How I Manage a Patient with a Newly Elevated PSA

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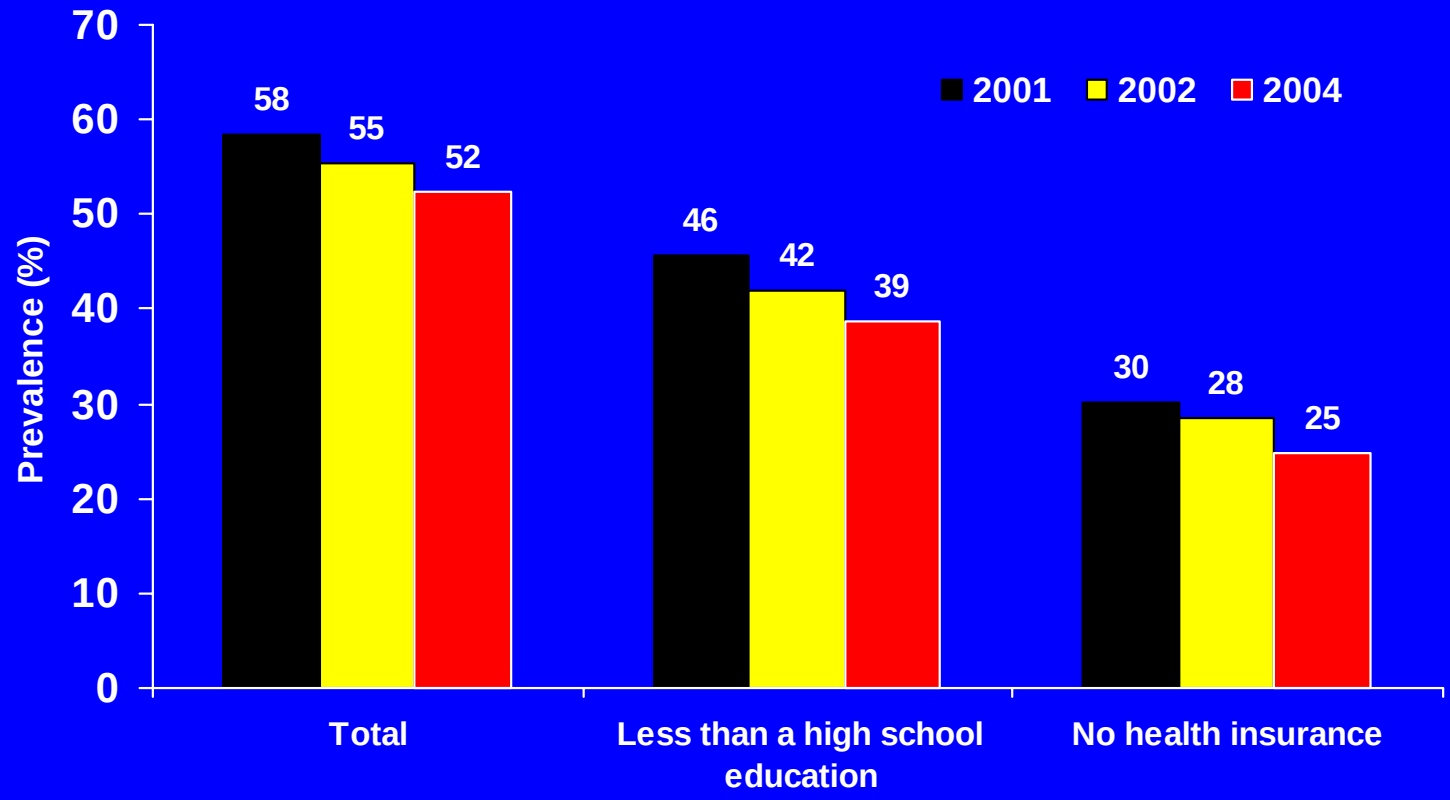
Recent* Prostate-Specific Antigen (PSA) Test Prevalence (%) Men 50 Years and Older, US, 2001-2004



*A prostate-specific antigen (PSA) test within the past year. Note: Data from participating states and the District of Columbia were aggregated to represent the United States.

Source: Behavioral Risk Factor Surveillance System Public Use Data Tape (2001, 2002, 2004), National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2002, 2003, 2005.

PSA Testing in Physicians

- **87%** of male physicians age ≥ 50 years had a PSA test

Chan EC et al J Gen Intern Med Epub Jan 20, 2006; Walsh PC J Urol 176:583, 2006

"There are several conditions that can cause the PSA to rise:"

- **Prostate cancer** – PSA increases and does not decrease without treatment
- **Benign prostatic hyperplasia (BPH)** - PSA increases (but more slowly than cancer) and does not decrease without treatment
- **Prostate inflammation (prostatitis)** – PSA increases up, sometimes dramatically, and then returns to baseline with or without treatment

Other Possible Causes Counfounding PSA

- Ejaculation
- Prostate manipulation
- Differences in PSA assay standardization
- Biologic variation

Nonetheless, PSA is a very useful aid for the early detection of prostate cancer

The traditional PSA cutoff for recommending a prostate biopsy is 4.0 ng/ml (I have used 2.5 since 1995)

Risk for Prostate Cancer on Needle Biopsy

- PSA 4 -10 ng/ml 25 to 40%
- PSA >10 ng/ml ~ 60%

Less Well Appreciated

- Median PSA for age group in men without prostate cancer

Median PSA in Men without Prostate Cancer: PSA Study (32,000 Men)

Age Group	Median PSA
40s	0.7
50s	0.9
60s	1.3
70s	1.7

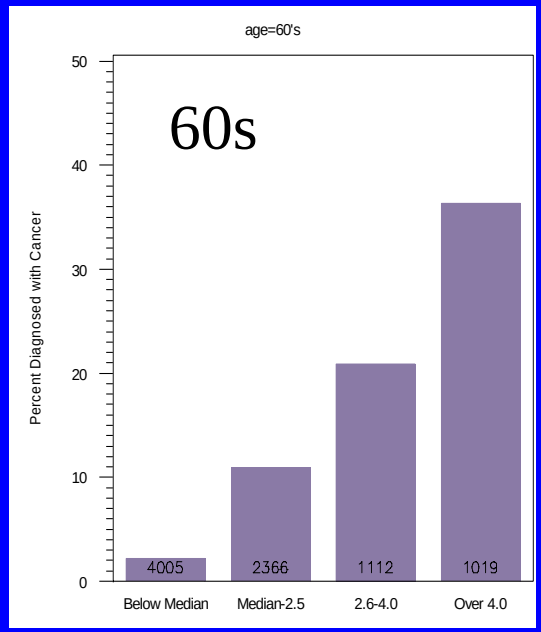
Loeb S et al J Urol 177:1745,2007; Loeb S et al J Urol:177:899, 2007; Loeb et al. Urology 67: 316,2006

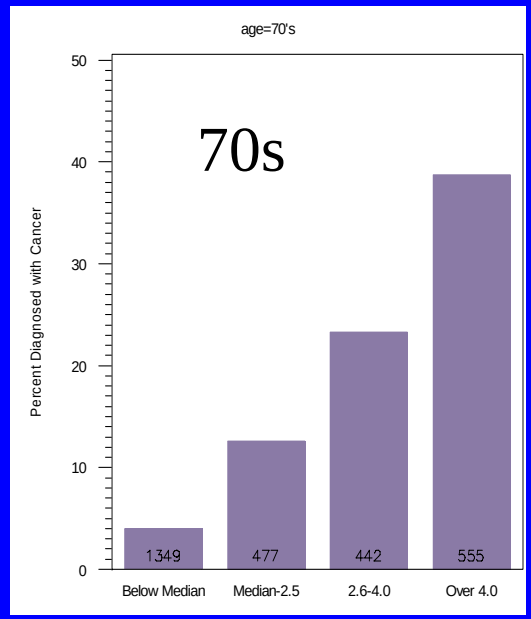
Baseline PSA Predicts Risk and Aggressiveness

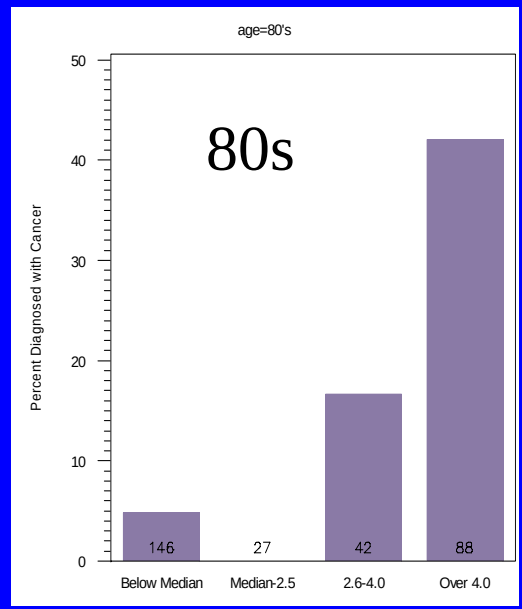
	PSA range ng/ml	Relative Risk
Age 50-59	< 0.9	1
	0.9-2.5	7
	2.6-4.0	27
	> 4.0	44

Loeb S, et al. Urology 67:316-20, 2006

Prostate Cancer Detection Rates by PSA Category



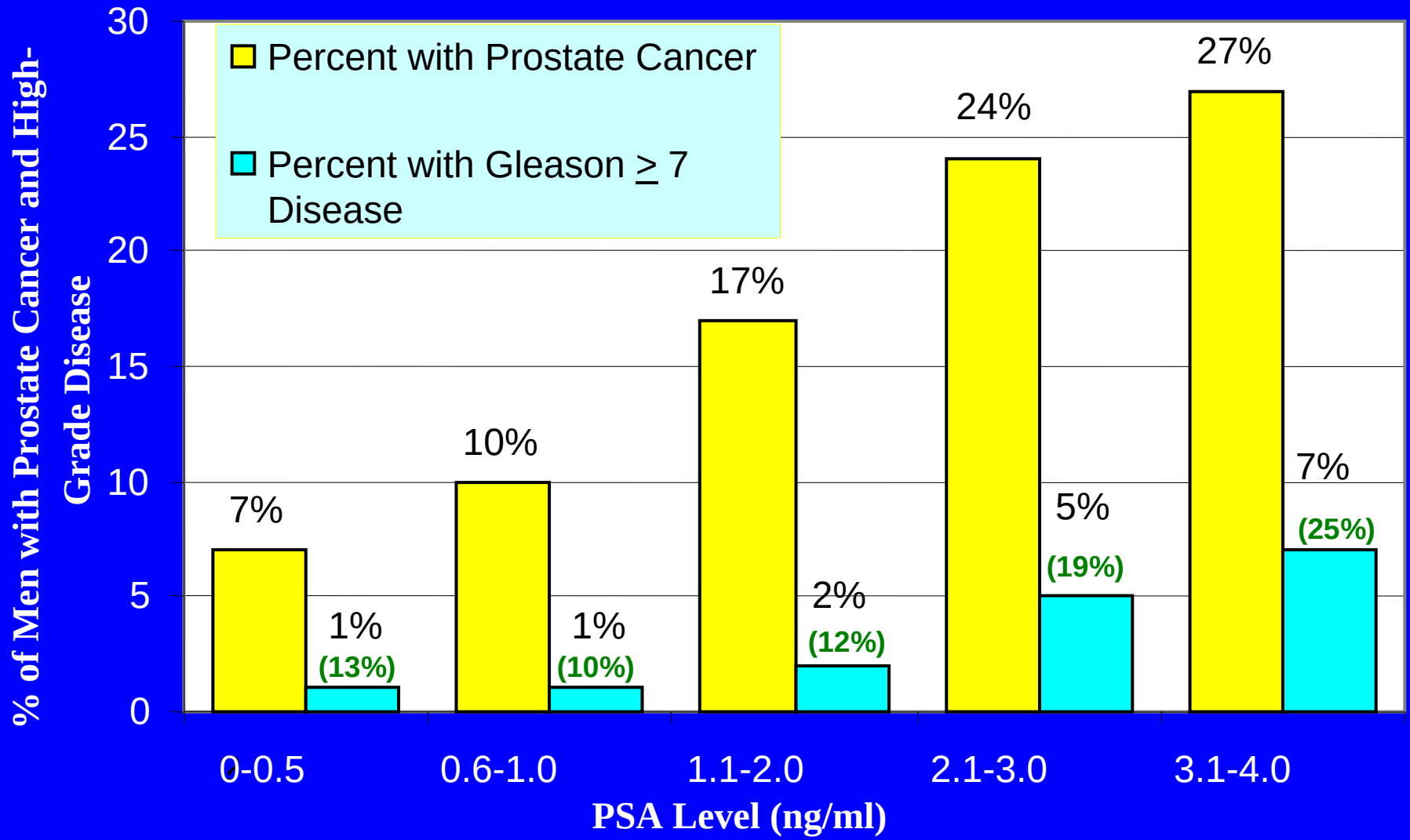




< median median-2.5ng/ml 2.6-4 ng/ml >4ng/ml

Data from PSA Study: 36,000 men followed for up to 12 years

Prevalence of Prostate Cancer with PSA ≤ 4.0 ng/ml.



Thompson IM, et al. N Engl J Med. 2004;350:2239-46.

PSA Conversion to > 4 ng/ml

	PSA	PSA	PSA	PSA
	0-1	**1-2**	**2-3**	**3-4**
2 yrs	0.5	2.5	**13**	**44**
4 yrs	1.4	6.6	**30**	**77**
5 yrs	1.6	7.6	**35**	**83**

Crawford D et al J Urol 167: 99, 2002 from PLCO Trial

How to Evaluate Possible Confounding from BPH

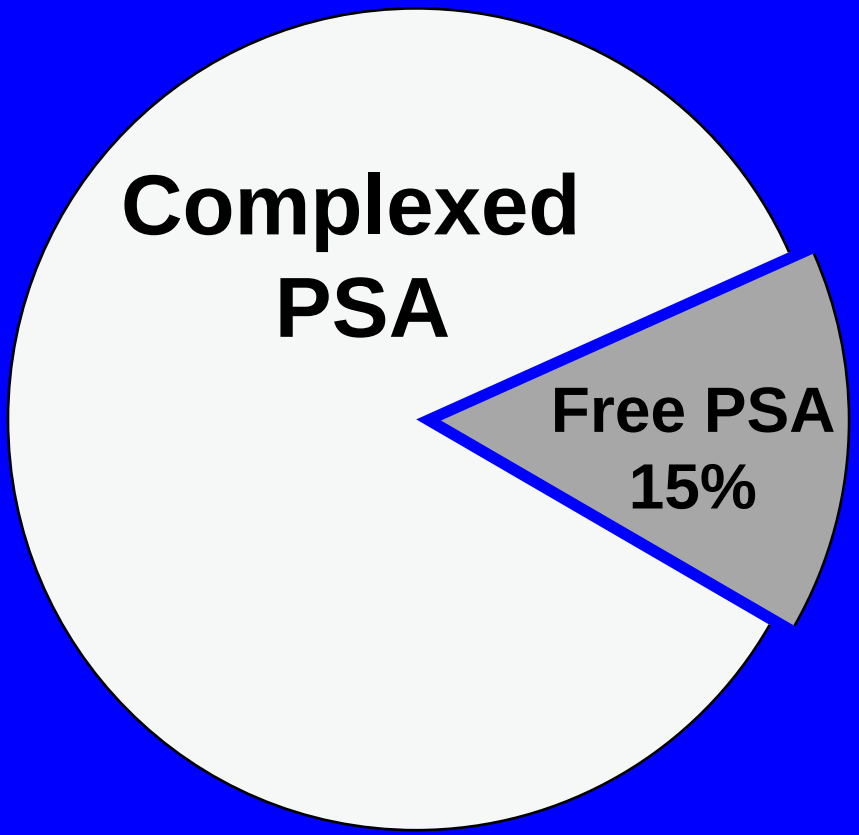
- Estimate **PSA velocity**
- Estimate **PSA density**
- Measure the **% of free PSA**

PSA Density (PSA / Prostate Volume)

- PSA density > 0.10 –0.15 is suspicious for cancer
- PSA density correlates with:
  - Tumor volume
  - Gleason grade
  - PSA velocity
  - Progression-free survival

Kundu SD et al, J Urol 177:505,2007

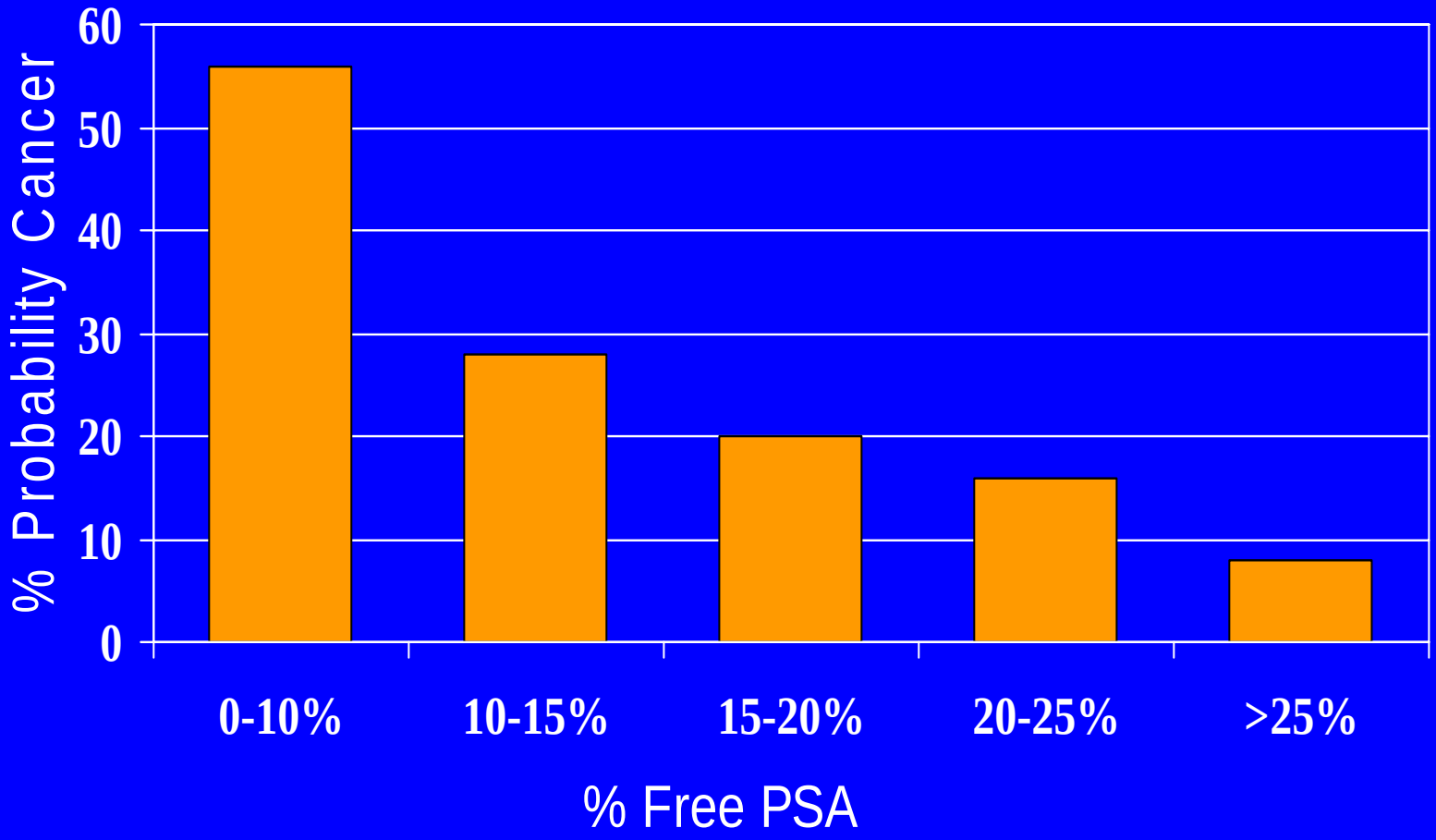
What is Free PSA in Serum?

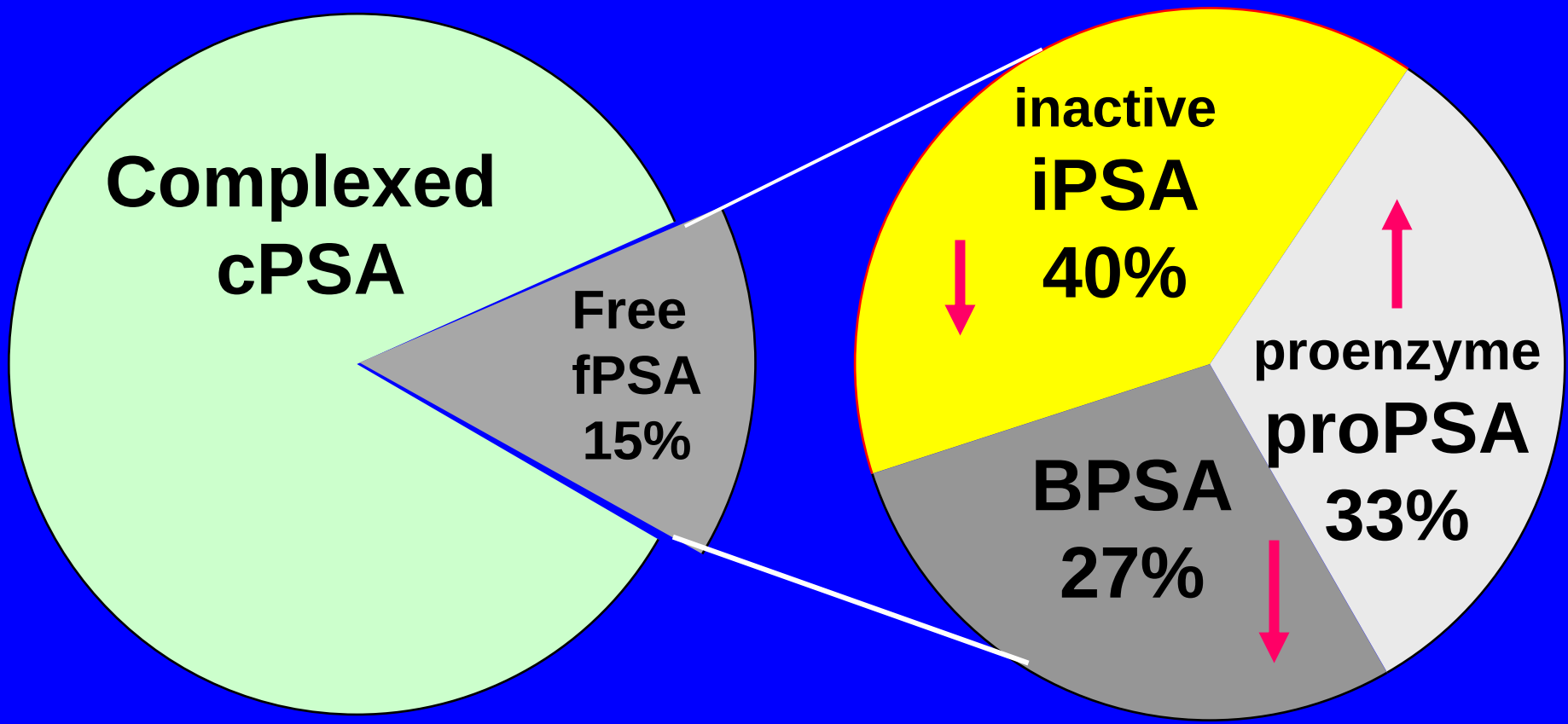


- Enzymatically inactive
- Does not complex with ACT
- Lower % in cancer

Probability of Cancer

PSA 4-10 ng/ml




Complexed
cPSA
Free
fPSA
15%
inactive
iPSA
40%
proenzyme
proPSA
33%
BPSA
27%

Evaluate Possible Confounding from Prostatic Inflammation

- Empiric trial of antibiotics
- Repeated PSA measurements estimating PSA kinetics

PSA Kinetic Parameters

- **PSA velocity**
  - Absolute change in PSA per year
  - Independent of baseline PSA value
- **PSA doubling time**
  - Relative change in PSA per year
  - A function of baseline PSA

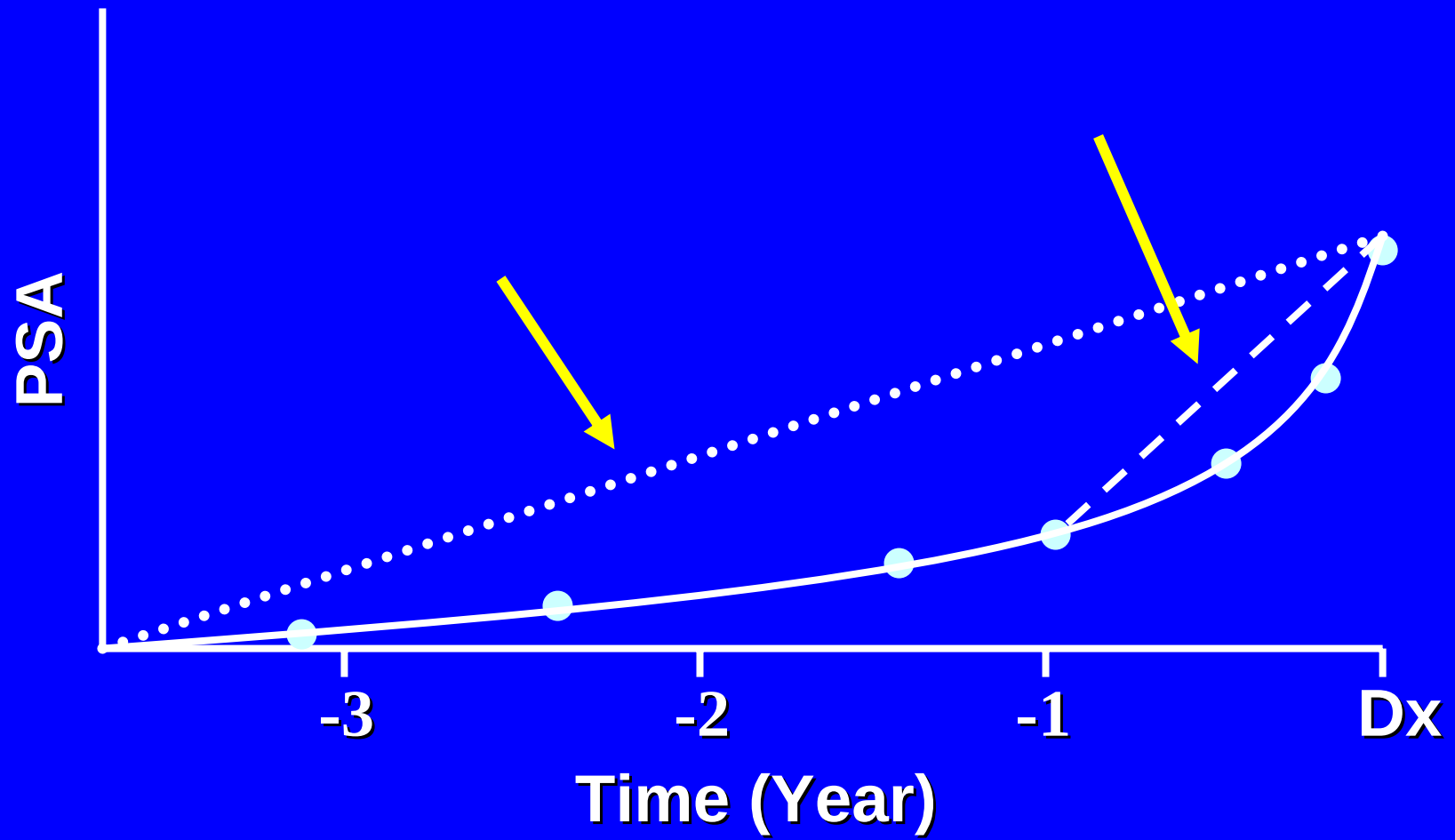
Calculating PSA Kinetic Parameters

- PSAV = (PSA2-PSA1)/time

- PSADT* = log2/((log PSA2 – log PSA1)/time)

Xu X et al, J Urol 176:2427, 2006

PSA Kinetics



Dependence on Baseline PSA

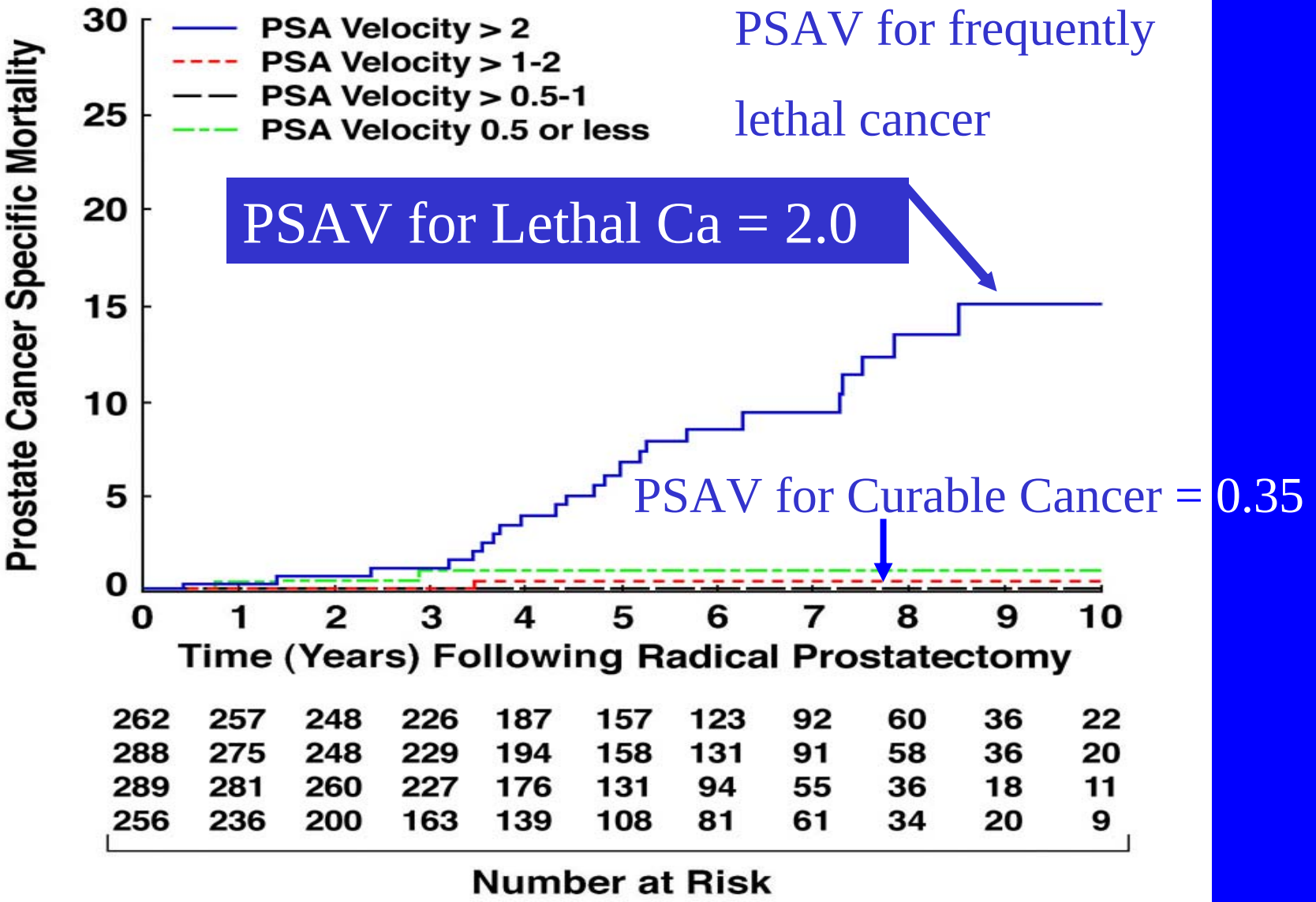
	PSA 1 (ng/ml)	PSA 2 (ng/ml)	PSAV (ng/ml/y)	PSADT (years)	% PSA Rise
Patient A	1.0	2.0	**1.0**	**1.0**	**100%**
Patient B	4.0	5.0	**1.0**	**4.0**	**25%**

PSA Velocity in PSA Study

	Median PSAV (ng/ml/yr)
Cancer	0.8
Non-Cancer Biopsy	0.1
No Biopsy	0.1

P<0.0001

PSAV for frequently lethal cancer



D'Amico et al, NEJM 351:125, 2004

Long-T PSAV >0.35 ng/ml/year Correlates with CaP-Specific Mortality Rate

- PSAV calculated in 980 men from Baltimore Longitudinal Study on Aging

- *PSAV >0.35 ng/ml/year associated with 5-fold increased risk prostate cancer death 15 or more years later*

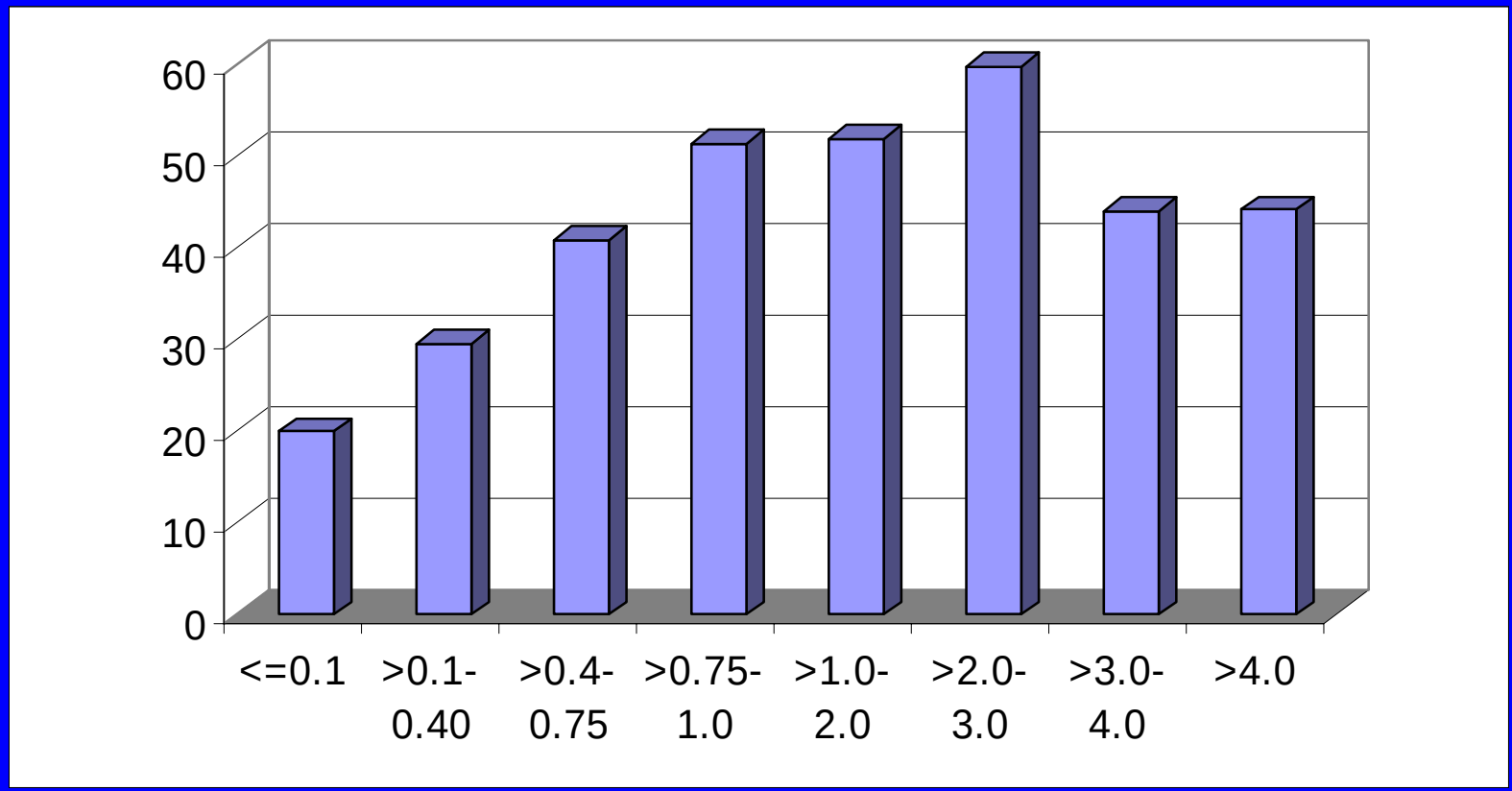
Carter HB et al. JNCI 2006; 98: 1521

PSA Velocity to Predict CaP

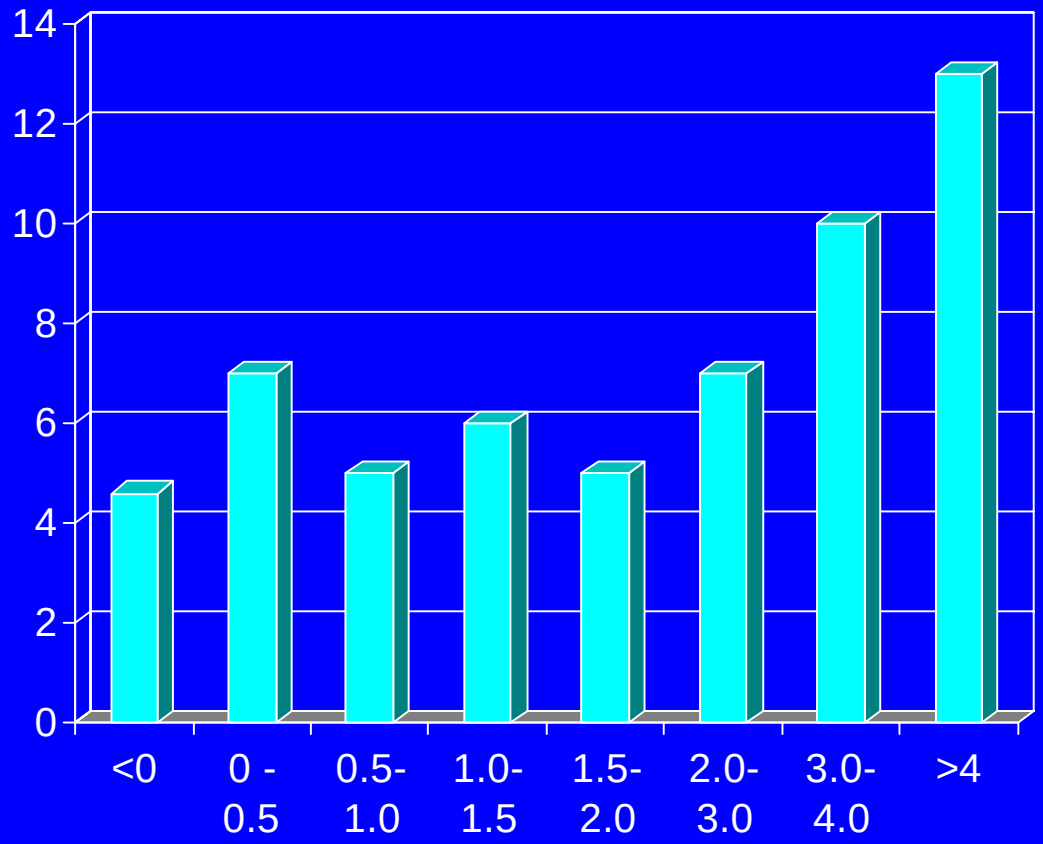
- Traditional PSAV cutoff for Bx = 0.75, established in men with PSA > 4 ng/ml
- If PSA < 4 ng/ml, a cutoff of 0.3-0.5 ng/ml/yr should be used
- 2006 National Comprehensive Cancer Center (NCCN) Guidelines recommend 0.5 ng/ml/year (0.35 in 2007)
- 2007 AUA may recommend 0.4 ng/ml/year

*Smith DS et al J Urol 1994 152 1163;Fang et al Urol 2002 59 889; Berger D, et al abstract 485, 2006.**

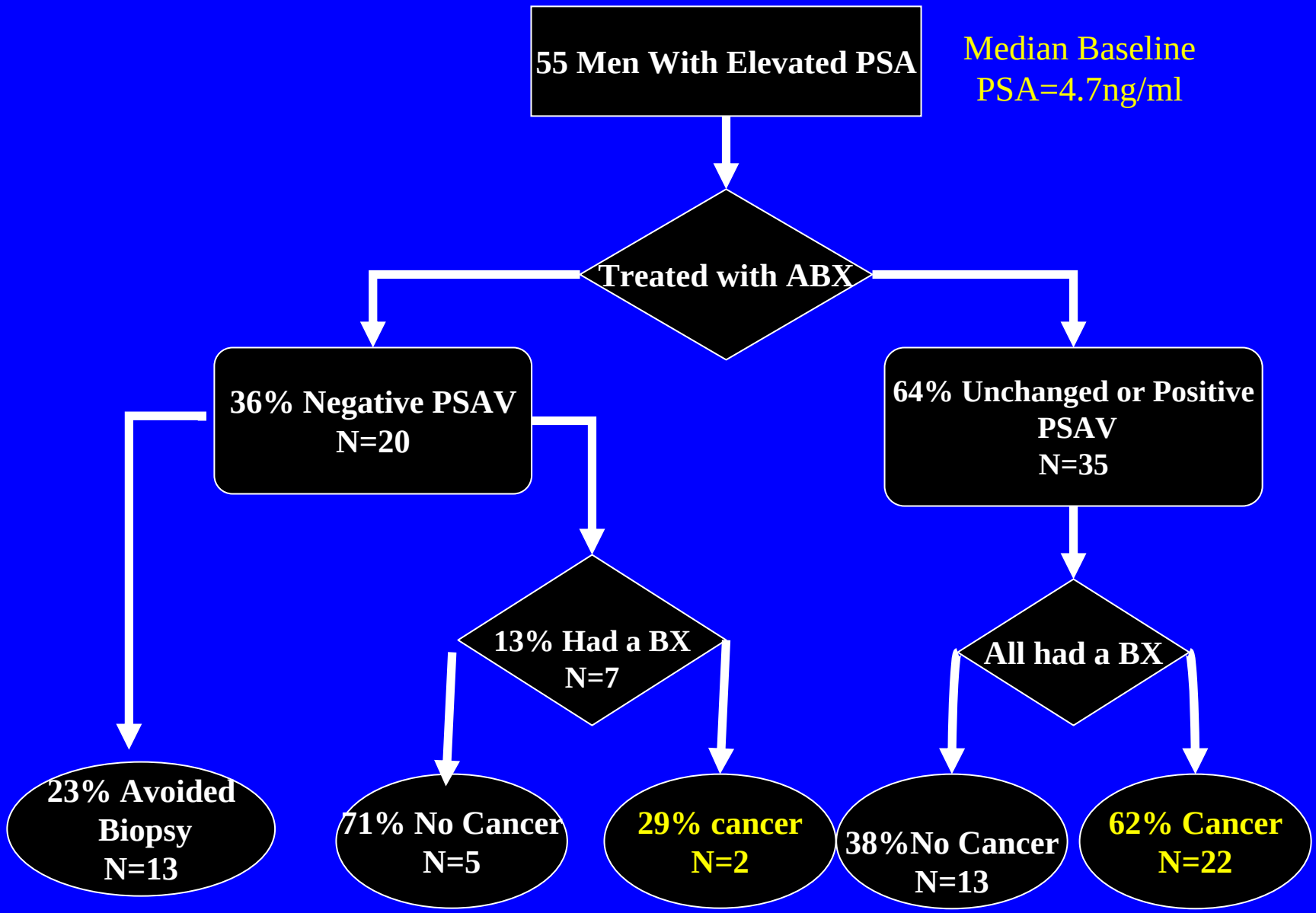
Cancer Detection Rate by PSAV



Rate of prostatitis on first biopsy, stratified by PSAV



Prospective Cohort Treated with an Empiric Antibiotics

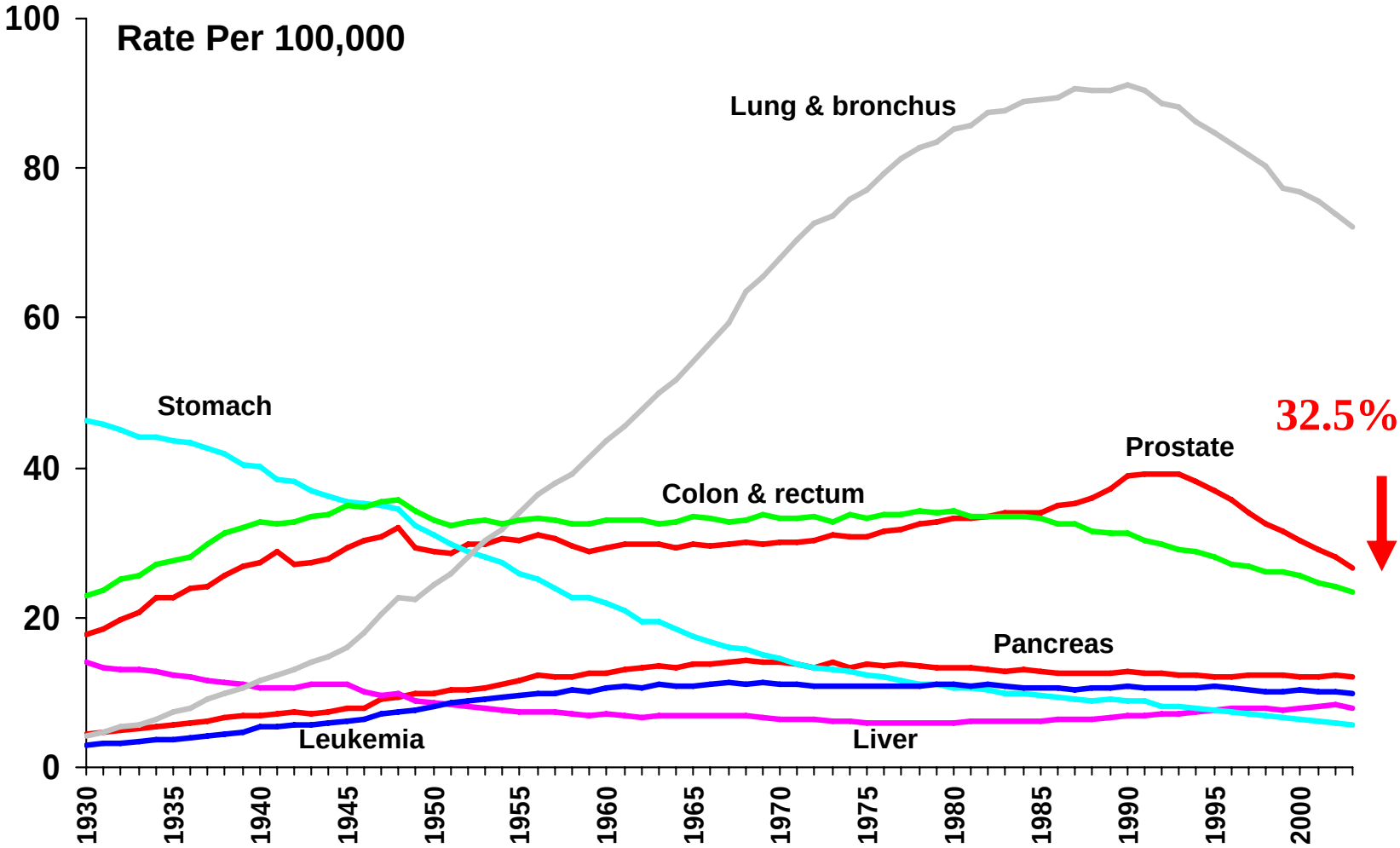


Different PSA Standards

- Hybritech 1986 (Clinical parameters established using this assay)
  - WHO 1999
- WHO-standardized assays give PSA levels ~23% lower
- Hybritech 4.0 = WHO 3.1
- Hybritech 2.5 = WHO 2.0
- Standardization bias affects: PSA cutoffs, PSAV, PSADT, PSA density, % free PSA

Sotelo R et al Urology 69:1143,2007

Cancer Death Rates*, for Men, US,1930-2003



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes 1960-2003, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

Jemal A et al, Cancer Epidemiol Biomarkers Prev 2005;14:590

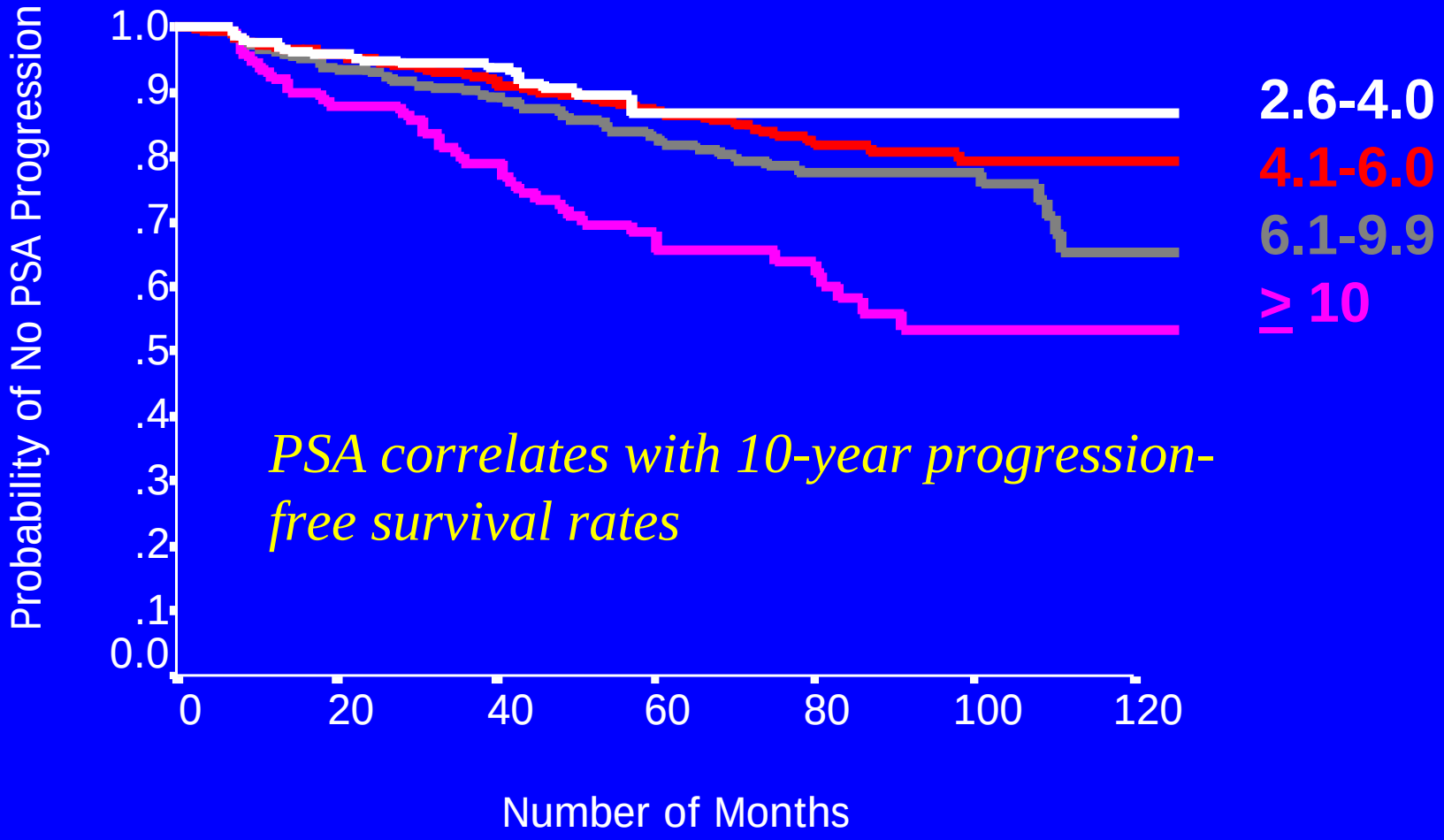
Examined relation of PSA screening to stage at diagnosis and prostate cancer death rates in 30 population-based US cancer registries (30 states, District of Columbia & Atlanta: ~ 68% of US population)

- *The more PSA testing, the less late-stage disease, and the lower the prostate cancer death rate*

PSA

- Cancers treated at lower PSA have better progression-free survival than those treated at higher PSA

T1c Patients with RRP by PSA at Diagnosis (PSA Follow-up Study)



Intelligent Use of PSA

- Start annual PSA testing at age 40 and track changes
- Know the standardization of PSA assays used
- Assess PCa risk using age-group median PSA values
- Use PSA density and % free or % complexed PSA to evaluate confounding from BPH
- Rule out prostatitis with antibiotics and repeat PSA measurements
- Use PSA velocity to identify more aggressive tumors
  - Use PSAV cutoff: 0.3–0.5 ng/ml/yr