Optimizing Surveillance of Low-Risk Prostate Cancer

Yates Coley, PhD
Postdoctoral Fellow
Department of Biostatistics, JHSPH
ryc@jhu.edu

October 22, 2015
Research sponsored by the Patrick C. Walsh Prostate Research Fund and PCORI Methods Grant “Bayesian Hierarchical Models for the Design and Analysis of Studies to Individualize Healthcare”
Outline

1. Motivation

2. Individualized Management of Low-Risk Prostate Cancer

3. Framework for Network of Active Surveillance Cohorts
Can we build a statistical model that integrates all the available data to inform clinical decision-making in a way that improves health outcomes in the long term?
Undiagnosed

Undx  PSA+  Bx

Diagnosed

Individualized Risk Assessment and Diagnosis

Individualized Treatment

AS  Tx
Outline

1. Motivation

2. Individualized Management of Low-Risk Prostate Cancer
   • Background
   • Statistical Model
   • Missing Data
   • Results

3. Framework for Network of Active Surveillance Cohorts
Active Surveillance of Prostate Cancer
Active Surveillance of Prostate Cancer

Key to Success:
Distinguish between indolent and lethal prostate cancer
Age (years)

PSA (ng/mL)

Reclassification

- No
- Yes

Biopsy Upgrading
Age (years) | PSA (ng/mL) | Reclassification | Biopsy Upgrading
---|---|---|---
64 | 1 | No
66 | 5 | No
68 | 10 | No
70 | 15 | No
72 | | No
Individualized Risk Assessment of Prostate Cancer

PCPTRC 2.0

**Enter Your Information**

<table>
<thead>
<tr>
<th>Race</th>
<th>Age</th>
<th>PSA Level</th>
<th>Family History of Prostate Cancer</th>
<th>Digital Rectal Examination</th>
<th>Prior Prostate Biopsy</th>
</tr>
</thead>
</table>

[Calculate Cancer Risk] [Clear Fields]

**PCPTRC 2.0 and Adjusted Risk Calculators**

- PCPTRC 2.0
- %freePSA
- Download the R Code

**PCPTRC 1.0 and Adjusted Risk Calculators**

- PCPTRC 1.0
- BMI
- PCA3
- Finasteride
- %freePSA
- [-2]proPSA
- %freePSA and [-2]proPSA
- Prostate Volume and Number of Biopsy Cores
- AUA Symptom Score
- Finasteride with Volume
- Finasteride with AUA Symptom Score
- Download the R Code


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http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp
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   - Background
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3. Framework for Network of Active Surveillance Cohorts
True Prostate Cancer State

True PSA

Random Variability

Measurement Error

Observed PSA

Biopsy Results
Latent Class

"True" Gleason score (6 vs. 7+)

True Prostate Cancer State

Random Variability

Measurement Error

True PSA

Observed PSA

Random Variability

Measurement Error

Biopsy Results

Measurement Error
Gold standard
True state observed after surgical removal

True Prostate Cancer State

Random Variability

True PSA

Measurement Error

Observed PSA

Biopsy Results

Measurement Error
Time-varying Biomarker

True Prostate Cancer State

Random Variability

Measurement Error

True PSA

Observed PSA

Time-varying Biomarker

Biopsy Results

Measurement Error
Discrete Time-to-Event

- True PSA
- Measurement Error
- Observed PSA
- Random Variability
- True Prostate Cancer Status
- Measurement Error
- Biopsy Results

Discrete Time-to-Event
True Prostate Cancer State

Biopsy Results

Observed PSA

Individual-Level Random Effects

Observed PSA

Biopsy Results

Time
With which group would this PSA trajectory be more consistent?

True Gleason 6

True Gleason 7+
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True Prostate Cancer State (Latent)

- Observed PSA
- Surgical Removal (Observe True State)
- Biopsy Results

Missing at Random
True Prostate Cancer State (Latent)

- Observed PSA
- Biopsy Results
- Surgical Removal (Observe True State)

Missing NOT at Random
True Prostate Cancer State (Latent) → Observed PSA → Surgical Removal (Observe True State)

Biopsy Results → Surgical Removal (Observe True State) → Observed PSA → True Prostate Cancer State (Latent)

Missing NOT at Random
True Prostate Cancer State (Latent)

Observed PSA

Receive Biopsy

Biopsy Results

Missing at Random
True Prostate Cancer State (Latent) → Observed PSA → Receive Biopsy → Biopsy Results → Missing NOT at Random
True Prostate Cancer State (Latent) → Observed PSA
       ↓                    ↓
Receive Biopsy          Biopsy Results

Missing NOT at Random
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   - Background
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   - Missing Data
   - Results

3. Framework for Network of Active Surveillance Cohorts
n=874

Curative Intervention n=318

Death n=19

Lost to Follow-up n=130

Active n=407
n=874

Curative Intervention n=318

Death n=19

Lost to Follow-up n=130

Active n=407

None due to Prostate Cancer
Most recent PSA or biopsy at least 2 years ago
n=874

Curative Intervention n=318

Death n=19

Lost to Follow-up n=130

Active n=407

Post-Surgery Gleason
6
7+

Final Biopsy
6
7+

66
30
17
48
(6 unknown)

Prostatectomy n=167
<table>
<thead>
<tr>
<th></th>
<th>Total Number Observations</th>
<th>Median # per patient</th>
<th>(25th, 75th)%ile # per patient</th>
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</thead>
<tbody>
<tr>
<td>PSA</td>
<td>10,425</td>
<td>10</td>
<td>(6, 16)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>2,741</td>
<td>3</td>
<td>(1, 4)</td>
</tr>
<tr>
<td>Years Follow-up (pre-RC)</td>
<td>4,980</td>
<td>5</td>
<td>(3, 8)</td>
</tr>
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- **160 Reclassifications**
  18% of patients
  <6% of all biopsies

- **67 received surgery**
  69 other treatment
  24 none
### Diagnosis

- **P(True Gleason 7+)**

  - 0%
  - 100%
  - 40%

- **Diagnosis**
  - 40%

- **5 Years Follow-up**
  - 0%
  - 100%
  - 2%

- **10 Years Follow-up**
  - 0%
  - 100%
  - 2%

### Age (years) vs. PSA (ng/mL)

- **PSA**:
  - 66, 68, 70, 72

- **Age**:
  - 64, 66, 68, 70, 72

### Probability Reclassification

- **0%**
- **25%**
- **50%**
- **75%**
- **100%**

### Biopsy Performed

- **No Biopsy**

- **All Available**

### Graphs

1. **PSA (ng/mL) vs. Age (years)**
2. **Probability Reclassification vs. Age (years)**
3. **P(Biopsy Upgrade) vs. Age (years)**
Diagnosis

5 Years Follow-up

P( Truly Gleason 7+ )

PSA (ng/mL)

Probability Reclassification

Age (years)

Biopsy Performed

No Biopsy

P ( Biopsy Upgrade )

P ( True Gleason 7+ )

P ( Lethal PCa )
I.O.P. Model
AUC = 0.75 (0.67, 0.83)

Unadjusted Model
AUC = 0.74 (0.64, 0.81)
Posterior P(Aggressive PCa)

Observed P(Aggressive PCa)

Patient with Gleason 7+
on post-surgery analysis

Patient with Gleason = 6
on post-surgery analysis

Observed Proportion with True Gleason 7+

Posterior P(True Gleason 7+)
Active Surveillance of Low-Risk Prostate Cancer - Decision Support Tool

Probability of Aggressive Prostate Cancer

Likely PSA Trajectory

Future Risk of Reclassification

Predictions given submitted data: probability of aggressive prostate cancer (top), PSA trajectory (bottom left), and risk of grade reclassification on future biopsy (bottom right)

https://rycoley.shinyapps.io/dynamic-prostate-surveillance
Dynamic Prediction Model

- Real-time predictions of cancer state for new patients
- Real-time updates of predictions for existing patients
- Can incorporate new scientific knowledge, biomarkers
- Over time, improve understanding of disease in the population by continuously updating model.
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   • Extensions in Single-Cohort Model
   • Extension to Multi-Cohort Model
Probability of True Gleason 7+ in Johns Hopkins AS Cohort
P(True Gleason 7+ in JH AS Cohort) = 20%
P(True Gleason 7+ in JH AS Cohort) = 20%
P(True Gleason 7+ in JH AS Cohort) = 20%
P(True Gleason 7+ in JH AS Cohort) = 20%

Are some patients (with similar PSA and biopsies) more likely to have a true Gleason 7+?
Regression Model for Patient-Specific Probability of True Gleason 7+
Patient’s probability of True Gleason 7+ may depend on:

- Genetic, biomarker
- Family History
- Race
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   • Extensions in Single-Cohort Model
   • Extension to Multi-Cohort Model
Separate modeling approach:
• No information shared across sites
• No sense of generalizability
Comparing JHMI and PASS Cohorts

1. Underlying Risk
2. Inclusion Criteria
3. Biopsy and PSA protocols
4. Reclassification criteria
5. Drop-out to treatment
Comparing JHMI and PASS Cohorts

Inoue and Etzioni (2015?)
Comparing JHMI and PASS Cohorts

1. Underlying Risk

2. Inclusion Criteria

3. Biopsy and PSA protocols

4. Reclassification criteria

5. Drop-out to treatment
Comparing JHMI and PASS Cohorts

1. Underlying Risk  
2. Inclusion Criteria
3. Biopsy and PSA protocols
4. Reclassification criteria
5. Drop-out to treatment

Do differences persist?
Comparing JHMI and PASS Cohorts

1. Underlying Risk
   Do differences persist?

2. Inclusion Criteria
   Why does it matter?

3. Biopsy and PSA protocols

4. Reclassification criteria

5. Drop-out to treatment
Probability Distribution over Proportion of Cohort with True Gleason Score 7+

Johns Hopkins Active Surveillance

CANARY PASS
Proportion of Cohort with True Gleason 7+
Proportion of Cohort with True Gleason 7+

Johns Hopkins Active Surveillance
Proportion of Cohort with True Gleason 7+
Johns Hopkins Active Surveillance

PROMISS

...
Proportion of Cohort with True Gleason 7+
Do cohorts with a lower proportion of true Gleason 7+ have characteristics in common?
Regression Model for Cohort-Specific Proportion of True Gleason 7+
Regression Model for Cohort-Specific Proportion of True Gleason 7+

Cohort’s expected proportion of True Gleason 7+ may depend on:
- Enrollment criteria
- Patient population
- Unobserved heterogeneity
Cohort-Specific Regression Model

Johns Hopkins Active Surveillance

CANARY PASS

...
Cohort-Specific Regression Model

Johns Hopkins Active Surveillance

CANARY PASS

Patient-Specific Regression Model
Cohort-specific effects can also be used for:

- Probability of performing a biopsy
- Sensitivity and specificity of biopsy Gleason scores
- Probability of prostatectomy
inelligent use of health information to individualize and integrate health care

http://hopkinsinhealth.jhu.edu/
Bayes Theorem

\[ P(\text{Hypothesis} \mid \text{Data}) = \frac{P(\text{Data} \mid \text{Hypothesis}) \times P(\text{Hypothesis})}{P(\text{Data})} \]
Bayes Theorem

\[
P(\text{Hypothesis} \mid \text{Data}) = \frac{P(\text{Data} \mid \text{Hypothesis}) \times P(\text{Hypothesis})}{P(\text{Data})}
\]

How probable is it that an individual has Gleason 7+ given their observed PSA and biopsy results?
Bayes Theorem

\[ P(\text{Hypothesis} | \text{Data}) = \frac{P(\text{Data} | \text{Hypothesis}) \times P(\text{Hypothesis})}{P(\text{Data})} \]

How probable is it that an individual has Gleason 7+ given their observed PSA and biopsy results?

Would we expect to see these PSA and biopsy results if an individual had Gleason 7+ CaP?