New trends in screening: MRI, biomarkers, germ line testing

Sao Paolo, Brazil
April 4 2019

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University of Toronto
A lot has changed since March 2017 (my last visit to this meeting)

- USPSTF recommendation D to C
- MRI prior to biopsy—Precision, MRI First
- Micro-ultrasound
- Focal therapy—HIFU approved in US, TULSA
- BRCA, DNA repair germ line testing
- Stampede, Horrad (Radiation for Met disease); Latitude, Arches, Spartan, Stampede, etc.
- Apalutamide, Daralutamide
- Immuno-Oncology—PDL, PDL1 inhibitors
- Each of these represents change and challenges
Many issues in early detection

• Screening—who, how, when
  • ? Role of germ line testing

• PSA here to stay--next step evolving:
  • Biopsy
  • MRI
  • High resolution ultrasound/Other imaging
  • Secondary molecular biomarker

• Biopsy: systematic/targeted/template

• Trans-rectal/trans-perineal
The power of PSA

- Greater impact on cancer detection, staging, prognosis, and monitoring for prostate cancer than any biomarker has had on any other cancer.
- More accessible, ubiquitous, quantitative, reproducible, and accurate than any other cancer biomarker.
- Compelling evidence for its effectiveness as a screening tool.
- PSA levels in mid-life predict lifetime risk of Pca metastasis/death with profound accuracy.
### Recommendations by major groups

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
<th>Commentsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF</td>
<td>2012: Against any testing</td>
<td>2018: Propose to move to ‘C’ recommendation based on reduced overtreatment due to adoption of active surveillance</td>
</tr>
<tr>
<td>AUA, ACS, ACP</td>
<td>Against routine testing</td>
<td>Informed discussion in those who wish; Age 40-50, not &gt; 75 yrs.</td>
</tr>
<tr>
<td>NCCN</td>
<td>For</td>
<td>PSA, DRE age 40; repeat q 5 yrs if PSA &lt; 1.0</td>
</tr>
<tr>
<td>EAU, UK, NZ</td>
<td>Against</td>
<td>Case by case evaluation and discussion</td>
</tr>
<tr>
<td>JUA</td>
<td>For</td>
<td>Baseline PSA age 40, annual after 50, no cutoff</td>
</tr>
<tr>
<td>Melbourne Consensus Statement</td>
<td>For</td>
<td>Baseline PSA mid-40s, annual after 50, no cutoff, separate Dx from Rx</td>
</tr>
</tbody>
</table>
Incidence of Cancer That Was Metastatic at First Presentation, United States, 1975–2012.

Conflicting recommendations: What is going on?

- Are prostate cancer clinicians too biased and tainted by their involvement in the field?
- Are folks on the USPSTF and CTFPHE biased against screening?
- Has the science moved ahead of the guidelines?
- Is the story just too complicated?
  - Many trade offs which are hard to quantify
  - Conflicting data
  - Flawed trials
  - Rapidly moving developments
The key facts

• Age adjusted mortality decreased 45% over the last 20 years (coincident with PSA testing)

• No comparable improvement in countries without prevalent PSA testing

• Properly performed large randomized trials show a 21-44% mortality reduction (29-56% among men actually screened)

• NNS with intermediate F/U 293 per death avoided

• NNT at 14 years : 12 (likely to decrease further with longer f/u)
  • Vs mammography:: NNS 111-235 age 50-70, NNT 10-14
  • Vs Colonoscopy: NNS 850
Results of the key screening trials

**ERSPC: NEJM 2009**
NNS 1410 NNT 48

**ERSPC: Lancet 2014**
NNS 781, NNT 27

**Goteborg Lancet Onc 2010**
NNS 293  NNT 12  CSM HR 0.56

**PLCO: NEJM 2009**

**PLCO Healthy men:  NNS 723; NNT 5** (Crawford D, JCO 2011:29:355-61)
Predictive value of early PSA

Vickers, Ulmert, Sjoberg et al, BMJ 2013:348, 12023

- 21,277 men aged 33-50, 74% participation
- Low rates of PSA testing
- 1369 clinical pca, 241 metastases, 163 cancer deaths
- Age 45-49:
  - median PSA 0.7,
  - top quartile PSA 1.1
  - top decile 1.6.
- Probability of mets at 20-25 yrs in men with PSA < 1.1 ~ 0.2%.
‘Smart PSA screening’

- 1st test age ~ 45 (pre BPH); if < 1, then repeat every 5 years
- Only 2-3 tests between ages 55-65
- Best data: 98 screened and 5 cancers detected to prevent one Pca death
- Screening above age 70 not recommended.
- Risk stratification for more intensive screening and conservative biopsy strategy
- Role for additional blood/urine markers.
- Active surveillance for most low risk disease
- Emerging role for MRI to replace biopsy
# Prostate biomarkers: Who to biopsy

## Serum
- PSA, Free vs Total
- PHI
- 4K
- Mitomics
- Telo PC

## Urine
- PCA3
- TMPRSS2-ERG
- Select MDx
- miR Scientific

## Germ line (saliva/buccal)
- Prompt
- Color

Not commercially available
Germ line testing: Risk assessment before PSA

**Advantages:**
- Once in a lifetime
- Inexpensive
- Increasingly validated
- Basis for rational strategy of subsequent testing
- Identification of proband benefits family, ie BRCA

**Disadvantage:**
- Only goes so far (ie, dietary/environmental factors not incorporated)
- Validation still pending
- Potential tsunami of genetic counselling needs
Color.com genetic testing for inherited DNA repair defects

Hereditary Cancer Test
Learn your risk for common hereditary cancers and how you can use that information.

Buy Color $249
Discounted pricing available for current clients Learn more

You must be at least 18 to use Color.

Color's BRCA Test
$149 $99

What's included in your Color test
- Saliva collection kit & prepaid return label
- BRCA1 and BRCA2 test report
- Expert genetic counseling
- Latest genetics news that matters to you

Buy Color

*You must be at least 18 to use Color. If you have a personal or family history of cancer, you may want to consider Color’s Hereditary Cancer Test. Learn more
Prompt - Prostate Genetic Score (PGS)

• Combination of over 30 PCa associated SNPs

• Validated in multiple populations and within the context of large clinical trials (REDUCE, PLCO and PCPT)

• Highly associated with a positive prostate biopsy ($p = 3.41 \times 10^{-8}$)

• Outperformed all existing biomarkers for overall PCa risk in the REDUCE study

Kader et al Eur Urol 2012
## Individual variables at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline (Age)</td>
<td>0.56</td>
</tr>
<tr>
<td>Digital rectal examination at baseline (DRE)</td>
<td>0.51</td>
</tr>
<tr>
<td>Total PSA levels at baseline</td>
<td>0.54</td>
</tr>
<tr>
<td>Free/total PSA ratio at baseline (f/t PSA)</td>
<td>0.54</td>
</tr>
<tr>
<td>Prostate volume at baseline (PV)</td>
<td>0.56</td>
</tr>
<tr>
<td>Number of cores sampled at base biopsy (No. of cores)</td>
<td>0.55</td>
</tr>
<tr>
<td>Family history at baseline (FH)</td>
<td>0.53</td>
</tr>
<tr>
<td>Genetic score based on 33 PCa risk SNPs (Genetic score)</td>
<td>0.59</td>
</tr>
</tbody>
</table>
This algorithm is only hypothetical and has not been validated.
Liquid assays to identify clinically significant prostate cancer

<table>
<thead>
<tr>
<th>Assay</th>
<th>PHI</th>
<th>4K score</th>
<th>PCA3</th>
<th>Select MDx</th>
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<tbody>
<tr>
<td>Company</td>
<td>Beckman Coulter</td>
<td>Opko</td>
<td>Hologic</td>
<td>MDx Health</td>
</tr>
<tr>
<td>Specimen</td>
<td>Blood</td>
<td>Serum</td>
<td>Post DRE urine</td>
<td>Urine</td>
</tr>
<tr>
<td>Method</td>
<td>RIA for tPSA, fPSA, pro PSA</td>
<td>RIA for PSA, fPSA, intact PSA, HK2</td>
<td>qPCR mRNA for PCA3</td>
<td>qPCR for DLX1, HOXC6</td>
</tr>
<tr>
<td>List Price US$</td>
<td>499</td>
<td>1900</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>AUC</td>
<td>0.73</td>
<td>0.82</td>
<td>0.68</td>
<td>0.89</td>
</tr>
</tbody>
</table>
5-year Diagnosis Rates Based on Initial PSA Level

Overall Study Population (21,500)
African Americans 19-fold increase in risk

15-fold increase in risk
7.85%
10.39%
0.51%

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

Pros and cons of ‘PSA > 1.5’ approach

• Simple and straightforward
• Appealing to primary care physicians
• Potential to reduce unnecessary biopsies
• Would capture almost all significant cancers

Caveats:

• Resource intensive
• ‘Medicalization of healthy’ (1 in three will be informed ‘you are at risk’)
• Unclear if biomarker or MRI should be next step
  • This is likely a financial/resource availability issue
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Ca Dx rate %</th>
<th>Accuracy %</th>
<th>Sens %</th>
<th>Spec %</th>
<th>PPV %</th>
<th>NPV %</th>
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<tr>
<td>Abd-Alazeez</td>
<td>2014</td>
<td>129</td>
<td>55</td>
<td>44</td>
<td>94</td>
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<td>89</td>
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<tr>
<td>Chamie</td>
<td>2014</td>
<td>115</td>
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<td>72</td>
<td>96</td>
<td>46</td>
<td>66</td>
<td>92</td>
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<tr>
<td>Sonn</td>
<td>2013</td>
<td>105</td>
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<td>50</td>
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<td>NR</td>
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<td>Abd-Alazeez</td>
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<td>54</td>
<td>63</td>
<td>53</td>
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<td>42</td>
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<td>79</td>
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<tr>
<td>Arumainayagam</td>
<td>2013</td>
<td>64</td>
<td>84</td>
<td>72-82</td>
<td>58-73</td>
<td>71-84</td>
<td>49-63</td>
<td>84-89</td>
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<tr>
<td>Kasivisvanathan</td>
<td>2013</td>
<td>182</td>
<td>79</td>
<td>57</td>
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<td>87</td>
<td>93</td>
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<td>Hoeks</td>
<td>2012</td>
<td>265</td>
<td>41</td>
<td>35</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
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<tr>
<td>Rais-Bahrami</td>
<td>2013</td>
<td>538</td>
<td>59</td>
<td>NR</td>
<td>94</td>
<td>28</td>
<td>38</td>
<td>91</td>
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<tr>
<td>Rouse</td>
<td>2011</td>
<td>114</td>
<td>60</td>
<td>86</td>
<td>95</td>
<td>84</td>
<td>68</td>
<td>98</td>
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<tr>
<td>Thompson</td>
<td>2014</td>
<td>150</td>
<td>61</td>
<td>33</td>
<td>96</td>
<td>50</td>
<td>50</td>
<td>96</td>
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<tr>
<td>Pannebianco</td>
<td>2015</td>
<td>1140</td>
<td>80</td>
<td>97</td>
<td>86</td>
<td>94</td>
<td>99</td>
<td>100</td>
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<tr>
<td>Ahmed Promis</td>
<td>2017</td>
<td>740</td>
<td>53</td>
<td>60</td>
<td>88</td>
<td>45</td>
<td>65</td>
<td>76</td>
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<tr>
<td>Klotz</td>
<td>2018</td>
<td>273</td>
<td>23</td>
<td>50</td>
<td>93</td>
<td>27</td>
<td>30</td>
<td>0.86</td>
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<td>Reviews</td>
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<td></td>
<td>De Rooij, AJR 2014</td>
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<td></td>
<td>Mowatt, HTA 2013</td>
<td></td>
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<td></td>
<td></td>
<td>0.85</td>
</tr>
</tbody>
</table>
## Randomized MRI studies: Systematic bx vs MRI and targeted bx

All studies: Median PSA ~6, median age ~64,

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Cohort</th>
<th>Biopsies avoided</th>
<th>Clinically significant Ca missed if only targeted Bx</th>
<th>GG ≥ 2 Targ vs systematic</th>
<th>GG 1 Targ vs systematic</th>
<th>Median # cores/pt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision NEJM 2018 Kasivisanathan</td>
<td>500</td>
<td>↑ PSA</td>
<td>28%</td>
<td></td>
<td>+ 12%</td>
<td>- 13% (9% vs 22%)</td>
<td>4 vs 12</td>
</tr>
<tr>
<td>MRI-First Lancet Onc 2018 Rouviere</td>
<td>251</td>
<td>↑ PSA</td>
<td>20%</td>
<td>11%</td>
<td>+ 2% (NS)</td>
<td>-14% (6% vs 20%)</td>
<td>3 vs 12</td>
</tr>
<tr>
<td>4M Eur Urol 2018 Van der Leest</td>
<td>626</td>
<td>↑ PSA</td>
<td>49%</td>
<td>4%</td>
<td>+ 2%</td>
<td>-11% (14% vs 25%)</td>
<td>3 vs 12</td>
</tr>
<tr>
<td>ASIST Euro Urol 2018 Klotz</td>
<td>275</td>
<td>Active Surv. (Confirm. Bx)</td>
<td>N/A (Syst vs Targ + Syst)</td>
<td>14%</td>
<td>-2%</td>
<td>-4%</td>
<td>N/A (median 2 targeted vs 12 systematic)</td>
</tr>
</tbody>
</table>

Message: 1 in 6 significant cancers will be missed if no biopsy with negative MRI
ASIST Trial Summary

Men with Gleason 6 Pca on surveillance. Randomize (within 6 - 12 months of initial biopsy) →

ARM 1
Active surveillance with 12-14 core biopsy at 9 months (6 - 13 months) after initial biopsy, and serial PSA determinations

ARM 2
Active surveillance with MR imaging and targeted and systematic biopsies at 9 months (6 - 13 months) after initial biopsy, and serial PSA determinations

• Pathologic Upgrading
• N of pts having treatment
• Clinical stage
• Number, size, location of radiographic lesions
• PSA failure post treatment
• Clinical progression

275 subjects will be accrued from three participating Canadian Urology Research Consortium (CURC) sites in an estimated time of 2 years. Primary analysis is planned at a year after randomization.
Artemis Image Guidance and Navigation

- 3D Image guidance & navigation for prostate biopsy
Percentages with No Cancer, GG!, and GG ≥ 2 by MRI score in AS population (ASIST study)

Precision study NEJM 2018
(Note: definition of CS Ca non- identical)
Conclusions of recent tsunami of MRI and biomarker publications

- MRI and targeted biopsy an improvement over systematic biopsies
- But NPV in average patient less than hoped for (~85%)
- Risk stratification for biopsy decision warranted
- Ballpark: If risk of high grade cancer < 10%, systematic biopsies can be avoided; otherwise they are still necessary
- In men with elevated PSA, whether MRI or biomarker comes next largely a function of resources/cost/availability/patient preference
Micro U/S vs. Conventional U/S

- Micro-ultrasound system **29 MHz**
  - vs conventional 6-9MHz systems

- **Resolution to** 70 μ (vs ~200 μ with conventional U/S)

- Real-time targeting of biopsies

Initial system developed by Stuart Foster and team, Sunnybrook Research Institute (Imaging Research)
Assigning a Risk Score (PRI-MUS) to each Prostate Region

<table>
<thead>
<tr>
<th>PRI-MUS 1</th>
<th>PRI-MUS 2</th>
<th>PRI-MUS 3</th>
<th>PRI-MUS 4</th>
<th>PRI-MUS 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small regular ducts</td>
<td>&quot;Swiss Cheese&quot;</td>
<td>Hyperechoic with/without ductal patches</td>
<td>Mild heterogeneity or Bright Echoes in hyperechoic tissue</td>
<td>Heterogeneous &quot;Cauliflower, smudgy or mottled&quot; or Bright Echoes (&quot;Starry Sky&quot;)</td>
</tr>
<tr>
<td>&quot;Swiss Cheese&quot;</td>
<td>Hyper, ductal patches</td>
<td>Mild heterogeneity, bright echoes in hyperechoic tissue</td>
<td>Bright Echoes</td>
<td>Irregular Shadowing, or Mixed-echo lesions, or Irregular Prostate / PZ border</td>
</tr>
<tr>
<td>&quot;Swiss Cheese&quot;</td>
<td>Hyper, ductal patches</td>
<td>Mild heterogeneity, bright echoes in hyperechoic tissue</td>
<td>Bright Echoes</td>
<td>Irregular Shadowing</td>
</tr>
<tr>
<td>&quot;Swiss Cheese&quot;</td>
<td>Hyper, ductal patches</td>
<td>Mild heterogeneity, bright echoes in hyperechoic tissue</td>
<td>Bright Echoes</td>
<td>Mixed Echo Lesion with Irregular Prostate border</td>
</tr>
<tr>
<td>&quot;Swiss Cheese&quot;</td>
<td>Hyper, ductal patches</td>
<td>Mild heterogeneity, bright echoes in hyperechoic tissue</td>
<td>Bright Echoes</td>
<td>Irregular Shadowing</td>
</tr>
</tbody>
</table>

1. Systematic Biopsy
2. Target Suspicious Region
Sunnybrook data

- N=75
- 48 were undiagnosed men at risk for Pca
- 27 previously treated with focal therapy with HIFU or TULSA for post treatment biopsies.
- Targeted and 12 core systematic biopsies
- 42/75 had prior MRI
Experience with Micro-Ultrasound

• 18 cases had positive biopsies, MRI, and micro-ultrasound guided biopsy

  • 11/18 had equivalent targets on both modalities
  • 1/18 negative on both (positive on systematic only)
  • 6/18 negative on MRI, positive for GG >=2 on micro-ultrasound targeted biopsy
  • 0/18 positive or higher GG on MRI target compared to micro-ultrasound

PATIENTS WITH POSITIVE BIOPSY RESULTS

- Both MRI and MicroUS
- Only Systematic
- Only MicroUS
- Only MRI

Sunnybrook
HEALTH SCIENCES CENTRE
## PPV by PRIMUS score

<table>
<thead>
<tr>
<th>PRIMUS score</th>
<th>All Pca (GG &gt;=1) (%)</th>
<th>GG2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>67</td>
</tr>
</tbody>
</table>
Rehabilitating PSA Screening.

1. Informed patient (good brochure)
2. Restrict testing to men who will benefit
   - Germline testing once in lifetime to assess risk is coming
3. Restrict biopsy to those with a compelling reason
   - Secondary molecular marker for elevated PSA
   - Emerging role of MRI to replace biopsy if normal
   - Result: Almost all men subjected to a biopsy will have a positive diagnosis
4. Active surveillance for low risk disease
5. Reduce morbidity of treatment
   - Centres of excellence
   - Focal therapy