Predictive and Prescriptive Models for Early Detection of Prostate Cancer
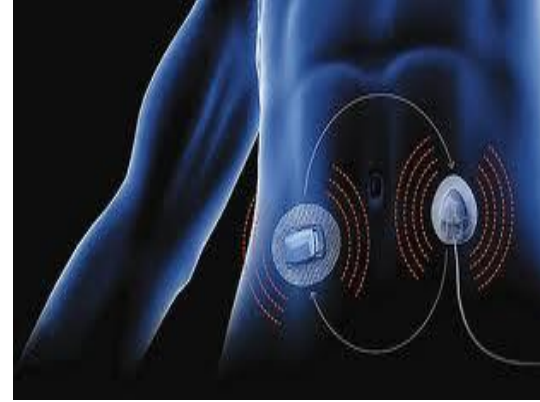
April 9, 2024

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University of Michigan

Chronic Diseases

Cancer

Diabetes

Kidney Disease
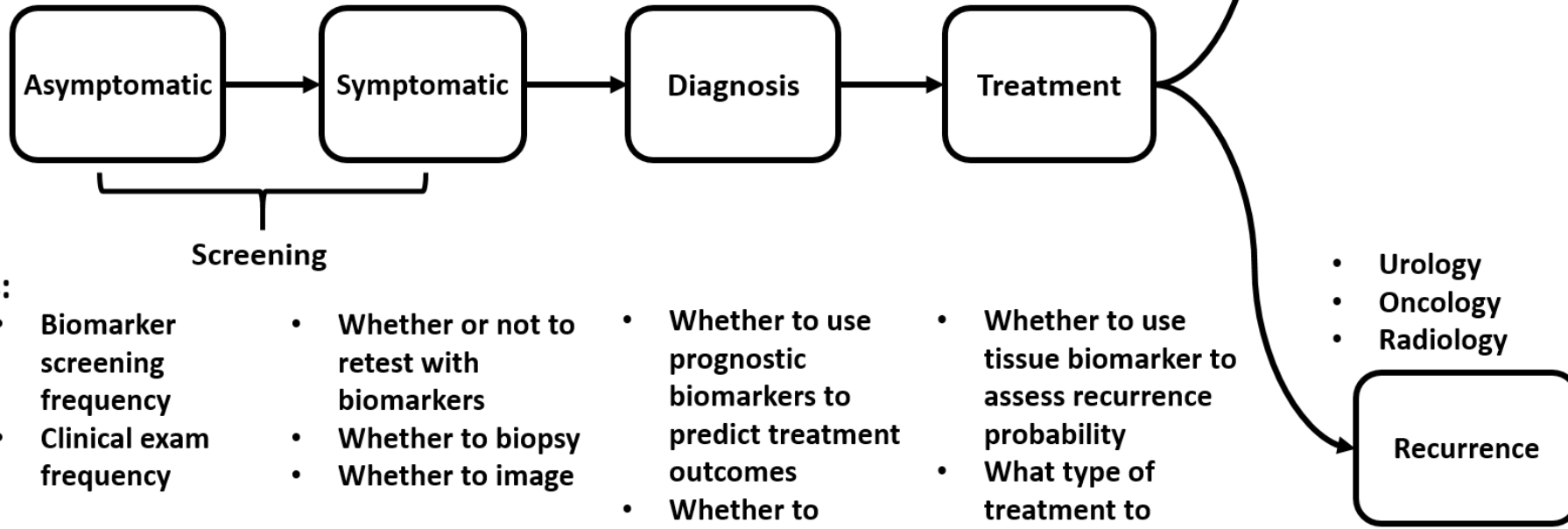
Heart Disease

Why prostate cancer?

- 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

- The care cycle for prostate cancer is a complex stochastic process with many clinical decisions

Prostate Cancer Care Cycle

Prostate Cancer Care Stages

Resources:

Asymptomatic:
- Primary care clinic
- Biomarkers/Labs

Symptomatic:
- Urology clinic
- Biomarkers/Labs
- Imaging/Radiology

Diagnosis:
- Urology clinic
- Biomarkers/Labs
- Imaging/Radiology
- Procedure center

Treatment:
- Surgery
- Radiology
- Hospital resources
- Specialty care

Post-Treatment Monitoring:
- Urology
- Radiology
- Biomarkers/labs
- Follow-up test frequency
- Imaging

Recurrence:
- Urology
- Oncology
- Radiology
- Salvage radiation therapy
- Chemotherapy

Stages: Asymptomatic → Symptomatic → Diagnosis → Treatment → Post-Treatment Monitoring / Recurrence

Screening (spans Asymptomatic and Symptomatic)

Decisions:

Asymptomatic:
- Biomarker screening frequency
- Clinical exam frequency

Symptomatic:
- Whether or not to retest with biomarkers
- Whether to biopsy
- Whether to image

Diagnosis:
- Whether to use prognostic biomarkers to predict treatment outcomes
- Whether to image to evaluate spread of cancer

Treatment:
- Whether to use tissue biomarker to assess recurrence probability
- What type of treatment to pursue

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Three Examples

1. Should new biomarkers be used for <u>early detection</u> of prostate cancer?

2. When should imaging be used for <u>staging</u> of prostate cancer?

3. What is the optimal strategy for <u>active surveillance</u> of low-risk prostate cancer?

1. Should new biomarkers be used for early detection of prostate cancer?

Prostate cancer screening

PSA Test Result

Biopsy Result

Biopsy +

Biopsy -

Y

N

PSA Test?

Y

N

Age 50

Age 51
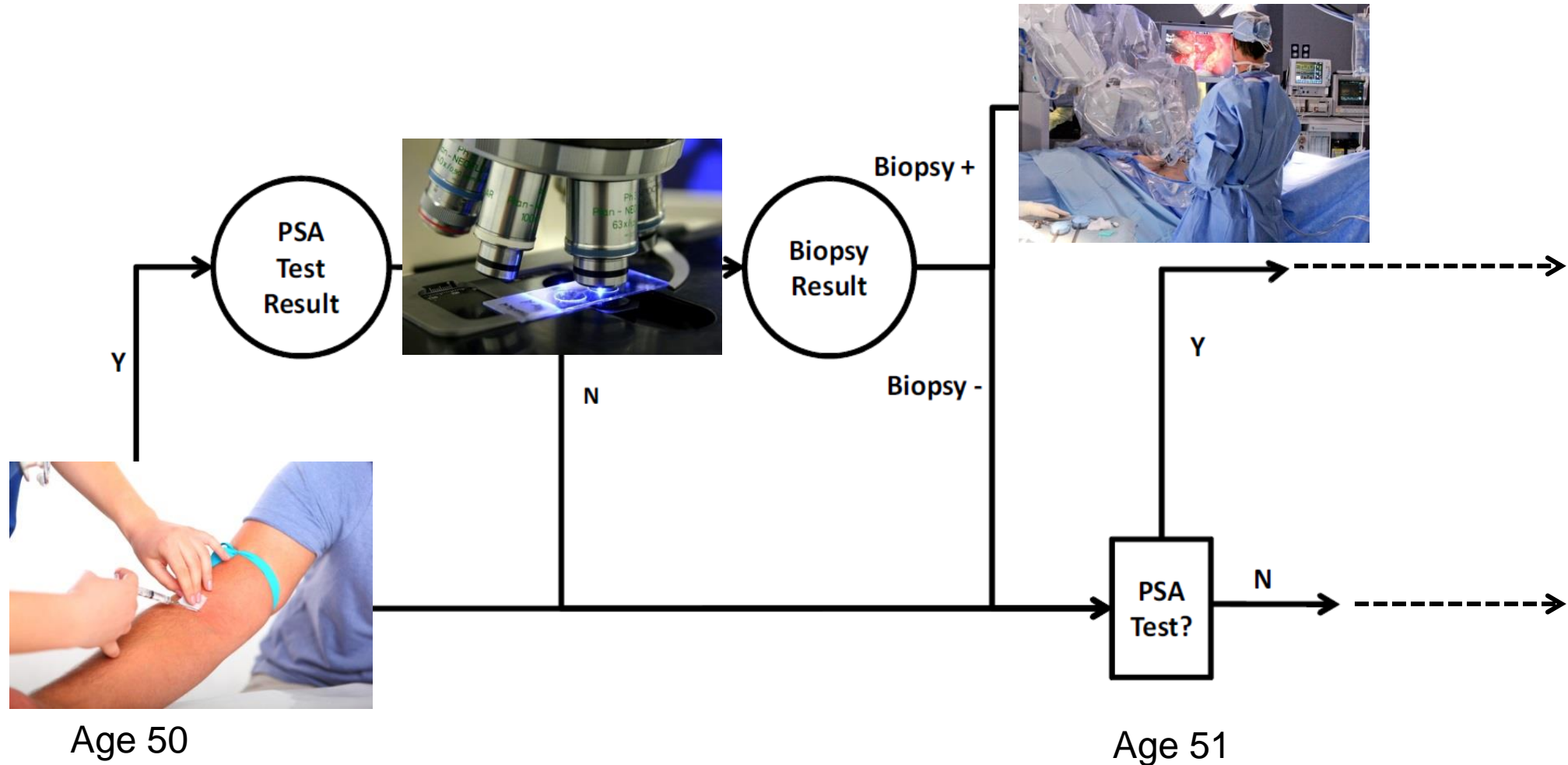
PSA screening model example
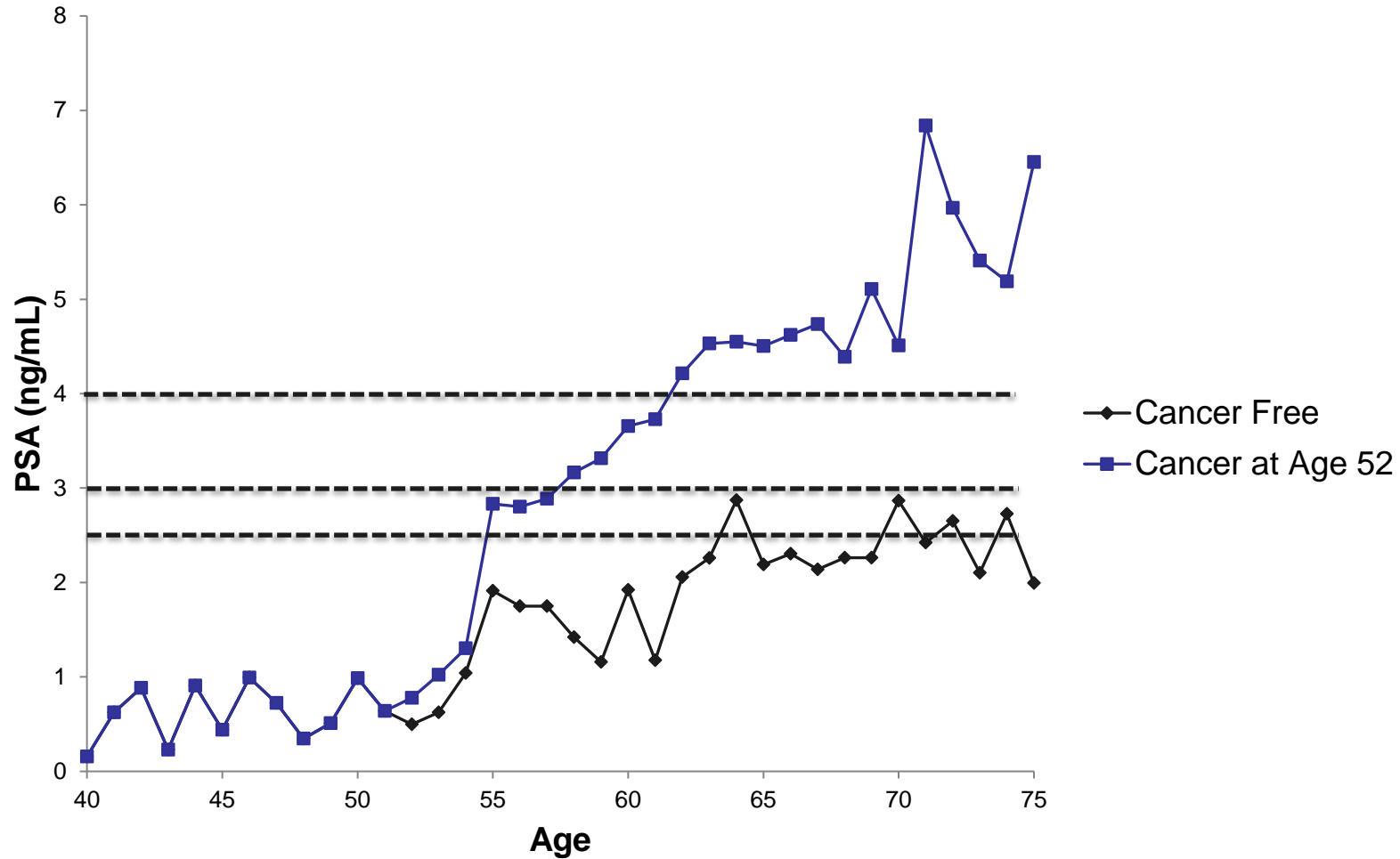
Underwood DJ, Zhang J, Denton BT, Shah ND, Inman BA. Simulation optimization of PSA-threshold based prostate cancer screening policies. *Health Care Management Science*.2012 15(4):293-309.

Urine-based biomarkers for prostate cancer

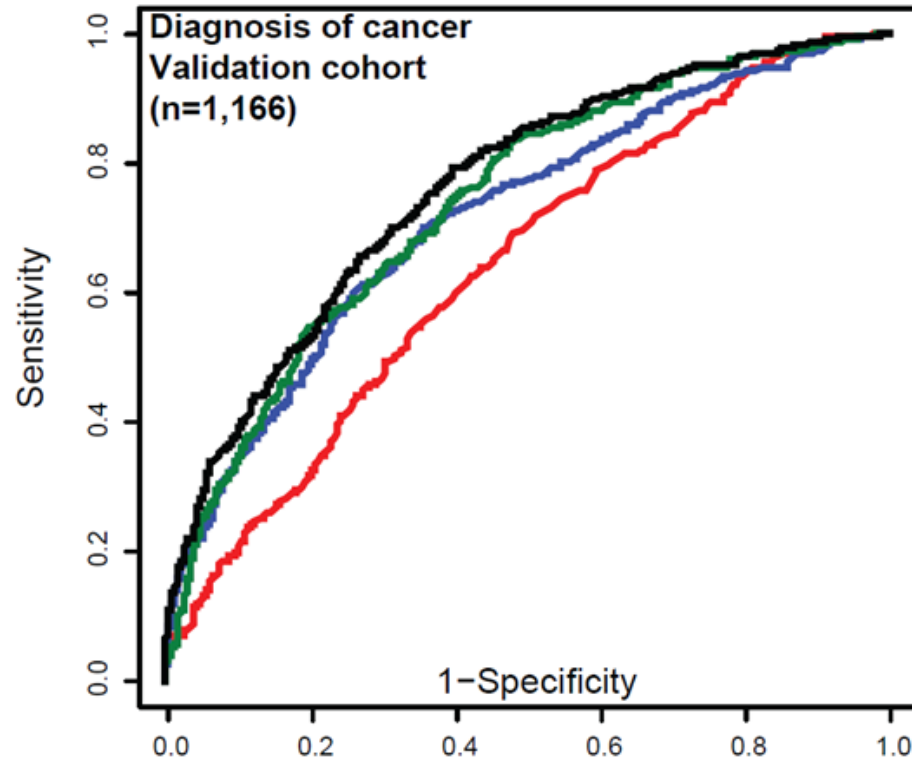**Detection of Cancer Cells Directly**

PSA Protein

Prostate Cells

PSA

PCA3

Prostate Cell
Cancer Cell
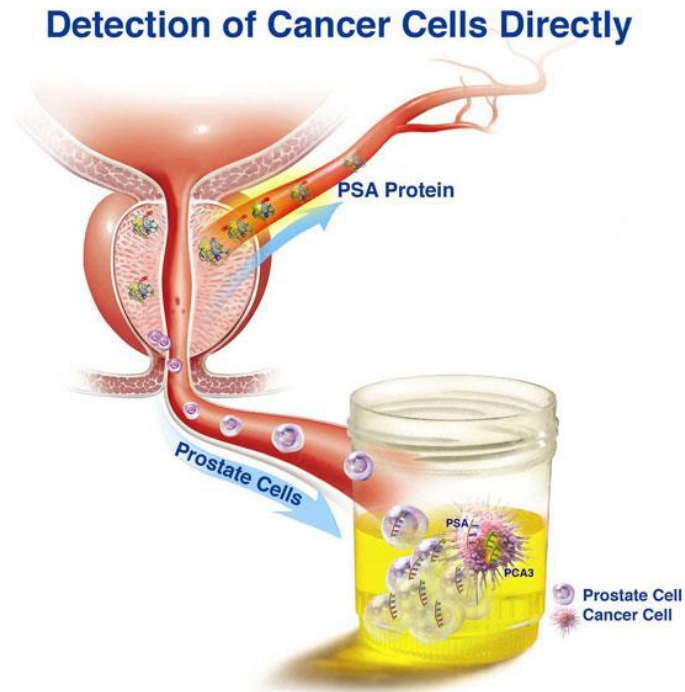
- PCA3 – urine test that received FDA approval in 2012 for repeat biopsy decisions

- T2:ERG – urine test in late-stage clinical validation

Improving predictions for prostate cancer

Diagnosis of cancer
Validation cohort
(n=1,166)

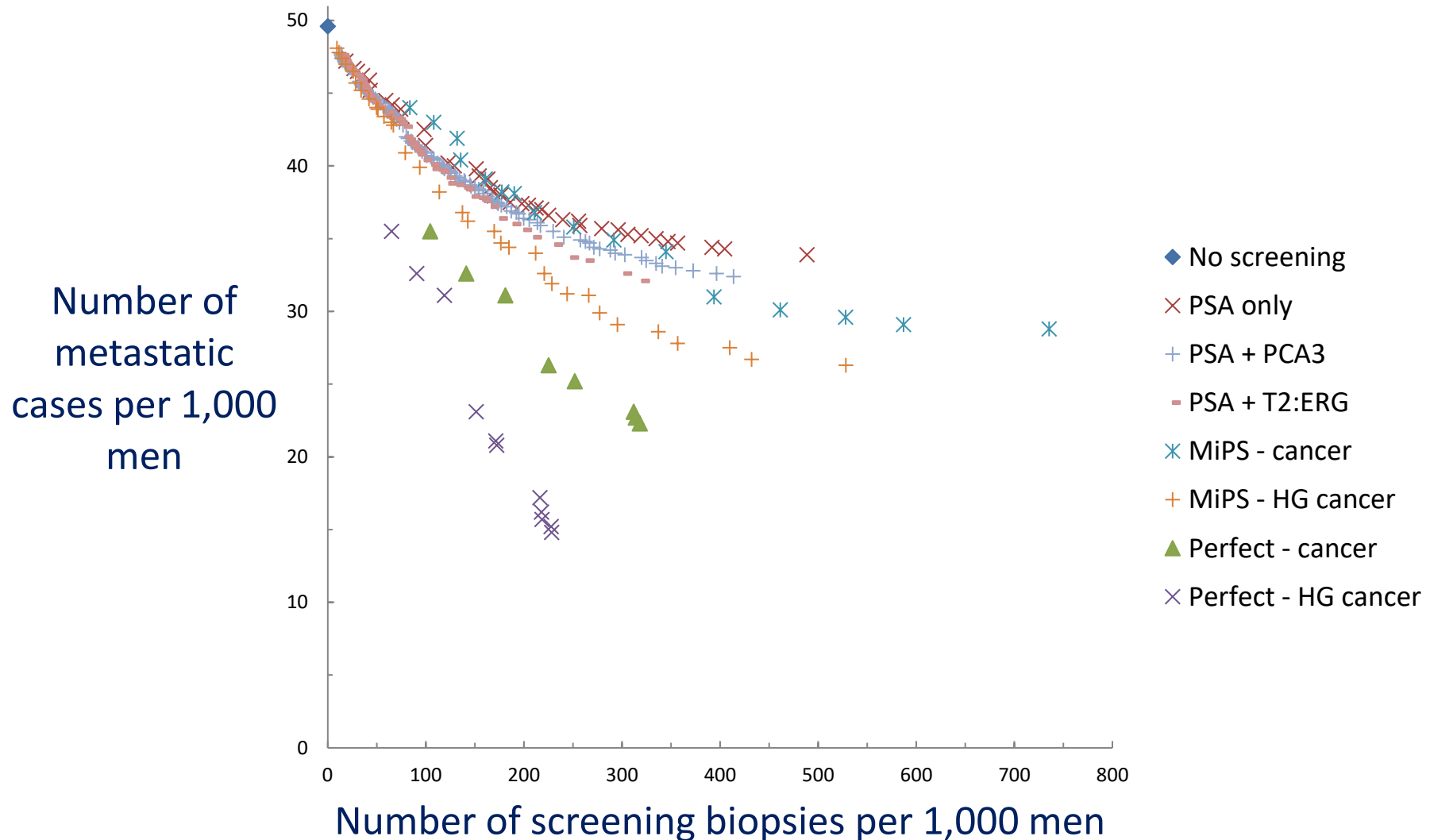|	Model	AUC
	PSA	0.585
	PSA+T2:ERG	0.666
	PSA+PCA3	0.712
	PSA+T2:ERG+PCA3	0.751

Tomlins SA, Day JR, Lonigro RJ, Hovelson DH, Siddiqui J, Kunju LP, Dunn RL, Meyer S, Hodge P, Groskopf J, Wei JT, Chinnaiyan AM. "Urine TMPRSS2:ERG + PCA3 for individualized prostate cancer risk assessment," *European Urology*, 70(1), 45-53, 2016

Natural history model
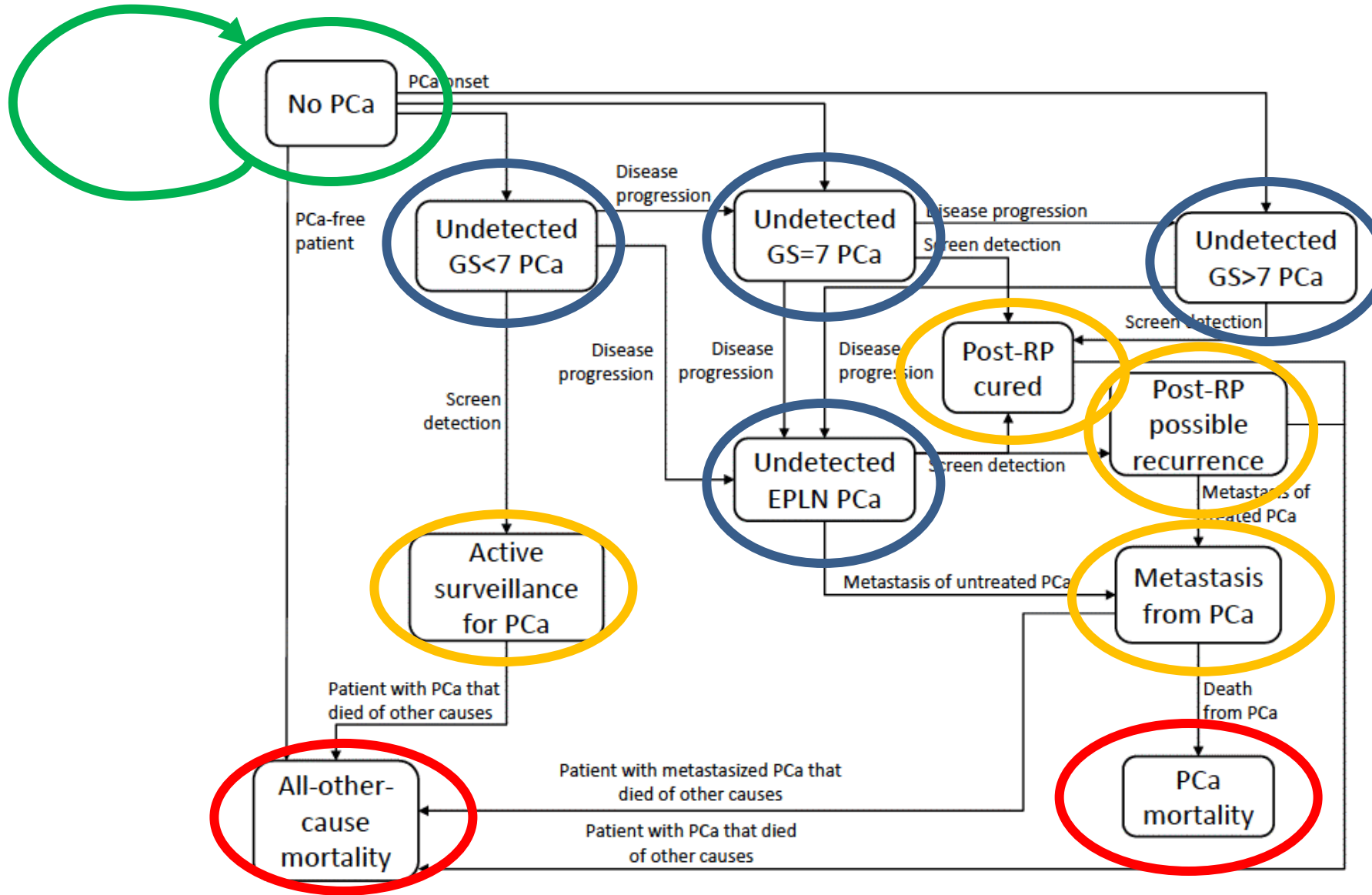
Barnett, et al. "Two-stage biomarker protocols for improving the precision of early detection of prostate cancer," *Medical Decision Making*, 37(7), 815-826, 2017

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High-grade cancer biomarkers could reduce biopsies and saves lives

Number of metastatic cases per 1,000 men

Number of screening biopsies per 1,000 men

Legend:
- ◆ No screening
- ✕ PSA only
- + PSA + PCA3
- ▬ PSA + T2:ERG
- ✳ MiPS - cancer
- + MiPS - HG cancer
- ▲ Perfect - cancer
- ✕ Perfect - HG cancer

2. When should imaging be used for <u>staging</u> of prostate cancer?

Imaging modalities

Bone Scan (BS)

- Detect bone metastasis

Computed Tomography (CT)

- Detects lymph node metastasis

Harms of <u>not</u> imaging

- Metastatic cancer may go undetected

- Missed diagnoses subject patients to unnecessary treatments (e.g., radical prostatectomy)

- Appropriate treatment (e.g., chemotherapy) is delayed

Harms of imaging

- Potentially <u>harmful radiation</u> exposure

- Incidental findings that require <u>painful and risky</u> follow-up procedures (e.g., bone biopsy)

- Blocks access to imaging resources for other patients and unnecessarily <u>increases healthcare costs</u>

# Michigan Urological Surgery Improvement Collaborative

- Physician-led, statewide collaborative

- Urology practices across Michigan (> 95% of urologists)

- Complete preoperative data for men with newly-diagnosed PCa

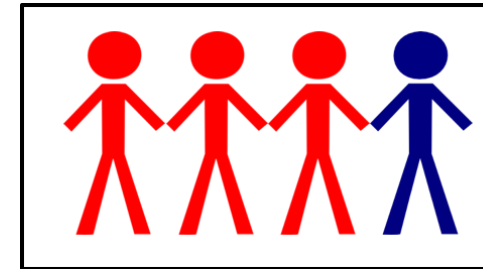# Factors associated with a positive BS and CT

- Age
- Race and ethnicity
- Prostate-specific antigen (PSA) (ng/ml)
- Clinical tumor stage (e.g., T1a/b/c, T2a/b/c and T3/4)
- Gleason score (GS)
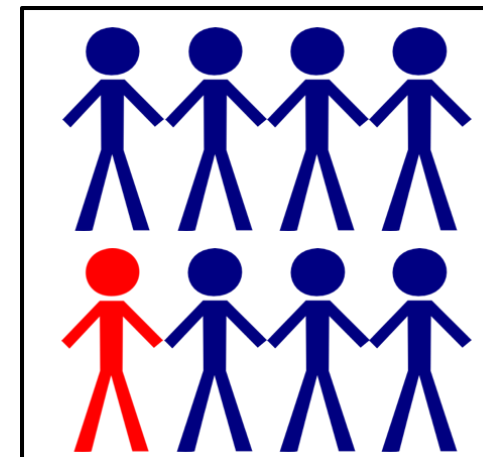- Pathology

Verification bias

Entire patient population
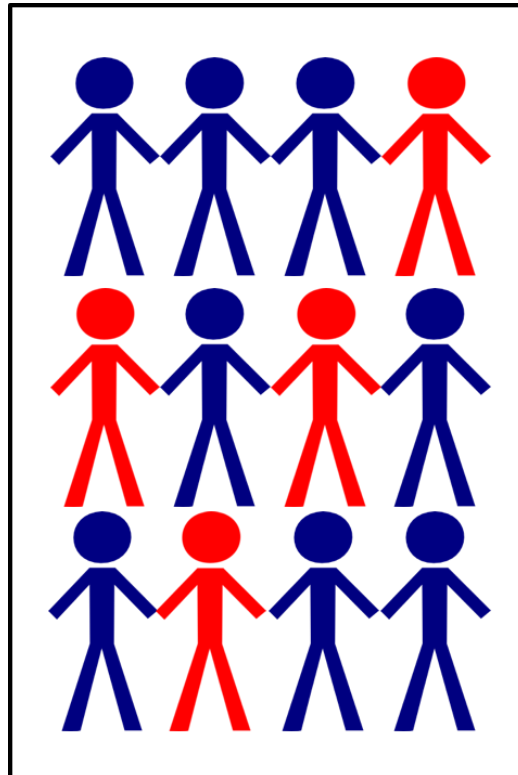
Patients who received imaging

Patients who did not receive imaging

Effects of verification bias

	Sensitivity	Specificity
Clinical guidelines		
Bone scan		
EAU	97.9	33.4
AUA	**97.9**	**43.5**
NCCN	97.9	40.8
Briganti's CART	89.6	45.4
CT scan		
EAU	98.4	36.5
AUA	**96.8**	**49.2**

Begg, C. B., Greenes, R. A. "Assessment of diagnostic tests when disease verification is subject to selection bias," *Biometrics*, 39:207, 1983.

Correcting for verification bias

Estimate sensitivity and specificity based on the entire population:

$$\Pr(Disease\ Present|G+)P(G+) + P(Disease\ Present|G-)P(G-)$$

$$P(G+|Disease\ Present) = \frac{P(Disease\ Present|G+)P(G+)}{P(Disease\ Present)}$$

$$\Pr(Disease\ \textbf{not}\ Present|G+)P(G+) + P(Disease\ \textbf{not}\ Present|G-)P(G-)$$

$$P(G-|Disease\ \textbf{not}\ Present) = \frac{P(Disease\ \textbf{not}\ Present|G-)P(G-)}{P(Disease\ \textbf{not}\ Present)}$$

Main Assumptions: Data missing at random; Factors considered by the guideline are the only factors that influence imaging decisions.

Begg, C.B., Greenes, R.A. Assessment of diagnostic tests when disease verification is subject to selection bias, *Biometrics*, 39 (207), 1983

Optimizing clinical guidelines, accounting for verification bias

- Two important challenges:
  - Learning from <u>unlabeled data</u>
    - In practice not all patients receive imaging at diagnosis
  - Learning from <u>imbalanced data</u>
    - A minority of patients has metastatic cancer

- To address these challenges, we combined:

  - <u>Semi-supervised</u> learning
  - <u>Cost-sensitive</u> learning

Cost-sensitive Laplacian Kernel Logistic Regression

Higher cost on missing metastatic cancers

$$f^* = \underset{f \in \mathcal{H}}{\operatorname{argmin}} \frac{1}{l} \sum_{i=1}^{l} \boxed{\delta \mathbb{1}_{\{y_i=1\}} \log\left(1 + e^{-f(\mathbf{x}_i)}\right)} + (1-\delta)\mathbb{1}_{\{y_i=-1\}} \log\left(1 + e^{f(\mathbf{x}_i)}\right)$$

$$+ \boxed{\gamma_{\mathcal{H}} \|f\|_{\mathcal{H}}^2} + \boxed{\gamma_{\mathcal{M}} \mathbf{f}^{\mathbf{T}} \mathbf{L} \mathbf{f}}$$

Avoid overfitting

Extract information from unimaged patients

Merdan, S., Barnett, C., Miller, D.C., Montie, J.E., Denton, B.T. "Data Analytics for Optimal Detection of Metastatic Prostate Cancer," *Operations Research,* 69 (3), 774-794, *2021*

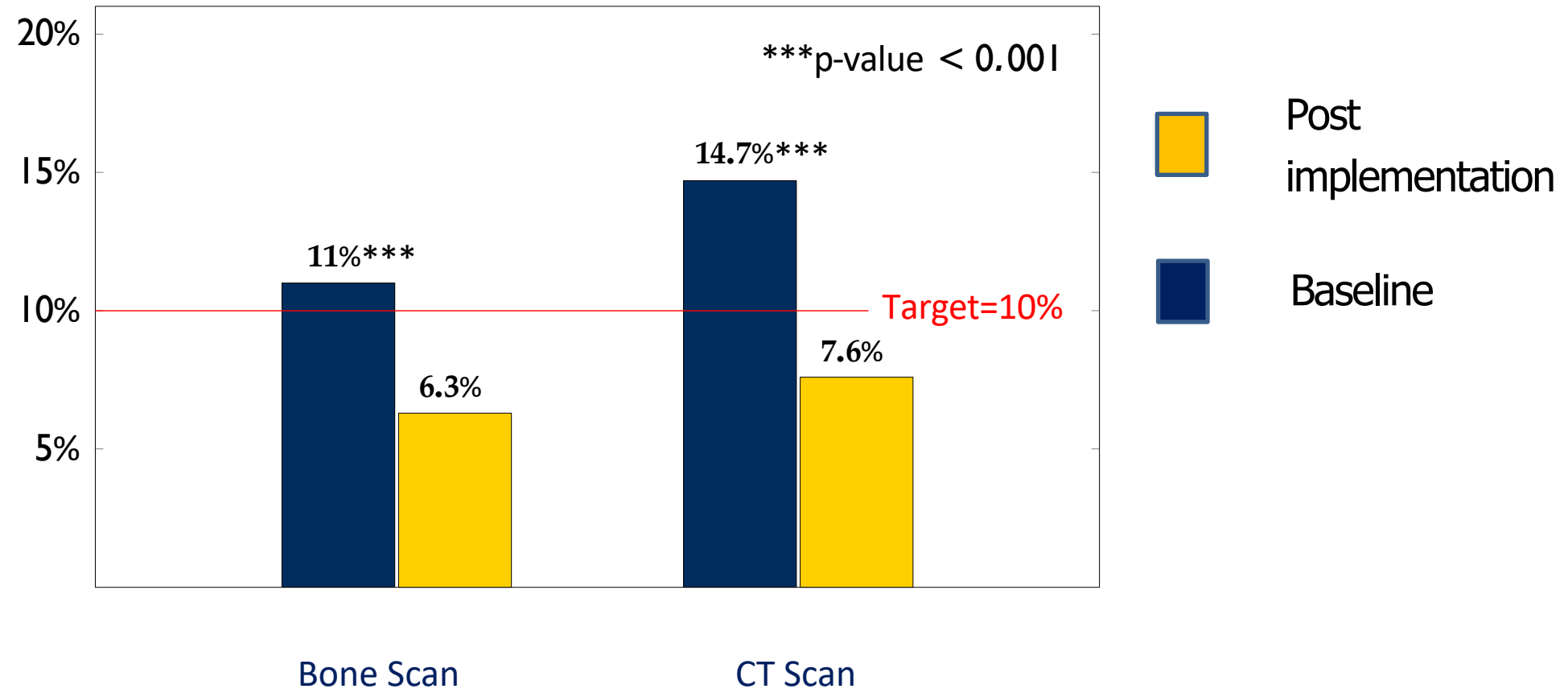# Imaging guideline performance

BS guideline design

CT scan guideline design

Percentage of patients with missed metastatic cancer

Briganti

NCCN

EAU

AUA

AUA

EAU

Number of negative studies per 1,000 men

Number of negative studies per 1,000 men
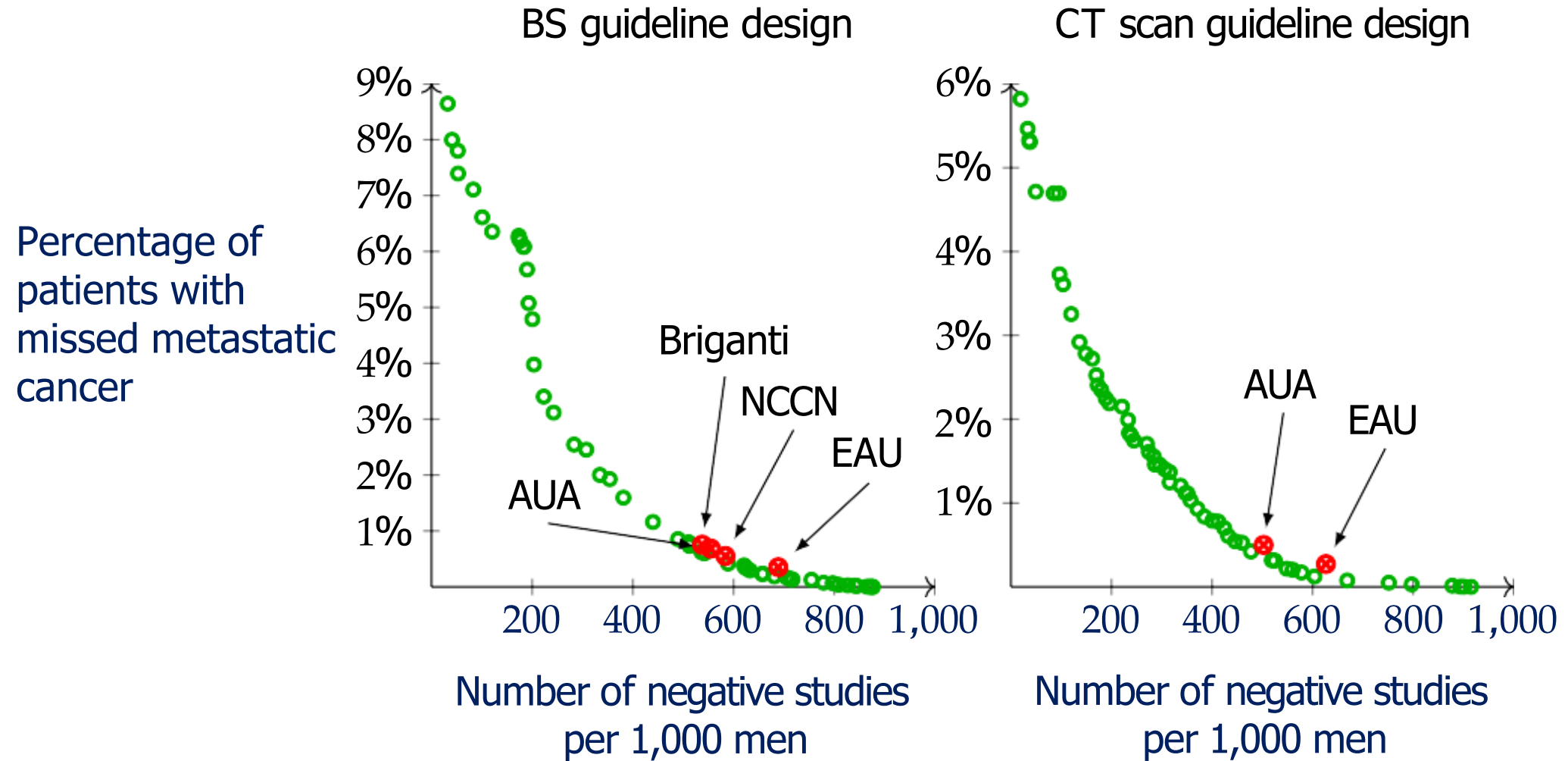
MUSIC state-wide decrease in imaging

Imaging rates for patients not fitting the criteria

***p-value < 0.001

Post implementation

Baseline

Bone Scan: Baseline 11%***, Post implementation 6.3%
CT Scan: Baseline 14.7%***, Post implementation 7.6%

Target=10%

3. What is the optimal strategy for <u>active surveillance</u> of low-risk prostate cancer?

Movember Foundation initiative

Global database for active surveillance:

- Includes >15,000 patients from 25 established AS cohorts worldwide
- Longitudinal observations of clinical and demographic characteristics

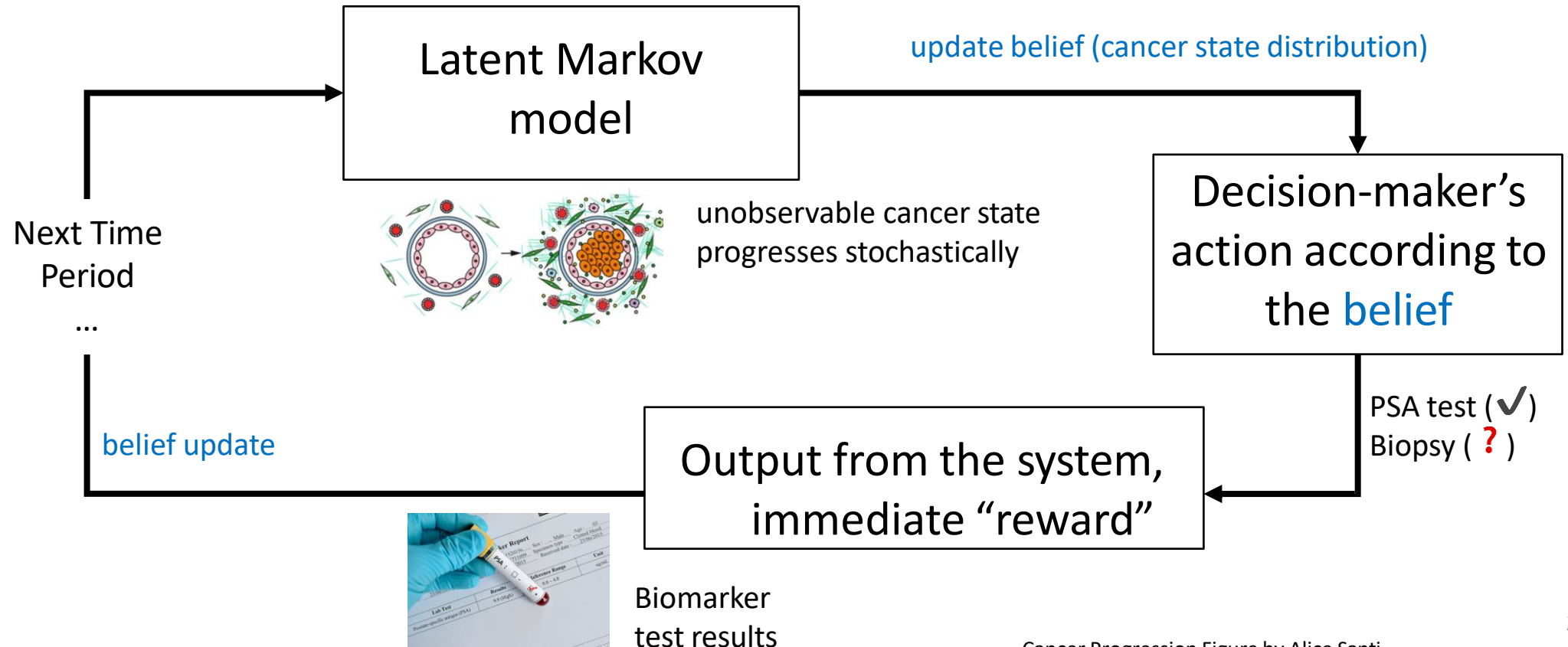We used the four most well known studies:

- Johns Hopkins (JH)
- University of California San Francisco (UCSF)
- University of Toronto (U of T)
- Prostate Cancer Research International Active Surveillance (PRIAS) project
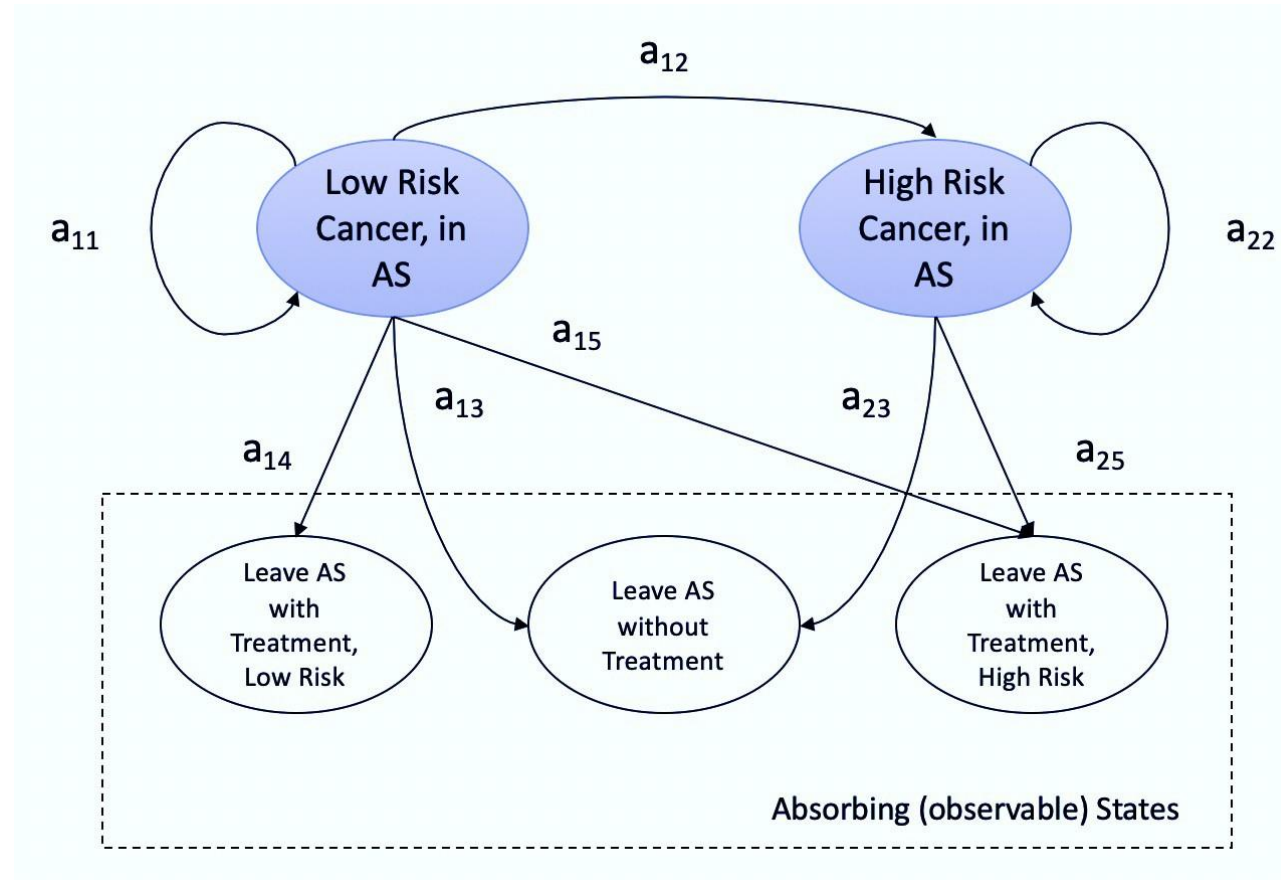
Movember Foundation initiative

Active surveillance

Active Surveillance (AS): monitoring "low-risk" prostate cancer patients with biomarkers and biopsies.

Latent Markov model

update belief (cancer state distribution)

unobservable cancer state progresses stochastically

Next Time Period ...

Decision-maker's action according to the belief

PSA test (✔)
Biopsy (❓)

belief update

Output from the system, immediate "reward"

Biomarker test results

Cancer Progression Figure by Alice Santi

Latent Markov model for prostate cancer AS

Learned Model Parameters

- Initial distribution at diagnosis

- Transition probability matrix

- Observation probabilities

Li, W. et al. "Comparison of biopsy under-sampling and annual progression using hidden Markov models to learn from prostate cancer active surveillance studies," *Cancer Medicine,* 9(24):9611-9619, 2020

Partially observable Markov decision process

Belief Vector:

$$b_i^t = P(S_t = i), \qquad i \in \{\text{Low Risk, High Risk}\}$$
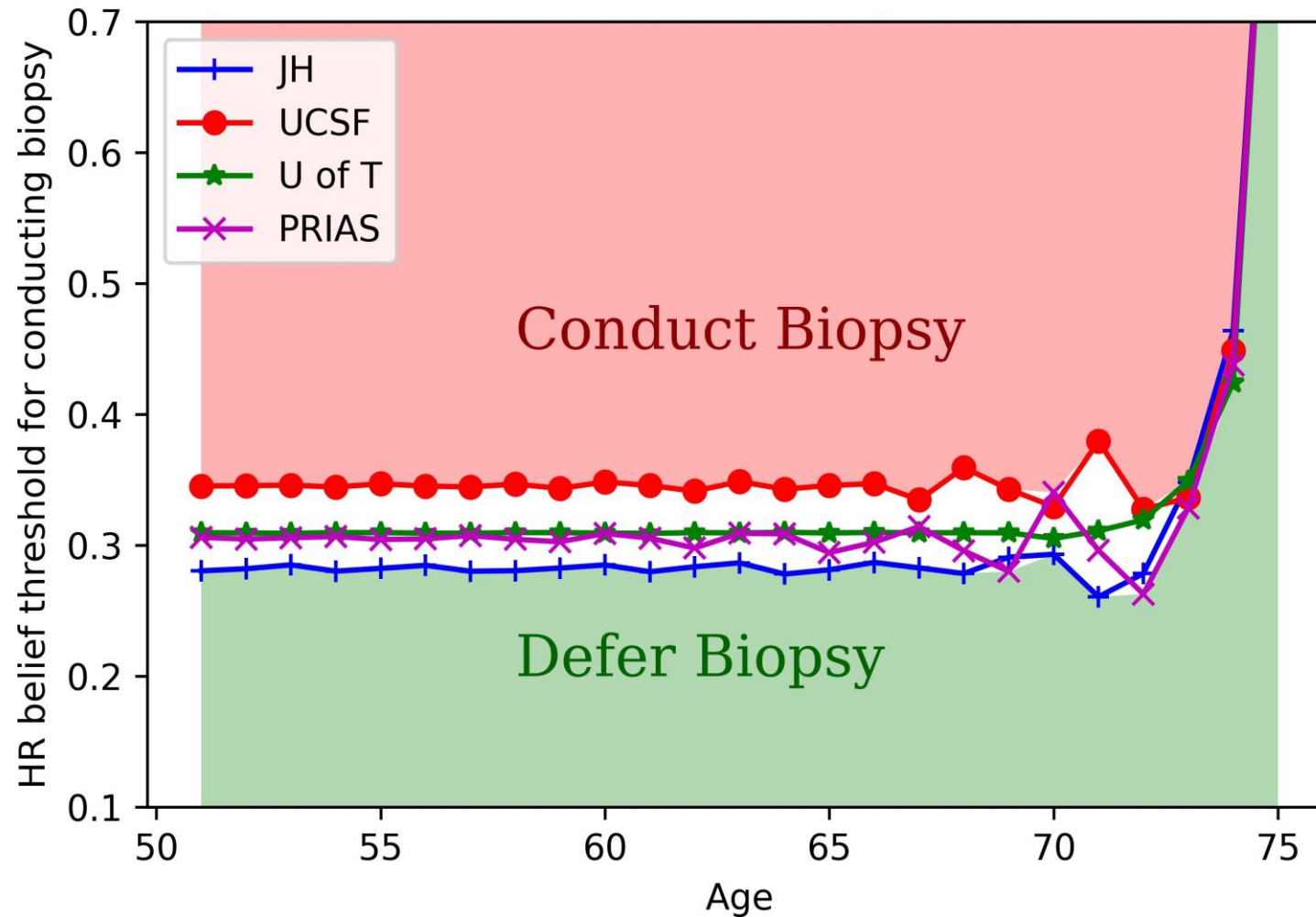
Optimality Equations:

$$V_t(b^t) = \max_{a_t}\{b^t r(a_t) + \sum_{o_t \in O} P(o_t | b^t, a_t) V_{t+1}(b^{t+1}(b^t | a_t, o_t))\}, \forall t, b_t$$

Optimal Decision:

$$a_t^*(b^t) = \arg \max_{a_t}\{b^t r(a_t) + \sum_{o_t \in O} P(o_t | b^t, a_t) V_{t+1}(b^{t+1}(b^t | a_t, o_t))\}$$

Optimal policies

Li W., Denton B.T., Morgan T.M.. "Optimizing Active Surveillance for Prostate Cancer Using Partially Observable Markov Decision Processes," *European Journal of Operational Research (in press),* 2022.

Recent adventures optimizing under ambiguity

Models for chronic disease to help resolve model ambiguity

1. **Steimle, L.**, Kauffman, D., Denton, B.T., "Multi-model Markov Decision Processes: A New Method for Mitigating Parameter Ambiguity," IISE *Transactions*, 53(10):1124-39, 2022

2. **Steimle, L**., Ahluwalia, V., Kamdar, C., Denton, B.T., "Decomposition Methods for Solving Multi-model Markov Decision Processes*," IISE Transactions,* 53 (12), 1295-1310, 2022

Working paper:

Li, W., Denton, B.T., "Multi-model Partially Observable Markov Decision Processes," Working Paper (available at *Optimization Online*), 2023

Recap

1. Should biomarkers be used for <u>early detection</u> of prostate cancer?

2. When should imaging be used for <u>staging</u> of prostate cancer?

3. What is the optimal strategy for <u>active surveillance</u> of low-risk prostate cancer?

Theme: personalization of medical decisions matters!

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MUSIC Collaborative