Utility of PSA and Current Prostate Cancer Diagnosis & Treatment

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Disclosure

- Sanofi
- Astellas
- Abvie
Objectives

- Brief overview of the prostate and PSA
- When to use PSA
- MRI and other predictive tools
- TRUS And MRI-fusion Biopsy
- Active Surveillance
- Treatment of local disease
- Treatment of metastatic disease
Where is it?

- Bladder
- Seminal Vesicles
- Prostate
- Urethra
- Rectum
- Anus
- Penis
- Vas Deferens
- Testis
- Scrotum
- Epididymis
- Tunica Vaginalis
### Prostate Cancer: Epidemiology

#### Estimated New Cases*

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>217,730</td>
<td>207,090</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,750</td>
<td>105,770</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>72,090</td>
<td>70,480</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>52,760</td>
<td>43,470</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>38,870</td>
<td>33,930</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>35,380</td>
<td>30,160</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>35,370</td>
<td>29,260</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,420</td>
<td>22,870</td>
</tr>
<tr>
<td>Leukemia</td>
<td>24,690</td>
<td>21,880</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,370</td>
<td>21,770</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>789,620</strong></td>
<td><strong>739,940</strong></td>
</tr>
</tbody>
</table>

#### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>86,220</td>
<td>71,080</td>
</tr>
<tr>
<td>Prostate</td>
<td>32,050</td>
<td>39,840</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>26,580</td>
<td>24,790</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,770</td>
<td>18,030</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>12,720</td>
<td>13,850</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,660</td>
<td>9,500</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,650</td>
<td>9,180</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10,710</td>
<td>7,950</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>10,410</td>
<td>6,190</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,210</td>
<td>5,720</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>299,200</strong></td>
<td><strong>270,290</strong></td>
</tr>
</tbody>
</table>

*Estimated cases and deaths are based on projections and may not reflect the actual number of cases and deaths.
Do you Screen?
PSA: Overdiagnosis and Overtreatment


*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
PSA: The Molecule

- Prostate
- Prostatic ducts
- Prostate Specific Antigen
- Absorption into the bloodstream

Types of PSA:
- Free PSA
- ACT bound PSA
- αMG bound PSA
PSA: Decreased Mortality

A. Age-adjusted prostate-cancer mortality (all ages)

C. Age-specific prostate-cancer mortality (65-74 years)

Oncology lancet 9:445
AAFP, USPSTF Issue Final Recommendation Against Routine PSA-based Screening for Prostate Cancer

Evidence Simply Does Not Support Test's Benefit, Says Task Force Co-chair

By Matt Brown

Posted: 5/22/2012, 4:00 p.m. -- The AAFP is **recommending against** performing prostate-specific antigen (PSA)-based screening for prostate cancer in asymptomatic men, a position that is in line with a **final recommendation** from the U.S. Preventive Services Task Force (USPSTF) that was published May 22 in the *Annals of Internal Medicine*. 
Since USPTF: Metastatic disease
Since USPTF: BX and RRP
Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

- N=20 000\(^1\)
- 3% contamination
- 14 yrs FU
- Bx if PSA > 3.5
- NNT=12 (NNT for Breast CA=20)

Goteborg: Mortality

↓44%
PLCO: USA

- N=76 000
- 52% contamination
- 9 yrs FU
- BX if PSA> 4.0
- No difference overall
  - <65 ans: ↓44% PC mortalité et NNT 5
ERSPC: Europe

- N=162 000\(^1\)
- 15% contamination
- 14 yr FU
- Bx if PSA>3.0
- NNT=48
- ↓40% M+
ERSPC: Mortality

![Graph showing mortality rates over years since randomization for control and screening groups, with a notable 20% reduction.]
USPTF 2017: longer follow-up of ERSPC = Improved PSA utility

<table>
<thead>
<tr>
<th>Years of monitoring</th>
<th>Number needed to screen to avoid 1 cancer-specific death</th>
<th>1 incidence of metastatic disease</th>
<th>Number needed to diagnose to avoid 1 cancer-specific death</th>
<th>1 incidence of metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>1,410</td>
<td>736</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>11</td>
<td>979</td>
<td>393</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td>13</td>
<td>781</td>
<td>333*</td>
<td>27</td>
<td>14*</td>
</tr>
</tbody>
</table>

*At a median follow-up duration of 12 years at four ERSPC centers

2017 PSA Recommendations

- **CUA**
  - PSA to those with >10yr
  - 50-70 yr
  - 45yr if Black, Family Hx

- **USPTF**: grade C for 55-69 (2017)

- **CTFPHC**: no
Table 102-0122 1, 2, 3, 4, 5
Health-adjusted life expectancy, at birth and at age 65, by sex and income, Canada and provinces occasional (years)

Selected items [Add/Remove data]
Sex = Males
Income group 6, 7 = All income groups
Characteristics 2, 3, 4, 8, 9, 10 = Life expectancy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Newfoundland and Labrador</td>
<td>At birth</td>
<td>75.3</td>
<td>75.8</td>
</tr>
<tr>
<td></td>
<td>At age 65</td>
<td>15.4</td>
<td>16.2</td>
</tr>
<tr>
<td>Quebec</td>
<td>At birth</td>
<td>76.4</td>
<td>78.2</td>
</tr>
<tr>
<td></td>
<td>At age 65</td>
<td>16.5</td>
<td>18.1</td>
</tr>
<tr>
<td>British Columbia</td>
<td>At birth</td>
<td>78.0</td>
<td>78.9</td>
</tr>
<tr>
<td></td>
<td>At age 65</td>
<td>18.0</td>
<td>18.9</td>
</tr>
</tbody>
</table>
Based on what you told us, your life expectancy is **87**, which you'll reach in the year **2034**.

Did you know that many Canadians are now outliving common life expectancies?

With at least **17 years** of retirement to look forward to, you need to plan for your money to last. To get help, review your results with an advisor.
When not to order PSA!

- Retention
- UTI
When to Send to URO?
COMPARISON OF DIGITAL RECTAL EXAMINATION AND SERUM PROSTATE SPECIFIC ANTIGEN IN THE EARLY DETECTION OF PROSTATE CANCER: RESULTS OF A MULTICENTER CLINICAL TRIAL OF 6,630 MEN

Serum Prostate-Specific Antigen in a Community-Based Population of Healthy Men

Establishment of Age-Specific Reference Ranges

Joseph E. Oesterling, MD; Steven J. Jacobsen, MD, PhD; Christopher G. Chute, MD, DrPH; Harry A. Guess, MD, PhD; Cynthia J. Girman, MS; Laurel A. Panser, MA, MS; Michael M. Lieber, MD

Table 2.—Age-Specific Reference Ranges* for Serum PSA Concentration, Prostatic Volume, and PSA Density

<table>
<thead>
<tr>
<th>Parameter</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum PSA concentration, ng/mL</td>
<td>0.0-2.5</td>
<td>0.0-3.5</td>
<td>0.0-4.5</td>
<td>0.0-6.5</td>
</tr>
</tbody>
</table>

*Reference ranges for healthy men age 40 through 80 years.
Detection: DRE
### Characteristics

<table>
<thead>
<tr>
<th>Race</th>
<th>Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60</td>
</tr>
<tr>
<td>PSA [ng/ml]</td>
<td>5</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>
<tr>
<td>Percent free PSA available?</td>
<td>No</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 a:
- 6% chance of high-grade prostate cancer,
- 18% chance of low-grade cancer,
- 76% 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.

Click [here](#) to watch a video overview of these results.
MRI: Pre BX utility
-T2W and DWI
Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study

Hashim U Ahmed*, Ahmed El-Shater Bosaily*, Louise C Brown*, Rhian Gabe, Richard Kaplan, Mahesh K Parmar, Yolanda Collaco-Moraes, Katie Ward, Richard G Hindley, Alex Freeman, Alex P Kirkham, Robert Oldroyd, Chris Parker, Mark Emberton, and the PROMIS study group†
### MRI Accuracy

<table>
<thead>
<tr>
<th>MP-MRI, % (95% CI)</th>
<th>TRUS-biopsy, % [95% CI]</th>
<th>Test ratio* [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary definition (Gleason score ≥4+3 or cancer core length ≥6 mm), prevalence of clinically significant cancer 230 (40% - 44%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity test</td>
<td>93 (88-96)</td>
<td>48 (42-55)</td>
<td>0.52 (0.45-0.60)</td>
</tr>
<tr>
<td>Specificity test</td>
<td>41 (36-46)</td>
<td>96 (94-98)</td>
<td>2.34 (2.08-2.68)</td>
</tr>
<tr>
<td>PPV</td>
<td>51 (46-56)</td>
<td>90 (83-94)</td>
<td>8.2 (4.7-14.3)</td>
</tr>
<tr>
<td>NPV</td>
<td>89 (83-94)</td>
<td>74 (69-78)</td>
<td>0.34 (0.21-0.55)</td>
</tr>
</tbody>
</table>
MRI if suspicion for PC after first BX
Wait 8 weeks!
Targeted BX if PIRADS 3-5
Trans-Rectal Biopsy
Biopsy Strategy

Figure 2 – Extended biopsy.
Gleason 3, 4, 5
MRI Fusion Rationale

- Target lesion specifically
- Identify GI7
- Avoid GI6
MRI Fusion Bx
Magnetic Resonance Imaging/Ultrasound-Fusion Biopsy Significantly Upgrades Prostate Cancer Versus Systematic 12-core Transrectal Ultrasound Biopsy

M. Minhaj Siddiqui a, Soroush Rais-Bahrami a, Hong Truong a, Lambros Stamatakis a, Srinivas Vourganti a, Jeffrey Nix a, Anthony N. Hoang a, Annerlein Walton-Diaz a, Brian Shuch a, Michael Weintraub a, Jochen Kruecker d, Hayet Amalou c, Baris Turkbey a, Maria J. Merino b, Peter L. Choyke b, Bradford J. Wood c, Peter A. Pinto a, b, c, *
Relationship Between Prebiopsy Multiparametric Magnetic Resonance Imaging (MRI), Biopsy Indication, and MRI-ultrasound Fusion–targeted Prostate Biopsy Outcomes

Xiaosong Meng, Andrew B. Rosenkrantz, Neil Mendhiratta, Michael Fenstermaker, Richard Huang, James S. Wysock, Marc A. Bjurlin, Susan Marshall, Fang-Ming Deng, Ming Zhou, Jonathan Melamed, William C. Huang, Herbert Lepor, Samir S. Taneja, Samir S. Taneja

![Bar chart showing cancer detection rate vs. multiparametric MRI suspicion score]
Thoughts on Treatment for Local Disease?
Therapie Standard

- Radiation
- surgery
  - Open
  - Lap
  - Robot

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UofT & Klotz: Active Surveillance (AS)

- Gleason 6
  - Risk of progression
  + Avoid ED et incontinence
cost
Klotz: AS failure

Dan Lewinshtein 2014
Klotz AS: Cancer specific Survival

Dan Lewinshtein 2014
Radical Prostatectomy versus Observation for Localized Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Michael K. Brawer, M.D., Karen M. Jones, M.S., Michael J. Barry, M.D., William J. Aronson, M.D., Steven Fox, M.D., M.P.H., Jeffrey R. Gingrich, M.D., John T. Wei, M.D., Patricia Gilhooly, M.D., B. Mayer Grob, M.D., Imad Nsouli, M.D., Padmini Iyer, M.D., Ruben Cartagena, M.D., Glenn Snider, M.D., Claus Roehrborn, M.D., Ph.D., Roohollah Sharifi, M.D., William Blank, M.D., Parikshit Pandya, M.D., Gerald L. Andriele, M.D., Daniel Culk, M.D., and Thomas Wheeler, M.D., for the Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group
PIVOT: RRP vs. AS

B Death from Prostate Cancer

- Proportion Who Died
- Years

No. at Risk
- Observation: 367, 341, 315, 288, 258, 176, 106, 26, 0
- Radical prostatectomy: 364, 352, 329, 300, 267, 187, 126, 36, 0

Radical prostatectomy vs. Observation
# Pivot: Sub Analysis

## Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Observation</th>
<th>Radical Prostatectomy</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events/total no.</td>
<td>no. of events/total no.</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>31/367</td>
<td>21/364</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>12/131</td>
<td>6/122</td>
<td>-</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>19/236</td>
<td>15/242</td>
<td>-</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>22/220</td>
<td>15/232</td>
<td>-</td>
</tr>
<tr>
<td>Black</td>
<td>7/121</td>
<td>5/111</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>2/26</td>
<td>1/21</td>
<td>-</td>
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<tr>
<td>Charlson score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19/220</td>
<td>14/224</td>
<td>-</td>
</tr>
<tr>
<td>≥1</td>
<td>12/147</td>
<td>7/140</td>
<td>-</td>
</tr>
<tr>
<td>Performance score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>25/310</td>
<td>18/312</td>
<td>-</td>
</tr>
<tr>
<td>1-4</td>
<td>6/57</td>
<td>3/57</td>
<td>-</td>
</tr>
<tr>
<td>PSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>15/241</td>
<td>14/238</td>
<td>-</td>
</tr>
<tr>
<td>&gt;10</td>
<td>16/125</td>
<td>7/126</td>
<td>-</td>
</tr>
<tr>
<td>RISK</td>
<td></td>
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</tr>
<tr>
<td>Low</td>
<td>4/148</td>
<td>6/148</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate</td>
<td>13/120</td>
<td>6/129</td>
<td>-</td>
</tr>
<tr>
<td>High</td>
<td>14/80</td>
<td>7/77</td>
<td>-</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>15/261</td>
<td>11/254</td>
<td>-</td>
</tr>
<tr>
<td>≥7</td>
<td>15/86</td>
<td>10/98</td>
<td>-</td>
</tr>
</tbody>
</table>

Graph showing hazard ratios for different subgroups with a focus on PSA levels.
Radical Prostatectomy: Anatomy
Radical Prostatectomy: LND
Radical Prostatectomy: Urethra Length
Radical Prostatectomy: Nerve Sparing
Robotic Prostatectomy
**Robot: Usage**

*Figure 1.* Trends in robotic (green curve) and open (red curve) RP. Blue curve indicates total.
Robot: Results Peri-op?

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MIRP</th>
<th>RRP</th>
<th>MIRP vs RRP, Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay, median (IQR)</td>
<td>2 (1-2)</td>
<td>3 (2-4)</td>
<td>0.67 (0.58-0.72)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heterologous blood transfusion, %</td>
<td>2.7</td>
<td>20.8</td>
<td>0.11 (0.06-0.17)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

JAMA 302:1557
Robot: BCR
## Robot: Functional Results

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MIRP</th>
<th>RRP</th>
<th>MIRP vs RRP, Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incontinence per 100 person-years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>15.9</td>
<td>12.2</td>
<td>1.3 (1.05-1.61)</td>
<td>.02</td>
</tr>
<tr>
<td>Procedures</td>
<td>7.8</td>
<td>8.9</td>
<td>0.87 (0.69-1.1)</td>
<td>.24</td>
</tr>
<tr>
<td><strong>Erectile dysfunction per 100 person-years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>26.8</td>
<td>19.2</td>
<td>1.40 (1.14-1.72)</td>
<td>.009</td>
</tr>
<tr>
<td>Procedure</td>
<td>2.3</td>
<td>2.2</td>
<td>1.05 (0.74-1.51)</td>
<td>.78</td>
</tr>
</tbody>
</table>
Radiotherapy
Mortality After Radical Prostatectomy or External Beam Radiotherapy for Localized Prostate Cancer

Metastatic Disease?

Mets to death 6 yr
Hormones
Firmagon: LHRH Receptor Blocker

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Firmagon: Rapid Testosterone block
Bone Protection
Superscan

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Pathologic Fracture & Spinal Compression
XGEVA\textsuperscript{Mc} : Prend pour cible et inhibe le ligand du RANK pour briser le cercle vicieux de destruction de l’os et prévenir les complications osseuses.

XGEVA\textsuperscript{Mc} prend pour cible le ligand du RANK et s’y fixe, ce qui prévient l’activation de ses récepteurs, RANK, sur les ostéoclastes.

En se liant au ligand du RANK, XGEVA\textsuperscript{Mc} inhibe la formation, la fonction et la survie des ostéoclastes.

XGEVA\textsuperscript{Mc} empêche la maturation des ostéoclastes, ce qui réduit la résorption osseuse et rompt le cercle vicieux de destruction de l’os.

2. Monographie de XGEVA\textsuperscript{Mc} (denosumab) Amgen Canada Inc. Mai 2011

Ne pas copier ni distribuer - © - Amgen Canada 2011
Denosumab: Bone Protection

![Graph showing percent change in BMD from baseline for Lumbar Spine, comparing Denosumab and Placebo. The graph indicates a difference at 24 mo, with 6.7 percentage points.](image)
Hormone Refractory Disease (CRPC)

Local Therapy
Androgen Deprivation

Therapies After LHRH Agonists and Antiandrogens

Chemotherapy

Asymptomatic
Nonmetastatic
Castrate Sensitive

Symptomatic
Metastatic
Castrate Resistant

Time

Death
Post-chemotherapy
Chemotherapy: Docetaxel

**Figure 1.** Kaplan–Meier Estimates of the Probability of Overall Survival in the Three Groups.
Abiraterone: 10X ketoconazole
Abiraterone: mechanism

Cholesterol → Desmolase

Pregnenolone → 17α OH-pregnenolone → DHEA

17α hydroxylase → c17-20 lyase

Progesterone → 17α OH-progesterone → Androstenedione

11β hydroxylase → Corticosterone

21 hydroxylase → Cortisol

18 hydroxylase

Aldosterone

Hypokalemia, Hypertension, Fluid overload

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Abiraterone in CRPC post-docetaxel

HR = 0.646 (0.54-0.77) \( P < 0.0001 \)

Abiraterone acetate:
14.8 months (95%CI: 14.1, 15.4)

Placebo:
10.9 months (95%CI: 10.2, 12.0)

De Bono et al, ESMO 2010

Dan Lewinshtein 2014
Enzalutamide
Enzalutamide in Metastatic Prostate Cancer before Chemotherapy

Enzalutamide: Progression Free Survival

Hazard ratio, 0.19 (95% CI, 0.15–0.23)
P<0.001
THANK YOU!