Prostate Cancer and Use of PSA

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The Wrong Call on Prostate Cancer Screening

By William J. Catalona
Tuesday, August 26, 2008; Page A13

Numerous media reports followed a federal task force's announcement this month that there is insufficient medical evidence to assess the risks and benefits of prostate cancer screening in men younger than 75 and that doctors should stop testing men over age 75 [" U.S. Panel Questions Prostate Screening: 'Dramatic' Risks for Older Men Cited," front page, Aug. 5].

It's important to note that consideration was not given to the overwhelming body of emerging evidence that screening with PSA tests and digital rectal exams saves lives. Rates of death from prostate cancer and rates of diagnosis at advanced stages have decreased markedly since testing became widespread.

As a physician and a researcher specializing in prostate cancer, I worry that this recommendation will result in delays in potentially lifesaving treatment and possibly the unnecessary loss of life.

The U.S. Preventive Services Task Force did not even recommend screening for men at higher risk because of race or family history. The task force reasoned that screening might harm more men than it

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The New York Times
Sunday, January 25, 2009
Health

Well
Tara Parker-Pope on Health

Will Older Men Give Up the PSA Test?

Men ages 75 and older should not be screened for prostate cancer. This is the important and definitive conclusion of the U.S. Preventive Services Task Force, which for the first time has made a specific recommendation about the value of screening for prostate cancer.

To many doctors, the new guidelines will not come as a shock. Quite a few believe that because prostate cancer often progresses slowly, not causing symptoms for 10 years or longer, it's inappropriate to look for it in healthy older men. A man aged 75 or older may well die of another cause long before his prostate cancer becomes a problem. And treatment of prostate cancer has significant drawbacks, often leading to impotence, incontinence and a variety of other complications that reduce a patient's quality of life.

But what doctors know and what happens in practice often are two different things.

Prostate screening involves a simple blood test to check for prostate-specific antigen, or PSA. Many doctors find it easier just to do a PSA test than take

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U.S. Panel Questions Prostate Screening
'Dramatic' Risks For Older Men Cited

By Rob Stein
Washington Post Staff Writer
Tuesday, August 5, 2008; Page A01

The blood test that millions of men undergo each year to check for prostate cancer leads to so much unnecessary anxiety, surgery and complications that doctors should stop testing elderly men, and it remains unclear whether the screening is worthwhile for younger men, a federal task force concluded yesterday.

In the first update of its recommendations for prostate cancer screening in five years, the panel that sets government policy on preventive medicine said that the evidence that the test reduces the cancer's death toll is too uncertain to endorse routine use for men at any age, and that the potential harm clearly outweighs any benefits for men age 75 and older.

Sprint
Today's forecast: Unlimited

Is cure possible?

Willet F. Whitmore, Jr

Is cure possible?

Is cure necessary?

Is cure possible only when it is not necessary?

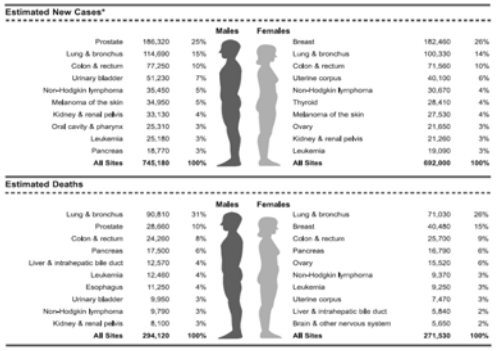
Willet F. Whitmore, Jr

Is cure possible?

Is cure necessary?

Willet F. Whitmore, Jr

Prostate Cancer Epidemiology



Estimated New Cases*

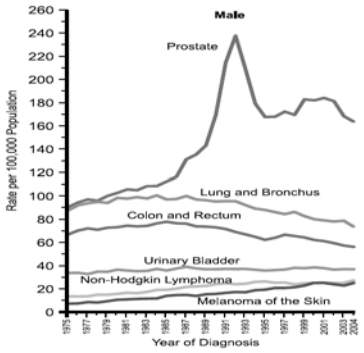
	Males			Females		
Prostate	186,320	25%		Breast	182,460	26%
Lung & bronchus	114,690	15%		Lung & bronchus	100,330	14%
Colon & rectum	77,250	10%		Colon & rectum	71,560	10%
Urinary bladder	51,230	7%		Uterine corpus	40,100	6%
Non-Hodgkin lymphoma	35,450	5%		Non-Hodgkin lymphoma	30,670	4%
Melanoma of the skin	34,950	5%		Thyroid	28,410	4%
Kidney & renal pelvis	33,130	4%		Melanoma of the skin	27,530	4%
Oral cavity & pharynx	25,310	3%		Ovary	21,650	3%
Leukemia	25,180	3%		Kidney & renal pelvis	21,260	3%
Pancreas	18,770	3%		Leukemia	19,090	3%
All Sites	**745,180**	**100%**		**All Sites**	**692,000**	**100%**

Estimated Deaths

	Males			Females		
Lung & bronchus	90,810	31%		Lung & bronchus	71,030	26%
Prostate	28,660	10%		Breast	40,480	15%
Colon & rectum	24,260	8%		Colon & rectum	25,700	9%
Pancreas	17,500	6%		Pancreas	16,790	6%
Liver & intrahepatic bile duct	12,570	4%		Ovary	15,520	6%
Leukemia	12,460	4%		Non-Hodgkin lymphoma	9,370	3%
Esophagus	11,250	4%		Leukemia	9,250	3%
Urinary bladder	9,950	3%		Uterine corpus	7,470	3%
Non-Hodgkin lymphoma	9,790	3%		Liver & intrahepatic bile duct	5,840	2%
Kidney & renal pelvis	8,100	3%		Brain & other nervous system	5,650	2%
All Sites	**294,120**	**100%**		**All Sites**	**271,530**	**100%**

American Cancer Society.: Cancer Facts and Figures 2008. Atlanta, Ga: American Cancer Society, 2008.

Age Adjusted Incidence



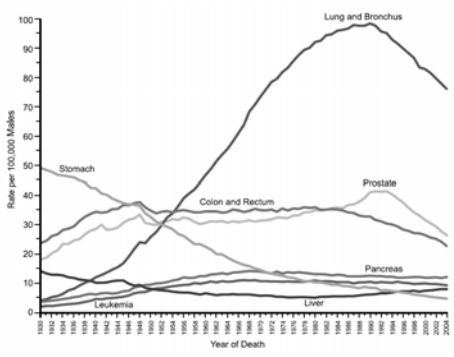
American Cancer Society.: Cancer Facts and Figures 2008. Atlanta, Ga: American Cancer Society, 2008.

Prostate Cancer

- Regional differences have been observed in prostate cancer incidence and mortality rates.
- Variable incidence rates may reflect variability in the intensity of early detection practices and use of PSA.
- Differences in aggregate mortality by regions of the United States have not been observed

American Cancer Society, 2008.
Potosky AL, et al.: J Natl Cancer, 1990.
Levy IG, et al.: CMAJ, 1993.

Age Adjusted Deaths



American Cancer Society.: Cancer Facts and Figures 2008. Atlanta, Ga: American Cancer Society, 2008.

Risk Factors

- Age
- Race
- Family history
- Dietary fat
- Lycopene
- Soy
- Smoking
- Androgen levels and receptor expression

Prostate Specific Antigen

- Discovered in 1979 by Wang et al
- Approved by FDA in 1986
- Produced by prostate and periuretheral glands epithelial cells
- Liquefaction of seminal coagulum
- Serine protease from the kallikrein family
- In serum, most is bound

Prostate Specific Antigen-Screening

- Disagreement exists over cut-point
- Too high a cut-point
  - Miss curable prostate cancer
- Too low a cut-point
  - Too many biopsies performed and insignificant cancer detected
- Fluctuation in PSA levels is very common 30-40%

Eastham, J, *et al.: JAMA, 2003*

Prostate Specific Antigen

- Inflammation, hyperplasia, neoplasia lead to disruption of physiological barriers and increased serum PSA levels
- Half life is 2-3 days
- Used for
  - Initial diagnosis of disease and screening
  - Monitor for recurrence after initial therapy
  - Prognosis of outcomes after therapy

PCPT

- There is no PSA value below which a man can be assured that he has no risk of prostate cancer
- Estimated sensitivity in the range of 70%
- 2,950 men PSA < 4.0 ng/mL or an normal DRE
- Final PSA determination and prostate biopsy after 7 years.
- Incidence of prostate cancer 15.2%
- High-grade cancer (defined as Gleason score ≥7) was seen in 15.8%
- In the placebo arm; a continuum of prostate cancer risk at all values of PSA

Thompson IM, et al.: N Engl J Med, 2004.

PSA Cut-Point

Table 3. Numbers (percentages) of prostate cancers and high-grade prostate cancers by PSA level*

PSA level, ng/mL	*N*	No. of prostate cancers (%)	No. of high-grade prostate cancers† (%)
0–1	1963	217 (11.1)	19 (1.0)
1.1–2	1640	337 (20.5)	43 (2.6)
2.1–3	775	205 (26.5)	44 (5.7)
3.1–4	510	153 (30.0)	48 (9.4)
4.1–6	481	234 (48.6)	70 (14.6)
>6	150	65 (43.3)	33 (22.0)
Total	5519	1211 (21.9)	257 (4.7)

Thompson, IM, *et al.*: JNCI, 2006

PSA Density

- Benson et al 1992
- Serum PSA level/prostate volume
- TRUS
- ≥0.15 will avoid 60% of biopsies but will miss 10% of cancers

Benson MC, J Urol, 1992.

PSA Derivatives

- Density
- Velocity
- Free to total

PSA Velocity

- Carter et al in 1992
- Rate of change over a period of 18-24 months
- Three measurements
- PSA 4-10ng/ml, PSAV ≥ 0.75 ng/ml/year will capture 95% of CaP patients
- PSA < 4ng/ml, PSAV ≥ 0.35

Carter HB, Cancer Res, 1992.

Free PSA

- Christensson et al in 1993
- Free/total 0.25 or less detected 95% of cancer and avoided 20% of unnecessary biopsies
- Most valuable when total PSA 4-10 ng/ml

Catalona WJ, JAMA 1998.

Prostate Cancer Screening

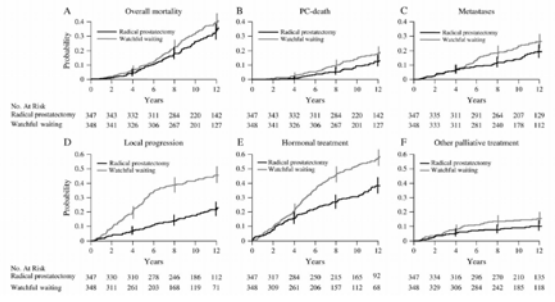
- Controversial:
  - lack of definitive evidence of benefit
  - Prostate cancer has a relatively slow course, Long term follow up is needed (>15 years).
  - Patient's age
  - Comorbidities
  - Treatments are associated with significant morbidity
  - No comparisons of efficacy between therapeutic options

Screening for Prostate Cancer

- 7.9% of all screened men will have an elevated PSA (>4ng/ml),
- 1/3 will be diagnosed with CaP

Data from PLCO

Radical Prostatectomy Versus Watchful Waiting in Localized Prostate Cancer: the Scandinavian Prostate Cancer Group-4 Randomized Trial



Bill-Axelson A, *et al.*: JNCI, 2008

Screening for Prostate Cancer: *Potential Harms*

- Additional medical visits
- Adverse effects of prostate biopsies
- Anxiety
- Over diagnosis
- Over treatment
- Morbidity and mortality associated with treatment
- Financial burden

Prostate Cancer Screening

- Sandblim G *et al :* A small randomized trial in Sweden evaluated the effects of screening men aged 50 to 69 years every 3 years; No difference at 15 years, statistical power?
- Concato J *et al:* A nested case-control study
  - Ten U.S. Department of Veterans Affairs med ctr
  - 71,661 patients
  - No benefit from screening by PSA or PSA and/or DRE (OR, 1.08; 95% CI, 0.71–1.64; *P* = .72) or for PSA and/or DRE (OR, 1.13; 95% CI, 0.63–2.06; *P* = .68).

Sandblom G, et al.: Eur Urol, 2004
Concato J, et al.: Arch Intern Med, 2006.

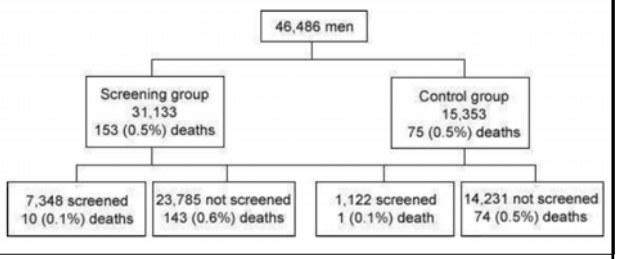
Screening for Prostate Cancer: *Potential Benefits*

- Early detection and treatment
- Improve cancer Specific Survival
- Alleviate symptoms of locally advanced disease

Randomized Prospective Clinical Trials: *The Canada Quebec Trial*

- A population-based trial that started in 1988.
- 46,193 men aged 45 to 80 years
- 30,956 were invited to be screened
- 7155 accepted and were screened. In the control group, 982 men were screened on annual bases.
- The cut-off is a PSA level of 3 ng/mL
- Intention-to- treat analysis was never done at 10 years

Randomized Prospective Clinical Trials:
The Canada Quebec Trial



Noncompliance bias, this study does not answer the question of whether early detection with PSA will reduce prostate cancer mortality

Randomized Prospective Clinical Trials:
The US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)

- **Both PSA positivity rates (range 7.7-8.8%) and DRE positivity rates (range 6.8-7.6%) were relatively constant over time**
- **PPV of a PSA level of >4.0 ng/mL decreased from 17.9% to 12.3%**
- **PPV for DRE (in the absence of a positive PSA test) was constant over time (2.9-3.6%)**
- **Cancer was diagnosed in 1902 men (4.9%)**
- **Determining the effect of PSA screening on prostate cancer mortality awaits further follow-up.**

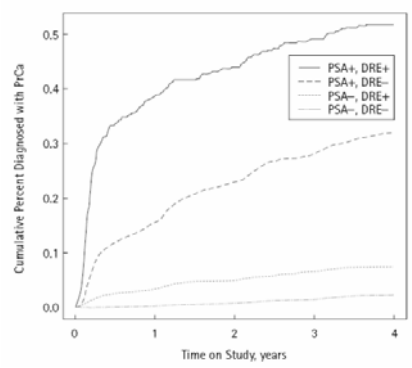
Grubb III *et al*. : BJUI, 2008

Randomized Prospective Clinical Trials:
The US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)

- **74,000 ages 55 to 74 years**
- **1:1 randomization to receive annual PSA and DRE screening to a total of 4 screens vs usual care in the community**
- **PSA cut-off is 4 ng/mL**
- **Follow-up of abnormal screening results was at the discretion of physicians**
- **Compliance with screening, 85%**

Grubb III *et al*. : BJUI, 2008

PLCO



Randomized Prospective Clinical Trials:
The European Randomized Study for Screening for Prostate Cancer

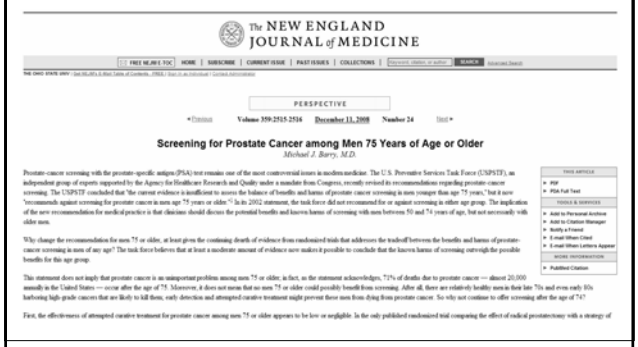
- Multicenter trial initiated in 1994
- 267,994 men in 8 countries.
- Method of recruitment, age of the enrollees, PSA cut-offs and the frequency of screening vary among the centers.
- Lead-time in Rotterdam section was 10.3 years
- ERSPC is designed to show or exclude at least a 25% reduction in prostate cancer mortality

When to Stop Screening

- US Preventive Services Task Force
  - Recently revised recommendations regarding prostate cancer screening (Dec 2008)

    "the current evidence is insufficient to assess the balance of benefits and harms of prostate cancer screening in men younger than age 75 years"

    "recommends against screening for prostate cancer in men age 75 years or older"
  - In 2002, no recommendation against screening in any age group



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Screening for Prostate Cancer among Men 75 Years of Age or Older

Michael J. Barry, M.D.

When to Stop Screening
Screening in Men Older than 75

Arguments to continue screening

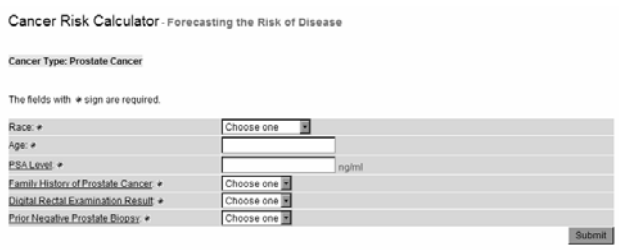
- 71% of prostate cancer deaths occur in men older than 75
- Many men in 70's and 80's are relatively healthy, high-grade cancers can still kill
- Death from prostate cancer is not the only important endpoint
  - Mobidity from prostate cancer may be prevented with local treatment

Barry, MJ, NEJM, 2008.

When to Stop Screening

- Arguments to stop screening
  - Most men > 75 will die from other causes
    - 1000 75-year old men, non-smokers, 19 expected to die of PCa, 430 expected to die of other causes
  - Long average lag-time between a detectable increase in PSA level and development of clinical disease
  - "Harms of screening increase with age
    - Increased PSA with age increases number of biopsies
    - Increased complications with treatments in older men
- Discussions may be individualized
- Results of screening trials will still not answer question of screening in older men as these men were excluded from these trials

NCI Prostate Cancer Risk Calculator



http://www.compass.fhcrc.org/edrnnci/bin/calculator/main.asp?t=prostate&sub=s1&m=&v=prostate&x=Prostate%20Cancer

- PSA for screening
  - to identify patients at high risk for prostate cancer
- Only way to establish diagnosis is through biopsy

TRUS/ Bx- What are the risks?

- Prostate biopsy is an office procedure, not requiring sedation
- Generally very-well tolerated
- No bowel prep necessary
- Peri-prostatic nerve block improves patient tolerability

Wein: Campbell – Walsh Urology, 9th ed., 2007.

TRUS/ Bx- What are the risks?

- **Side effects:**
  - **Hematuria, 20% - 60%, >1 day 14.7%, clot retention in 0.7%**
  - **Rectal bleeding, <2 days 2.2%, >2 days or requiring intervention 0.7%**
  - **Hematospermia, 9 -50%**
  - **Fever/ sepsis/ prostatitis 0.1%/ 1.0%**
  - **Urinary retention 0.2%**

Wein: Campbell – Walsh Urology, 9th ed., 2007.

Treatment for Clinically-Localized Prostate Cancer

- **Active surveillance**
- **Surgery**
  - **Open**
  - **Laparoscopic**
  - **Robotic**

Office-based Screening Procedure

- **Colonoscopy**
  - **Sedation**
  - **Bowel prep**
- **Complications- overall 0.3%, 2% with polypectomy**
  - **Hematochezia, 1.5 – 3%**
  - **Bowel perforation, 0.1 – 0.3%**
  - **Localized peritonitis**
  - **Sepsis**
  - **Death in 1/ 16,000 cases**

Feldman: Sleisenger & Fordtran's Gastroentinestinal and Liver Disease, 8th ed., 2006.

Treatment for Clinically-Localized Prostate Cancer

- **Radiation**
  - **EBRT**
  - **Brachytherapy**
- **Experimental**
  - **Cryoablation**
  - **HIFU**
  - **Focused therapy**

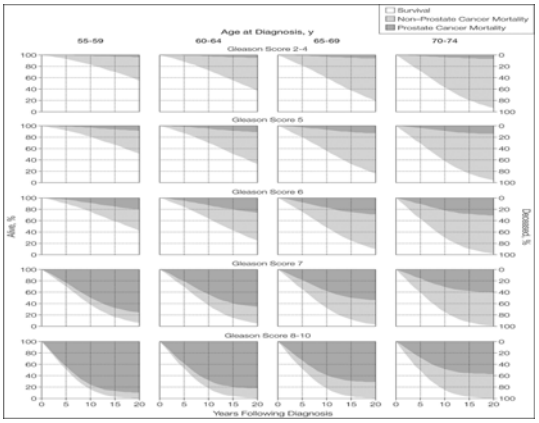
Selecting Treatment

- **Balance risk:**
  - **Posed by the health and age of the patient**
    - **Competing causes for death**
    - **Life expectancy**
  - **Posed by the cancer and its treatment**
    - **Any treatment for prostate cancer associated with potential decrement in quality of life**

Active Surveillance for PCa

- **Not all prostate cancer *should* be treated**
  - **Klotz, et al:**
    - **300 patients**
    - **F/U 8 years**
    - **Overall survival 85%, Disease-specific survival 99.3%**
  - **San Francisco**
    - **500 patients on surveillance**
    - **24% received secondary treatment a median of 3 years (range 1-17 years) after initiating surveillance**

Thong et al, J Urol, 2008.
Berglund et al, J Urol, 2008.



Albertsen, P. C. et al. JAMA 2005;293:2095-2101.

Active Surveillance for PCa

- **Risk of understaging / undergrading**
  - **27% upgraded or upstaged on immediate rebiopsy**
  - **18-20% of lowest risk on biopsy, upgraded or upstaged at prostatectomy**

Thong et al, J Urol, 2008.
Berglund et al, J Urol, 2008.

Who is a Candidate for Surveillance?

- Identify men who are at 'good risk'
  - Published criteria vary from institution to institution
  - Criteria used at OSU
    - PSA ≤ 10 ng/ml
    - Gleason score ≤ 6
    - Clinical stage T1 to T2a
    - %positive cores <20%
    - Extent cancer in any core <50%
    - PSA prior to biopsy relatively stable (PSAv <2)

PSA After Prostatectomy

- Detectable PSA following prostatectomy is associated with eventual disease recurrence in most patients
- PSA should be undetectable (<0.08 ng/ml)
- Median interval from PSA recurrence to clinical mets is 8 years (30% of patients)
- Median interval from clinical mets to prostate cancer death is 5 years
  - Prognosis affected by many factors including Gleason grade

Pound et al, JAMA, 1999.

Use of PSA after Treatment for Cancer

- Rise of PSA after treatment is an early indicator of disease recurrence
  - Biochemical recurrence (BCR) is a state of disease preceding clinical metastasis
  - Further treatment may be prompted by rise in PSA
    - After prostatectomy
      - Salvage radiotherapy
      - Androgen deprivation therapy
    - After radiotherapy
      - Androgen deprivation therapy
      - Cryotherapy
      - Salvage prostatectomy
  - Overall impact of salvage therapy on survival is uncertain

PSA After Radiation or Cryoablation

- After radiation, PSA declines slowly
- Nadir reached after median of 17 months
- A lower nadir PSA (especially undetectable) associated with improved long-term progression-free (biochemical) survival

PSA After Radiation or Cryoablation

- **Definition of biochemical failure:**
  - **ASTRO definition– 3 consecutive rises in PSA above nadir**
  - **Phoenix definition – 0.2 ng/ml rise above nadir**
  - **Both definitions delay diagnosis of PSA rise and can impact and confound results in trials attempting to compare surgery and radiation**

PSA After Androgen Deprivation Therapy

- **In men with metastatic prostate cancer treated with androgen deprivation therapy**
  - **Nadir PSA and %PSA decline at 3 and 6 mo predict PFS**
    - **Ability to attain undetectable PSA and PSA decline >90% at 3 and 6 mo more likely to experience prolonged PFS**
- **In men with metastatic prostate cancer on second-line treatments**
  - **% PSA decline correlates with disease survival**
    - **'Castrate-resistant' prostate cancer-- >50% decline in PSA at 8 wks after 2nd-line treatments associated with improved survival**

Patterns of PSA Rise After Definitive Therapy

- **In setting of biochemical failure after surgery or radiation, pattern of PSA rise can help distinguish between local and distant recurrence**
  - **More likely distant recurrence:**
    - **PSA fails to fall to undetectable after surgery or rises despite RT or cryotherapy**
    - **Rises within 12 months of local treatment**
    - **PSA doubling time <6 months**
  - **More likely local recurrence or persistent disease:**
    - **Biochemical recurrence noted late (>24 months)**
    - **PSA doubling time >12 months**

PSA Use

- **Proven benefits of PSA:**
  - **Prognostication**
  - **Detection of recurrence after definitive therapy**
  - **Following response to treatments for metastatic disease**

PSA Use

- Proven benefits of PSA:
  - Prognostication
  - Detection of recurrence after definitive therapy
  - Following response to treatments for metastatic disease
  - Screening?

Current Recommendations for Screening

- National organizations in US
  - AUA
  - ACS
  - NCCN (NCI)
  - AMA
  - Federal Task Force
- Europe
- Canada

Current Recommendations for Screening

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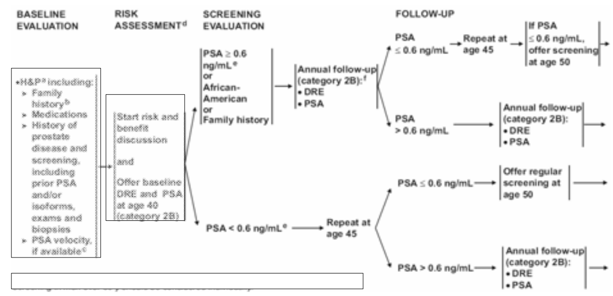
- Canada

A Practical Approach to PSA Screening

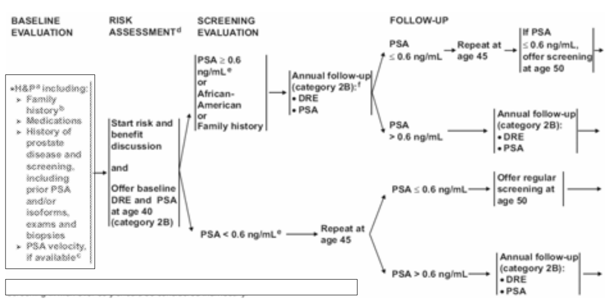
- Establish a baseline PSA early
  - Identify early aggressive disease to target for curative therapy
- Identify a group of patients more likely to need screening

Whittemore et al, J Urol, 2005.
Catalona et al, Ann Int Med, 2006.

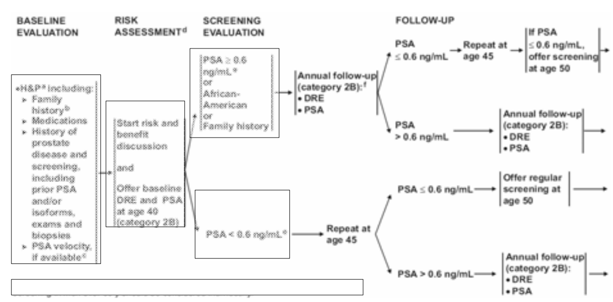
NCCN Clinical Guideline



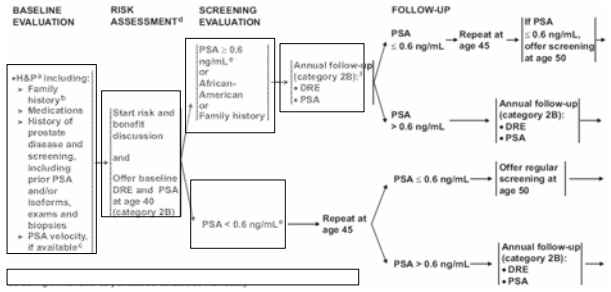
NCCN Clinical Guideline



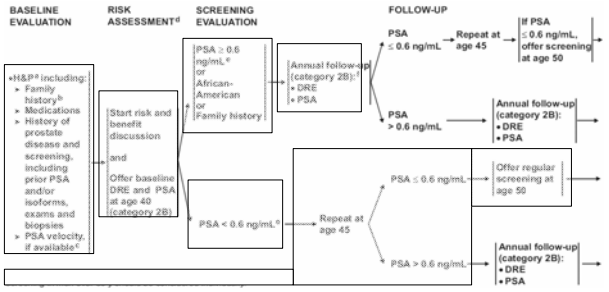
NCCN Clinical Guideline



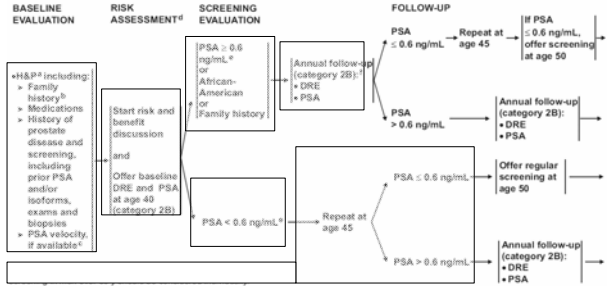
NCCN Clinical Guideline



NCCN Clinical Guideline



NCCN Clinical Guideline



Who to Screen

- **Consider starting evaluation at 40 in all men with an initial PSA/ DRE**
- **Start annual screening with PSA/ DRE after discussion of risks/ benefits**
  - **If PSA >0.6 ng/ml**
  - **+ Family history**
  - **African American**
- **If PSA <0.6 ng/ml, retest at 45**
  - **If still <0.6 at 45, defer annual screening until 50**

When to Consider TRUS/Bx

- Indications for initial biopsy
  - Positive DRE
  - PSA >2.5
    - Age
    - Comorbid conditions
    - %free PSA
    - Prostate size
    - Family history
    - African-American
  - Rising PSA > 0.35 ng/ml/yr if PSA <2.5

When It Comes to Prostate Cancer:

"Diagnostically aggressive"

"Therapeutically conservative"

Peter T. Scardino, MD

When It Comes to Prostate Cancer:

"Diagnostically aggressive"

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Is cure possible?

Is cure necessary?

Is cure possible only when it is not necessary?

Willet F. Whitmore, Jr

Is cure possible? Yes

Is cure necessary?

Is cure possible only when it is not necessary?

Willet F. Whitmore, Jr

Is cure possible? Yes

Is cure necessary? Not always

Is cure possible only when it is not necessary? Not always in 2009

Willet F. Whitmore, Jr

Is cure possible? Yes

Is cure necessary? Not always

Is cure possible only when it is not necessary?

Willet F. Whitmore, Jr

Conclusions

- **PSA is not perfect screening test**

  (But it is the best we have)
- **PSA screening for prostate cancer detects cancers earlier and at a lower stage where curative therapies more effective**
- **Randomized studies are pending**
- **PSA is a valuable tool in prognostication and following prostate cancer patients**