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 can be safely surveilled | Treatable locoregional phase that improves survival | Fatal #2 cause of male cancer death |

Prostate cancer is a spectrum

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Prostate cancer is a spectrum

What can we do to impact this?

Incidental detection on autopsy in the majority of old men
Indolent stage that can be safely surveilled
Treatable locoregional phase that improves survival
Fatal #2 cause of male cancer death

Prostate cancer is a spectrum

Prevent Screen Diagnose Treat Survivorship

Incidental detection on autopsy in the majority of old men
Indolent stage that can be safely surveilled
Treatable locoregional phase that improves survival
Fatal #2 cause of male cancer death
### Prostate Cancer is a Spectrum

<table>
<thead>
<tr>
<th>Prevent</th>
<th>Screen</th>
<th>Diagnose</th>
<th>Treat</th>
<th>Survivorship</th>
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### Screening

| Incidental detection on autopsy in the majority of old men | Indolent stage that can be safely surveilled | Treatable locoregional phase that improves survival | Fatal #2 cause of male cancer death |

Google Images: Permission to Reuse
Screening = PSA*

*Pretty Much

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

Google Images: Permission to Reuse
**PSA: Historical Perspective**

- **1960**: Flocks identifies that the human prostate has unique antigens

**PSA: Historical Perspective**

- **1960**: Hara identifies a unique antigen in the semen
PSA: Historical Perspective

- 1960
- 1970
- Ablin discovers PSA – prostate specific antigen
- 1980
- 1990
- 2000
- 2012
- 2019

Rao et al. BJU Int 2008

PSA: Historical Perspective

- 1960
- 1970
- 1980
- Wang & Chu improve our understanding of PSA and optimize clinical testing
- 1990
- 2000
- 2012
- 2019

Rao et al. BJU Int 2008
PSA: Historical Perspective

- 1960
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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

- 1960
- 1970
- 1980
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- 2000
- 2012
- 2019

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

Widespread screening and treatment

What has PSA done?

SEER Registry Public Data
Screening dramatically increased incidence

Prostate cancer mortality has halved
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

Deaths


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

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

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

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

USPSTF Grade I – insufficient evidence for PSA

A gap between incidence and mortality

SEER Registry Public Data
Prostate cancer is a spectrum

- **Incidental** detection on autopsy in the majority of old men
- **Indolent** stage that can be safely surveilled
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"THE GAP" between incidence and mortality
Prostate cancer is a spectrum

Incidental detection on autopsy in the majority of old men

Indolent stage that can be safely surveilled

Treatable locoregional phase that improves survival

Fatal #2 cause of male cancer death

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

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2009 Revelations

<table>
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<tr>
<th>Trial</th>
<th>PLCO</th>
<th>ERSPC</th>
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<tr>
<td>Location</td>
<td>US</td>
<td>Europe</td>
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<td>Participants</td>
<td>76,685 men 55-74 (PLCO)</td>
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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)


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?

- 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

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By 2019, screening was looking better and better

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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%


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

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


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).

A changing tide

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

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

### Screening recommendations

<table>
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<th>Society</th>
<th>Summary of recommendation</th>
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<tr>
<td>USPSTF</td>
<td>Men 55-69 shared decision making</td>
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<tr>
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<tr>
<td>NCCN</td>
<td>Men 45-75 shared decision making</td>
</tr>
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### Shared decision making

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

**Benefits**

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**Harms**

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

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
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.

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.