relative Survival Rate	93%	85%
Median Age at Diagnosis	71 yr	64 yr
Median Age at Death	77 yr	68 yr

Issues to Address

- Does PSA screening of asymptomatic men reduce mortality from prostate cancer?
- Should PSA screening of the general population be routine practice?
- How should the effectiveness of PSA screening in the population be measured?
- Who should be screened? Different for high risk groups?
- What are the side effects of screening?

Does PSA screening reduce mortality?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D., Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D., Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D., Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S., Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D., Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D., Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., and Christine D. Berg, M.D., for the PLCO Project Team*

N ENGL J MED 360;13 NEJM.ORG MARCH 26, 2009

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial
- Prostate component: designed to determine effect of annual PSA and DRE on mortality from CaP
- 4 prior publications
  - Design: Prorok et al, *Control Clin Trials* 2000
  - Prelim: Andriole et al and Grubb et al, *J Natl Cancer Inst* 2005, *BJU Int* 2008
  - Biopsy results: *J Urol* 2005

Study Design

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- From 1993 – 2001
- Age: 55-74 yrs
- 76,693 men
  - 38,343 annual PSA screening
  - 38,350 usual care (control)
- 10 study centers (U.S.)
- Primary exclusion criteria
  - History of PLCO cancer
  - Current cancer treatment
  - Beginning in 1995, > 1 PSA test in previous 3 yrs

Study Design

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- Screening Group
  - Annual PSA for 6 yrs, DRE 4 yrs
  - All tests performed at single lab
  - PSA > 4.0 ng/mL considered positive
- Control Group
  - Usual care (in some cases included PSA)

Study Design

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- Primary endpoint: cause-specific mortality
- Secondary endpoints
  - PLCO cancer incidence
  - Staging, survival
- Independent panel reviewed all deaths
- Primary statistical analysis
  - Intention-to-screen comparison of prostate cancer mortality between the 2 groups

Study Design

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- Event rates (ratio of # events : person-yrs)
  - Events: cancer diagnosis and mortality
- Confidence intervals for rate ratios
- Independent safety panel, q6mos
- November 2008
  - Unanimously recommended that the current results be reported
  - Due to lack of benefit after 7-10 yrs f/u

Results

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Table 1. Characteristics of the Subjects at Baseline.*

Variable	Screening Group (N = 38,343)	Control Group (N = 38,350)
	percent	
Age		
55–59 yr	32.3	32.3
60–64 yr	31.3	31.3
65–69 yr	23.2	23.2
70–74 yr	13.2	13.2
Race or ethnic group†		
Non-Hispanic white	86.2	83.8
Non-Hispanic black	4.5	4.3
Hispanic	2.1	2.1
Asian	4.0	3.9
Other	0.8	0.9
Missing data	2.4	5.0
Enlarged prostate or benign prostatic hyperplasia	21.4	20.5
Previous prostate biopsy	4.3	4.3
Family history of prostate cancer	7.1	6.7
PSA test within past 3 yr		
Once	34.6	34.3
Two or more times	9.4	9.8
Digital rectal examination within past 3 yr		
Once	32.8	31.9
Two or more times	22.2	22.0

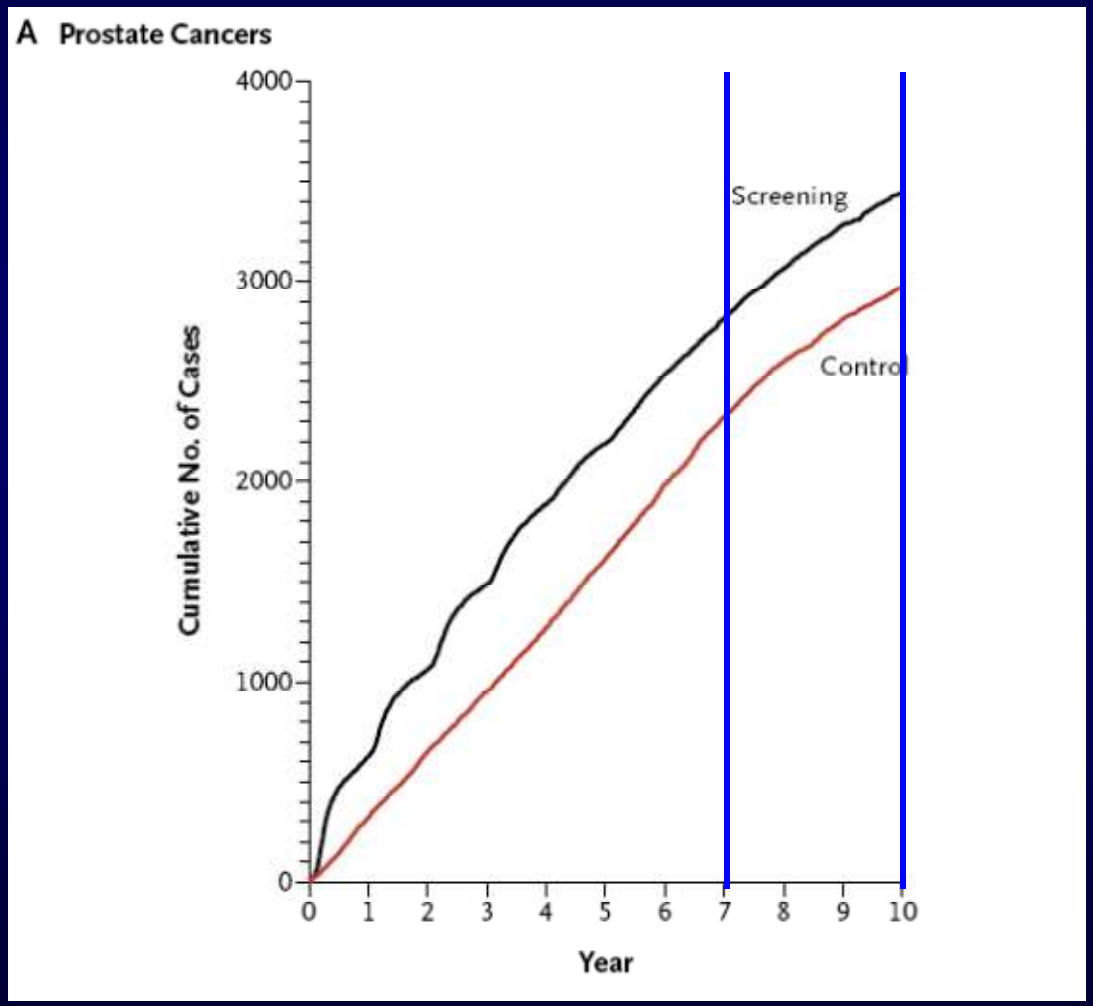
Results

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- Median f/u: 11.5 yrs
- 7 yrs (vital stats known for 98%)
- 10 yrs (vital stats for 67%)
- Compliance
  - 85% PSA, 86% DRE
- Control group
  - Rate of PSA testing (contamination): 52% by 6th yr (40% in 1st yr)
  - Rate of DRE 41-46%

Results

Mortality Results from a Randomized Prostate-Cancer Screening Trial



- 7 years
  - 2 yrs after screening stopped
  - Screen: 2820 cancers
  - Control: 2322
  - Rate ratio: 1.22, CI 1.16 – 1.29
- 10 years
  - Screen: 3452
  - Control: 2974
  - RR: 1.17, CI 1.11 – 1.22

Results

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Table 2. Tumor Stage, Histopathological Type, and Gleason Score for All Prostate Cancers at 10 Years, According to Method of Detection and Time of Diagnosis.*

Variable	Screening Group					Control Group	
	According to Method of Detection					All Subjects (N=3452)	All Subjects (N=2974)
	Never Screened (N=154)	*After Screening (N=875)*	*Outside of Screening Protocol (N=374)*	*Screen Detected at Baseline (N=549)*	*Screen Detected at Yr 1–Yr 5 (N=1500)*		
	number (percent)						
Clinical stage							
I	1 (0.6)	5 (0.6)	8 (2.1)	2 (0.4)	2 (0.1)	18 (0.5)	15 (0.5)
II	138 (89.6)	838 (95.8)	347 (92.8)	516 (94.0)	1458 (97.2)	3297 (95.5)	2790 (93.8)
III	5 (3.2)	7 (0.8)	3 (0.8)	12 (2.2)	22 (1.5)	49 (1.4)	56 (1.9)
IV	10 (6.5)	20 (2.3)	9 (2.4)	19 (3.5)	15 (1.0)	73 (2.1)	79 (2.7)
Unknown	0	5 (0.6)	7 (1.9)	0	3 (0.2)	15 (0.4)	34 (1.1)
Histopathological type							
Adenocarcinoma							
Any	144 (93.5)	824 (94.2)	346 (92.5)	511 (93.1)	1375 (91.7)	3200 (92.7)	2802 (94.2)
Acinar	9 (5.8)	48 (5.5)	25 (6.7)	36 (6.6)	124 (8.3)	242 (7.0)	158 (5.3)
Other	1 (0.6)	3 (0.3)	3 (0.8)	2 (0.4)	1 (0.1)	10 (0.3)	14 (0.5)
Gleason score on biopsy†							
2–4	11 (7.1)	1.7 (1.9)	36 (9.6)	64 (11.7)	94 (6.3)	222 (6.4)	137 (4.6)
5–6	78 (50.6)	500 (57.1)	228 (61.0)	278 (50.6)	963 (64.2)	2047 (59.3)	1656 (55.7)
7	39 (25.3)	252 (28.8)	74 (19.8)	132 (24.0)	318 (21.2)	815 (23.6)	779 (26.2)
8–10	16 (10.4)	95 (10.9)	25 (6.7)	55 (10.0)	98 (6.5)	289 (8.4)	341 (11.5)
Unknown	10 (6.5)	11 (1.3)	11 (2.9)	20 (3.6)	27 (1.8)	79 (2.3)	61 (2.1)

Treatment

Mortality Results from a Randomized Prostate-Cancer Screening Trial

	Screen	Control
Stage II		
RP	44%	40%
XRT	22%	21%
XRT + ADT	18%	21%
Stage III		
XRT	24%	16%
XRT + ADT	47%	52%

Results

Mortality Results from a Randomized Prostate-Cancer Screening Trial

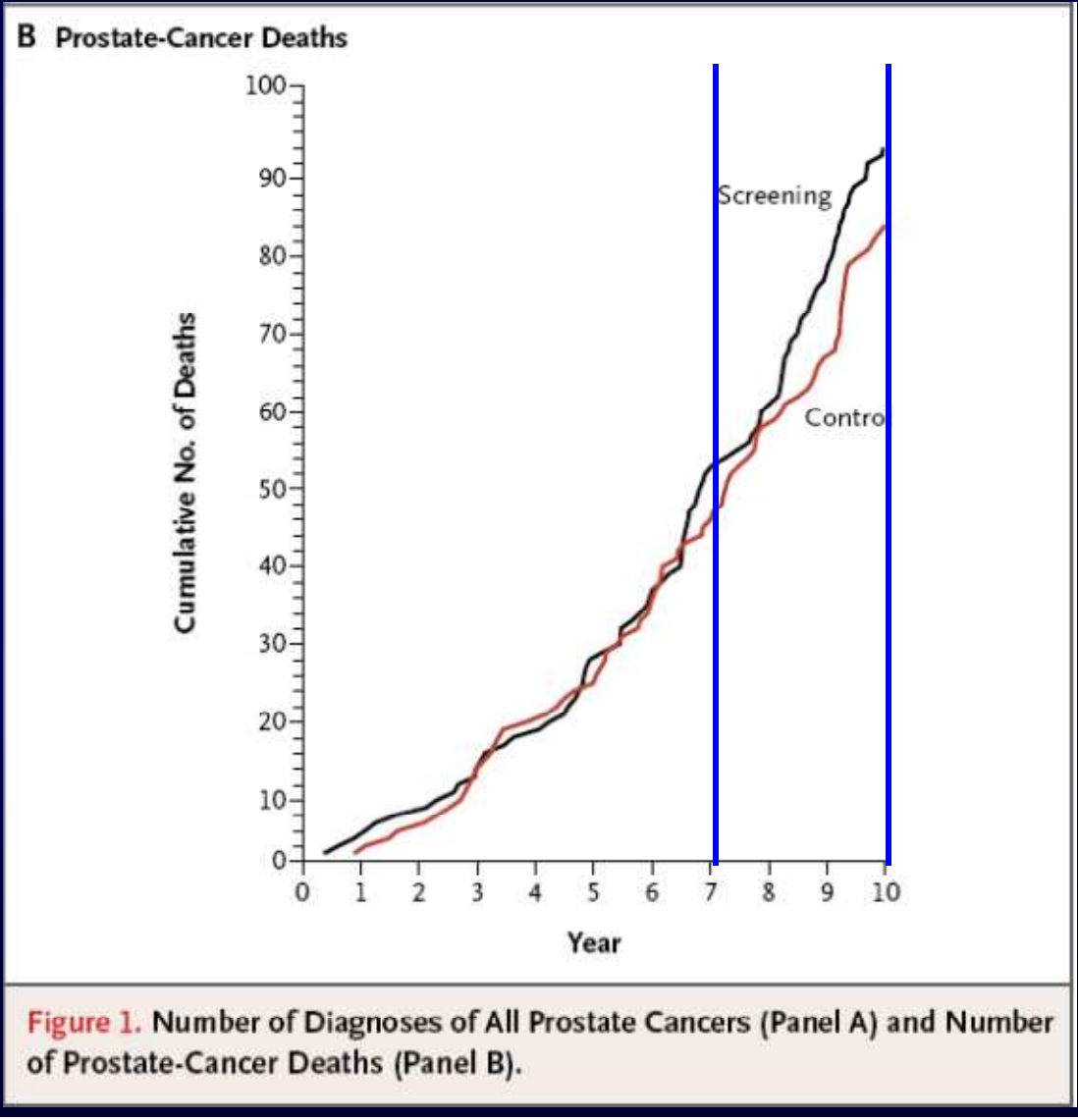


Figure 1. Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B).

- 7 years
  - Screen: 50 deaths
  - Control: 44
  - RR 1.13, CI 0.75 – 1.70
- 10 years
  - Screen: 92 deaths
  - Control: 82
  - RR: 1.11, CI 0.83 – 1.50
- No difference in stage at death

Results

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Table 3. Death Rates from Prostate Cancer per 10,000 Person-Years at 10 Years. *

Variable	Years after Randomization									
	1	2	3	4	5	6	7	8	9	10
Screening group										
Cumulative deaths — no.	3	6	12	16	26	35	50	59	76	92
Cumulative person-yr — no.	37,864	75,292	112,234	148,635	184,490	219,752	254,295	287,196	316,244	340,230
Death rate	0.8	0.8	1.1	1.1	1.4	1.6	2.0	2.1	2.4	2.7
Control group										
Cumulative deaths — no.	1	4	12	18	23	34	44	56	65	82
Cumulative person-yr — no.	37,838	75,231	112,123	148,444	184,154	219,135	253,317	285,777	314,463	338,083
Death rate	0.3	0.5	1.1	1.2	1.2	1.6	1.7	2.0	2.1	2.4
Rate ratio (95% CI)	3.00 (0.31–28.82)	1.50 (0.42–5.31)	1.00 (0.45–2.22)	0.89 (0.45–1.74)	1.13 (0.64–1.98)	1.03 (0.64–1.65)	1.13 (0.75–1.70)	1.05 (0.73–1.51)	1.16 (0.83–1.62)	1.11 (0.83–1.50)

Discussion

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- PSA screening: 22% increase in rate of CaP diagnosis (at 7yrs)
- At 7 and 10 yrs, death rate from CaP was very low
- Screening was associated with no reduction in CaP mortality

Problems

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- PSA < 4.0 threshold
- Contamination
  - 52% control group was screened with PSA
- Baseline PSAs
  - 44% pts in both groups had undergone 1 or more PSA tests at baseline
- Follow-up too short
- Improved treatment
  - Fewer deaths in both groups, blunting effect of screening

Future

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- Follow-up of at least 13 yrs is planned
- Effect of screening on quality of life
  - Incontinence
  - Sexual dysfunction

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

Screening and Prostate-Cancer Mortality in a Randomized European Study

- European Randomized Study of Screening for Prostate Cancer (ERSPC)
- Begun in early 1990s
- Ages 50-74 yrs
  - Core age 55-69 yrs
- 7 European countries
- 182,000 men
  - Randomized into screened and control groups
  - Core age group 162,387

Study Design

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Study Design

Screening and Prostate-Cancer Mortality in a Randomized European Study

- All centers except Finland (n=80,379), subjects were randomized in 1:1 ratio
- Independent international committee reviewed all deaths
- Most centers used PSA cutoff of 3.0 ng/mL
  - Finland: used 4.0, those in 3-3.9 range used ratio of fPSA:total (≤ 0.16)
  - Italy: used 4.0, those in 2.5-3.9 had DRE and TRUS

Study Design

Screening and Prostate-Cancer Mortality in a Randomized European Study

- PSA cutoff
  - Belgium: PSA < 10 until 1995
- TRUS/Bx
  - Most used sextant biopsies
  - Finland: 10-12 cores beginning in 2002
- Screening interval
  - 4 yrs (6/7 centers, 87% subjects)
  - 2 yrs Sweden
  - 7 yrs Belgium (due to interruption of funding)

Study Design

Screening and Prostate-Cancer Mortality in a Randomized European Study

- No central pathologic review for biopsies
- Trea ntly differ

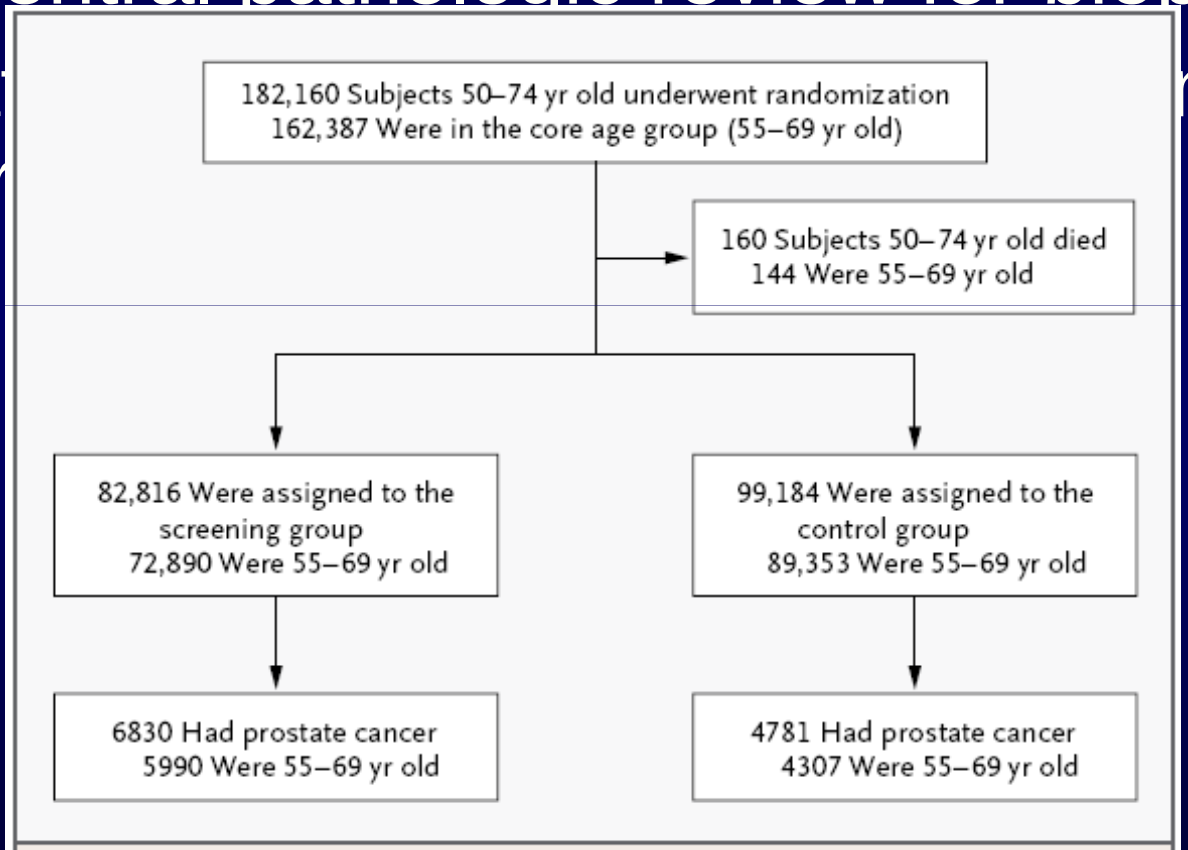


Figure 1. Enrollment and Outcomes, According to Age Group at Randomization.
The predefined core age group for this study included 162,243 men between the ages of 55 and 69 years.

Study Design

Screening and Prostate-Cancer Mortality in a Randomized European Study

- Analysis was based on the core age group and intention-to-screen
- Study had a power of 86% to detect a difference of 25% or more on CaP mortality with a P-value of 0.05
- Contamination of control group: 20%
- Compliance: 82%

Results

Screening and Prostate-Cancer Mortality in a Randomized European Study

Table 1. Numbers of Subjects and Results of Screening, According to Study Center.*

Variable	The Netherlands	Belgium	Sweden	Finland	Italy	Spain	Switzerland	Total
	November 1993–March 2000	June 1991–December 2003	June 1991–December 2003	January 1996–January 1999	October 1996–October 2000	February 1996–June 1999	September 1998–August 2003	June 1991–December 2003
Total no. of subjects	34,833	8562	11,852	80,379	14,517	2197	9903	162,243
Screening group — no. (%)	17,443 (50.1)	4307 (50.3)	5,901 (49.9)	31,970 (39.8)	7,265 (50.0)	1056 (48.1)	4948 (50.0)	72,890 (44.9)
Control group — no. (%)	17,390 (49.9)	4255 (49.7)	5,951 (50.1)	48,409 (60.2)	7,252 (50.0)	1141 (51.9)	4955 (50.0)	89,353 (55.1)
Age at randomization — yr								
All subjects								
Mean	61.9	63.0	59.8	59.6	62.2	61.0	61.6	60.8
Median	61.7	63.0	59.7	58.7	61.8	60.4	61.1	60.1
Screening group								
Mean	61.9	63.0	59.8	59.6	62.2	60.5	61.6	60.9
Median	61.7	63.0	59.7	58.7	61.7	59.7	61.0	60.3
Control group								
Mean	62.0	63.0	59.8	59.6	62.2	61.4	61.7	60.7
Median	61.7	63.1	59.7	58.7	61.9	61.1	61.2	59.9
First round of screening — no. (%)	16,502 (94.6)	3795 (88.1)	3,649 (61.8)	20,796 (65.0)	4,961 (68.3)	1056 (100)	4721 (95.4)	55,480 (76.1)
Screening interval — yr	4	4–7	2	4	4	4	4	NA
Screened at least once — no. (%)	16,502 (94.6)	3876 (90.0)	4,466 (75.7)	23,608 (73.8)	5,675 (78.1)	1056 (100)	4740 (95.8)	59,923 (82.2)
No. of screening tests performed	34,526	6042	14,848	48,900	11,377	1846	8923	126,462
Positive PSA tests — no. (%)	7,707 (22.3)	984 (16.3)	2,751 (18.5)	5,528 (11.3)	1,267 (11.1)	354 (19.2)	1846 (20.7)	20,437 (16.2)
Biopsies — no. (%)	6,929 (89.9)	728 (74.0)	2,382 (86.6)	4,991 (90.3)	828 (65.4)	263 (74.3)	1422 (77.0)	17,543 (85.8)
Prostate cancers								
Total detected in screening group — no. (%)	1,736 (10.0)	363 (8.4)	697 (11.8)	2,493 (7.8)	280 (3.9)	68 (6.4)	353 (7.1)	5,990 (8.2)
Detected during screening — no.	1,521	182	550	1,477	180	60	265	4,235
Detected outside of screening protocol — no.	215	181	147	1,016	100	8	88	1,755
Positive predictive value of screening — %†	22.0	25.0	23.1	29.6	21.7	22.8	18.6	24.1
Total detected in control group — no. (%)	685 (3.9)	252 (5.9)	421 (7.1)	2,632 (5.4)	133 (1.8)	24 (2.1)	160 (3.2)	4,307 (4.8)

Results

Screening and Prostate-Cancer Mortality in a Randomized European Study

- 126,462 PSA tests performed
  - Average of 2.1 per subject screened
- False-positive rate (based on bx): 76%
- Biopsy results
  - Gleason 6 or less
    - Screened: 72%
    - Control: 55%
  - Gleason 7 or more
    - Screened: 28%
    - Control: 45%

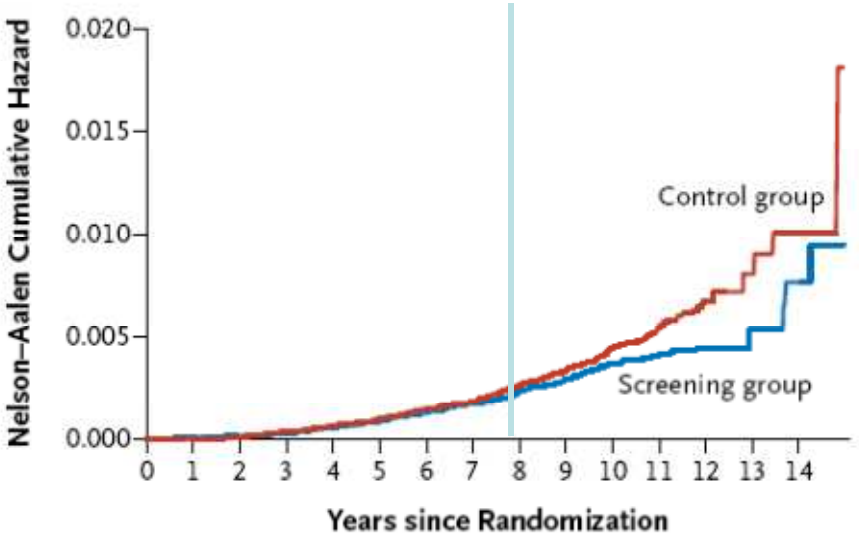
Results

Screening and Prostate-Cancer Mortality in a Randomized European Study

- Median f/u: 8.8 yrs
- Deaths from CaP
  - Screened: 214
  - Control: 326
- Absolute difference b/w screened and control group: 0.71 CaP deaths per 1000 men
- 20% reduction in CaP deaths in screened group
- To prevent 1 CaP death
  - 1410 men would need to be screened
  - 48 men would need to be treated

Results

Screening and Prostate-Cancer Mortality in a Randomized European Study



No. at Risk

Screening group	65,078	58,902	20,288
Control group	80,101	73,534	23,758

Figure 2. Cumulative Risk of Death from Prostate Cancer.

As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. Deaths that were associated with interventions were categorized as being due to prostate cancer. The adjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95% CI, 0.65 to 0.98; P=0.04). The Nelsen–Aalen method was used for the calculation of cumulative hazard.

Problems

Screening and Prostate-Cancer Mortality in a Randomized European Study

- Non-uniform study design
- Interim analysis
- 20% reduction marginally statistically significant (P=0.04)

Conclusions

Screening and Prostate-Cancer Mortality in a Randomized European Study

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- Contamination: PLCO study
  - Modest increase in cancers detected in screened arm (20%)
- PSA cutoff lower in ERSPC study
- Result: 2x as many cases in screened arm
- Short f/u for both studies

Conclusions

Screening and Prostate-Cancer Mortality in a Randomized European Study

Mortality Results from a Randomized Prostate-Cancer Screening Trial

- Mortality from CaP in screened populations in the first 10 yrs is modest
- Overdiagnosis
- Overtreatment

Conclusion

- Prostate cancer screening is controversial
- More cost-effective means at targeting high risk populations may be more reasonable
- We await longer term results of randomized screening trials
- While we await results of screening trials, we continue to improve prostate cancer treatment with cancer control and quality of life as our primary aims.
- Improved Biomarkers

REBUTTAL

Does PSA Screening Reduce Mortality

- ERSPC – YES!! 20% reduction in mortality in only 7-10 years
- Would be greater if:
  - A.) 12 core biopsies done
  - B.) Yearly screening done
  - C.) Cutoff of PSA 2.5ng/dl used

- PLCO: NO but WHY?
  - A.) Contamination of Control Group
  - B.) Cutoff of PSA 4 not realistic
  - C.) Only sextant biopsies

Should PSA Screening be Recommended

- AUA and ACS say YES!!
- Question of screening an easy one, question of treatment is a more difficult one
- Active surveillance under utilized

How Should Effectiveness of PSA Screening be Measured?

- Significant reduction in Prostate Cancer Mortality since inception of PSA screening
- To save one CaP death=1400 men screened and 48 treated
- Similar overtreatment burden in breast cancer
- Breast cancer: need to screen 2500 women to save one death
- Colon cancer: need to screen 2000 to save one death

Should PSA screening be Risk Stratified?

- Family history
- Race/Ethnicity

Side Effects of PSA Screening

- Screening should be Dissociated from Treatment
- Psychological Factors
- Urological counseling critical

Future

- Molecular profiling
- Better Treatment
- New Markers

What is PCA3?

- PCA3 is an mRNA that is highly over-expressed in prostate cancer cells
  - 60-100x higher in 90% of prostate cancers compared with benign prostate tissue
- Also known as PCA^{DD3} or $DD3^{PCA}$
- Originally identified in 1999 by Bussemakers et al.

Bussemakers MJG, Van Bokhoven A, Verhaegh GW et al. DD3: A new prostate-specific gene, highly over-expressed in prostate cancer. Cancer Res. 59, 5975–5979 (1999).

de la Taille A. Progensa PCA3 test for prostate cancer detection. Expert Rev Mol Diagn. 2007 Sep;7(5):491-7.

How was PCA3 identified?

- Extracted RNA from both benign and cancer tissue from patients undergoing prostatectomy
- cDNAs were prepared and 11 cDNAs were identified that were differentially expressed between benign and malignant tissue
- PCA3 was chosen from among the 11 because of the high level of expression in tumor compared to benign tissue
- RT-PCR was used to further examine PCA3
  - Low expression in benign prostate tissue
  - No expression in normal tissues from a wide variety of other sites (brain, kidney, pancreas, etc.)
- Mapped to chromosome 9q21-22
- No indicator of function, could be a noncoding RNA

de la Taille A. Progensa PCA3 test for prostate cancer detection. Expert Rev Mol Diagn. 2007 Sep;7(5):491-7.

PCA3 Assay

- Makes use of transcription-mediated amplification (TMA) technology
  - An isothermal nucleic acid-based method that can amplify RNA or DNA targets a billion-fold in < 1hr
- Measures PCA3 mRNA and KLK3 mRNA in first-catch urine sample collected following prostate manipulation
  - [PCA3 mRNA]/[KLK3 mRNA] x 1000 = PCA3 score

Why is KLK3 mRNA also measured?

- KLK3 is the gene that encodes PSA
  - KLK3 has not been shown to be upregulated in prostate cancer
- Acts to normalize the amount of prostate cells and mRNA released into the urine following prostate manipulation

PCA3 Assay

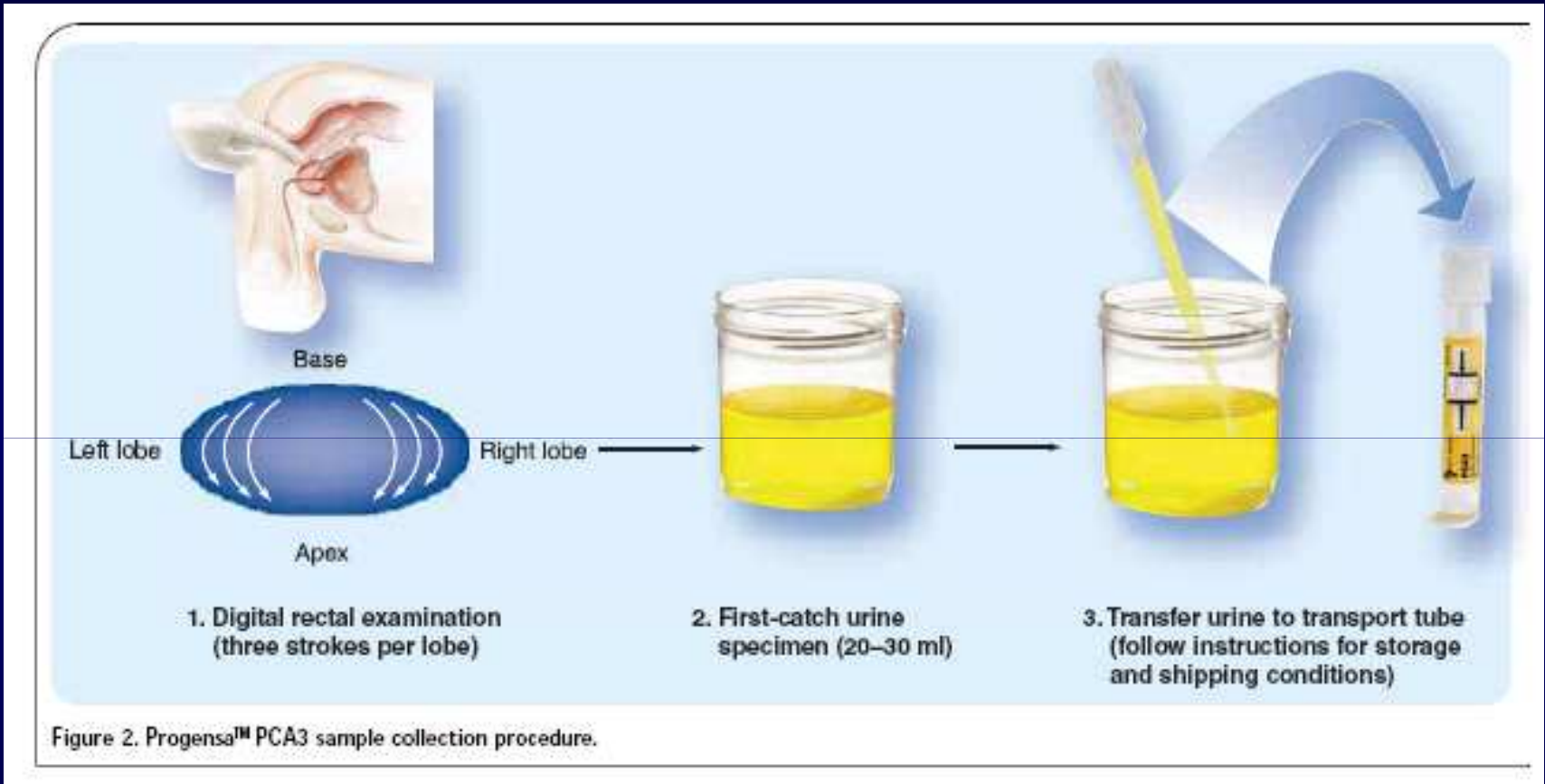


Figure 2. Progensa™ PCA3 sample collection procedure.

- Yields specimen with sufficient RNA for analysis 97% of the time

PCA3: A Molecular Urine Assay for Predicting Prostate Biopsy Outcome

Ina L. Deras,*,† Sheila M. J. Aubin,*,† Amy Blase,† John R. Day,† Seongjoon Koo,† Alan W. Partin,† William J. Ellis,‡ Leonard S. Marks,§ Yves Fradet,¶ Harry Rittenhouse† and Jack Groskopf†,‖

From Gen-Probe, Inc. (ILD, SMJA, AB, JRD, SK, HR, JG), San Diego and Urological Sciences Research Foundation (LSM), Los Angeles, California, The Johns Hopkins Medical Institutions (AWP), Baltimore, Maryland, University of Washington (WJE), Seattle, Washington, and Diagnocure Inc. and Université Laval, Quebec City, Quebec, Canada (YF)

How does PCA3 perform?

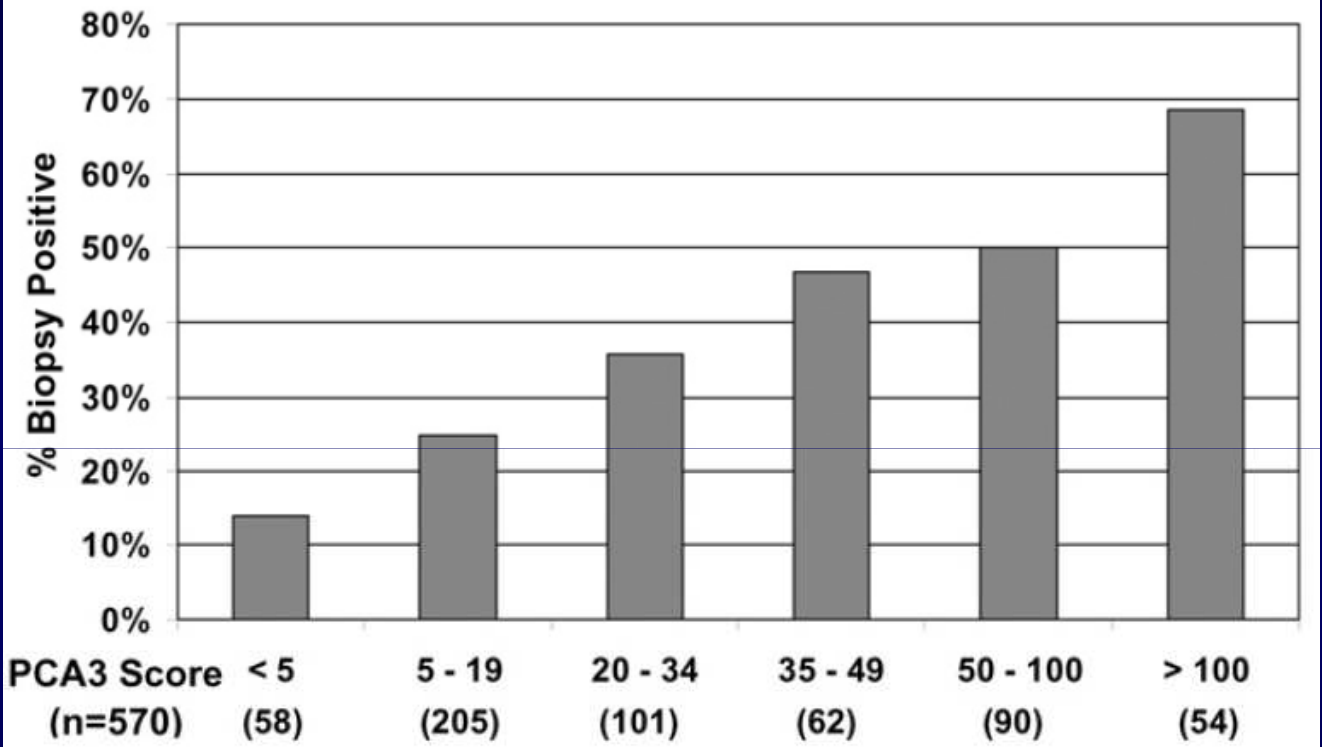


FIG. 1. Percent of men with positive biopsy by PCA3 score. Values in parentheses indicate sample size.

Deras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, Ellis WJ, Marks LS, Fradet Y, Rittenhouse H, Groskopf J. PCA3: A Molecular Urine Assay for Predicting Prostate Biopsy Outcome. J Urol. 2008 Feb 21; [Epub ahead of print]

How does PCA3 perform relative to PSA?

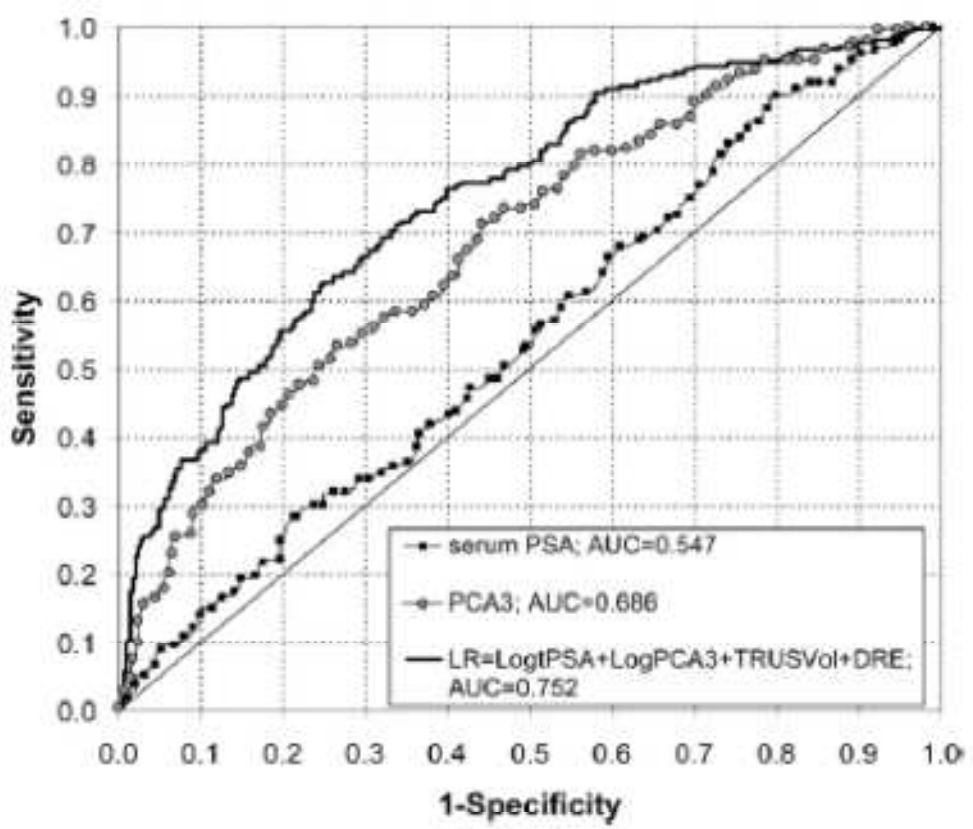


FIG. 5. ROC curve analysis of serum PSA, PCA3 score and LR algorithm in 553 men. LR incorporated terms log(PCA3 score), log(PSA), prostate volume on transrectal ultrasound (*TRUSVol*) and DRE result.

Deras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, Ellis WJ, Marks LS, Fradet Y, Rittenhouse H, Groskopf J. PCA3: A Molecular Urine Assay for Predicting Prostate Biopsy Outcome. J Urol. 2008 Feb 21; [Epub ahead of print]

Unlike PSA, PCA3 does not appear to be affected by prostate volume

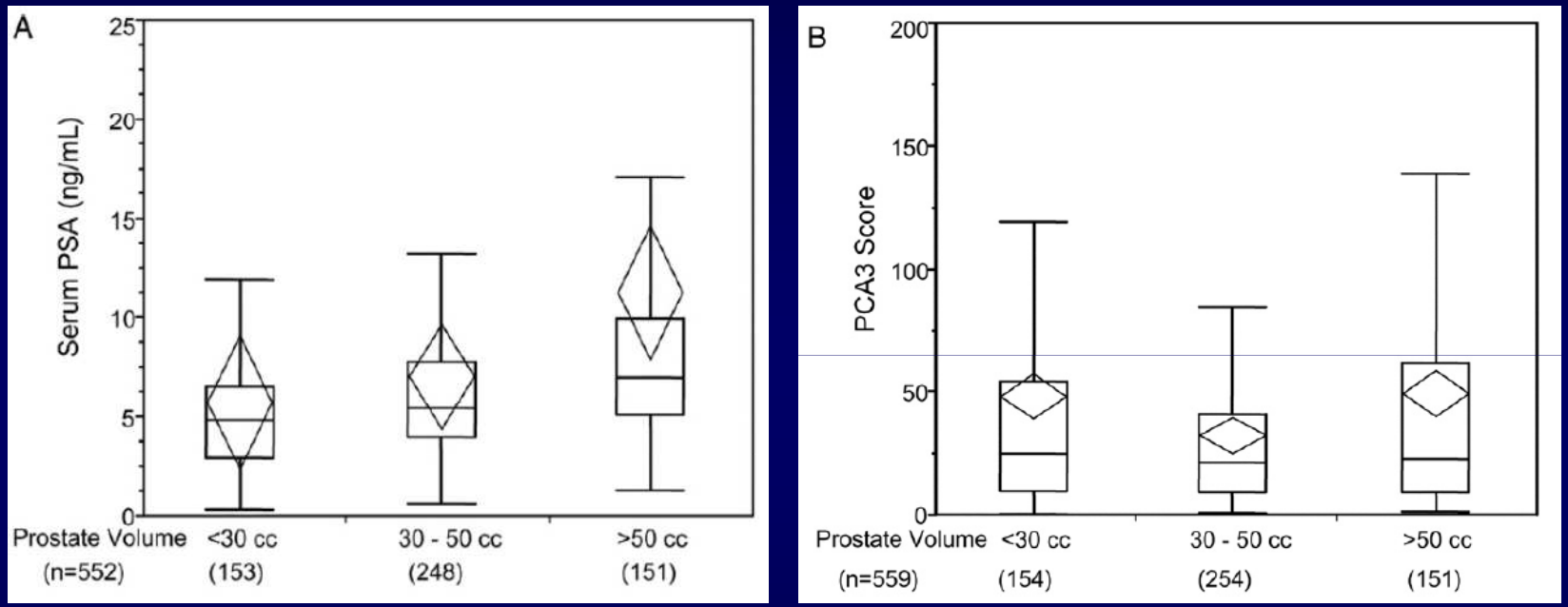


FIG. 4. *A*, serum PSA by PV. *B*, PCA3 score by PV. Boxes indicate these results suggest that the PCA3 score could be combined 25th and 75th quartiles. Vertical lines indicate 1.5 IQR. Horizontal lines in box represents median. Sides of diamonds represent mean. Top and bottom of diamonds represent 95% CI. Values in parentheses indicate sample size.

Deras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, Ellis WJ, Marks LS, Fradet Y, Rittenhouse H, Groskopf J. PCA3: A Molecular Urine Assay for Predicting Prostate Biopsy Outcome. J Urol. 2008 Feb 21; [Epub ahead of print]

PCA3 performance in men undergoing first time biopsy and those with prior negative biopsy

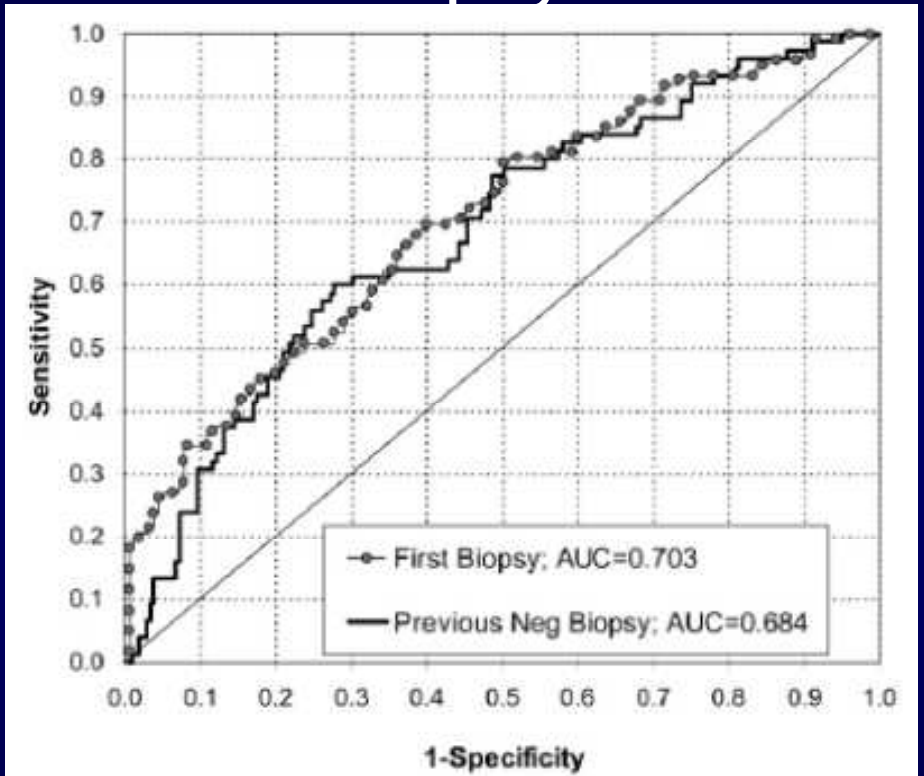


FIG. 2. ROC curve analysis in 277 men undergoing first biopsy and in 280 with previous negative biopsy. ROC curve shows plot of sensitivity as function of false-positive rate (1 − specificity). PCA3 score was analyzed with prostate biopsy used as comparison method.

Deras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, Ellis WJ, Marks LS, Fradet Y, Rittenhouse H, Groskopf J. PCA3: A Molecular Urine Assay for Predicting Prostate Biopsy Outcome. J Urol. 2008 Feb 21; [Epub ahead of print]

Sensitivity and Specificity

TABLE 3. *PCA3 assay sensitivity and specificity at various cutoffs*

PCA3 Cutoff	% Sensitivity	% Specificity
5	96	14
10	85	32
15	77	47
20	71	56
25	63	61
30	56	70
35	54	74
40	49	78
45	44	82
50	40	83
55	38	86
60	33	89
65	32	91
70	26	92
75	25	94
80	22	94
85	22	94
90	20	95
95	18	95
100	18	95

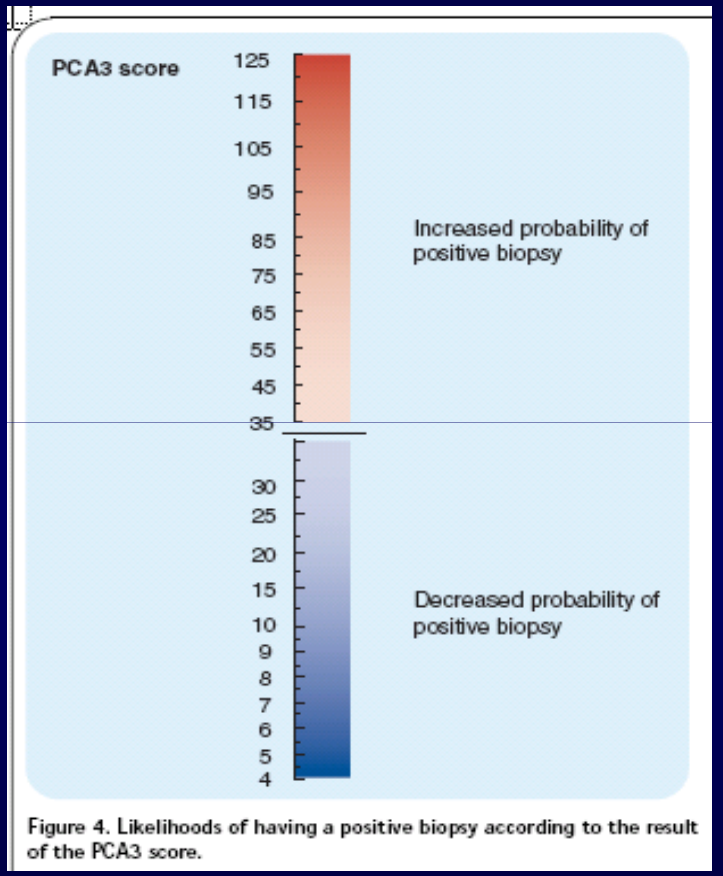


Figure 4. Likelihoods of having a positive biopsy according to the result of the PCA3 score.

Deras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, Ellis WJ, Marks LS, Fradet Y, Rittenhouse H, Groskopf J. PCA3: A Molecular Urine Assay for Predicting Prostate Biopsy Outcome. J Urol. 2008 Feb 21; [Epub ahead of print]

de la Taille A. Progensa PCA3 test for prostate cancer detection. Expert Rev Mol Diagn. 2007 Sep;7(5):491-7.

Conclusions

- In this study the urinary PCA3 assay improved diagnostic accuracy for CaP detection.
- The quantitative PCA3 score was found to be directly related to the probability of positive biopsy.
- The test performed similarly regardless of serum PSA level and the PCA3 score was not influenced by PV or by whether the patient had undergone previous negative biopsy.
- In addition to other prostate markers and patient data,the PCA3 test can provide valuable information to guide physicians in the diagnosis of CaP.

EPCA-2: A Highly Specific Serum Marker for Prostate Cancer

Eddy S. Leman, Grant W. Cannon, Bruce J. Trock, Lori J. Sokoll, Daniel W. Chan, Leslie Mangold, Alan W. Partin, and Robert H. Getzenberg

- Early prostate cancer antigen (EPCA) is a nuclear matrix protein identified in prostate cancers
- Initial assessment of EPCA-2 as a serum marker for the detection of PCa and to examine its sensitivity and specificity
- Characterization of an assay and was not designed to determine the efficacy of this assay in screening men for PCa
- Sensitivity and specificity values are not necessarily reflective of a screening population

Urology, 69: 714-20, 2007

Table 1. Sample profiles

Sample Population	Sample Size (n)	Sex	Age Range (yr)	Median Age (yr)	Gleason Score ≥7 (%)	Mean Total PSA (ng/mL ± SD)	Mean EPCA-2.22 (ng/mL ± SD)
Healthy (PSA <2.5 ng/mL)	33	M	51–82	63	NA	1.12 ± 0.59	15.18 ± 2.39
Healthy (PSA ≥2.5 ng/mL, negative biopsy for prostate cancer)	30	M	45–71	63	NA	8.77 ± 6.66	14.12 ± 2.79
BPH (mean American Urological Association Symptom Score 24)	35	M	40–84	58	NA	1.34 ± 0.96	25.86 ± 4.72
Prostate cancer, organ confined	40	M	45–67	59	27.5	5.35 ± 2.53	33.90 ± 4.18
Prostate cancer, nonorgan confined	40	M	43–70	58	52.5	7.15 ± 4.69	42.81 ± 6.74
Prostate cancer (PSA <2–5 ng/mL)	20	M	46–81	57.5	23.1	1.72 ± 0.62	32.17 ± 2.65
Normal women	10	F	23–55	42.5	NA	NA	22.70 ± 3.15
Benign breast disease	9	F	36–68	50	NA	NA	22.00 ± 6.42
Breast cancer (Stage I–IV)	10	F	37–82	51	NA	NA	22.37 ± 5.62
Benign colon	9	4M, 5F	42–75	56	NA	NA	19.58 ± 6.04
Colorectal cancer (Stage I–IV)	10	8M, 2F	47–87	63	NA	NA	19.89 ± 5.26
Benign liver disease	10	3M, 7F	27–74	49.5	NA	NA	20.82 ± 5.44
Liver cancer	10	9M, 1F	51–76	65.5	NA	NA	21.48 ± 5.69
Benign pancreatic	10	6M, 4F	17–85	64	NA	NA	19.58 ± 4.89
Pancreatic cancer (Stage I–IV)	10	7M, 3F	60–80	71	NA	NA	22.14 ± 5.74
Benign renal disease	10	4M, 6F	18–69	44.5	NA	NA	18.22 ± 6.05
Renal cancer (Stage I–IV)	9	8M, 1F	45–71	62	NA	NA	16.99 ± 5.44
Bladder cancer (Stage I–IV, pT1N0M0-pT3N0Mx)	9	8M, 1F	58–80	69	NA	NA	21.70 ± 4.68
Benign lung disease	9	4M, 5F	35–71	56	NA	NA	18.48 ± 7.71
Lung cancer (Stage IB–IV)	9	7M, 2F	49–78	69	NA	NA	18.20 ± 5.98

PSA = prostate-specific antigen; EPCA = early prostate cancer antigen; M = male; NA = not applicable; BPH = benign prostatic hyperplasia; F = female.

- Group 1 = 33 men with a PSA level less than 2.5 ng/mL and normal DRE presumed to have a normal prostate gland, but a biopsy sample was not taken.
- Group 2 = 30 men with a PSA level of 2.5 ng/mL and normal DRE who underwent 12 core biopsy with negative result
- Group 3 = 40 men with organ confined prostate cancer
- Group 4 = 40 men with non-organ confined prostate cancer
- Group 5 = 20 patients with prostate cancer and a PSA < 2.5 ng/ml
- Group 6 = 35 men with a normal PSA concentration who were diagnosed with highly symptomatic BPH (IPSS > 20). No prostate bx.

EPCA-2 assay

- Indirect enzyme-linked immunosorbent assay (ELISA)
  - Anti-epitope antibody for EPCA-2
- Established the optimal conditions and cutoff point as 30ng/mL
- EPCA-2 assay was highly specific in discriminating between people with and without PCa

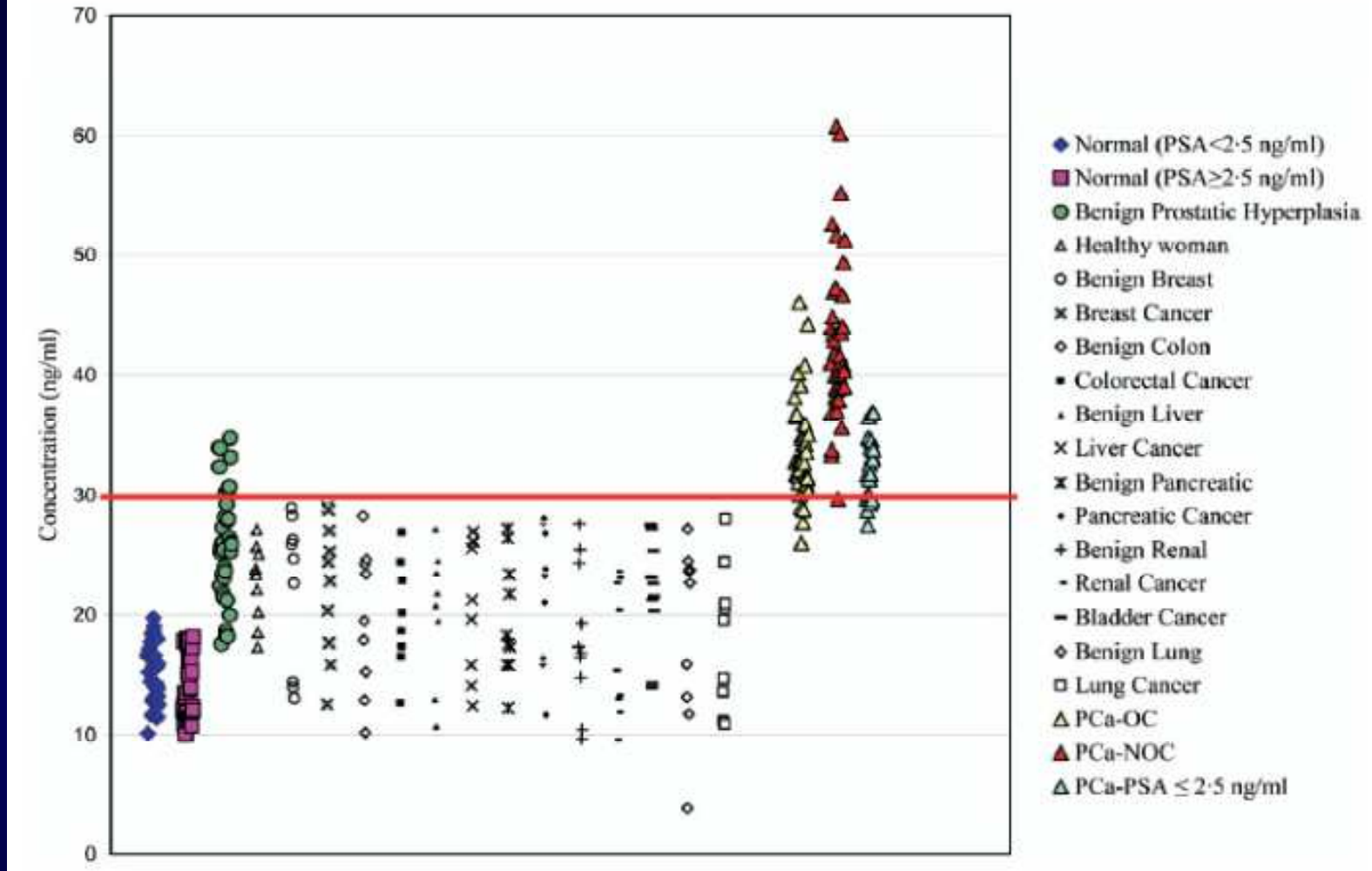


Figure 1. Serum analysis of EPCA-2 in study populations. Total of 330 serum samples screened for EPCA-2.22. Indirect ELISAs showed that EPCA-2.22 has cutoff of 30 ng/mL or greater at estimated concentration. Cutoff represented by red line across graph.

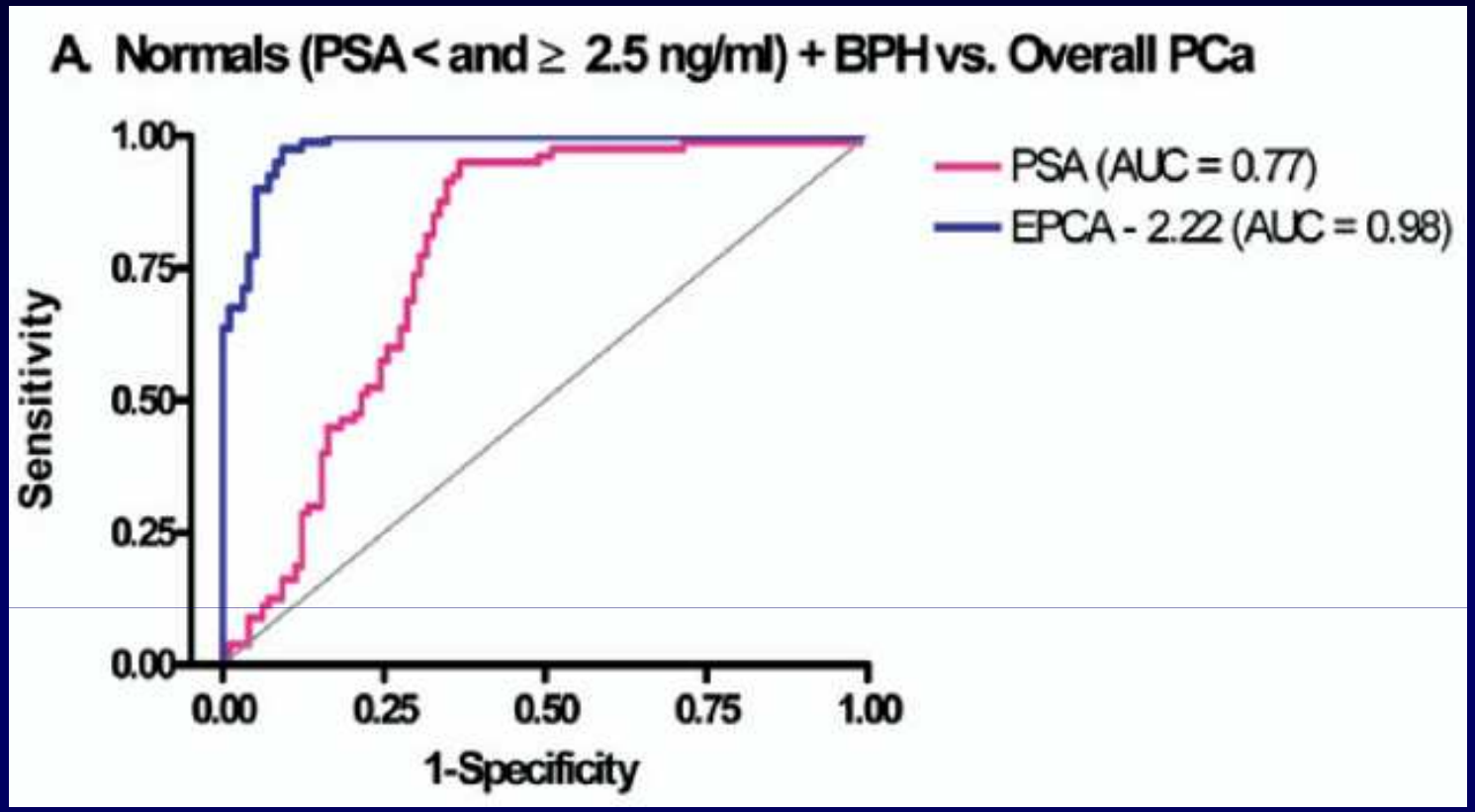
Table 2. Sensitivity and specificity of PSA and EPCA-2.22

	PSA Cutoff (ng/mL)		EPCA 2.22 (30 ng/mL Cutoff) (95% CI; n)
	2.5 (95% CI; n)	4.0 (95% CI)	
Specificity in selected population(%)			
Normal (PSA <2.5 and ≥2.5 ng/mL) and BPH (n = 98)	65 (55–75; 64/98)	70 (60–79)	92 (85–96; 90/98)
Normal (PSA <2.5 and ≥2.5 ng/mL), BPH, other benign diseases and other cancer (n = 232)	NA*	NA*	97 (93–99; 225/232)
Sensitivity in selected population† (%)			
PCa-OC (n = 40)	90 (76–97; 36/40)	58 (41–73; 23/40)	90 (76–97; 36/40)
PCa-NOC (n = 40)	90 (76–97; 36/40)	80 (64–91; 32/40)	98 (87–100; 39/40)
PCa-OC and PCa-NOC (n = 80)	90 (81–96; 72/80)	69 (57–79; 55/80)	94 (86–98; 75/80)

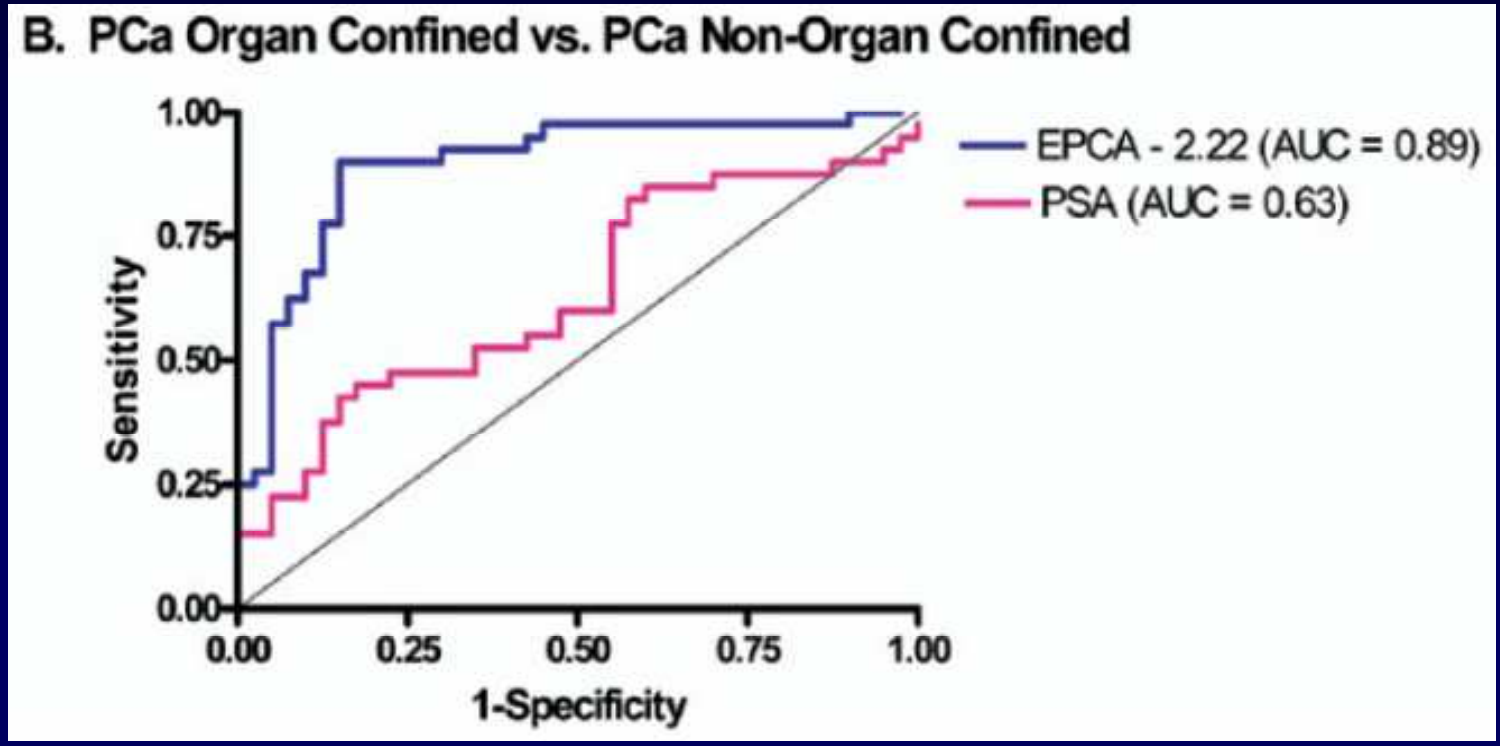
CI = confidence interval; PCa = prostate cancer; OC = organ confined; NOC = non organ confined; other abbreviations as in Table 1. Data in numerator/denominator format indicate numbers available for specificity and sensitivity calculations.

* PSA not measured in other control groups that included normal women, as well as various benign and cancer serum samples.

† These values pertain to 80 patients with prostate cancer who were selected based on their OC-PCa or NOC-PCa status, but not to the separate subgroup of 18 patients with prostate cancer deliberately selected with PSA levels <2.5.



- Area under the curve was significantly greater for EPCA-2 than for PSA (P<0.001)
  - EPCA-2 had significantly greater accuracy than did PSA



- EPCA-2 was highly accurate in differentiating between localized and extracapsular disease ($P<0.0001$)

Conclusion

- EPCA-2 has great potential as a serum-based biomarker for prostate cancer
- Additional validation studies are needed to show the performance of EPCA-2 in a more representative population

Other potential biomarkers

- Gene fusion/translocation markers: (TMPRSS2-ERG, TMPRSS2-ETV1)
- Proteomic profiling
- PSCA: a prostate specific glycoprotein expressed on the cell surface. PSCA RNA can be detected in serum and has been shown to correlate with prostate cancer risk in small studies
- AMACR: isomerase expressed in virtually all prostate cancers. Detected by immunohistochemistry. Helpful in distinguishing benign tissue from cancer in difficult pathology cases

Other potential biomarkers

- HK2: Overexpression of HK2 have been reported in prostate cancer tissue and has been used in combination with free and total PSA to improve specificity and sensitivity (mixed results)

- Hepsin: Overexpression in up to 90% of tumors, but not detectable in serum or urine → currently limited role for this reason