Optimizing Surveillance of Low-Risk Prostate Cancer: An Application of Precision Medicine and Learning Health Systems at Johns Hopkins

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Outline

1. Patient-Centered Medicine

2. Individualized Management of Low-Risk Prostate Cancer

3. Learning Health Systems
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?
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. Patient-Centered Medicine

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

3. Learning Health Systems
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

Graph showing the relationship between PSA levels and age.
Age (years)

PSA (ng/mL)

Reclassification

- Yes
- No

Biopsy Upgrading
Age (years)

PSA (ng/mL)

64
66
68
70
72

Yes

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Biopsy Upgrading

Reclassification

No

Yes
Age (years)

PSA (ng/mL)

Reclassification

No

Yes

Biopsy Upgrading

No

Yes

10

64

66

68

70

72
1. Patient-Centered Medicine

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3. Learning Health Systems
True Prostate Cancer State → True PSA → Observed PSA

Random Variability → True PSA

Measurement Error → Observed PSA

Measurement Error → Biopsy Results

Biopsy Results → Measurement Error

Measurement Error → True PSA
Latent Class

“True” Gleason score (6 vs. 7+)

True Prostate Cancer State

Random Variability

True PSA

Measurement Error

Observed PSA

Measurement Error

Biopsy Results

Random Variability

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

Biopsy Results

Measurement Error

Time-varying Biomarker
Discrete Time-to-Event

True Prostate Cancer Status

Random Variability

True PSA

Measurement Error

Observed PSA

Biopsy Results

Measurement Error

Discrete Time-to-Event
True Prostate Cancer State

Individual-Level Random Effects

Observed PSA

Biopsy Results

Biopsy Results

Observed PSA

Observed PSA

Time
True Prostate Cancer State

Observed PSA

Observed PSA

Observed PSA

Biopsy Results

Biopsy Results

Individual-Level Random Effects

Time
**True Gleason 6**

**True Gleason 7+**

The graphs illustrate the relationship between age and PSA levels, with a focus on the incidence of biopsy upgrades and reclassification. The data points suggest a trend where PSA levels and biopsy upgrade frequency increase with age, particularly noticeable in the True Gleason 7+ category.
With which group would this PSA trajectory be more consistent?
True Prostate Cancer State

Observed PSA

Biopsy Results

Linear Mixed Effects Model

Individual-Level Random Effects

Observed PSA

Time
Pooled Logistic Regression

Observed PSA

Observed PSA

Biopsy Results

Biopsy Results

True Prostate Cancer State

Time
Bayes Theorem

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

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

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

How probable is it that an individual has Gleason 7+ given their observed PSA and biopsy results?
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   • Background
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True Prostate Cancer State (Latent)

Observed PSA

Surgical Removal (Observe True State)

Biopsy Results

Missing at Random

(Rubin 1976; Little and Rubin 2014)
True Prostate Cancer State (Latent)

Observed PSA

Surgical Removal (Observe True State)

Biopsy Results

Missing NOT at Random

(Rubin 1976; Little and Rubin 2014)
True Prostate Cancer State (Latent)

Observed PSA

Surgical Removal (Observe True State)

Biopsy Results

Pr (Surgical Removal = 1 | Time, Age, PSA, Previous Biopsy Results, Cancer State)

(Rubin 1976; Little and Rubin 2014)
True Prostate Cancer State (Latent) → Observed PSA → Receive Biopsy → Biopsy Results

Missing at Random

(Rubin 1976; Little and Rubin 2014)
True Prostate Cancer State (Latent) → Observed PSA → Receive Biopsy → Biopsy Results

Missing NOT at Random

(Rubin 1976; Little and Rubin 2014)
Pr (Biopsy Performed = 1 | Time, Age, PSA, Previous Biopsy Results, Cancer State)

(Rubin 1976; Little and Rubin 2014)
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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
n=874

- Curative Intervention n=318
- Death n=19
- Lost to Follow-up n=130
- Active n=407

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
Other Intervention n=151
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>
</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
Probability Reclassification

P(Gleason 7+)

0% 25% 75% 100%

Age (years)

PSA (ng/mL)

0% 25% 50% 100%

Probability Reclassification

PSA (ng/mL)

0% 25% 50% 75% 100%

Age (years)

Biopsy Performed

Biopsy Upgraded

No Biopsy

Probability Reclassification

P(Biopsy Upgrade)

0% 25% 50% 75% 100%

Age (years)

Biopsy Performed

No Biopsy

Probability Reclassification

PSA (ng/mL)

0% 25% 50% 75% 100%

Age (years)
Diagnosis

P(True Gleason 7+)

Age (years)

PSA (ng/mL)

P(Biopsy Upgrade)

P(Lethal PCa)

P(True Gleason 7+)

Age (years)
Diagnosis

5 Years Follow-up

Age (years)

PSA (ng/mL)

P(Gleason 7+)

P(Biopsy Upgrade)

P(True Gleason 7+)

P(Lethal PCa)
Adjusted for Informative Missingness
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

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
- Over time, improve understanding of disease in the population by continuously updating model.
- Can incorporate new scientific knowledge, biomarkers
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Learning Health Systems

- “Science, information, incentives, and culture are aligned for continuous improvement and innovation”
- “Best practices seamlessly embedded in the care process”
- “Patients and families are active participants in all elements”
- “New knowledge captured as an integral by-product of the care experience”
In a learning health care system, research influences practice and practice influences research.
Dynamic Prediction Model

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Hopkins in Health

intelligent use of health information to individualize and integrate health care

http://hopkinsinhealth.jhu.edu/
Papers
