Optimal Design of Biomarker-Based Screening Strategies for Early Detection of Prostate Cancer

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Prostate Cancer

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
Physicians use biomarker tests to screen healthy men for asymptomatic, early-stage cancer.

Catching cancer at an early stage can increase a patient’s chance of survival and decrease the cost of treatment.

Prostate-specific antigen (PSA) test is the biomarker that is most commonly used for prostate cancer screening.
New Biomarker Tests

T2:ERG
- Urine test
- In late stage clinical validation

PCA3
- Urine test
- FDA approved for repeat biopsy

More than a dozen other prostate cancer biomarkers have been discovered.
“Sophisticated new prostate cancer tests are coming to market that might supplement the unreliable PSA test, potentially saving tens of thousands of men each year from unnecessary biopsies, operations and radiation treatments.” - The New York Times


“The existing clinical biomarkers for PCa are not ideal, since they cannot specifically differentiate between those patients who should be treated immediately and those who should avoid over-treatment.”

Harms and Benefits

- Longer life expectancy with early detection and treatment
- Unnecessary biopsies and overtreatment
- High costs of biomarker tests, biopsy and treatment
Harms and Benefits

- Longer life expectancy with early detection and treatment
- Unnecessary biopsies and overtreatment
- High costs of biomarker tests, biopsy and treatment

Conflicting guidelines for PSA screening

- American Urological Association (AUA, 2013)
- American Cancer Society (ACS, 2010)
- National Comprehensive Cancer Network (NCCN, 2010)
- U.S. Preventive Services Task Force (USPSTF, 2008, revised 2011, revised 2012,...)
Research Questions

- Can optimization models help inform clinical screening decisions?
- Can biomarkers be used for minimally invasive early detection of prostate cancer?
- What factors influence the effectiveness of prostate cancer screening?
Men 40 years and older receive routine annual PSA tests

Physician (and patient) decides whether to refer for biopsy
Typical Screening Process

- **PSA Test Result**
  - **Biopsy Result**
    - **Biopsy +**
    - **Biopsy -**
  - **PSA Test?**
    - **Epoch t+1**

**Michigan**

Brian Denton

Prostate Cancer Screening
Markov transitions between prostate cancer states:

- No cancer (NC) → **Unobservable**
- Cancer present but not detected (C) → **Unobservable**
- Cancer detected (T) → Treated immediately after detected
- Death (D) → Prostate cancer and other cause mortality
Objective: maximize expected benefits minus costs:

- Societal willingness to pay, $\beta$ dollars/QALY
- $Reward = \beta \times QALY - Cost\ of\ Screening\ and\ Treatment$

Three decisions at each decision epoch:

- Defer biomarker testing (DP)
- Defer biopsy (DB)
- Biopsy (B)
POMDP Notation

- $t$: decision epochs every 6 months from age 40 to age 95
- $s_t$: health state at start of epoch $t$
- $o_t$: biomarker observation at start of epoch $t$
- $p_t(s_{t+1}|s_t, a_t)$: transition probability between health states $s_t$ to $s_{t+1}$
- $q_t(o_t|s_t), \forall s_t \in S, o_t \in O$: probability of observing PSA level $o_t$ in health state $s_t$ in epoch $t$
- $r_t(s_t, a_t)$: reward at epoch $t$
Sequential Updating of Cancer Risk

Biomarker test results are observed over time:

\[
\begin{align*}
\text{Pr}(s_t) & \xrightarrow{\text{Pt}} \tilde{s}_{t+1} \xrightarrow{\text{Qt}} \tilde{o}_{t+1} \xrightarrow{\text{Pr}(s_{t+1})} \\
\end{align*}
\]

The probability a patient is in a given health state at epoch \( t \) is estimated using the entire history of observations:

\[
Pr_{t+1}(s_{t+1}) = \frac{q_{t+1}(o_{t+1}|s_{t+1}) \sum_{s_t \in S} p_t(s_{t+1}|s_t, a_t)Pr_t(s_t)}{\sum_{s_{t+1} \in S} q_{t+1}(o_{t+1}|s_{t+1}) \sum_{s_t \in S} p_t(s_{t+1}|s_t, a_t)Pr_t(s_t)}
\]
Annual Rewards: Societal Perspective

- $r_t(\text{NC, DP}) = \beta$
- $r_t(\text{NC, DB}) = \beta - c_p$
- $r_t(\text{NC, B}) = \beta(1 - \mu) - c_b$
- $r_t(\text{C, DP}) = \beta$
- $r_t(\text{C, DB}) = \beta - c_p$
- $r_t(\text{C, B}) = \beta(1 - \mu - f\epsilon) - c_b - f \cdot c_t$

<table>
<thead>
<tr>
<th>$f$</th>
<th>Biopsy detection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>Utility decrement of biopsy</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Annual utility decrement after treatment</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Societal willingness to pay per QALY</td>
</tr>
<tr>
<td>$c_p$</td>
<td>Cost of a PSA test</td>
</tr>
<tr>
<td>$c_b$</td>
<td>Cost of a biopsy</td>
</tr>
<tr>
<td>$c_t$</td>
<td>Cost of prostate cancer treatment</td>
</tr>
</tbody>
</table>
Decisions are based on risk of prostate cancer by selecting among the three possibilities: *defer PSA test, PSA test, or biopsy*

\[ v_t(Pr_t(C)) = \max \{ v_t(Pr_t(C), DP), v_t(Pr_t(C), DB), v_t(Pr_t(C), B) \} \]

**Properties:**
- For any policy the sequence of \( Pr_t(C) \) is a Markov process
- \( v_t(Pr_t(C)) \) is piecewise linear convex
Optimality Equations

Select among three actions: *defer testing*, *PSA test only*, or *biopsy*

\[ v_t(Pr_t(C)) = \max \{ v_t(Pr_t(C), DP), v_t(Pr_t(C), DB), R_t(Pr_t(C)) \} , \forall t \]

where

\[ R_t(Pr_t(C)) = (1 - Pr_t(C))\bar{R}_t(NC) + Pr_t(C)((1 - f)\bar{R}_t(C) + f\bar{R}_t(T)) - \beta \mu - c_b \]
Optimality Equations

Select among three actions: *defer testing, PSA test only, or biopsy*

\[ v_t(Pr_t(C)) = \max \{v_t(Pr_t(C), DP), v_t(Pr_t(C), DB), R_t(Pr_t(C))\} , \forall t \]

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- \[ v_t(Pr_t(C), DB) = r_t(Pr_t(C), DB) + \sum_{o_{t+1} \in O} v_{t+1}(Pr_{t+1}(C))p_t(o_{t+1}|Pr_t(C), DB) \]
Optimality Equations

Select among three actions: defer testing, PSA test only, or biopsy

\[ v_t(Pr_t(C)) = \max \{v_t(Pr_t(C), DP), v_t(Pr_t(C), DB), R_t(Pr_t(C))\}, \forall t \]

where

- \[ R_t(Pr_t(C)) = (1 - Pr_t(C))\bar{R}_t(NC) + Pr_t(C)((1 - f)\bar{R}_t(C) + f\bar{R}_t(T)) - \beta\mu - c_b \]
- \[ v_t(Pr_t(C), DB) = r_t(Pr_t(C), DB) + \sum_{o_{t+1} \in O} v_{t+1}(Pr_{t+1}(C))p_t(o_{t+1}|Pr_t(C), DB) \]
- \[ v_t(Pr_t(C), DP) = r_t(Pr_t(C), DP) + v_{t+1}(Pr_{t+1}(C))p_t(Pr_{t+1}(C)|Pr_t(C), DP) \]
**Proposition**

The incremental benefit of an additional PSA test in expected QALYs is non-negative.

**Theorem**

The optimal biopsy referral policy is of control-limit type such that

\[
a_t^*(Pr_t(C)) = \begin{cases} 
W, & \text{if } Pr_t(C) \leq Pr_t^*(C) \\
B, & \text{if } Pr_t(C) > Pr_t^*(C). 
\end{cases}
\]

---

Theorem

There exists a finite age, \( N \), at which it is optimal to discontinue biopsy referral if and only if the following condition is satisfied:

\[
\bar{R}_N(T) - \bar{R}_N(C) \leq \mu/f.
\]

Corollary

If \( a^*_t(Pr_t(C)) = W, \forall Pr_t(C) \in [0, 1], \forall t \geq N \), PSA screening should be discontinued.

Basic Idea: approximate the value function with a combination of inner and outer linearization subject to a fixed computing budget

(d) A minimal $\alpha$-vector set  
(e) A lower bound  
(f) An upper bound
Lower Bound

\[ L^*_t = \arg \min_{L_t \subseteq W_t} \int_{x \in \Pi} \left( \max_{w \in W_t} w \cdot x - \max_{\ell \in L_t} \ell \cdot x \right) f_t(x) dx \]

s.t.

\[ |L_t| \leq c \]

**LB heuristic:**

**Step 1.** Initialize \( \widehat{L}_T \) as the true minimal \( \alpha \)-vector set, \( L_T \). Set \( t = T - 1 \). Sample belief point sets, \( N_t \), for \( t = 1, \ldots, T \).

**Step 2.** Using \( \widehat{L}_{t+1} \) find the dominating \( \alpha \)-vector at all the belief points in \( N_t \) and estimate a probability of dominance.

**Step 3.** Select \( c \) vectors with highest probability. Let \( t = t - 1 \). If \( t = 1 \) stop; otherwise return to Step 2.
Upper Bound

\[ U^*_t = \arg \min_{U_t \subseteq Y_t} \int \left( \min_{g_u \in [0,1], \forall u \in U} \left\{ \sum_{u \in U} v_t(u)g_u \left| \sum_{u \in U} g_u u = x, \sum_{u \in U} g_u = 1 \right\} \right) f_t(x) dx \]

s.t.

\[ |U_t| \leq k, \]

**UB heuristic:**

**Step 1.** Compute the value functions at all the points in \( N_T \). Let \( t = T - 1 \).

**Step 2.** Estimate the value function for all belief points in \( N_t \) using inner linearization for the value functions of all the points in \( N_{t+1} \).

**Step 3.** Let \( t = t - 1 \). If \( t = 1 \) stop; otherwise return to start of Step 2.
From patient perspective
- $\epsilon = 0.145$
- $\mu = 0.05$

From societal perspective
- $\beta = 50,000$
- $\epsilon = 0.145$
- $\mu = 0.05$

---

## Screening Benefit from the Patient Perspective

<table>
<thead>
<tr>
<th>$\epsilon$</th>
<th>$\mu$</th>
<th>Benefit over no PSA screening (QALYs/person)</th>
<th>Benefit over traditional guideline (QALYs/person)</th>
<th>Screening stopping age</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>0.01</td>
<td>0.289</td>
<td>0.292</td>
<td>&gt; 84</td>
</tr>
<tr>
<td>0.05</td>
<td>0.05</td>
<td>0.271</td>
<td>0.312</td>
<td>&gt; 84</td>
</tr>
<tr>
<td>0.1</td>
<td>0.1</td>
<td>0.253</td>
<td>0.340</td>
<td>&gt; 84</td>
</tr>
<tr>
<td>0.145</td>
<td>0.01</td>
<td>0.148</td>
<td>0.151</td>
<td>77</td>
</tr>
<tr>
<td>0.05</td>
<td>0.05</td>
<td><strong>0.131</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>0.165</strong></td>
<td>76</td>
</tr>
<tr>
<td>0.1</td>
<td>0.1</td>
<td>0.116</td>
<td>0.204</td>
<td>75</td>
</tr>
<tr>
<td>0.24</td>
<td>0.01</td>
<td>0.044</td>
<td>0.047</td>
<td>61</td>
</tr>
<tr>
<td>0.05</td>
<td>0.05</td>
<td>0.032</td>
<td>0.073</td>
<td>60</td>
</tr>
<tr>
<td>0.1</td>
<td>0.1</td>
<td>0.025</td>
<td>0.113</td>
<td>60</td>
</tr>
</tbody>
</table>

**Table:** Comparison of optimal screening vs. no screening and the traditional guideline for 40-year-old healthy men

<sup>1</sup>Base case: annual incremental benefit of 293,000 QALYs for U.S. population
### Table: Sensitivity analysis of the total costs of the optimal policy and the traditional guideline for 40-year-old healthy men

<table>
<thead>
<tr>
<th>$\beta$</th>
<th>costs</th>
<th>Cost of the optimal policy (U.S. $/person)</th>
<th>Cost of the traditional guideline (U.S. $/person)</th>
<th>Screening stopping age</th>
</tr>
</thead>
<tbody>
<tr>
<td>100,000</td>
<td>−20%</td>
<td>904</td>
<td>764</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>base case</td>
<td>1104</td>
<td>956</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>+20%</td>
<td>1274</td>
<td>1147</td>
<td>72</td>
</tr>
<tr>
<td>50,000</td>
<td>−20%</td>
<td>768</td>
<td>764</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>base case</td>
<td>882</td>
<td>956</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>+20%</td>
<td>989</td>
<td>1147</td>
<td>69</td>
</tr>
<tr>
<td>25,000</td>
<td>−20%</td>
<td>583</td>
<td>764</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>base case</td>
<td>642</td>
<td>956</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>+20%</td>
<td>658</td>
<td>1147</td>
<td>65</td>
</tr>
</tbody>
</table>

1 Base case: annual cost saving of 166 million dollars for the U.S. population
Sensitivity Analysis of Expected QALYs

Figure: Expected QALYs of 40 year old male with $Pr_{40}(C) = 0$
Incorporating New Biomarker Tests

T2:ERG
- Distinguishes between low and high grade cancers

PCA3
- FDA approved for use in combination with PSA
Expanded Prostate Cancer Treatment Options

Radical Prostatectomy
- Surgical removal of the prostate
- Appropriate when the cancer is contained in the prostate

Active Surveillance
- Treatment option for patients with low-risk prostate cancer
- Delays and possibly avoids curative treatment until evidence of disease progression
Depending on which core state the patient is in, we sample from the appropriate probability distribution for their biomarker results.
Multiple Biomarker-Based Screening

Sequential biomarker threshold-based policies:

\[ Pr(PCA) = \logit^{-1}(-\beta_0 + \beta_1 \times PSA + \beta_2 \times PCA3 + \beta_3 \times T2:ERG) \]
Numerical Experiments

- No Screening, PSA threshold, PSA+PCA3 threshold, PSA + T2ERG threshold, PSA+PCA3+T2ERG Risk Score
- All combinations of biopsy thresholds for PSA, PCA3, T2ERG, increments of .05 for risk scores
- Screening frequency based on published 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</td>
<td>-</td>
<td>Ross et al. (2000)</td>
</tr>
<tr>
<td>S5</td>
<td>40,45</td>
<td>2</td>
<td>Ross et al. (2000)</td>
</tr>
<tr>
<td></td>
<td>50-75</td>
<td>-</td>
<td></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>
Results: Public Health Perspective

No Screening

PSA only

PSA + PCA3

PSA + T2:ERG

MiPS: Cancer

MiPS: HG Cancer

Perfect Biomarker: Cancer

Perfect Biomarker: HG Cancer

Expected QALYs

77.94  77.99  78.04  78.09  78.14  78.19
Results: Patient Perspective

- No Screening
- PSA only
- PSA + PCA3
- PSA + T2:ERG
- MiPS - Cancer
- MiPS - HG Cancer
- Perfect Biokmarker - Cancer
- Perfect Biomarker - HG Cancer

Number of Metastatic Cases per 1,000 Men

Number of Screening Biopsies per 1,000 Men

AUA
Conclusions

- Fast approximations for POMDPs for PCa screening can achieve near optimal solutions

- Combining multiple biomarkers can increase quality adjusted life years, reduce the probability of metastasis, and reduce the probability of receiving a biopsy

- Factors that most influence the effectiveness of prostate cancer screening are: accuracy of high grade cancer detection, other cause mortality, and cancer incidence
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PSA growth model developed by Gulati et al. (2010):

\[
\log\{y_i(t)\} = \beta_0 + \beta_1 t + \beta_2(t - t_{oi})I(t > t_{oi}) + \epsilon,
\]

where:

- \(y_i(t)\) is the PSA level for individual \(i\) at age \(t\)
- \(t = 0\) corresponds to age 35
- \(t_{oi}\) is the age at onset of a preclinical tumor for individual \(i\)
- Individual intercepts and slopes are given by \(\beta_{ki} \sim N(\mu_k, \sigma_k^2)\) for \(k = 0, 1, 2\)

## Model Validation

<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>0.028 (0.027, 0.029)</td>
<td>0.026</td>
<td>Howlader et al. (2012)</td>
</tr>
<tr>
<td>Expected lifespan for 40-year-old man (yr.)</td>
<td>38.03 (37.92, 38.14)</td>
<td>37.7</td>
<td>Elizabeth (2010)</td>
</tr>
<tr>
<td>Overall diagnosis rate</td>
<td>0.106 (0.104, 0.109)</td>
<td>0.159</td>
<td>Howlader et al. (2012)</td>
</tr>
</tbody>
</table>
| Biopsy-detectable prostate cancer prevalence | Age  
50: 8%  
60: 19%  
70: 33%  
80: 49%  
89: 62%  
Age  
50: 13%  
60: 22%  
70: 36%  
80: 51%  
89: 65% | Haas et al. (2007)     |
Experiments: 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\}