

Prostate Cancer Screening: Perspectives in 2019

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Case presentation

- A 55 year old healthy Caucasian male presents to your office for his annual health assessment.
- He denies any urinary symptoms and has no family history of cancer.
- Should we screen him for prostate cancer?

Objectives

- What is prostate cancer screening?
- Why should we screen for prostate cancer?
- Who, when, how, and where should we screen for prostate cancer?

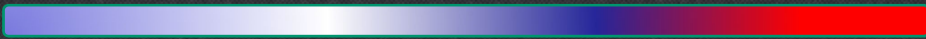
Prostate cancer is important!

- #1 most common cancer
- #2 cause of male cancer death

- In the US (2019):
 - 174,650 cases
 - 31,620 deaths

American Cancer Society Statistics, CA Cancer J Clin 2019, non-melanoma skin not included

Prostate cancer is a spectrum



Incidental
detection
on autopsy
in the
majority of
old men

Indolent
stage that
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Treatable
locoregional
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Fatal
#2 cause of
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Prostate cancer is a spectrum

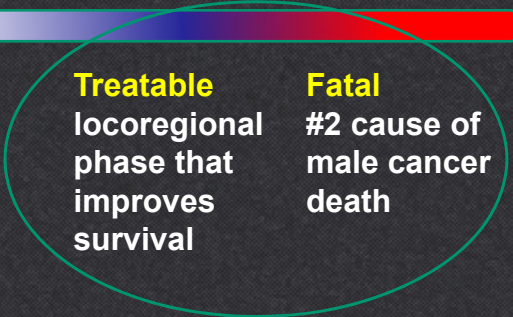


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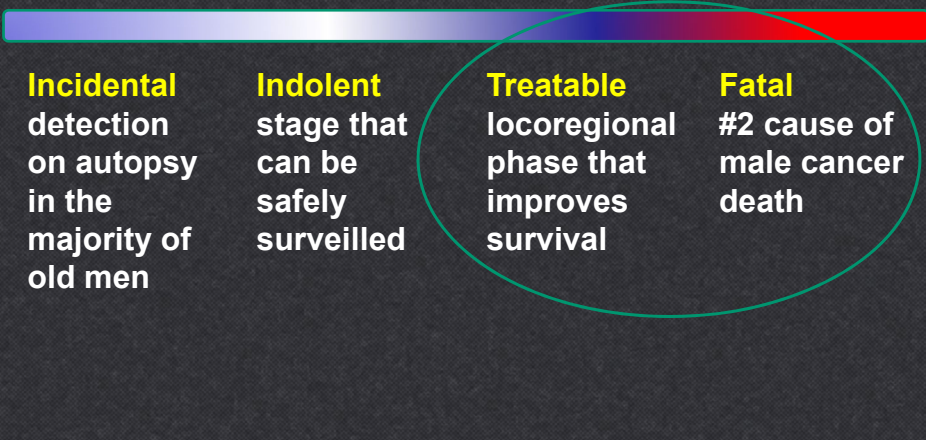
Prostate cancer is a spectrum

What can we do to impact this?



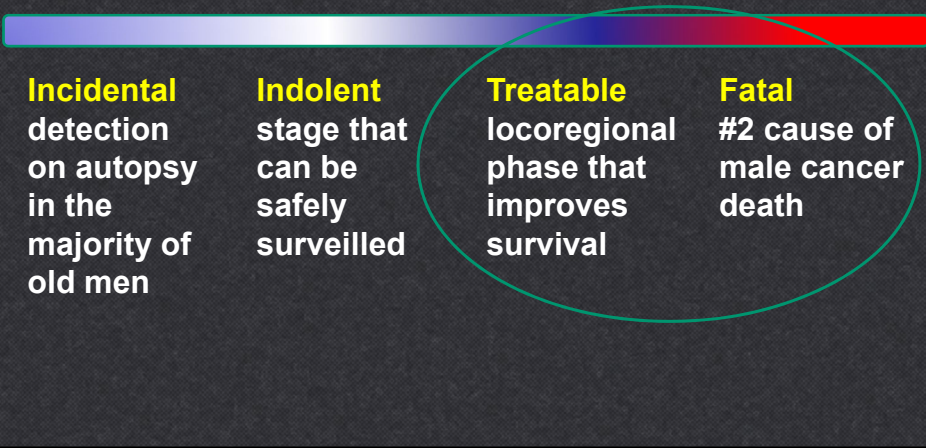
Prostate cancer is a spectrum

Prevent Screen Diagnose Treat Survivorship

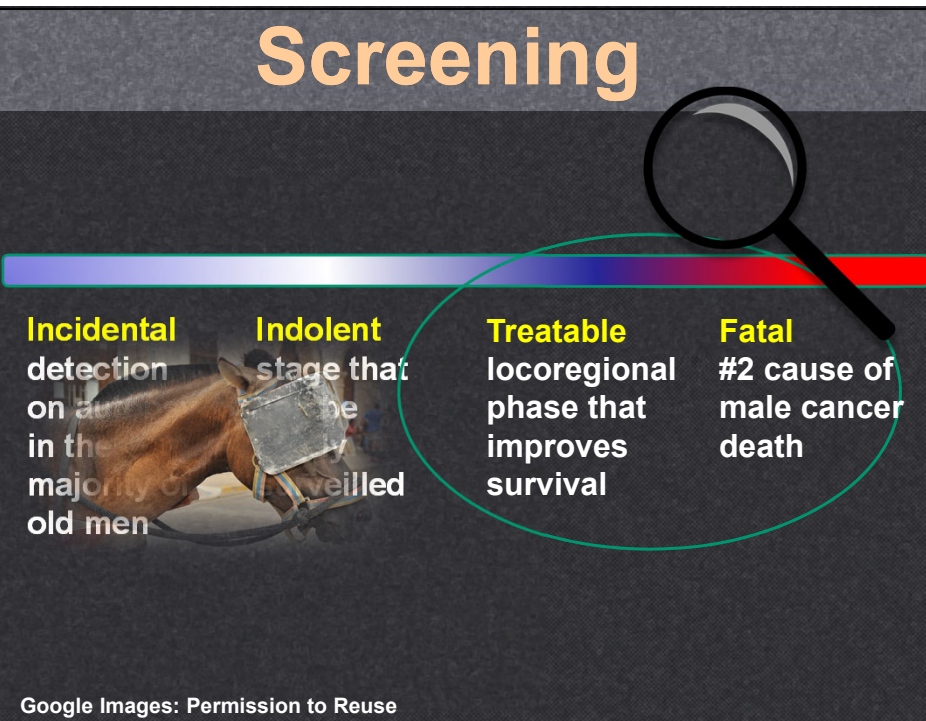


Prostate cancer is a spectrum

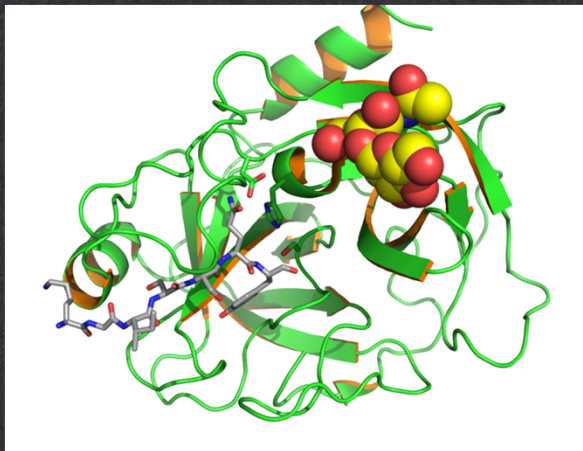
Prevent **Screen** Diagnose Treat Survivorship



Screening

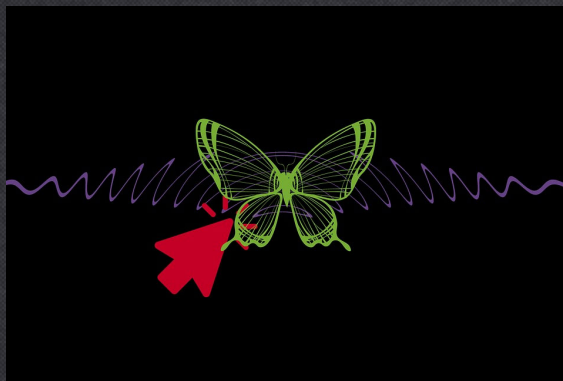


Screening = PSA*



*Pretty Much

Modern PSA screening is based on
large part on certain key events...



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PSA: Historical Perspective



1960 ➤ Flocks identifies that the human prostate has unique antigens

Rao et al. BJU Int 2008

PSA: Historical Perspective



1960 ➤ Hara identifies a unique antigen in the semen

Rao et al. BJU Int 2008

PSA: Historical Perspective



Ablin discovers PSA – prostate specific antigen

Rao et al. BJU Int 2008

PSA: Historical Perspective



Wang & Chu improve our understanding of PSA and optimize clinical testing

Rao et al. BJU Int 2008

PSA: Historical Perspective



Stamey publishes a clinical report on the use of PSA in the New England Journal of Medicine
-correlation with stage and tumor volume
-correlation with treatment response

Rao et al. BJU Int 2008

PSA: Historical Perspective



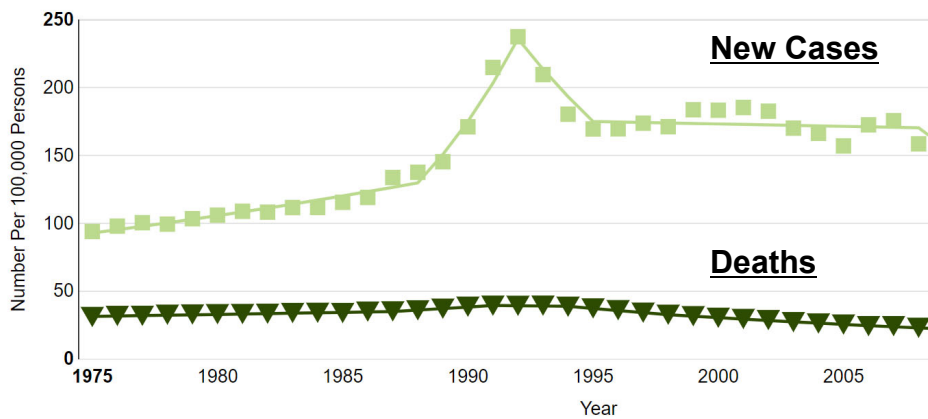
FDA approval of PSA for the early detection of prostate cancer
Numerous nonrandomized studies supporting its use

Rao et al. BJU Int 2008

PSA: Historical Perspective

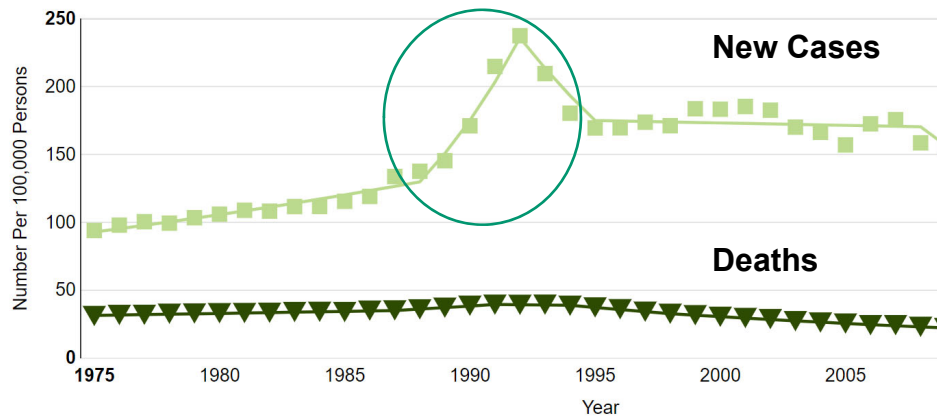


What has PSA done?



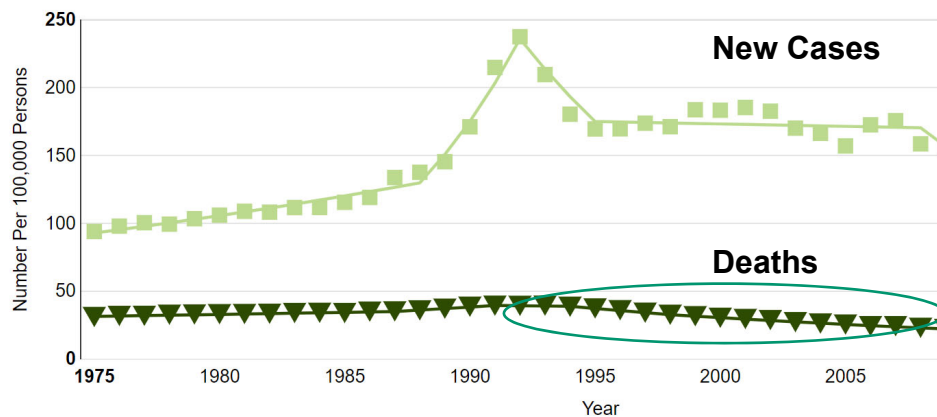
SEER Registry Public Data

Screening dramatically increased incidence



SEER Registry Public Data

Prostate cancer mortality has halved

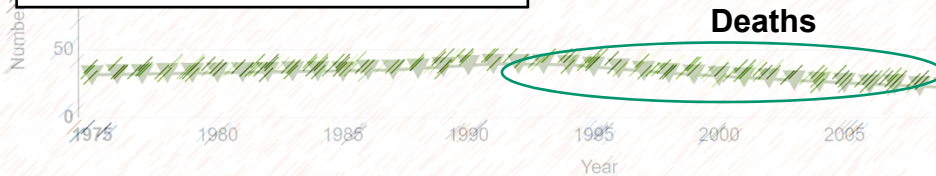


SEER Registry Public Data

Prostate cancer mortality has halved

Also coinciding with...
Better surgery
Better medications
Better biopsies and risk stratification
Better imaging

Models estimated that **45-70%** of this mortality reduction is from screening



Cancer Causes Control. 2008 Mar;19(2):175-81. Epub 2007 Nov 20.

PSA has profoundly impacted medicine

Prostate cancer is the most common cancer in men and the second most common cause of cancer death in men

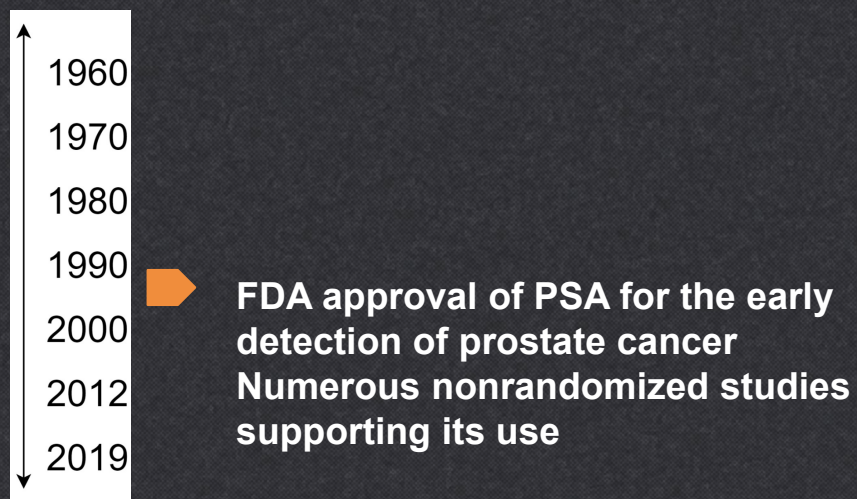
Models estimated that **45-70%** of a two-fold reduction in prostate cancer mortality relates to PSA screening

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The END

*What's the problem – why not just do it??
Why are we even talking about this?*

PSA: Historical Perspective



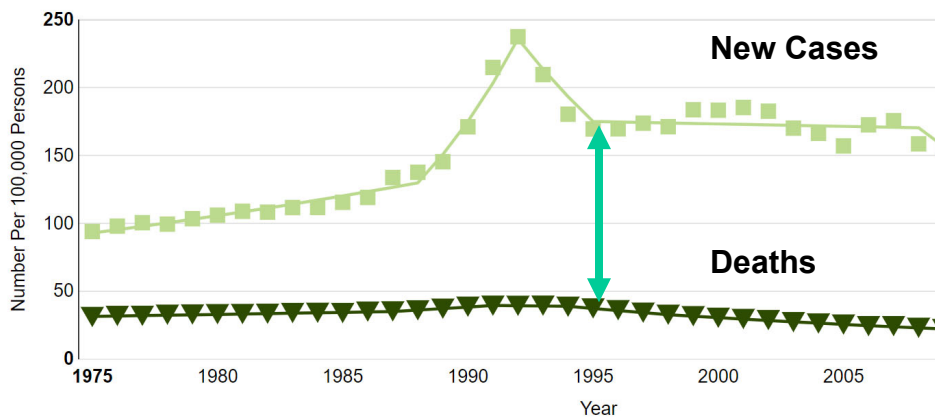
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PSA: Historical Perspective



USPSTF Grade I – insufficient evidence for PSA

A gap between incidence and mortality



SEER Registry Public Data

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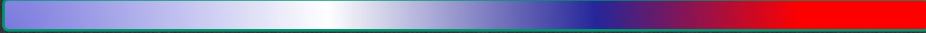
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“THE GAP”
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We were treating **ALL** these men in the '90s and '00s

PSA has profoundly impacted medicine

Prostate cancer is the most common cancer in men and the second most common cause of cancer death in men

We were screening many men and treating most men with prostate cancer with expensive and toxic treatments, without high-level evidence of benefit

American Cancer Society Statistics, CA Cancer J Clin 2019, non-melanoma skin not included

PSA: Historical Perspective



2 major randomized screening studies reported in the New England Journal of Medicine

Schroder et al NEJM 2009, Andriole et al NEJM 2009

2009 Revelations

Trial	PLCO	ERSPC
Location	US	Europe
Participants	76,685 men 55-74	162,243 men 55-69
Intervention	Annual PSA	PSA every 4 years
Finding	No impact on prostate cancer mortality	Reduction of 1 prostate cancer death per 1410 screened and 48 treated

PSA: Historical Perspective



USPSTF – grade “D”
recommendation, the harms
outweigh the benefits **without**
regard to age, race, family history

The USPSTF Decision

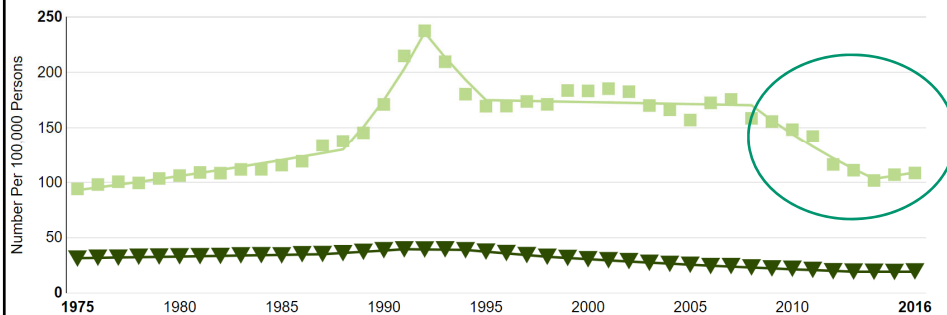
ERSPC
1410 men to screen
48 to treat
to save 1 life from
prostate cancer

PLCO Lack of survival
benefit
Harms of biopsy including
infection (2-4% sepsis)
Psychological impacts
Harms of treatment including
erectile dysfunction (most)
and incontinence (10%)

Benefits

Harms

Reduced screening decreased incidence



We have **MANY** studies that show that screening, biopsies, diagnoses of prostate cancer decreased following the 2012 recommendations.

This was even **more pronounced in high-risk groups** (African American men, those with a family history)

Eapen Curr Op Urol (2017)

USPSTF Skepticism

- The USPSTF had no representation from any doctor who actually deals with prostate cancer (urologist, medical oncologist, radiation oncologist).
- Those who dealt with the disease had concerns...

What about this?

Deaths
per
100,000



Incidence of more aggressive cancer declined by 25%
→ **What will happen to these undetected cases??**

Prostate biopsy series started showing a 33% higher rate of more aggressive disease
→ **Can these patients be as successfully managed??**

Metastatic prostate cancer increased by 92% from 2004 to 2013 and median PSA at presentation of doubled
→ **Does this relate to changes in screening practice??**

Barocas J Urol (2015); Banerji J Urol (2016); Weiner Pros Can Pros Dis (2016)

PLCO Death Knell



We realize 90% of men in the non-screening arm of the PLCO had a PSA before or during the trial (Shoag et al. NEJM 2016)

90% rate of contamination in PLCO trial

Shoag NEJM (2016)

2019 Revelations

Trial	PLCO	ERSPC
Location	US	Europe
Participants	76,574 men	162,243 men 55-69
Intervention	Annual PSA testing	PSA every 4 years
Finding	No improvement in prostate cancer mortality	Reduction of 1 prostate cancer death per 1410-570 screened and 48-18 diagnosed

By 2019, screening was looking better and better

Trial	ERSPC Pilot	Goteborg	ERSPC
Location	Rotterdam	Goteborg	Europe

Hugosson Eur Urol (2019), Osses Eur Urol (2019), Hugosson Eur Urol (2018)

By 2019, screening was looking better and better

Trial	ERSPC Pilot	Goteborg	ERSPC
Location	Rotterdam	Goteborg	Europe
Follow up	19 years	18 years	16 years
Number to screen	101	231	570
Number to diagnose	3	10	18

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By 2019 diagnosis has also changed

- Using MRI following elevated PSA:
 - **reduces** biopsy by 28% and insignificant cancer by 13%
 - **increases** significant cancer diagnosis by 12%
- Additional biomarkers may
 - **reduce** biopsy rates by 24-34%
- Biopsy via the perineum (transperineal) rather than rectum (transrectal) **reduces** post-biopsy infection
 - From 2-4% (transrectal) to <<1%

Kasivisvanathan NEJM (2018), Sathianathan J Urol (2018), Stefanova J Urol (2019)

By 2019 treatment has also changed

- Multiple large studies now show appropriate patients have a **clear benefit to treatment** (PIVOT, SCPG4, PROTECT)
- Active surveillance is being increasingly employed for low-risk cases – **overtreatment reduced**
- Focal therapies with minimal quality of life impact are on the horizon
- Surgery and radiation advances continue

Butler NEJM (2019), Wilt NEJM (2016), Hamdy NEJM (2016), Bil-Axelson NEJM (2018)

Earlier screening

We can stratify men by a baseline PSA in their **40s**:

PSA > **1.7** ng/dL - 8.7 odds of lethal prostate cancer

82% deaths in those with PSA above median (**0.7** ng/dL)

In African American men, PSA > **1.7** ng/dL - odds 174 for aggressive prostate cancer compared to those under 0.7 ng/dL

Preston JCO (2016), Preston Eur Urol (2019)

Increasing recognition of high-risk groups

Certain men are at high risk

- African American men
 - incidence 60% higher, **death rate is double**
- BRCA / Lynch
 - 2-6 fold risk
- Family history
 - Father or brother – 2 fold risk
 - 2 first degree relatives – 5 fold risk

Only 4% in PLCO were African American and 7% had a family history. We can move up discussions of screening to 40 (multiple guidelines are supportive).

Segal Ca J Clin (2019) Schroder NEJM (2009) Steinberg GD Prostate (1990) Castro JCO (2013)

A changing tide



➤ USPSTF – grade “C”
recommendation, shared decision
making on PSA screening

Principles of a good screening test

1. Important **disease...second leading cause of cancer death in men**
2. Acceptable treatment...**improving**
3. Access to diagnosis and treatment...**improving**
4. Recognizable early stage...**improved understanding of indolence**
5. Suitable test...**improving use of tests other than PSA**
6. Acceptable test...**improving use of MRI, transperineal biopsy**
7. Understood natural history...**improving**
8. Agreed on policy on whom to treat as patients...**improving**
9. Acceptable cost...**generally**
10. Continuous process...**improving understanding when to start/stop**

• Wilson, James Maxwell Glover, Gunnar Jungner, and World Health Organization. "Principles and practice of screening for disease." (1968).

Screening recommendations

Society	Summary of recommendation
USPSTF	Men 55-69 shared decision making
AUA	Men 55-69 shared decision making
NCCN	Men 45-75 shared decision making
ACS	Men starting 40-50 based on risk shared decision making
ACP	Men 50-69 shared decision making
AAFP	Men 55-69 shared decision making

Society Websites

Shared decision making

Screening has a **survival benefit**
 Treatment has a **survival benefit**
 We are better at reducing
 overscreening, overdiagnosis,
 overtreatment

Harms of biopsy
 Psychological
 impacts
 Harms of treatment
 Overdiagnosis and
 overtreatment still
 exist

Benefits

Harms



Use of the digital rectal exam

- The data doesn't show a clear benefit for DRE in the *screening* setting
- Optional ... but we definitely see many high-grade tumors with a low PSA and abnormal DRE
- It is not debated that it is important in the workup of *elevated PSA / prostate cancer*

Naji Ann Fam Med (2018)

Practical recommendations

- Discussion regarding screening beginning in the 40s, continue until 70s
 - Focus on **younger** rather than older
- Interval can be varied based on risk – between 1 and 4 years
 - Yearly may just be the most practical
- Be more vigilant in those at risk (AA, FHx, BRCA, Lynch)
- Double PSA in those on finasteride (Proscar) or dutasteride (Avodart)
- Repeat the PSA in 4-6 weeks if elevated
- Perform DRE for an elevated PSA
- Do not perform PSA with an acute UTI or recent Foley

Back to the case...

Recommendation: Shared decision making on PSA

Discuss it before you do it, as well as the rationale and limitations. May use a decision aid if visit time is limited.

Discussions should be tailored to age and PSA is de-emphasized in comorbid and older men. Many older and comorbid men should NOT be screened.

Those with a family history, BRCA/Lynch, and African American men are HIGH RISK and our screening studies do not apply. I would recommend screening these men.

Back to the case...

Indications for urology referral:

Know your urologist's practice patterns. Err on the side of referring; most of us don't biopsy or subsequently treat unless necessary.

PSA>2 in 40s

PSA>3 in 50s and 60s

PSA>4 in 70s

Abnormal digital rectal exam

Please err on the side of screening and referring African Americans, family history & susceptible germlines.

My indications to biopsy are MUCH higher but I would order an MRI in many of these men