A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

Prostate Cancer and Primary Care
The Role of Shared Decision Making in Screening and Treatment

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  - Advisory Board/Speaker – Astellas

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  - Other – Wife Employee – Ferring

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  - Research/Consulting – Astellas, Bayer, Dendreon, Ferring, Janssen,
    Medivation, Sanofi, Millennium

• Ronald Tutrone, MD, FACS
  - Speaker/Research – Dendreon, Valeant, Medivation, Bayer, Janssen

Part 1: Prevalence and Screening –

Finding Those at Risk
To Screen or Not to Screen
That is the Question

Matt T. Rosenberg, MD
E. David Crawford, MD
William Shakespeare

I am so CONFUSED

Matt T. Rosenberg, MD
E. David Crawford, MD
200,000 un-named PCPs
Objectives

- Recognize the prevalence, risk factors and impact of prostate cancer.
- Compare the USPSTF and AUA guidelines on screening.
- Understand sharing decision making.
- Define the role of the PCP in treating patients with localized and metastatic disease.

Pre-test Question 1

On a scale of 1 to 5:
Please rate how confident you would be treating a patient with Prostate Cancer:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Steve is a 46 year old Chinese male with a family history of prostate cancer in his brother. He is concerned about his risk factors. You advise him of all the following are true about Prostate Cancer **except**:

1. High prevalence in all males, but low mortality
2. Low prevalence in Asian American males
3. Father with cancer confers greater risk than a brother with prostate cancer
4. Incidence is linked with dietary factors

According the USPSTF recommendations regarding prostate cancer screening, which of the following is **true**?

1. Do not routinely screen with a PSA, but still use the DRE
2. Use both the PSA and the DRE on all patients of appropriate age
3. Do not routinely screen with either the PSA or DRE
4. Routinely use the PSA, but not the DRE
Pre-test Question 4

According the AUA guidelines on prostate cancer screening, which of the following is **false**?

1. Screen men 55-69 years of age
2. Screen men 70 years of age and older with a 5 year life expectancy
3. Use an individualized approach to screen patients less that 55 years of age
4. Consider increasing screening interval depending on PSA and age
5. Use shared decision making approach

Pre-test Question 5

The tenets of shared decision making include all the following **except**?

1. Provision of information
2. Directing patient decision making with evidence based medicine
3. Elicitation of patient perception
4. Guiding final decision making
Max is a 63 year old with a slightly high PSA (4.1 ng/ml) noted at his yearly PE. He had read something online regarding biomarkers and was hoping you could help him understand them. Which of the following statements most adequately represents your impression of this tool?

1. Don’t know, never heard of them
2. Replaces the need for biopsy
3. Evaluates risk of having aggressive prostate cancer
4. Only useful in men with a PSA greater than 6 ng/ml

Henry has castrate resistant prostate cancer and is prescribed abiraterone acetate by the Urologist. Which of the following side effects should the PCP be aware of?

1. Hypokalemia and hypotension
2. Hyperkalemia and hypotension
3. Hypokalemia and hypertension
4. Hyperkalemia and hypertension
Pre-test Question 8

Sal is a 75 y/o man with prostate cancer on Androgen Deprivation therapy. His PSA is very suppressed at 0.1 but he presents complaining of bad hot flashes. All of the following may offer him some relief except:

1. Clonidine
2. Gabapentin
3. Spironolactone
4. Depot Provera
5. Venlafaxine

*ARS Question

Regarding early detection of prostate cancer, I am:

1. Supportive of routine screening of at-risk men who have a >10yr life expectancy
2. Supportive of selective screening
3. Do not support any form of screening
4. Unsure and the jury is still out
Normal Prostate Anatomy

Benign Prostatic Hyperplasia

WebMD Accessed March 19, 2015
Stage 1 Prostate Cancer  
**T1N0M0**

- Found by needle biopsy (done for a high PSA level) or in a small amount of tissue during surgery for other reasons.
- Situated in one-half or less of one lobe of the prostate.
- The PSA level is lower than 10 and the Gleason score is 6 or lower.


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Stage 2A Prostate Cancer  
**T2N0M0**

- Found by needle biopsy or in a small amount of tissue during surgery for other reasons. The PSA level is lower than 20 and the Gleason score is 7.
- Found by needle biopsy or in a small amount of tissue during surgery for other reasons. The PSA level is at least 10 but lower than 20 and the Gleason score is 6 or lower.
- Found in one-half or less of one lobe of the prostate. The PSA level is at least 10 but lower than 20 and the Gleason score is 6 or lower.
- Found in one-half or less of one lobe of the prostate. The PSA level is lower than 20 and the Gleason score is 7; or
- Found in more than one-half of one lobe of the prostate.

Stage 2B Prostate Cancer

- Found in opposite sides of the prostate. The PSA can be any level and the Gleason score can range from 2 to 10
- Cannot be felt during a digital rectal exam and cannot be seen in imaging tests. The PSA level is 20 or higher and the Gleason score can range from 2 to 10
- Cannot be felt during a digital rectal exam and cannot be seen in imaging tests. The PSA can be any level and the Gleason score is 8 or higher

Stage 3 Prostate Cancer

T3 NOMO

Cancer has spread beyond the outer layer of the prostate and may have spread to the seminal vesicles. The PSA can be any level and the Gleason score can range from 2 to 10
Stage 4 Prostate Cancer
T1-4 N+M+

- The cancer has spread beyond the seminal vesicles to nearby tissue or organs, such as the rectum, bladder, or pelvic wall
- May have metastasized to distant parts of the body including lymph nodes or bones
- PSA can be any level

Gleason Grade: sum of worst 2 patterns

http://www.aboutcancer.com/proad.htm
Accessed March 23, 2015

http://www.webmicroscope.net/webmicroscope/gleason/gleasonscale.gif
Accessed March 19, 2015
Section 1 – Prostate Cancer Basics

- Prevalence
- Risk factors
- Impact

US Incident and Mortality Rates Common Malignancies in Males

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Incidence (annual)</th>
<th>Mortality (annual)</th>
<th>% Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>233,000</td>
<td>29,480</td>
<td>12.65</td>
</tr>
<tr>
<td>Lung and Bronchus</td>
<td>116,000</td>
<td>86,930</td>
<td>74.94</td>
</tr>
<tr>
<td>Colorectal</td>
<td>71,930</td>
<td>26,270</td>
<td>36.52</td>
</tr>
<tr>
<td>Bladder</td>
<td>56,390</td>
<td>11,170</td>
<td>19.81</td>
</tr>
<tr>
<td>Melanoma</td>
<td>43,890</td>
<td>9,710</td>
<td>22.12</td>
</tr>
<tr>
<td>Kidney</td>
<td>39,140</td>
<td>8,900</td>
<td>22.74</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>38,270</td>
<td>10,470</td>
<td>27.36</td>
</tr>
</tbody>
</table>

Adapted from Cancer Facts and Figures – 2014, American Cancer Society
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

The Lifetime Risk of Prostate Cancer in the United States

Diagnosis → 17%

Prevalence

Top 10 Cancer Sites: 2011, Male, United States—All Races

- Prostate: 128.3
- Lung and Bronchus: 73.0
- Colon and Rectum: 46.1
- Urinary Bladder: 35.1
- Melanomas of the Skin: 25.3
- Non-Hodgkin Lymphoma: 22.6
- Kidney and Renal Pelvis: 21.0
- Oral Cavity and Pharynx: 17.0
- Leukemias: 16.5
- Pancreas: 13.8

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Prevalence

Top 10 Cancer Sites: 2011, Male, United States – White

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>117.2</td>
</tr>
<tr>
<td>Lung and Bronchus</td>
<td>72.5</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>44.9</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>37.1</td>
</tr>
<tr>
<td>Melanomas of the Skin</td>
<td>28.0</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>23.1</td>
</tr>
<tr>
<td>Kidney and Renal Pelvis</td>
<td>21.1</td>
</tr>
<tr>
<td>Oral Cavity and Pharynx</td>
<td>17.4</td>
</tr>
<tr>
<td>Leukemias</td>
<td>15.8</td>
</tr>
<tr>
<td>Pancreas</td>
<td>13.7</td>
</tr>
</tbody>
</table>

Prevalence

Top 10 Cancer Sites: 2011, Male, United States – Black

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>194.7</td>
</tr>
<tr>
<td>Lung and Bronchus</td>
<td>87.3</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>55.0</td>
</tr>
<tr>
<td>Kidney and Renal Pelvis</td>
<td>23.2</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>19.1</td>
</tr>
<tr>
<td>Liver and Intrahepatic Bile Duct</td>
<td>16.3</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>16.2</td>
</tr>
<tr>
<td>Pancreas</td>
<td>16.2</td>
</tr>
<tr>
<td>Oral Cavity and Pharynx</td>
<td>14.8</td>
</tr>
<tr>
<td>Stomach</td>
<td>13.9</td>
</tr>
</tbody>
</table>

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Prevalence

Top 10 Cancer Sites: 2011, Male, United States—Asian/Pacific Islander

- Prostate: 67.1
- Lung and Bronchus: 45.3
- Colon and Rectum: 38.3
- Liver and Intrahepatic Bile Duct: 20.0
- Non-Hodgkin Lymphoma: 15.3
- Urinary Bladder: 14.4
- Stomach: 14.1
- Oral Cavity and Pharynx: 10.8
- Kidney and Renal Pelvis: 10.7
- Pancreas: 10.2

Rates per 100,000#


Prevalence

Top 10 Cancer Sites: 2011, Male, United States—American Indian/Alaska Native

- Prostate: 62.2
- Lung and Bronchus: 47.8
- Colon and Rectum: 33.5
- Kidney and Renal Pelvis: 18.2
- Urinary Bladder: 13.9
- Liver and Intrahepatic Bile Duct: 12.9
- Non-Hodgkin Lymphoma: 11.6
- Oral Cavity and Pharynx: 10.9
- Pancreas: 9.9
- Leukemias: 8.2

Rates per 100,000#

Prevalence

Top 10 Cancer Sites: 2011, Male, United States—Hispanic

- Prostate: 104.4
- Colon and Rectum: 43.1
- Lung and Bronchus: 42.5
- Kidney and Renal Pelvis: 20.0
- Urinary Bladder: 19.5
- Non-Hodgkin Lymphoma: 19.3
- Liver and Intrahepatic Bile Duct: 18.8
- Stomach: 13.2
- Leukemias: 12.5
- Pancreas: 12.3

Accessed March 19, 2015

Risk Factors: *Reality vs Myth*

- Age
- Race/ethnicity
- Geography
- Family
- Gene changes
- Diet
- Workplace exposures
- Prostatitis
- Obesity
- Sexually transmitted diseases
- Vasectomy

Accessed March 19, 2015
AGE is a Risk Factor

- Very rare in men younger than 40
- Rises rapidly after age 50
- 6 in 10 cases found in men over the age of 65

Race/ethnicity is a Risk Factor

- Increased prevalence
  - African-American
  - Caribbean men of African ancestry
- Decreased prevalence
  - Asian-American
  - Hispanic/Latino
- Increased mortality
  - African-American

Accessed March 19, 2015
**Geography** is a Risk Factor

- More common
  - North America
  - Europe (northwestern)
  - Australia
  - Caribbean Islands
- Less common
  - Asia
  - Africa
  - Central America
  - South America

Accessed March 19, 2015

**Family History** is a Risk Factor

- Immediate family member with prostate cancer more than doubles risk
  - Higher if brother affected than father
- Multiple relatives with prostate cancer increases risk, especially if young when diagnosed

Accessed March 19, 2015
Inherited Gene Changes may be Risk Factors

- BRCA1 or BRCA2 less than 2% of cancers
- Lynch syndrome (hereditary non-polyposis colorectal cancer)

Diet can be a Risk Factor

- Increased risk in
  - Red meat consumption
  - High fat dairy products
  - Low consumption of fruits and vegetables
  - Excess calcium

Accessed March 19, 2015
Obesity is and isn’t a Risk Factor

- No linkage found in overall prevalence
- Decreased risk of low-grade prostate cancer
- Higher risk of more aggressive prostate cancer

Smoking is not a Risk Factor

Accessed March 19, 2015
**Workplace exposures** may be a Risk Factor

- Firefighters exposed to toxic combustion products may increase their risk of prostate cancer
- Agent Orange

[43]

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**Inflammation of the prostate** is not yet known to be a Risk Factor

- No link found yet
- Inflammation is often seen in biopsy samples that contain cancer
- Active area of research

[44]
**Sexual transmitted infections** are not known to be Risk Factors

- Studies have not agreed
- Research ongoing

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**Prior Vasectomy** is not a known Risk Factor

- Research ongoing
- Probably not associated

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Accessed March 19, 2015
Impact of Prostate Cancer

- Possibly fatal
- Emotional toll
- Symptoms

Urinary and Excretory Symptoms

- Difficulty stopping and starting urine flow
- Urine flow that is weak or intermittent
- Nocturia
- Incontinence
- Pain or burning during urination or bowel movements
- Difficulty have a bowel movement
- Hematuria
Sexual Symptoms

• Problems obtaining an erection
• Painful ejaculation
• Hematospermia

Symptoms of Advanced Disease

• Swelling in legs (nodal involvement)
• Frequent pain in the thighs, hips, abdomen, or lower back
• Bone pain
• Fatigue or weakness
• Unexplained weight loss
• Nausea, vomiting, or reduced appetite
Section 2 – Screening Guidelines

- Why do we screen for cancer?
- What is PSA?
- Is the PSA accurate?
- What has been the historical result of prostate cancer screening?
- ERSP and PLCO
  - Why they were done?
  - What were the results?
- USPSTF Recommendations
- AUA Recommendations

Definition of Screening

“The systematic application of a test or inquiry, to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventive action, amongst persons who have not sought medical attention on account of symptoms of that disorder”

OR SIMPLY PUT

Testing an asymptomatic patient for early disease detection

United Kingdom National Screening Committee (2004)
Screening for Prostate Cancer: DRE

Screening for Prostate Cancer: Labs

- **1936**: Elevated acid phosphatase described in the prostate
- **1970**: PSA discovered
- **1980**: PSA found to be elevated in men with prostate cancer
- **1986**: PSA approved by FDA for monitoring cancer recurrence
- **1994**: PSA approved for screening in conjunction with DRE
- **2005**: Discovery of antibodies that act as a new biomarker for prostate cancer
Interpreting the PSA Level

- PSA is prostate specific. Elevations occur with
  - Cancer (poor sensitivity)
  - Benign prostatic hypertrophy
  - Prostatitis
    - Antibiotics decrease PSA in 30% if infected
  - Trauma, instrumentation
  - Does not increase with sex or DRE
- 15% variation week to week
- Assay variability up to 20%
- Statins decrease PSA by ~ 4%
- Finasteride/Dutasteride can decrease PSA approximately 50%

The Benefit of Screening with PSA
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You Don’t Help Most Men with Prostate Cancer When You Find It

Death from prostate cancer
Metastatic disease develops
Cancer spreads to lymph nodes
Cancer spreads beyond prostate
Cancer detectable: PSA >4 ng/mL
Prostate cancer develops

Annual PSA and DRE

Only this man benefits

Zone of detection when cure is possible

Prevalence of prostate cancer among men with a PSA level ≤4.0 ng/mL

% of men with prostate cancer and high-grade disease

- Percent with prostate cancer
- Percent with Gleason ≥7 disease

A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

### Sensitivity and Specificity of PSA

<table>
<thead>
<tr>
<th>PSA</th>
<th>N</th>
<th>CaP</th>
<th>HGCaP</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.5</td>
<td>486</td>
<td>32 (6.6%)</td>
<td>4 (12.5%)</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>0.6-1.0</td>
<td>791</td>
<td>80 (10.1%)</td>
<td>8 (10.0%)</td>
<td>93%</td>
<td>2%</td>
</tr>
<tr>
<td>1.1-2.0</td>
<td>998</td>
<td>170 (17%)</td>
<td>20 (11.8%)</td>
<td>73%</td>
<td>33%</td>
</tr>
<tr>
<td>2.1-3.0</td>
<td>482</td>
<td>115 (23.9%)</td>
<td>22 (19.1%)</td>
<td>37%</td>
<td>73%</td>
</tr>
<tr>
<td>3.1-4.0</td>
<td>193</td>
<td>52 (26.9%)</td>
<td>13 (25.0%)</td>
<td>12%</td>
<td>92%</td>
</tr>
</tbody>
</table>


### Assessing Risk of Prostate Cancer

Pienta K. Urology. 2009;73(S5A):11-20

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NACE - Emerging Challenges in Primary Care: 2015

Prostate Cancer - 30
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

Is the Use of PSA the Reason for Decreased Mortality?

Many Reasons for the Reduction in Prostate Cancer Mortality

- Early detection / screening?
- Better therapy (radiation, surgery)
- Earlier use of hormonal therapy
- Other
  - Lifestyle changes
  - Medication use (statins / cox-2 inhibitors)
Many Reasons for the Reduction in Prostate Cancer Mortality

- Early detection / screening? How can we be sure we are right?
- Better therapy (radiation, surgery)
- Earlier use of hormonal therapy
- Other
  - Lifestyle changes
  - Medication use (statins / cox-2 inhibitors)

American (PLCO) Study

- Design
  - 76693 men
  - Yearly PSA vs no PSA
- Results
  - After 13 years of follow up there was no mortality benefit for organized annual screening compared to opportunistic screening

American Study - Debate

- Large number pre-screened resulting in contaminated control group
- Single point cut point for PSA
- Was the length of follow up long enough?

European Study

- Design
  - 182,000 men
  - PSA every 4 years, no DRE

- Results
  - 25% reduction in metastatic disease
  - 20% reduction in mortality
  - 1055 men needed to be screened for 11 years to save one man from prostate cancer

European Study - Debate

• Combination of 7 studies in 5 countries
  – 5 studies showed no benefit
  – Dutch and Swedish studies did
• Was the length of follow up long enough?

Benefit Over Time May Increase

Figure 2. Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.

Why is this so hotly debated?

- **OVERDIAGNOSIS** - 50% of men found to have prostate cancer would not have symptoms in their lifetime
  - Turned into unnecessary patients
  - Unpleasant outcomes
    - ED
    - Incontinence
    - Biopsy, surgery, radiation, chemotherapy complications
- **UNDIAGNOSIS** – there will be men with a missed opportunity for survival

USPSTF Guidelines Prostate Cancer Screening

- PSA screening is a “D” recommendation
- Physicians should not order PSA screening unless they are prepared to engage in shared decision making that enables an informed choice by patients

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AUA Guidelines

- 55-69 years of age
- 70 years of age and older with a 10 to 15 year life expectancy
- Patients less that 55 years of age use an individualized approach
- Consider increasing screening interval depending on PSA and age
- Use shared decision making approach


PSA Screening Recommendations of Major Societies

<table>
<thead>
<tr>
<th>Organization</th>
<th>Who To Screen</th>
<th>Screening Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF, 2012</td>
<td>Should not be offered, consider shared decision making</td>
<td>na</td>
</tr>
<tr>
<td>AUA, 2013</td>
<td>55-69 y or ≥ 70 with 10 to 15 y life expectancy, use shared decision making approach (SDMA); &lt; 55 y individualize approach</td>
<td>Consider 2 y interval over annual; may individualize depending on initial level</td>
</tr>
<tr>
<td>ASCO, 2012</td>
<td>Men with life expectancy &gt; 10 y, SDMA</td>
<td>none</td>
</tr>
<tr>
<td>ACS, 2010</td>
<td>&gt;50 y at average risk with 10 y life expectancy use SDMA; 45 y high risk, 40 y very high risk</td>
<td>Annual if ≥ 2.5 ng/m; biannual if &lt; 2.5 ng/ml; Biopsy if &gt; 4 ng/dl; individualize 2.5-4 ng/ml</td>
</tr>
<tr>
<td>ACP, 2013</td>
<td>&gt;50 y at average risk with 10 y life expectancy use SDMA; 45 y high risk, 40 y very high risk</td>
<td>Consider longer intervals than yearly</td>
</tr>
<tr>
<td>EAU, 2013</td>
<td>Baseline PSA ≥ 40 – 45 y</td>
<td>2-4 y with PSA &gt; 1µg/L at 45-59 y and up to 8 y if PSA &lt; 1µg/L</td>
</tr>
</tbody>
</table>

Section 3 – Shared Decision Making

• Who is affected by them?
• What is Shared Decision Making?
• Are they able to be implemented as designed?
• What have been the results of the recommendations?

Who is affected by this?
Who is Ordering PSA tests?

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>Internal Medicine</td>
<td>64.9</td>
</tr>
<tr>
<td>Family Medicine</td>
<td>23.7</td>
</tr>
<tr>
<td>Urology</td>
<td>6.1</td>
</tr>
<tr>
<td>Hem/Onc</td>
<td>1.3</td>
</tr>
</tbody>
</table>


Which Guidelines Do Primary Care Follow?

<table>
<thead>
<tr>
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<td>&lt;55 yrs and ≥50 with 10 to 15 y life expectancy, use shared decision making approach (SDMA); &lt; 55 y individualize approach</td>
<td>Consider 2 y interval over annual; may individualize depending on initial level</td>
</tr>
</tbody>
</table>

69% chose USPSTF vs 4% chose AUA

The AAFP Website

Recommendation

Do not routinely screen for prostate cancer using a prostate-specific antigen (PSA) test or digital rectal exam.

• There is convincing evidence that PSA-based screening leads to substantial over-diagnosis of prostate tumors.

• Many tumors will not harm patients, while the risks of treatment are significant.

• Physicians should not offer or order PSA screening unless they are prepared to engage in shared decision making that enables an informed choice by patients.

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Patients Read This

Great News For Guys: No More Invasive Prostate Exams!

1 in 7 men will be diagnosed with prostate cancer during his lifetime.

……...and this

FORBES Magazine November 2013

Prostate Cancer: GET THE FACTS

Other than skin cancer, prostate cancer is the most common cancer in American men.

1 in 6 men will be diagnosed with prostate cancer during his lifetime.

Prostate cancer can be a serious disease, but most men diagnosed with prostate cancer do not die from it. In fact, more than 2.5 million men in the United States who have been diagnosed with prostate cancer at some point are still alive today.

238,590 Estimated new cases this year.

Prostate cancer incidence rates increase in men until about age 70 and decline thereafter.

1 in 4 Newly diagnosed cancers each year are prostate cancer cases.

About 60% of all prostate cancer cases are diagnosed in men 65 years of age or older.

93% of prostate cancers are discovered in the local or regional stages, for which the 5-year relative survival rate approaches 100%.

……...and this

FORBES Magazine November 2013

Great News For Guys: No More Invasive Prostate Exams!
Tenets of Shared Decision Making

• Provision of information
  – Balanced and evidence based
  – Harms and benefits of each option

• Elicitation of patient’s perspective
  – Asking about prior experiences
  – Understanding and discussing concerns
  – Delineating preferences regarding screening options

• Guiding final decision making (without directing)


Can they be implemented according to design?
Is Shared Decision Making Common?

**The Patient Perspective**

- Shared decision making is an uncommon occurrence in PSA screening
- Most PSA screening occurs with incomplete or no physician-patient discussion of its associated advantages, disadvantages, and uncertainty
- The absence of shared decision making applies not only to PSA screening but even more so to nonscreening
- Men who reported being fully informed about advantages, disadvantages, and uncertainty had a lower likelihood of undergoing high-intensity screening


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Is Shared Decision Making Common?

**The Physician’s Perspective**

- Variability in use of informed decision-making can be attributed to beliefs about screening, including medicolegal risk
- Physicians who do not engage their patients in discussions about the potential harms and benefits of screening should consider changing their practice styles
- Efforts to educate physicians about the shared decision-making process should include countering the beliefs that perpetuate routine screening

Result of Physician Education

• Physicians studied performed poorly in many aspects of counseling regarding prostate cancer screening eliciting patients’ perspectives and in shared decision making.

• 90% of physicians self reported that they took patients’ perspectives into account.

• Paid intervention physicians showed somewhat more shared decision making and tended to provide more neutral guidance.

• Intervention just for physicians may not be sufficient to optimize shared decision making, the patient must also be educated independently.

Pairing Provider and Patient Education

• No differences in standardized patient–reported indices of shared decision making.

• Most physicians (64%) lectured the standardized patient about prostate cancer screening, rather than engaging in a 2-way discussion (28%).

• Movement from a pro screening bias toward neutral counseling about prostate cancer screening.
The Implementation of Shared Decision Making Has Failed in Other Diseases as Well

<table>
<thead>
<tr>
<th>Variable</th>
<th>Breast CA</th>
<th>Colorectal (W)</th>
<th>Colorectal (M)</th>
<th>Prostate CA</th>
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<td>Discussed reasons to have test (pros)</td>
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<td></td>
<td></td>
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<tr>
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<td>41</td>
<td>33</td>
<td>48</td>
</tr>
<tr>
<td>Some/a lot</td>
<td>53</td>
<td>59</td>
<td>67</td>
<td>51</td>
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<td>Discussed reasons not to have test (cons)</td>
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<td>87</td>
<td>87</td>
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<tr>
<td>Some/a lot</td>
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<td>13</td>
<td>14</td>
<td>7</td>
</tr>
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</table>


What are the results of these recommendations?
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

Proportion of men with PSA screening by patient characteristics

<table>
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<th>Postrecommendation N=26338</th>
<th>P value</th>
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<td>#</td>
<td>%</td>
<td>#</td>
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<tr>
<td>Total</td>
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<td>2004</td>
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<td>40 – 49</td>
<td>394</td>
<td>5.64</td>
<td>376</td>
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<tr>
<td>50 – 59</td>
<td>720</td>
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<td>816</td>
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<tr>
<td>60 – 69</td>
<td>508</td>
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<td>621</td>
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<tr>
<td>70 - 79</td>
<td>184</td>
<td>7.86</td>
<td>191</td>
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</table>


Individual Physician Screening Practices: Before and After USPSTF Recommendation

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Increased</th>
<th>Decreased</th>
<th>No Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family Medicine (n=52)</td>
<td>6 (11.5%)</td>
<td>13 (25.0%)</td>
<td>33 (63.5%)</td>
</tr>
<tr>
<td>Internal Medicine (n=85)</td>
<td>20 (23.5%)</td>
<td>33 (38.8%)</td>
<td>32 (37.7%)</td>
</tr>
<tr>
<td>Total (n=137)</td>
<td>26 (19.0%)</td>
<td>46 (33.6%)</td>
<td>65 (47.4%)</td>
</tr>
</tbody>
</table>

### Additional emerging evidence supports these trends

Oregon Health Sciences University study looked at pre-USPSTF and post-USPSTF PSA screening rates in their large primary care network in and around Portland, OR

- From EMR data abstracted Jan. 2008 – December 2013
- Included: Men over age 40 seen as new patients in Family or Internal Medicine clinics
- Excluded: Men with dx of PCa or those who had seen a urologist
- Overall PSA testing rate 2008 – 2012 (N=9160) 14%
- Overall PSA testing rate after May 2012 (N=3185) 7% (p<0.0001)
- Age 40-49 4.2% rate → 4.4% NS
- Age 50-59 19.2% rate → 8.5% (p<0.0001)
- Age 60-69 19.3% rate → 7.7% (p<0.0001)
- Age >70 10.2% rate → 9.3% NS

*Slide courtesy of Tim Stumpf*

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### Is this a problem?

- Patient perspective
- PCP perspective
- Urologist perspective
Is this a problem?

• Patient perspective

Patient Preference Matters

Unknown Status Without Screening

Normal by Screening

There is a significant quality-of-life benefit gained through screening and is strongly supported by patients

A Jury of “My Peers”

Patients had extensive training on prostate cancer on over a weekend

- Government should not focus on public campaign or widespread screening
- Effort should be made to educate GPs
- Patients should have access to test
  - 45% would not test
  - 55% would definitely test or consider testing


Is this a problem?

- PCP perspective
American Board of Internal Medicine

The 36 calendar months of full-time internal medicine residency education:

Must include at least 30 months of training in general internal medicine, subspecialty internal medicine and emergency medicine. Up to four months of the 30 months may include training in areas related to primary care, such as neurology, dermatology, office gynecology, or office orthopedics.


ACGME Recommendations for a Family Practice Residency

• IV.A.5.b).(5).(d) Surgical Subspecialties: In addition to the general surgery experience, residents must have adequately structured, hands-on educational experiences in the following subspecialty areas: otorhinolaryngology, to include oral health, urology, and ophthalmology. This must be in addition to resident experience with continuity patients during routine care in FMC and must involve disorders that are commonly seen in a family physician’s office.

www.acgme.org/acgmeweb/Portals/0/PFAssets/ProgramRequirements/120pr07012007.pdf.(accessed 1-29-14)
The Goldilocks Effect

Too much information or too little information results in providers adopting a
“screen all”
or
“screen none”

The Struggle for the PCP

<table>
<thead>
<tr>
<th>Reasons to Screen</th>
<th>Reason to Not Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liability</td>
<td>Guidelines</td>
</tr>
<tr>
<td>Patient Request</td>
<td>Future Quality Measures</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>Uncertainty</td>
</tr>
</tbody>
</table>

There is a movement to markedly limit or stop screening ....by whatever means needed

• Empower the patient
• Tailor the message to their cultural background
• Assess and manipulate their readiness
  – Small group forums
  – Previsit phone calls
  – Celebrities


In the current form the USPSTF recommendations represent a losing proposition for primary care and their patients
PHYSICIAN TO THE PRESIDENT
THE WHITE HOUSE
June 12, 2014

MEMORANDUM FOR:  JAY CARNEY
ASSISTANT TO THE PRESIDENT AND
WHITE HOUSE PRESS SECRETARY

FROM:          RONNY L. JACKSON, MD, FAAEM
PHYSICIAN TO THE PRESIDENT AND
DIRECTOR, WHITE HOUSE MEDICAL UNIT

SUBJECT:   The President’s Periodic Physical Exam
Lipid Panel:
Total cholesterol  213 (mg/dL)
Triglycerides     47 (mg/dL)
HDL cholesterol   72 (mg/dL)
LDL cholesterol   137 (mg/dL)
VLDL cholesterol  9 (mg/dL)
Cholesterol to HDL ratio  3.0

Fasting Blood Glucose:  95 (mg/dL)
Vitamin D:           22.9 (ng/ml)
PSA:                 1.15 (ng/ml)

Is this a problem?

• Urologist perspective
“Death of PSA screening”
Consequences of USPSTF recommendation

Will we return to pre-PSA era when most men were diagnosed with advanced incurable disease?

Gomella, LG “Celebrating the Death of PSA screening” CJU December 2011

A Simple Schema?

• Information for patient must be based on evidence and be beyond dispute
• Patient should be presented with a clear framework for a decision
• Schema should be appropriate for primary care
  – Should not assume provider has detailed knowledge of disease
  – Should not require more than a few minutes

Make Intelligent and Personalized Decisions

• Avoid PSA tests in men with little to no gain, as suggested in the AUA guidelines
  – Focus on age
  – Focus on health
  – Focus on quality measures
• Referral to high volume centers
• Do not treat those who do not need treatment
  – We (primary care) need a risk calculator?

Common Sense

• Shouldn’t the gold standard in prostate cancer screening be set by those treating it?
• Do we actually have enough evidence to be sure beyond any doubt?
• Using evidence-based medicine is not a defense when advanced CaP is diagnosed and screening was not offered
• The USPSTF should have criticized the response to the PSA test results
Treat too much or too little?

- Serum PSA has a high false positive rate
- Over 1 million prostate biopsies performed annually in the US
  - 75% biopsies have low-grade indolent (Gleason 6) or no prostate cancer
  - Serious complications of biopsies include infection and hospitalization
- Following the USPSTF recommendations misses an opportunity to detect and treat men with high grade prostate cancer (Gleason grade ≥ 7)
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

Using PSA More Intelligently

Initial PSA Predicts Future Risk
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

Using PSA as a Predictor

![Graph showing the risk of prostate cancer (PCa) based on baseline PSA levels.](image)


Reality Check on the USPSTF Guidelines

Let's not throw the baby out with the bath water.
Part 2: Shared Decision Making – Initial and Ongoing Treatment Strategies

Message from USPSTF
And other organizations following the lead

- PSA screening is a “D” recommendation
- Physicians should not order PSA screening unless they are prepared to engage in shared decision making that enables an informed choice by patients
- What to do?

Prostate Cancer: Current Needs

- Refine PSA
- Increase the probability of an initial positive biopsy
- Reduce the number of unnecessary repeat biopsies by better distinguishing benign from malignant disease
- Stratify low risk from higher risk tumors
- Will PCMs (Prostate Cancer Markers) improve the answer: Yes

Time for Change
Not one fits all

- Precision medicine
- Selection Medicine
- Stratifying medicine
- Genomic Medicine
- Personalized Diagnosis and Therapy
What is a biomarker?
A molecule that can be found in blood, tissue or body fluids that is a sign of a normal or abnormal process

PCM Buckets
Ways Forward

- Educate those who order PSAs-Primary Care
- Define a PSA level with little risk
- Identify those who need further evaluation by a Urologist

Who is Ordering PSA Tests in United States?

We need to educate and target who is ordering PSAs

- Internal Medicine: 64.9%
- Family Medicine: 23.7%
- Urology: 6.1%
- Hem/Onc: 1.3%

A lot of candidates, few selected
No wonder confusion.

PSA
ProPSA/PHI
CTC
hK2
Chromogranin
NSE
TGFβ
PSMA
AMACR
EPCA
hK1I
Leptin
MIF
VEGF
ZAG
...

Ways Forward

• PSA Levels
• Improving the Performance of the test and find cancers that need to be treated
• Eliminate needless repeat biopsies, but don’t miss a threatening cancer
Defining PSA Levels and Improving Performance

Patients and Methods:
- 350,000 HMO-Henry Ford System
- Men in system 1997-2008
- Initial PSA between 1-5ng/ml
- Minimum 5 years follow-up
- No 5 ARIs

Results:
- Mean age -55 Mean PSA 1.0 African American 29%
- Detected Cancer: 2%
  21, 502 men eligible

What is the Appropriate PSA Level?

Prostate-specific antigen 1.5–4.0 ng/ml: a diagnostic challenge and danger zone
E. David Crawford, Judd H. Moul*, Kyle O. Rove, Curtis A. Pettaway*, Lois E. Lamatera and Alex Hughes
University of Colorado, Anschutz Medical Campus, Aurora, CO; Division of Urologic Surgery, Duke University Medical Center, Durham, NC; MD Anderson Cancer Center, University of Texas, Houston, TX, and Josephine Ford Cancer Center, Henry Ford Medical Centers, Detroit, MI, USA
Accepted for publication: 20 January 2011

BJU Best Clinical Paper

A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

5-year Diagnosis Rates Based on Initial PSA Level

Overall Study Population (21,500)

- African Americans 15-fold increase in risk 10.32%
- 15-fold increase in risk 7.85%
- Percent developing prostate cancer 0.51%
- Percent developing prostate cancer 7.85%
- Estimated Area C = 0.8725

A first PSA test threshold of 1.5 - 4.0 ng/mL, represents the Early-Warning PSA Zone
Patients with PSA ≥1.5 ng/mL have an increased risk of developing PC


Early Detection
A Way Forward

- PSA treated like other lab tests, lipids, electrolytes, weight, and BP-Routine
- Informed decision when tests are abnormal
- 70% of men require no discussion-based on our screening data on 150,000 men.
- Men’s Health broader issue > 1.5ng/ml surrogate for BPH, Prostatitis, Prostate cancer.
Early Detection
A Way Forward

- PSA Levels- > 1.5 ng/ml-Evaluate
- Improving the Performance of the test and find cancers that need to be treated
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

PSA Performance

- Beckman Coulter phi
- For men with tPSA between 2–10 ng/mL and non suspicious DRE for PCa

PSA Isoforms

- Beckman Coulter phi
- For men with tPSA between 2–10 ng/mL and non suspicious DRE for PCa

PSA

- Marker release from tumor
- Prostate tumor
- Blood sample
- Measure PSA protein in serum

PCa3 score

- Measure PCA3 and PSA mRNA from cells
- PCA3 Score = PCA3/PSA mRNA x 10^-3

A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

Percent of Men with Positive Biopsy by PCA3 Score First Biopsy


PSA PERFORMANCE 4Kscore

- 4Kscore™ Prostate Cancer Test
- Prostate cancer test
- Based on the following panel of kallikrein markers:
  - Total PSA
  - Free PSA
  - Intact PSA
  - Human Kallikrein 2 (HK2)

OPKO
OURlab
**4K Score**
Finding a **significant cancer**

### 4 Kallikreins

<table>
<thead>
<tr>
<th>Components</th>
<th>Results</th>
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<tbody>
<tr>
<td>4 Kallikreins</td>
<td>% risk of having aggressive prostate cancer</td>
</tr>
<tr>
<td>Total PSA</td>
<td>for an individual patient</td>
</tr>
<tr>
<td>Free PSA</td>
<td></td>
</tr>
<tr>
<td>PSA HK2</td>
<td></td>
</tr>
<tr>
<td>Age, DRE, and prior biopsy status</td>
<td></td>
</tr>
</tbody>
</table>

### Outperforms PSA

The 4Kscore Test has the accuracy of a prostate biopsy for aggressive prostate cancer.

### 4Kscore Test enhances total PSA in predicting aggressive prostate cancer in subset of men with PSA 16-20ng/mL

<table>
<thead>
<tr>
<th>Total PSA</th>
<th>DRE</th>
<th>4Kscore Test Result</th>
<th>Biopsy Result</th>
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<tbody>
<tr>
<td>16.1</td>
<td>Normal</td>
<td>69%</td>
<td>7</td>
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<td>16.4</td>
<td>Normal</td>
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<td>16.4</td>
<td>Normal</td>
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<td>20.0</td>
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<td>98%</td>
<td>9</td>
</tr>
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</table>

Need reference
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

4Kscore predicting the probability of distant metastases within 20 years

Ways Forward

- PSA Levels -1.5ng/ml
- Improving the Performance of the test and find cancers that need to be treated - PHI, PCA3, 4 K
- Eliminate needless repeat biopsies, but don’t miss a threatening cancer
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

TRUS Biopsies

- Anxiety
- Repeat Biopsies
- Infections
- Miss Cancers

- Who to rebiopsy
- ConfirmMDX and PCA3

Improve Biopsy Outcomes

Epigenetic Field Effect

ConfirmMDx detects an epigenetic field effect associated with the presence of cancer at the DNA level

- **Field effect** around a cancer lesion can be present despite normal appearance under the microscope
- **Absence of methylation** changes helps rule out malignancy
- **Presence of methylation** changes indicates increased risk for malignancy
  - GSTP1 – DNA detoxification
  - APC – apoptosis
  - RASSF1 – cell cycle regulation

Addressing False-Negative Biopsy Concerns

ConfirmMDx provides actionable information to improve patient risk stratification and decisions on repeat biopsy:

- **RULE OUT** prostate-cancer-free men from undergoing unnecessary repeat biopsies

- **RULE IN** those who require repeat biopsies and potential treatment

Pivotal Trial: Second Validation Study

![Image of journal cover for Pivotal Trial]

Document Clinical Trial

![Image of document clinical trial graph]

ConfirmMDx provides actionable information to improve patient risk stratification and decisions on repeat biopsy.
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

Where ConfirmMDx Fits

**Patient Profile**: Men considered for repeat prostate biopsy.

- Assay performed on residual tissue from previous negative biopsy
- Does not require repeat patient visit

---

Family Practitioner

- **PSA 5 years**
  - Routine Lab/PSA
  - PSA > 1.5

- **PSA < 1.5**
  - Further Investigation from PCP or Urologist
  - ConfirmMDx

Urologist

- **GS ≥ 3+4**
  - Consider Tx
  - Genomic Markers

- **GS 6 or ≥ 4+3**
  - TRUS Bx

- **ConfirmaMDx**
  - Genomic Markers

- **Low Risk**
  - MP MRI

©2014 E. David Crawford, MD
Current Initial Approach: Localized Prostate Cancer
Counseling the Man as to Treatment options for local disease

- Two big I’s
- Most local treatment have similar survival rates
- Age a factor-long term risks of XRT
- Long term risk of Hormonal therapy

Medical Management Of Advanced Prostate Cancer: 2015

Where we have been

- 1 modern chemotherapy drug with a clear survival benefit (docetaxel, 2004)

Where we are

- 7 newly approved agents for prostate cancer in the past 36 months

Where we are going

- Optimal timing and use (combination) of these new therapies
7 new agents: what are they?

• Degarelix (Firmagon)-New LHRH antagonist
• Sipuleucel-T (Provenge)-Immunotherapy
• Denosumab (Prolia, Xgeva)-Bone-targeted therapy
• Abiraterone (Zytiga)-Androgen biosynthesis inhibitor
• Cabazitaxel (Jevtana)-Microtubule inhibitor
• Enzalutamide (Xtandi)-Antiandrogen
• Radium-223 (Alpharadin)-Alpha-emitter

New Agents

• How does it work?
• When do we use it?
• Expected outcomes?
• What are the side effects?
• What should the PCP watch for?
ADT-Androgen Deprivation Therapy
Degarelix: Direct Mechanism of Action of an GNRH Antagonist

Cardiovascular risks of ADT

GnRH antagonist linked to lower CV event, death risk

The gonadotropin-releasing hormone (GnRH) antagonist degarelix (Firmagon) may be associated with lower risk of a cardiovascular event or death compared to commonly prescribed luteinizing hormone-releasing hormone (LHRH) agonists, data presented at the European Association of Urology annual congress in Milan, Italy indicate.

The data are based on a pooled analysis of 2,328 men with prostate cancer from six prospective, randomized trials. Analysis of the data also revealed that men in the studies treated with degarelix had significantly higher overall survival and improved disease control as evidenced by fewer disease-related deaths, which was associated with lower cardiovascular events and death.
A GnRH-receptor agonist induces necrosis in atherosclerotic plaques.

Anki Knutsson et al. Abstract #558
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

The Role of the FSH System in the Development and Progression of Prostate Cancer

E. David Crawford, MD, Rob O. Raw, MD, Andrew V. Schally, PhD, M.D.In. (Mehl), Difords, Jerome G. Reik, MD, PhD, Nortman L. Block, MD, Thomas J.R. Freifelder, PhD, David N. Dabade, PhD, and Donna C. Marshall, RN, MS, PhD

Abstract

This article describes relationships between follicle-stimulating hormone (FSH), vascular endothelial growth factor (VEGF), and other mediators of prostate cancer, in order to help optimize treatment decisions. A summary of the latest results from the FSH publication congress abstract database was conducted using combinations of the key words prostate cancer, follicle-stimulating hormone, vascular endothelial growth factor, antiandrogenic growth hormone releasing hormone (GHRH) receptor agonist/biological, and angiogenesis. This was followed by a consensus meeting of prostate cancer experts to discuss current knowledge surrounding FSH and the relevant evidence for its role in the tumor FSH system to encompass all aspects of FSH, including the synthesis, release, and circulating levels of FSH itself, as well as its receptor and receptor signaling.

FSH Publication

FSH is a 30 kDa homodimeric glycoprotein that belongs to a class of proteins that includes luteinizing hormone (LH), thyrotropin-stimulating hormone, and human chorionic gonadotropin. Structurally, these glycoproteins share a common alpha subunit, but have unique alpha subunits that confer receptor specificity. FSH binds to the FSH receptor, which belongs to the G-protein coupled superfamilily characterized by their 7 hydrophobic transmembrane domains, membrane-spanning domains, and intracellular domains.

BPH

GS 6 normal prostate BPH

NACE - Emerging Challenges in Primary Care: 2015
Prostate Cancer - 79
Degarelix (Firmagon)

- How does it work? - Lowers T, ADT
- When do we use it? Rising PSA, Advanced
- Expected outcomes? Palliation
- What are the side effects? Hot flashes and others
- What should the PCP watch for? Cardiovascular, Osteoporosis others

What you need to know about treating side effects of ADT

- 1-Sexual dysfuction
- 2-Osteoporosis
- 3-Vasomotor symptoms
- 4-Changes in body composition/metabolism
- 5-Cardiovascular and Diabetes
- 6-Gynecomastia/Body image
Testosterone: Target Organs

- brain
  libido, mood, cognition
- heart
  cardiovascular health
- liver
  protein synthesis
- kidney
  stimulation of erythropoietin production
- bone
  strength and density
- skin
  hair growth, balding, sebum production
- muscle
  strength, volume, energy reduction in visceral fat
- male sexual organs
  penile growth, spermatogenesis, erection, prostate growth and function
- bone marrow
  stimulation of stem cells
- liver
  protein synthesis
- kidney
  stimulation of erythropoietin production
- bone
  strength and density

Abdominal Obesity and Sarcopenia during ADT

GnRH Agonists Significantly Increase Serum Lipids in Men with CaP


Diabetes and CHD During ADT: Causal or Casual Relationship?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diabetes Mellitus</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency of association</td>
<td>All studies</td>
<td>Studies controversial</td>
</tr>
<tr>
<td>Mechanism(s)</td>
<td>Obesity</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>Insulin resistance</td>
<td>↑ LDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Triglycerides (neutral?)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ HDL (protective?)</td>
</tr>
</tbody>
</table>
Practical Recommendations: Diabetes

- **Screening**
  - Consider testing in all men treated with ADT at baseline and yearly thereafter while receiving ADT
    - Recommended test: glycated hemoglobin (HbA1c)
    - Prediabetes=HbA1c 6.5-7.0%; diabetes=HbA1c >7%
  - Management of pre-diabetes
    - Treat other CHD risk factors
    - Repeat testing at least yearly
    - Lifestyle interventions (with follow-up counseling):
      - 5–10% weight loss
      - ≥150 min/week of moderate physical activity


Practical Recommendations: Cardiovascular Disease

- **Screening**
  - Fasting lipoproteins at baseline, 1 year, then every 5 years
  - Assign target LDL based on major CHD risk factors (NCEP ATP III) (national cholesterol program adult treatment program)
- **Treatment**
  - Emphasis on primary prevention
  - Tobacco cessation
  - Treatment of hypertension per AHA guidelines
  - Lifestyle interventions: reduce saturated fat and cholesterol, increase physical activity, and weight control
  - Low-dose aspirin in men with 10-year CHD risk ≥10%
  - Statins as first line for hyperlipidemia if lifestyle fails to meet target

Prevention and Treatment of Osteoporosis in Men

- Obtain a DXA baseline before starting ADT therapy and every 2 years
- Counsel men on importance of:
  - Exercise
  - Prevention of falls
  - Calcium and vitamin D supplements
  - Quitting smoking
  - Decrease alcohol intake

Supplementation

- **Vitamin D**
  - Recommend 1000 IU – 2000 IU daily
- **Calcium Supplementation**
  - Recent research: calcium supplementation of >1000 mg increased risk of CVD mortality by 20% in men.
  - New recommendation: obtain most of calcium through diet, supplement, if needed, with calcium 600 mg daily

Pharmacological Treatment

- **Oral Bisphosphonate**
  - Alendronate (Fosamax®, Fosamax Plus®): 70mg PO Qwk
  - Risedronate (Actonel®): 35 mg PO Qwk

- **IV Bisphosphonates**
  - ADT: Zoledronic acid (Reclast®): 5 mg/yr
  - Mets: Zoledronic acid (Zometa®): 4 mg q mo

- **RANK ligand inhibitor**
  - ADT/osteo: Denosumab (Prolia®): 60 mg SC Q 6 mo
  - Mets: Denosumab (Xgeva®): 120 mg SC Q mo

But in 2010-2012 only about 3.4% of men were on bisphosphonates w/ADT


Practical Recommendations:
Osteoporosis

- **Screening**
  - BMD testing for all men on ADT;
  - Baseline, after 1 year of ADT, then every 2 years

- **Treatment**
  - Exercise; Prevention of falls; quit smoking; decrease alcohol intake
  - Calcium (1,000 mg daily) and vitamin D (1,000 IU daily)
  - Drug therapy if age ≥50 and any of:
    - Personal history of hip or vertebral fracture, OR
    - T-score ≤−2.5 at the femoral neck or spine, OR
    - WHO algorithm 10-year probability of a hip fracture ≥3% OR 10-year probability of a major osteoporosis fracture ≥20%

Hot Flashes (Vasomotor Instability)

- 50% to 80% of men
- Sudden perceived increase in temperature, reddening of the skin, sweating, occasionally chills
- Triggers: usually spontaneous, hot liquids, temperature changes
- Altered hypothalamic thermoregulation


Hot Flashes: Therapies

- Estrogens
- Megestrol acetate
- Clonidine
- Progesterones (Megesterol, Depot Progesterone)
- Antidepressants (Venlafaxine, Paroxetine)
- Neuromodulators (Gabapentin)
- Alternative therapies (lifestyle, soy, flaxseed, acupuncture)

Eur Urol. 2014 Aug 2. [Epub ahead of print]
Definition of CRPC (Castrate Resistant Prostate Cancer)

CRPC

- Castrate testosterone levels (<50 ng/dl)
- 3 × PSA rises 1 week apart
  (2 × levels 50% > nadir and >2 ng/mL)
- PSA progression despite consecutive HTs
- AA withdrawal for ≥4 weeks (flutamide)
  or ≥6 weeks (bicalutamide)

- CRPC responds to secondary hormonal manipulation
- True HRPC is resistant to all hormonal measures

*For bone lesions, progression/appearance of ≥2 lesions on bone scan or soft tissue lesions (RECIST).
*Either AA withdrawal or one secondary hormonal therapy (HT).
AA = androgen; HRPC = hormone-resistant Pca; RECIST = Response Evaluation Criteria In Solid Tumors

7 new agents: what are they?

- Degarelix (Firmagon)-New LHRH antagonist
- Sipuleucel-T (Provenge)-Immunotherapy
- Denosumab (Prolia, Xgeva)-Bone-targeted therapy
- Abiraterone (Zytiga)-Androgen biosynthesis inhibitor
- Cabazitaxel (Jevtana)-Microtubule inhibitor
- Enzalutamide (Xtandi)-Antiandrogen
- Radium-223 (Alpharadin)-Alpha-emitter
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

Sipuleucel-T Dendritic Cell Vaccine

- **Mechanism of action**
  - Induces an immune response targeted against prostatic acid phosphatase (PAP)
- **Mode of delivery**
  - Intravenously (IV)
- **Dosing frequency**
  - 3 complete doses, given at approximately 2-week intervals
- **FDA Approval date**
  - April, 2010
- **Indication**
  - Sipuleucel-T is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer

| Leukapheresis |
| (every 2 weeks x 3) |
| Product sent from clinic → manufacturing plant |
| Culture |
| (40 hours) |
| Antigen loading; Antigen processing |
| Dendritic cell expresses PAP on cell surface |
| Delivery |
| (product infused within 2 days) |
| T-cell activation |
| T-cells attack tumor cells (95% of tumor cells express PAP) |

Provenge * Prescribing Information. Dendreon Corporation, Seattle, WA, USA, 2011.

Optimal timing for treatment of metastatic castration-resistant prostate cancer (mCRPC): sequencing and identifying parameters of early progression with sipuleucel-T

E. David Crawford, M.D.¹, Adam S. Kibel, M.D.¹, Neal D. Shore, M.D., F.A.C.S.³

¹University of Colorado Anschutz Medical Campus, Aurora, Colorado; ²Dana-Farber Cancer Institute, Boston, MA; ³Atlantic Urology Clinics, Myrtle Beach, SC

Immunotherapy vs Cytotoxic Chemotherapy

Crawford ED et al. AUA 2013. Abstract #960
Optimal timing for treatment of metastatic castration-resistant prostate cancer (mCRPC):
sequencing and identifying parameters of early progression with sipuleucel-T

E. David Crawford, M.D.¹, Adam S. Kibel, M.D.², Neal D. Shore, M.D., F.A.C.S.³
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Patients in the lowest PSA quartile had greatest OS benefit with sipuleucel-T

<table>
<thead>
<tr>
<th>Baseline PSA ng/mL</th>
<th>≤22.1 (n=128)</th>
<th>&gt;22.1 to 50.1 (n=128)</th>
<th>&gt;50.1 to 134.1 (n=128)</th>
<th>&gt;134.1 (n=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS, months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>41.3</td>
<td>27.1</td>
<td>20.4</td>
<td>18.4</td>
</tr>
<tr>
<td>Control</td>
<td>28.3</td>
<td>20.1</td>
<td>15.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Difference, months</td>
<td>13.0</td>
<td>7.1</td>
<td>5.4</td>
<td>2.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>(0.51, 0.85)</td>
<td>(0.74, 1.17)</td>
<td>(0.81, 1.24)</td>
<td>(0.84, 1.29)</td>
</tr>
</tbody>
</table>

- Although all PSA quartile groups in IMPACT showed a benefit from sipuleucel-T treatment, those in the lowest PSA quartile benefitted the most in terms of OS.
- The magnitude of treatment effect in patients in the lowest quartile appeared to be greater than those in the highest quartile (13.0 vs. 2.8 months median OS benefit, respectively).

Crawford ED et al. AUA 2013. Abstract #960

Sipuleucel T

- How does it work? Immune PAP
- When do we use it? Advanced CRPC
- Expected outcomes? Improved survival
- What are the side effects? Fever, Chills
- What should the PCP watch for? PSA will not go down, drug well tolerated
Chemotherapy

Docetaxel

Cabazitaxel

Taxanes

- How does it work? DNA-microtubule
- When do we use it? Advanced CRPC
- Expected outcomes? Pain relieve and survival
- What are the side effects? WBC, Anemia, nail, cachexia
- What should the PCP watch for? Drug reasonably well tolerated
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

Range of an α-emitting Radiopharmaceutical Compared to a β-emitter

Short range of α-particles could reduce bone marrow exposure

\[\text{Range of } \alpha\text{-particle (short range – ~2 to 10 cell diameters)}^1\]

\[\text{Range of } \beta\text{-particle (long range – 10 to 1000 cell diameters)}^2\]


ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design

**PATIENTS**

- N=921
  - Confirmed Symptomatic CRPC
  - ≥2 bone metastases
  - No known visceral metastases
  - Post-docetaxel or unfit for docetaxel*

**STRATIFICATION**

- Total ALP:
  - <220 U/L vs. ≥220 U/L
  - Bisphosphonate use: Yes vs. No
  - Prior docetaxel: Yes vs. No

**TREATMENT PHASE**

- Radium-223 dichloride (50 kBq/kg) + best standard of care†
- Placebo (saline) + best standard of care†

- 6 injections at 4-week intervals

- >100 centers in 19 countries
- Planned follow-up is 3 years

*Unfit for docetaxel includes patients who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable
†Best standard of care defined as a routine standard of care at each center, eg. local external beam radiotherapy, corticosteroids, anti-androgens, estrogens (e.g., stilbestrol), estramustine, or ketoconazole

Radium 223

- How does it work? Alpha emitter
- When do we use it? Bone mets, pain
- Expected outcomes? Improved survival, pain relieve
- What are the side effects? rare
- What should the PCP watch for? CBC

Sources of Androgen Production

Androgens are produced at 3 sites
- Testes
- Adrenal glands
- Prostate tumor cells
Major steps forward: Androgen Anilation

- Inhibition of production
- Blocking the receptor
- Abiraterone
- Enzalutimide

Enzalutamide: An Androgen Receptor Inhibitor

1. Inhibits binding of androgens to AR
2. Inhibits AR nuclear translocation
3. Inhibits AR-mediated DNA binding

AR = androgen receptor; T = testosterone.
Adapted from Tran et al. *Science*. 2009;324:787-790
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

Prostate Cancer Disease Continuum and Enzalutamide Phase 3 Trials

Enzalutamide

- How does it work? Blocks T antiandrogen
- When do we use it? Advanced
- Expected outcomes? Survival, pain relief
- What are the side effects? Fatigue, seizures
- What should the PCP watch for? Above
Abiraterone Acetate

- Pregnenolone derivative
- Irreversible, high affinity inhibitor of CYP17A
- Inhibits testosterone production in testis, adrenal glands and prostate cells
- Two phase III trials Pre- and post-docetaxel

MW = 391.55
3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene

Abiraterone Acetate: Androgen Biosynthesis Inhibitor

Cholesterol  \[\rightarrow\] Pregnenolone  \[\rightarrow\] 170H-Pregnenolone  \[\rightarrow\] DHEA

\[\rightarrow\] \[\rightarrow\] \[\rightarrow\] \[\rightarrow\]

\[\text{Aldosterone}\] \[\text{Aldosterone}\] \[\text{Cortisol}\] \[\text{Androstenedione}\] \[\text{Testosterone}\] \[\text{DHT}\]

\[\text{Abiraterone}\] \[\text{Abiraterone}\]
A Primary Care Approach to Prostate Cancer - The Role of Shared Decision Making in Screening and Treatment

**Abiraterone Acetate: Why Do We Need the Steroid?**

- Co-administration of a corticosteroid suppresses ACTH drive, resulting in a reduction in the incidence and severity of mineralocorticoid adverse reactions.
- A prednisone dosage of 12.5 to 10 mg/day is physiologically equivalent to endogenous cortisol levels produced daily by the adrenal glands in individuals not on chronic steroid therapy and whose adrenals are otherwise unimpaired.


**COU 301: Abiraterone Acetate Phase III Trial in mCRPC Post-Chemotherapy**

- Phase III, multinational, multicenter, randomized, double-blind, placebo-controlled study

- **Progressive mCRPC**
- Failed 1 or 2 chemotherapy regimens, one of which contained docetaxel (N=1195)

- **Primary endpoint:** OS (25% improvement; HR 0.8)
- **Secondary endpoints (ITT):** TTPP, rPFS, PSA response

bid = twice daily; BPI = brief pain inventory; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITT = intent to treat; PFS = progression-free survival; TTPP = time to PSA progression; rPFS = radiographic PFS

COU 301: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Abiraterone Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>10.9</td>
<td>14.8</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.646</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.54-0.77</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

2 prior chemo OS: 14.0 months abiraterone acetate vs 10.3 months placebo¹
1 prior chemo OS: 15.4 months abiraterone acetate vs 11.5 months placebo¹
Updated results: 4.6-month difference in median survival with abiraterone acetate²


COU 302: Abiraterone Acetate
Phase III Trial in Chemonaïve mCRPC

- Progressive chemonaïve mCRPC patients
- Asymptomatic or mildly symptomatic (N = 1088)
- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs 1

Abiraterone Acetate 1000 mg daily
Prednisone 5 mg bid
n = 546

Placebo daily
Prednisone 5 mg bid
n = 542

Primary Endpoints:
- rPFS by central review
- OS

Secondary:
- Time to opiate use (cancer-related pain)
- Time to initiation of chemotherapy
- Time to ECOG PS deterioration
- Time to PSA progression

Abiraterone

- How does it work? Lowers T
- When do we use it? Advanced CRPC
- Expected outcomes? Survival, pain decrease
- What are the side effects? Hypokalemia, HTN
- What should the PCP watch for? Electrolyes, Vital signs

Abiraterone acetate:
Physical exam: routine standard/thorough evaluation assure BP and K+ are controlled prior to starting treatment
Labs: In addition T/PSA: monthly potassium
Also LFTs q 2 week x 3 months; q 1 month thereafter

MONITORING PATIENTS
Summary of Monitoring
FAMILY PRACTICE/UROLOGY
SHARED CARE

7 new agents: what are they?

- Degarelix (Firmagon)-New LHRH antagonist
- Sipuleucel-T (Provenge)-Immunotherapy
- Denosumab (Prolia, Xgeva)-Bone-targeted therapy
- Abiraterone (Zytiga)-Androgen biosynthesis inhibitor
- Cabazitaxel (Jevtana)-Microtubule inhibitor
- Enzalutamide (Xtandi)-Antiandrogen
- Radium-223 (Alpharadin)-Alpha-emitter
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<table>
<thead>
<tr>
<th>Monitoring Requirement</th>
<th>LUPRON® leuprolide acetate</th>
<th>CASODEX® bicalutamide</th>
<th>ZYTIGA® abiraterone acetate</th>
<th>PROVENGE® sipuleucel-T</th>
<th>XTANDI® enzalutamide</th>
<th>ZOMETA® zoledronic acid</th>
<th>TAXOTERE® docetaxel</th>
<th>XGEVA® denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hepatotoxicity</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Cardiovascular indications</td>
<td></td>
<td>✓</td>
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<tr>
<td>Mineralo-corticoi dex</td>
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<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Bone health</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Osteonecrosis of the jaw/ Hypoakarima</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Renal toxicity</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
<td></td>
<td></td>
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<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Cutaneous/ neurologic reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Treatment Side Effects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUPRON® leuprolide acetate</td>
<td>Hot flashes, injection site reaction, testicular shrinkage, difficulty urinating, fatigue</td>
</tr>
<tr>
<td>CASODEX® bicalutamide</td>
<td>Hot flashes, pain, asthenia, constipation, infection, nausea, edema, diarrhea</td>
</tr>
<tr>
<td>ZYTIGA® abiraterone acetate</td>
<td>Fatigue, joint swelling, edema, hot flush, diarrhea, vomiting, cough</td>
</tr>
<tr>
<td>PROVENGE® sipuleucel-T</td>
<td>Chills, fatigue, fever, back pain, nausea, joint ache, headache</td>
</tr>
<tr>
<td>XTANDI® enzalutamide</td>
<td>Fatigue, back pain, diarrhea, arthralgia, hot flush, edema, headache, upper respiratory infection</td>
</tr>
<tr>
<td>ZOMETA® zoledronic acid</td>
<td>Nausea, fatigue, anemia, bone pain, constipation, fever, vomiting</td>
</tr>
<tr>
<td>TAXOTERE® docetaxel</td>
<td>Infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy</td>
</tr>
<tr>
<td>XGEVA® denosumab</td>
<td>Fatigue, asthenia, hypophosphatemia, and nausea</td>
</tr>
</tbody>
</table>

199

200
Summary

• Prostate Cancer is prevalent
• Screening is important, if done correctly
• PSA is valuable
• Biomarkers improve screening by assigning risk
• Treatment after biopsy depends on risk of high grade tumor
• The partnership of the PCP in treatment is essential to assist with the process

The End
Thanks
*ARS Question*

Regarding early detection of prostate cancer, I am:

1. Supportive of routine screening of at-risk men who have a >10yr life expectancy
2. Supportive of selective screening
3. Do not support any form of screening
4. Unsure and the jury is still out

---

**Post-test Question 1**

On a scale of 1 to 5:

Please rate how confident you would be treating a patient with Prostate Cancer:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Steve is a 46 year old Chinese male with a family history of prostate cancer in his brother. He is concerned about his risk factors. You advise him of all the following are true about Prostate Cancer except:

1. High prevalence in all males, but low mortality
2. Low prevalence in Asian American males
3. Father with cancer confers greater risk than a brother with prostate cancer
4. Incidence is linked with dietary factors

According the USPSTF recommendations regarding prostate cancer screening, which of the following is true?

1. Do not routinely screen with a PSA, but still use the DRE
2. Use both the PSA and the DRE on all patients of appropriate age
3. Do not routinely screen with either the PSA or DRE
4. Routinely use the PSA, but not the DRE
According the AUA guidelines on prostate cancer screening, which of the following is false?

1. Screen men 55-69 years of age
2. Screen men 70 years of age and older with a 5 year life expectancy
3. Use an individualized approach to screen patients less that 55 years of age
4. Consider increasing screening interval depending on PSA and age
5. Use shared decision making approach

The tenets of shared decision making include all the following except?

1. Provision of information
2. Directing patient decision making with evidence based medicine
3. Elicitation of patient perception
4. Guiding final decision making
Max is a 63 year old with a slightly high PSA (4.1 ng/ml) noted at his yearly PE. He had read something online regarding biomarkers and was hoping you could help him understand them. Which of the following statements most adequately represents your impression of this tool?

1. Don’t know, never heard of them
2. Replaces the need for biopsy
3. Evaluates risk of having aggressive prostate cancer
4. Only useful in men with a PSA greater than 6 ng/ml

Henry has castrate resistant prostate cancer and is prescribed abiraterone acetate by the Urologist. Which of the following side effects should the PCP be aware of?

1. Hypokalemia and hypotension
2. Hyperkalemia and hypotension
3. Hypokalemia and hypertension
4. Hyperkalemia and hypertension
Sal is a 75 y/o man with prostate cancer on Androgen Deprivation therapy. His PSA is very suppressed at 0.1 but he presents complaining of bad hot flashes. All of the following may offer him some relief except:

1. Clonidine
2. Gabapentin
3. Spironolactone
4. Depot Provera
5. Venlafaxine

Which of the statements below describes your approach to treating Prostate Cancer?

1. I do not treat patients with Prostate Cancer, nor do I plan to this year.
2. I did not treat patients with Prostate Cancer, but as a result of attending this course I’m thinking of doing this now.
3. I do treat patients with Prostate Cancer and this course helped me change my methods.
4. I do treat patients with Prostate Cancer and this course confirmed that I don’t need to change my methods.