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. 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

• Heterogeneity
Statistical Challenges in Precision Medicine

• Heterogeneity

• Latent Health State Prediction
Statistical Challenges in Precision Medicine

• Heterogeneity
• Latent Health State Prediction
• Integrate Multiple Data Sources
Statistical Challenges in Precision Medicine

- Heterogeneity
- Latent Health State Prediction
- Integrate Multiple Data Sources
- Informative Missing Data Patterns
Statistical Challenges in Precision Medicine

• Heterogeneity
• Latent Health State Prediction
• Integrate Multiple Data Sources
• Informative Missing Data Patterns
• Data Visualization
Statistical Challenges in Precision Medicine

- Heterogeneity
- Latent Health State Prediction
- Integrate Multiple Data Sources
- Informative Missing Data Patterns
- 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

• Majority of prostate tumors are indolent
Active Surveillance of Prostate Cancer

- Majority of prostate tumors are indolent
- Risk of permanent, significant 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

• Majority of prostate tumors are indolent
• Risk of permanent, significant 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)

Age (years) vs. PSA (ng/mL)
PSA (Every 6-12 Months)

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

- PSA levels are plotted against age.
- PSA levels are measured every 6-12 months.
- The graph shows a trend in PSA levels over the years.

[Graph showing PSA levels over ages 63 to 67]
Prostate Biopsy (Annually)

![Graph showing prostate biopsy information]

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

- **PSA (ng/mL)**

- **Biopsy Upgrade**
  - 6
  - 7+

- **Biopsy Gleason**
  - 10

*Prostate Biopsy (Annually)*
Prostate Biopsy (Annually)

- Cancer
- Normal tissue

Age (years)

PSA (ng/mL)

Biopsy Upgrade

Biopsy Gleason

6

7+
Individualized Risk Assessment of Prostate Cancer
PCPTRC 2.0

Enter Your Information

Race
Age
PSA Level
Family History of Prostate Cancer
Digital Rectal Examination
Prior Prostate Biopsy

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


http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp
Individualized 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
- Continuously update model estimates as new patient data are observed
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3. Local and Multi-Cohort Implementation
True Prostate Cancer State

True PSA

Measurement Error

Observed PSA

Biopsy Results

Measurement Error

Biologic Variability
Latent Class

“True” Gleason score (6 vs. 7+)

True Prostate Cancer State

True PSA

Measurement Error

Observed PSA

Measurement Error

Biopsy Results

Biologic Variability
True Prostate Cancer State

Biologic Variability

Measurement Error

True PSA

Observed PSA

Partially-Latent Observed after surgical removal

Biopsy Results
Time-varying Biomarker

Biologic Variability

True PSA

Measurement Error

Observed PSA

True Prostate Cancer State

Measurement Error

Biopsy Results

Measurement Error

Time-varying Biomarker
True Prostate Cancer State

Biologic Variability

Measurement Error

True PSA

Observed PSA

Measurement Error

Binary Outcome

Biopsy Results
Biologic Variability

True PSA

Measurement Error

Observed PSA

Receive Biopsy

Biopsy Results

Measurement Error

True Prostate Cancer State
True Prostate Cancer State

Biologic Variability

Measurement Error

Biologic Variability

Measurement Error

True PSA

Observed PSA

Receive Biopsy

Biopsy Results

Constant Assumption for Identifiability
Likelihood
Likelihood

Cancer State
Likelihood

Cancer State

Individual Effects | Cancer State

PSA | Covariates, Individual Effects
Likelihood

Cancer State

Individual Effects | Cancer State

PSA | Covariates, Individual Effects

\( \prod \text{years} \)

Receive Bx | Covariates, Past PSA and Bx

Bx Gleason | Bx Received, Covariates, Cancer State

Bx: Biopsy
Likelihood

Bayesian Estimation:
Posterior Probability of True Gleason 7+

Cancer State

Individual Effects | Cancer State

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Bx Gleason | Bx Received, Covariates, Cancer State

Bx: Biopsy
Likelihood

Cancer State

Individual Effects | Cancer State

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

Bx: Biopsy
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   • Results

3. Local and Multi-Cohort Implementation
Measurement Error

Biologic Variability

True PSA

Observed PSA

Receive Biopsy

Biopsy Results

Measurement Error

True Prostate Cancer State
Measurement Error

Observed PSA

Receive Biopsy

Biopsy Results

Missing NOT At Random

True Prostate Cancer State

True PSA

Biologic Variability

PSA Measurement Error

Receive Biopsy

Missing NOT At Random
Likelihood

Cancer State

Individual Effects | Cancer State

PSA | Covariates, Individual Effects

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

Bx Gleason | Bx Received, Covariates, Cancer State

Bx: Biopsy
Prostate Cancer

True Prostate Cancer State

Biologic Variability

True PSA

Measurement Error

Observed PSA

Surgical Removal (Observe True State)

Measurement Error

Biopsy Results
True Prostate Cancer State

Biologic Variability

True PSA

Measurement Error

Observed PSA

Surgical Removal (Observe True State)

Measurement Error

Biopsy Results
True Prostate Cancer State

True PSA

Observed PSA

Measurement Error

Surgical Removal (Observe True State)

Biopsy Results

Missing NOT At Random

Measurement Error

Biologic Variability
Likelihood

- Cancer State
- Individual Effects | Cancer State
- PSA | Covariates, Individual Effects
- Receive Bx | Covariates, Past PSA and Bx, Cancer State
- Bx Gleason | Bx Received, Covariates, Cancer State
- Surgery | Covariates, Past PSA and Bx, Cancer State
Outline

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   - Results

3. Local and Multi-Cohort Implementation
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</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
<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>6</td>
<td>30 (31%)</td>
</tr>
<tr>
<td>7+</td>
<td>17 (26%)</td>
</tr>
<tr>
<td>7+</td>
<td>48 (74%)</td>
</tr>
</tbody>
</table>

(6 unknown)
### Pre-surgery Biopsy Results

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### Post-Surgery Gleason

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<tr>
<th>True Cancer State</th>
<th>6</th>
<th>7+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity = 50%</td>
<td>62%</td>
<td>72%</td>
</tr>
<tr>
<td>Specificity = 71%</td>
<td>80%</td>
<td>88%</td>
</tr>
</tbody>
</table>
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

Last Biopsy
Patient with Gleason ≥7 on post-surgical analysis

Patient with Gleason = 6 on post-surgical analysis
Probability of True Gleason 7+:
6%

Projected PSA Trajectory

Risk of Biopsy Gleason 7+

Biopsy Upgrade:
No
Yes
6
7+
https://rycoley.shinyapps.io/dynamic-prostate-surveillance
Active Surveillance of Low-Risk Prostate Cancer - Decision Support Tool

Predicted True Prostate Cancer State

58.8%  23.8%  9%  8.4%

Gleason 6  3+4  4+3  8+

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://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
Outline

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
Thank you!
Questions?

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False Positive Rate

True Positive Rate

I.O.P. Specificity = 77% 86% 93%

Non - I.O.P. Specificity = 71% 81% 89%

AUC = 0.67 0.75 0.83

AUC = 0.64 0.71 0.81
Posterior P(Aggressive Prostate Cancer)

Frequency

Observed Cancer State
- Unobserved
- Indolent
- Aggressive

Final Biopsy
- Gleason 6
- Gleason 7+

Posterior P(Aggressive Prostate Cancer)
Observed Cancer State

- Aggressive (Gleason≥7)
- Indolent (Gleason=6)
- Unobserved/No Surgery
Informative Missing Data Approaches

Shared Parameter Model (Wu and Carroll 1988)
Random effect from mixed model related to censoring process
[Censoring time | RE] [Response | RE]

(L Albert and Folmmann 2009)

Latent Class Drop-out Model (Roy 2003, 2007)
Discrete shared parameter: unobserved latent class
[Latent class | censoring time] [Response | latent class]
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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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

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*
\[
L(\rho, \beta, \xi, \sigma^2, \nu, \gamma, \omega; (\mu_k, \Sigma_k), k = 0, 1; \tilde{b}_i, i = 1, \ldots, n; \eta_i, i = 1, \ldots, n; s = 0 | \\
\eta_i, i = n_{s=0} + 1, \ldots, n; (Y_i, X_i, Z_i), (B_i, U_i), (R_i, V_i), (S_i, W_i), i = 1, \ldots, n)
\]

\[
= \prod_{i=1}^{n} \rho_{\eta_i} (1 - \rho)^{1 - \eta_i} f(Y_i | X_i, Z_i, \beta, \xi, \tilde{b}_i, \sigma^2) g(\tilde{b}_i | \mu_{\eta_i}, \Sigma_{\eta_i})
\]

\[
\prod_{j=1}^{J_i} P(B_{ij} = 1 | \eta_i, U_{ij}, \nu)^{B_{ij}} P(B_{ij} = 0 | \eta_i, U_{ij}, \nu)^{1 - B_{ij}}
\]

\[
(P(R_{ij} = 1 | \eta_i, V_{ij}, \gamma)^{R_{ij}} P(R_{ij} = 0 | \eta_i, V_{ij}, \gamma)^{1 - R_{ij}})^{B_{ij}}
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PSA | Covariates, Individual Effects
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\textbf{Bx Gleason | Bx Received, Covariates, Cancer State}
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(5)

Surgery | Covariates, Past PSA and Bx, Cancer State
Comparing JH and Canary Cohorts

Canary PASS

JH AS

Inoue and Etzioni (2014)
Estimated Effectiveness

Heterogeneity in Risk in HIV prevention

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

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