Precision Medicine, Learning Health Systems, and Low Risk Prostate Cancer Care

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Shifting Healthcare Landscape

- Patients’ health problems are increasingly complex
- Number, type of available treatments for particular conditions has increased
- Amount of data available on individuals has increased—genetic, epigenetic, biomarkers, mobile health tracking
- Economic, quality concern pressures on health care delivery systems

(Gabriel and Normand, 2012)
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 2011)
Active Surveillance of Prostate Cancer
Active Surveillance of Prostate Cancer

Keys to Success
1. Identify potentially lethal cancer when present
2. Identify indolent cancer as such
3. Maintain patient engagement
Active Surveillance of Prostate Cancer

Keys to Success
1. Identify potentially lethal cancer when present
2. Identify indolent cancer
3. Maintain patient engagement
Active Surveillance of Prostate Cancer

**Keys to Success**

1. Identify potentially lethal cancer when present
2. Identify indolent cancer
3. Maintain patient engagement
Active Surveillance of Prostate Cancer

**Keys to Success**
1. Identify potentially lethal cancer when present
2. Correctly diagnose indolent cancer
3. Maintain patient engagement

**Patient Priorities**
1. Avoid negative side effects of curative intervention
2. Limit the number, frequency of painful biopsies
3. Reduce anxiety
Active Surveillance of Prostate Cancer

Keys to Success
1. Identify potentially lethal cancer

Core Concepts in Precision Medicine:
• Focus on patient-centered outcomes
• Avoid unnecessary procedures

1. Avoid negative side effects of curative intervention
2. Limit the number, frequency of painful biopsies
3. Reduce anxiety
Age (years)

PSA (ng/mL)

Reclassification

Yes
No

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Age (years)

PSA (ng/mL)

64 66 68 70 72

Yes

No

Reclassification

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Core Concepts in Precision Medicine:

• Use information from various data sources collected over time
Core Concepts in Precision Medicine:

- Use data from population to make inference about individual patient
Probability of biopsy result given true cancer state

- **Indolent Biopsy**
  - True Indolent: 94%
  - True Lethal: 38%

- **Lethal Biopsy**
  - True Indolent: 6%
  - True Lethal: 62%
Core Concepts in Precision Medicine:

- Use findings of scientific research to inform data analysis

<table>
<thead>
<tr>
<th>PSA (ng/mL)</th>
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<th>True Lethal</th>
</tr>
</thead>
<tbody>
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</table>
True Prostate Cancer Status

Random Variability

True PSA

Measurement Error

Observed PSA

Biopsy Results

Measurement Error
Latent Class

- Indolent
- Lethal

True Prostate Cancer Status

Random Variability

Measurement Error

True PSA

Observed PSA

Biopsy Results

Measurement Error
Gold standard
Pathologic analysis observed in subset

True Prostate Cancer Status

Random Variability

True PSA

Measurement Error

Biopsy Results

Observed PSA

Measurement Error
Time-varying Biomarker

True Prostate Cancer Status

Random Variability

Measurement Error

True PSA

Observed PSA

Biopsy Results

Measurement Error

Time-varying Biomarker
Repeated Outcome Measure

True Prostate Cancer Status

Random Variability

True PSA

Measurement Error

Observed PSA

Measurement Error

Biopsy Results
PSA Trajectories

Indolent Class

Lethal Class

 Mean  Individual

PSA (ng/mL)  Age (years)

50 55 60 65 70 75 80 85

0.5 1 5 10

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Core Concepts in Precision Medicine:

- Recognize heterogeneity, unobserved predictors
With which group would this PSA trajectory be more consistent?
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 aggressive cancer?

How probable is it that an individual has aggressive cancer given their observed PSA and biopsy results?
True Prostate Cancer Status

Observed PSA

Observed PSA

Individual-Level Effects

Observed PSA

Biopsy Results

Biopsy Results

Time

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Surgical Removal (Observe True State)

Observed PSA

Biopsy Performed

Biopsy Results

True Prostate Cancer State (Latent)
Surgical Removal

(Observe True State)

True Prostate Cancer State (Latent)

Observed PSA

Biopsy Results

Biopsy Performed

“Missing Not at Random”
(Little and Rubin, 2014)

Surgical Removal (Observe True State)
Core Concepts in Precision Medicine:

- Understand limitations of observational data
- Use appropriate statistical methods
Core Concepts in Precision Medicine:

• Provide information, not prescriptions
Core Concepts in Precision Medicine:

- Predictions should be dynamic, updated with additional information
Decision Support Tool

Prognosis for Active Surveillance Patients

These plots show your anticipated PSA trajectory (left) and risk of reclassification (right) based on your diagnostic characteristics. Green bands represent uncertainty in these estimates.

http://rycoley.shinyapps.io/prediction-app
Core Concepts in Precision Medicine:

- Decision support tools (clinician- and patient-facing)
- Use of technology, appropriate design
Dynamic Prediction Model

- Real-time predictions of cancer state for new patients
- Real-time updates of predictions for existing patients
- Overtime, understanding of disease at population-level improves
- Example of a learning health care system
“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.”
Learning Health Systems

Challenges

- Informed consent framework
- Patient privacy
- Data infrastructure
- Data standardization
- Statistical methods
- Culture shift to promote transparency, communication, collaboration
intelligent use of health information to individualize and integrate health care
Thank you!

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Missing Data Mechanisms

Missing Completely at Random
Missingness independent of outcome
Missing Data Mechanisms

**Missing Completely at Random**

Missingness independent of outcome

\[ P(\text{Reclassification} \mid \text{True State}) \]
Missing Data Mechanisms

**Missing Completely at Random**
- Missingness independent of outcome

**Missing at Random**
- Missingness independent on outcome conditional on observed predictors
Surgical Removal (Observe True State)

True Prostate Cancer State (Latent)

Observed PSA

Biopsy Performed

Biopsy Results

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Missing Data Mechanisms

**Missing Completely at Random**

Missingness independent of outcome

**Missing at Random**

Missingness independent on outcome conditional on observed predictors

\[
P(\text{Reclassification} \mid \text{True State}) = \frac{P(\text{Reclassification} \mid \text{True State, Biopsy}) \times P(\text{Biopsy} \mid \text{Observed Predictors})}{P(\text{Observed Predictors})}
\]
Missing Data Mechanisms

**Missing Completely at Random**
Missingness independent of outcome

**Missing at Random**
Missingness independent on outcome conditional on observed predictors

**Missing Not at Random**
Missingness dependent on outcome, even after conditioning on observed predictors
True Prostate Cancer State (Latent) → Observed PSA → Biopsy Performed → Biopsy Results → Surgical Removal (Observe True State)
Missing Data Mechanisms

Missing Completely at Random

Missingness independent of outcome

$$P(\text{Reclassification} \mid \text{True State}) =$$
$$P(\text{Reclassification} \mid \text{True State, Biopsy}) \times P(\text{Biopsy} \mid \text{Observed Predictors, True State})$$

Missing Not at Random

Missingness dependent on outcome, even after conditioning on observed predictors
AUC = 0.74
AUC = 0.72

False positive rate
True positive rate

Unadjusted
I.O.P.