Incidence rates, US Men


*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Mortality Rates, US Men

Cancer Death Rates* Among Men, US, 1930-2009

*Age-adjusted to the 2000 US standard population.
National Center for Health Statistics, Centers for Disease Control and Prevention.
Clinical Stage at Diagnosis

ACoS Survey 1982

Percent

Stage

A
B
C
D
Unknown

Percentages for each stage are shown in the diagram.
Clinical Stage at Diagnosis
National Prostate Cancer Detection Project 1992

Percent

Stage

A1  A2  B1  B2  C  D
PSA-based Screening Limitations

• Low specificity
  – PSA is “prostate specific” but not “prostate cancer specific”
  – Most men with “elevated” PSA do not have prostate cancer
What are the Harms of Screening?

- Acute complications
- Overdiagnosis
- Overtreatment
Screen & Treat Everybody

Early PSA Era

Current Era

Don’t Screen or Treat Anyone

The Goal: Selective Screening & Therapy
• Age and health of the patient
• Risk of having cancer
• Biologic potential of the tumor
• Patient and family desire
Prostate Cancer in 2014

• Most newly diagnosed prostate cancer is not life threatening and does not require immediate treatment

• Lifetime risk of diagnosis: 17%
• Lifetime risk of dying: 3%
Outcomes with Active Surveillance

Prostate Cancer Death

Comparative Mortality

Klotz et al, JCO 28:126, 2010
FAQ

What’s the best way to treat my prostate cancer?
Active Surveillance

• After diagnosis, monitoring disease status and not treating unless the tumor becomes more aggressive

• Goals:
  – Avoid side effects of therapy
  – Apply curative therapy only in those who need it

• Watchful Waiting
  – No monitoring, treat only if symptoms develop, intervene to palliate symptoms (not cure)
Active Surveillance is Underutilized

Barriers to Adopting Surveillance

• Economic/Professional
  – Doctors get trained & paid to treat, not watch

• Legal
  – Failure to diagnose or cure

• Anxiety
  – Patient, family, doctors

• Uncertainties in clinical tools to predict
  – True biologic potential at diagnosis
  – True biologic progression after initiating surveillance (“when to pull the trigger”)

Active Surveillance

Initial Bx & Risk Categorization
- Comorbidity & Life Expectancy
- Patient desire

Re-biopsy to improve accuracy of risk classification

Periodic re-evaluation for change in risk categorization

Intervention
- Change in risk categorization
- Worry over PSA
- Patient desire
## NCCN Risk Groups

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low (Epstein Criteria)</td>
<td>T1c, PSA &lt; 10, Gl 6, &lt; 3 scores &amp; no core ≥ 50%, PSAD &lt; 0.15</td>
</tr>
<tr>
<td>Low</td>
<td>T1-T2a, PSA &lt; 10, Gl 6</td>
</tr>
<tr>
<td>Intermediate</td>
<td>T2bc or Gl 7 or PSA 10-20</td>
</tr>
</tbody>
</table>
# New Biomarkers

## Who to Biopsy
- PSA
- PCA3
- PHI
- TMPRSS2-ERG
- 4K

## Who to Rebiopsy
- PCA3
- Confirm MDx
- PCMT

## Who to Watch or Treat
- OncotypeDX
- Prolaris
- Promark
- Decipher
Precision Medicine

FOR IMMEDIATE RELEASE

REPORT CALLS FOR CREATION OF A BIOMEDICAL RESEARCH AND PATIENT DATA NETWORK FOR MORE ACCURATE CLASSIFICATION OF DISEASES, MOVE TOWARD 'PRECISION MEDICINE'

WASHINGTON — A new data network that integrates emerging research on the molecular makeup of diseases with clinical data on individual patients could drive the development of a more accurate classification of disease and ultimately enhance diagnosis and treatment, says a new report from the National Research Council. The "new taxonomy" that emerges would define diseases by their underlying molecular causes and other factors in addition to their traditional physical signs and symptoms. The report adds that the new data network could also improve biomedical research by enabling scientists to access patients' information during treatment while still protecting their rights. This would allow the marriage of molecular research and clinical data at the point of care, as opposed to research information continuing to reside primarily in academia.

...link(age) of molecular data to health outcomes in order to allow more precise clinical decision making that is tailored to individual patients
Localized Primary Tumor

Genomic signatures in the primary tumor are predictive of biological potential

Time

Metastatic Disease
Conventional Pre-Treatment Models Stratify “Average” Risks at the Population Level
...But Individual Risk Varies Widely for Patients Within Each Clinical Risk Group
The Promise of Genomics

Clinical Risk Groups

- Very Low
- Low
- Intermediate

Favorable Biology
Very Low Risk

Unfavorable Biology
Intermediate Risk

INDIVIDUAL RISK
Challenges in Choosing Candidates for Active Surveillance

1. How well does Gleason grade predict true biological potential?
2. How accurately does the biopsy capture the biology of the whole prostate?
Oncotype Dx Overcomes Heterogeneity and Multifocality
Prototype GPS Stratifies Outcomes in Cleveland Clinic Development Study

AUA Low Risk

<table>
<thead>
<tr>
<th>AUA Risk Group</th>
<th>RS Group</th>
<th>Risk of Clinical Recurrence by 12 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Low</td>
<td>Low RS</td>
<td>2.2%</td>
</tr>
<tr>
<td>Low Int</td>
<td>Int RS</td>
<td>4.0%</td>
</tr>
<tr>
<td>Low High</td>
<td>High RS</td>
<td>10.3%</td>
</tr>
<tr>
<td>Low Overall</td>
<td>Overall</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

Clinical Failure = local recurrence, metastasis or death
Prototype GPS Stratifies Outcomes in Cleveland Clinic Development Study

AUA Intermediate Risk

Clinical Failure = local recurrence, metastasis or death

<table>
<thead>
<tr>
<th>AUA Risk Group</th>
<th>RS Group</th>
<th>Risk of Clinical Recurrence by 12 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Int</td>
<td>Low RS</td>
<td>2.8%</td>
</tr>
<tr>
<td>Int</td>
<td>Int RS</td>
<td>6.2%</td>
</tr>
<tr>
<td>Int</td>
<td>High RS</td>
<td>19.4%</td>
</tr>
<tr>
<td>Int</td>
<td>Overall</td>
<td>11.9%</td>
</tr>
</tbody>
</table>

RM-Corrected Estimates

RS Low (16% of pts.)
RS Int (38% of pts.)
RS High (47% of pts.)
GPS Incorporates Multiple Biologic Pathways Predictive of Prostate Cancer Aggressiveness

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

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

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

These genes predict for:
1. Metastasis & Death when measured in RP specimens
2. Dominant pattern 4 & EPE/SV/LN+ in biopsy specimens
Successful Validation of GPS: Improved Risk Discrimination with Addition of GPS to NCCN

Multivariate Analysis
NCCN p-value = 0.002
GPS p-value = 0.001

Cooperberg et al, AUA 2013
Combining Biologic & Clinical Information Refines Risk Stratification for Individual Patients

Population-Based Clinical Risk Assessment

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>VERY LOW RISK</th>
<th>LOW RISK</th>
<th>INTERMEDIATE RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% (N=37)</td>
<td>49% (N=191)</td>
<td>41% (N=160)</td>
<td></td>
</tr>
</tbody>
</table>

GPS Provides Biologic Risk Information

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>VERY LOW RISK</th>
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<th>INTERMEDIATE RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPS=8</td>
<td>84%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPS=25</td>
<td>75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPS=51</td>
<td>57%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

More Individualized Biologic and Clinical Risk Assessment

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>VERY LOW RISK</th>
<th>LOW RISK</th>
<th>INTERMEDIATE RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26% (N=100)</td>
<td>31% (N=119)</td>
<td>44% (N=169)</td>
<td></td>
</tr>
</tbody>
</table>

UCSF Validation Study

NCCN Risk Classification

- 10% Very Low-risk
- 49% Low-risk
- 41% Intermediate Risk

GPS

- Adds more accurate risk assessment by combining biological and clinical risk factors
- Predicted which patients have risk consistent with their NCCN clinical risk group
- 26% of men in the NCCN Low-risk group had more indolent biology and likelihood of favorable pathology consistent with Very Low-risk
- 10% of men in the NCCN Low-risk group had more aggressive biology and likelihood of favorable pathology consistent with Intermediate risk
- Identified patients in the NCCN Very Low-risk group who had more aggressive biology, with likelihood of favorable pathology consistent with Low and Intermediate risk disease
- Identified patients with Intermediate risk who had more indolent biology, predicted to be consistent with Low-risk disease
- Enables more accurate identification of a larger population of patients who can more confidently choose active surveillance
- Precisely identifies a patient's tumor biology and refines the population-based clinical risk assessment with a more personalized risk assessment

Cooperberg et al, AUA 2013
More Accurate Risk Discrimination Delivers Confident Decision Making

Clinical Criteria

Biologic Criteria

Actionable Information

Marker

0 100

- VERY LOW
- LOW
- INTERMEDIATE

- More favorable
- Consistent with clinical criteria
- Less favorable

ACTIVE SURVEILLANCE

IMMEDIATE TREATMENT

More Accurate Risk Discrimination Delivers Confident Decision Making
Case 1

- 53yo healthy WM
- PSA 4.38
- DRE normal Vol = 48cc (PSAD = 0.09)

1. Prostate, right, multiple needle biopsies - Benign prostatic tissue.

2. Prostate, left, multiple needle biopsies - Adenocarcinoma of the prostate, Gleason score 3+3=6, involving one out of six cores (30% of single core; 3 mm).

Meets NCCN Very Low Risk criteria
Interpretation of GPS for this clinical NCCN VERY LOW risk patient:

Likelihood of Favorable Pathology* 88% (95% CI: 75%-95%)

CONSISTENT WITH clinical criteria alone. In the expected range of NCCN VERY LOW risk.**

Freedom from High-Grade Disease (dominant Gleason pattern 4 or any pattern 5): 93% (95% CI: 82%-98%)
Freedom from Non-Organ-Con fined Disease (pathologic T3 stage): 95% (95% CI: 84%-98%)
Case 2

- 50 yo WM       Normal DRE
- PSA 4.8       PSAD 0.12
- Biopsy: 5% 1 core GI 3 + 3
  10% 1 core GI 3 + 4

Really wants Active Surveillance
Case 2

Interpretation of GPS for this clinical NCCN INTERMEDIATE\(^1\) risk patient:

- **Likelihood of Favorable Pathology**
  - **65%** (95% CI: 55%-73%)

  CONSISTENT WITH clinical criteria alone. In the expected range of NCCN INTERMEDIATE risk.**

Freedom from High-Grade Disease (dominant Gleason pattern 4 or any pattern 5):
- **85%** (95% CI: 77%-90%)

Freedom from Non-Organ-Confined Disease (pathologic T3 stage):
- **78%** (95% CI: 69%-84%)

RP Path:
- **GI 3 + 4 (35% pattern 4)**
- **1.5cm max dimension**
- Focal EPE
- Neg SV, nodes
Cases 3 & 4

Pt A: 63 yo WM
- PSA 5.7
- DRE normal
- Gleason 6, 2/12 cores
  - 40% & 60% each
- PSAD 0.12
- Med controlled BP & cholesterol

Pt B: 57 yo WM
- PSA 8.4
- DRE normal
- Gleason 6, 1/12 cores
  - 10% of core
- PSAD 0.16
- Mild LUTs on α blocker

Both meet NCCN Low Risk Criteria
Cases 3 & 4

**Patient A**
Moves from Low to Very Low risk
Likelihood of Favorable Path 81%

**Patient B**
Moves from Low to Intermediate risk
Likelihood of Favorable Path 66%

---

On Surveillance
Negative biopsy @1 yr

Radical Prostatectomy
GI 3 + 4, EPE
Case 5

- 75yo healthy Hispanic
- PSA 16 (12-14 range last sev yrs)
- DRE normal   vol = 72 cc   PSAD 0.22

FINAL DIAGNOSIS

Prostate, left mid, biopsy  
- Prostatic adenocarcinoma, Gleason score 3+4=7 in one out of two tissue fragments, involving less than 5% and less than 1 mm.  
- Perineural invasion present.

Prostate, left base, biopsy (B)  - Benign fibromuscular tissue.

Prostate, left lateral mid, biopsy (C)  - Benign prostatic tissue.

Prostate, left lateral base, biopsy (D)  - Benign prostatic tissue.

Prostate, right apex and right base, biopsies (E & F)  - Benign prostatic tissue.

Prostate, right lateral base, biopsy (G)  - Focal high-grade prostatic intraepithelial neoplasia.

Meets NCCN Intermediate Risk criteria
Interpretation of GPS for this clinical NCCN INTERMEDIATE risk patient:

Likelihood of Favorable Pathology*
50% (95% CI: 41%-59%)

CONSISTENT WITH clinical criteria alone. In the expected range of NCCN INTERMEDIATE risk.**

Freedom from High-Grade Disease (dominant Gleason pattern 4 or any pattern 5): 72% (95% CI: 63%-79%)
Freedom from Non-Organ-Confined Disease (pathologic T3 stage): 65% (95% CI: 56%-73%)

Case 5
Case 5

Gleason score: Primary 4, Secondary 4, Tertiary 3
Total Gleason Score: 8
% of 4 and/or 5: 91-100%
% of 3: 1-10% (less than 5%)

Areas of involvement: Left mid to base, lateral
Principal area of involvement: Left mid lateral
Focality: Unifocal
Proportion (percentage) of prostate involved by tumor: 10%
Greatest dimension of larger tumor nodule: 1.6 cm

Extraprostatic extension (EPE): Two foci, established
Location (specify site): Left posterolateral base
Degree of max penetration (mm): 1 mm

Seminal vesicles invasion (SVI): Not identified
Case 6

- 64yo healthy WM
- ED responds to PDE5
- PSA 11.3
- DRE normal Vol = 75cc (PSAD = 0.15)
- Bx: Gl 3+3 2/12 cores 1 & 2mm
Case 12

MR negative

RP:
GI 4+3, EPE
M, SV, N neg
How will this help manage patients?

- Initial Biopsy
  - Gene Signature “good” → Surveillance → Repeat Biopsy
    - Gene Signature “good”
  - Gene Signature “bad” → Treatment
Newly diagnosed?

Does my prostate cancer need to be treated?
# 2 Year Cost of Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active surveillance</td>
<td>$2,500</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>$17,000</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>$22,000</td>
</tr>
<tr>
<td>3-D conformal radiotherapy</td>
<td>$24,000</td>
</tr>
<tr>
<td>IMRT</td>
<td>$54,000</td>
</tr>
<tr>
<td>Proton-beam radiotherapy</td>
<td>&gt; $100,000</td>
</tr>
</tbody>
</table>

Rand Corp. NY Times 2009
QOL after Rx for Prostate Cancer

- Physical
- Fatigue
- Pain
- Incontinence
- Frequency
- Stream
- Diarrhea
- Rectal urgency
- Libido
- Impotence

Capsure Database, n = 2252
Hey! How do you know if a woman has been working at a computer?

The Men's Knot

How?
Theres "white out" on the screen!

Thppfft!

Ha! Ha!

You dumb hypocrites.
YOU MOCK THE HALF OF HUMANITY THAT MAKES YOUR GRACELESS EXISTENCE BEARABLE.
MEN SHOULD PAUSE FOR ONE MOMENT AND TAKE ANOTHER LONG HARD LOOK AT THE VERY THING THAT BRINGS MEANING TO THEIR MEANINGLESS LIVES.