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

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EDRN Prostate and GU Collaborative Team:

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Frederick Hutchinson and MD Anderson DMCC: Z Feng, J Dahlgren

Hologics/Genprobe: J Groskopf Beckman/Coulter: D Broyles, B Cook

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

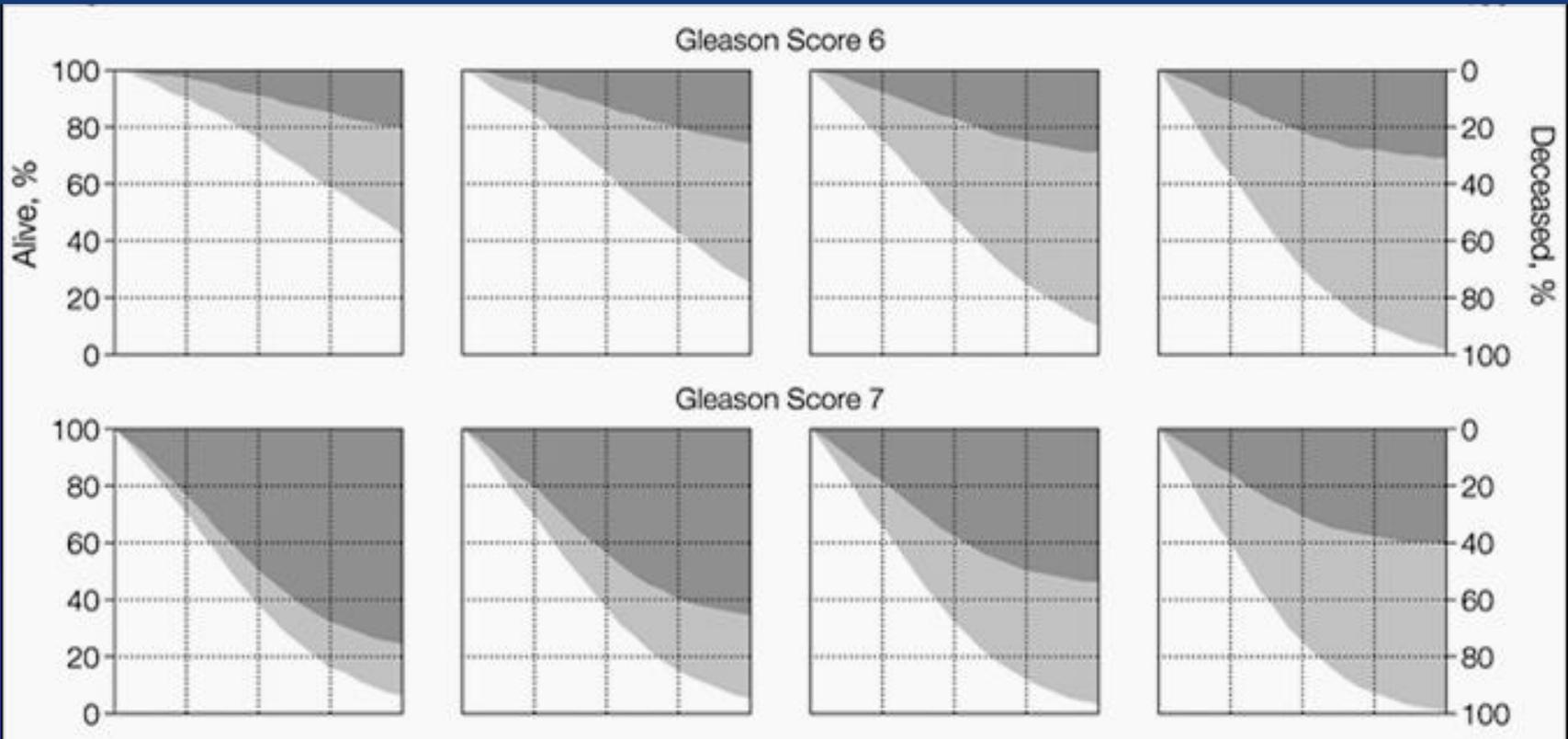
- Prostate, Lung, Colon and Ovarian Screening Trial (PLCO; Andriole et al NEJM 2009)
 - No survival benefit
 - **BUT** 52% + screening contamination in control arm
 - Only 1/3 of men with abnormal PSA/DRE underwent biopsy
- European Randomized Screening trial in Prostate Cancer (ERSPC; F Schroeder et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

phi Serum Test to Improve Detection of Aggressive Prostate Cancer

Prostate Health Index (*phi*)

$$\text{Phi} = [-2] \text{pro-PSA} / \text{free PSA} * \text{total PSA}$$

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

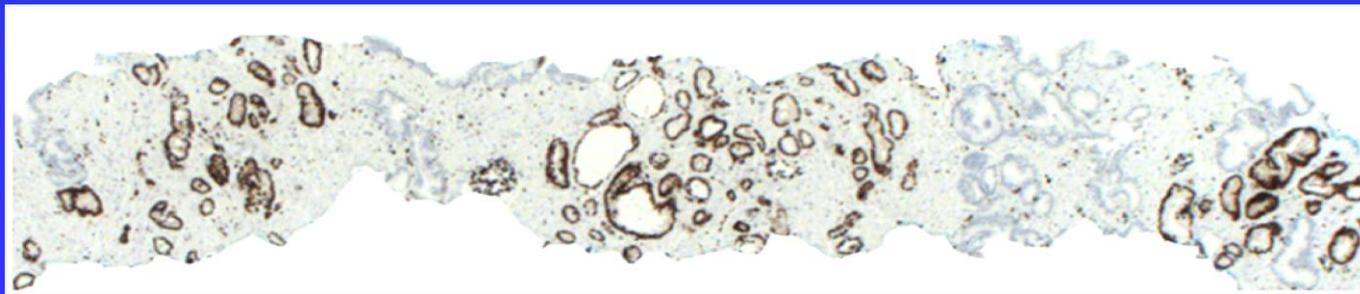


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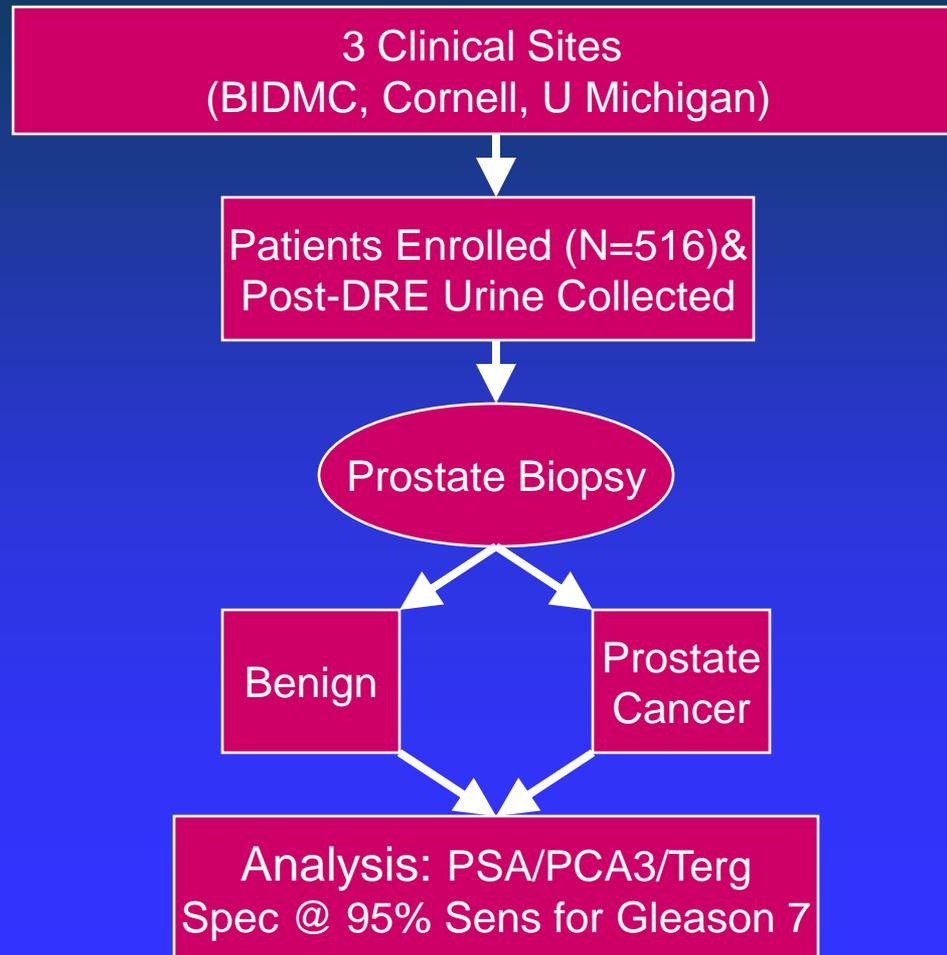
Urinary RNA Testing to Refine Prostate Ca Detection

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

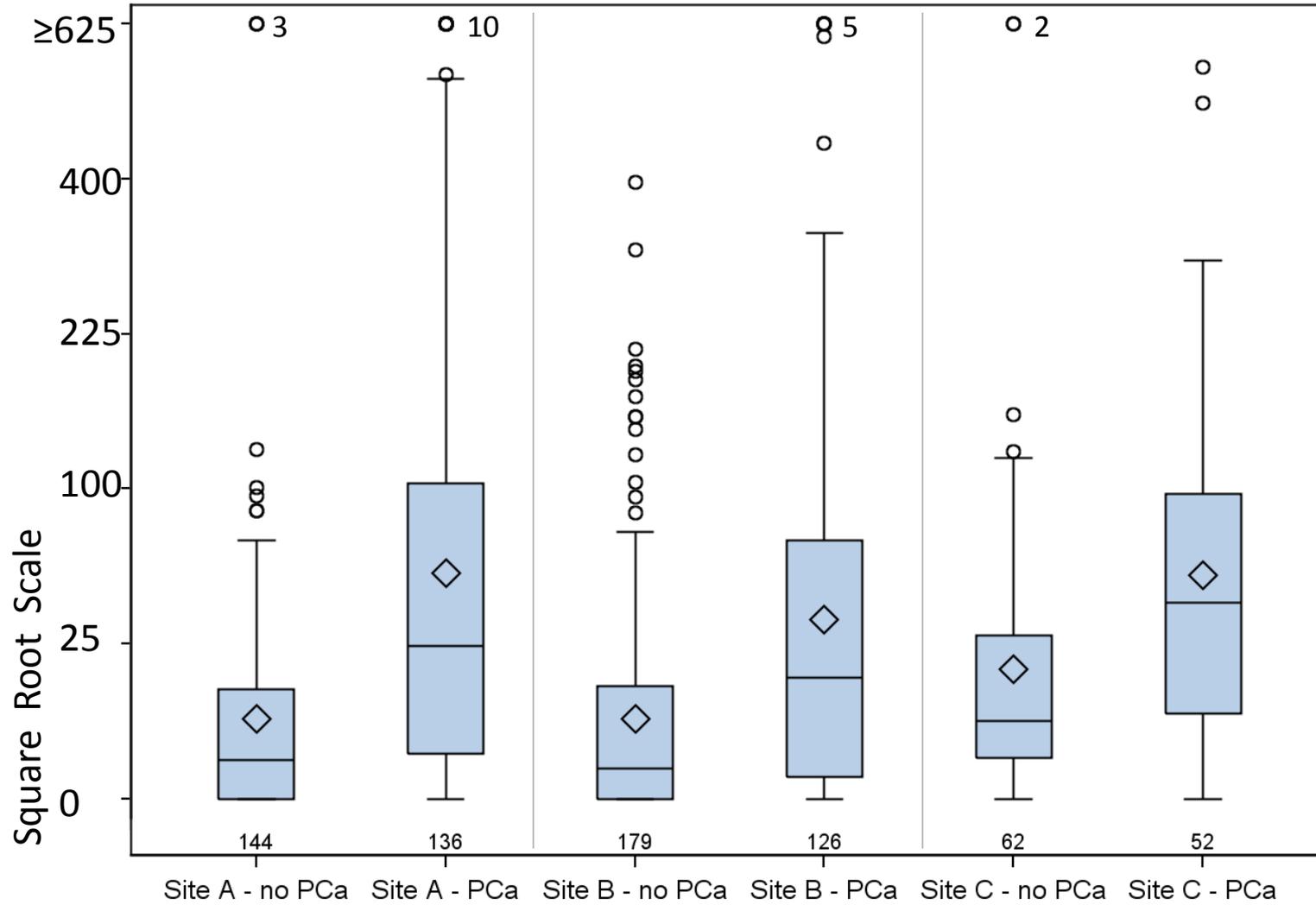
- Gene rearrangement (deletion or translocation) in ~ half of prostate cancers (Tomlins et al, Science, 2005)
- TMPRSS2-Erg RNA detected in post-DRE urine sediment by RT-PCR (Laxman et al 2006); adopted for clinical grade/commercial platform by Genprobe (now Hologic)
- Possible combination with PCA3 suggested (Hessels et al 2007)



Emory-Harvard-Michigan-Cornell EDRN CVC Prospective Study of Urine PCA3 + Terg to Detect $Gleason \geq 7$ Prostate CA



(AIM 1) Urinary T2erg by Site and Biopsy Diagnosis



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