PSA Testing: Simplified at Last?

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Objectives

The learning objectives

- Explain the role of PSA testing in the early detection of prostate cancer;
- Cite current guidelines on PSA testing in symptomatic and asymptomatic men; and
- Provide patient education aids to assist individualized decision making.

Learn your perception of practice barriers or challenges they may face with regard to these objectives including opportunities for resolution.
Have you had your PSA test?
*Tuum Est* is often translated as “It is yours” or “It is up to you”.

*Cuum Est* has no apparent meaning in Latin. While there’s no way of knowing how or why the mistake was made, the confusion would appear to arise from obtaining a trademark on the original UBC logo.
**Prostate Cancer Demographics**

**Lifetime risk of**
- Diagnosis with PCa is ~10%-15%
- 10-15% of men will die from pCa
- 85% will die from other causes

**Autopsy**
- 5% at age <30
- 60% by age >79 years
- Bell KJ et al. Int J Cancer. 2015

Many men with prostate cancer never experience symptoms and, without screening, would never know they have the disease.

**5y OS**
- organ confined ~ 98%
- metastatic disease is ~ 30% - 50%
Prostate cancer is many things

Cancer than needs no treatment

Life threatening disease

Public health concern

Staggeringly profitable industry
PSA
PSA

Glycoprotein - 10X greater production by PCa cells. In cancer tissue, barriers between glands and capillary are disrupted, so more PSA is released into the serum.

**PSA elevations can precede clinical disease by >5 to 10 years**

The 5-alpha reductase inhibitors lower PSA levels by 50%

**PCa**

- BPH
- Subclinical inflammation
- Prostate biopsy
- Cystoscopy
- TURP
- Urinary retention
- Ejaculation
- DRE
- Perineal trauma
- Prostatic infarction

**PSA is not a good screening test for PCa**

PSA does not distinguish between clinically indolent cancers and those that may go on to cause death.
75% of PCa are detected in the gray zone (PSA 4-10)
50% of PCa with PSA 10 are outside prostate
### Age-based Reference Ranges for PSA Test

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### Age-specific Median PSA

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Will come back to this.
SCREENING

Testing Healthy People
without symptoms
PSA is not covered by MSP
### BENEFITS

1. Reduced disease specific and overall mortality

2. Improved future QOL: Less invasive treatment:
   1. lower stage Ca, treatment is less toxic/complex

3. Reduced cancer development:
   Dx of pre-cancerous lesions can be successfully treated: colon, lung, cervix.

### HARMS

1. False-positive results
   Morbidity, anxiety, waste money and waste time

2. Labeling
   Patients live longer with the knowledge of cancer, Life insurance affected

3. Over-diagnosis:
   Some cancer would never have been diagnosed, or caused symptoms if patients hadn’t been screened

4. Overtreatment
   Harm form the treatment, investigations
Sensitivity

Probability: person with the disease is correctly identified by the test

PSA testing (cut-off 4.0 ng/mL) has a sensitivity of 65-80%, which implies that 20-35% of PCa are missed.

Efforts to improved sensitivity had failed:
Age-adjusted reference ranges
PSA velocity (rate of change over time)
Free/total PSA ratio
PSA density (PSA level relative to gland volume)
PCA3 Pca antigen 3 gene
Lead time bias:
Disease is detected earlier, there is an appearance of longer survival,

Length time bias:
PSA finds slower growing cancers and misses aggressive PCa

Bias is a significant issue in PSA screening.
pCa incidence in PSA era

Effects ADT ? PSA screening

Effects of PSA screening

Mortality reduction

PSA approval

Year of diagnosis

Age-adjusted rate per 100,000
The goal of PSA Screening is to identify high-risk, localized Pca that can be successfully treated, thereby preventing the morbidity and mortality associated with advanced or metastatic prostate cancer.

PSA screening
The confusion
The controversy
The opinions
Approach for GPs
Why confusion?

1. 3(or 4) screening RTC - contradictory results

2. USPSTF (US preventative task force)
   - Issued PSA screening recommendations
   - Recommendations changed:
     - 2008 - “I” - insufficient evidence for or against
       “D” - against for men >75 y
     - 2012 - “D” against for all men
     - 2017 - “C” discussion about pros and cons

3. Other professional organizations have their own recommendations

PCa screening confusion
**PLCO trial** of organized vs opportunistic screening
90% of had PSA in control group I usual care arm
Death from Pca after 15 years 4.8 and 4.6 /1000 person-years

**ERSPC trial**, NNS - 781 (55 -69 y) to prevent
1 man from dying of pCca after 13 years.
3 men from having metastatic Pca

**Goteborg Trial** - 20,000 men (50–64)
absolute reduction of Pca death 0.52%
NNS (invite) was 231
NND (diagnose) 10 to prevent one death

**CAP trial** single invitation PSA-based screening in the UK (0.5 M men). 34% of invited men had PSA
At 10 years, mortality was the same (absolute risk, 0.30 and 0.31 per 1000 person-years)
2012 - USPSTF recommendation was against screening
10 y benefits for 1000 men (50-65) q1-4y

<table>
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<tr>
<th>Event</th>
<th>Per 1000 men</th>
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<tr>
<td>Die (pCa) no Screening</td>
<td>5</td>
</tr>
<tr>
<td>Die with screening</td>
<td>4</td>
</tr>
<tr>
<td>Did not die because of screening</td>
<td>1</td>
</tr>
<tr>
<td>Complications of bx</td>
<td>120</td>
</tr>
<tr>
<td>Men asymptomatic from Pca</td>
<td>110</td>
</tr>
<tr>
<td>CVS complications</td>
<td>3</td>
</tr>
<tr>
<td>ED</td>
<td>20</td>
</tr>
<tr>
<td>Incontinence</td>
<td>10</td>
</tr>
<tr>
<td>Death due to treatment</td>
<td>&lt;1</td>
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1,000 men screened.

Of these:

100-120 get false-positive results that may cause anxiety and lead to biopsy
(Possible side effects of biopsies include serious infections, pain, and bleeding)

110 get a prostate cancer diagnosis, and of these men:

• at least 50 will have treatment complications, such as infections, sexual dysfunction, or bladder or bowel control problems

• 4-5 die from prostate cancer (5 die among men who do not get screened)

• 0-1 death from prostate cancer is avoided

Absolute reduction in PC mortality

Goteborg trial - 14 y Follow up

**Goteborg trial** - 1000 men and 14 y follow up -
9 will die with NO screening
4 will die WITH screening

**Red** - died despite PSA screening
**Open Red** - death prevented because of screening
**Gray** - men alive regardless of screening.

P Carroll JCO 2011
Screening for Prostate Cancer
US Preventive Services Task Force Recommendation Statement

PSA-testing in 1000 men age 55-69 and 13 y fu will prevent 1.3 deaths 3 cases of metastatic disease

C recommendation - "there is at least moderate certainty that the net benefit is small."

- PCa is indolent
- 5 - 10y lead time associated with PSA testing,
- Immediate burden of screening and treatment, including harms from over diagnosis and overtreatment, and potentially have lifelong consequences.

New recommendation: PLCO trial: >90% of the control group had PSA
USPSTF 2018

- PSA +
- BX +
- RP or RT
- AS

Of 1,000 Men Offered PSA-Based Screening

- 240 Get a Positive PSA Result which may indicate prostate cancer

- Of those, 100 Get a Positive Biopsy showing definite cancer

- 80* Choose Surgery or Radiation Treatment

- ED & Incontinence

- 3** Avoid Cancer Spreading to Other Organs
- 1* Avoids Death From Prostate Cancer***
- 5* Die From Prostate Cancer Even After Surgery or Treatment
**BENEFITS**

1. Reduced disease specific and overall mortality
2. Improved future QOL: Less invasive treatment: lower stage Ca, treatment is less toxic/complex
3. Reduced cancer development: Dx of pre-cancerous lesions can be successfully treated: colon, lung cervix.

**HARMS**

1. False-positive results: Morbidity, anxiety, waste money and waste time
2. Labeling: Patients live longer with the knowledge of cancer, Life insurance affected
3. Over-diagnosis: Some cancer would never have been diagnosed, or caused symptoms if patients hadn’t been screened
4. Overtreatment: Harm form the treatment, investigations
MEN AGED 55-69

GRADE C RECOMMENDATION

SELECTIVELY OFFER OR PROVIDE PSA SCREENING BASED ON PROFESSIONAL JUDGMENT AND PATIENT VALUES.

THERE IS MODERATE CERTAINTY THAT THE NET BENEFIT IS SMALL FOR SOME MEN.
BENEFITS?   HARMS

BENEFITS?   HARMS
MEN AGED 70 AND OLDER
GRADE D RECOMMENDATION

CLINICIANS SHOULD DISCOURAGE USE OF PSA SCREENING.

THERE IS MODERATE CERTAINTY THAT THE BENEFITS DO NOT OUTWEIGH THE EXPECTED HARMs.
PSA screening
CONTRAVERSY
Impact of the 2012 “D” PSA recommendation

PSA screening decreased by 25%
Decrease in Biopsy by ~30%
Decrease incidence of PCa by 30%
Decrease of all risk disease

**Missing high grade PCa**

- Focused on harms of biopsy
- Disregard that low risk ca will managed by active surveillance

Halperen JAMA 2016
Effect of the USPSTF Grade D Recommendation against Screening for Prostate Cancer on Incident Prostate Cancer Diagnoses in the United States

Daniel A. Barocas,*† Katherine Mallin, Amy J. Graves, David F. Penson,
Reanalysis of USA trial – based on comorbidities at baseline

Men stratified by co-morbidities

Q: would men in good health would benefit more from screening

- Minimal co-morbidity was seen in only 35% men

E. D Crawford at al JCO Feb 2011
NNS - number need to screen to prevent one death

PC
specific mortality Reduction by 50%

NNS 723
NNT 5

Results changed from NO mortality Reduction to 50% mortality reduction

E. D Crawford at a JCO Feb 2011
NNS – number needed to screen to prevent 1 death

Length of follow up is critical

Loeb et al. JCO 2011  Hugosson et al. Lancet Oncology 2010
The Genitourinary Cancer Tumour Group (GUTG) of the BCC and the Vancouver Prostate Centre (VPC) recommend

Asymptomatic men 50-55 years of age or older, with an estimated life expectancy of more than 10 years, who are well informed about the risks of over-diagnosis and over-treatment, consider PSA testing for the early diagnosis of prostate cancer.

The GUTG and VPC do not support unselected, population-wide PSA screening because of the potential for over-diagnosis, over-treatment and detriment to quality adjusted survival.
Abnormal results trigger referral to urologists.

<table>
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The most cost-effective and evidence-based strategy is for PSA testing every 4 years from age 55 to 70 years.

**Urologist: Biopsy consideration:** life expectancy, co-morbidities, prostate co-conditions (e.g. large BPH, prostatitis), PSA velocity, DRE findings, patient risk factors and preference.
Result

The chance to find prostate cancer with further study as indicated on the outside ring is 8%.

If your risk falls into the white area, you have a lower than average risk of finding prostate cancer with further study. If your risk is in the yellow area, you might consider consulting your family physician to have the PSA content determined in your blood. Some family physicians will also carry out a rectal examination to determine if your prostate is normal to palpation.

If you know your PSA level, select Risk Calculator 2. You can access this from the top right of this panel.

60y
No urinary symptoms
No family history

Risk 8%

60y
Has urinary symptoms
and family history

Risk 11.5%
WHAT CAN YOU DO IN YOUR PRACTICE?
What is a GP to do?

¼ GPs are confident in their knowledge about PSA screening

**Low correlation between confidence and knowledge**

Less than a half of primary care physicians are compliant with the recommendations of PSA screening - discuss: pros and cons

Fear of missing cancer

- Screen all or none

Tasian GE at al Urol Oncology: 2012 30(2)
1. Information must be based on evidence, and be beyond dispute

2. Patient should be presented with a clear framework for a decision

   Decision aids provide a large number of estimates and ask the pt to somehow integrate this into the choice

2. The schema must be appropriate for the primary care and should not assume that the provider has a detailed knowledge of the subject
FACTS

- PCa is very common
- Most men will not die from PCa
- PSA testing will reduce small the risk of dying from PCa
- Most PCa found by screening are indolent and may not need treatment

Key take home messages

- Goal of PSA screening is to find aggressive PCa
- Most cancers found by PSA screening are indolent and may not need any treatment
- If you have PSA test, you may be diagnosed with indolent PCa, and may experience pressure to treat it

Decision

- If you are confident that you would only accept treatment for aggressive PCa, than PSA screening is for you
SMART SCREENING
PSA screening reduce met pCa and increase cause specific survival (age 50-69)

Pca diagnosis must incorporate Active Surveillance concept

Baseline PSA testing age 40-50

Older men in good health with life expectancy >10 should not be denied PSA test
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PSA does not distinguish between clinically indolent cancers and those that may go on to cause death.
PSA at age <50 - Malmö study

1974 to 1986, >21,277 men age 50 in Malmö were enrolled onto a cardiovascular study

18 y later, 498 were later diagnosed with pCa

A single PSA test at age 44-50 predicts clinically diagnosed prostate cancer.

• This raises the possibility of risk stratification for PCA screening

Hans Lilja JCO 2007
PSA testing at 45-50 y

Baseline PSA can predict the PC in 18-25 years

PSA > 1.5 at age <50
Life time chance of >60%

PSA <0.7 at age <50
Life time chance of pCa ,10%

Fig 2. Predicted probability of a prostate cancer diagnosis before age 75 years by population-based centiles of prostate-specific antigen (PSA) measured at age 44 to 50 years, with 95% CIs.

Hans Lilja JCO 2007
Baseline PSA can predict the PC in 18-25 years

Baseline PSA level from men in their 40s above the age-adjusted median value is a strong predictor of future risk of prostate cancer; those with a PSA value below the median (0.6 to 0.7ng/mL) are at very low risk while those above the median are at higher risk. 

At the present time, it is uncertain how and whether to incorporate this information into a PSA testing algorithm.

Hans Lilja JCO 2007
Smart PSA Screening

Start at Age ~45 - 50, repeat in 1 year

- If PSA <1 - Then every 4 yearly
- If PSA >1 - test q 2 years

Monitor PSA doubling time

DRE

Stop when life expectancy <10yrs - Comorbidity

Incorporate active surveillance
SUMMARY
PSA screening Benefits and Harms

Harms:
- False positive PSA
- Biopsy complication (Sepsis 1-2%)
- Anxiety
- QOL?
- Cost $$$$$ - (MRI)

Harms:
- Over diagnosis
- Over treatment
- Surgical complications
- Incontinence
- Sexual dysfunction
- Urinary dysfunction
- Rectal dysfunction
**Benefits**

Only for age 55-69

Mortality reduction

~20% in 10 years

Reduction in Metastatic Pca

Diagnosis of potentially aggressive pCa
**PSA for early detection**

**WHY?**  If they wish to be tested and are well informed of harms and benefits

**WHO?**  age >50

**WHEN?**  q2-4 y

**STOP?**  >70

Abnormal results should trigger referral to a urologist.

**Higher risk for PCA screening at age 40 to 45**
1. African American origin
2. Family history of PCA
3. BRCA1 or BRCA2

**SMART Screening**
Baseline PSA age 45-50
Screening Trials

Important points - cautionary note

Contamination in Screening Trials (controls had PSA)
NO trials have results to show the difference between
NO PSA screening vs PSA screening

All trials were investigating opportunistic vs organized
PSA screening
Before PSA era ~700 men
Surgery reduced CSM by 11% at 22y
Greater effect younger and higher grade pCa.

Early PSA era ~700 men
Surgery reduced CSM by 3% at 12y
20% had post surgical complications and 1% death

PSA era: 1643 men
No difference in PCM or OS
AS - Mets 6% vs 3% and progression 22 vs 8%
Calling the buffalo

Where is the wisdom we have lost in knowledge, and where is the knowledge we have lost in information?

T.S. Eliot