Using Markov Models to Estimate the Impact of New Prostate Cancer Biomarkers

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Department of Industrial and Operations Engineering
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Industrial and Operations Engineering

IOE Department Statistics:

- Awarded over 6,500 bachelor's degrees
- Awarded more than 2,577 master's degrees
- Awarded 476 doctoral degrees
- 528 undergraduates
- 208 graduate students
- 31 faculty members (many interested in healthcare)
- Department ranked #2 in US News
My Research Interests

• Development and validation of quantitative models for comparative effectiveness

• Cost-Effectiveness of new technologies

• Predictive models for medical decision making
Prostate cancer is the most common cancer among men

• 60-80% of men will eventually develop prostate cancer
• 1 in 7 men will be diagnosed during his lifetime
• 1 in 36 men will die of prostate cancer
Prostate cancer screening is controversial

• Longer life expectancy with early detection and treatment
• Unnecessary biopsies and overtreatment
• High cost of screening, biopsy and treatment
Conflicting guidelines for PSA screening

- American Urological Association (AUA, 2013)
- American Cancer Society (ACS, 2014)
- National Comprehensive Cancer Network (NCCN, 2014)
- U.S. Preventive Services Task Force (USPSTF, 2008, revised 2011, revised 2012,...)
Can new biomarkers improve prostate cancer screening?

- PCA3 – urine test that received FDA approval in 2012 for repeat biopsy decisions
- T2:ERG – urine test in late stage clinical validation
M Cubed Project

“Measuring the costs and benefits of new biomarkers”

- Christine Barnett, MEng
- James Montie, MD
- Todd Morgan, MD
- Scott Tomlins, MD, PhD
- John Wei, MD
Research Questions

• Should new biomarkers be used for prostate cancer screening?

• What factors influence the effectiveness of new biomarkers for prostate cancer screening?
Predicting prostate cancer diagnosis

Markov Model

Markov model states: no cancer (NC), undiagnosed cancer (C), treatment (T), metastasis (M), and death (D).

State T is an aggregate of multiple prostate-cancer states: organ-confined (OC), extraprostatic (EP), and lymph-node positive (LN). Transitions represented by arrows.


PSA growth model

Statistical model:

\[
\log(y_i(t)) = \beta_{0i} + \beta_{1i}t + \beta_{2i}(t - t_{oi})I_C
\]

- \( y_i(t) \) is the PSA level for individual \( i \) at age \( t \)
- \( t_{oi} \) is the age at onset of preclinical tumor for individual \( i \)
- \( I_C \) indicator function for cancer (1=cancer, 0=no cancer)
- Individual intercepts and slopes: \( \beta_{ki} \sim N(\mu_k, \sigma_k^2), k = 0,1,2 \)

PSA model example

![PSA model example graph showing PSA levels against age. The graph includes two lines: one for Cancer Free and another for Cancer at Age 52. The PSA levels are measured in ng/mL.](image-url)
Prostate cancer screening model

Age 50

PSA Test Result

Biopsy Result

Biopsy +

Biopsy -

PSA Test?

Age 51
Microsimulation

Model Outputs:
- Time to reach state D (PCa or “Other Cause”)
- Quality adjusted life span
- Probability of reaching state M
- Probability of having a biopsy
## Model parameter estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual prostate-cancer incidence rate</td>
<td>0.0023—0.117</td>
</tr>
<tr>
<td>Annual other-cause mortality rate</td>
<td>0.0022—0.3468</td>
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<td>Annual metastasis rate for patients who have undergone radical prostatectomy</td>
<td>0.0067—0.0092</td>
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<td>Annual metastasis rate for patients with undiagnosed prostate cancer</td>
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<tr>
<td>Annual prostate-cancer-specific mortality rate for patients with metastasized prostate cancer</td>
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<tr>
<td>Prostate biopsy detection rate</td>
<td>0.8</td>
</tr>
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Heijnsdijk et al. 2012. “Quality of Life Effects of Prostate-Specific Antigen Screening,” NEJM, 367(7), 595-605
Model validation

“Essentially, all models are wrong, but some are useful”
-George Box

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Model Estimate</th>
<th>Literature Estimate</th>
<th>Literature Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall prostate cancer death rate</td>
<td>0.027 (0.026, 0.028)</td>
<td>0.026</td>
<td>Howlader et al. (2012)</td>
</tr>
<tr>
<td>Expected lifespan for 40-year-old man (yr.)</td>
<td>37.1 (36.99, 37.21)</td>
<td>37.7</td>
<td>Elizabeth (2010)</td>
</tr>
<tr>
<td>Overall diagnosis rate</td>
<td>0.185 (0.182, 0.188)</td>
<td>0.159</td>
<td>Howlader et al. (2012)</td>
</tr>
<tr>
<td>Biopsy-detectable prostate cancer prevalence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr.)</td>
<td>Prevalence</td>
<td>Age (yr.)</td>
<td>Prevalence</td>
</tr>
<tr>
<td>50</td>
<td>8%</td>
<td>50</td>
<td>13%</td>
</tr>
<tr>
<td>60</td>
<td>18%</td>
<td>60</td>
<td>22%</td>
</tr>
<tr>
<td>70</td>
<td>33%</td>
<td>70</td>
<td>36%</td>
</tr>
<tr>
<td>80</td>
<td>49%</td>
<td>80</td>
<td>51%</td>
</tr>
<tr>
<td>89</td>
<td>61%</td>
<td>89</td>
<td>65%</td>
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<td>Haas et al. (2007)</td>
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</table>
Comparison to ERSPC Trial

- Comparison of ERSPC reported results to model-based results at 9, 11, and 13 years of follow-up
- Adherence based on portion of patients receiving first PSA test
Number needed to screen with PSA

- Cohort of 1M men from varying risk groups
- Number needed to screen projected out to end of life of cohort
Model Extensions for New Biomarkers

• Distinction between cancer grades on the basis of Gleason score

• Distinction between treatment options

• Quality of life determined by treatment modalities
Treatment options

• Radical Prostatectomy:
  – For patients with localized cancer, Gleason score $\geq 7$

• Active Surveillance:
  – For patients with Gleason score = 6, delays and possibly avoids curative treatment until evidence of disease progression
Screening with multiple biomarkers

Option 1:

- PSA?
  - PSA$>y$: Biopsy
  - $x\leq$PSA$\leq y$:
    - B$\geq z$: Biopsy
    - B$< z$: No Biopsy
  - PSA$< x$: No Biopsy

Option 2:

- PSA
- PCA3
- T2ERG

MiPS

- All Cancer Risk Score
- High Grade Risk Score
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<tr>
<td>QALY decrement for PSA screening</td>
<td>0.00019</td>
</tr>
<tr>
<td>QALY decrement for prostate biopsy procedure</td>
<td>0.00577</td>
</tr>
<tr>
<td>QALY decrement for prostate cancer diagnosis</td>
<td>0.01667</td>
</tr>
<tr>
<td>QALY decrement for radical prostatectomy</td>
<td>0.24667</td>
</tr>
<tr>
<td>Annual QALY decrement for 9-year postrecovery period for radical prostatectomy</td>
<td>0.05</td>
</tr>
<tr>
<td>Annual QALY decrement for patients with metastatic cancer</td>
<td>0.4</td>
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Screening strategy types

- No Screening
- PSA
- PSA + PCA3
- PSA + T2:ERG
- MiPS
- MiPS
- HG MiPS
- Perfect
- HG Perfect
## Screening schedules

<table>
<thead>
<tr>
<th>Schedule Label</th>
<th>Range of Ages (yr)</th>
<th>Screening Interval (yr)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>40-75</td>
<td>5</td>
<td>Ross et al. (2000)</td>
</tr>
<tr>
<td>S2</td>
<td>50-75</td>
<td>2</td>
<td>Ross et al. (2000)</td>
</tr>
<tr>
<td>S3</td>
<td>50-75</td>
<td>1</td>
<td>Ross et al. (2000), Andriole et al. (2009)</td>
</tr>
<tr>
<td>S4</td>
<td>40,45 50-75</td>
<td>-</td>
<td>Ross et al. (2000)</td>
</tr>
<tr>
<td>S5</td>
<td>40,45 50-75</td>
<td>1</td>
<td>Ross et al. (2000)</td>
</tr>
<tr>
<td>S6</td>
<td>55-69</td>
<td>1</td>
<td>Heijnsdijk et al. (2012)</td>
</tr>
<tr>
<td>S7</td>
<td>55-74</td>
<td>1</td>
<td>Heijnsdijk et al. (2012)</td>
</tr>
<tr>
<td>S8</td>
<td>55-69</td>
<td>4</td>
<td>Heijnsdijk et al. (2012)</td>
</tr>
<tr>
<td>S9</td>
<td>55</td>
<td>-</td>
<td>Heijnsdijk et al. (2012)</td>
</tr>
<tr>
<td>S10</td>
<td>60</td>
<td>-</td>
<td>Heijnsdijk et al. (2012)</td>
</tr>
<tr>
<td>S11</td>
<td>65</td>
<td>-</td>
<td>Heijnsdijk et al. (2012)</td>
</tr>
</tbody>
</table>
Biopsy thresholds

- PSA: \{1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 6.5\}
- PCA3: \{19, 25, 35, 55, 75\}
- T2:ERG: \{7, 10, 30, 50, 100\}
- MiPS: \{0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50\}

# of screening strategies = (# of screening types) × (# of screening schedules) × (# of biopsy thresholds) = 1,439
Quality adjusted lifespan
Detection of high-grade cancers is most important

- Number of metastatic cases per 1,000 men
- Number of screening biopsies per 1,000 men

Graph showing the relationship between the number of screening biopsies and the number of metastatic cases per 1,000 men. The graph includes multiple lines and markers representing different screening methods: No screening, PSA only, PSA + PCA3, PSA + T2:ERG, MiPS - cancer, MiPS - HG cancer, Perfect - cancer, and Perfect - HG cancer.
High-grade MiPS simultaneously reduces biopsies and metastatic cases

Number of screening biopsies per 1,000 men

Number of metastatic cases per 1,000 men
High-grade MiPS simultaneously reduces biopsies and metastatic cases

- Annual screening ages 55-69, risk threshold of 0.50
  - Number of screening biopsies per 1,000 men: 36
  - Number of metastatic cases per 1,000 men: 37

- Screening once every two years ages 55-69, PSA threshold of 4 ng/mL
  - Number of screening biopsies per 1,000 men: 38
  - Number of metastatic cases per 1,000 men: 38
High-grade MiPS simultaneously reduces biopsies and metastatic cases

- ↓ biopsies by 32%
- ↓ metastatic cases by 2%

- ↓ biopsies by 14%
- ↓ metastatic cases by 7%
Conclusions

• New biomarkers used in conjunction with PSA could reduce unnecessary biopsies (and overtreatment) and development of metastatic cancer

• High grade cancer biomarkers are much more valuable than “any cancer” biomarkers
Assessment of Long-Term Outcomes Associated With Urinary Prostate Cancer Antigen 3 and TMPRSS2:ERG Gene Fusion at Repeat Biopsy

Selin Merdan, MEng\(^1\); Scott A. Tomlins, MD, PhD\(^2,3\); Christine L. Barnet, MEng\(^1\); Todd M. Morgan, MD\(^3\);
James E. Montie, MD\(^3\); John T. Wei, MD\(^3\); and Brian T. Denton, PhD\(^1,3\)

**BACKGROUND:** In men with clinically localized prostate cancer who have undergone at least 1 previous negative biopsy and have elevated serum prostate-specific antigen (PSA) levels, long-term health outcomes associated with the assessment of urinary prostate cancer antigen 3 (PCA3) and the transmembrane protease, serine 2 (TMPRSS2)-v-ets erythroblastosis virus E26 oncogene homolog (avian) (ERG) gene fusion (T2:ERG) have not been investigated previously in relation to the decision to recommend a repeat biopsy.

**METHODS:** The authors performed a decision analysis using a decision tree for men with elevated PSA levels. The probability of cancer was estimated using the Prostate Cancer Prevention Trial Risk Calculator (version 2.0). The use of PSA alone was compared with the use of PCA3 and T2:ERG scores, with each evaluated independently, in combination with PSA to trigger a repeat biopsy. When PCA3 and T2:ERG score evaluations were used, predefined thresholds were established to determine whether the patient should undergo a repeat biopsy. Biopsy outcomes were defined as either positive (with a Gleason score of <7, 7, or >7) or negative. Probabilities and estimates of 10-year overall survival and 15-year cancer-specific survival were derived from previous studies and a literature review. Outcomes were defined as age-dependent and Gleason score-dependent 10-year overall and 15-year cancer-specific survival rates and the percentage of biopsies avoided. **RESULTS:** Incorporating the PCA3 score (biopsy threshold, 25; generated based on the urine PCA3 level normalized to the amount of PSA messenger RNA) or the T2:ERG score (biopsy threshold, 10; based on the urine T2:ERG level normalized to the amount of PSA messenger RNA) into the decision to recommend repeat biopsy would have avoided 55.4% or 64.7% of repeat biopsies for the base-case patient, respectively, and changes in the 10-year survival rate were only 0.93% or 1.41%, respectively. Multi-way sensitivity analyses suggested that these results were robust with respect to the model parameters. **CONCLUSIONS:** The use of PCA3 or T2:ERG testing for repeat biopsy decisions can substantially reduce the number of biopsies without significantly affecting 10-year survival. **Cancer 2015;000:000-000. © 2015 American Cancer Society.**

**KEYWORDS:** prostate cancer antigen 3, prostate cancer, repeat biopsy, survival, TMPRSS2:ERG, transmembrane protease, serine 2-ETS-related gene fusion, urinary biomarkers.
Other Research

- Predictive models:
  - Imaging guidelines in MUSIC
  - Biopsy outcome prediction
  - Active surveillance choice model

- Cost-effectiveness of MRI

- Active surveillance model for studying alternative active surveillance strategies
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• David Miller
• James Montie
• Todd Morgan

Scott Tomlins
Daniel Underwood
John Wei
Jim Wilson

My website: http://btdenton.engin.umich.edu/

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