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

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

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Outline

1. What is Precision Medicine?

2. Individualized Management of Low-Risk Prostate Cancer

3. Local and Multi-Cohort Implementation
Goal: Develop statistical framework to integrate all available data to inform clinical decision-making in a way that improves health outcomes.
Statistical Challenges in Precision Medicine
Statistical Challenges in Precision Medicine

• Variability
Statistical Challenges in Precision Medicine

• Variability

• Latent Health State Prediction
Statistical Challenges in Precision Medicine

• Variability
• Latent Health State Prediction
• Missing Data
Statistical Challenges in Precision Medicine

- Variability
- Latent Health State Prediction
- Missing Data
- Data Visualization
Statistical Challenges in Precision Medicine

- Variability
- Latent Health State Prediction
- Missing Data
- Data Visualization
- Real-time Analysis
Outline

1. What is Precision Medicine?

2. Individualized Management of Low-Risk Prostate Cancer
   • Clinical Motivation
   • Statistical Model
   • Informative Missing Data Patterns
   • Results

3. Local and Multi-Cohort Implementation
Active Surveillance of Prostate Cancer
Active Surveillance of Prostate Cancer

• Many prostate tumors are indolent
Active Surveillance of Prostate Cancer

• Many prostate tumors are indolent
• Risk of permanent side effects with surgery, radiation therapy
Active Surveillance of Prostate Cancer

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• AS is alternative to treatment
Active Surveillance of Prostate Cancer

- Many prostate tumors are indolent
- Risk of permanent side effects with surgery, radiation therapy
- AS is alternative to treatment
- Key to success: Correctly differentiate between aggressive and indolent tumors
PSA (Every 6-12 Months)
PSA (Every 6-12 Months)

- **PSA (ng/mL)**
- **Age (years)**

The graph shows the PSA levels (in ng/mL) for different ages (in years) from 63 to 67. The trend indicates a general decrease in PSA levels with age.
Prostate Biopsy (Annually)

Age (years)

Biopsy Gleason

Biopsy Upgrade
Prostate Biopsy (Annually)

- **Cancer**
- **Normal tissue**

**Age (years)**
- 63
- 64
- 65
- 66
- 67
- 68
- 69
- 70

**Biopsy Upgrade**
- 6
- 7+

**Biopsy Gleason**
- 6
Age (years) vs. PSA (ng/mL)

Biopsy Upgrade

Biopsy Gleason 7+

No

Yes
## Individualized Risk Assessment of Prostate Cancer

**PCPTRC 2.0**

### Enter Your Information

<table>
<thead>
<tr>
<th>Information</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
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<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>PSA Level</td>
<td>ng/ml</td>
</tr>
<tr>
<td>Family History of Prostate Cancer</td>
<td></td>
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<tr>
<td>Digital Rectal Examination</td>
<td></td>
</tr>
<tr>
<td>Prior Prostate Biopsy</td>
<td></td>
</tr>
</tbody>
</table>

### 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/uroriskcalc.jsp
Individually Decision Support for JH AS Patients
Individualized Decision Support for JH AS Patients

• Predict true state, not biopsy result
Individualized Decision Support for JH AS Patients

• Predict true state, not biopsy result
Individualized Decision Support for JH AS Patients

• Predict true state, not biopsy result

• Continuously update model estimates as new patient data is observed
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True Prostate Cancer State

Biologic Variability

True PSA

Measurement Error

Observed PSA

Biopsy Results

Measurement Error
Latent Class

“True” Gleason score (6 vs. 7+)

True Prostate Cancer State

Biologic Variability

True PSA

Measurement Error

Observed PSA

Biopsy Results

Measurement Error
True Prostate Cancer State

Biologic Variability

Measurement Error

Partially-Latent

Observed after surgical removal

True PSA

Observed PSA

Measurement Error

Biopsy Results
Time-varying Biomarker

True Prostate Cancer State

True PSA

Measurement Error

Observed PSA

Biopsy Results

Measurement Error

Biologic Variability
Biologic Variability

True PSA

Measurement Error

Observed PSA

Receive Biopsy

Biopsy Results

Measurement Error

Constant Assumption for Identifiability

True Prostate Cancer State
Why a time constant cancer state?

Inoue et al. (2014) *Statistics in Medicine*
Why a time constant cancer state?

• True state observed at most once

Inoue et al. (2014) *Statistics in Medicine*
Why a time constant cancer state?

• True state observed at most once
• Data insufficient to model both grade progression and misclassification

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- 65-70% upgrading from misclassification

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- Data insufficient to model both grade progression and misclassification
- 65-70% upgrading from misclassification
- Rate of progression sensitive to priors

Inoue et al. (2014) *Statistics in Medicine*
Why a time constant cancer state?

- True state observed at most once
- Data insufficient to model both grade progression and misclassification
- 65-70% upgrading from misclassification
- Rate of progression sensitive to priors
- Modified interpretation of true state

Inoue et al. (2014) Statistics in Medicine
Likelihood
Likelihood

Cancer State
Likelihood

Cancer State

PSA | Covariates, Individual Effects

Individual Effects | Cancer State
Likelihood

Cancer State

PSA | Covariates, Individual Effects

Individual Effects | Cancer State

\[ \prod \text{years} \]

Receive Bx | Covariates, Past PSA and Bx

Bx Gleason | Bx Received, Covariates, Cancer State

Bx: Biopsy
Bayesian Estimation:
Posterior Probability of True Gleason 7+

Cancer State

PSA | Covariates, Individual Effects

Individual Effects | Cancer State

Receive Bx | Covariates, Past PSA and Bx

Bx Gleason | Bx Received, Covariates, Cancer State

Bx: Biopsy
Likelihood

Cancer State

PSA | Covariates, Individual Effects

Individual Effects | Cancer State

\[ \prod \text{Receive Bx} | \text{Covariates, Past PSA and Bx} \]

\[ \text{Bx Gleason} | \text{Bx Received, Covariates, Cancer State} \]

Similar to Joint Latent Class Model of Lin et al. (2002) *JASA*
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Biologic Variability

Measurement Error

True PSA

Observed PSA

Receive Biopsy

Biopsy Results

Missing NOT At Random

PSA Measurement Error

Receive Biopsy Missing NOT At Random

27
Likelihood

Cancer State

PSA | Covariates, Individual Effects

Individual Effects | Cancer State

\[ \prod \text{years} \]

Receive Bx | Covariates, Past PSA and Bx, Cancer State

Bx Gleason | Bx Received, Covariates, Cancer State

Bx: Biopsy
True Prostate Cancer State

True PSA

Biologic Variability

Measurement Error

Observed PSA

Surgical Removal (Observe True State)

Biopsy Results

Measurement Error
True Prostate Cancer State

True PSA

Biologic Variability

Measurement Error

Observed PSA

Surgical Removal (Observe True State)

Biopsy Results

Measurement Error
Prostate Cancer

True PSA

Observed PSA

Surgical Removal (Observe True State)

Missing NOT At Random

Biopsy Results

Measurement Error

True Prostate Cancer State

Biologic Variability

Measurement Error

29
Likelihood

Receive Bx | Covariates, Past PSA and Bx, Cancer State

Surgery | Covariates, Past PSA and Bx, Cancer State

Bx: Biopsy
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3. Local and Multi-Cohort Implementation
<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</td>
<td>4,980</td>
<td>5</td>
<td>(3, 8)</td>
</tr>
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- **160 Biopsy Upgrades**: 18% of patients <6% of all biopsies
- **67 received surgery**: 69 other treatment 24 none
Post-Surgery Gleason

<table>
<thead>
<tr>
<th>Biopsy Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-surgery Gleason</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7+</td>
</tr>
</tbody>
</table>

(6 unknown)
### Post-Surgery Gleason

<table>
<thead>
<tr>
<th>Pre-surgery Biopsy Gleason</th>
<th>Post-Surgery Gleason</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>66 (69%)</td>
</tr>
<tr>
<td></td>
<td>30 (31%)</td>
</tr>
<tr>
<td>7+</td>
<td>17 (26%)</td>
</tr>
<tr>
<td></td>
<td>48 (74%)</td>
</tr>
</tbody>
</table>

**Sensitivity:**
- 50%  
- 62%  
- 72%

**Specificity:**
- 71%  
- 80%  
- 88%
Specificity = 86% (77.93%) at Sensitivity = 62%

AUC = 0.67 0.75 0.83
Specificity = 77% 86% 93% at Sensitivity = 62%

AUC = 0.67 0.75 0.83

True Positive Rate

False Positive Rate

Last Biopsy
Observed Fraction Gleason ≥ 7 on post-surgical analysis

Observed P(Aggressive PCa)

Posterior P(Aggressive PCa)

Observed P(Aggressive Prostate Cancer)

Posterior P(Gleason ≥ 7)

Patient with Gleason ≥ 7 on post-surgical analysis

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

Predicted True Prostate Cancer State

Gleason 6

Likely PSA Trajectory

Future Risk of Grade Reclassification

Predictions given submitted data: probability of true Gleason Score (top), PSA trajectory (bottom left), and risk of grade reclassification on future biopsy (bottom right).

This tool is designed for men with lower risk prostate cancer diagnoses who choose Active Surveillance (AS) instead of early treatment. In AS, serial PSA measurements and repeated biopsies are used to monitor disease state. Treatment is typically recommended after grade reclassification on biopsy, i.e., a biopsy with a Gleason score of 7 or higher. Here, we use PSA and biopsy measurements to predict a patient’s true underlying cancer state—what would be observed if he were to have his prostate surgically removed. We draw a distinction between Gleason scores of 3+4 and 4+3 but combine Gleason scores of 8-10. (Few patients in AS have Gleason scores above 7.)

We also provide predictions of a patient’s anticipated PSA trajectory and risk of grade reclassification to inform expectations and decision-making. For example, patients and clinicians may decide to delay future biopsies if the likelihood of reclassification is low. Alternatively, clinicians may recommend a biopsy if future PSA values exceed what was expected. Darker shading in prediction intervals above indicate more likely values.

https://rycoley.shinyapps.io/dynamic-prostate-surveillance

https://github.com/aaronjfisher/in-clinic-updates-PSA
Coley et al. (2016) arXiv:1508.07511
“A Bayesian Hierarchical Model for Prediction of Latent Health States from Multiple Data Sources with Application to Active Surveillance of Prostate Cancer”

rycoley/prediction-prostate-surveillance
1. What is Precision Medicine?

2. Individualized Management of Low-Risk Prostate Cancer

3. Local and Multi-Cohort Implementation
• Assessment plan for outcomes and attitudes
• Assessment plan for outcomes and attitudes
• Real-time predictions for new patients, updates for existing patients
• Assessment plan for outcomes and attitudes
• Real-time predictions for new patients, updates for existing patients
• Over time, improve understanding of disease in patient population by continuously updating model
• Assessment plan for outcomes and attitudes
• Real-time predictions for new patients, updates for existing patients
• Over time, improve understanding of disease in patient population by continuously updating model
• Can incorporate new scientific knowledge, biomarkers
OSLER inHealth
(Open Source Learning Environment in R)

- Latent health state to predict
  - Constant and time-varying
  - Uni- and multivariate
  - Binary, categorical, ordered
- Multiple clinical data sources
- Interventions, treatment
- Informative missing data
Heterogeneity in Risk in HIV prevention

- Van Damme et al. 2012
- Thigpen et al. 2012
- Marrazzo et al. 2013
- Baeten et al. 2012
- Abdool Karim et al. 2011
- Abdool Karim et al. 2010

- TDF gel
- TDF
- TDF–FTC
- BufferGel
- 0.5% PRO 2000 gel

Estimated Effectiveness
Some Subjects at Risk

Cox Model Estimate of Effectiveness

Effectiveness=0, Null Hyp.

True Effectiveness=0.5

Var=1/2

Var=1

Var=5

P(No Risk)

8%

29%

78%

Effectiveness=0, Null Hyp.
HPTN 035: 0.5% PRO 2000 Gel
(Abdool Karim et al. (2011))

Effectiveness (95% CI)

Cox Model
0.27 (-0.12, 0.52)

Compound Poisson Frailty Model
0.37 (-0.05, 0.63)

Coley and Brown (2016) Statistics in Medicine
Thank you!
Questions?

**Yates Coley**, PhD
Postdoctoral Fellow
Department of Biostatistics, JHSPH
ryc@jhu.edu
rycoley.com
Observed Rate of Outcome
Posterior Probability of Outcome
Observed Cancer State
- Aggressive (Gleason ≥ 7)
- Indolent (Gleason = 6)
- Unobserved/No Surgery