COLLEGE OF ENGINEERING
INDUSTRIAL & OPERATIONS ENGINEERING
UNIVERSITY OF MICHIGAN

Predictive and Prescriptive Models for Early Detection of Prostate Cancer

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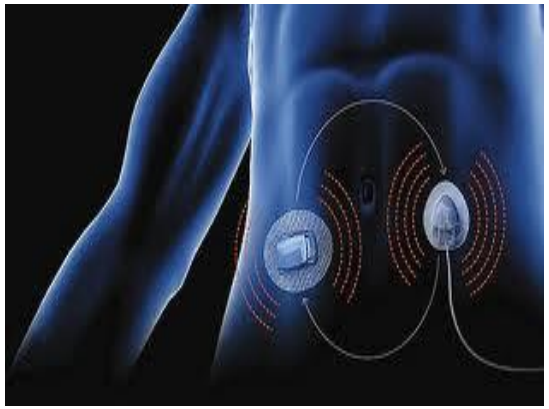
Chronic Diseases

Cancer

Diabetes



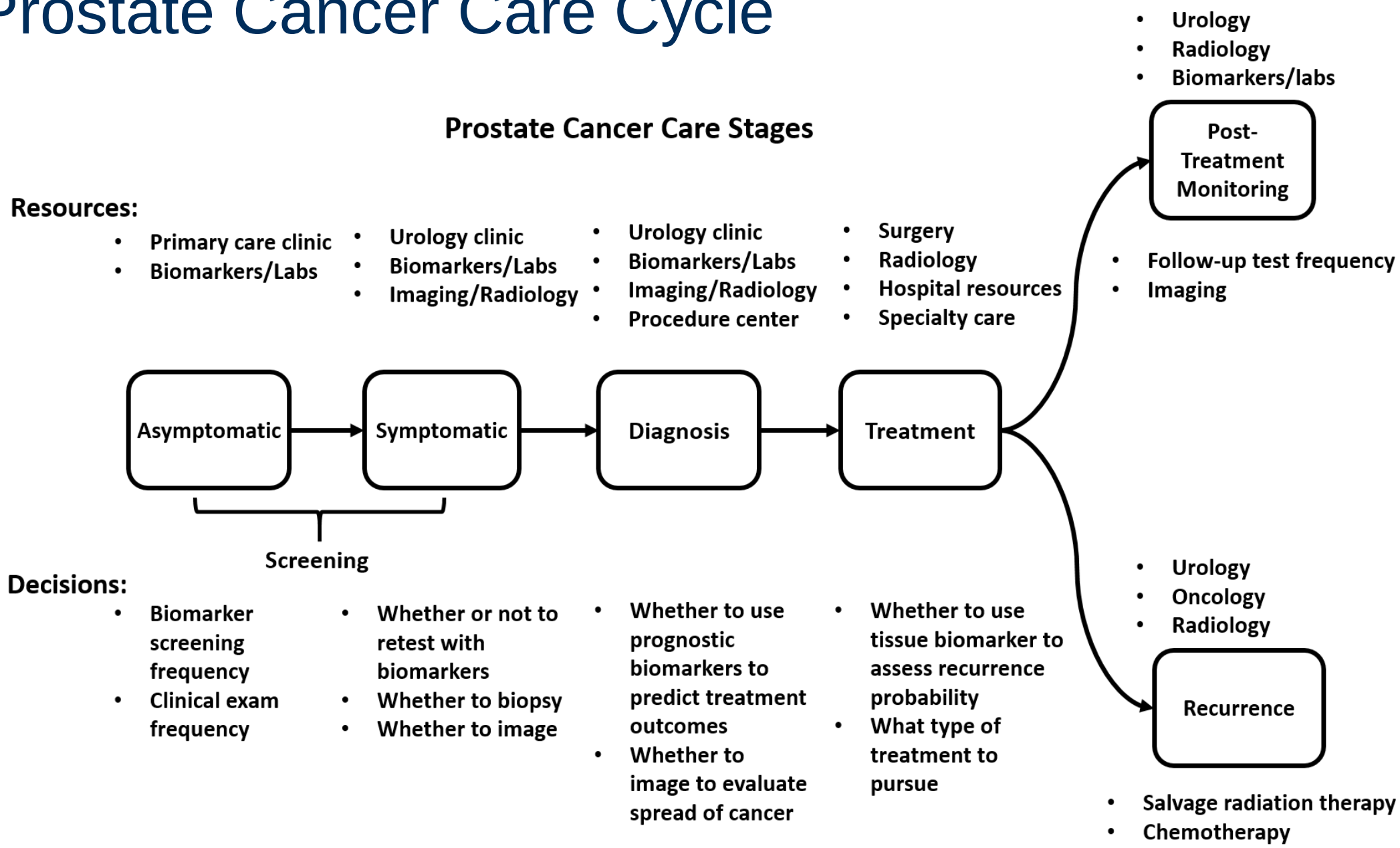
Kidney Disease

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



Three Examples

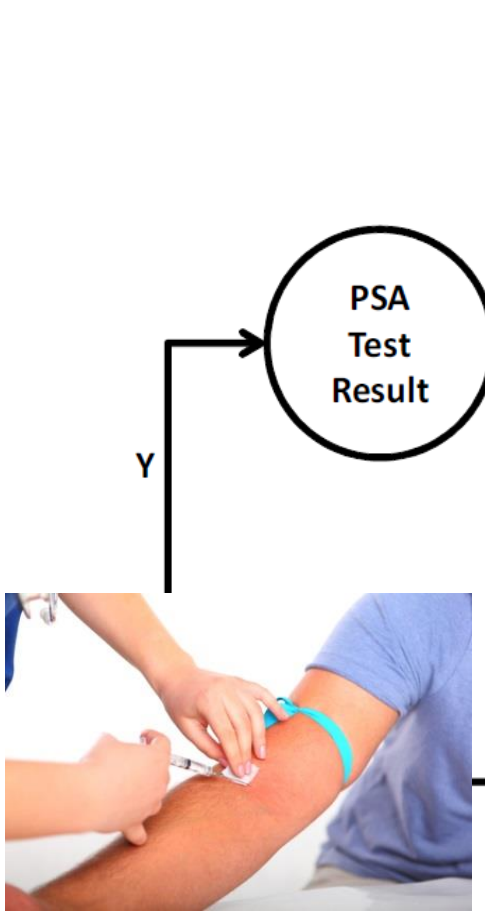
1. Should new biomarkers be used for early detection of prostate cancer?

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

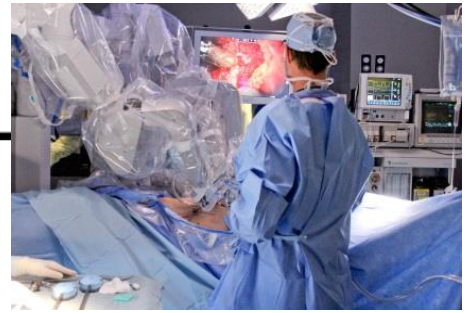
3. What is the optimal strategy for active surveillance of low-risk prostate cancer?

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

Prostate cancer screening



Age 50



PSA Test Result

Y

N

Biopsy Result

Biopsy +

Biopsy -

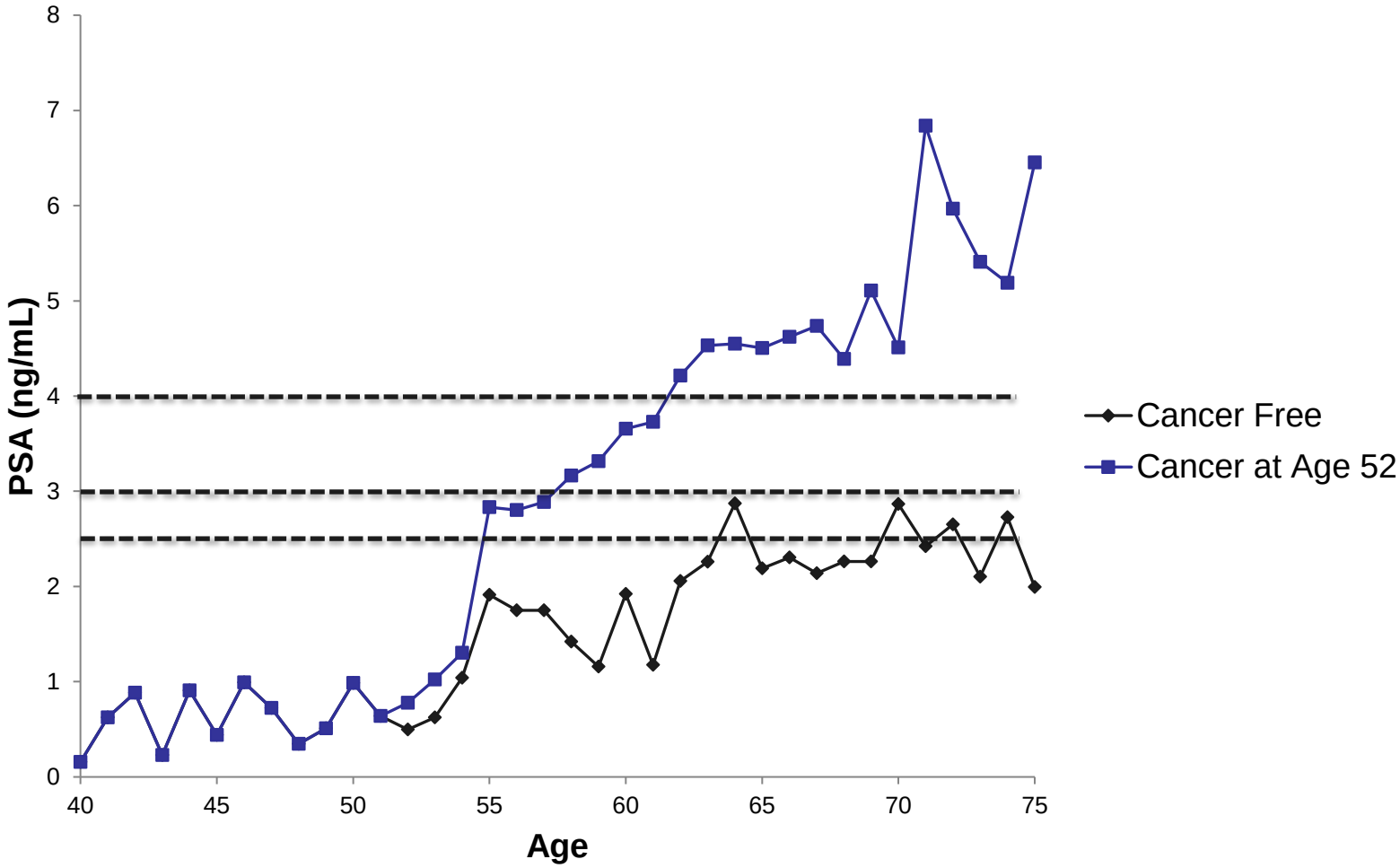
Y

PSA Test?

N

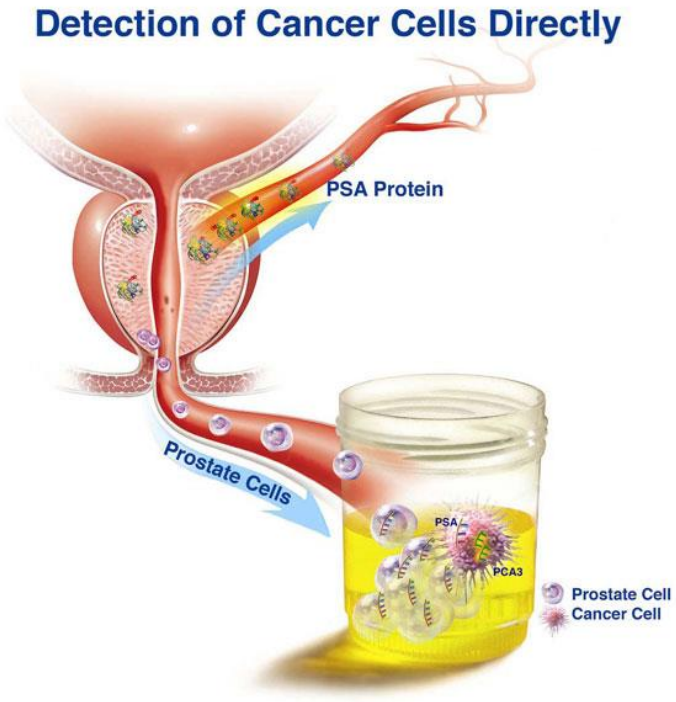
Age 51

PSA screening model example



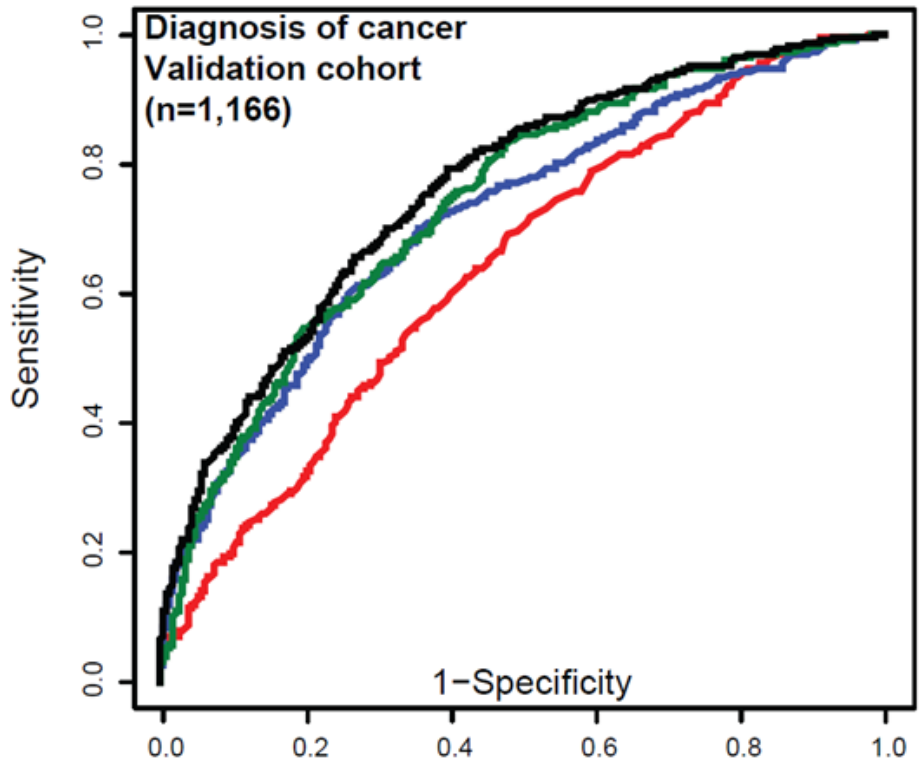
Underwood DJ, Zhang J, Denton BT, Shah ND, Inman BA. Simulation optimization of PSA-threshold based prostate cancer screening policies. *Health Care Management Science*.2012 15(4):293-309.

Urine-based biomarkers for prostate cancer



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

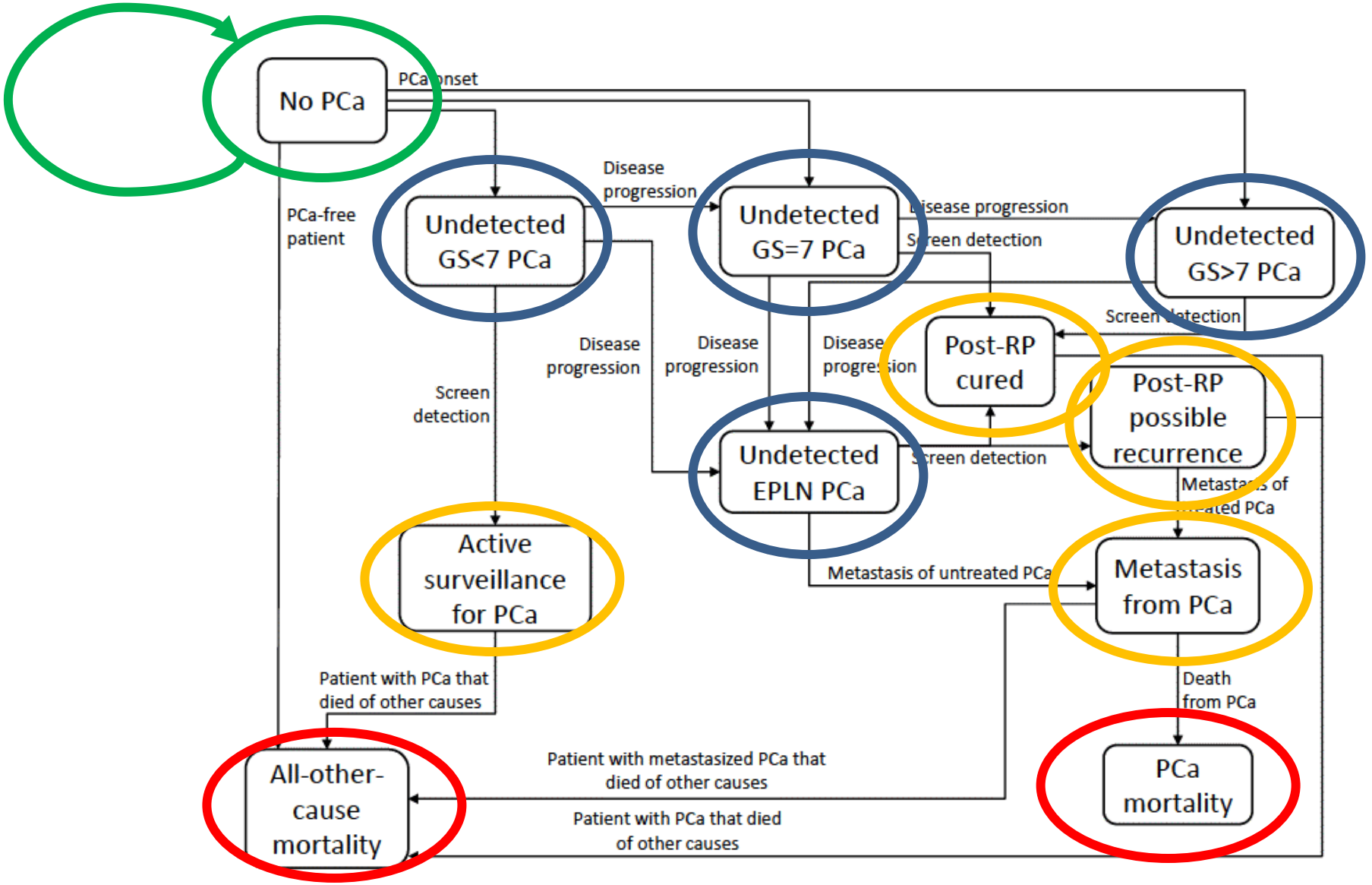
Improving predictions for prostate cancer



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

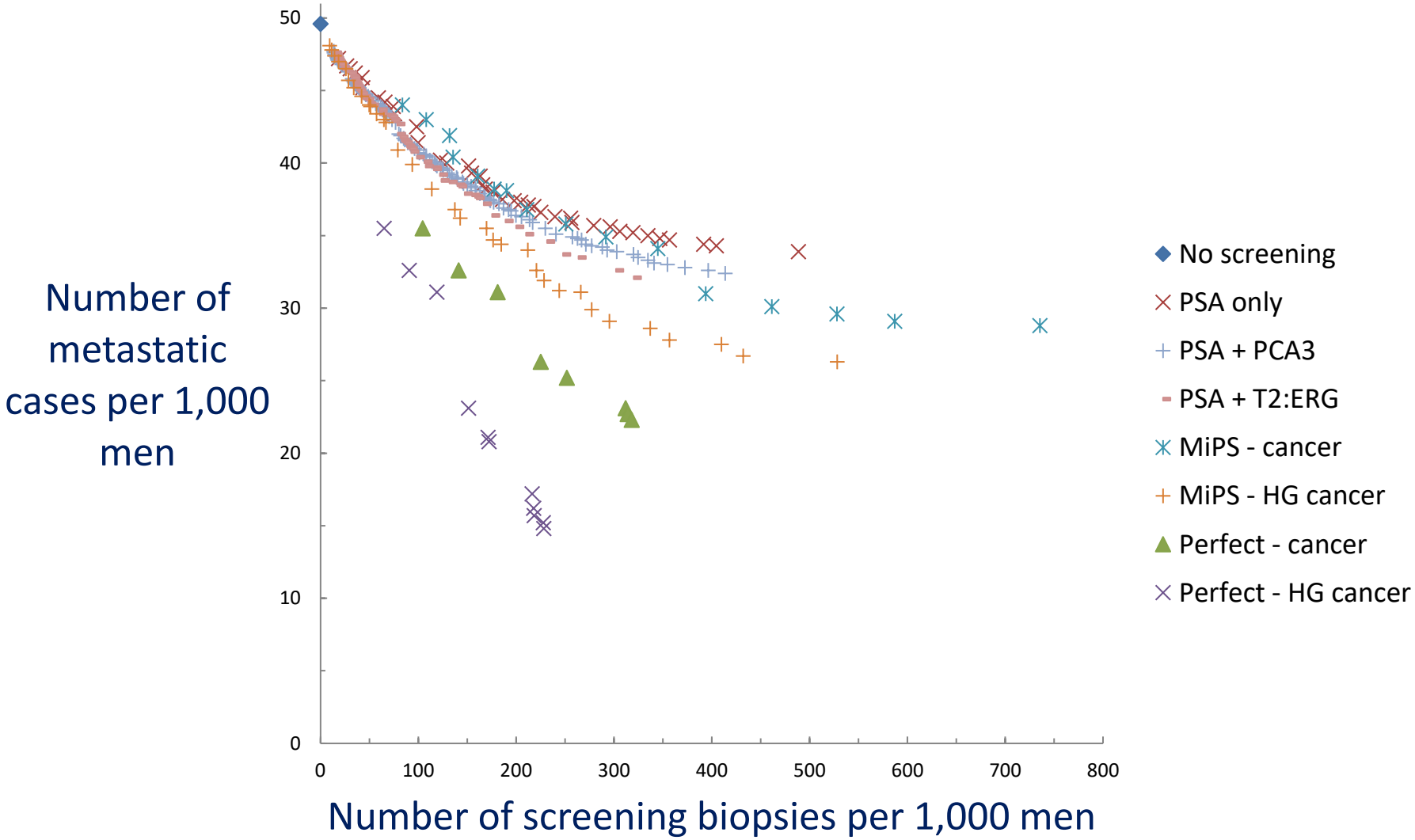
Tomlins SA, Day JR, Lonigro RJ, Hovelson DH, Siddiqui J, Kunju LP, Dunn RL, Meyer S, Hodge P, Groskopf J, Wei JT, Chinnaiyan AM. "Urine TMPRSS2:ERG + PCA3 for individualized prostate cancer risk assessment," *European Urology*, 70(1), 45-53, 2016

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

High-grade cancer biomarkers could reduce biopsies and saves lives



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

Imaging modalities

Bone Scan (BS)

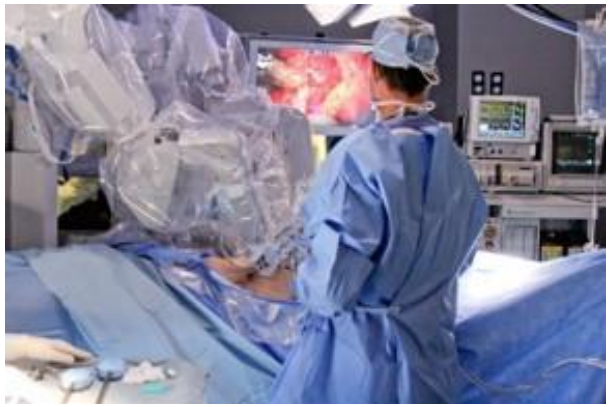
- Detect bone metastasis

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

Choosing Wisely®
An initiative of the ABIM Foundation

- 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

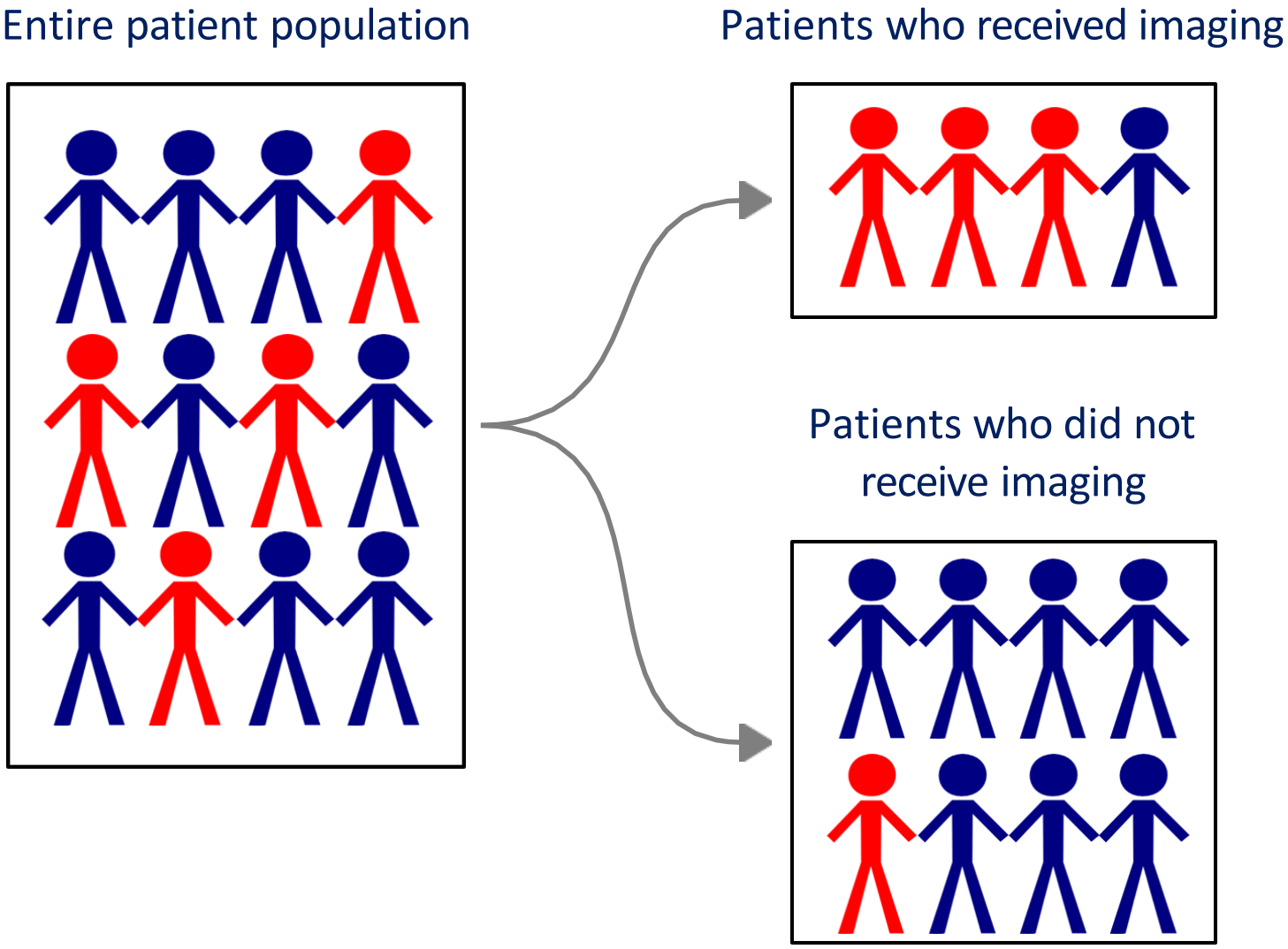
Michigan Urological Surgery Improvement Collaborative

- 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

Clinical guidelines	Sensitivity	Specificity
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:

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

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

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

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

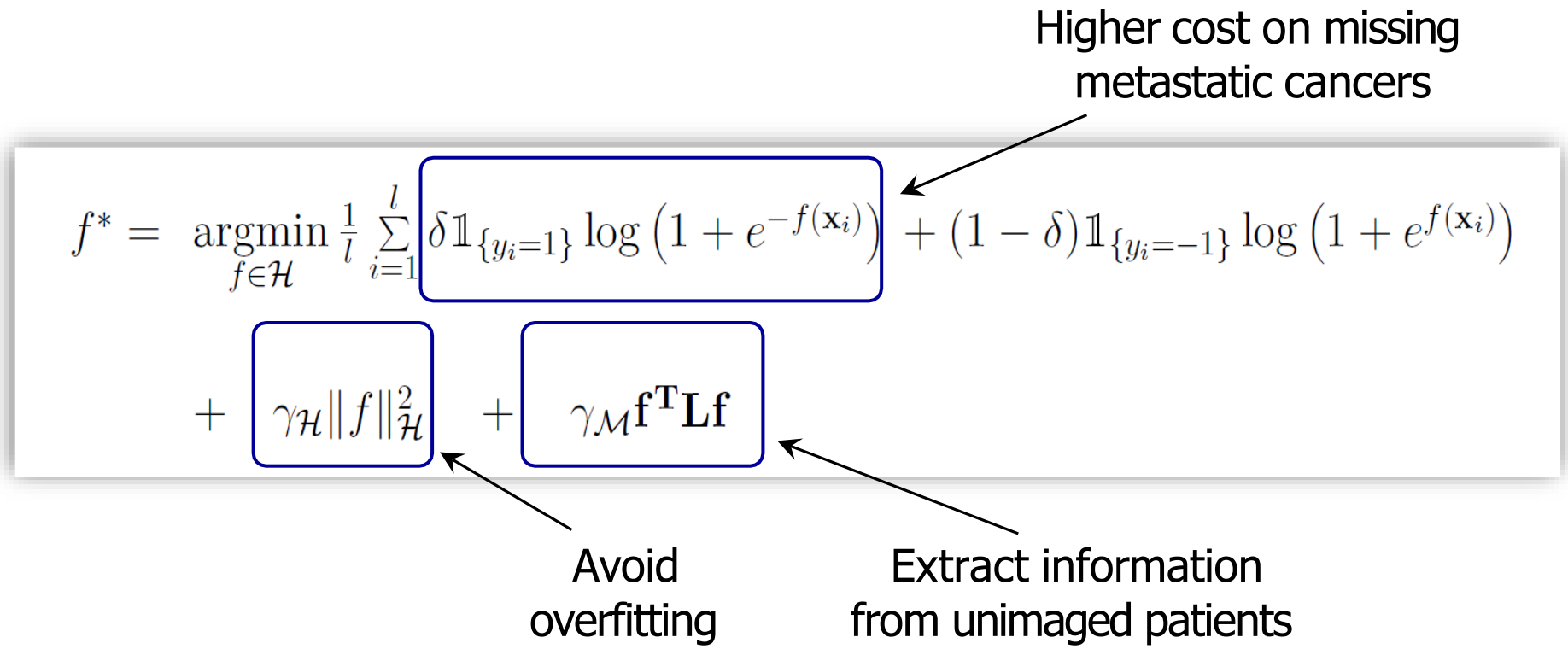
Main Assumptions: Data missing at random; Factors considered by the guideline are the only factors that influence imaging decisions.

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

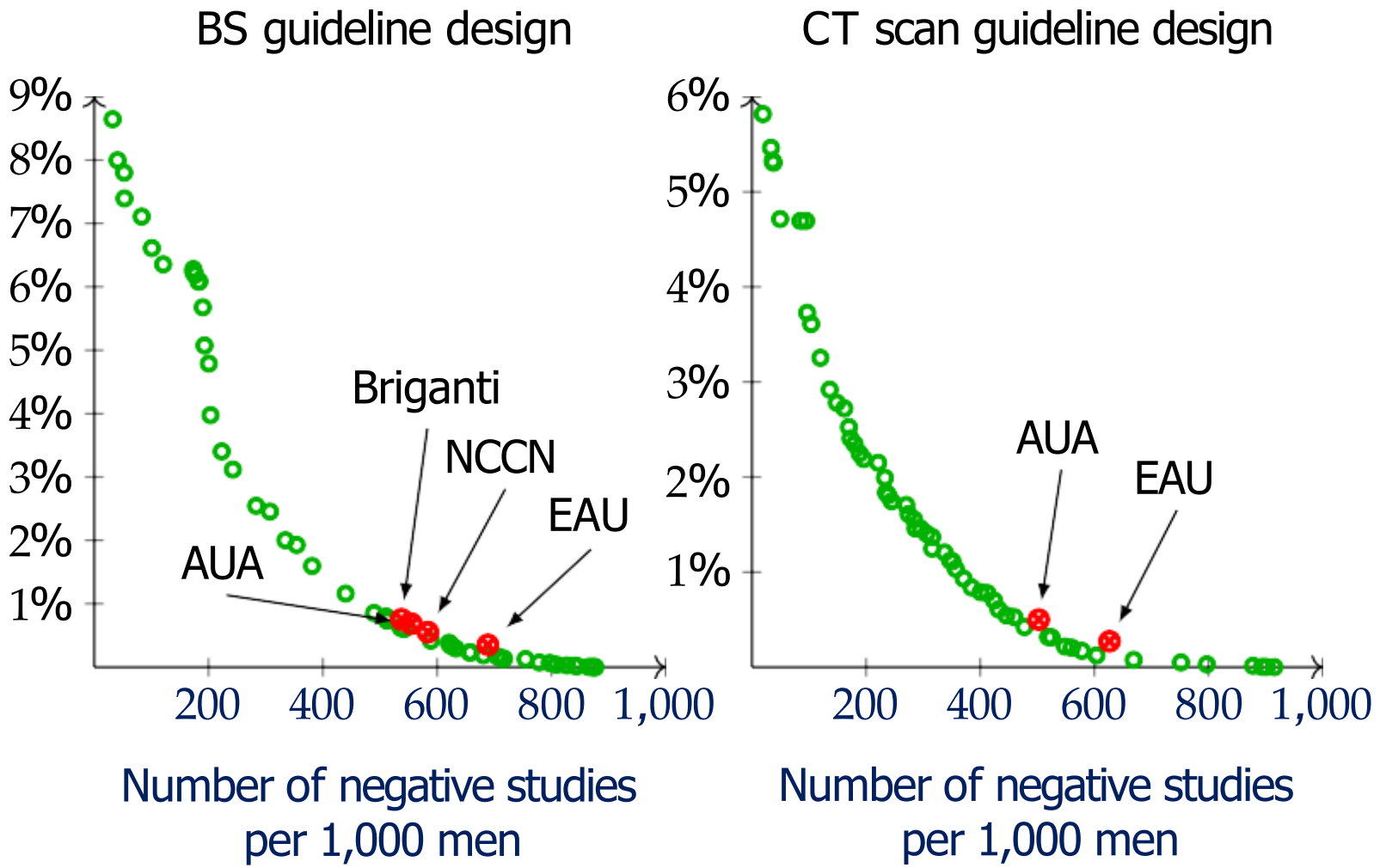
Cost-sensitive Laplacian Kernel Logistic Regression



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*

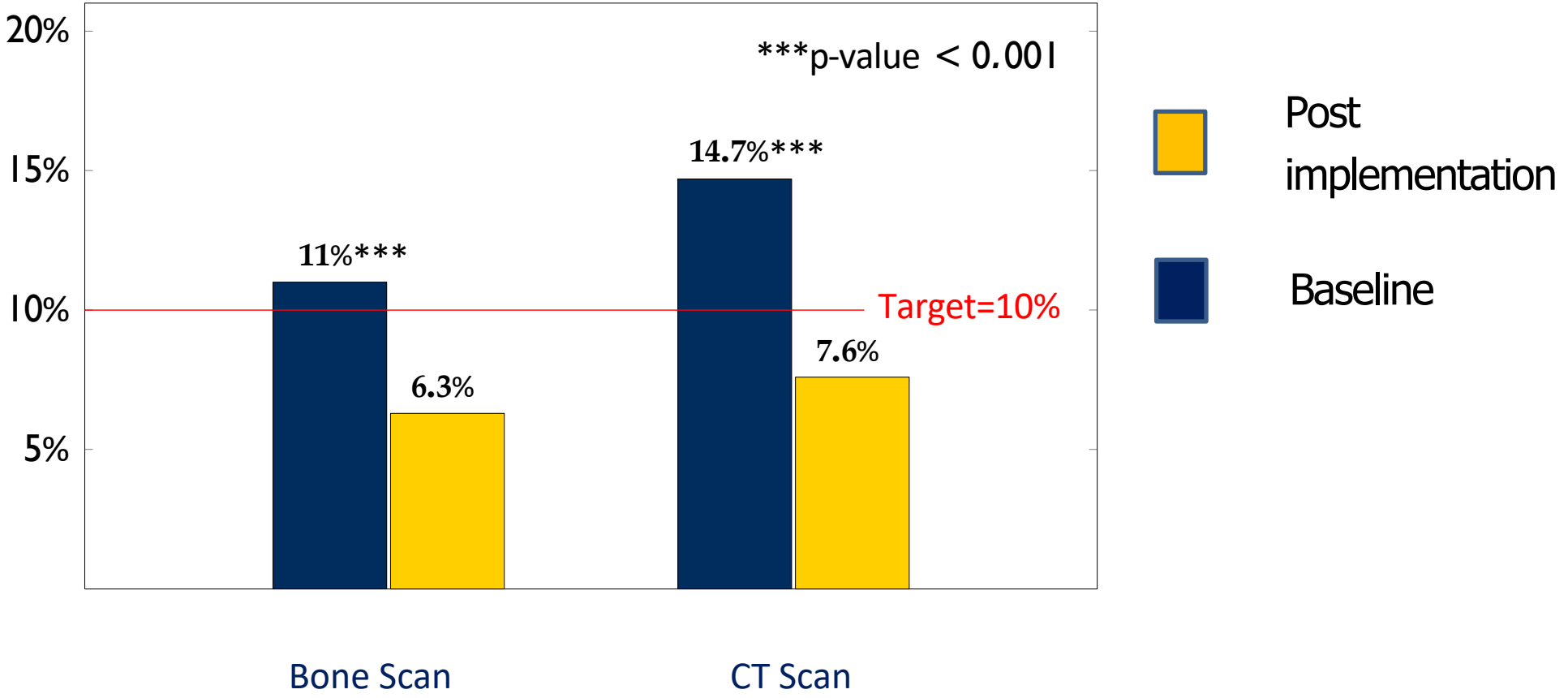
Imaging guideline performance

Percentage of patients with missed metastatic cancer



MUSIC state-wide decrease in imaging

Imaging rates for patients not fitting the criteria



3. What is the optimal strategy for active surveillance 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

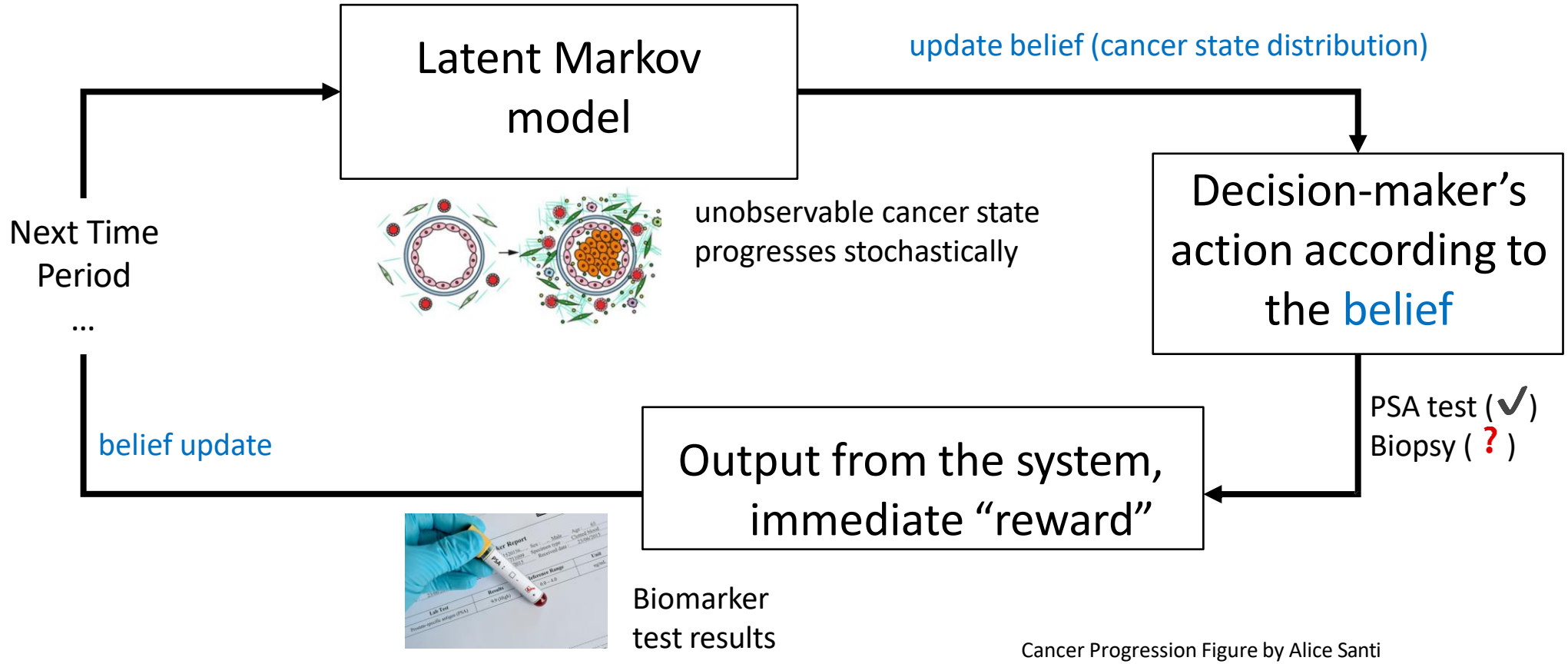
We used the four most well known studies:

- 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

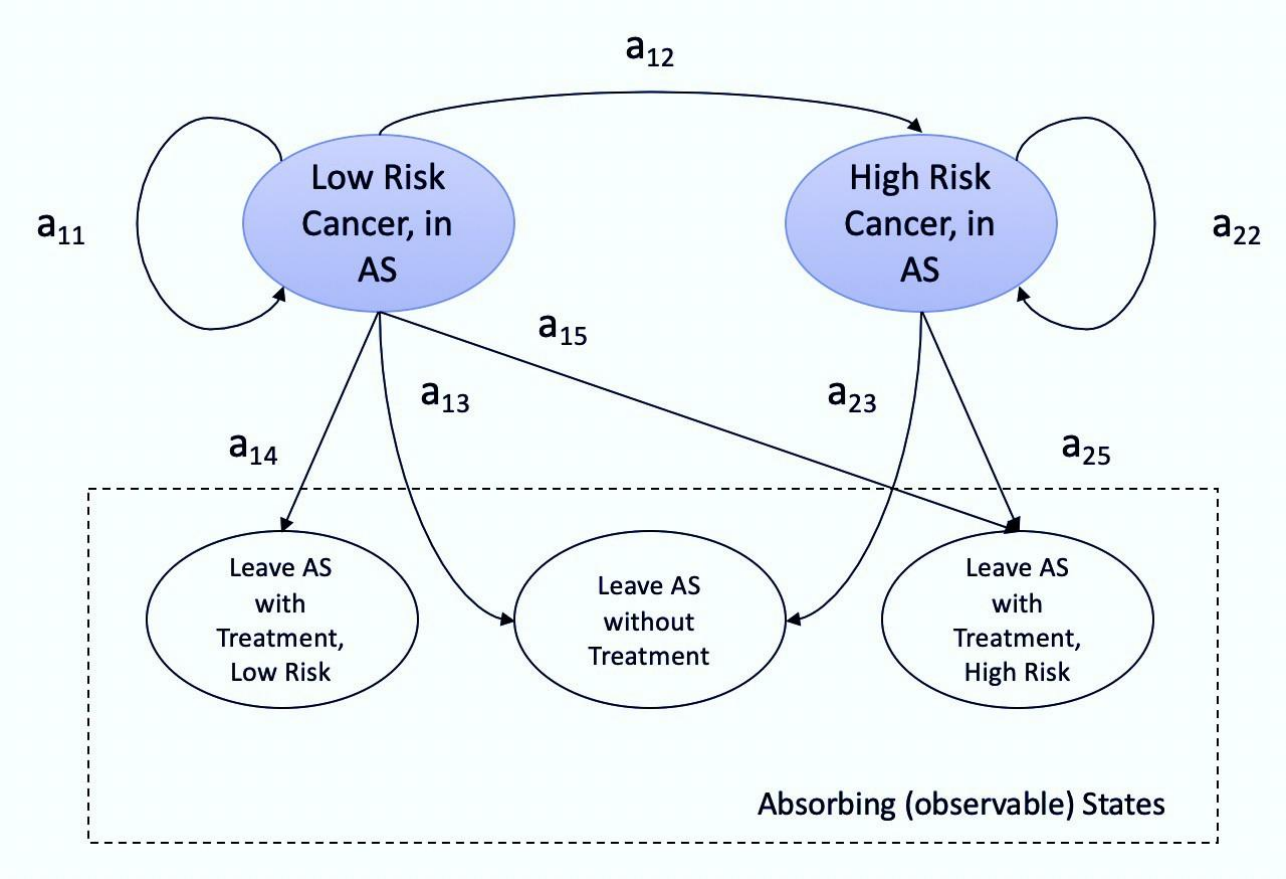
Active surveillance

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



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:

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

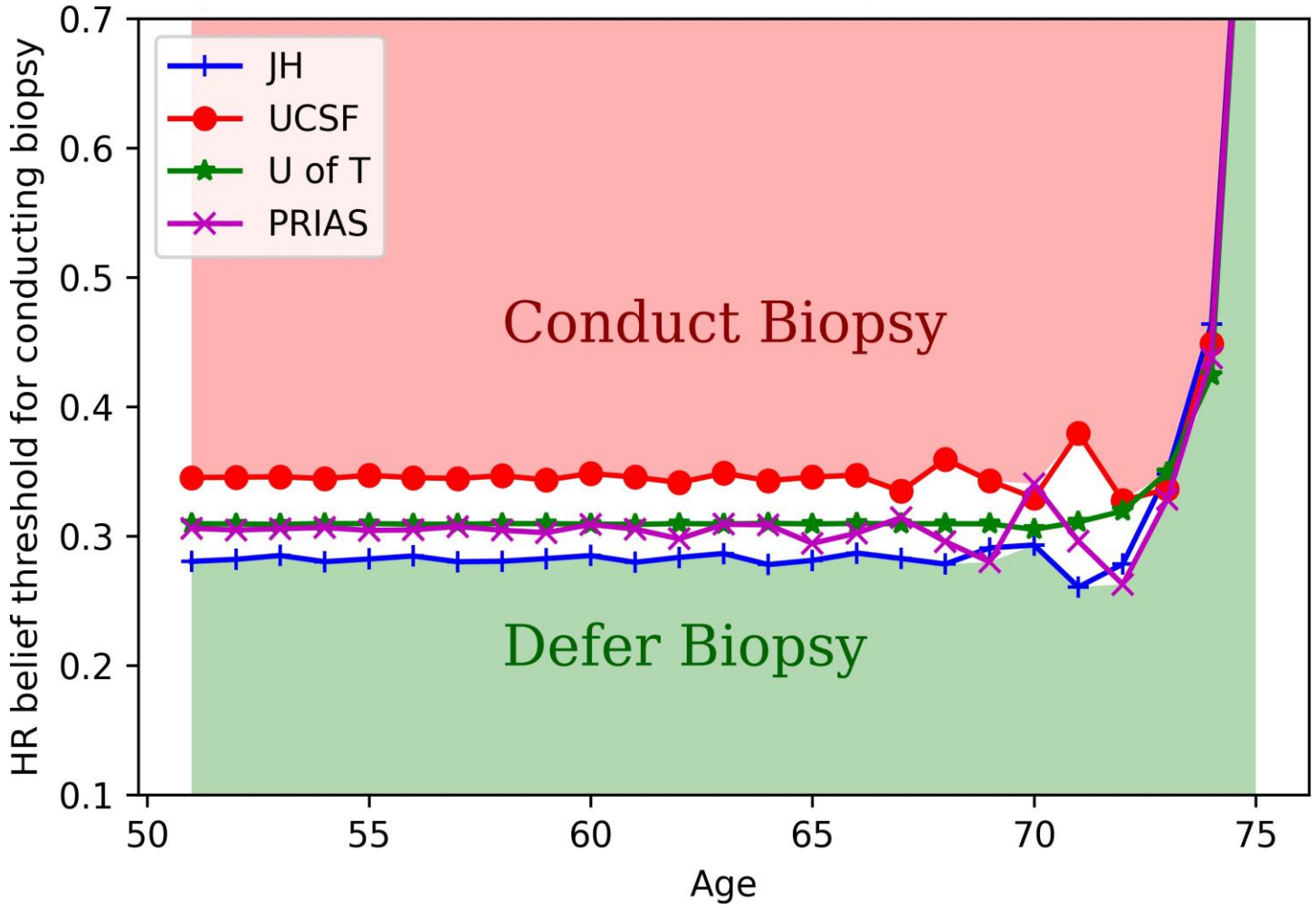
Optimality Equations:

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

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 (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 early detection of prostate cancer?

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

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

Theme: personalization of medical decisions matters!

Acknowledgments

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MUSIC Collaborative