No financial disclosures
Case Presentation

62 yo white man without significant past medical history presents for annual preventive visit. He has no family history of prostate cancer. He has mild urinary hesitancy and his prostate is mildly enlarged without induration or nodules. His PSA has been gradually rising:
- 2011: 2.35
- 2013: 2.17
- 2017: 3.75
- 2019: 4.51
Where do we go from here?

What’s New in Prostate Cancer Screening?

Key Questions

• Do we have any new evidence for or against screening?
• Do we have anything better than the PSA?
• What about the good old digital rectal exam?
• Are we doing any better identifying who needs to be treated?
• What do the experts recommend?
Prostate Cancer Incidence & Mortality Over the Decades

Source: Seer 9 areas & US Mortality Files (National Center for Health Statistics, CDC, Feb 2018)

Estimated New Cases

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>259,660</td>
<td>50%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>195,463</td>
<td>35%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>76,880</td>
<td>15%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>81,760</td>
<td>17%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>57,223</td>
<td>11%</td>
</tr>
<tr>
<td>Kidney &amp; ureter</td>
<td>44,123</td>
<td>9%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>41,060</td>
<td>9%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>30,144</td>
<td>6%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>20,825</td>
<td>4%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>20,841</td>
<td>4%</td>
</tr>
<tr>
<td>All sites</td>
<td>872,879</td>
<td>18%</td>
</tr>
</tbody>
</table>

Estimated Deaths

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>40,763</td>
<td>5%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>31,821</td>
<td>4%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>19,855</td>
<td>4%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>23,263</td>
<td>9%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>21,800</td>
<td>7%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>13,150</td>
<td>4%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>13,150</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; ureter</td>
<td>11,610</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,954</td>
<td>3%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>7,612</td>
<td>3%</td>
</tr>
<tr>
<td>All sites</td>
<td>250,514</td>
<td>100%</td>
</tr>
</tbody>
</table>

CA Cancer J Clin 2019;69:7-34.
Do we have any new evidence for or against prostate cancer screening?

Is Prostate Screening Still Controversial?
Mortality Results from a Randomized Prostate-Cancer Screening Trial

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

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
- NNS to prevent 1 case of metastatic cancer: ~350
- Number needed to diagnose to save 1 life: 27
  - Major issue of over-diagnosis & over-treatment

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

415,000 British men 50-69 randomized to a single offer to screen vs usual care (info sheet on request)
• One-time screen & then followed for 10 yrs
• Men dx’d with prostate cancer randomized to treatment vs active surveillance
Single PSA Screen vs Control: CAP Trial Results

CAP Trial: Problems

- Wasn’t a study of screening effectiveness; it examined the impact of offering screening
  - Only 1/3rd took them up on it vs 10-15% of controls
  - Likelihood of seeing a difference from the control group was very low!
- 10 year f/u is relatively short for prostate cancer
  - Though unlikely to see a difference even with longer f/u given low % screened
- Many diagnosed with cancer not treated as aggressively as in U.S.
- Designed to study the impact of a single screen
  - Not generalizable to serial screening strategies
Do we have anything better than the PSA?

Test Characteristics of the PSA

- Using a PSA threshold of $\geq 4.0$ ng/ml for referral for biopsy:
  - Sensitivity: 72%
  - Specificity: 93%
  - Positive Predictive Value: 25%
- 15-28% of men with PSA < 4 ng/ml will have prostate cancer on biopsy
  - 15% of these are high-grade
- False positives caused by:
  - BPH – the biggie
  - Prostatitis (often asymptomatic)
  - Ejaculation, long bike rides, probably not the DRE
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”?
Beyond PSA (alone)

- PSA Velocity
- PSA Density
- % Free PSA
- Prostate Health Index (PHI)
- 4K Test
- Multiparametric MRI (mpMRI)

PSA Velocity

- Velocity > 0.35 ng/dl per year associated with greater likelihood of death from prostate cancer in one study
- BUT: Didn’t predict cancer on biopsy any better than absolute PSA level in most recent study
- Best role may be in predicting need for repeat biopsy after initial negative biopsy

JNCI 2006;98:152127; Br J Cancer 2018;118:266-76.
PSA Density

- PSA/Prostate Volume = PSA density
- Men with BPH have lower PSA density than men with cancer
  - Could help to differentiate the two
- Doesn’t add much predictive value to % free PSA (fPSA)
- Requires a trans-rectal u/s
- Hasn’t gained much traction in initial evaluation of elevated PSA’s

% Free PSA (fPSA)

- The higher the % free PSA, the lower the risk of cancer
  - PSA produced by cancer cells is more likely to be complexed to a glycoprotein)
- FDA approved indication: PSA between 4 & 10 ng/dl with normal DRE
- Using a fPSA threshold of <25% detects 95% of cancers & reduces biopsy rate by 20%
  - But most men with elevated PSA’s have fPSA levels below 25% (ie, they need a biopsy)
Prostate Health Index (PHI)

- Combination of total PSA, free PSA, and proPSA tests
- Discriminates between high-grade cancer vs low-grade or no cancer
  - Higher score ≈ higher cancer risk
- A PHI score cut-off of 24 reduces biopsies by 36% at a cost of missing 2.5% of high-grade cancers (Gleason ≥7)
- FDA approved for PSA values between 4 & 10 ng/dl
- Epic ordering:
  - Miscellaneous non-genetic sendout to Mayo
  - LAB3926
  - Indicate PHI11 & red top in notes


4K Score

- Another combo test: total PSA, fPSA, human kallikrein 2, & ‘intact’ PSA
- Also factors in age, DRE result, and prior biopsy status
- Demonstrated to significantly improve accuracy & reduce need for biopsy, compared with PSA
- No optimal cut-off threshold for biopsy vs no-biopsy, just provides a probability of high-grade cancer.
Multiparametric MRI vs Standard Biopsy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MRI-Targeted Biopsy Group (N=251)</th>
<th>Standard Biopsy Group (N=248)</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy outcome — no. (%)</td>
<td></td>
<td></td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>PET-avidity below or equal to 0.1 mm cMRI</td>
<td>14 (56)</td>
<td>6</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>17 (34)</td>
<td>52 (49)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Atypical small acinar proliferation</td>
<td>0</td>
<td>5 (2)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>High-grade prostatic intraepithelial neoplasia</td>
<td>4 (2)</td>
<td>10 (4)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3+3</td>
<td>23 (9)</td>
<td>55 (22)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3+4</td>
<td>37 (15)</td>
<td>35 (14)</td>
<td>12 (4 to 20)</td>
<td>0.003</td>
</tr>
<tr>
<td>3+5</td>
<td>7 (3)</td>
<td>6 (2)</td>
<td>1 (1)</td>
<td>0.75</td>
</tr>
<tr>
<td>4+3</td>
<td>18 (7)</td>
<td>19 (8)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>4+4</td>
<td>13 (5)</td>
<td>6 (2)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>4+5</td>
<td>7 (3)</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>0.007</td>
</tr>
<tr>
<td>5+5</td>
<td>5 (2)</td>
<td>6 (2)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>No biopsy</td>
<td>4 (2)</td>
<td>3 (2)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Withdrawn from trial</td>
<td>5 (2)</td>
<td>13 (5)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Clinically significant cancer — no. (%)</td>
<td>95 (38)</td>
<td>64 (26)</td>
<td>12 (10 to 20)</td>
<td>0.006</td>
</tr>
<tr>
<td>Modified intention to treat analysis — no.</td>
<td>93/135 (69)</td>
<td>88/235 (37)</td>
<td>12 (10 to 20)</td>
<td>0.007</td>
</tr>
<tr>
<td>Per-protocol analysis — no./total no. (%)</td>
<td>92/235 (39)</td>
<td>62/253 (25)</td>
<td>12 (10 to 20)</td>
<td>0.007</td>
</tr>
<tr>
<td>Locally insignificant cancer — no. (%)</td>
<td>23 (9)</td>
<td>55 (22)</td>
<td>13 (10 to 20)</td>
<td>0.001</td>
</tr>
<tr>
<td>Maximum cancer core length (mm)</td>
<td>1.8 (1.5)</td>
<td>2.8 (2.1)</td>
<td>1.0 (0 to 2.1)</td>
<td>0.053</td>
</tr>
<tr>
<td>Core positive for cancer — no./total no. (%)</td>
<td>422/8767 (44)</td>
<td>513/2788 (18)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Men who did not undergo biopsy — no. (%)</td>
<td>73 (31)</td>
<td>16 (6)</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

### Multiparametric MRI vs Standard Biopsy

#### Complications

<table>
<thead>
<tr>
<th></th>
<th>MRI-Guided Biopsy</th>
<th>Standard Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median # of core biopsies</td>
<td>4*</td>
<td>12</td>
</tr>
<tr>
<td>Blood in urine (%)</td>
<td>30%</td>
<td>63%</td>
</tr>
<tr>
<td>Blood in semen (%)</td>
<td>32%</td>
<td>60%</td>
</tr>
<tr>
<td>Post-procedural pain (%)</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>Rectal bleeding (%)</td>
<td>14%</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Among men who underwent biopsy

---

**mpMRI: Caveat**

- Not yet routinely covered by insurance prior to biopsy except Medicare
- Requires peer-to-peer
- More likely to get covered if:
  - PSA>10
  - Abnormal PHI or 4K test
  - Subsequent biopsy confirms cancer diagnosis
    - But that’s a $3000 crapshoot...
What about the good old digital rectal exam?

The Digital Rectal Exam

- 2018 meta-analysis: sensitivity 51%, specificity 59% (primary care docs)
  - About the same as flipping a coin
- One survey: ½ of medical school graduates never performed a DRE
- Only ½ of primary care docs are confident in their ability to detect prostate cancer with DRE
- Inter-examiner reliability between urologists to identify suspicious nodules is fair at best ($\kappa = 0.22$)
- Major guidelines now make DRE optional for primary screen
  - Still makes sense to do it for abnormal PSA’s, symptoms

Are we doing any better identifying who needs to be treated?

“It may be more inconvenient, but the ‘Reverse Prostate Exam’ is a lot less embarrassing for the both of us.”
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

---

Overdiagnosis & Overtreatment: the PSA Quandary

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

-- Willet Whitmore, MD, “1990
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 progresses
  - In the US, PSA done every 6 months & biopsy annually
  - In the US, Gleason 7 generally offered treatment, NOT active surveillance
- Reduces risk of overtreatment
ProtecT Trial: Treatment vs “Active Monitoring”


ProtecT: Survival in treated vs active surveillance groups

A price to pay for active surveillance?

Active Surveillance: Are we creating a cohort of anxious men who are in “cancer limbo”?

Table 3. Predicted risk of anxiety by overall health score and time on active surveillance in 413 patients

<table>
<thead>
<tr>
<th>Overall Health Score</th>
<th>Median % Predicted Risk (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 Yrs</td>
</tr>
<tr>
<td>4</td>
<td>39 (28–49)</td>
</tr>
<tr>
<td>6</td>
<td>30 (24–36)</td>
</tr>
<tr>
<td>8</td>
<td>23 (19–27)</td>
</tr>
<tr>
<td>10</td>
<td>17 (11–22)</td>
</tr>
</tbody>
</table>
What do the experts recommend?

**Prostate Cancer Screening Guidelines**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Range</td>
<td>55-69 Recommends against screening &gt; 70 (D rec)</td>
<td>55-69 Individualize 40-54 based on (+) FH, AA race</td>
<td>50-74 45 if AA or (+) FH No screening if life expectancy &lt;10 yrs</td>
</tr>
<tr>
<td>No separate rec for (+) FH or AA</td>
<td>Individualize over age 70 (only if life expectancy &gt;10 y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening Tool</td>
<td>PSA without DRE</td>
<td>PSA (no mention of DRE)</td>
<td>PSA +/- DRE</td>
</tr>
<tr>
<td>Screening Interval</td>
<td>Not defined</td>
<td>2 yrs (consider 4 yrs if PSA &lt;1)</td>
<td>2 yrs (PSA &lt;2.5), 1 yr (PSA 2.5-4)</td>
</tr>
</tbody>
</table>

So, how do you do informed/shared decision-making in 5 minutes or less?

• Provide the core information needed for an informed decision
• Provide dichotomous “values matching” scenarios
• Assign homework

Core elements for an informed decision

• PSA testing can find prostate cancer before you have symptoms
• Early detection may reduce your chances of suffering or dying from prostate cancer
• There is a good chance that if we find prostate cancer, it would never have caused problems during your lifetime.
• If we find one of these low-grade prostate cancers, you won’t need treatment, but you’ll need to undergo yearly biopsies
• Treating prostate cancer frequently leads to erectile dysfunction, urinary leakage, and/or bowel problems.

PSA screening can detect cancer at an earlier stage than if no screening is performed.

PSA screening can reduce 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: this can be painful & anxiety-producing.

PROS

CONS

To Help Our Patients Decide:

Values Matching Scenarios

“You might want to be tested if you value finding cancer early, you’re willing to be diagnosed with a cancer that we may not treat, and you’re willing to risk significant injury to sexual, urinary, or bowel function if we do have to treat.”

“You might not want to be tested if you place a higher value on avoiding the potential harms of screening, such as anxiety about finding a cancer we don’t treat, or injury to sexual, urinary or bowel function.”
Assign homework
Prostate Cancer

Should I Get Screened for Prostate Cancer?

In 2018, the U.S. Preventive Services Task Force (USPSTF) made the following recommendation:

- Men who are 55 to 69 years old should make individual decisions about being screened for prostate cancer with a prostate-specific antigen (PSA) test.
- Before making a decision, men should talk to their doctor about the benefits and harms of screening for prostate cancer, including the benefits and harms of other tests and treatment.
- Men who are 70 years old and older should not be screened for prostate cancer routinely.

This recommendation applies to men who:

- Are at average risk for prostate cancer.
- Are at increased risk for prostate cancer.
- Do not have symptomatic prostate cancer.
- Have never been diagnosed with prostate cancer.

Prostate Cancer Screening: Making the Best Choice

WELCOME TO

Prostate Cancer Screening: Making the Best Choice

Click here to get started

Content updated January 2014
Quality-Adjusted Life-Years (QALYs) Gained by Lifetime Prostate Cancer Screening of 1000 Men Based on Utilities (Values)


Case Presentation

62 yo white man without significant past medical history presents for annual preventive visit. He has no family history of prostate cancer. He has mild urinary hesitancy and his prostate is mildly enlarged without induration or nodules. His PSA has been gradually rising:

- 2011: 2.35
- 2013: 2.17
- 2017: 3.75
- 2019: 4.51

Where do we go from here?
### Characteristics

<table>
<thead>
<tr>
<th>Race</th>
<th>Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62</td>
</tr>
<tr>
<td>PSA [ng/ml]</td>
<td>4.51</td>
</tr>
<tr>
<td>Family History of Prostate Cancer</td>
<td>No</td>
</tr>
<tr>
<td>Digital rectal examination</td>
<td>Normal</td>
</tr>
<tr>
<td>Prior biopsy</td>
<td>Never had a prior biopsy</td>
</tr>
</tbody>
</table>

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

Based on the provided risk factors, a prostate biopsy performed would have:
- **65% chance of high-grade prostate cancer.**
- **16% chance of low-grade cancer.**
- **19% 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.

---

### Characteristics

<table>
<thead>
<tr>
<th>Race</th>
<th>Other Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62</td>
</tr>
<tr>
<td>PSA [ng/ml]</td>
<td>4.51</td>
</tr>
<tr>
<td>Family History of Prostate Cancer</td>
<td>No</td>
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About 2 to 4% of men undergoing biopsy will have an infection that may require hospitalization.

Please consult your physician concerning these results.
Options

• Repeat – appropriate, but probably won’t change much (current value consistent with rate of rise)
• Other tests to refine risk assessment: % free PSA, PHI, 4K, mpMRI
• Biopsy

Take-Home Points

• Prostate cancer screening probably does save lives.
• Prostate cancer screening definitely subjects many men to unnecessary treatment that poses significant risk to urinary, sexual & bowel health.
• We have a growing array of tools to refine cancer probability and avoid unnecessary biopsy, including free PSA, prostate health index, & mpMRI.
• Active surveillance is a powerful tool to reduce unnecessary treatment – but leaves men with untreated cancer & its associated anxiety.
• Men need to know what they’re getting into before screening.
Useful Resources

- Prostate cancer risk calculator: [www.riskcalc.org/PCPTRC](http://www.riskcalc.org/PCPTRC)
- CDC patient info: [https://www.cdc.gov/cancer/prostate/index.htm](https://www.cdc.gov/cancer/prostate/index.htm)
- Georgetown decision aid: [http://prostatedecision.georgetown.edu](http://prostatedecision.georgetown.edu)

Thank you!