COLLEGE OF ENGINEERING
INDUSTRIAL & OPERATIONS ENGINEERING
UNIVERSITY OF MICHIGAN

Predictive and Prescriptive Models for Early Detection of Prostate Cancer

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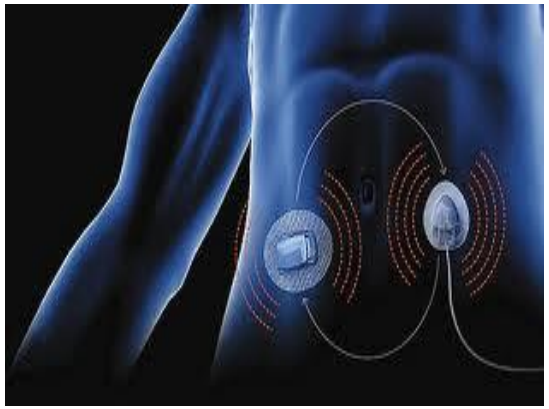
Chronic Diseases

Cancer

Diabetes



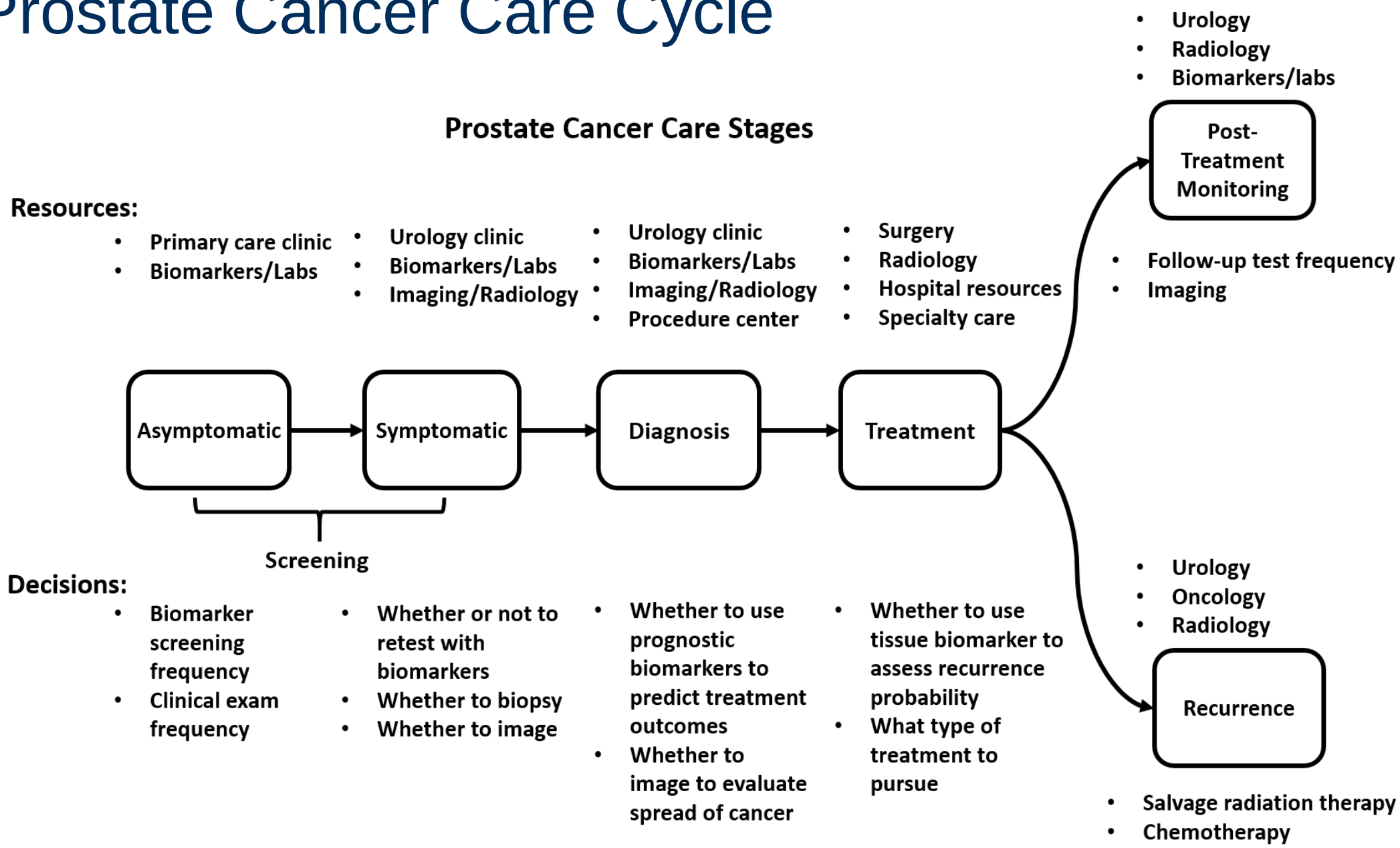
Kidney Disease

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 Screening and Early Detection

Zhang, Z., Denton, B.T., Morgan, T., “Optimization of Active Surveillance Strategies for Heterogeneous Patients with Prostate Cancer,” *Production and Operations Management* 31(11); 4021-4037, 2022, 2022.

Barnett, C., Davenport, M.S., Montgomery, J.S., Kunju, L.P., Denton, B.T., Piert, M., “18F-choline PET/mpMRI for Detection of Significant Prostate Cancer: Part 2. Cost-Effectiveness Analysis,” *Journal of Nuclear Medicine, 60*(12), 1705-1712, 2019.

Barnett, C.L., Tomlins, S.A., Underwood**,** D.J., Morgan, T.M., Montie, J.E., Wei, J.T., Denton, B.T., “Two-Stage Biomarker Protocols for Improving the Precision of Early Detection of Prostate Cancer," *Medical Decision Making, 37*(7), 815-826*,* 2017.

Merdan, S., Tomlins, S.A., , **Barnett, C.L., Underwood, D.J.**, Morgan, T.M., Montie, J.E., Wei, J.T., Denton, B.T., “Assessment of Long Term Outcomes Associated with Urinary Prostate Cancer Antigen 3 and TMPRSS2:ERG Gene Fusion at Repeat Biopsy," *Cancer,* 122(22), 4071-4079, 2015.

Zhang, J., Denton, B.T., Balasubramanian, H., Inman, B., Shah, N., “Optimization of Prostate Biopsy Decisions,‘’ *Manufacturing & Service Operations Management*, 14(4): 529-547, 2012.

Two Examples – Diagnosis and Treatment

1. When should imaging be used for staging of prostate cancer?

2. What is the optimal strategy for active surveillance of low-risk prostate cancer?

1. When should imaging be used for staging of prostate cancer?

Imaging modalities

Bone Scan (BS)

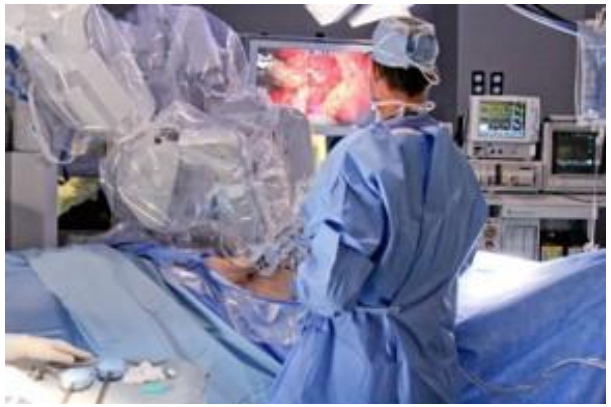
- Detect bone metastasis

Computed Tomography (CT)

- Detects lymph node metastasis

Harms of not 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 harmful radiation exposure
- Incidental findings that require painful and risky follow-up procedures (e.g., bone biopsy)
- Blocks access to imaging resources for other patients and unnecessarily increases healthcare costs

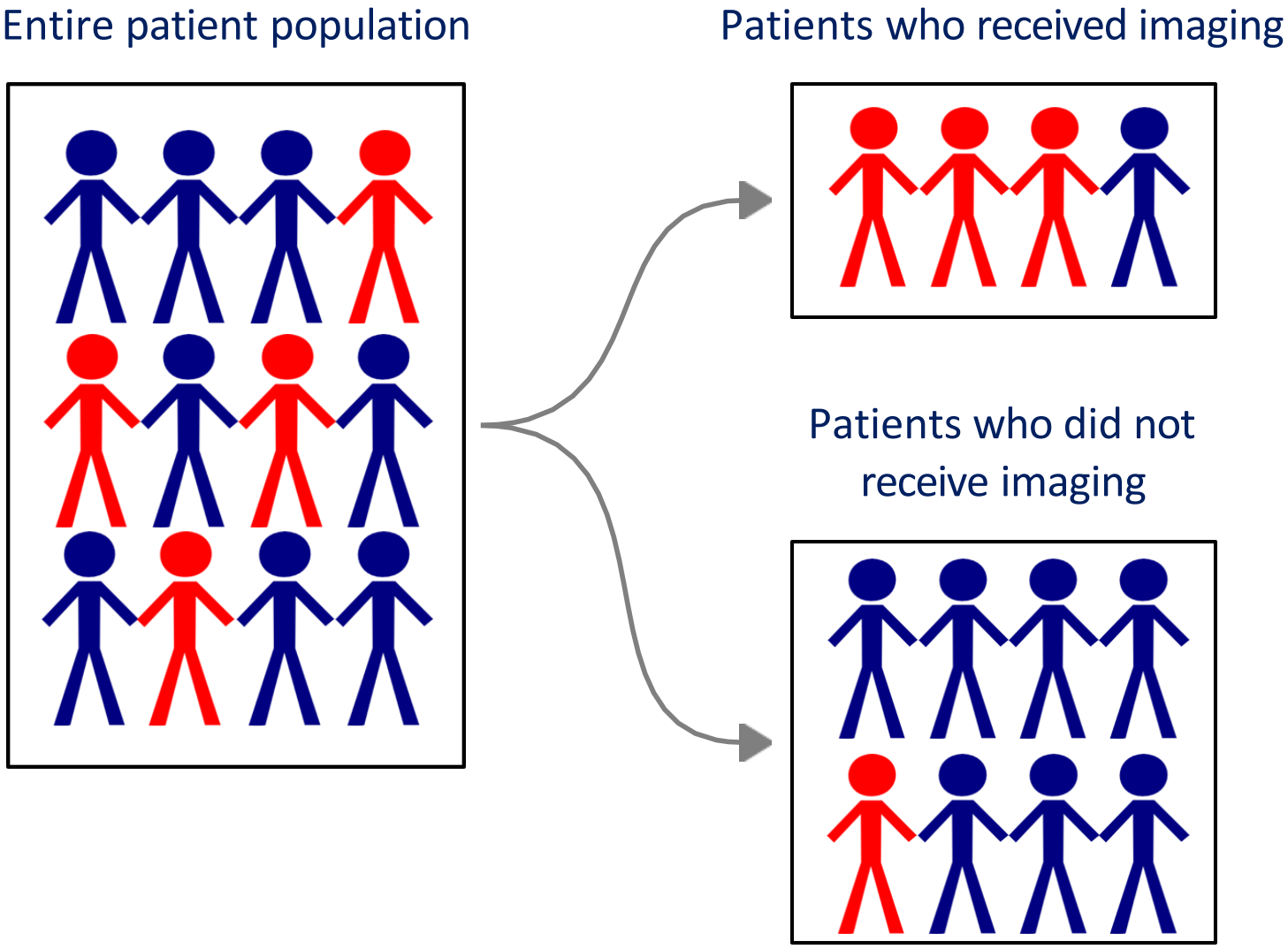
Michigan Urological Surgery Improvement Collaborative

- 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



Effects of verification bias

	Uncorrected		Bias-corrected	
	Sensitivity	Specificity	Sensitivity	Specificity
Clinical guidelines				
Bone scan				
EAU	97.9	33.4	84.5	75.7
AUA	97.9	43.5	81.2	82.0
NCCN	97.9	40.8	82.3	80.9
Briganti's CART	89.6	45.4	79.3	83.3
CT scan				
EAU	98.4	36.5	89.9	74.4
AUA	96.8	49.2	87.2	82.5

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:

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

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

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

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

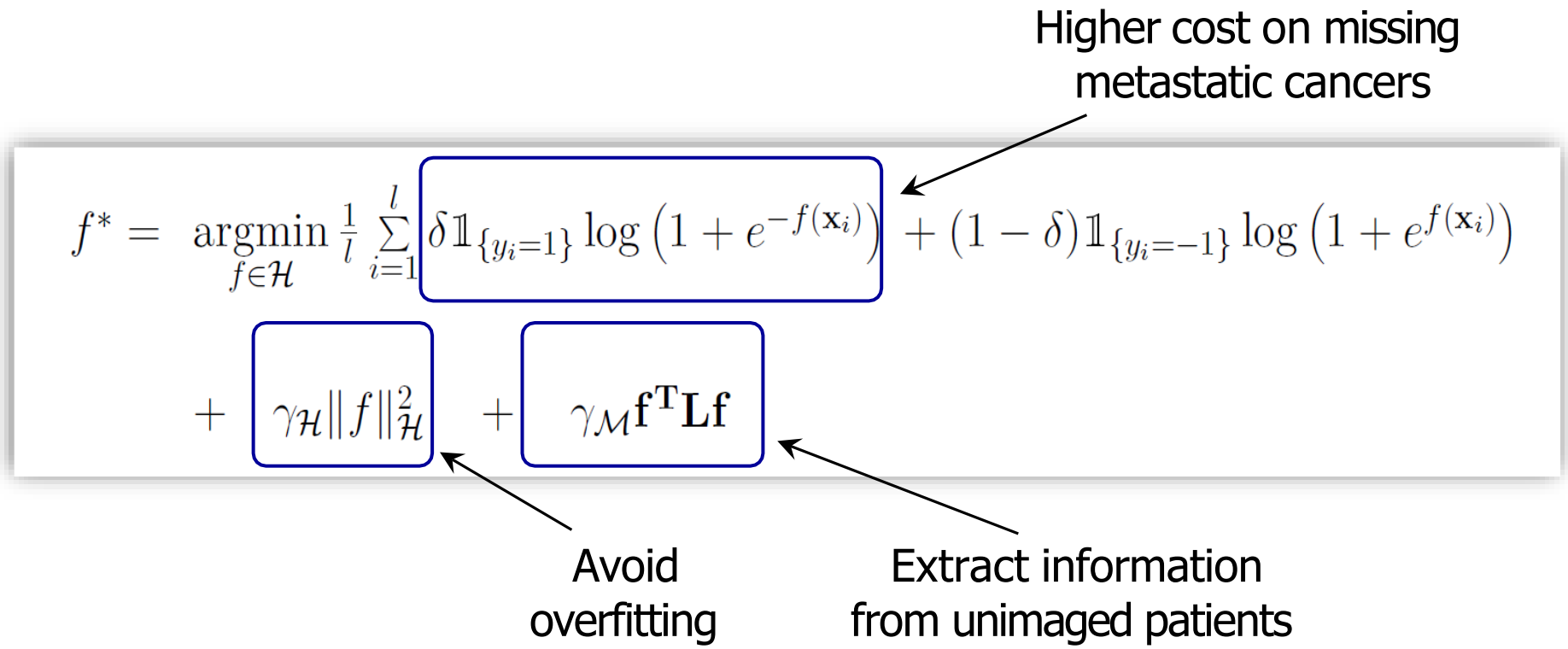
Main Assumptions: Data missing at random; Factors considered by the guideline are the only factors that influence imaging decisions.

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 unlabeled data
    - In practice not all patients receive imaging at diagnosis
  - Learning from imbalanced data
    - A minority of patients has metastatic cancer
- To address these challenges, we combined:
  - Semi-supervised learning
  - Cost-sensitive learning

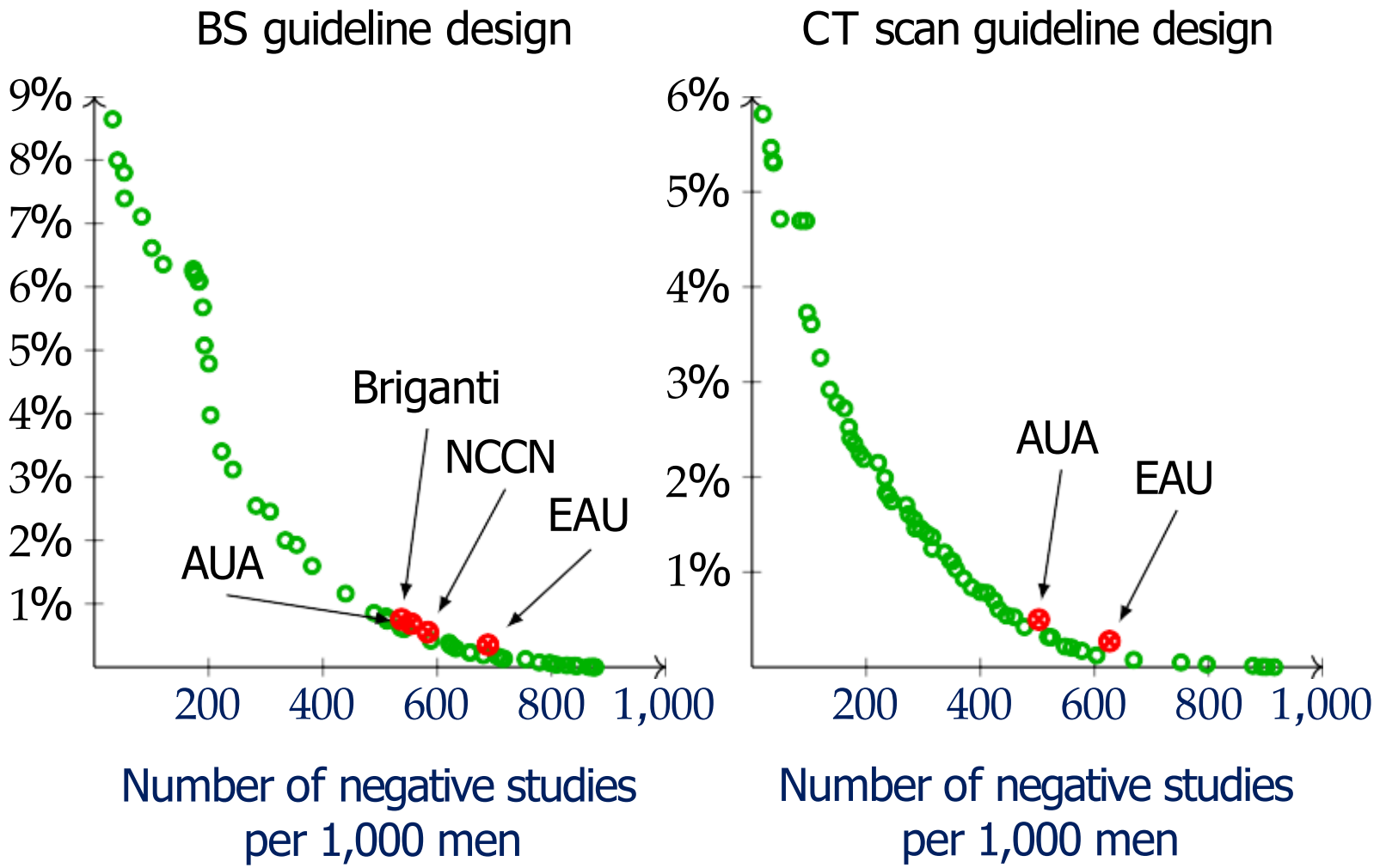
Cost-sensitive Laplacian Kernel Logistic Regression



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*

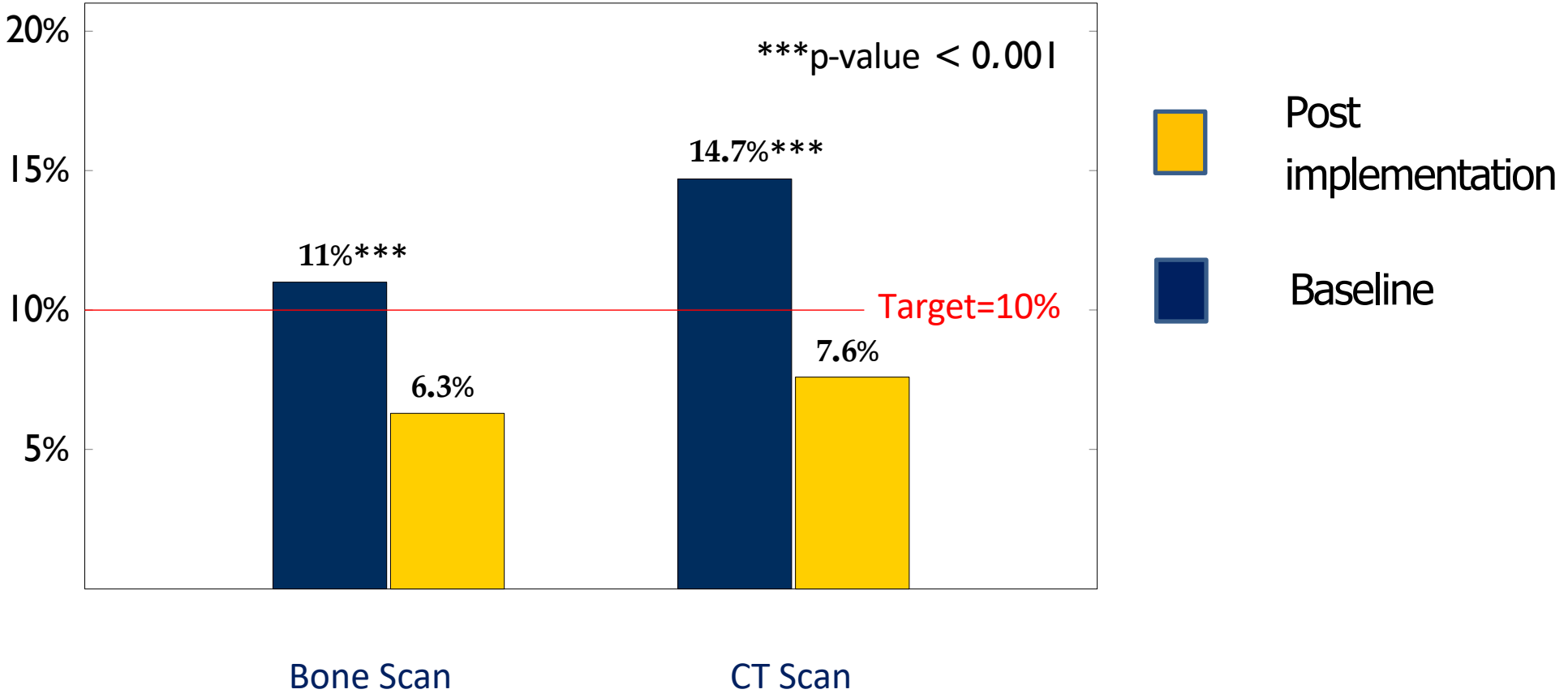
Imaging guideline performance

Percentage of patients with missed metastatic cancer



MUSIC state-wide decrease in imaging

Imaging rates for patients not fitting the criteria



2. What is the optimal strategy for active surveillance of low-risk prostate cancer?

Movember Foundation

Global database for active surveillance:

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

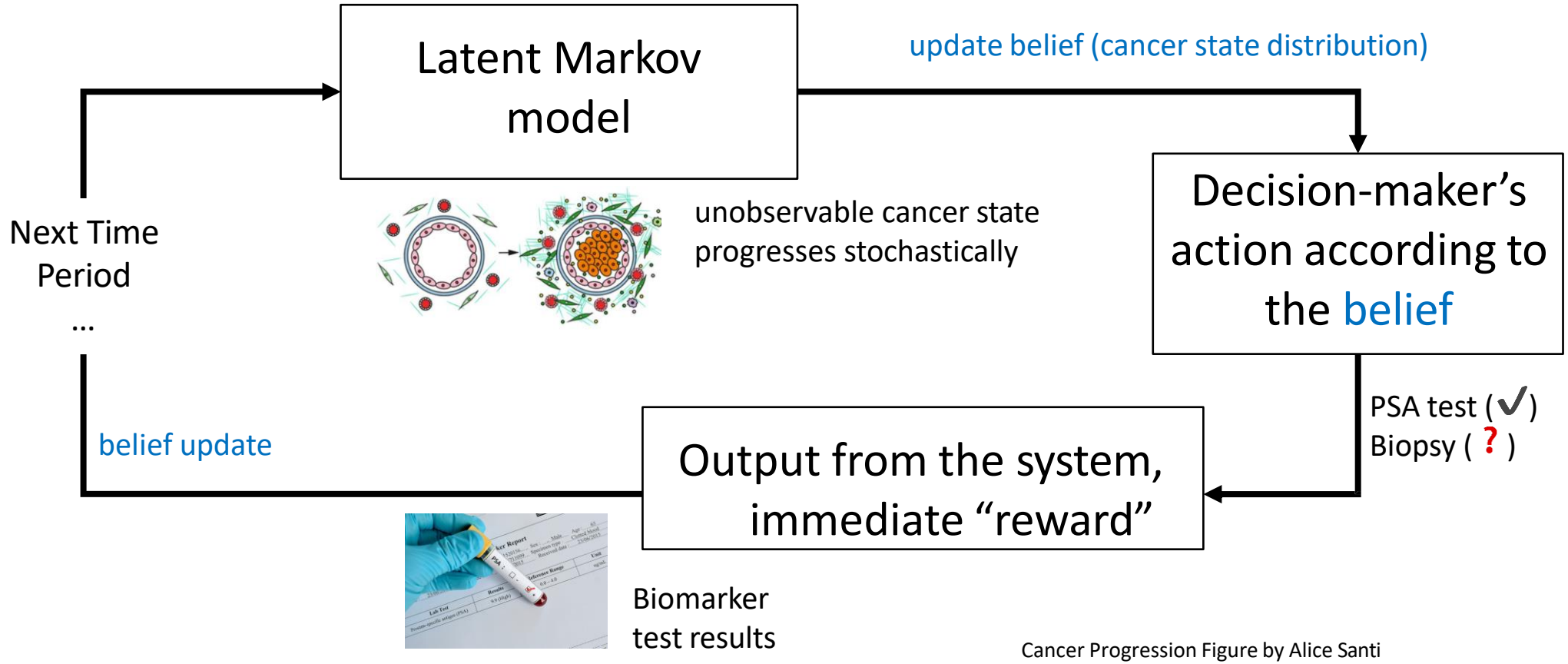
We used the four most well known studies:

- 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

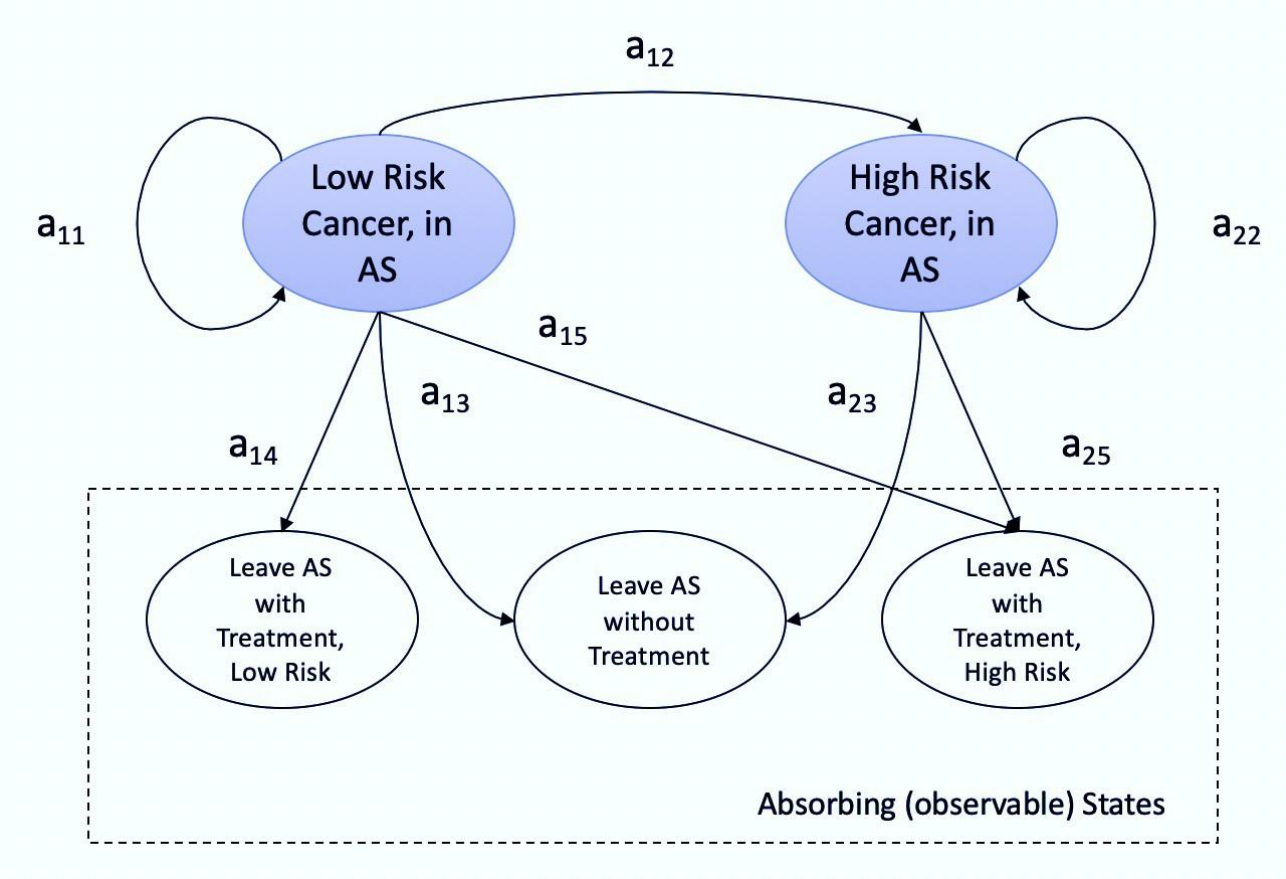
Active surveillance

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



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:

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

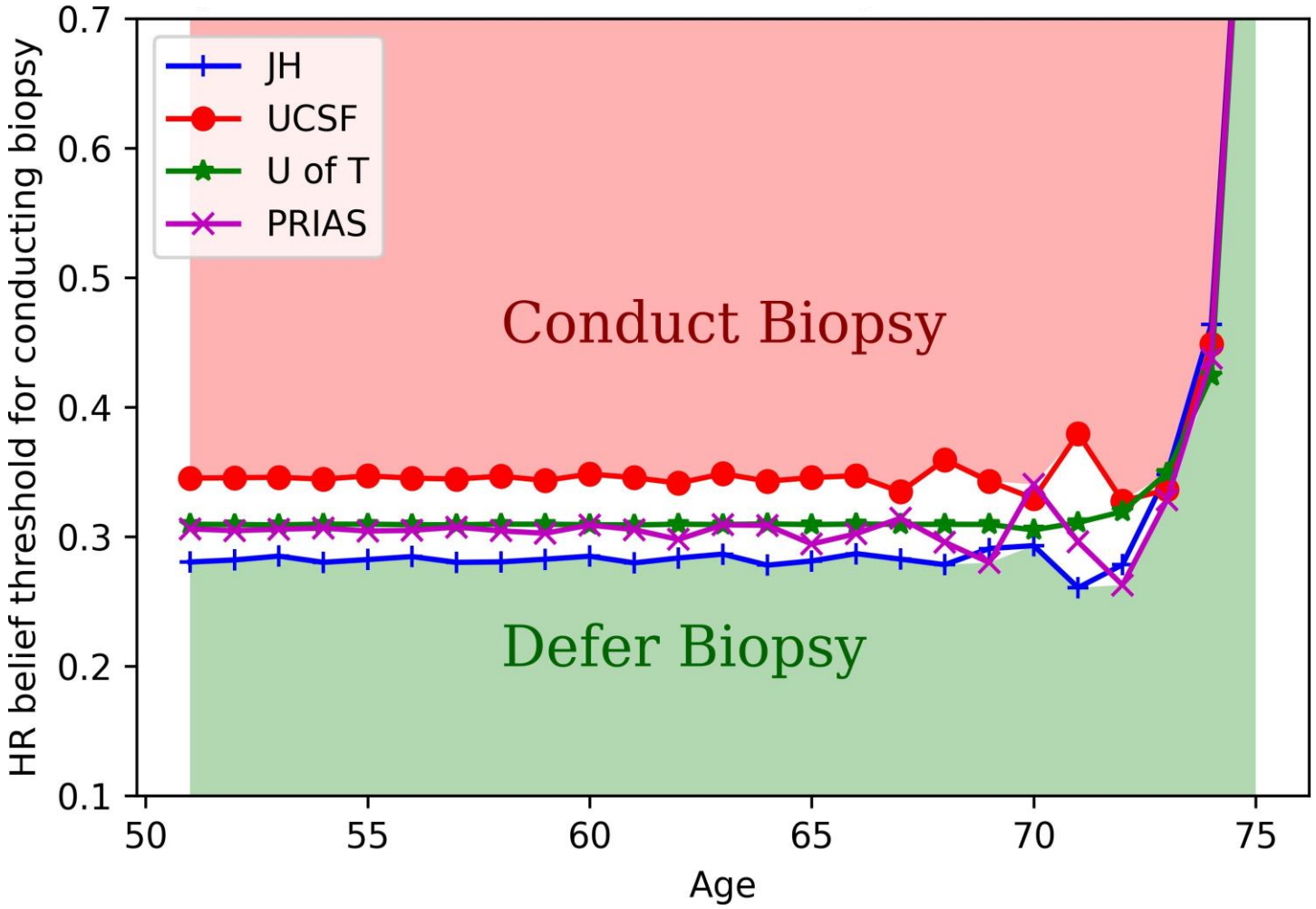
Optimality Equations:

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

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*, 350(1), 386-399, 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, 2021

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, 2021

A forthcoming study addresses this for active surveillance:

Li, W., Denton, B.T., “Multi-model Partially Observable Markov Decision Processes,” Submitted to *INFORMS Journal On Computing*, 2023

Recap

1. When should imaging be used for staging of prostate cancer?

2. What is the optimal strategy for active surveillance of low-risk prostate cancer?

Theme: personalization of medical decisions matters!

Acknowledgments

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