New Blood and Urine Tests to Improve Detection of Aggressive Prostate Cancer: Progress from the NCI Early Detection Research Network

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Patient Advocate: Merel Grey
Background

- USPSTF Grade D recommendation against PSA testing due to over-detection & over-treatment of indolent cancers
- American Cancer Society
- AUA: Screening advisable for men ages 50 – 70 after discussion of risk/benefit

Problem/Dilemma

“one-size-fits-all” – no guidance for risk factors (family history, african-american race, obesity, symptoms)
“baby thrown out with bathwater” – in effort to reduce over-treatment, discarding reduction of prostate cancer deaths
Randomized Clinical Trials Evaluating PSA Screening

**Randomized Prostate Ca screening trials with survival endpoint**

- Prostate, Lung, Colon and Ovarian Screening Trial (PLCO; Andriole et al NEJM 2009)
  - No survival benefit
  - **BUT** 52% + screening contamination in control arm
  - Only 1/3 of men with abnormal PSA/DRE underwent biopsy

- European Randomized Screening trial in Prostate Cancer (ERSPC; F Schroeder et al NEJM 2009)
  - Significant survival benefit
  - 1400 men screened for each life saved
  - 40 treated per life year saved @ 9yrs
  - 12 treated per life saved @ 14yrs (Hugosson et al Lancet Oncology 2010)

*Many unnecessary biopsies; unnecessary/excess treatment !!*
Natural History of *Untreated* Prostate Cancer

*only a minority of Gleason 6 cancers can spread or be fatal*

**Age:**
- 55-59
- 60-64
- 65-69
- 70-74

Years of Follow-up After Diagnosis (5,10,15,20 yrs)
Prostate Health Index (phi)

$Phi = [-2]pro-PSA \div free\ PSA \times total\ PSA$

Less impact of prostate size/BPH (than total PSA)

Ready for Clinical Use?

1. FDA-approved, commercially available clinical assay
2. Beckman pivotal trial (Catalona et al J Urology 2011)
3. NCI-EDRN study + validation (Sanda et al, J Urology 2015)
NCI Early Detection Research Network *phi* Study: Predicting Gleason ≥ 7 Prostate Ca on Initial Biopsy

**Method**
- 963 men at 6 sites (569 prevalidation+394 validation)
- before initial biopsy
- Any total PSA
- Endpoint: predict Gleason ≥ 7 Pca

**Results**
- Improved accuracy over PSA (ROC AUC 0.81)
- At *phi* > 25:
  - Sensitivity = 95%
  - Specificity = 36% for Gleason ≥ 7 PCa
  - (PSA specificity = 17%)
- Avoids 25% of biopsies in validation cohort

*Sanda et al J Urology 2015*
Urinary RNA Testing to Refine Prostate Ca Detection

TMPRSS2:ERG Mutation is in **one-half** of prostate cancers:

- Gene rearrangement (deletion or translocation) in ~ half of prostate cancers (Tomlins et al, Science, 2005)
- TMPRSS2-Erg RNA detected in post-DRE urine sediment by RT-PCR (Laxman et al 2006); adopted for clinical grade/commercial platform by Genprobe (now Hologics)
- Possible combination with PCA3 suggested (Hessels et al 2007)
Emory-Harvard-Michigan-Cornell  EDRN CVC Prospective Study of Urine PCA3 + Terg to Detect *Gleason ≥ 7* Prostate CA

3 Clinical Sites  
(BIDMC, Cornell, U Michigan)

Patients Enrolled (N=516) & Post-DRE Urine Collected

Prostate Biopsy

Benign  
Prostate Cancer

Analysis: PSA/PCA3/Terg  
Spec @ 95% Sens for Gleason 7
(AIM 1) Urinary T2erg by Site and Biopsy Diagnosis

Square Root Scale

<table>
<thead>
<tr>
<th>Site</th>
<th>No PCa</th>
<th>PCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site A</td>
<td>144</td>
<td>136</td>
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<tr>
<td>Site B</td>
<td>179</td>
<td>126</td>
</tr>
<tr>
<td>Site C</td>
<td>62</td>
<td>52</td>
</tr>
</tbody>
</table>
Combining Urine Tests for PCA3 and T:erg Mutation to Refine Prostate Cancer Detection: EDRN Validation Trial (AUA Annual Meeting 2015)

A. Multicenter Prevalidation Study urine test combining T:erg and PCA3 RNA
   - N = 518; 5 urology practice sites
   - Improved specificity of detecting Gleason 7+ from 18% to 38% (at 95% sensitivity)
   - PCA3 score > 20, T:erg score > 7

B. Validation in separate multicenter cohort
   - N = 561; 11 sites (nationwide U.S.)
   - Specificity ↑ to 33% from 16% PSA alone (p=0.04)

C. Cost Impact Study
   - Terg+PCA3 urine test may reduce healthcare costs