Prostate Cancer: Screening, Treatment, and Survivorship

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Associate Professor of Surgery, USUHS
Madigan Army Medical Center

No Disclosures – These views are my own and not that of the DoD.
Anatomy and Physiology

- Trigone of urinary bladder
- Neck of urinary bladder
- Fundus of urinary bladder
- Vesical fascia
- Rectovesical pouch
- Rectum
- Seminal vesicle
- Prostate and capsule
- Rectoprostatic (Denonvilliers') fascia
- Sphincter urethrae muscle
- Bulbourethral gland (Cowper)
- Perineal body
- Bulbospongiosus muscle
- Deep perineal (investing or Gallaudet's) fascia
- Superficial perineal (Colles') fascia
- Buck's fascia
- Septum of soroctum
- Superficial (dartos) fascia of penis and scrotum
- Scrotum of penis and external urethral meatus
- Prepuce
- Navicular fossa
- Corpus spongiosum
- Corpus cavernosum
- Deep (Buck's) fascia of penis
- Inferior (arcuate) pubic ligament
- Fundiform ligament of penis
- Suspensory ligament of penis
- Pubic symphysis
- Apex of urinary bladder
- Body of urinary bladder
- Urachus
- Glans of penis and external urethral meatus.
Trends in Cancer Incidence Rates* Among Males, US, 1975-2012

*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting. †Includes the intrahepatic bile duct.

Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2015.
THE FREQUENCY OF CARCINOMA AND INTRAEPITHELIAL NEOPLASIA OF THE PROSTATE IN YOUNG MALE PATIENTS

W. A. SAKR,* G. P. HAAS, B. F. CASSIN, J. E. PONTES AND J. D. CRISSMAN

From the Departments of Pathology and Urology, Harper Hospital, Wayne State University School of Medicine and Medical Examiner’s Office, Wayne County, Detroit, Michigan

<table>
<thead>
<tr>
<th>Histology</th>
<th>Pt. Age (yrs.)</th>
<th>Totals (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>10–19</td>
<td>20–29</td>
</tr>
<tr>
<td>Prostatic intraepithelial neoplasia:</td>
<td></td>
<td></td>
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<tr>
<td>Low grade:</td>
<td></td>
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<tr>
<td>Black pts.</td>
<td>0/10</td>
<td>2/28</td>
</tr>
<tr>
<td>White pts.</td>
<td>0/2</td>
<td>1/7</td>
</tr>
<tr>
<td>Totals</td>
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<td>3/35</td>
</tr>
<tr>
<td>High grade:</td>
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<tr>
<td>Black pts.</td>
<td>0/10</td>
<td>0/28</td>
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<tr>
<td>White pts.</td>
<td>0/2</td>
<td>0/7</td>
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<tr>
<td>Totals</td>
<td>0/12</td>
<td>0/35</td>
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<tr>
<td>Histological Ca:</td>
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<tr>
<td>Black pts.</td>
<td>0/10</td>
<td>0/28</td>
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<tr>
<td>White pts.</td>
<td>0/2</td>
<td>0/7</td>
</tr>
<tr>
<td>Totals</td>
<td>0/12</td>
<td>0/35</td>
</tr>
</tbody>
</table>

All values are reported as number of patients/total (%).
But, PCA remains a dread disease!

29,480 prostate cancer deaths in 2014
Trends in Cancer Death Rates* Among Males, US, 1930-2012

*Age-adjusted to the 2000 US standard population.
NOTE: Due to International Classification of Diseases coding changes, numerator information for colorectal and lung cancers has changed over time.
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2015.
Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriele, M.D., Robert L. Grubb III, M.D., Saundra S. Buys, M.D.,
PLCO Trial Design

• 1993-2001 randomized 76,693 men to annual PSA testing for 6 years, annual DRE for 4 years. PSA > 4 – ‘positive’ or usual community care.

• At study entry, 44% of men had undergone one or more PSA tests.
  – Cumulative death rate from PCA 25% lower in those who underwent ≥ 2 PSA tests at baseline.
PSA and Prostate Cancer Screening Controversial

• On October 6, the U.S. Preventive Services Task Force (USPSTF) issued draft recommendations that downgraded the prostate-specific antigen (PSA) test to a “D” status. May it was finalized.

• Other organizations (American Cancer Society, American Urological Association, and others) continue to endorse prostate cancer screening after discussion with the individual.
Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D.,

182,160 Subjects 50–74 yr old underwent randomization
162,387 Were in the core age group (55–69 yr old)

160 Subjects 50–74 yr old died
144 Were 55–69 yr old

82,816 Were assigned to the screening group
72,890 Were 55–69 yr old

6830 Had prostate cancer
5990 Were 55–69 yr old

99,184 Were assigned to the control group
89,353 Were 55–69 yr old

4781 Had prostate cancer
4307 Were 55–69 yr old
Study design

• Collection of designs.
  – Recruitment and randomization differed.
  – Age range varied (50-54, 55-74, 55-69…)
  – Randomization varied (1:1, 1:1.5…)
  – PSA cutoff varied (2.5, 3.0, 4.0, 10!)
  – Varying use of DRE
  – Varying biopsy (6, 10, 12)
  – Screening interval 94 years, 2 years, 7 years)
  – No central pathology review
  – Treatment not standardized. Differed for control and screening groups at some sites.
• **Grade D designation**

• On October 6, 2011 draft recommendations. May, 2012 it was finalized.

• Other organizations (American Cancer Society, American Urological Association, and others) continue to endorse prostate cancer screening after discussion with the individual
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Total PSA Tests</td>
<td>6692 (1115)</td>
<td>6195 (885)</td>
<td>5506 (918)</td>
</tr>
<tr>
<td>Prostate Biopsy</td>
<td>97 (16)</td>
<td>111 (16)</td>
<td>112 (19)</td>
</tr>
<tr>
<td>Prostate Cancer Cases</td>
<td>48 (8)</td>
<td>58 (8)</td>
<td>24 (6)</td>
</tr>
<tr>
<td>Prostatectomies</td>
<td>23 (4)</td>
<td>32 (5)</td>
<td>25 (4)</td>
</tr>
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</table>

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>PSA Tests</td>
<td>8954 (1492)</td>
<td>7942 (1135)</td>
<td>8010 (1135)</td>
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<tr>
<td>Prostate Biopsy</td>
<td>75 (13)</td>
<td>70 (10)</td>
<td>25 (4)</td>
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<tr>
<td>PSA Referrals</td>
<td>94 (16)</td>
<td>98 (14)</td>
<td>50 (8)</td>
</tr>
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</table>
### PSA Tests

**Month**

- Feb-11
- Jun-11
- Sep-11
- Dec-11
- Apr-12
- Jul-12
- Oct-12
- Jan-13

**PSA Tests**

- MAMC
- Multicare
- Linear(MAMC)
- Linear(Multicare)

**PSA Tests (Monthly Average)**

- Pre-Draft
- Draft
- Final

<table>
<thead>
<tr>
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<th>Draft</th>
<th>Final</th>
<th>Total Change (Pre-Draft to Final)</th>
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</thead>
<tbody>
<tr>
<td>MAMC PSA</td>
<td>- 20%</td>
<td>+ 0.04%</td>
<td>- 18% (P=0.2)</td>
</tr>
<tr>
<td>Multicare PSA</td>
<td>- 24%</td>
<td>+ 18%</td>
<td>- 11% (P=0.4)</td>
</tr>
<tr>
<td></td>
<td>Pre-Draft</td>
<td>Draft</td>
<td>Final</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td><strong>MAMC Biopsy</strong></td>
<td>16</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td><strong>MAMC Prostate Cancer Cases</strong></td>
<td>8</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td><strong>MAMC Prostatectomies</strong></td>
<td>4</td>
<td>5</td>
<td>4</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Pre-Draft</th>
<th>Draft</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multicare Biopsy</strong></td>
<td>13</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td><strong>Multicare PSA Referrals</strong></td>
<td>16</td>
<td>14</td>
<td>8</td>
</tr>
</tbody>
</table>
Methods | We examined PSA screening data from the 2000, 2005, 2010, and 2013 National Health Interview Survey (NHIS)

Figure. Prevalence of Prostate-Specific Antigen Screening From National Health Interview Survey (2000, 2005, 2010, and 2013)

- USPSTF recommendations against screening men ≥75 y (2008)
- USPSTF recommendations against screening all men (2012)

% of Prostate-Specific Antigen Screening

- Age group, y
  - 50-74
  - ≥75

Year

- 2000
- 2005
- 2010
- 2013

No. surveyed

- With age ≥75 y
  - 2000: 761
  - 2005: 834
  - 2010: 707
  - 2013: 984

- With age 50-74 y
  - 2000: 3937
  - 2005: 4277
  - 2010: 3891
  - 2013: 5366

Error bars indicate 95% confidence intervals.
DESIGN AND SETTINGS  Ecologic study of age-standardized prostate cancer incidence (newly diagnosed cases/100,000 men aged ≥50 years) by stage from 2005 through 2012 using data from 18 population-based Surveillance, Epidemiology, and End Results (SEER) registries and PSA screening rate in the past year among men 50 years and older without a history of prostate cancer who responded to the 2005 (n = 4580), 2008 (n = 3476), 2010 (n = 4157), and 2013 (n = 6172) National Health Interview Survey (NHIS).
Materials and Methods: We identified incident cancers diagnosed between January 2010 and December 2012 in NCDB (National Cancer Database). We
The *national experiment* in PSA screening. How did we get a cutoff value of 4.0?

Lifetime risk of prostate cancer in 1985 – 8%  
About 8% of screened men had PSA > 4.0  
PSA > 4.0 ng/ml – 25% PPV.  
Felt to be an acceptable PPV.  
Screening series conducted  
Lo and behold: if you biopsy older men, you find prostate cancer.  
Screening proliferated
5519 men
All had prostate biopsy and
- PSA and DRE at time of biopsy
- At least 2 prior PSA values
**Fig. 3:** Forest plot of risk factors for prostate cancer and for high-grade prostate cancer (Gleason score ≥ 7) if a prostate biopsy is performed. PSA = prostate-specific antigen, DRE = digital rectal examination.
How to find the risk calculator

1. Google ‘prostate cancer risk calculator’

2. Click on top ‘hit’
1. **Risk of Biopsy-Detectable Prostate Cancer**

The Cancer Risk Calculator for Prostate Cancer was developed based upon 5519 men in the placebo group of the Prostate Cancer Prevention Trial. ...

deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp - 6k - Cached - Similar pages

2. **The Sunnybrook prostate cancer risk calculator** « THE “NEW ...**

The Sunnybrook prostate cancer risk calculator. Posted on May 28, 2008 by E. Michael D. ("Mike") Scott. A new online calculator, developed by a Canadian ...

prostatecancerinfolink.net/2008/05/28/the-sunnybrook-prostate-cancer-risk-calculator/ - 23k - Cached - Similar pages

3. **The Sunnybrook prostate cancer risk calculator** « THE “NEW ...**

The Sunnybrook prostate cancer risk calculator is the second online prostate cancer risk assessment tool "that allows men to assess their risk for prostate cancer. ..."
Risk of Biopsy-Detectable Prostate Cancer

Fields marked with asterisks (*) are required.

<table>
<thead>
<tr>
<th>Enter Your Information</th>
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</thead>
<tbody>
<tr>
<td>* Race</td>
</tr>
<tr>
<td>* Age</td>
</tr>
<tr>
<td>* PSA Level ? ng/ml</td>
</tr>
<tr>
<td>* Family History of Prostate Cancer</td>
</tr>
<tr>
<td>* Digital Rectal Examination ?</td>
</tr>
<tr>
<td>* Prior Prostate Biopsy ?</td>
</tr>
<tr>
<td>* Is the patient taking finasteride?</td>
</tr>
</tbody>
</table>

Calculate Cancer Risk
Prostate Biopsy
Prostate Cancer

Staging

• Stage T1
  – Nonpalpable prostate cancer
  – Detected only on pathologic examination
    • Incidentally noted after
      – Transurethral resection for benign hypertrophy (T1a and T1b) or
      – On biopsy obtained because of an elevated PSA (T1c-the most common clinical stage at diagnosis)

• Stage T2
  – Palpable tumor
  – Appears to be confined to the prostatic gland (T2a if one lobe, T2b if two lobes)

• Stage T3
  – Tumor with extension through the prostatic capsule (T2a if focal, T2b if seminal vesicles are involved)

• Stage T4
  – Invasion of adjacent structures
    • Bladder neck
    • External urinary sphincter
    • The rectum
    • The levator muscles
    • The pelvic sidewall

• Nodal metastases
  – Can be microscopic and can be detected only by biopsy or lymphadenectomy, or they can be visible on imaging studies

• Distant metastases
  – Predominantly to bone
  – Occasional visceral metastases occur.
Prostate Cancer

Staging

• Stage T1
  – Nonpalpable prostate cancer
  – Detected only on pathologic examination

• Stage T2
  – Palpable tumor
  – Appears to be confined to the prostatic gland (T2a if one lobe, T2b if two lobes)

• Stage T3
  – Tumor with extension through the prostatic capsule (T2a if focal, T2b if seminal vesicles are involved)

• Stage T4
  – Invasion of adjacent structures
Prostate Cancer

Treatment

• Localized
  – Surgery
    • Traditional
    • Robotic
  – Radiation
    • Brachytherapy
    • External beam
  – Cryotherapy
  – Watchful waiting

• Advanced
  – Androgen Deprivation
  – Castrate Refractory
Albertsen’s Competing Risks

JAMA, May 4, 2005—Vol 293, No. 17
Bill-Axelson’s Active Surveillance vs. Prostatectomy


B  Death from Prostate Cancer, Total Cohort

<table>
<thead>
<tr>
<th>Years</th>
<th>Watchful waiting</th>
<th>Radical prostatectomy</th>
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<tbody>
<tr>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>3</td>
<td>0.1</td>
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<tr>
<td>6</td>
<td>0.2</td>
<td>0.2</td>
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<tr>
<td>9</td>
<td>0.5</td>
<td>0.5</td>
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<tr>
<td>12</td>
<td>0.6</td>
<td>0.6</td>
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<tr>
<td>15</td>
<td>0.6</td>
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P=0.01 by Gray’s test

No. at Risk

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<thead>
<tr>
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<th>Radical prostatectomy</th>
<th>Watchful waiting</th>
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<td>339</td>
<td>348</td>
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<td>214</td>
<td>192</td>
<td>121</td>
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<tr>
<td>192</td>
<td>109</td>
<td>96</td>
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## PIVOT Trial

### Death from Any Cause

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Observation</th>
<th>Radical Prostatectomy</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
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</thead>
<tbody>
<tr>
<td>Overall</td>
<td>183/367</td>
<td>171/364</td>
<td>0.88 (0.71–1.08)</td>
<td>0.85</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
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<tr>
<td>&lt;65 yr</td>
<td>50/131</td>
<td>43/122</td>
<td>0.89 (0.59–1.34)</td>
<td>0.85</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>133/236</td>
<td>128/242</td>
<td>0.84 (0.63–1.08)</td>
<td>0.85</td>
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<tr>
<td>Race:</td>
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<tr>
<td>White</td>
<td>119/220</td>
<td>117/232</td>
<td>0.84 (0.65–1.08)</td>
<td>0.81</td>
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<tr>
<td>Black</td>
<td>53/121</td>
<td>46/111</td>
<td>0.93 (0.62–1.38)</td>
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<tr>
<td>Other</td>
<td>11/26</td>
<td>8/21</td>
<td>0.85 (0.34–2.11)</td>
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<td>Charlson score:</td>
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<tr>
<td>0</td>
<td>86/220</td>
<td>82/224</td>
<td>0.90 (0.66–1.21)</td>
<td>0.79</td>
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<tr>
<td>≥1</td>
<td>97/147</td>
<td>89/140</td>
<td>0.84 (0.63–1.13)</td>
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<td>Performance score:</td>
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<td>0</td>
<td>146/310</td>
<td>139/312</td>
<td>0.89 (0.71–1.13)</td>
<td>0.66</td>
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<tr>
<td>1–4</td>
<td>37/57</td>
<td>32/52</td>
<td>0.82 (0.51–1.31)</td>
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<td>PSA:</td>
<td></td>
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<tr>
<td>≤10</td>
<td>101/241</td>
<td>110/238</td>
<td>1.03 (0.79–1.35)</td>
<td>0.04</td>
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<td>&gt;10</td>
<td>77/125</td>
<td>61/126</td>
<td>0.67 (0.48–0.94)</td>
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<td>Risk:</td>
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<tr>
<td>Low</td>
<td>54/148</td>
<td>62/148</td>
<td>1.15 (0.80–1.66)</td>
<td>0.07</td>
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<td>Intermediate</td>
<td>70/120</td>
<td>59/129</td>
<td>0.69 (0.49–0.98)</td>
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<td>High</td>
<td>49/80</td>
<td>42/77</td>
<td>0.74 (0.49–1.13)</td>
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<td>Gleason score:</td>
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<tr>
<td>&lt;7</td>
<td>125/261</td>
<td>113/254</td>
<td>0.86 (0.67–1.12)</td>
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<td>≥7</td>
<td>47/86</td>
<td>50/98</td>
<td>0.84 (0.56–1.25)</td>
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</tr>
</tbody>
</table>
Randomize Prior to Pelvic Lymph Node Dissection (PLND)
PLND within 8 weeks of Registration

(+) Off-Study

ARM I
Surgery

Radical Prostatectomy (retropubic or perineal)

FOLLOW

Death

Progression

ARM II
Radiotherapy

External Radiation
6600 cGy/34 fractions
TDF 200 cGy fractions
M-F (7-10 weeks)

FOLLOW

Progression

Death

Off-Study

(-) Proceed with Treatment Assigned
SWOG 8890

Study accrual: 6 patients over 21 months.

Closed to accrual
Prostate Cancer

Treatment

• Require individualization
  – Must take into account
    • Patient's comorbidity
    • Life expectancy
    • Likelihood of cure
    • Personal preferences
      – Based on an understanding of potential morbidity associated with each treatment
• A multidisciplinary approach (recommended)
  – Integrate
    » Surgery
    » Radiation therapy
    » Androgen deprivation
    » Behavioral therapy
Changes in Quality of Life after Primary Treatment for Prostate Cancer.

Patient-Specific Meta-Analysis of Multiple Studies to Predict Pathologic Outcomes in Clinically Localized Prostate Cancer Using a 17-Gene Genomic Prostate Score

Brand T,1 Cooperberg M,2 Sesterhenn I,3 Simko J,2 Zhang N,4 Crager M,4 Maddala T,4 Lawrence HJ,4 Febbo P,4 Chan J,2 Carroll P,2 Srivastava S,5 and Cullen J5

1Madigan Army Medical Center, Tacoma, WA; 2University of California, San Francisco, San Francisco, CA; 3Joint Pathology Center, Silver Spring, MD; 4Genomic Health, Inc., Redwood City, CA; 5Center for Prostate Disease Research, Rockville, MD
17-Gene Oncotype DX® Genomic Prostate Score

Genes Associated with Worse Outcome
- Stromal Response
  - BGN
  - COL1A1
  - SFRP4
- Proliferation
  - TPX2

Genes Associated with Better Outcome
- Androgen Signaling
  - AZGP1
  - FAM13C
  - KLK2
  - SRD5A2
- Cellular Organization
  - FLNC
  - GSN
  - GSTM2
  - TPM2

Reference Genes
- ARF1
- GPS1
- ATP5E
- PGK1
- CLTC

GPS (scaled 0-100) =
- {Stromal Response Group}
- {Androgen Signaling Group}
- {Cellular Organization Group}
+ {Proliferation}
Each gene is individually weighted in the final algorithm
Evaluable population in UCSF Study
N=395

6 (2%) excluded for pT2+

Evaluable population in CPDR Study
N=402

13 (3%) excluded for central biopsy GS 4+3
7 (2%) excluded for unevaluable RP slides
39 (10%) excluded for pT2+

Eligible for meta-analysis for AP endpoint
N=389

Eligible for meta-analysis for AP endpoint
N=343

Included in meta-analysis
N=732
Risk Profiles for GPS and CAPRA Score
Treatment for Systemic Disease
Hormone Therapy
Treatment after Hormone Therapy

- Enzalutamide
- Abiraterone
- Sipulicel-T
- Xofigo
- Xgeva, Zometa
- Docetaxel
- Clinical Trial