MICHIGAN ENGINEERING
UNIVERSITY OF MICHIGAN

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

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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

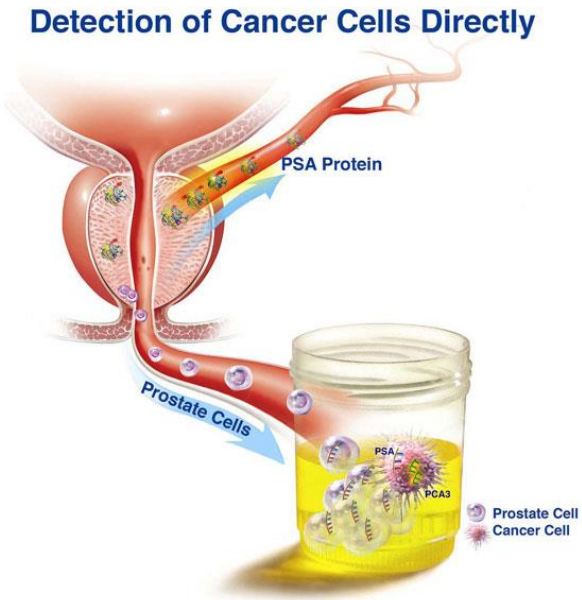
Prostate cancer screening is controversial

- 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?



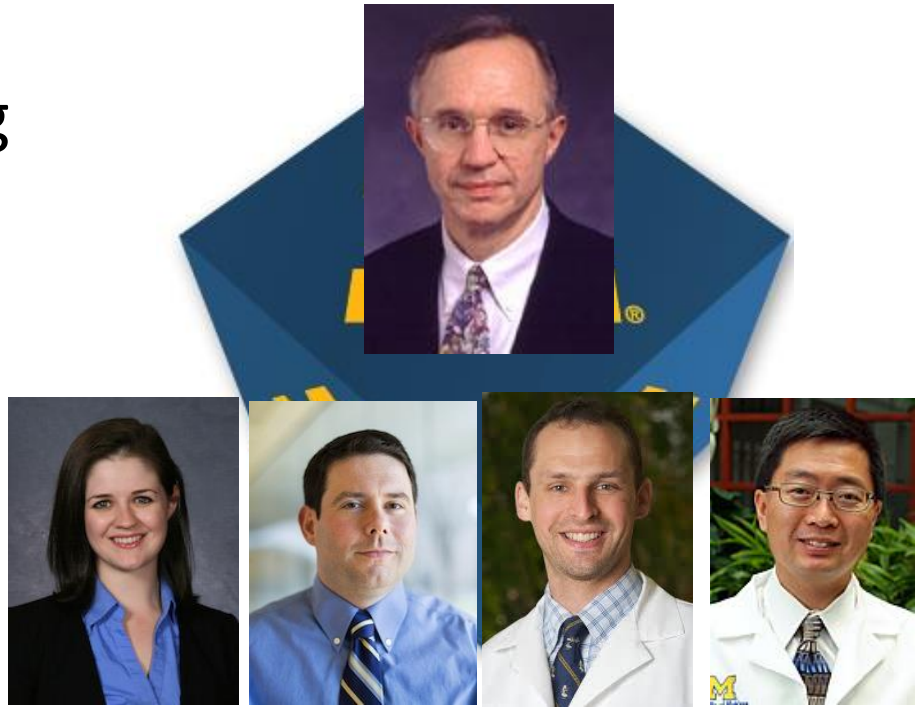
- PCA3 – urine test that received FDA approval in 2012 for repeat biopsy decisions
- T2:ERG – urine test in late stage clinical validation

M Cubed Project

harms

"Measuring the ~~costs~~ and benefits of new biomarkers"

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

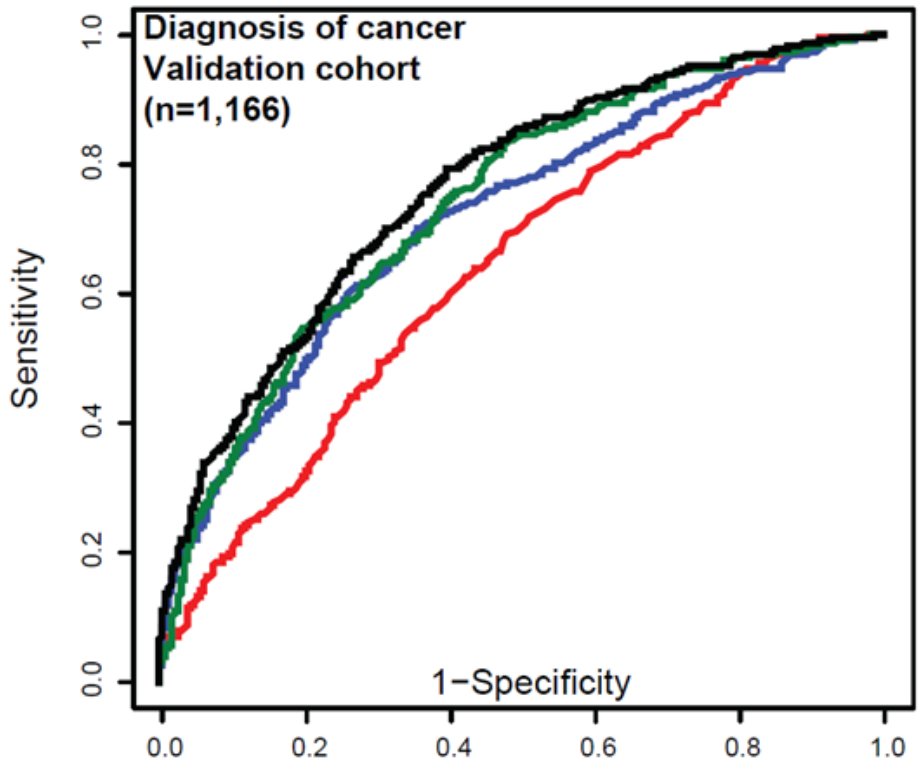


Research Questions

- 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



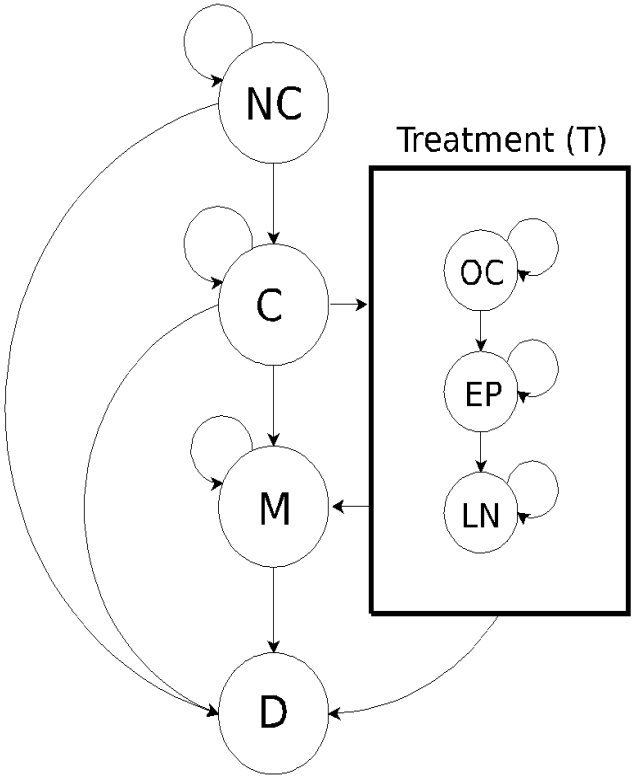
Model	AUC
PSA	0.585
PSA+T2:ERG	0.666
PSA+PCA3	0.712
PSA+T2:ERG+PCA3	0.751

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 Urol. In Press.

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.



D. J. Underwood, J. Zhang, B. T. Denton, N. Shah, and B. Inman. Simulation optimization of PSA-threshold based prostate cancer screening policies. Health Care Management Science, 15(4):293–309, 2012

Zhang, J., Denton, B.T., Balasubramanian, H., Inman, B., Shah, N., "Estimating the True Value of PSA Tests for Prostate Cancer Detection," *Medical Decision Making*, 32(2), 337-349, 2012.

PSA growth model

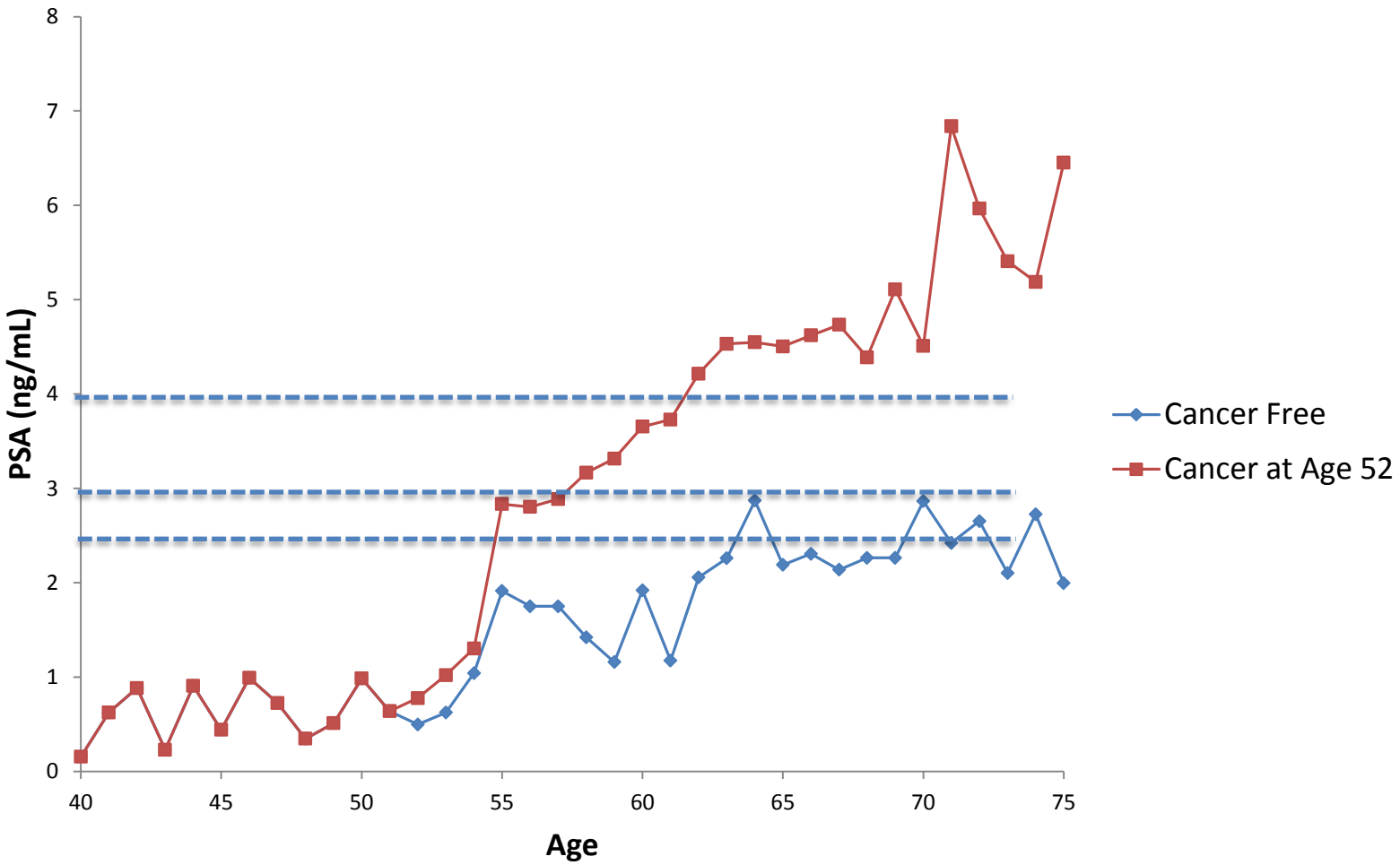
Statistical model:

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

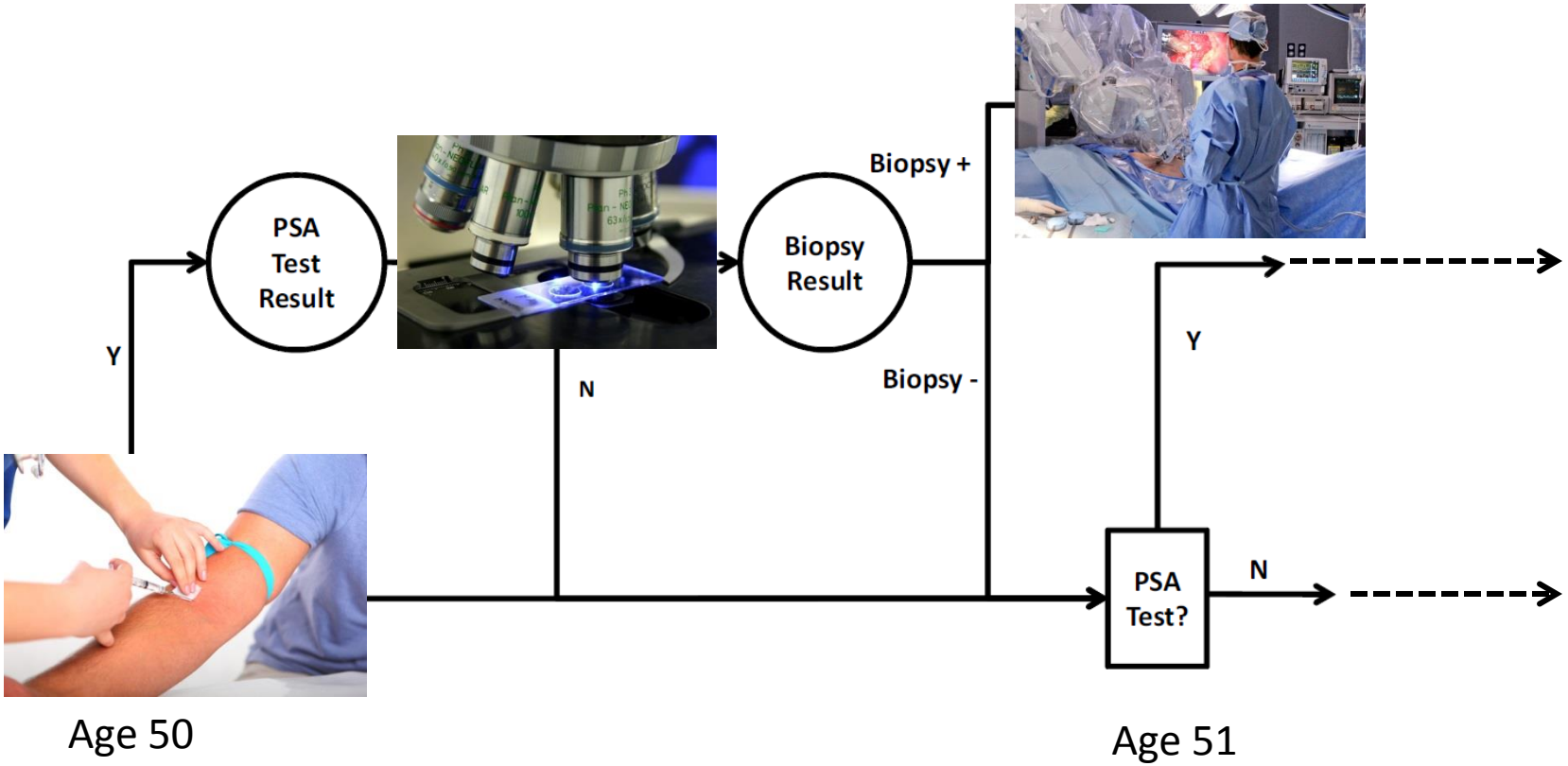
- $y_i(t)$ is the PSA level for individual i at age t
- t_{oi} is the age at onset of preclinical tumor for individual i
- I_C indicator function for cancer (1=cancer, 0=no cancer)
- Individual intercepts and slopes: $\beta_{ki} \sim N(\mu_k, \sigma_k^2), k = 0,1,2$

Gulati R, Inoue L, Katcher J, Hazelton W, Etzioni R. Calibrating disease progression models using population data: a critical precursor to policy development in cancer control. Biostatistics. 2010;11(4):707-719.

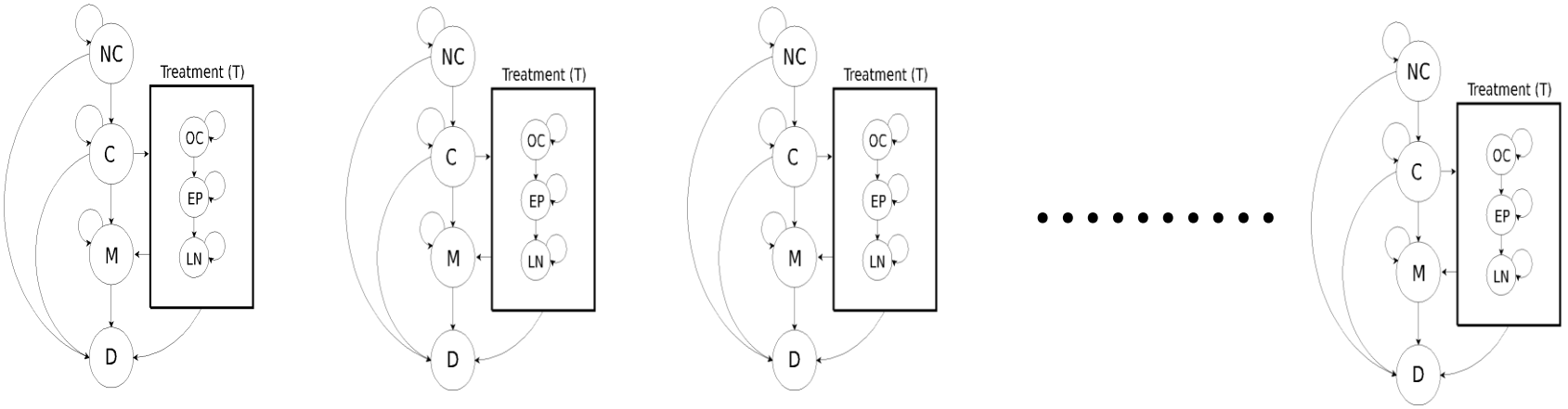
PSA model example



Prostate cancer screening model



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

Parameter	Values
Annual prostate-cancer incidence rate	0.0023—0.117
Annual other-cause mortality rate	0.0022—0.3468
Annual metastasis rate for patients who have undergone radical prostatectomy	0.0067—0.0092
Annual metastasis rate for patients with undiagnosed prostate cancer	0.0694
Annual prostate-cancer-specific mortality rate for patients with metastasized prostate cancer	0.0705—0.0742
Prostate biopsy detection rate	0.8

Heijnsdijk et al. 2012. “Quality of Life Effects of Prostate-Specific Antigen Screening,” NEJM, 367(7), 595-605

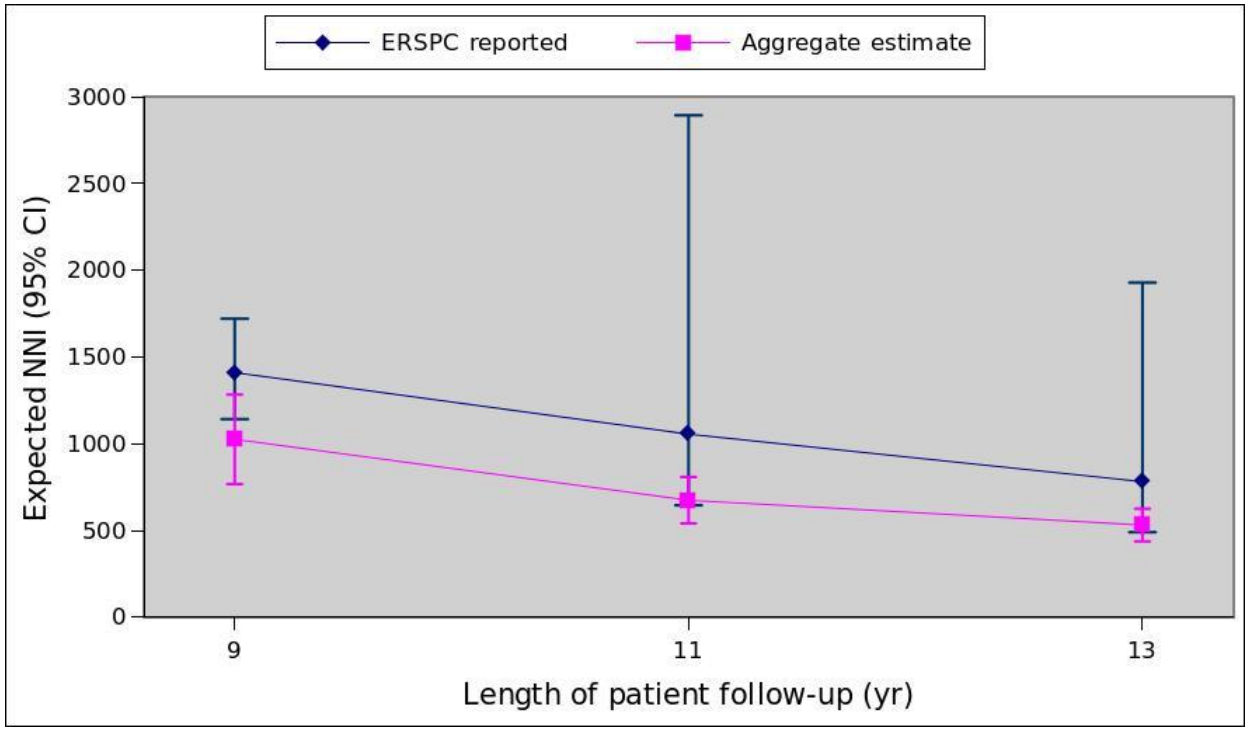
Model validation

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

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

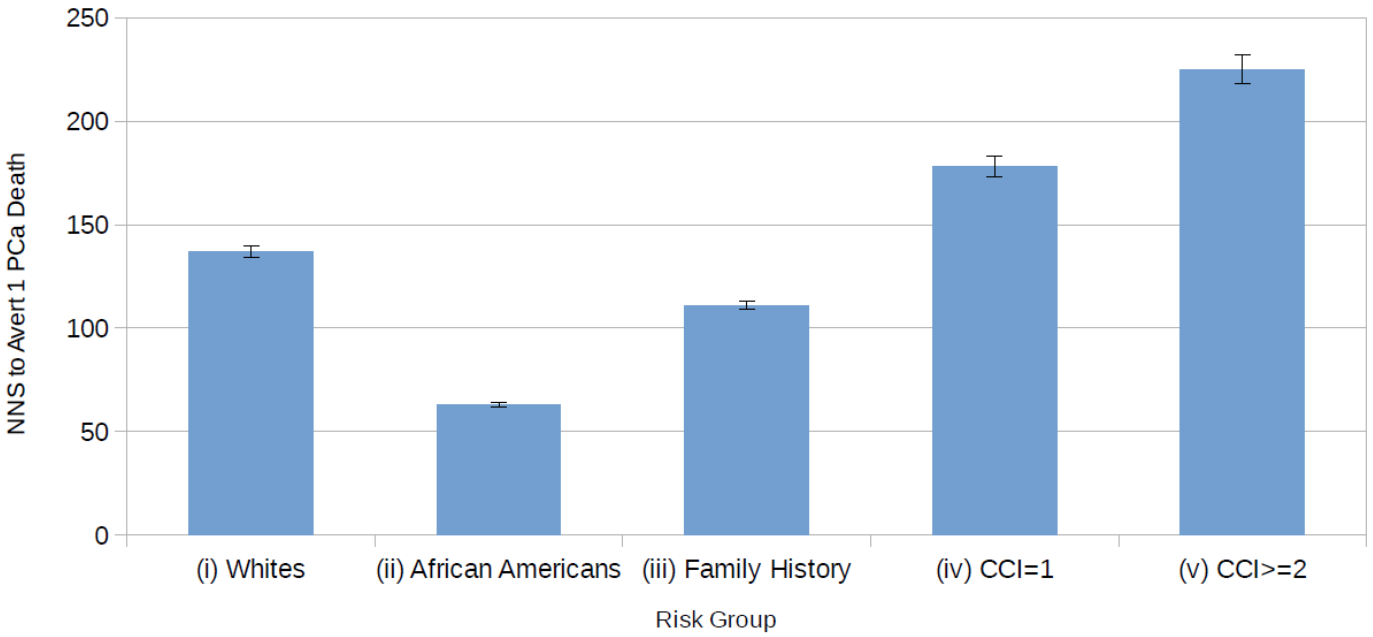
Comparison to ERSPC Trial

- 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

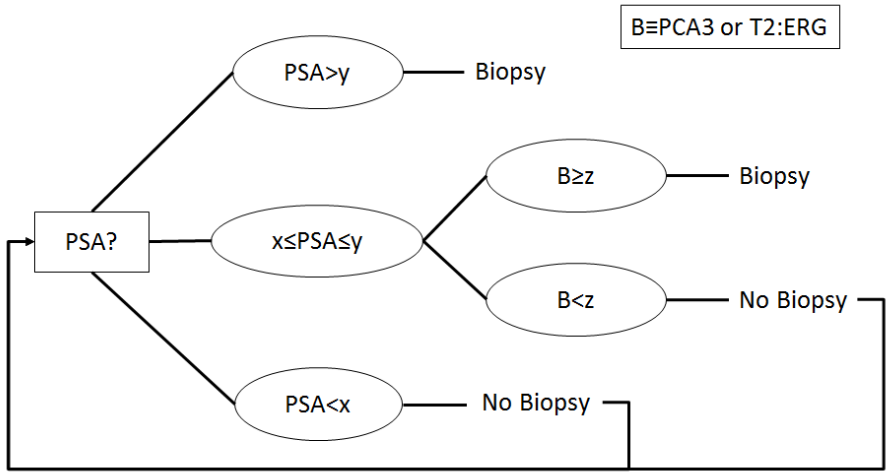
- Distinction between cancer grades on the basis of Gleason score
- Distinction between treatment options
- Quality of life determined by treatment modalities

Treatment options

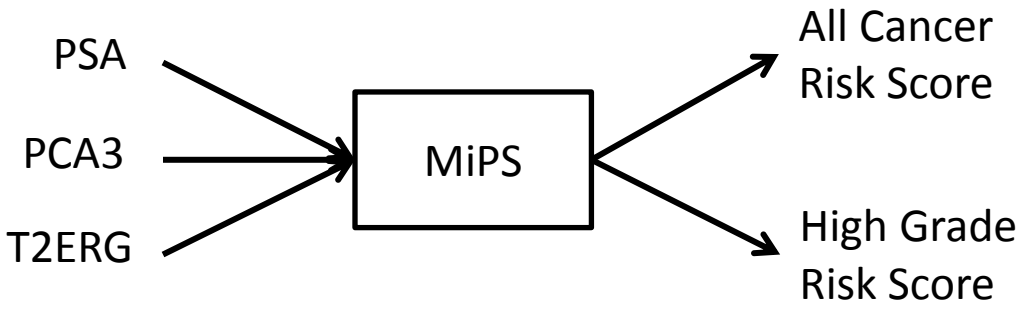
- Radical Prostatectomy:
  - For patients with localized cancer, Gleason score ≥ 7
- Active Surveillance:
  - For patients with Gleason score = 6, delays and possibly avoids curative treatment until evidence of disease progression

Screening with multiple biomarkers

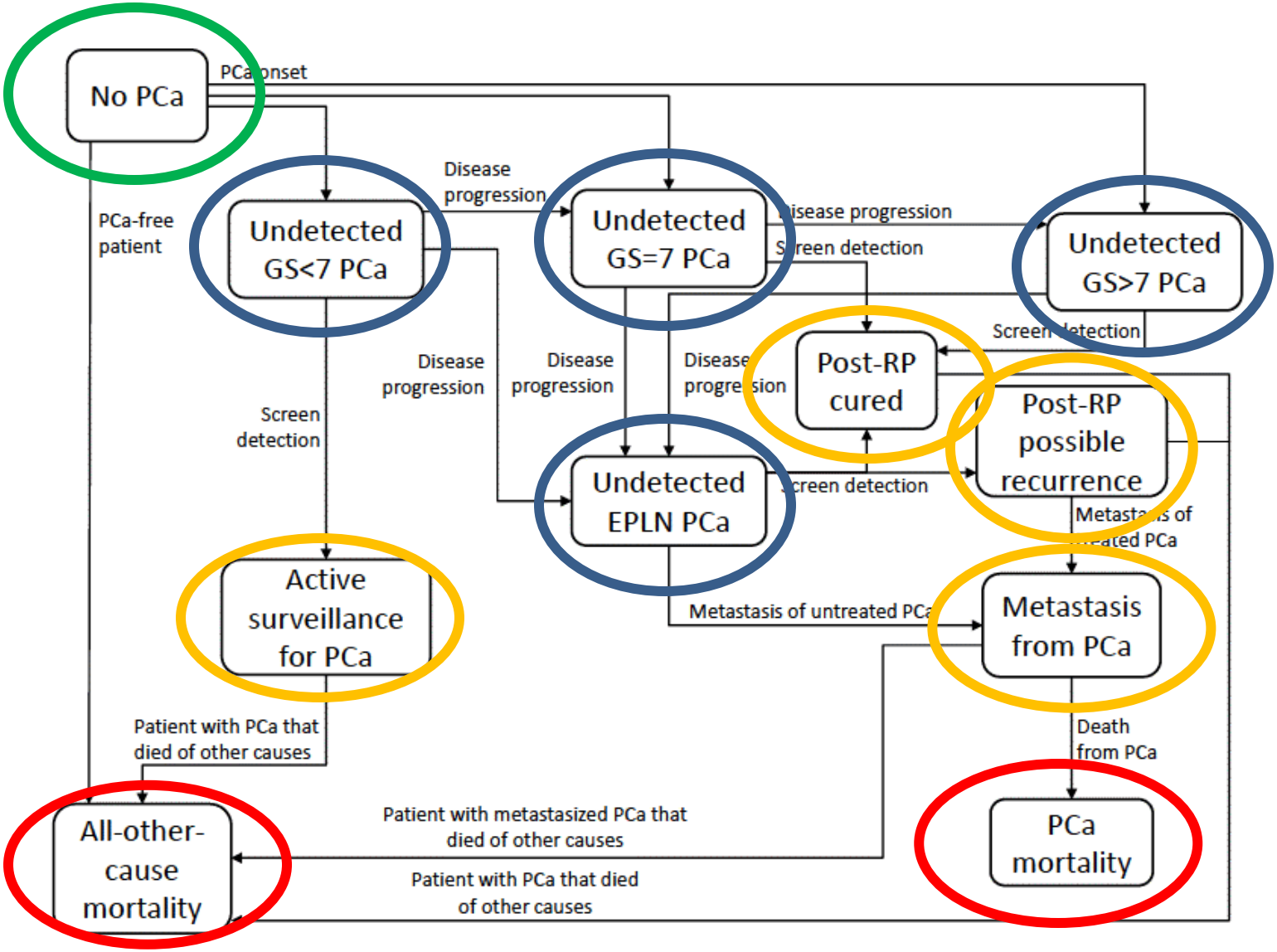
Option 1:



Option 2:



Complete natural history model



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Annual prostate-cancer-specific mortality rate for patients with metastasized prostate cancer	0.0705—0.0742
Prostate biopsy detection rate	0.8
QALY decrement for PSA screening	0.00019
QALY decrement for prostate biopsy procedure	0.00577
QALY decrement for prostate cancer diagnosis	0.01667
QALY decrement for radical prostatectomy	0.24667
Annual QALY decrement for 9-year postrecovery period for radical prostatectomy	0.05
Annual QALY decrement for patients with metastatic cancer	0.4

Heijnsdijk et al. 2012. “Quality of Life Effects of Prostate-Specific Antigen Screening,” NEJM, 367(7), 595-605

Screening strategy types

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

Screening schedules

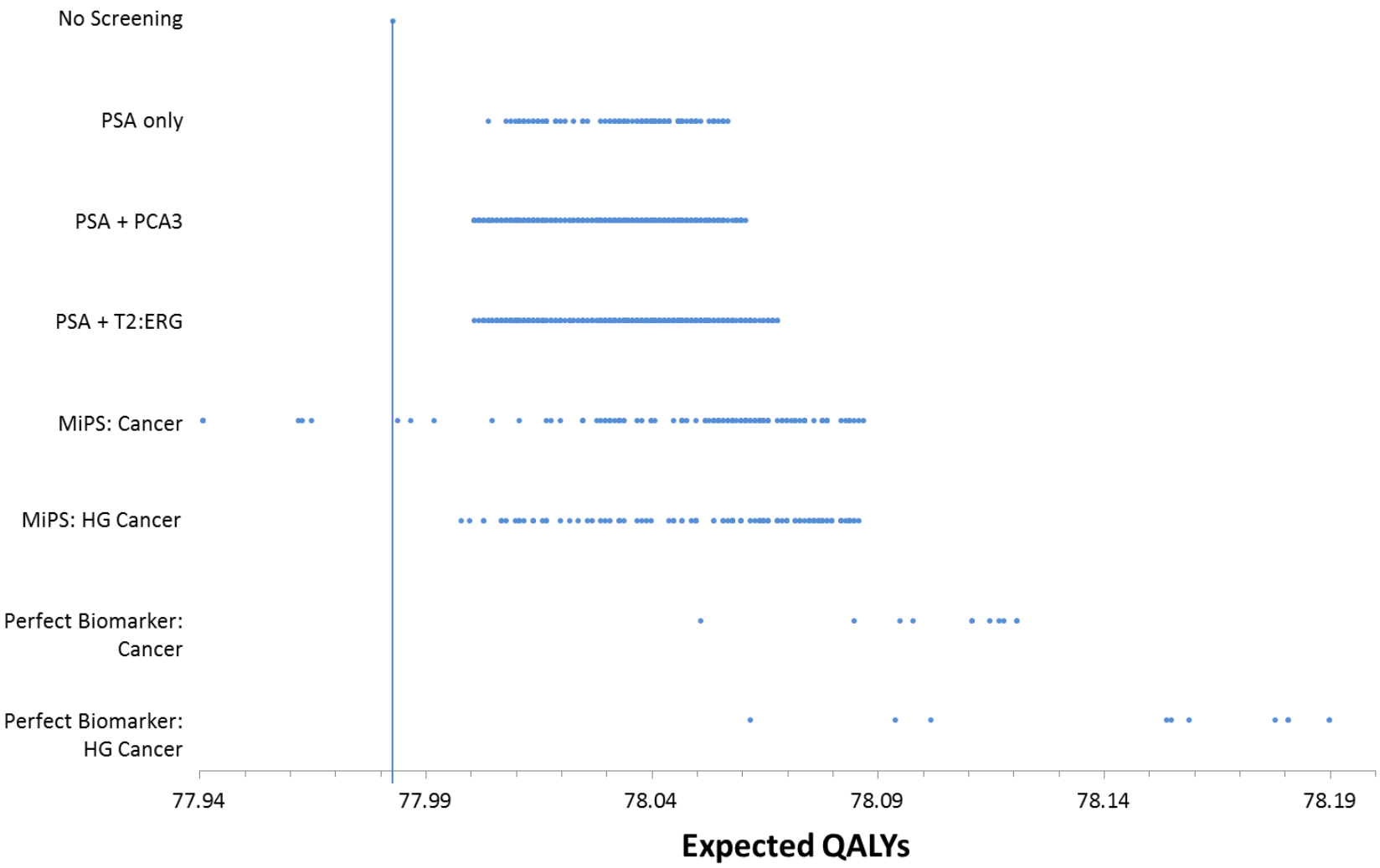
Schedule Label	Range of Ages (yr)	Screening Interval (yr)	Source
S1	40-75	5	Ross et al. (2000)
S2	50-75	2	Ross et al. (2000)
S3	50-75	1	Ross et al. (2000), Andriole et al. (2009)
S4	40,45 50-75	- 2	Ross et al. (2000)
S5	40,45 50-75	- 1	Ross et al. (2000)
S6	55-69	1	Heijnsdijk et al. (2012)
S7	55-74	1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

Biopsy thresholds

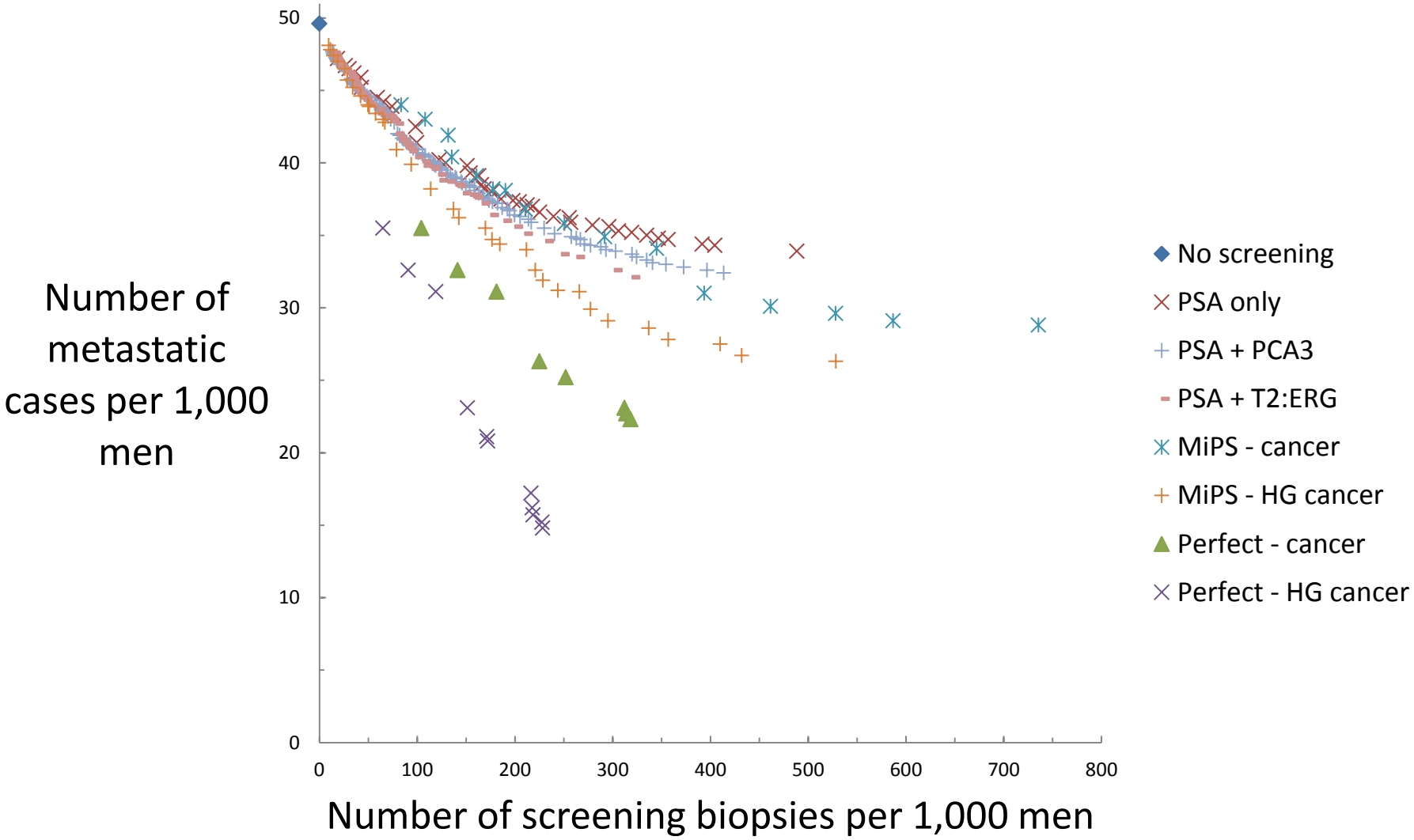
- PSA: {1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 6.5}
- PCA3: {19, 25, 35, 55, 75}
- T2:ERG: {7, 10, 30, 50, 100}
- MiPS: {0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50}

# of screening strategies = (# of screening types)×(# of screening schedules)×(# of biopsy thresholds) = **1,439**

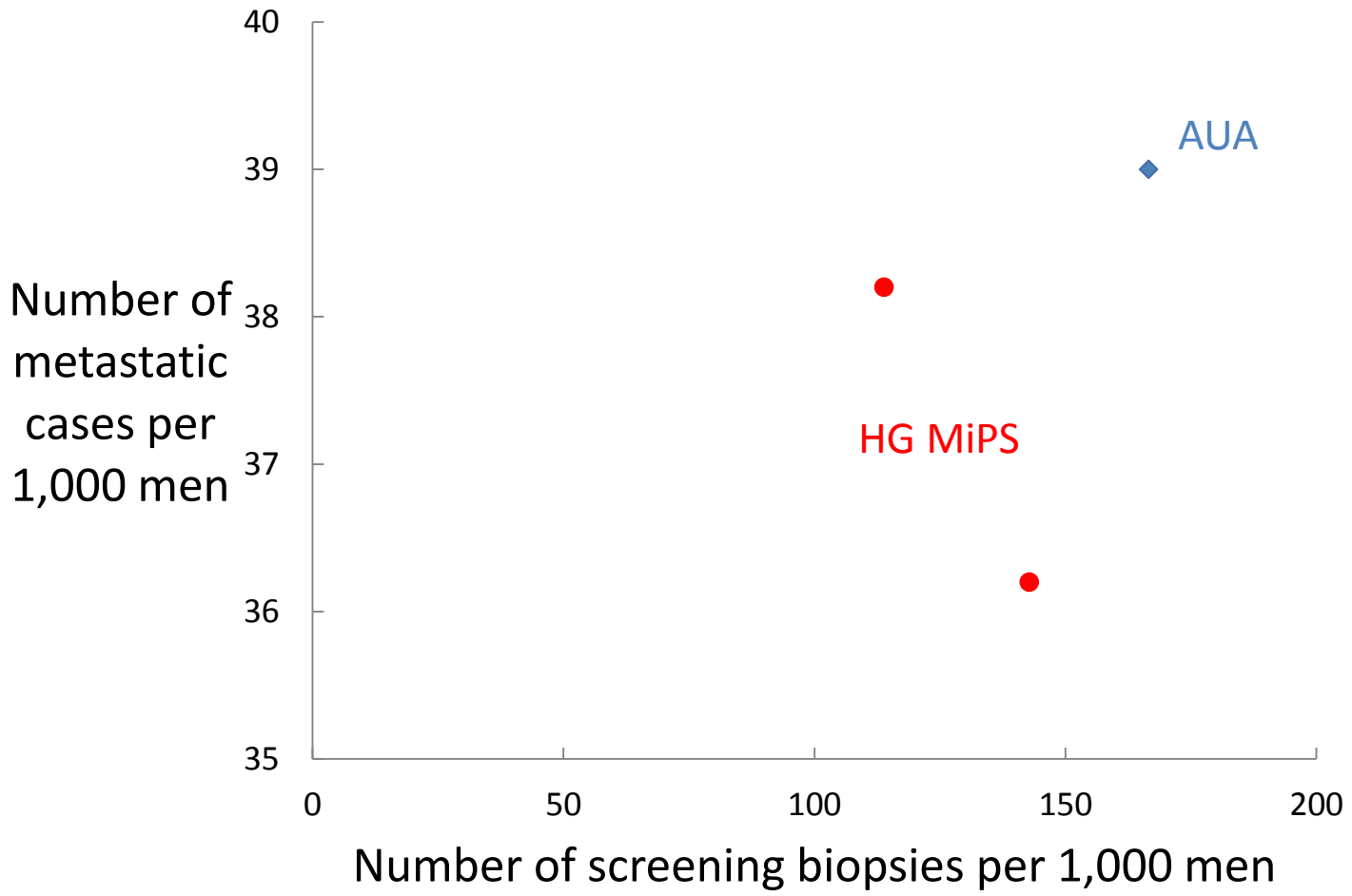
Quality adjusted lifespan



Detection of high-grade cancers is most important



High-grade MiPS simultaneously reduces biopsies and metastatic cases



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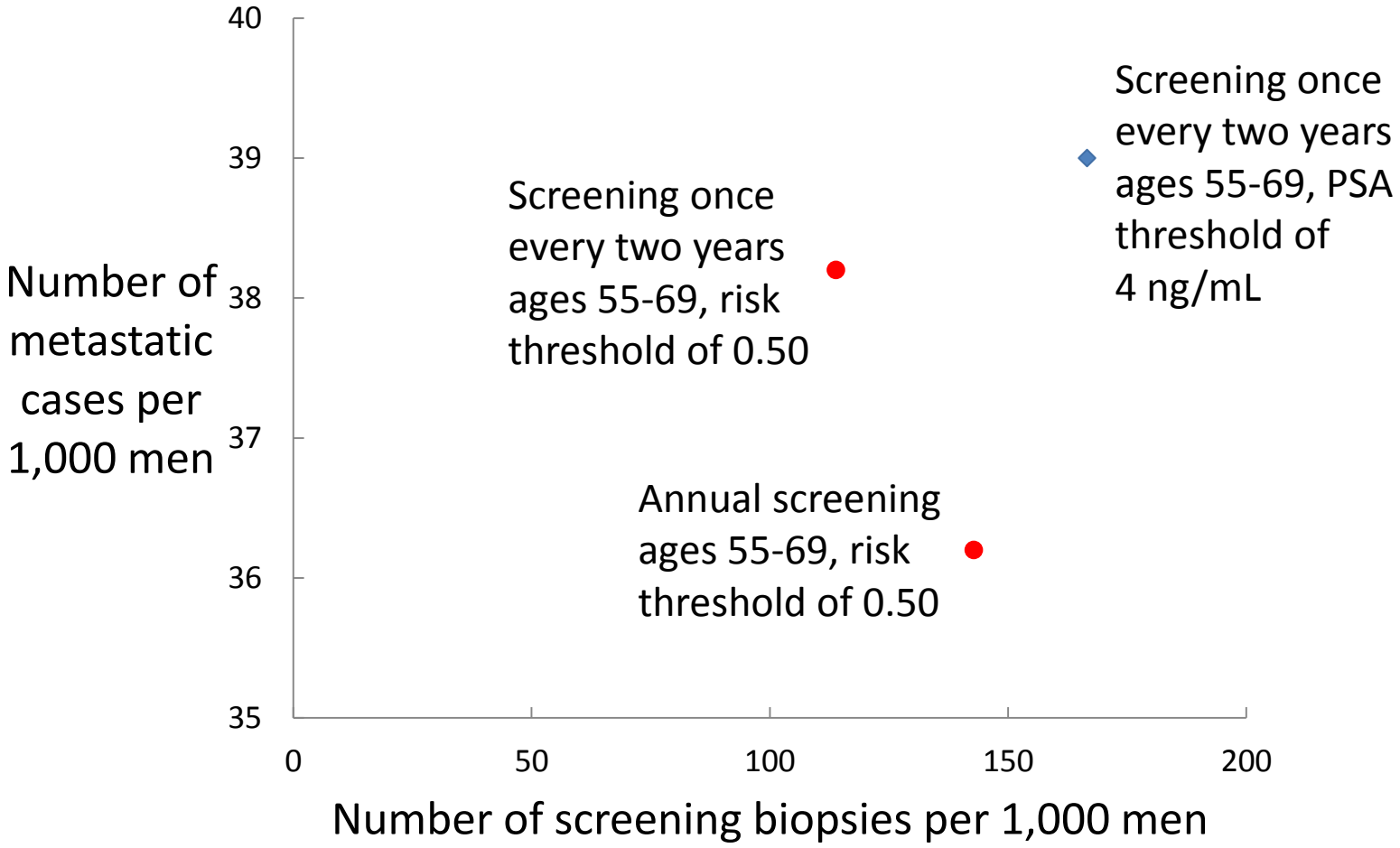

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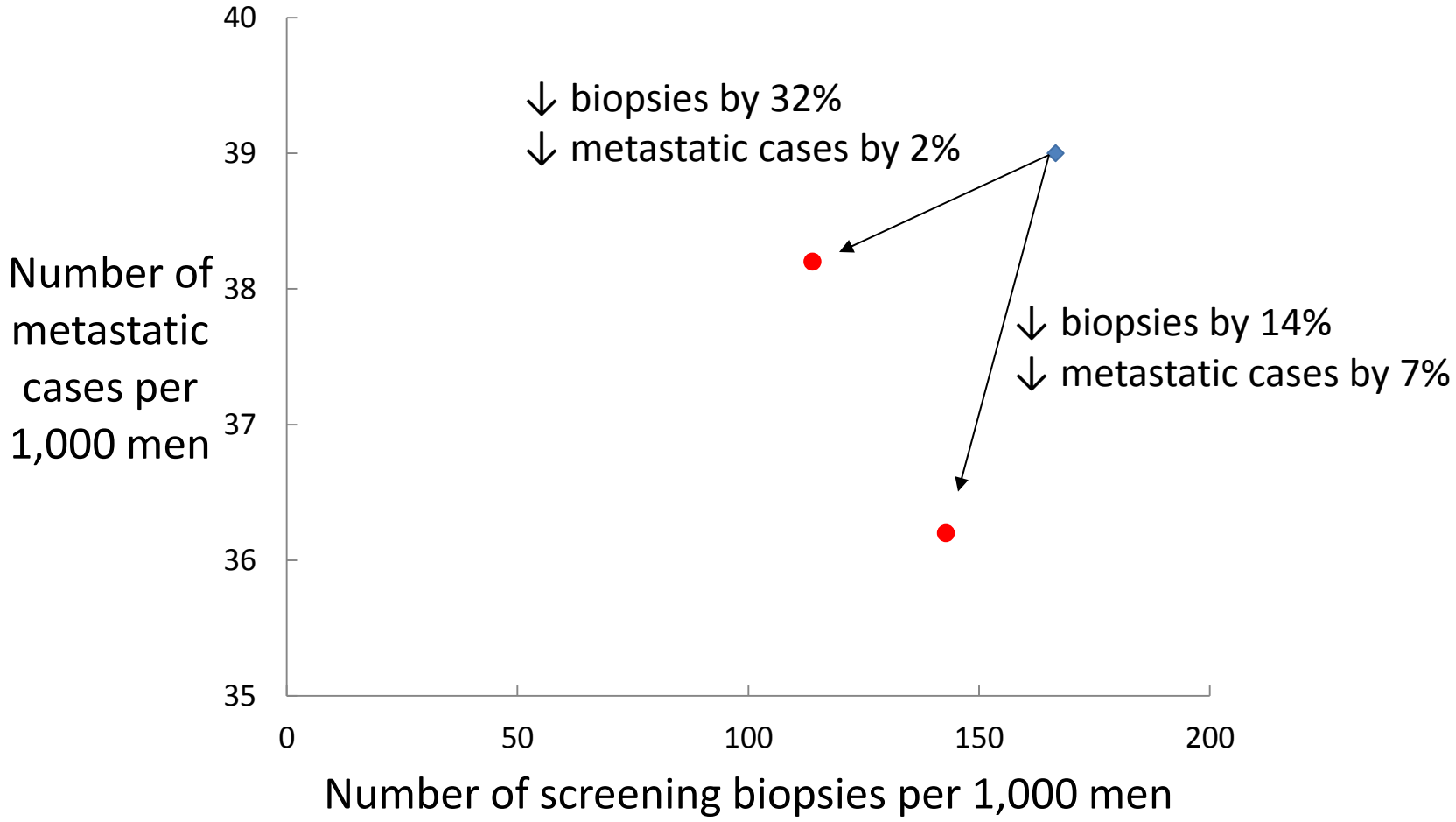

Conclusions

- 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

Original Article

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. Barnett, 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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- Todd Morgan

Scott Tomlins

Daniel Underwood

John Wei

Jim Wilson

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

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