




Prospects for Prostate Cancer Screening

Dialogue for Action
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Dr. Brooks has no relationships
or conflicts to disclose that
influence the content of today's
presentation.



Prostate Cancer Screening

- Fraught with controversy
 - Evidence is mixed on the balance of benefits vs harms
- Major shortcomings with current standard-of-care tests

Digital Rectal Exam

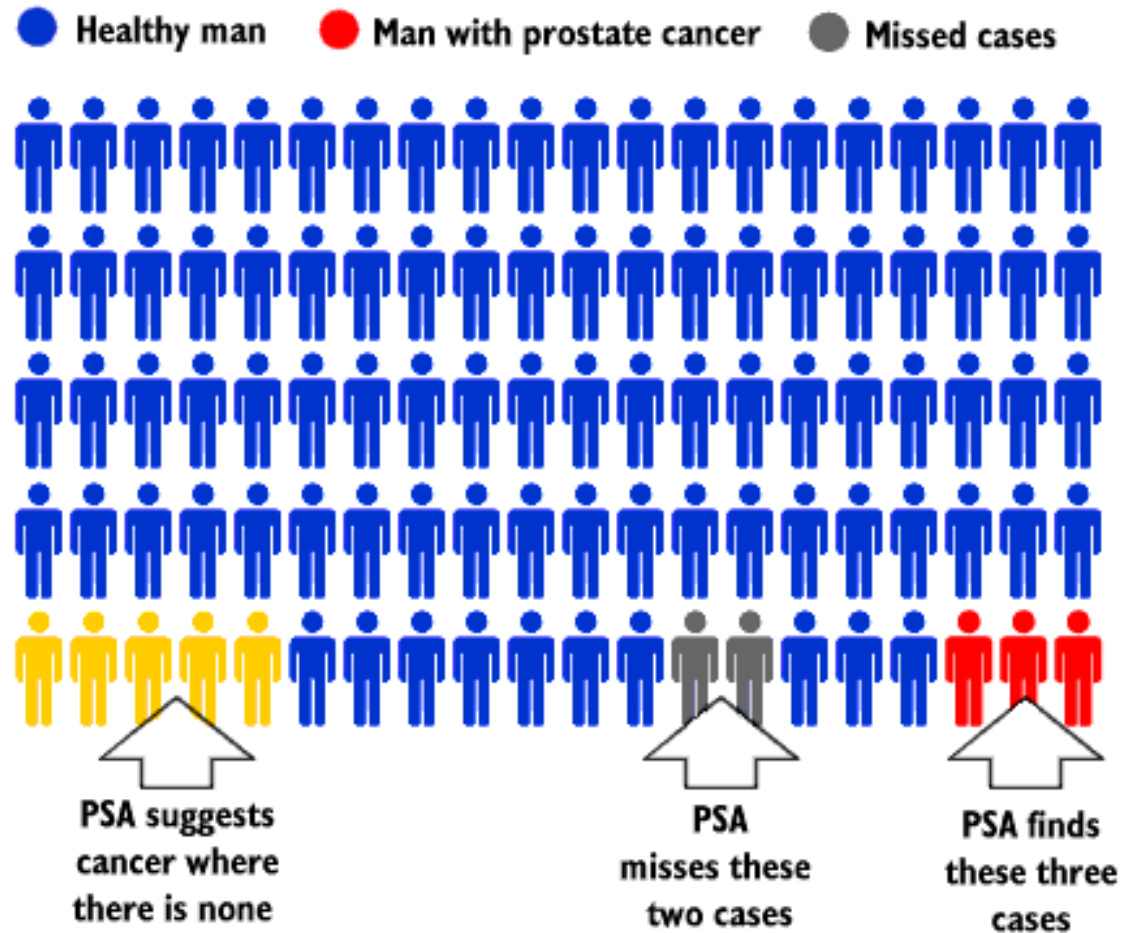




Prostate Specific Antigen

- Not “specific” for cancer (most elevations due to benign disease)
- False positive and false negative results occur frequently
- Over diagnosis of low-risk cancers, often leading to over treatment
- Treatment related complications are common, life-altering

PSA Screening Outcomes





Treatment Risks/Harms

Estimates from 2011 USPSTF review:

- 90% of diagnosed men choose active treatment
 - 195,000 men each year
 - 38% radiation
 - 40% prostatectomy
- 5/1000 men die within 30 day of prostatectomy
- 200-300/1000 treated men experience impotence, incontinence or both

Home PSA Screening



Not available in the U.S. - yet



New Tests for Prostate Cancer

These new tests:

- are adjuncts to PSA, not replacements
- assist in determining:
 - Who to biopsy
 - Who needs repeat biopsy
 - Who is likely/unlikely to benefit from treatment
- fall into two broad categories
 - Biomarkers
 - Imaging approaches



Tests for Who To Biopsy

- Biomarkers
 - Prostate Health Index (phi)
 - 4KScore
- Imaging
 - Multiparametric MRI (mpMRI)



Prostate Health Index (phi)

- Blood is tested for truncated proPSA (p2PSA) molecule
- If this molecule is present the phi is calculated based on a formula involving three biomarkers (p2PSA, free PSA and standard PSA)
- phi is intended to distinguish PCa from benign prostatic conditions in men with a total serum PSA between 4 and 10 ng/ml.
- Depending on the phi score a man is categorized as having a low, medium or high risk of aggressive prostate cancer

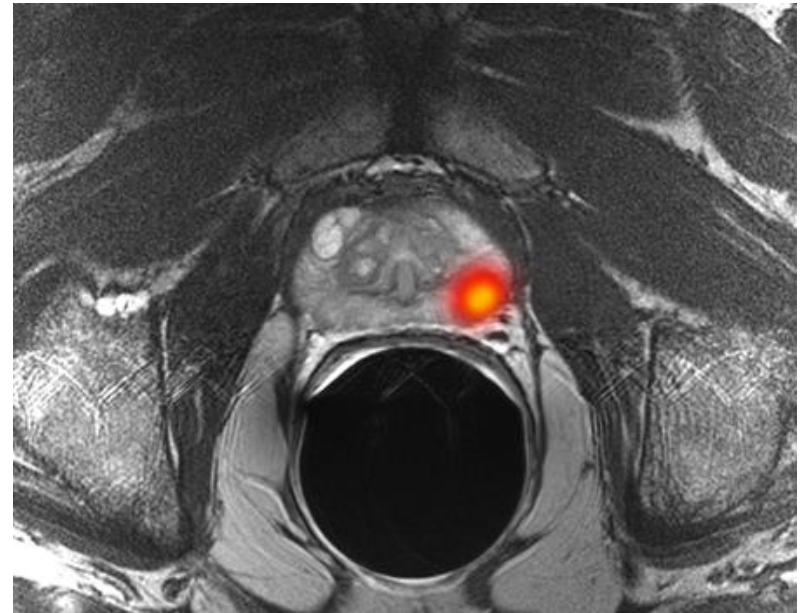


4KScore

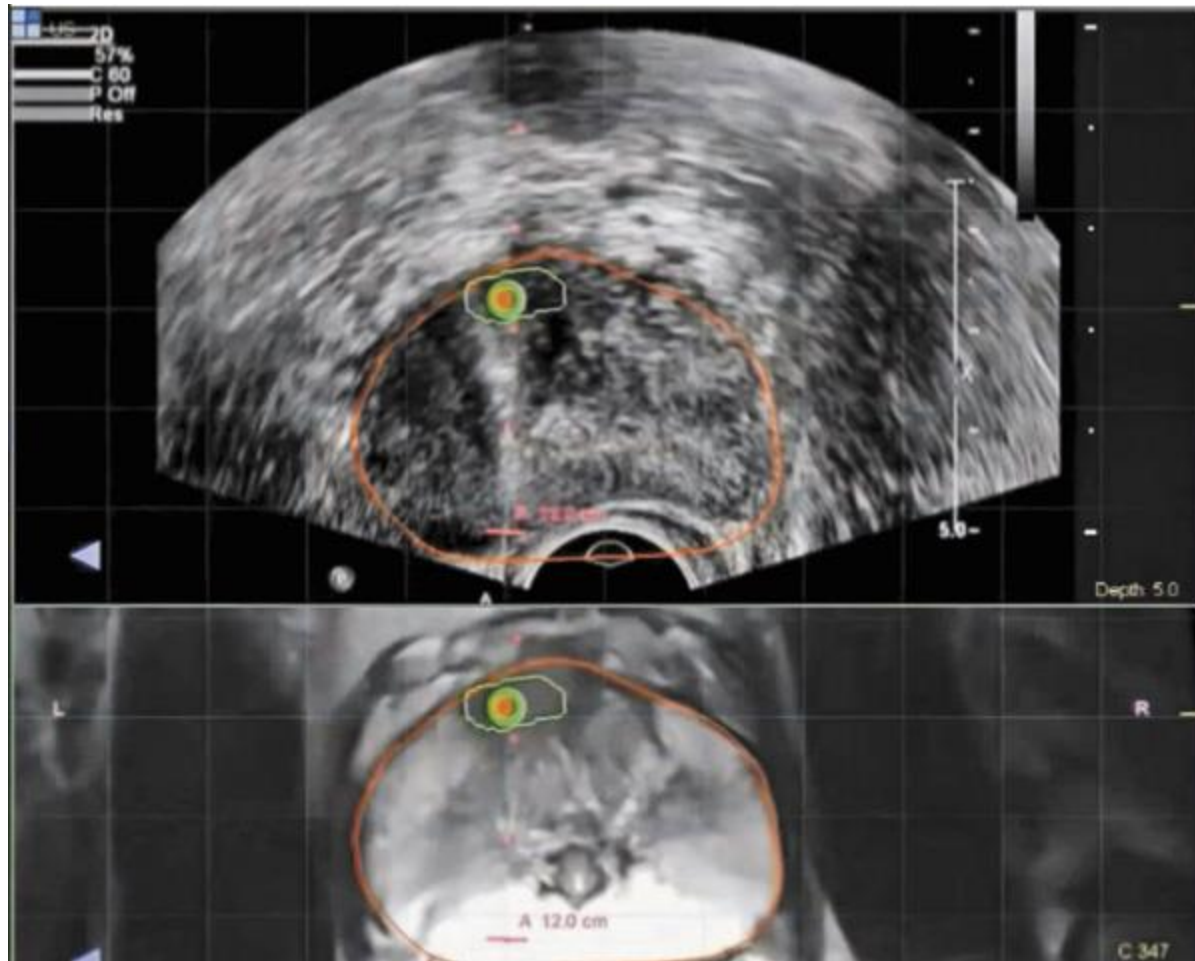
- Measures plasma levels of four different prostate-derived kallikrein proteins:
 - Total PSA
 - Free PSA
 - Intact PSA, and
 - Human Kallikrein 2 (hK2)
- These biomarkers are combined with a patient's age, DRE and prior biopsy status to calculate the probability of finding a Gleason Score 7 or higher prostate cancer.
- Recent study in 1012 men scheduled for biopsy estimated a reduction of 30–58% in the number biopsies depending on the threshold chosen.


Multiparametric MRI (mp-MRI)

- Integrates traditional T2-weighted imaging with 1 or more functional techniques (diffusion-weighting, dynamic contrast-enhancement, spectroscopy)
- Provides information about the biochemical and metabolic status of the tissue, angiogenesis and other parameters
- Used for cancer detection, assessment of tumor aggressiveness, localization and staging, search for tumor recurrence
- Role in active surveillance?



Mp-MRI/MRI-TRUS fusion biopsy





Tests for Who To re-Biopsy

- PCA3
- Markers of tumor “field effect”
 - DNA methylation assay
 - Mitochondrial DNA deletion assay

PCA3

- Measures the concentration of prostate cancer gene 3 (PCA3) and PSA RNA molecules and calculates the PCA3 RNA/PSA RNA (PCA3 score)
- PCA3 gene is overexpressed in PCa, but not in BPH or normal prostate
- FDA-approved for men who have a suspicion of PCa based on PSA level and/or DRE and/or one or more negative biopsy results.



Image - <http://harleystreetinternational.com/article.php?id=28>



Markers of Tumor “Field Effect”

- Intended to distinguish patients who have a true-negative biopsy from those who may have occult cancer by detecting PCa in specimens that appear histologically benign through a ‘halo effect’ (molecular changes at the DNA level in cells that are adjacent to cancer foci).
- Test of biopsy specimens to assess:
 - I. DNA methylation (ConfirmMDx)
 - Blinded multicenter study of 483 men with initial negative biopsy determined this test to have a negative predictive value of > 90%.¹
 - Recent study indicates potential ability to also identify tumor aggressiveness.²
 - II. Mitochondrial DNA deletion (Prostate Core Mitomic Test, “PCMT”)³

¹Stewart et al. J of Urology 2013; ²Gaston, European Association of Urology 2014 ³Robinson et al. Prostate Cancer Prostatic Dis. 2013



Tests to clarify Who to Treat

Differentiate low- from high-risk cancers; assist with decision making re: active surveillance vs immediate treatment

- Imaging tests
 - mpMRI
- Genomic tests
 - Marker panels
 - Gene mutations

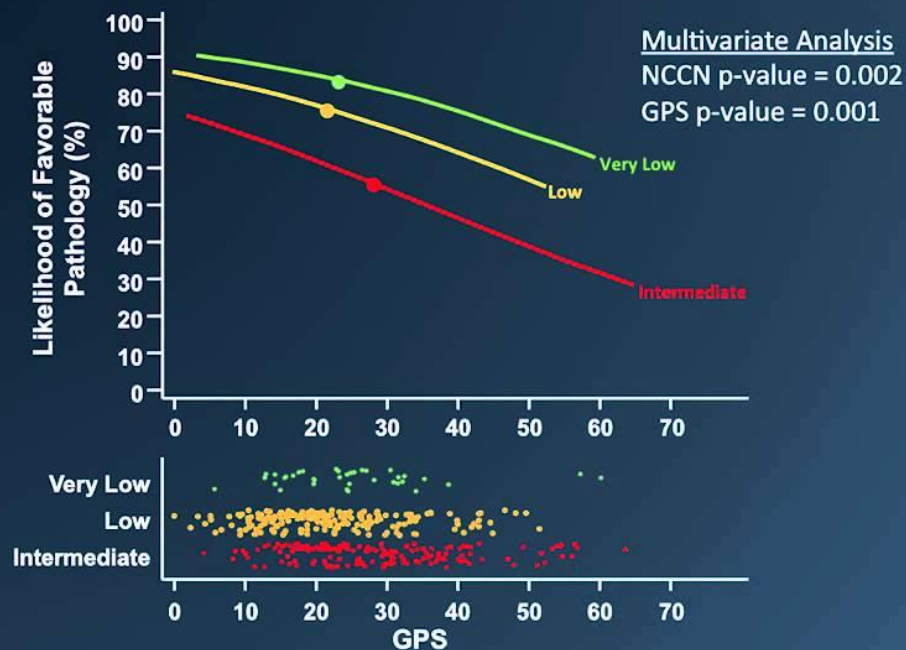


Genomic Tests

- Identify combination of molecular markers in biopsy or prostatectomy specimens that predict for biochemical recurrence, metastasis, or death. Tests measure:
 - Cancer gene expression resulting in genomic prostate score (Oncotype DX)
 - Tumor cell growth characteristics, giving cell cycle progression score (Prolaris)
 - Markers associated with aggressive PCa resulting in genomic classifier score (Decipher)

RNA expression profile: Oncotype DX

Successful Validation of GPS: Improved Risk Discrimination with Addition of GPS to NCCN



Metastasis Risk Stratification: Decipher

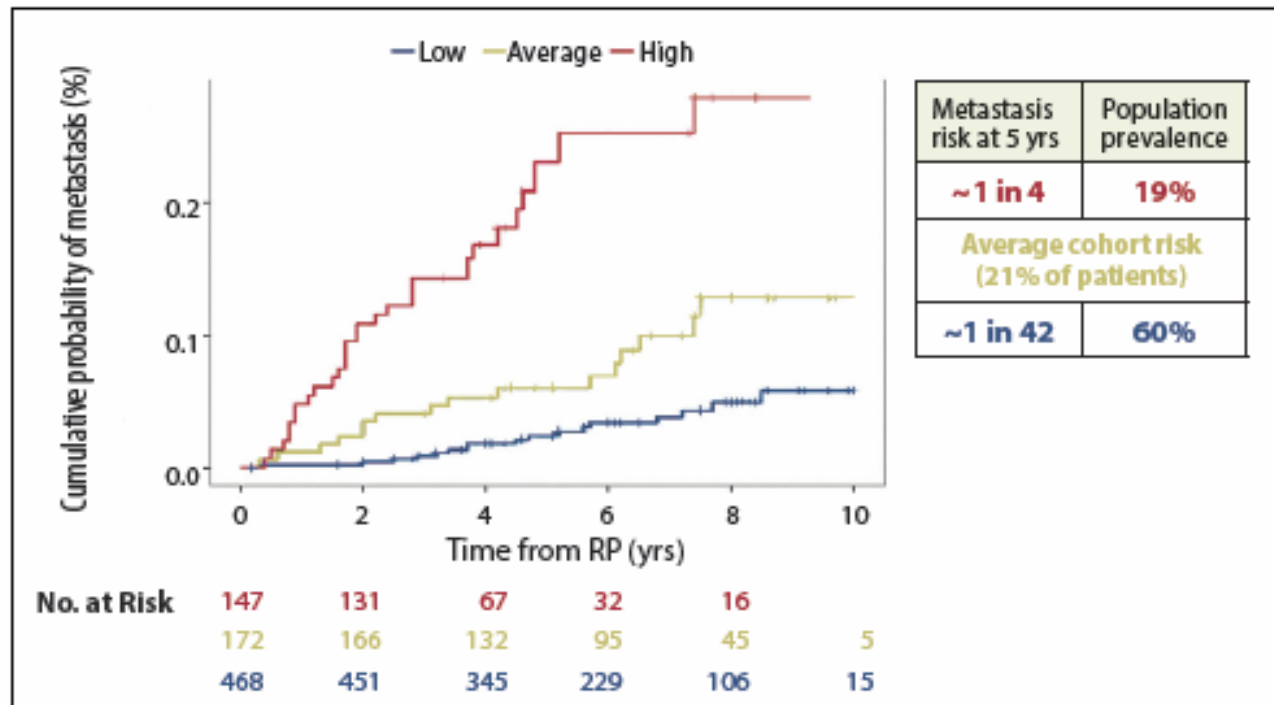


Figure 6: Risk Stratification of Prostate Cancer Patients Using Decipher, a Prognostic Genomic Marker Test—The Decipher test measures expression levels of multiple markers that are known to be associated with aggressive prostate cancer. Decipher scores are used to stratify an individual patient's risk of clinical metastasis following radical prostatectomy (RP). The blue, tan, and red lines show men classified by Decipher as low-, moderate-, and high-risk; the risk of metastasis at 5 years post RP is approximately 1 in 4 for the high-risk patients. Adapted from Karnes et al. 2013.[38]

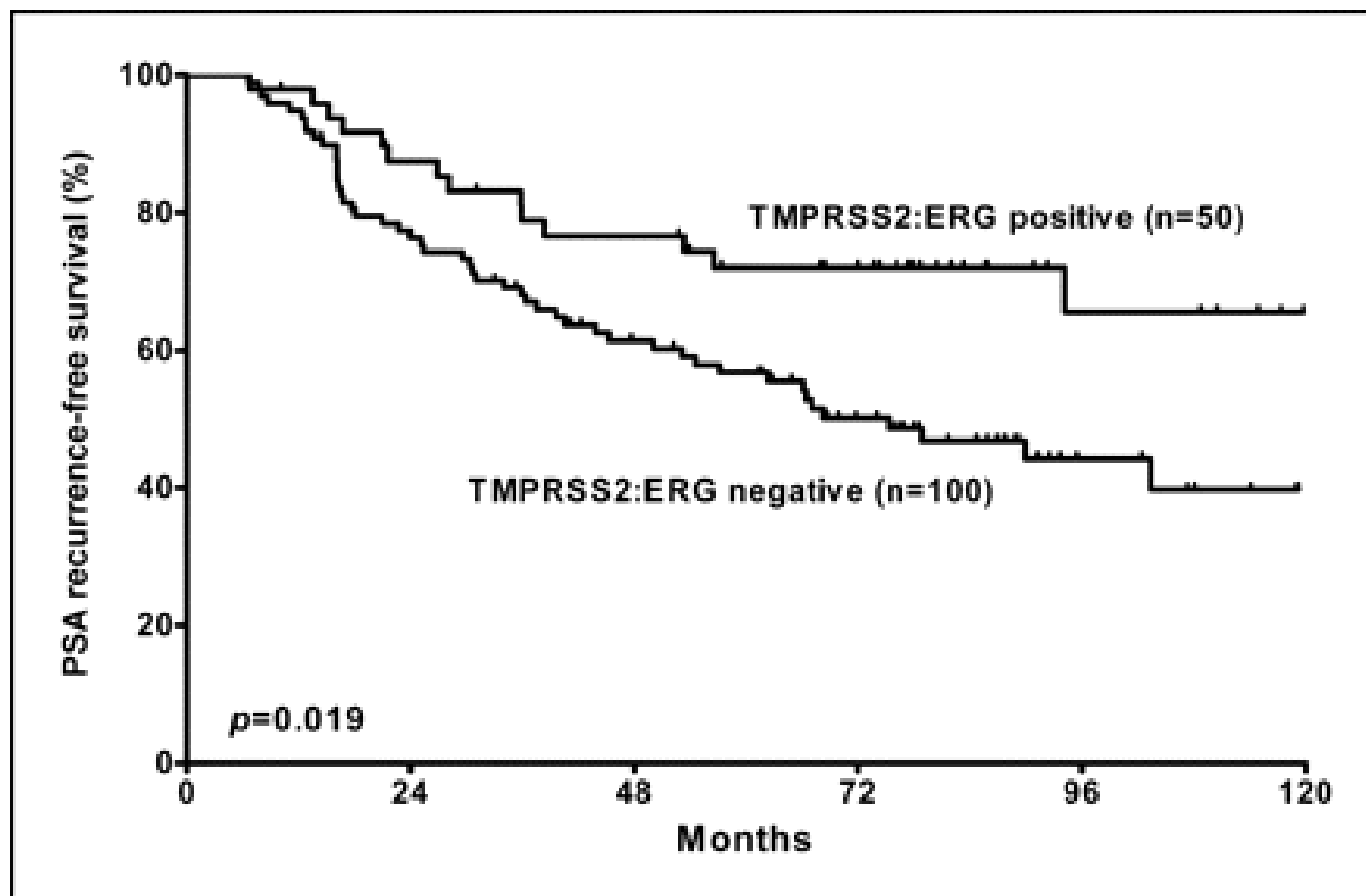


Genomic Tests

Tests for gene mutations

- PTEN tumor suppressor gene deletion
 - Loss associated with disease progression and metastasis
- Urine TMPRSS2-ERG (or T2-ERG) gene fusion
 - Low sensitivity but high specificity
 - May be more useful when combined with other markers (i.e. PCA3, PTEN)

TMPRSS2:ERG fusion



Outi R. Saramäki et al. Clin Cancer Res 2008;14:3395-3400

Successor to PSA?: Canine Detection

AUA 2014

- Volatile organic compounds associated with prostate cancer
- PCa sensitivity 98.6%-100%
- Specificity was 98.6%-98.7% ¹



Photograph: Emma Jeffery/Medical Detection Dogs/PA

Similar findings in prior studies of prostate cancer, as well as colorectal, lung, breast and other cancer sites²

¹Journal of Urology; Published Online: September 25, 2014; ²McColloch, J of Vet Behav 2010