Precision Medicine, Learning Health Systems, and Improving Surveillance of Low-Risk Prostate Cancer

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Outline

1. What is Precision Medicine?

2. Individualized Management of Low-Risk Prostate Cancer

3. Toward a Learning Health System
1. Given my personal characteristics, conditions, and preferences, what should I expect will happen to me?

2. What are my options, and what are the benefits and harms of those options?

3. What can I do to improve the outcomes that are most important to me?

4. How can the health care system improve my chances of achieving the outcomes that I prefer?

(Washington and Lipstein *NEJM* 2011)
ONE-SIZE FITS ALL
STORE
SALE
Outline

1. What is Precision Medicine?

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

3. Toward a Learning Health System
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)

64
66
68
70
72

Reclassification

No
Yes

Biopsy Upgrading

No
Yes
Age (years) vs. PSA (ng/mL) relationship. The data points indicate a trend where PSA levels increase with age, peaking around 68 years. The inset image shows a blood sample, possibly related to the PSA testing context.
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True Prostate Cancer State

Random Variability

True PSA

Measurement Error

Observed PSA

Biopsy Results

Measurement Error
Latent Class

“True” Gleason score (6 vs. 7+)

True Prostate Cancer State

Random Variability

True PSA

Measurement Error

Observed PSA

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

True PSA

Measurement Error

Observed PSA

Measurement Error

Biopsy Results

Time-varying Biomarker
Discrete Time-to-Event

True Prostate Cancer Status

Random Variability

True PSA

Measurement Error

Observed PSA

Measurement Error

Biopsy Results

Discrete Time-to-Event
True Prostate Cancer State

Biopsy Results

Observed PSA

Individual-Level Random Effects

Biopsy Results

Observed PSA

Observed PSA

Biopsy Results

Time
With which group would this PSA trajectory be more consistent?
True Prostate Cancer State

Biopsy Results

Biopsy Results

Time
\[ L_i \propto P(\text{Cancer State}_i) \]

\[ \times f(\text{PSA}_i | X_i, Z_i, \text{Random Effects}_i) \cdot g(\text{Random Effects}_i | \text{Cancer State}_i) \]

\[ \times \prod_j P(\text{Biopsy Upgrade}_{ij} | W_{ij}, \text{Cancer State}_i) \]
\[ L_i \propto P(\text{Cancer State}_i) \]

\[ \times f(\text{PSA}_i \mid X_i, Z_i, \text{Random Effects}_i) g(\text{Random Effects}_i \mid \text{Cancer State}_i) \]

\[ \times \prod_j P(\text{Biopsy Upgrade}_{ij} \mid W_{ij}, \text{Cancer State}_i) \]

**Pooled Logistic Regression**
We then proceed as above to get a re-weighted posterior for the latent variables of patient $k$.

\[
L_i \propto P(\text{Cancer State}_i) \\
\times f(\text{PSA}_i | X_i, Z_i, \text{Random Effects}_i) g(\text{Random Effects}_i | \text{Cancer State}_i) \\
\times \prod_j P(\text{Biopsy Upgrade}_{ij} | W_{ij}, \text{Cancer State}_i)
\]
We then proceed as above to get a re-weighted posterior for the latent variables of patient $k$.

$$L_i \propto P(\text{Cancer State}_i)$$

$$\times f(\text{PSA}_i \mid X_i, Z_i, \text{Random Effects}_i) \times g(\text{Random Effects}_i \mid \text{Cancer State}_i)$$

$$\times \prod_j P(\text{Biopsy Upgrade}_{ij} \mid W_{ij}, \text{Cancer State}_i)$$

Partially-latent class
We then proceed as above to get a re-weighted posterior for the latent variables of patient $k$.

**Partially-latent class**

\[
L_i \propto P(\text{Cancer State}_i) \times f(\text{PSA}_i | X_i, Z_i, \text{Random Effects}_i) \times g(\text{Random Effects}_i | \text{Cancer State}_i) \times \prod_j P(\text{Biopsy Upgrade}_{ij} | W_{ij}, \text{Cancer State}_i)
\]

**Bayesian Estimation:**

Posterior Probability of True Gleason 7+
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True Prostate Cancer State (Latent)

- Observed PSA

- Biopsy Results
True Prostate Cancer State (Latent) → Observed PSA → Surgical Removal (Observe True State) → Biopsy Results → Missing at Random
True Prostate Cancer State (Latent)

Observed PSA

Surgical Removal (Observe True State)

Biopsy Results

Missing NOT at Random
$L_i \propto P(\text{Cancer State}_i)\times f(\text{PSA}_i | X_i, Z_i, \text{Random Effects}_i)g(\text{Random Effects}_i | \text{Cancer State}_i)\times \prod_j P(\text{Biopsy Upgrade}_{ij} | W_{ij}, \text{Cancer State}_i)\times P(\text{Surgery}_{ij} | \text{History}_{ij}, W_{ij}, \text{Cancer State}_i)$

Pooled Logistic Regression
True Prostate Cancer State (Latent) → Observed PSA → Biopsy Results
True Prostate Cancer State (Latent) → Observed PSA → Receive Biopsy → Biopsy Results

Missing NOT at Random
\[ L_i \propto P(\text{Cancer State}_i) \]

\[ \times f(\text{PSA}_i | X_i, Z_i, \text{Random Effects}_i) g(\text{Random Effects}_i | \text{Cancer State}_i) \]

\[ \times \prod_j P(\text{Biopsy Here}_{ij} | \text{History}_{ij}, W_{ij}, \text{Cancer State}_i) \]

\[ \times P(\text{Biopsy Upgrade}_{ij} | \text{Biopsy Here}_{ij}, W_{ij}, \text{Cancer State}_i) \]

\[ \times P(\text{Surgery}_{ij} | \text{History}_{ij}, W_{ij}, \text{Cancer State}_i) \]
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n=874

Curative Intervention n=318

Death n=19

Lost to Follow-up n=130

Active n=407

Other Intervention n=151

Prostatectomy n=167
n=874

Curative Intervention n=318

Death n=19

Lost to Follow-up n=130

Active n=407

Prostatectomy n=167

Final Biopsy

<table>
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<tr>
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<th>6</th>
<th>7+</th>
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<tbody>
<tr>
<td>Post-Surgery Gleason</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>30</td>
</tr>
<tr>
<td>7+</td>
<td>17</td>
<td>48</td>
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</table>

(6 unknown)
<table>
<thead>
<tr>
<th></th>
<th>Total Number Observations</th>
<th>Median # per patient</th>
<th>IQR # per patient</th>
</tr>
</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

5 Years Follow-up

- P(True Gleason 7+)
- PSA (ng/mL)
- Probability Reclassification
- Biopsy Performed
- No Biopsy

- P(Biopsy Upgrade)
- P(Lethal PCa)

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

0.0 0.2 0.4 0.6 0.8 1.0

Patient with Gleason 7+
on post-surgery analysis

Observed Proportion with True Gleason 7+

Posterior P(True Gleason 7+)

Patient with Gleason = 6
on post-surgery analysis
Active Surveillance of Low-Risk Prostate Cancer - Decision Support Tool

Diagnosis

PSA 4
Age 60
Year 1
PSA 5
Biopsy No Grade Reclassification
Year 2
PSA 6
Biopsy No Biopsy
Year 3
PSA 5
Biopsy No Biopsy

Submit

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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   • Definition
   • Extensions in Single-Cohort Model
   • Extension to Multi-Cohort Model
   • Opportunities for Data Scientists
Learning Health Systems

“A learning health care system is one in which science, information, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the care process, patients and family active participants in all elements, and new knowledge captured as an integral by-product of the care experience.”
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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

Regression Model for Patient-Specific Probability of True Gleason 7+
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Network of Active Surveillance Cohorts

Johns Hopkins Active Surveillance

CANARY PASS
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+
Network of Active Surveillance Cohorts

Johns Hopkins Active Surveillance

CANARY PASS
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

Cohort-Specific Regression Model

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
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Challenges to Creating Learning Health Systems:

- Informed consent framework
- Privacy guarantees
- Network interoperability
- Data infrastructure
- Data standardization
- Statistical methods
- Culture shift within and across institutions to promote transparency, communication, collaboration
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”
Hopkins inHealth

intelligent use of health information to individualize and integrate health care

http://hopkinsinhealth.jhu.edu/