

# Prostate Cancer Screening: A Paradigm for Prioritizing Patient Preferences

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# The Story of Mr. S



# Learning Objectives

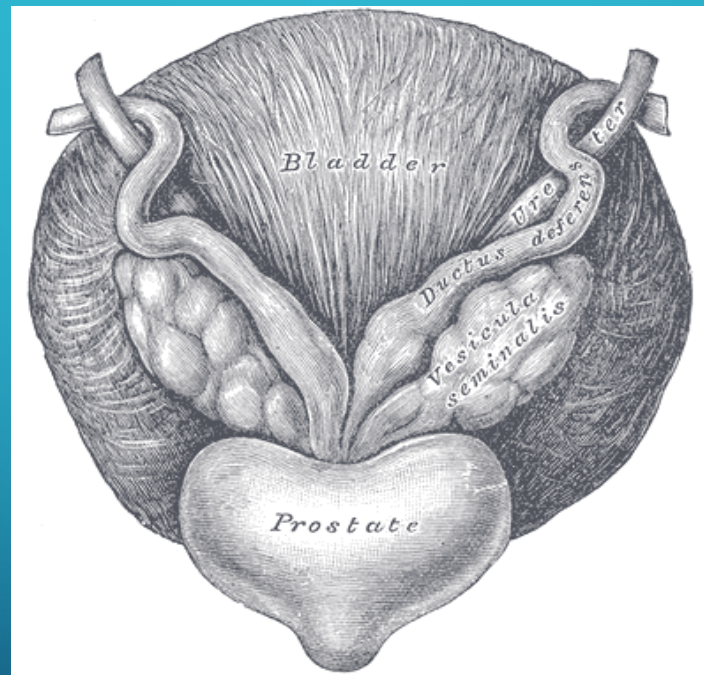
By the end of this lecture, participants will be able to:

- Discuss the benefits, risks, burdens, and uncertainties of prostate cancer screening
- Understand the concepts of over-diagnosis and over-treatment, as they relate to cancer screening
- Appreciate the importance of integrating patient values into decision making related to cancer screening
- Utilize decision aids either as a provider or a patient to facilitate cancer screening & other medical decisions

# Learning Objectives, generalized

- What is shared decision making?
- Why does it matter?
- Why is it so hard?
- How can we do it better?

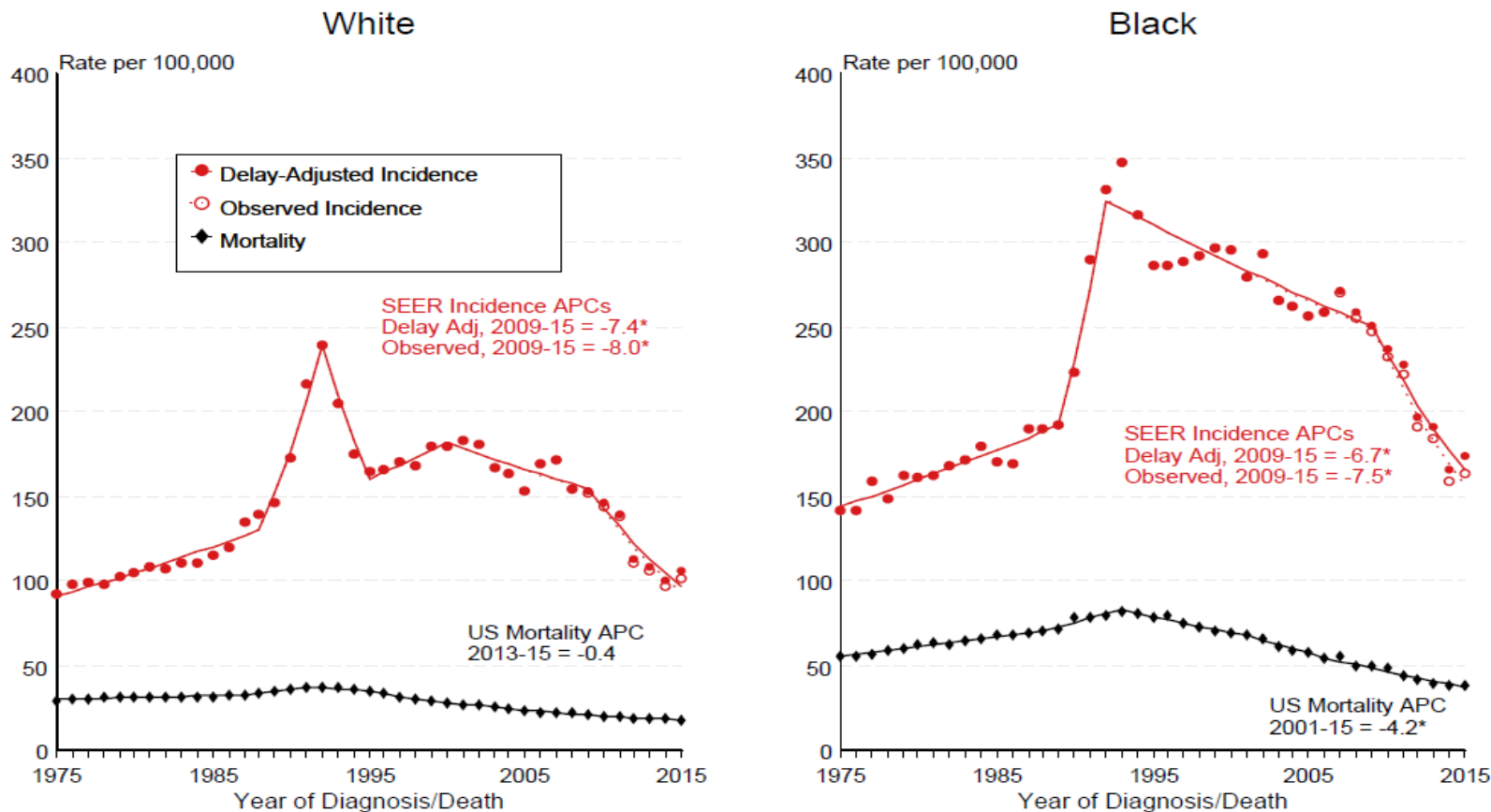
# First, a little about prostate cancer



Henry Vandyke Carter, Gray's Anatomy, 1918 edition

# Prostate Cancer Incidence & Mortality Over the Decades

SEER Observed Incidence, SEER Delay Adjusted Incidence and US Death Rates<sup>a</sup>  
Cancer of the Prostate, by Race



Source: SEER 9 areas and US Mortality Files (National Center for Health Statistics, CDC).

<sup>a</sup> Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).

Regression lines and APCs are calculated using the Joinpoint Regression Program Version 4.6, February 2018, National Cancer Institute. The APC is the Annual Percent Change for the regression line segments. The APC shown on the graph is for the most recent trend.

\* The APC is significantly different from zero ( $p < 0.05$ ).

# Prostate Cancer

- #1 cancer diagnosed in men; #2 cause of cancer death behind lung cancer
- 165,000 newly diagnosed in 2018, 30,000 deaths
- Lifetime risk of being diagnosed with prostate cancer: 1 in 9
- About 1 in 40 men die of prostate cancer
  - Many more men die WITH than from prostate cancer

# The PSA

- First blood test to become widely used for cancer screening
  - First used for screening in 1987
  - Widespread use by ~ 1990
- Glycoprotein produced by prostate cells
  - Production & release into the bloodstream increased in prostate cancer
- Definitely can find prostate cancer before it becomes symptomatic in many individuals



# The problems with PSA Screening

- Does it save lives?
- False positives
- False negatives
- Overdiagnosis & overtreatment
- Harms of evaluating elevated PSA levels with biopsy
  - About 3% have some complication (infection or bleeding)
  - 0.5% risk of hospitalization for infection (Medicare data)
- Harms of treating screen-detected cancer

“The current state of prostate cancer may not be good medicine but it sure is good business – there are more people making a living from prostate cancer than there are dying from it”

-- Willet Whitmore, MD  
Chair of Urology, Memorial Sloan-Kettering  
1951-1984

Does PSA screening save lives?

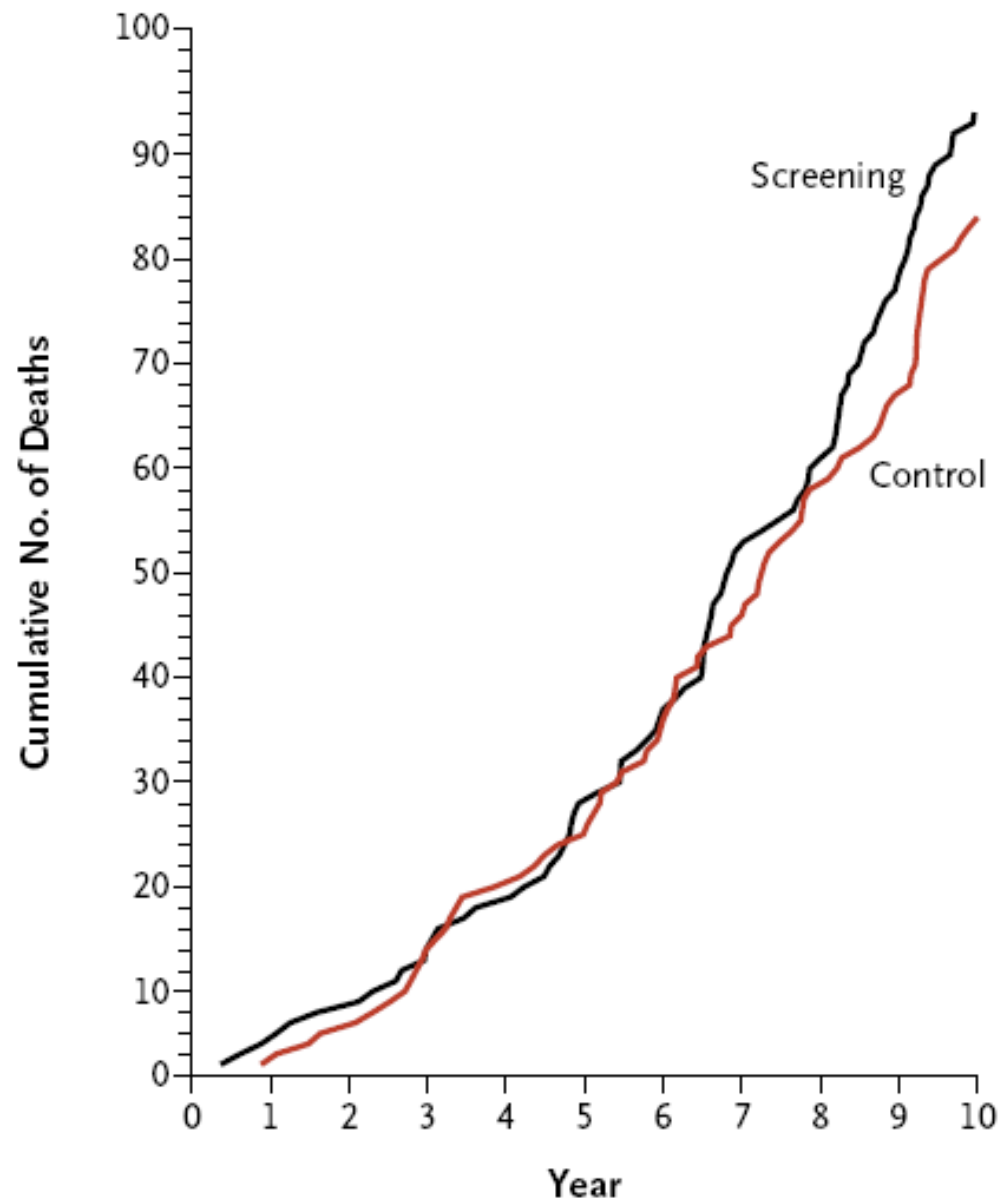
ORIGINAL ARTICLE

# Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., Robert L. Grubb III, M.D., Sandra S. Buys, M.D.,

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

## B Prostate-Cancer Deaths



ORIGINAL ARTICLE

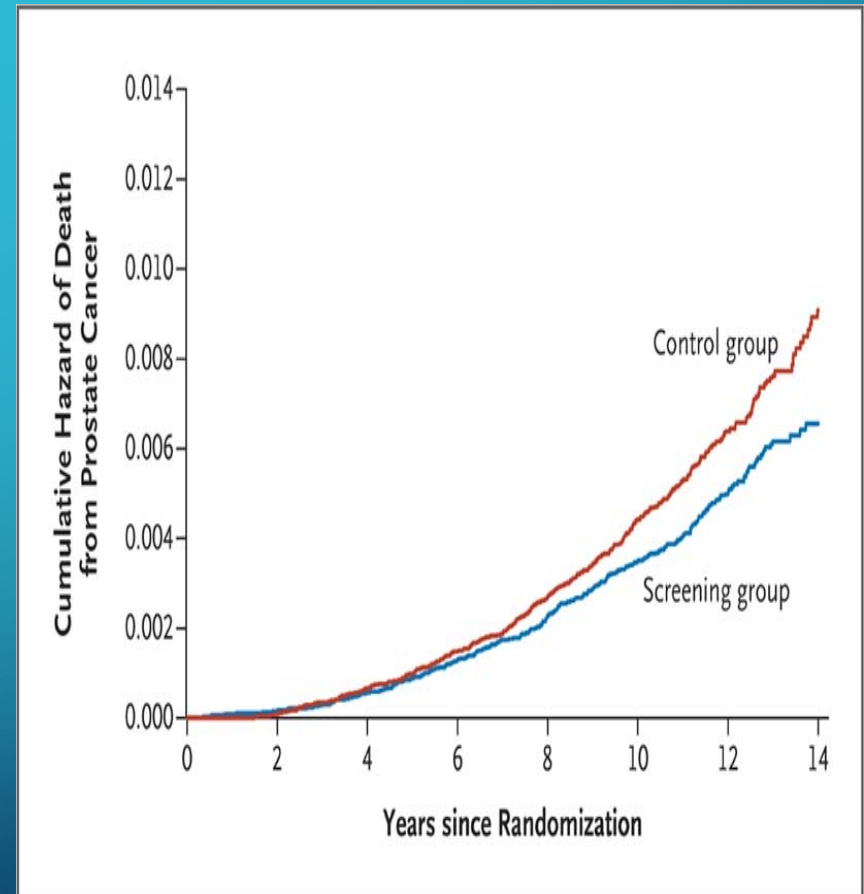
# Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D.,

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

# ERSPC Results

- Prostate cancer death rate 27% lower in screened group ( $p = 0.0001$ ) at 13 yrs
- Number needed to screen to save 1 life 781
- Number needed to diagnose to save 1 life: 27
  - Major issue of over-diagnosis & over-treatment
- No impact on overall mortality



## Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials

Alex Tsodikov, PhD; Roman Gulati, MS; Eveline A.M. Heijnsdijk, PhD; Paul F. Pinsky, PhD; Sue M. Moss, PhD; Sheng Qiu, MS; Tiago M. de Carvalho, MS; Jonas Hugosson, MD; Christine D. Berg, MD; Anssi Auvinen, MD; Gerald L. Andriole, MD; Monique J. Roobol, PhD; E. David Crawford, MD; Vera Nelen, MD; Maciej Kwiatkowski, MD; Marco Zappa, PhD; Marcos Luján, MD; Arnauld Villers, MD; Eric J. Feuer, PhD; Harry J. de Koning, MD; Angela B. Mariotto, PhD; and Ruth Etzioni, PhD

- Controlled for differences in study design
- Both studies led to a ~ 25-32% reduction in prostate cancer mortality with screening compared with no screening

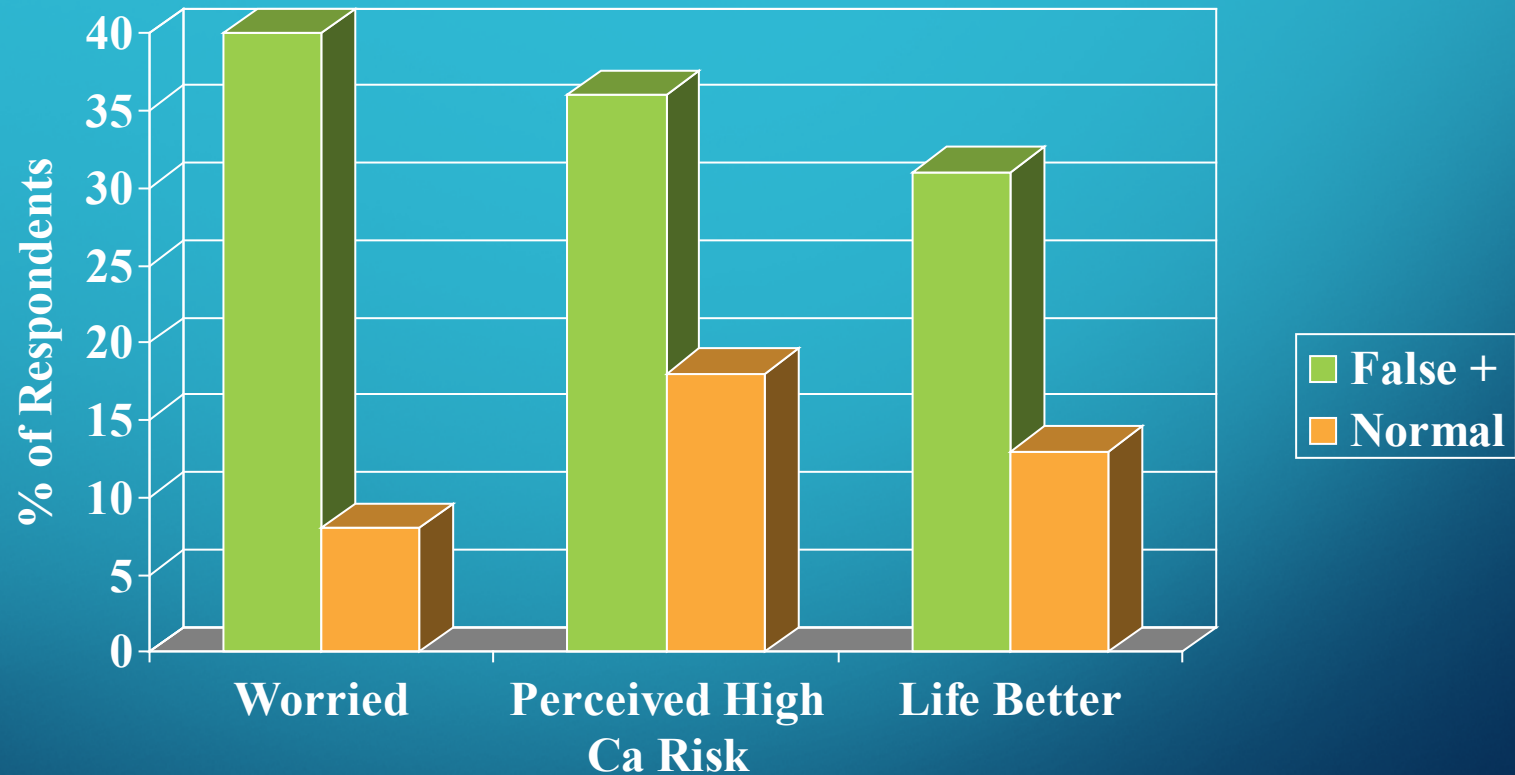


# The problem of false positive PSA tests

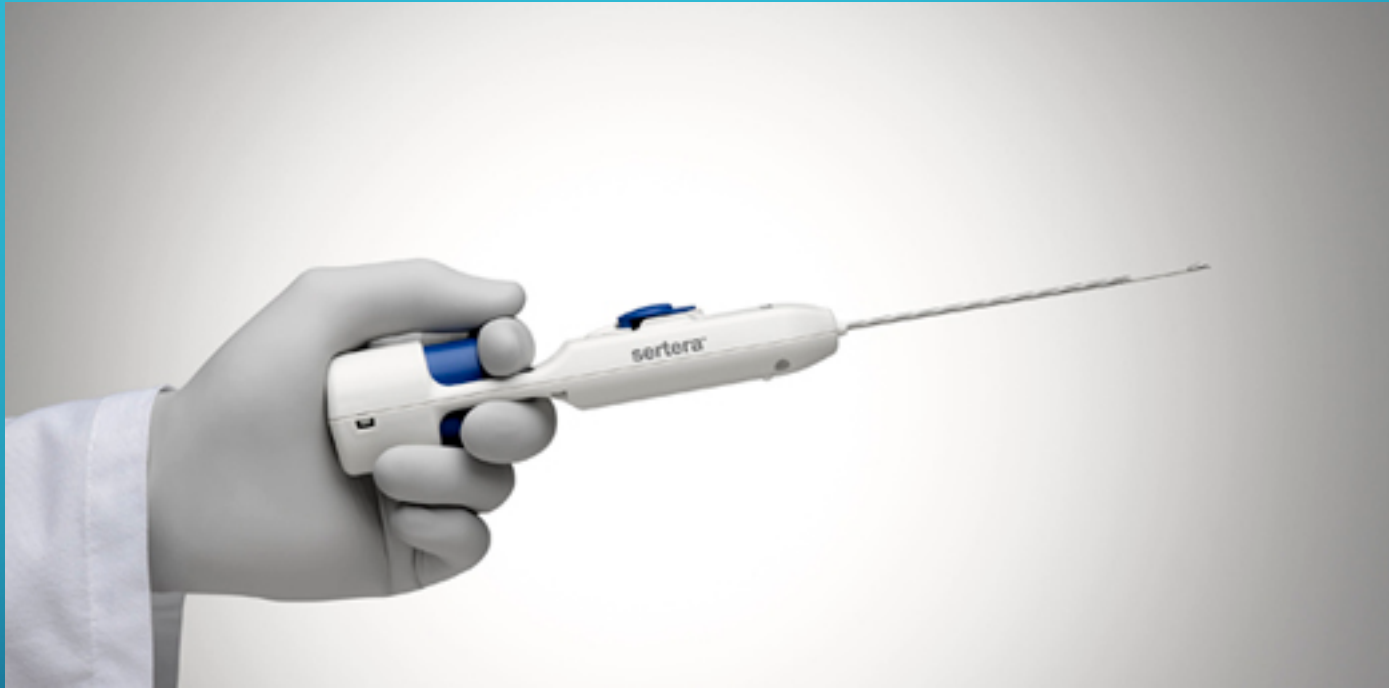
# Causes of a False Positive PSA Test

- Benign prostatic hypertrophy
- Prostate inflammation/infection
  - May not be symptomatic
- Ejaculation
- Urinary catheters
- Digital rectal exam?
- Bicycle riding?
  
- 13% false positive rate after 4 screens

# Impact of a False (+) PSA\*



\*High PSA led to normal biopsy vs normal PSA controls, surveyed 6 weeks later



Does this look like “dodging a bullet”?

# The problem of false negative PSA's

*An inconvenient truth...*

# Conventional Wisdom



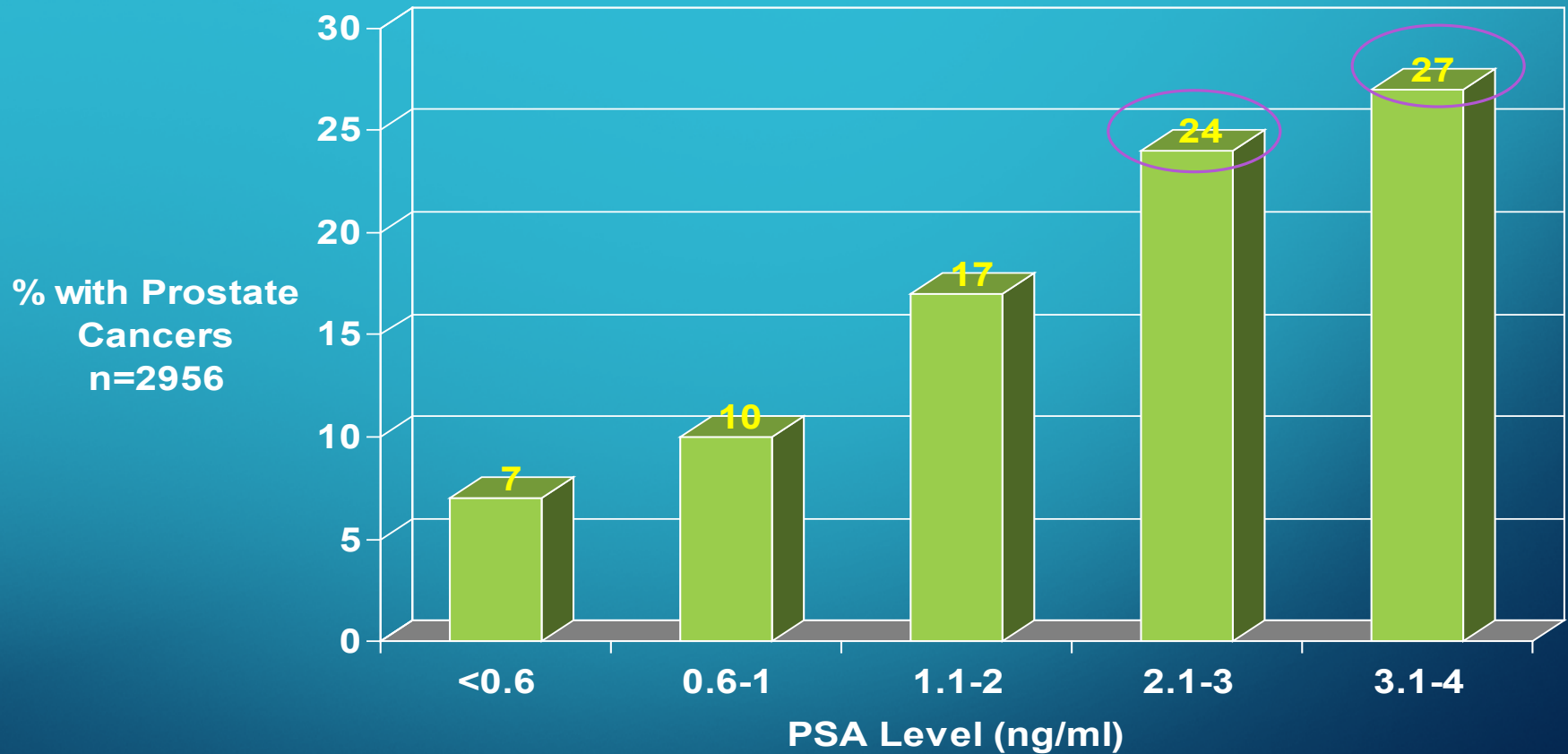
PSA>4.0

“Your PSA is elevated.  
You need a biopsy.”

PSA<4.0

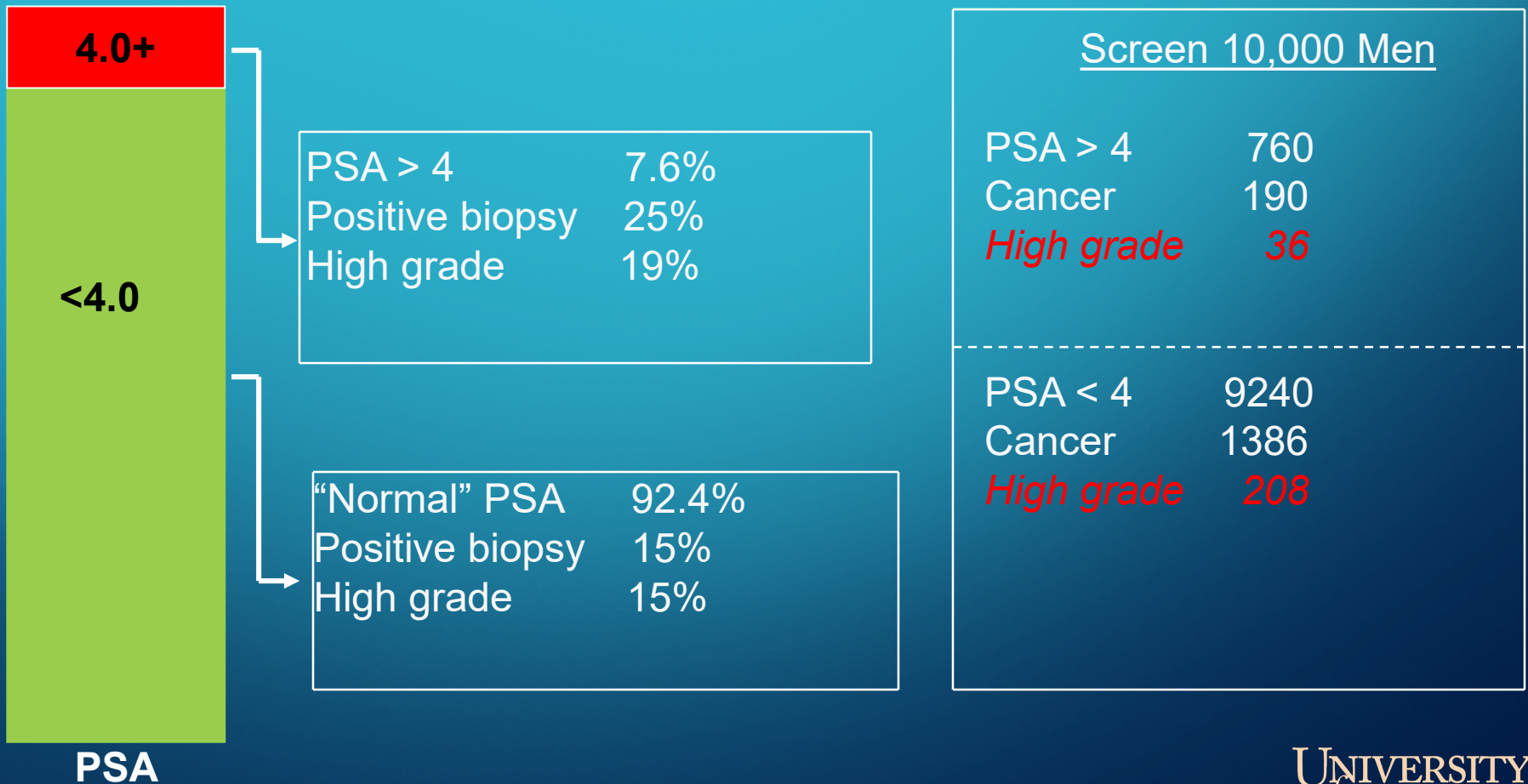
“Your PSA is normal.  
No testing is necessary.”

# Prostate Ca in Men with PSA < 4.0 ng/ml



Adapted from Thompson I. N Engl J Med 2004;350:2239-46;

# Population Screening with PSA: Disconcerting Outcomes





*Bottom line: there is no PSA level that reliably discriminates between cancer and non-cancer, so we somewhat arbitrarily pick 4.0 ng/dl*

# Attempts to better discriminate between true & false positives

- PSA Velocity
- % Free PSA
- 4K score
- Prostate health index
- Multi-parametric prostate MRI
- Digital rectal exam?



"It may be more inconvenient, but the 'Reverse Prostate Exam' is a lot less embarrassing for the both of us."

# Overdiagnosis & Overtreatment: the PSA Quandary

“When cure is possible, is it necessary?  
And when cure is necessary, is it possible?”

-- Willet Whitmore, MD, ~1990

# Overdiagnosis and Overtreatment

- Overdiagnosis
  - The diagnosis of prostate cancers through screening that would not have been diagnosed during the man's lifetime if screening had not occurred
  - Estimates range from 23% to 42% of screen-detected cancers
- Overtreatment
  - The treatment of screen-detected prostate cancers that never would have become clinically apparent during the man's lifetime in the absence of screening
  - Active surveillance and watchful waiting have the potential to significantly decrease overtreatment

# Harms of treating prostate cancer detected through screening

# Long-term Outcomes of Treating Localized Prostate Cancer

## Survey Responses on Selected Items Regarding Urinary, Bowel, and Sexual Function

**Table 2. Survey Responses on Selected Items Regarding Urinary, Bowel, and Sexual Function.\***

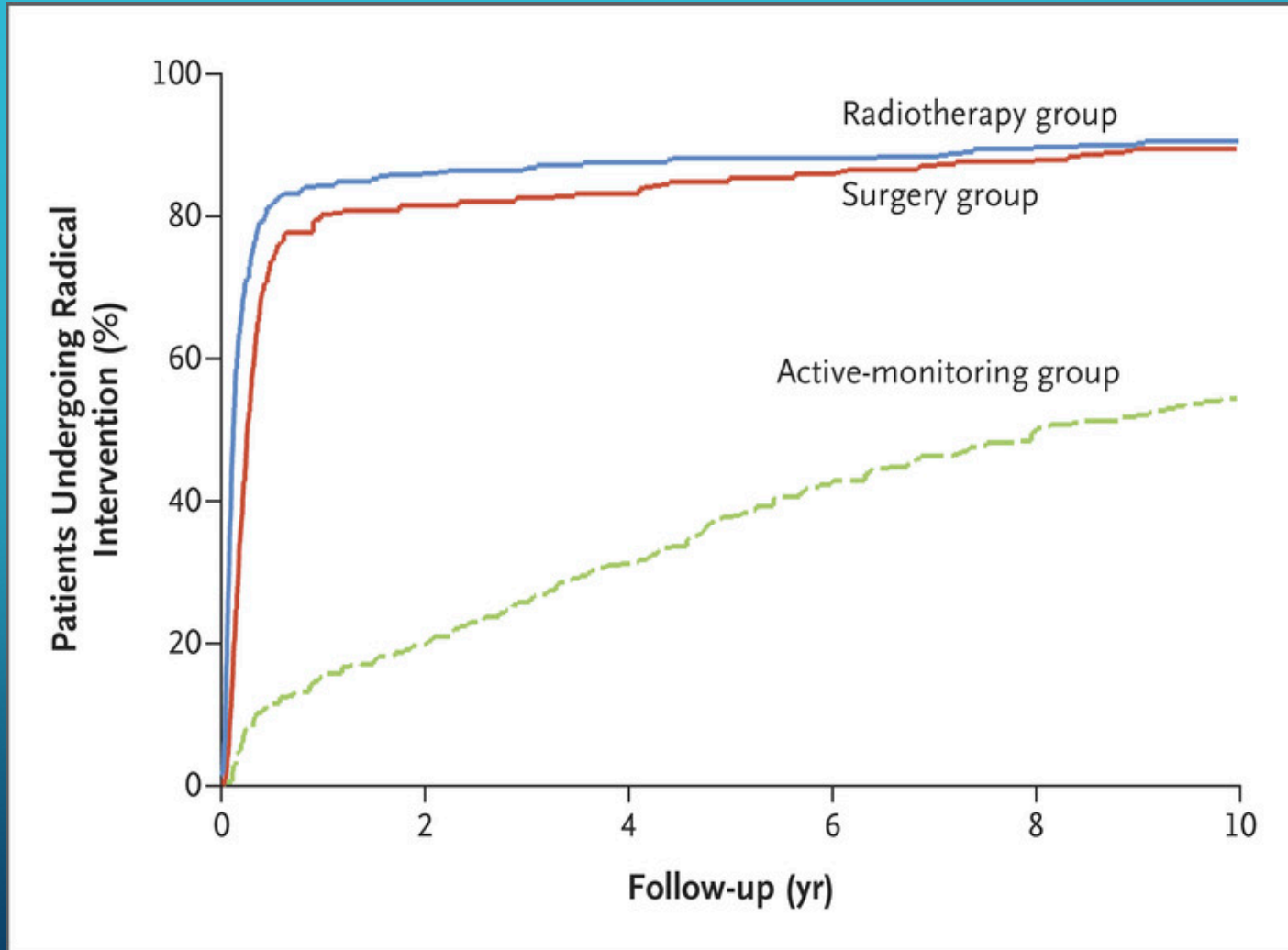
Outcome	Prostatectomy	Radiotherapy
	<i>percent</i>	
<b>Urinary incontinence</b>		
No control or frequent urinary leakage		
2 yr	9.6	3.2
5 yr	13.4	4.4
15 yr	18.3	9.4
Bothered by dripping or leaking urine‡		
2 yr	10.6	2.4
5 yr	12.9	2.9
15 yr	17.1	18.4
<b>Sexual function</b>		
Erection insufficient for intercourse		
2 yr	78.8	60.8
5 yr	75.7	71.9
15 yr	87.0	93.9
Bothered by sexual dysfunction‡		
2 yr	55.5	48.2
5 yr	46.7	39.7
15 yr	43.5	37.7
<b>Bowel function</b>		
Bowel urgency		
2 yr	13.6	34.0
5 yr	16.3	31.3
15 yr	21.9	35.8
Bothered by frequent bowel movements, pain, or urgency‡		
2 yr	2.9	7.9
5 yr	4.4	5.8
15 yr	5.2	16.0

# Emerging strategy to mitigate harm: “Active Surveillance”

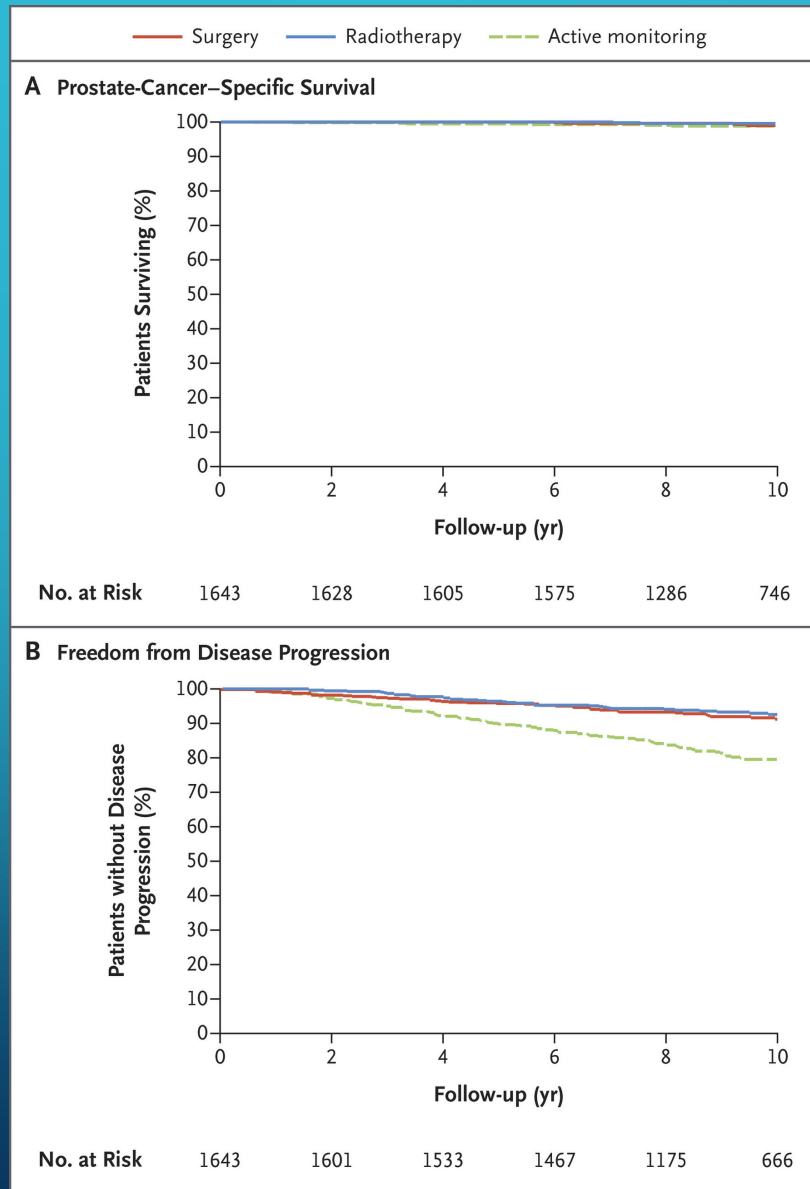
- Patients with low/intermediate grade cancers offered option to monitor cancer with PSA & periodic biopsies
  - Initiate treatment if cancer progress
- Reduces risk of overtreatment
- Are we creating a cohort of anxious men who are in “cancer limbo”?



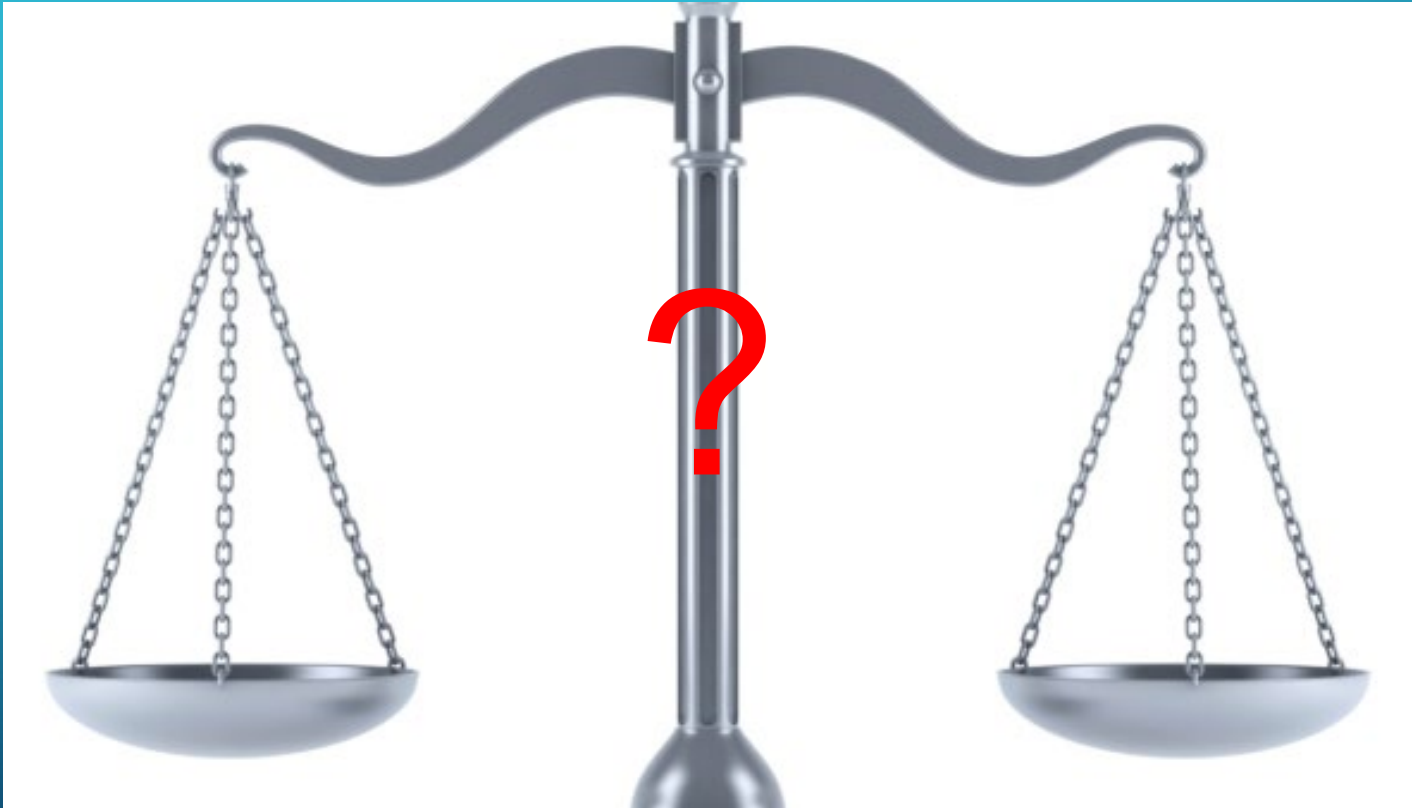
# ProtecT Trial: Treatment vs “Active Monitoring”



# A price to pay for active monitoring?



# How can we help patients balance the benefits & harms?



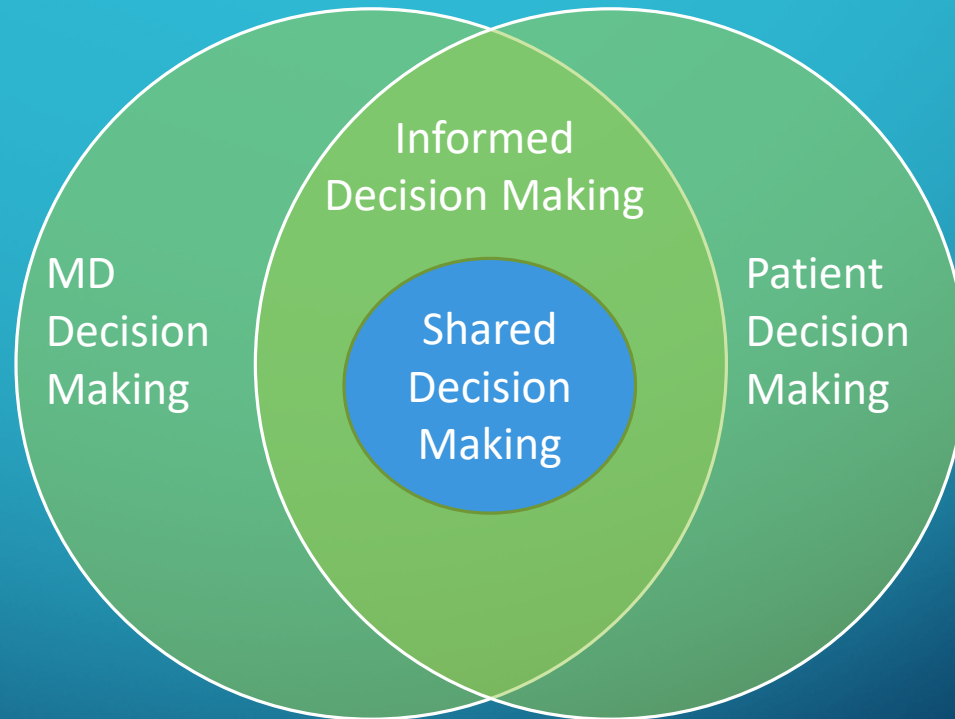
# Some Useful Concepts for Striking the Balance

- Informed vs shared decision making
- Health literacy & numeracy
- Decision aids
- Values matching scenarios

# Informed vs Shared Decision Making

- Core elements of informed decision making include:
  - Understanding the *benefits, risks, uncertainties* of the intervention
  - Integrating patient's *values* into decision
  - Choosing a level of participation in the decision (role preference)
- Shared decision making incorporates the physician/provider into informed decision making by:
  - Helping the patient integrate their values into the decision
  - Taking on more or less of the decision-making process based on patient's role preference

# Context of Shared Decision Making



# Other situations where shared decision making is warranted

*Just to name a few*

- Hormone replacement therapy for menopausal symptoms
- Treatment options for early-stage breast cancer (ductal carcinoma in-situ)
- “Statin” therapy for hyperlipidemia in older patients
- Cancer chemotherapy when life extension is measured in weeks to months
- Cardiac catheterization vs medication management for stable angina
- Treatment options for early-stage prostate cancer

# Health Literacy & “Numeracy”: the Challenges

- Only 54% of high-school & college-educated white women correctly estimated the likely number of “heads” on 1000 coin flips
  - 1/3 of respondents answered “under 300 heads”
- Under 50% of underserved central Virginia men understood the terms “erection” & “impotent”
  - *Only 5% understood the term “incontinence”*



So what can we do to promote truly informed & shared decision making?

# Assign Homework: Patient Decision Aids

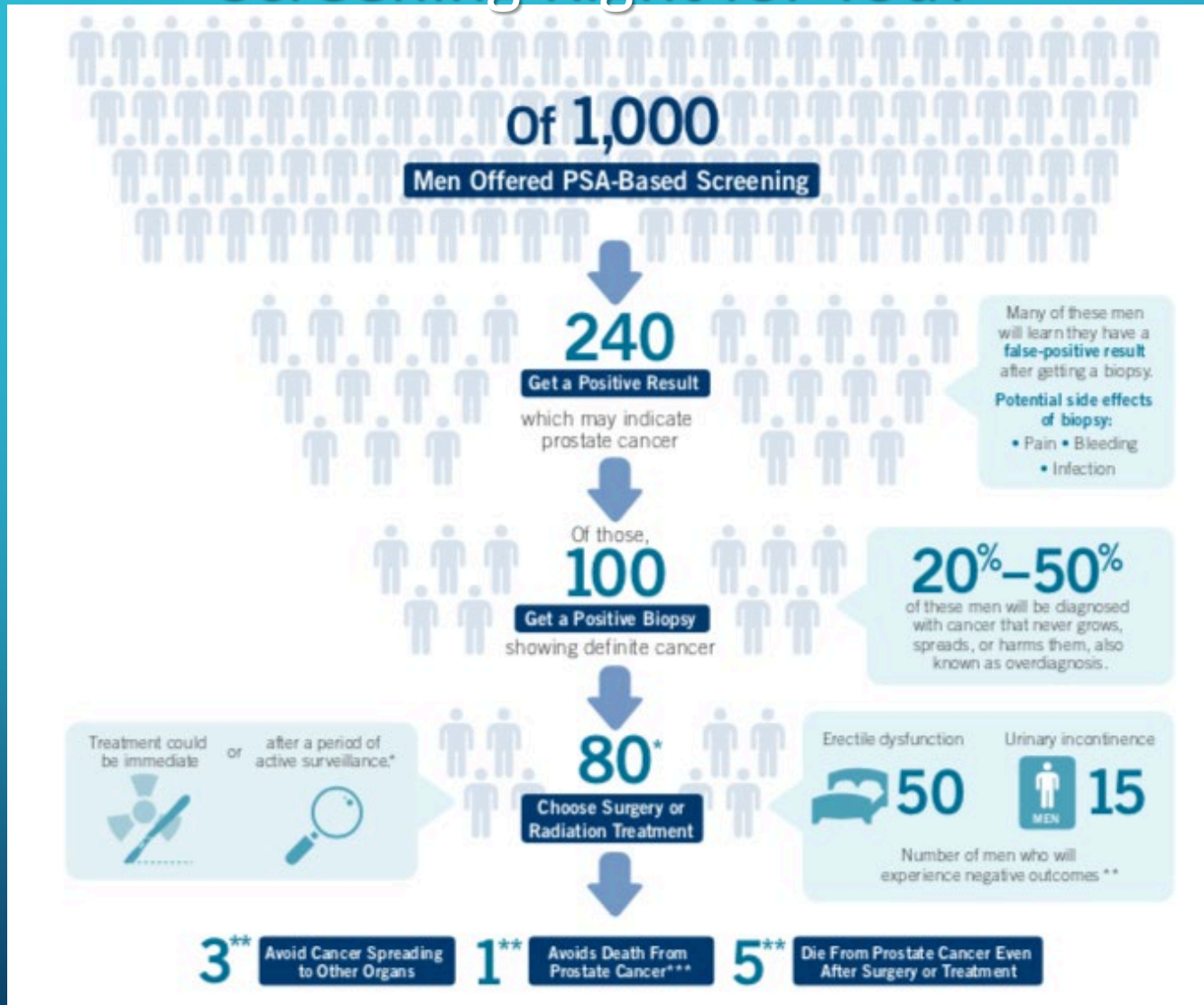
- “Should I get screened for prostate cancer?”
  - CDC web-based information
- “Prostate cancer screening: Should you get a PSA test?”
  - Mayo booklet, on-line
- “Should I Be Tested for Prostate Cancer?”
  - American Cancer Society, on-line
- Prostate Cancer Screening: Making the Best Choice
  - Georgetown University interactive web-based tool



- PSA screening detects cancer at an earlier stage than if no screening is performed.
- PSA screening reduces the risk of dying from prostate cancer and from developing metastatic prostate cancer.

- Some cancers detected by screening would never have become apparent during the man's lifetime (**overdiagnosis**).
- The PSA has **false-positives** & false-negatives.
- A high PSA requires a **prostate biopsy** - biopsies are painful & may cause infection or bleeding.
- Treatment for prostate cancer often leads to **urinary, sexual, or bowel problems**.
- **Not all prostate cancers need immediate treatment**, but they will require periodic blood tests and biopsies to determine the need for future treatment.

# US Preventive Services: “Is Prostate Cancer Screening Right for You?”



# Gold Standard for Informed Decision Making

<http://prostatedecision.georgetown.edu/>

# To Help Our Patients Decide: Values Matching Scenarios

- “You might want to be tested if you value finding cancer early, you are willing to be treated without definite expectation of benefit, and you are willing to risk significant injury to sexual, urinary, or bowel function.”
- “You might *not* want to be tested if you place a higher value on avoiding the potential harms of screening, such as anxiety or injury to sexual, urinary or bowel function.”



Shared decision making is not over once the decision to screen has been made...

# Case #1

- A 65 yo white man with well-controlled hypertension presents for his annual check-up. He has no family history of prostate cancer.
- After learning the potential risks & benefits, he chooses to be screened for prostate cancer:
  - PSA: 1.0; DRE: abnormal (nodule)
- He would generally be referred for biopsy...



# Decision making *after* the PSA

## Scenario #1

### Characteristics

Race

Caucasian

Age

65

PSA [ng/ml]

1.0

Family History of Prostate Cancer

No

Digital rectal examination

Abnormal

Prior biopsy

Never had a prior biopsy

Percent free PSA available?

PCA3 available?

T2:ERG available?

Calculate Risk

Result [More Information](#)

### Risk of prostate cancer if biopsy were to be performed

Based on the provided risk factors a prostate biopsy performed would have a:



2% chance of high-grade prostate cancer,



12% chance of low-grade cancer,



86% chance that the biopsy is negative for cancer.

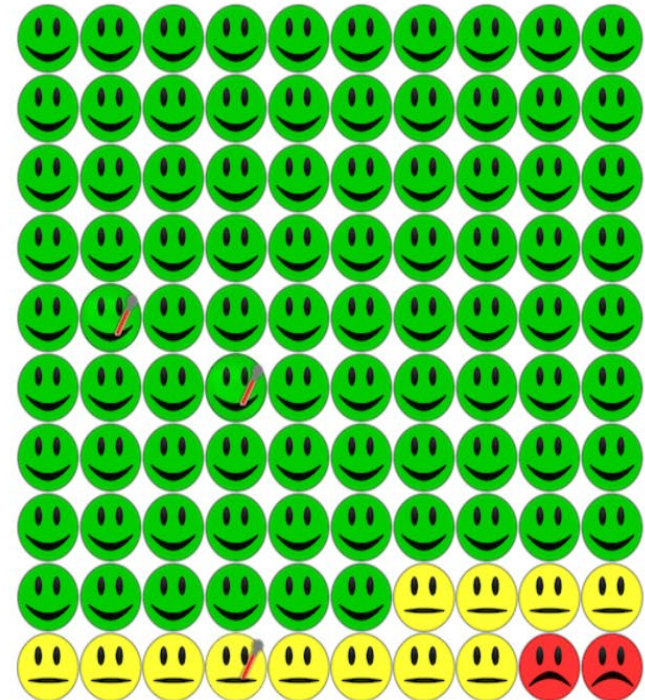


About 2 to 4% of men undergoing biopsy will have an infection that may require hospitalization.

Please consult your physician concerning these results.

If you are Caucasian, click [here](#) for a new update to the PCPTRC that incorporates detailed family history into a risk of prostate cancer calculation.

If you are Caucasian, click [here](#) for a research calculator that allows the incorporation of up to five single-nucleotide polymorphisms (SNP).



# Case #2

- A 65 year old black man with well-controlled hypertension presents for his annual check-up. No family history of prostate cancer.
- After learning of the potential risks & benefits, he also elects to be screened for prostate cancer:
  - PSA 2.5; DRE normal
- He would generally be reassured that his testing is normal...

# Decision making *after* the PSA: *Scenario #2*

## Characteristics

Race

African American

Age

65

PSA [ng/ml]

2.5

Family History of Prostate Cancer

No

Digital rectal examination

Normal

Prior biopsy

Never had a prior biopsy

Percent free PSA available?

PCA3 available?

T2:ERG available?

Calculate Risk

Result

More Information

## Risk of prostate cancer if biopsy were to be performed

Based on the provided risk factors a prostate biopsy performed would have a:



10% chance of high-grade prostate cancer,



17% chance of low-grade cancer,

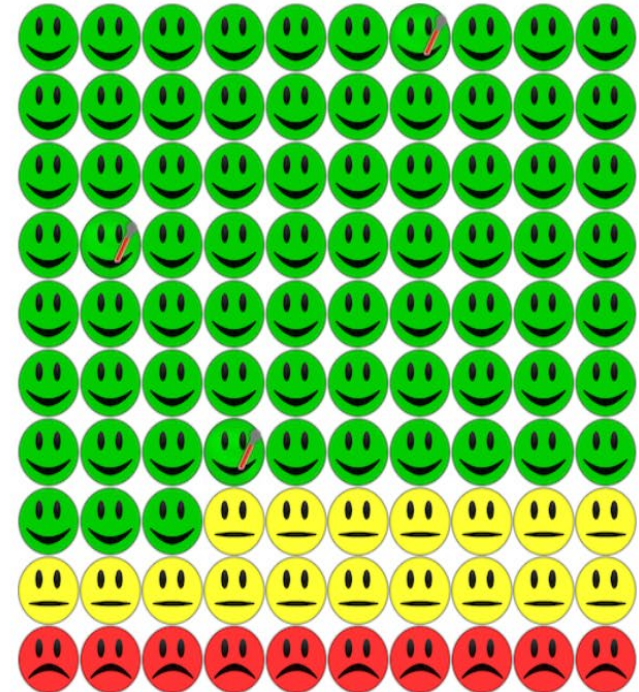


73% chance that the biopsy is negative for cancer.



About 2 to 4% of men undergoing biopsy will have an infection that may require hospitalization.

Please consult your physician concerning these results.



Make a Gift to Support Prostate Cancer Research

# Case #3

- A 72 yo man on hemodialysis with congestive heart failure presents for routine f/u. He remains very active, is feeling well, and is interested in prostate cancer screening...

## Case #3 (continued)

- This man's life expectancy is well below 10 years; you counsel him that finding & treating prostate cancer is more likely to harm him than help him.

# Does Informed/Shared Decision Making Work?

- Improves knowledge of pros/cons of screening
- ***Lowers decisional conflict***
  - men are happier with their decision than men who don't participate in informed decision making

# Quantifying the benefit-harm balance: Quality-Adjusted Life Years (QALYs)

- Combines length and quality of life into single unit
- Involves valuing health states on an interval scale with maximum value of 1 (perfect health) and value of 0 equal to death
- Used to weight life expectancy (“life years”)
- $QALY = (QoL) \times (length\ of\ life)$
- QOL estimates derive from research asking men to quantify specific health states related to prostate cancer (eg, erectile dysfunction from treatment)

# QALY example #1: treatment = living longer & better

- QOL with treatment: 0.9 (with 1.0 being perfect)
- QOL without treatment 0.7 (eg, painful bone metastases)
- Life expectancy with treatment: 10 years
- Life expectancy without treatment: 9 years
- QALYs gained = QALYs with treatment  
- QALYs without treatment  
 $= (0.9 \times 10) - (0.7 \times 9)$   
 $= 9 - 6.3$   
 $= 2.7$  QALYs gained



## QALY example #2: treatment = living longer, but not necessarily better

- QOL with treatment: 0.6 (due to treatment harms)
- QOL without treatment 0.7 (due to disease harms)
- QALYs 'gained' = QALYs with treatment  
- QALYs without treatment  
=  $(0.6 \times 10) - (0.7 \times 9)$   
=  $6 - 6.3$   
=  $-0.3$ , ie, 0.3 QALYs **LOST**

“The patient may not be dead but he wishes he was.”

-- Willet Whitmore, MD

*The* NEW ENGLAND  
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

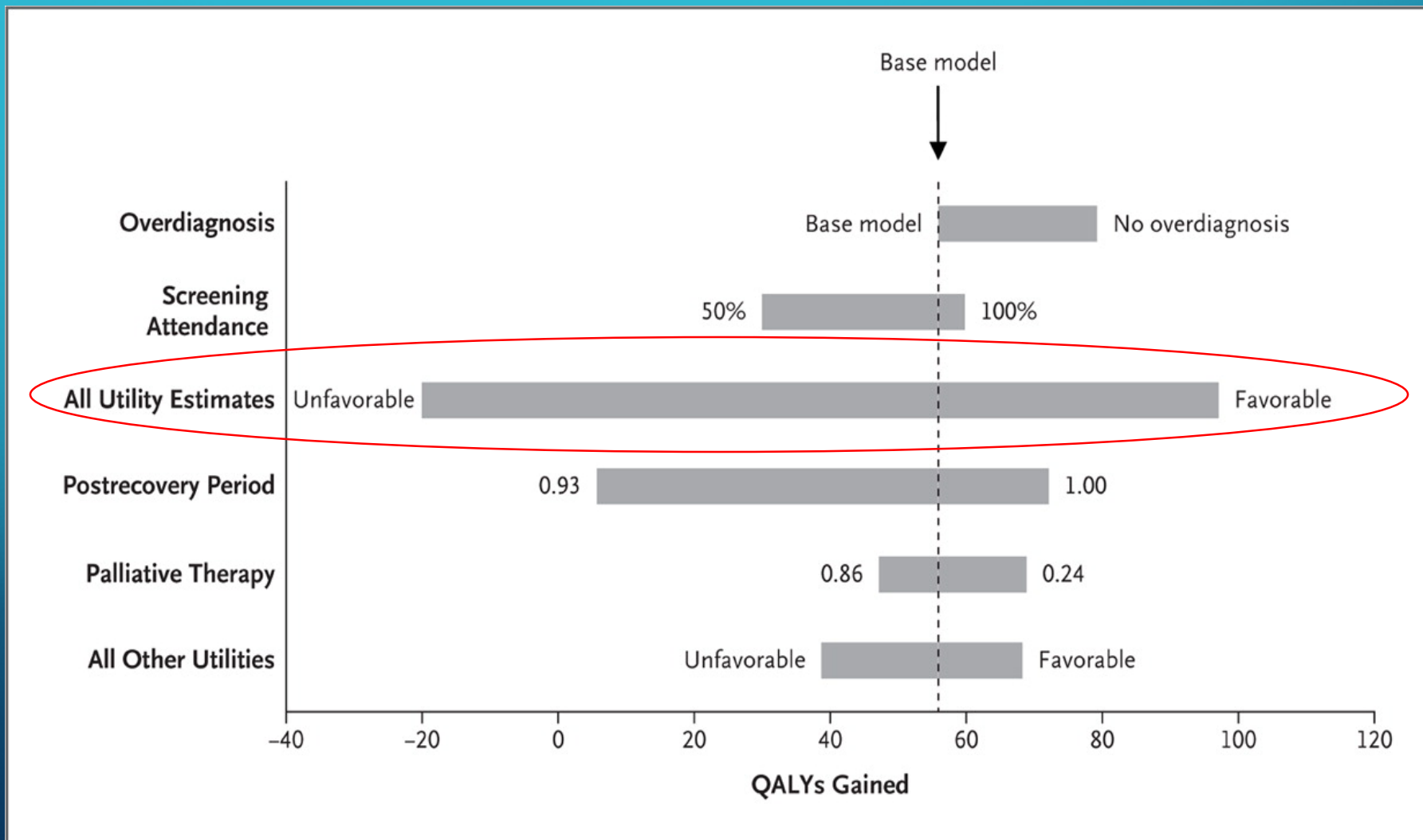
AUGUST 16, 2012

VOL. 367 NO. 7

## Quality-of-Life Effects of Prostate-Specific Antigen Screening

Eveline A.M. Heijnsdijk, Ph.D., Elisabeth M. Wever, M.Sc., Anssi Auvinen, M.D., Jonas Hugosson, M.D., Stefano Ciatto, M.D.,\* Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Arnaud Villers, M.D., Alvaro Páez, M.D., Sue M. Moss, Ph.D., Marco Zappa, M.D., Teuvo L.J. Tammela, M.D., Tuukka Mäkinen, M.D., Sigrid Carlsson, M.D., Ida J. Korfage, Ph.D., Marie-Louise Essink-Bot, Ph.D., Suzie J. Otto, Ph.D., Gerrit Draisma, Ph.D., Chris H. Bangma, M.D., Monique J. Roobol, Ph.D., Fritz H. Schröder, M.D., and Harry J. de Koning, M.D.

# Effect of Modeling Assumptions on Quality-Adjusted Life-Years (QALYs) Gained by Lifetime Prostate Cancer Screening of 1000 Men



# Take Home Points

- Many “routine” medical interventions have significant potential benefits *and* harms
- Shared decision-making is critical when
  - The benefit-harm balance is too close to call
  - The harms are heavily value-dependent
- Shared decision-making isn’t easy
- We have good tools & need to use them

# The Story of Mr. S Epilogue



# THANK YOU!

