

Biomarcatori in oncologia: cut-off o valutazione dinamica ?

Un esempio paradigmatico:

**il PSA nella diagnosi del
carcinoma prostatico**

Il valore tradizionalmente accettato oltre il quale eseguire una biopsia prostatica

4 ng/mL

Sensibilità: £ 80% (**20%** di tumori non identificati)

Specificità: £ 60% (**40%** di biopsie non necessarie)

Non ha una accuratezza diagnostica soddisfacente per la neoplasia prostatica

Cut-off positivo/negativo Limiti

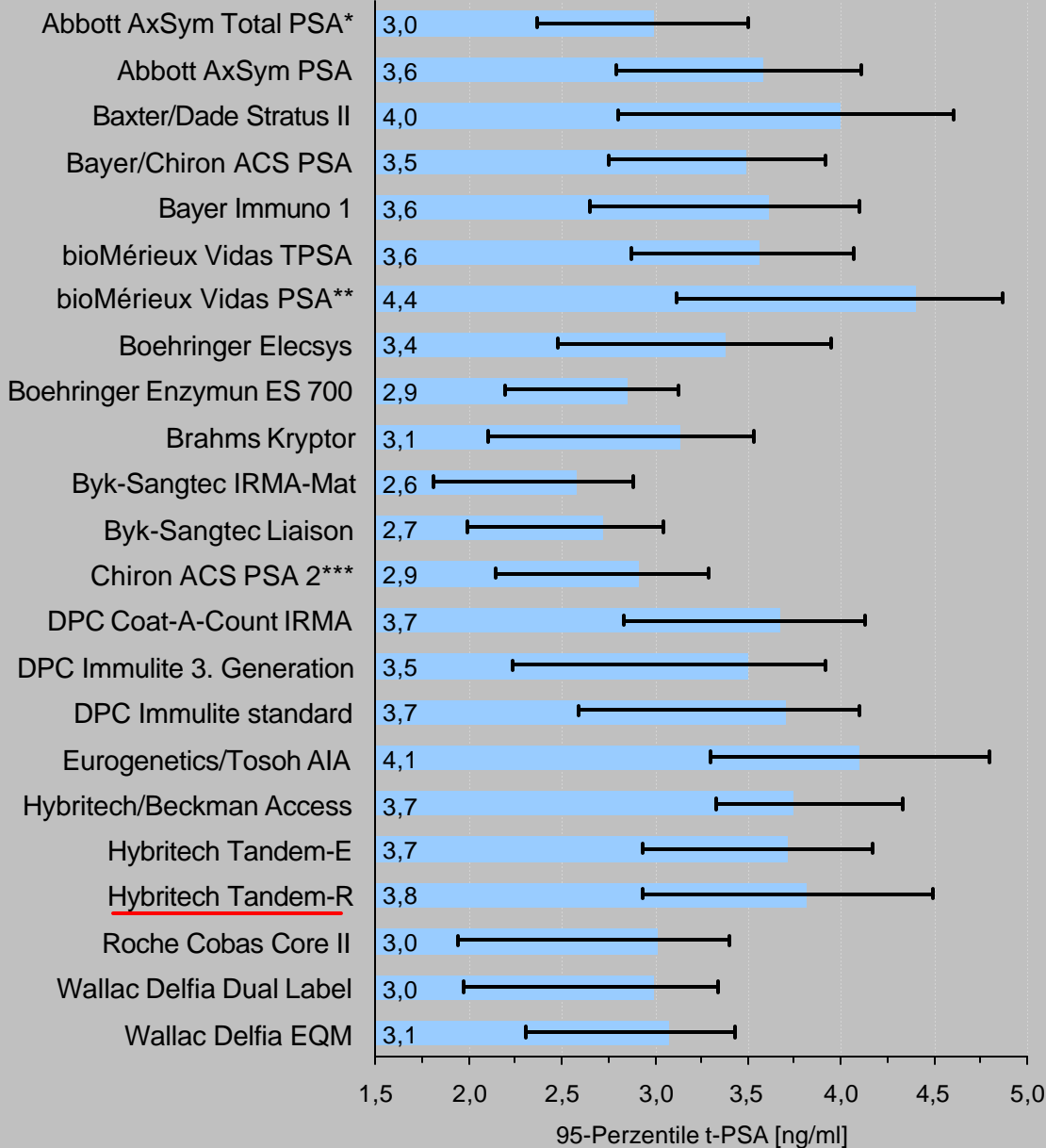
- Analitici
- Clinici

The clinical impact of different assays for prostate specific antigen

A. Semjonow, G. De Angelis, F. Oberpenning, HP. Schmid, B. Brandt, L. Hertle

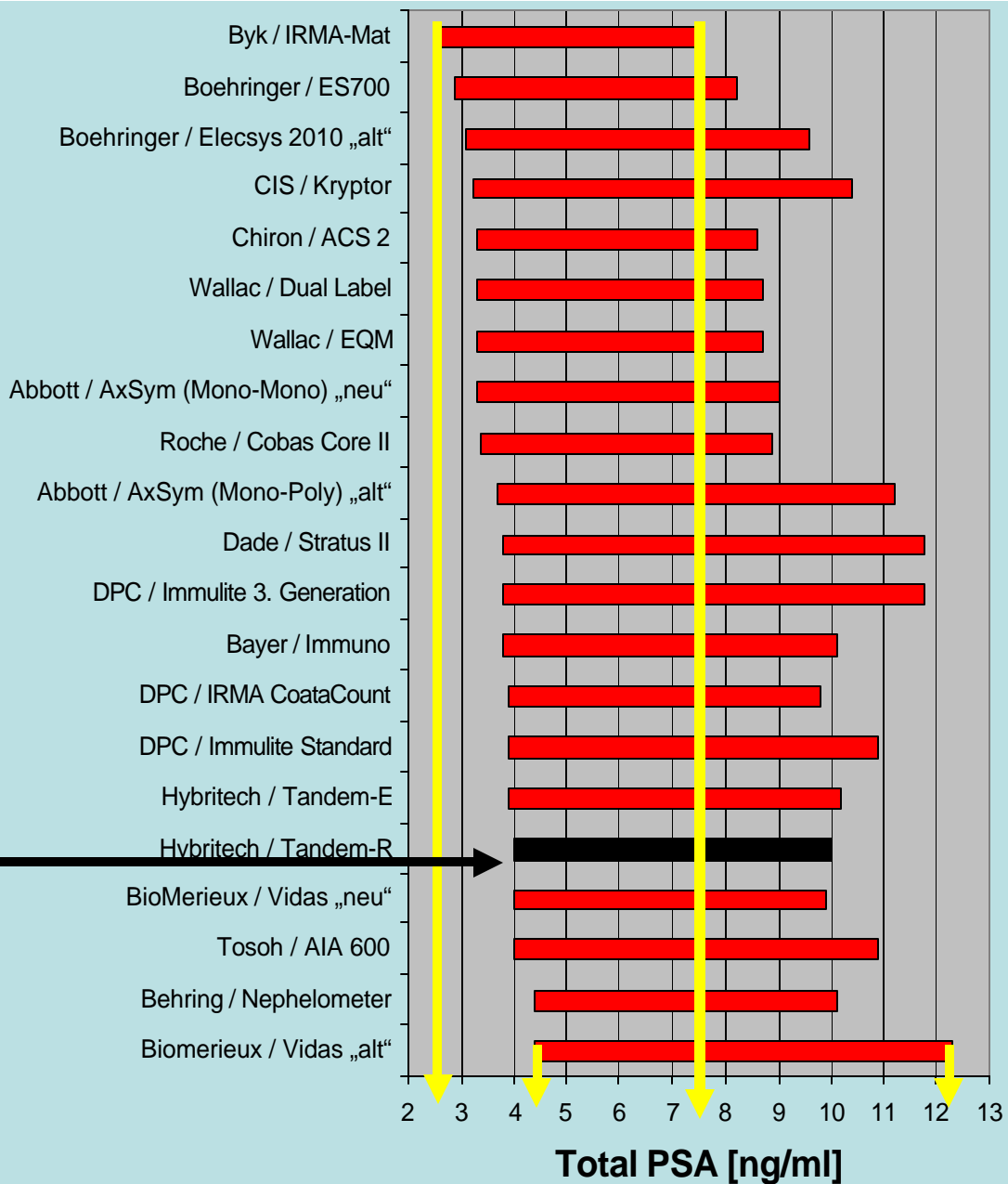
BJU International 86, 590-597, 2000

589 men
clinically NED
23 t-PSA assays



Fornara & Semjonow: PSA: Der Weg
zum Befund, Zuckschwerdt Verlag
München, 2002

Cut-offs equivalent to traditional 4-10



Fornara & Semjonow: PSA: Der Weg
zum Befund, Zuckschwerdt Verlag
München, 2002

Recalibration to WHO standards

- Differences among the assays are due to the use of different antibodies, assay format or calibration
- The WHO calibration of PSA assays was supposed to reduce this inter-assay variability to the minimum to limit the possible clinical implications of such variations

The clinical impact of WHO standardization of PSA assays

J.S. Blanchet, T. Brinkmann

JMB 27: 161–168, 2008

Recalibration to WHO standards

- Recalibration of an immunoassay to a new standard is expected to modify the concentration values obtained following the calibration

Total Access PSA based on the measurements with the traditional Hybritech calibration and the new WHO-aligned calibration

	All patients (n=641)	PCa patients (n=336)
Total PSA, $\mu\text{g/L}$		
<u>tPSA-Hyb</u>	5.27 (0.26–29.5)	5.61 (0.46–29.5)
<u>tPSA-WHO</u>	4.03 (0.21–23.2)	4.31 (0.36–23.2)

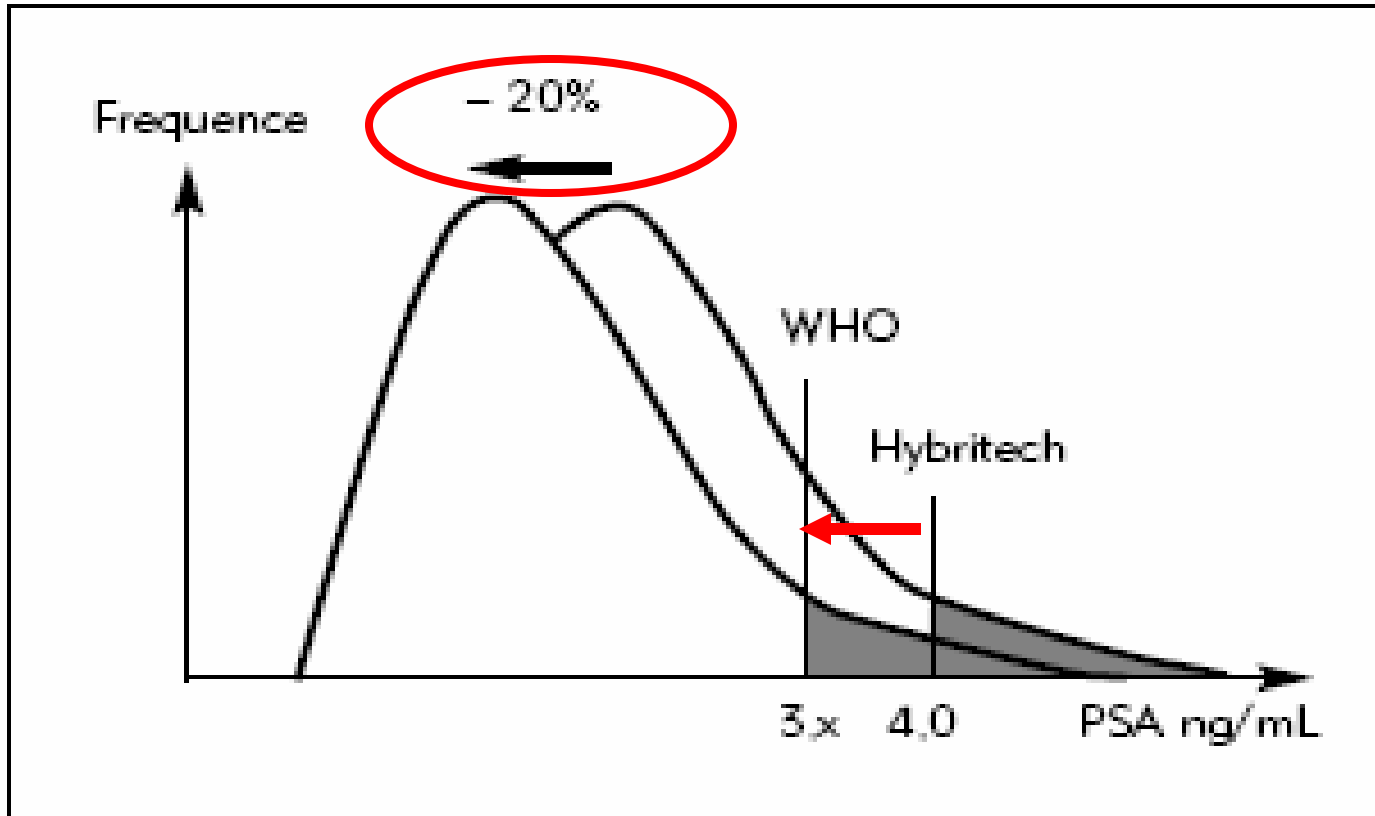
Recalibration to WHO standards

- Calibration to the WHO standard could lead to a proportional negative bias in mass units of approximately 20% compared with the non-WHO calibrated assay

Distribution of patients according to the tPSA cut-off value. Unadjusted WHO clinical cut-off

	<u>Hybritech Calibration</u>		
<u>WHO Calibration</u>	4.0 ng/mL	> 4.0 ng/mL	Total
≤ 4.0 ng/mL	47	38 (15%)	85
> 4.0 ng/mL	0	170	170
Total	47	208	255

Impact of different PSA standardization on the cut-off definition and clinical interpretation of results



Recalibration to WHO standards

- An appropriate clinical decision point of 3.1 ng/mL was identified to preserve the clinical performance of the assay calibrated to the WHO standard

Distribution of patients according to the tPSA cut-off value. Adjusted WHO clinical cut-off

	Hybritech Calibration		
	≤ 4.0 ng/mL	> 4.0 ng/mL	Total
≤ 3.1 ng/mL	47	0	85
> 3.1 ng/mL	0	208	170
Total	47	208	255

Clinical performance of the WHO and Hybritech calibrated Access tPSA assays using an appropriate cut-off

tPSA Calibration (ng/mL)	Hybritech ≤ 4.0	Hybritech > 4.0
WHO ≤ 3.1	5 616	0
WHO > 3.1	0	1 014
Total samples	5 616	1 014
Relative agreement	100%	100%

Different prostate-specific antigen assays give different results on the same blood sample: an obstacle to recommending uniform limits for prostate biopsies

C. Stephan, J. Kramer, H-A. Meyer, G. Kristiansen, S. Ziemer, S. Deger, M. Lein, S. A. Loening, K. Jung

BJU International 99,1427–143, 2007

Classification of 314 men with and 282 without PCa using fixed tPSA thresholds of 2.5 and 4.0 ng/mL for the three tPSA assays calibrated against the WHO standard

Selected Threshold	% of classified patients		
	AxSym	Centaur	Elecsys
2.5 ng/mL			
True positive	92	90	93
True negative	41	40	34
4.0 ng/mL			
True positive	73	70	81
True negative	23	57	51

Recalibration to WHO standards

- Even WHO calibrated assays do not deliver similar tPSA values
- Thus, calibration might be an important, but not the exclusive factor, to improve the harmonization among the various assays
- The 3.1 ng/mL cut-off cannot be applied to any WHO calibrated tPSA assay, since an appropriate clinical decision point should be defined for each tPSA assay

Cut-off positivo/negativo Limiti

- Analitici
- Clinici

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E possibile migliorare l'efficacia diagnostica del PSA variando il valore soglia ?

es. 2.5 ng/ml ?

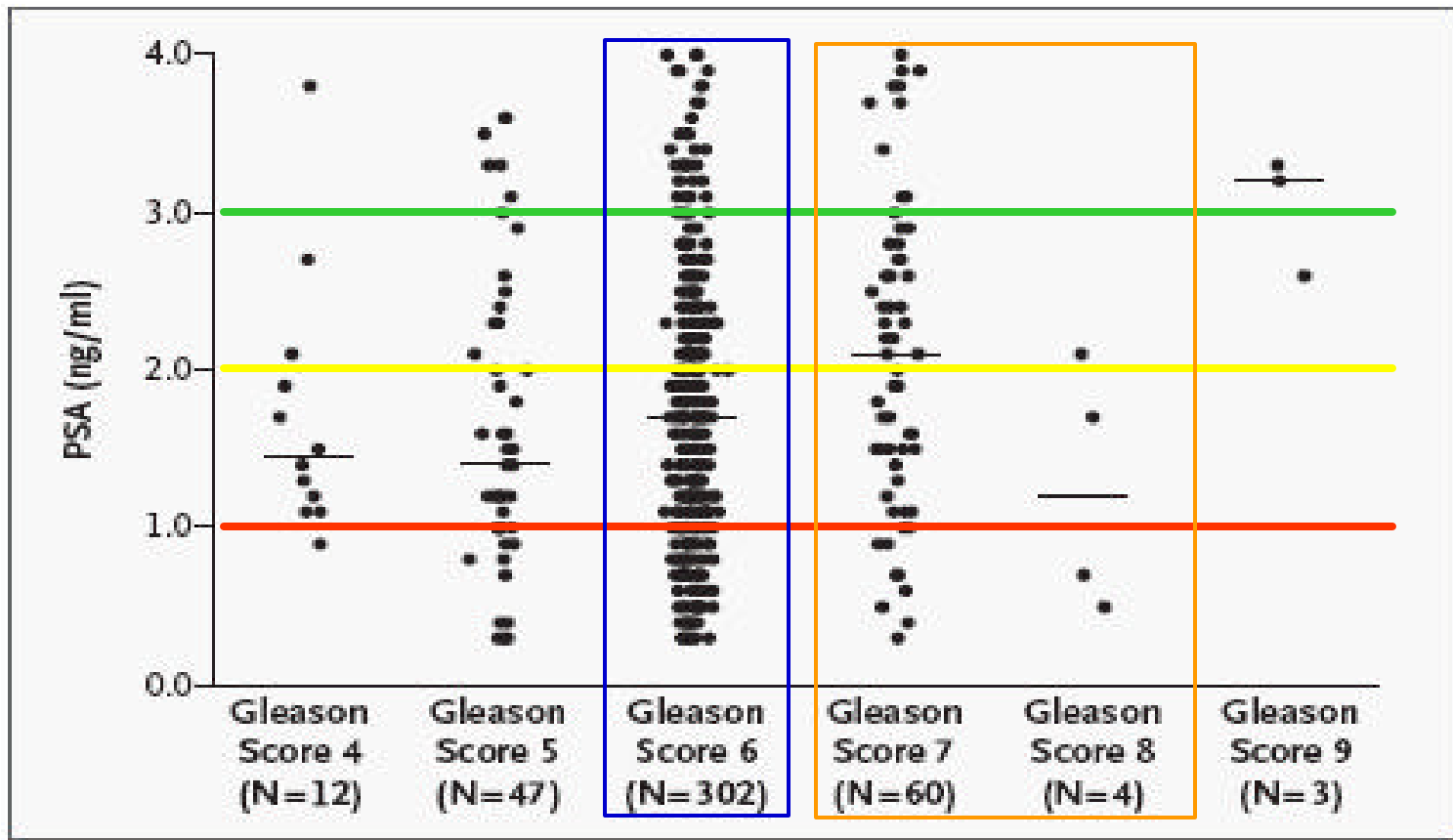
Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level \geq 4.0 ng/ml

IM. Thompson, D.K. Pauler, P.J. Goodman, C.M. Tangen, M. Scott Lucia, H.L. Parnes, L.Minasian, L.G. Ford, S.M. Lippman, E.D. Crawford, J.J. Crowley, C.A. Coltman, Jr.

N Engl J Med 350:2239-46, 2004

- 18,882 men enrolled in the prevention trial
- 9459 were randomly assigned to receive placebo and had an annual measurement of PSA and a DRE
- Among these 9459 men, 2950 men **never had a PSA level of more than 4.0 ng/ml** or an abnormal DRE, had a final PSA determination, and underwent a prostate biopsy after being in the study for 7 years
- Among the 2950 men (age 62 to 91), **prostate cancer** was diagnosed **in 449** (15.2 %)

PSA Values among the 449 Men with Prostate Cancer, According to the Gleason Score



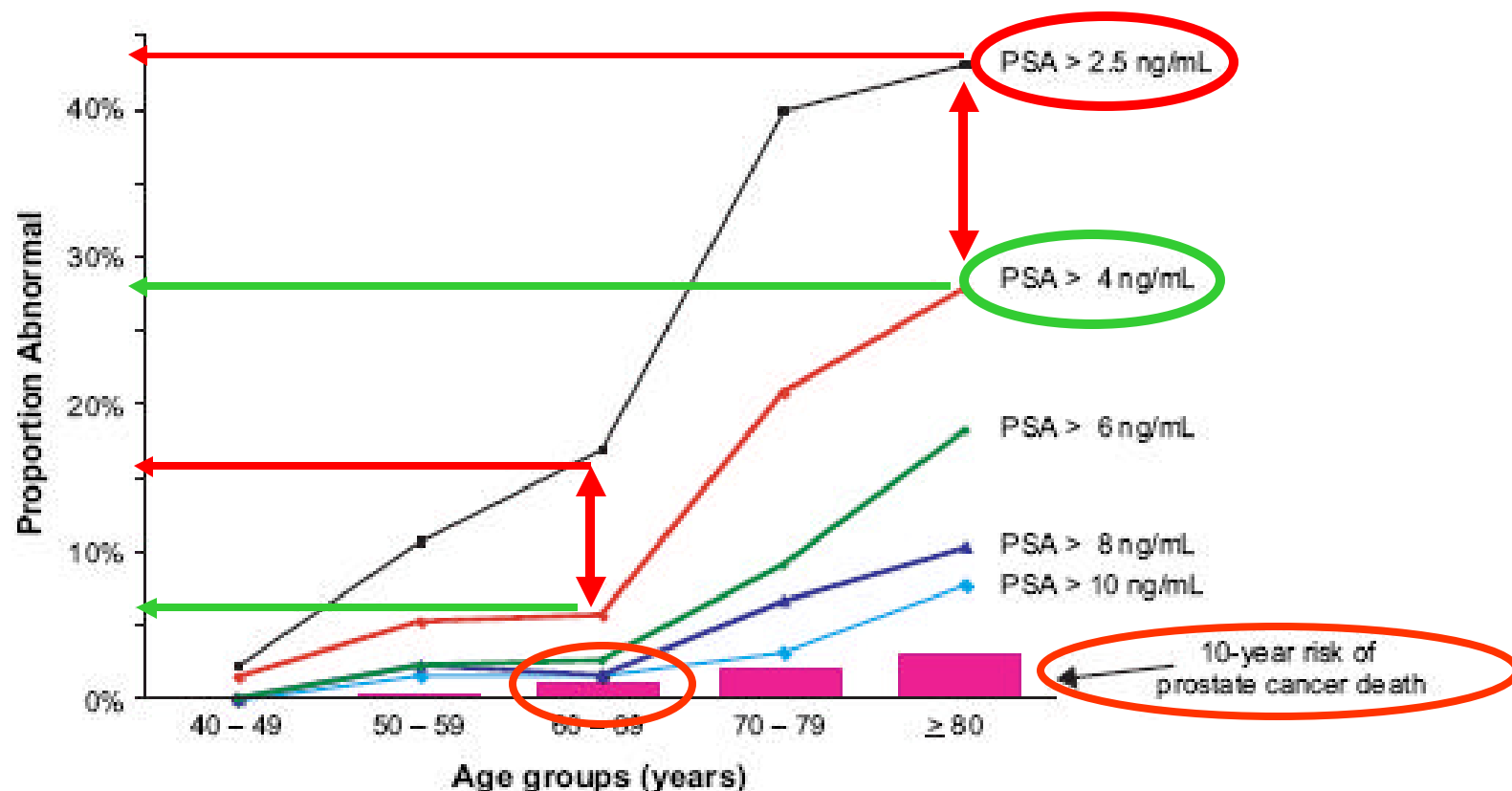
- Reassuring a man with a PSA of 2.1 that he does not have cancer is inaccurate.
- He actually has a 23.8% chance of sextant biopsy identifying prostate cancer.

**Prostate Specific Antigen levels in USA:
implications of various definition of abnormal**

Welch HG, Schwartz LM, Woloshin S

J Natl Cancer Inst 2005; 97:1132-37

Proportion of screen-eligible American men of different age groups who would be labeled as abnormal by PSA threshold



Welch HG, Schwartz LM, Woloshin S, *J Natl Cancer Inst* 2005; 97:1132-37

Data from NHNES

(National Health and Nutrition Examination Survey)

- Lowering the PSA threshold to 2.5 ng/mL would double the number of men defined as abnormal, to up to 6 million
- For context, only 0.9% of men over their 60 are expected to die from prostate cancer
- Until there is evidence that the screening is effective, increasing the number of men recommended for prostate biopsy – and the number of potentially diagnosed and treated unnecessarily – would be a mistake

There is no legitimate PSA cut-off point

- A threshold is scientifically and statistically baseless in the screening or diagnosis setting and is completely meaningless for any patient who has undergone treatment for prostate cancer
- Flagging PSA results as “normal” or “abnormal” is no longer justifiable.
- Laboratories should eliminate any artificial PSA cut-off value when reporting results

(Jones JS, Eur Urol 2008;53,10–12)

Perchè i criteri decisionali dicotomici sono deboli?

I criteri basati sul valore soglia derivano dalla chimica clinica e sono finalizzati a definire i limiti di un intervallo di equilibrio omeostatico

Nella biologia della cellula neoplastica la produzione e il rilascio di biomarcatori correlati alla estensione o alla aggressività non sono necessariamente associabili al concetto di omeostasi

I criteri decisionali dicotomici basati su un valore soglia potrebbero non avere un razionale biologico

Cut-off positivo/negativo

Ci serve davvero un valore soglia negativo/positivo?

**Una alternativa possibile:
i criteri decisionali dinamici**

Criteri dinamici

Razionale biologico

- La cinetica di crescita del tumore è diversa da quella dei tessuti normali
- La produzione e il rilascio di biomarcatori da parte del tumore dovrebbe essere sufficientemente elevata da essere evidenziabile dalla cinetica di crescita

Razionale clinico

- I biomarcatori vengono confrontati longitudinalmente nel singolo paziente (nessuna necessità di confronto con valori di riferimento)
- E' possibile ottenere informazioni cliniche rilevanti anche con valori molto bassi se in rapida crescita

Criteri decisionali dinamici

Analisi delle variazioni del PSA nel tempo nel singolo paziente

PSA Velocity

PSA Velocity

Campi di applicazione

- Diagnosi/screening
- Risk assesment
- Prognosi

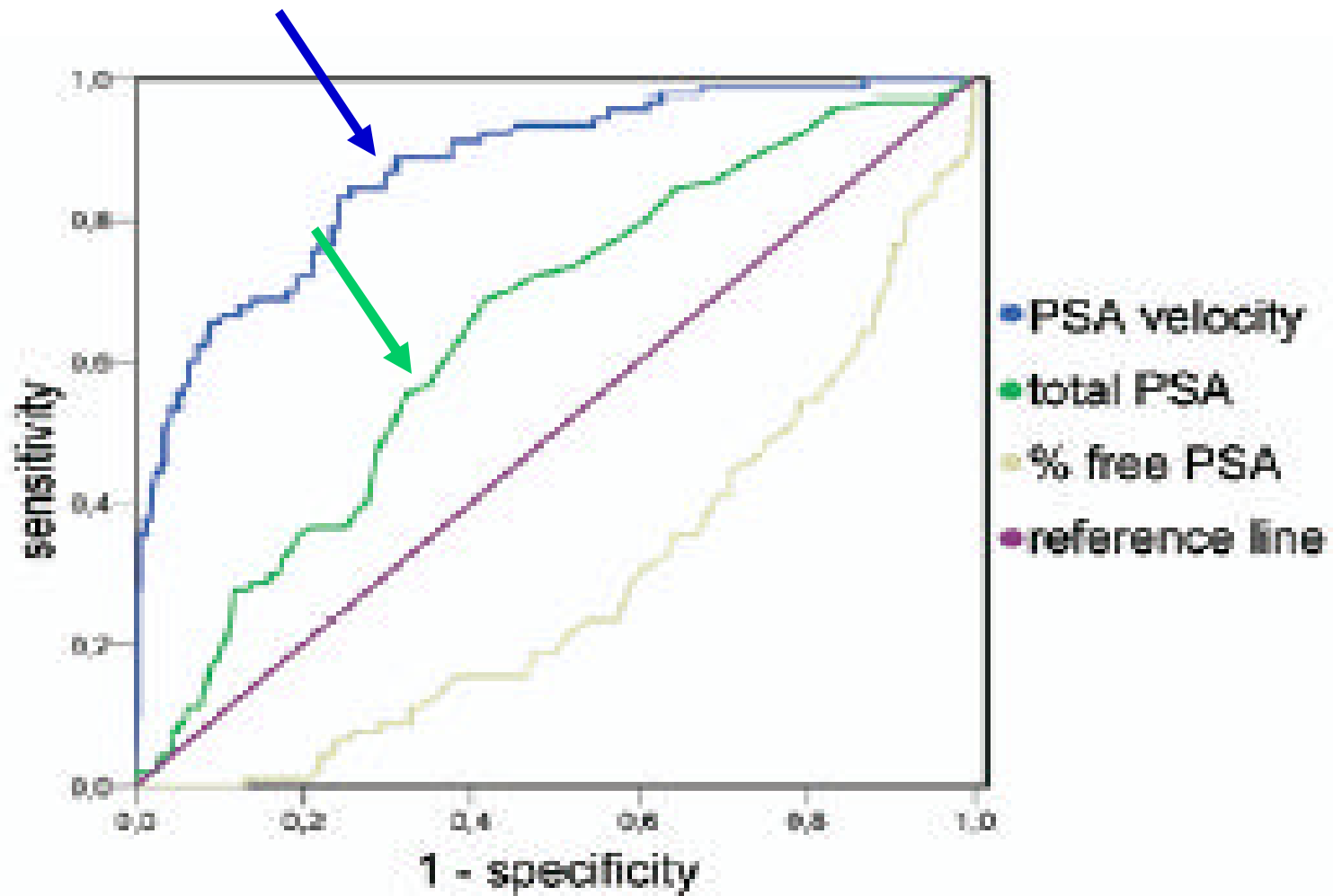
Large-Scale Study of Clinical Impact of PSA Velocity: Long-Term PSA Kinetics as Method of Differentiating Men with from Those without Prostate Cancer

A.P. Berger, M. Deibl, A. Strasak, J. Bektic, A.E. Pelzer, H. Klocker, H. Steiner, G. Fritsche, G. Bartsch, and W. Horninger

UROLOGY 69:134–138, 2007

- **4272** subjects without malignancies undergoing PSA testing at least every second year.
- Over a total period of 10 years **528** men who underwent PSA testing over 6 to 10 years (minimum: 6) were eventually diagnosed with prostate cancers.

(A.P. Berger, et al, UROLOGY 69:134–138, 2007)



(A.P. Berger, et al, UROLOGY 69:134–138, 2007)

- A mean PSAV of **0.4 ng/mL/yr** or more during a 3-year period or longer may indicate the presence of tumor and thus warrants biopsy.
- Patients with a Gleason score < 7 had lower PSAV (**0.34 ng/mL/yr**) than those with Gleason score 7 (**0.46 ng/mL/yr**) and those with a Gleason score > 8 or more (0.74 ng/mL/yr).

(A.P. Berger, et al, UROLOGY 69:134–138, 2007)

Does PSA velocity predict prostate cancer in pre-screened populations?

FH Schroder, MJ Roobol, TH van der Kwast, R Kranse, CH Bangma

Eur Urol. 2006 Mar;49(3):460-5

- Data from the European Randomized Study of Screening for Prostate Cancer Rotterdam are used.
- **588** consecutive participants were identified who presented at their first screening with PSA values <4.0 and who progressed to PSA values >4.0 ng/ml four years later

Schroder FH, et al, Eur Urol. 2006 Mar;49(3):460-5

The use of PSAV **does not improve** the PPV of the PSA cut-off of 4.0 ng/ml, nor the odds ratio for identifying prostate cancer with respect to the cut-off value of 4.0 ng/ml in secondary screening after four years

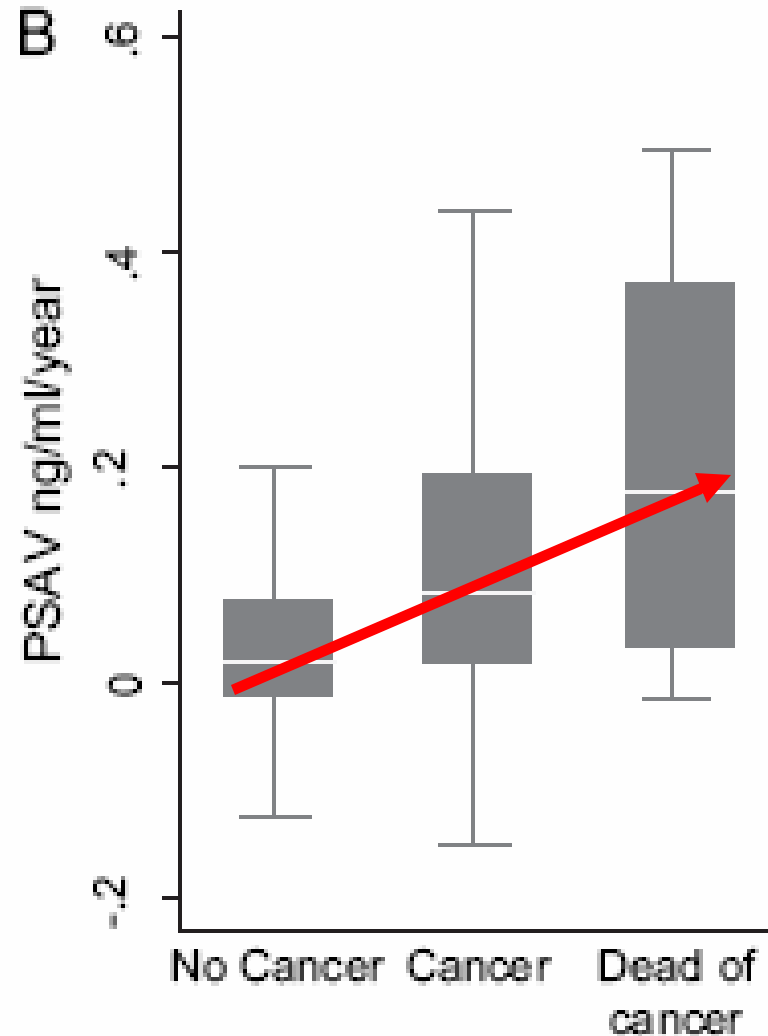
Schroder FH, et al, Eur Urol. 2006 Mar;49(3):460-5

Detection of Life-Threatening Prostate Cancer With Prostate-Specific Antigen Velocity During a Window of Curability

*H.B. Carter, L. Ferrucci, A. Kettermann, P. Landis, E.J.
Wright, J.I. Epstein, B.J. Trock , E.J. Metter*

J Natl Cancer Inst 2006;98:1521 – 27

Distributions of PSA velocity at **10 – 15 years** before diagnosis for each study group.



(Carter et al, J Natl Cancer Inst 2006;98:1521)

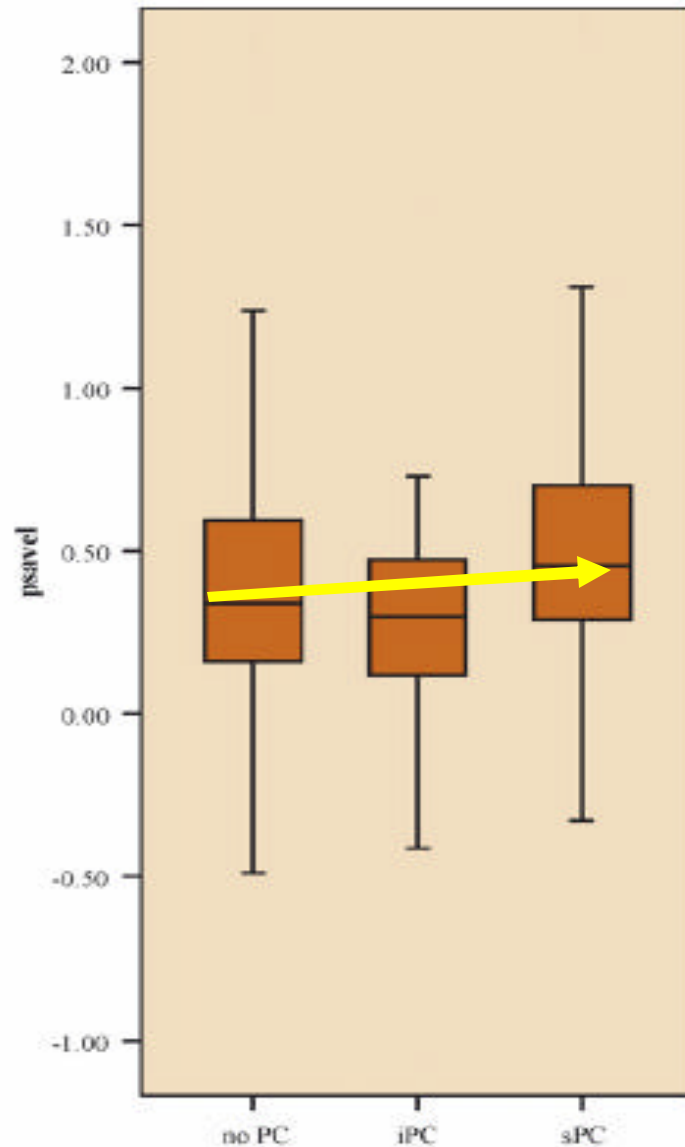
Is Prostate-Specific Antigen Velocity Selective for Clinically Significant Prostate Cancer in Screening? European Randomized Study of Screening for Prostate Cancer (Rotterdam)

T. Wolters, M.J. Roobol, C.H. Bangma, F.H. Schroder

European Urology, March 11, 2008

Prostate-specific antigen velocity (ng/ml/yr) in men without prostate cancer (PC) (n = 1776), men with indolent disease, i.e PCa that would not have been diagnosed in the absence of screening (iPC n = 108) and men with significant PCa (sPC n = 333).

(Wolters et al, European Urology, 2008)



PSA Velocity

Studi diversi, anche se condotti da gruppi affidabili su casistiche consistenti, portano a risultati significativamente diversi

Perche?

Is Prostate-Specific Antigen Velocity Useful in Early Detection of Prostate Cancer? A Critical Appraisal of the Evidence

*R.D. Etzioni , D.P. Ankerst , N.S. Weiss , L.Y. T. Inoue ,
I.M. Thompson*

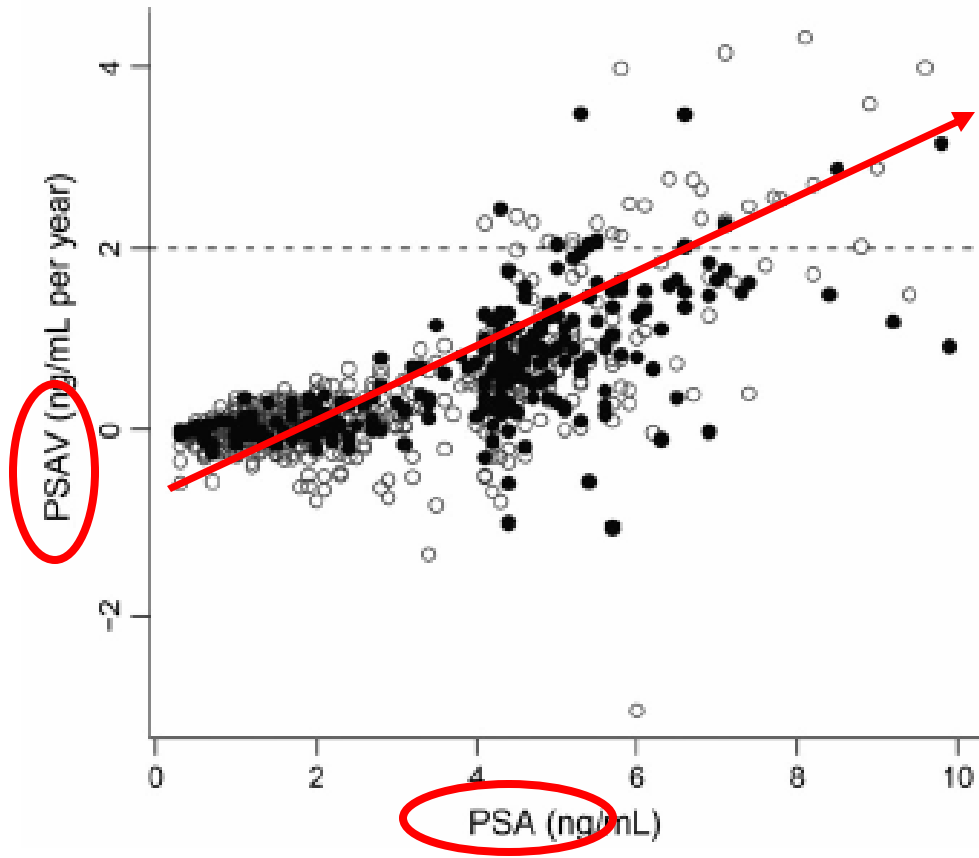
J Natl Cancer Inst 2007;99: 1510 – 5

Role of PSAV in early detection remains a matter of controversy

Variables affecting PSAV

1. PSA level
2. Mode of PCa detection
3. Type of study (association vs classification studies)
4. Timing, cut-off, method of calculating ...

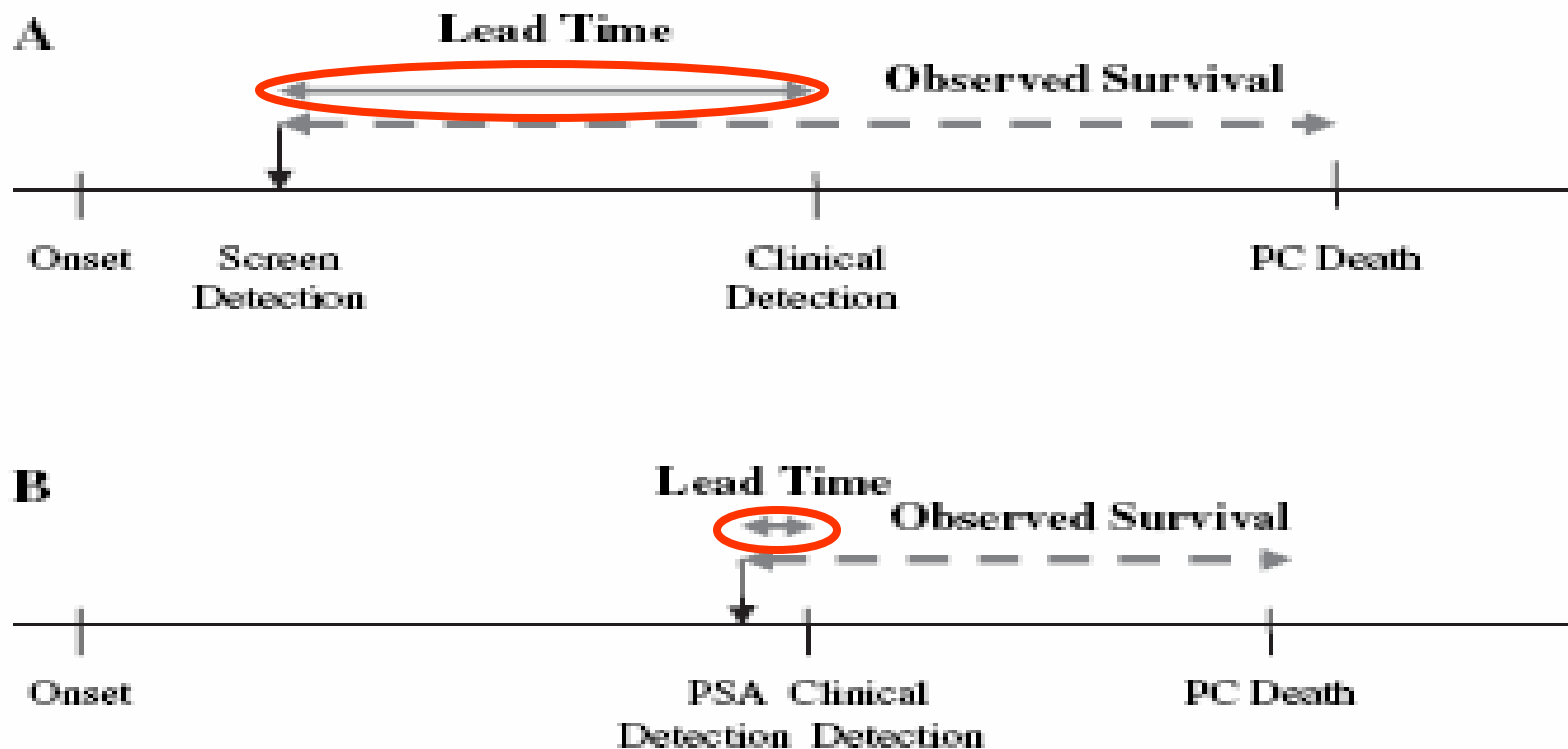
1. PSA level



PSA and PSA velocity (PSAV) from the Prostate Cancer Prevention Trial. Closed circles PCa; open circles, participants with a negative biopsy (Spearman's correlation coefficient, $r = .70$)

2. Mode of PCa detection

- Prospective screening trials, (PCPT and ERSPC)
- Survival or prognostic studies, which may or may not include serial screening of all patients.



A) Patients with screen-detected prostate cancers (PC) are likely to have lower PSAV at diagnosis, and their survival includes long lead time. **B**) Patients with prostate cancers detected close to their date of clinical presentation are likely to have higher PSAV at diagnosis, and their survival includes only a short lead time.

3. Type of study

Association studies

- is PSAV correlated with high-risk disease?

Classification studies

- does PSAV enable us to reliably distinguish high-risk from low-risk patients and individuals with prostate cancer from those without the disease?

Type of study

- **Association studies** use regression techniques to quantify dependence between a marker and an outcome
- **Classification studies** aim to quantify the sensitivity, specificity, and diagnostic accuracy of the marker in detecting disease

Even if a marker such as PSAV is independently associated with disease risk or with the risk of high-grade cancer, it may not substantially increase diagnostic accuracy

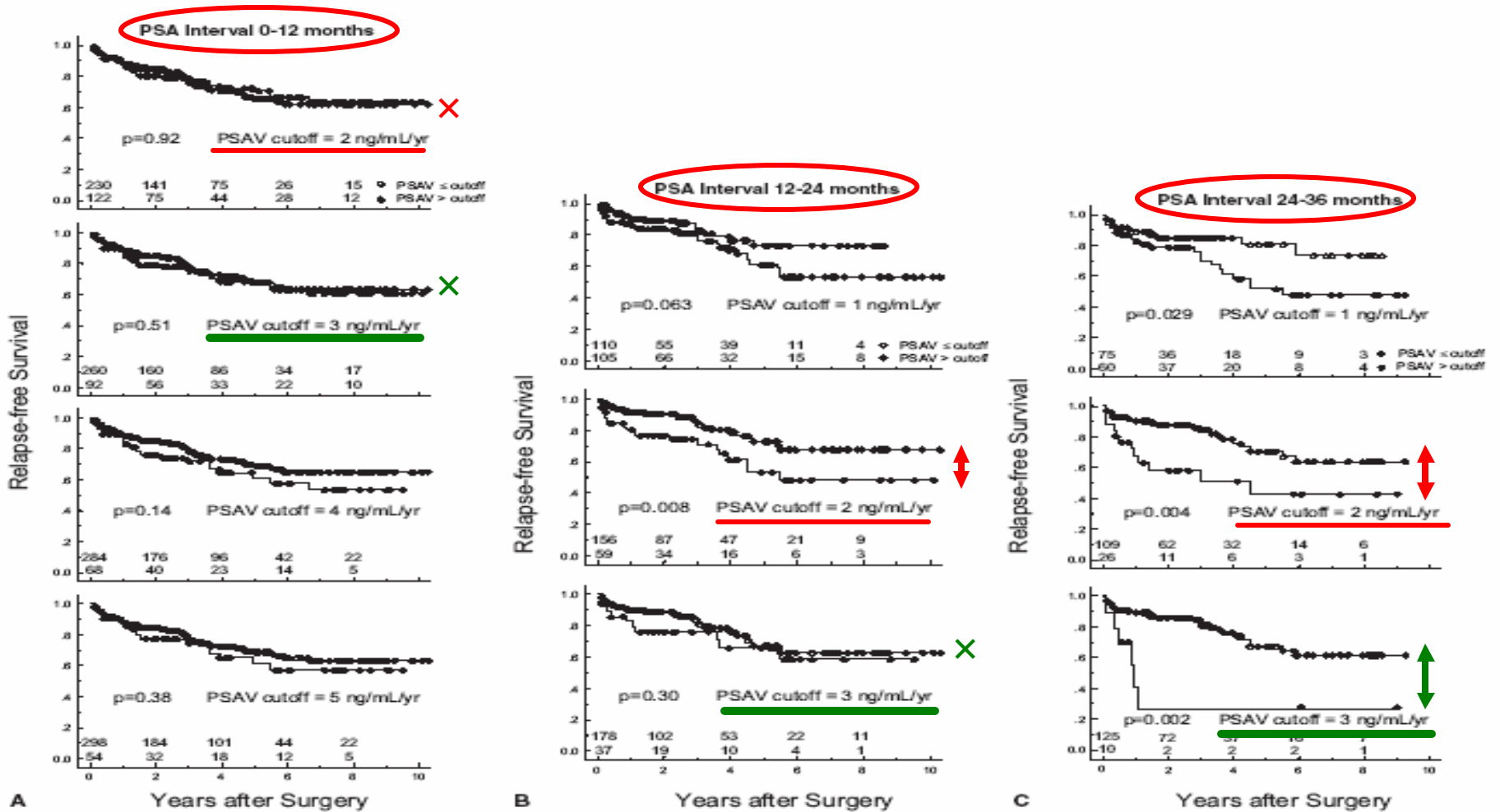
4. Timing, cutoff, method of calculation

Optimal Timing, Cutoff, and Method of Calculation of Preoperative Prostate-Specific Antigen Velocity to Predict Relapse After Prostatectomy: A Report from SEARCH

C.R. King, S.J. Freedland, M.K. Terris, W.J. Aronson, C.J. Kane, C.L. Amling, and J.C. Presti, Jr

UROLOGY 69: 732–737, 2007

Effect on PSAV of **timeframe** of the PSA used and the PSAV cutoff levels



(King et al UROLOGY 69: 732–737, 2007)

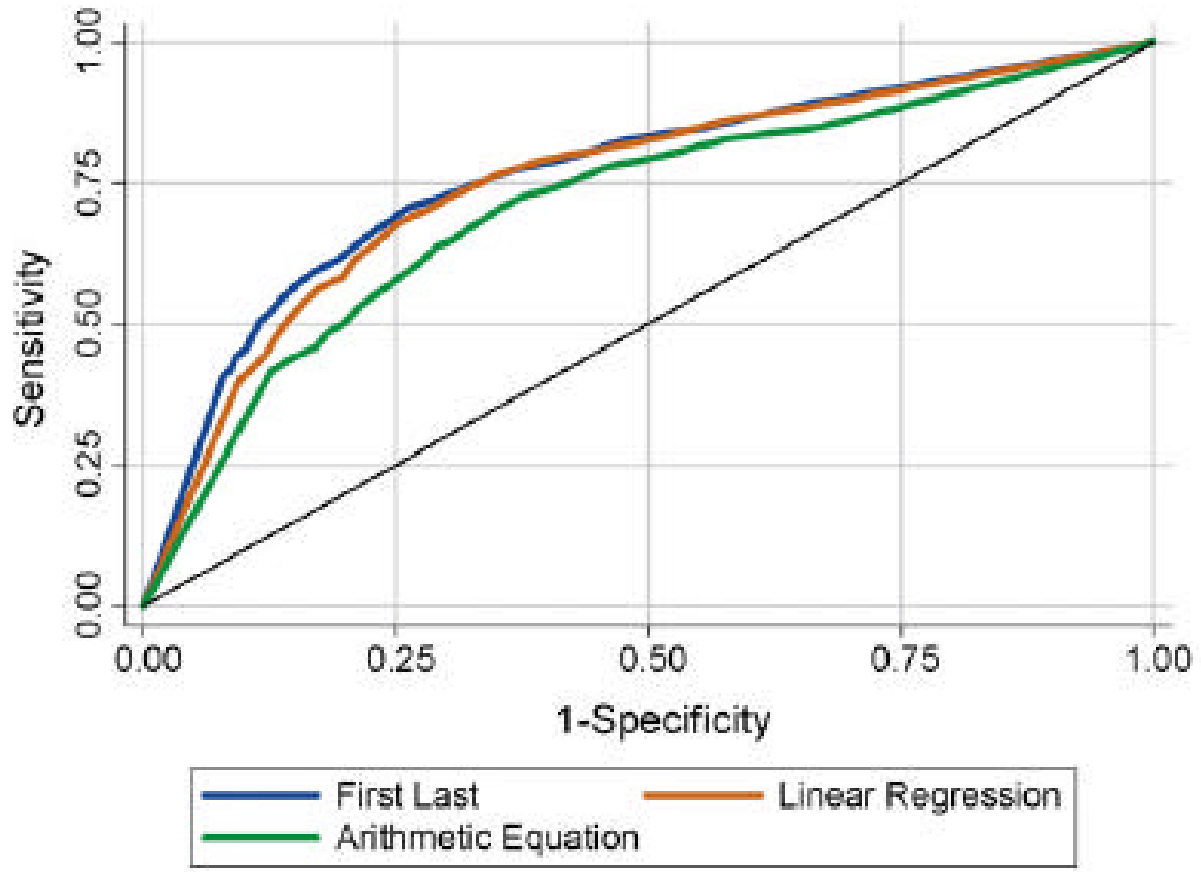
Methods of Calculating Prostate-Specific Antigen Velocity

*D. Connolly, A. Black , L.J. Murray, G. Napolitano, A
Gavin, P.F. Keane*

Eur Urol 52, 1044–1051, 2007

- Population-based database of PSA results
- 2204 men with initial PSA < 10.0 ng/ml and a subsequent diagnosis (716 PCa, 1488 BPH)
- 3 PSA tests before diagnosis carried out over a minimum of 18 mo were included.
- PSAV was calculated by using three methods:
 1. Arithmetic equation of change in PSA over time
 2. Linear regression
 3. Rate of PSA change using first and last values only

ROC curves of three methods of PSA velocity calculation for prostate cancer diagnosis



- The method used to calculate PSAV can produce markedly different results from the same PSA data, which may affect the decision to proceed with prostate biopsy

PSA Velocity

Margini di miglioramento: standardizzazione

- Disegno dello studio
- Frequenza di campionamento
- Distanza fra i campionamenti
- Variabilità analitica e biologica
- Algoritmi di calcolo
- Livelli decisionali

Conclusioni

Criteri basati sul cut-off

- Basi scientifiche ed epidemiologiche deboli
- Utilità clinica fortemente ridimensionata

Criteri dinamici

- Razionale biologico e clinico forte
- Bassa generalizzabilità per carenza di standardizzazione
- Impiego clinico non ancora raccomandabile

Biomarcatori in oncologia 2008 e criteri decisionali: dove siamo ?

