Modeling as a translational tool for early detection

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EDRN Steering Committee Meeting October 27 2020
Modeling, Biomarkers, Implementation Science

A tale of prostate cancer

1156 THE NEW ENGLAND JOURNAL OF MEDICINE April 25, 1991

MEASUREMENT OF PROSTATE-SPECIFIC ANTIGEN IN SERUM AS A SCREENING TEST FOR PROSTATE CANCER

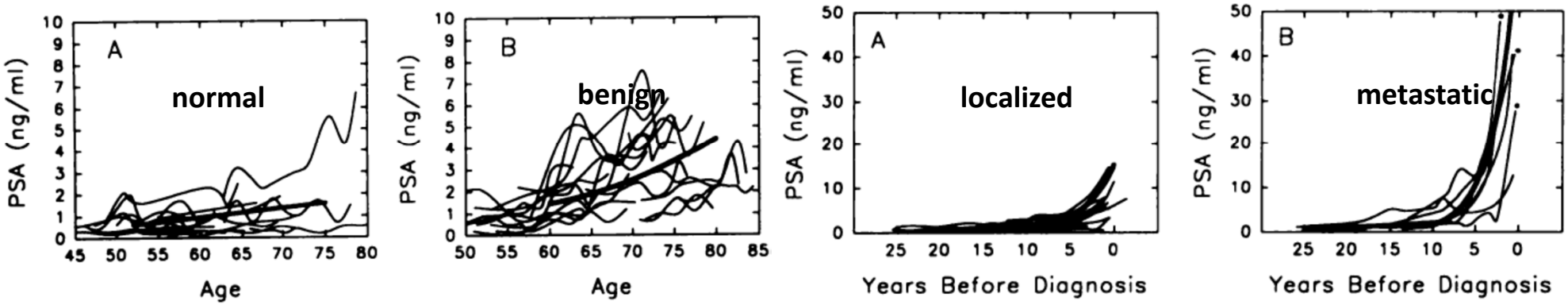
WILLIAM J. CATALONA, M.D., DEBORAH S. SMITH, PH.D., TIMOTHY L. RATLIFF, PH.D., KATHY M. DODDS, R.N., DOUGLAS E. COPLEN, M.D., JERRY J.J. YUAN, M.D., JOHN A. PETROS, M.D., AND GERALD L. ANDRIOLE, M.D.

Conclusions : The combination of measurement of the serum PSA concentration and rectal examination, with ultrasonography performed in patients with abnormal findings, provides a better method of detecting prostate cancer than rectal examination alone.

[CANCER RESEARCH 52, 3323–3328, June 15, 1992]

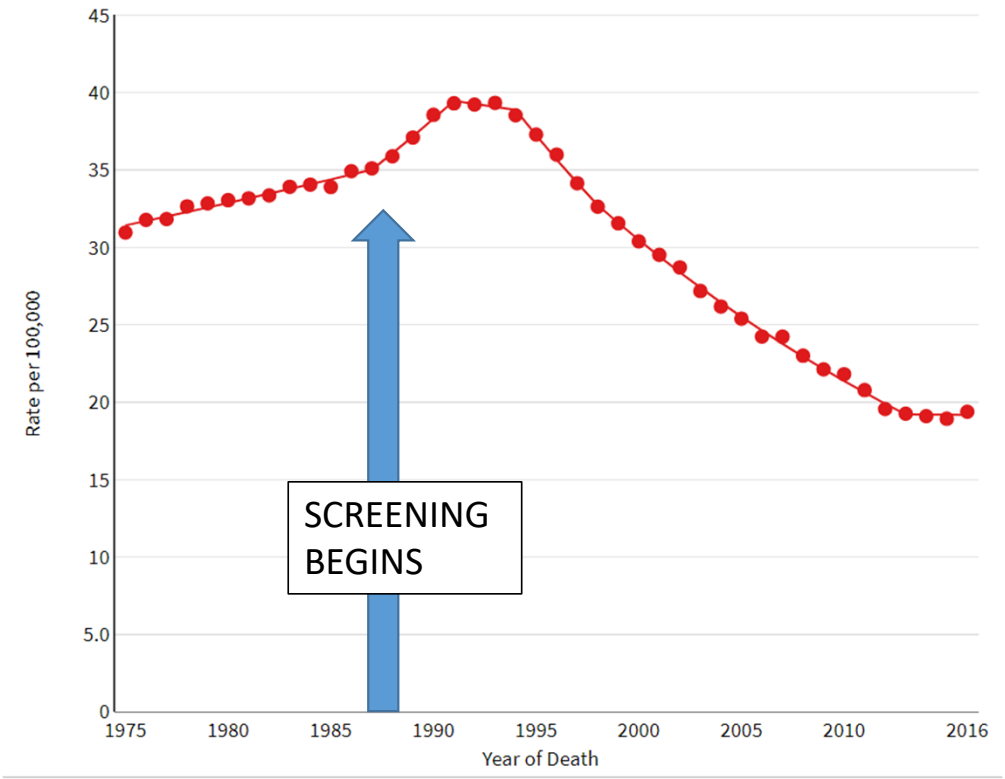
Estimation of Prostatic Growth Using Serial Prostate-specific Antigen Measurements in Men with and without Prostate Disease[1]

H. Ballentine Carter,[2] Christopher H. Morrell, Jay D. Pearson, Larry J. Brant, Constantine C. Plato, E. Jeffrey Metter, Daniel W. Chan, James L. Fozard, and Patrick C. Walsh

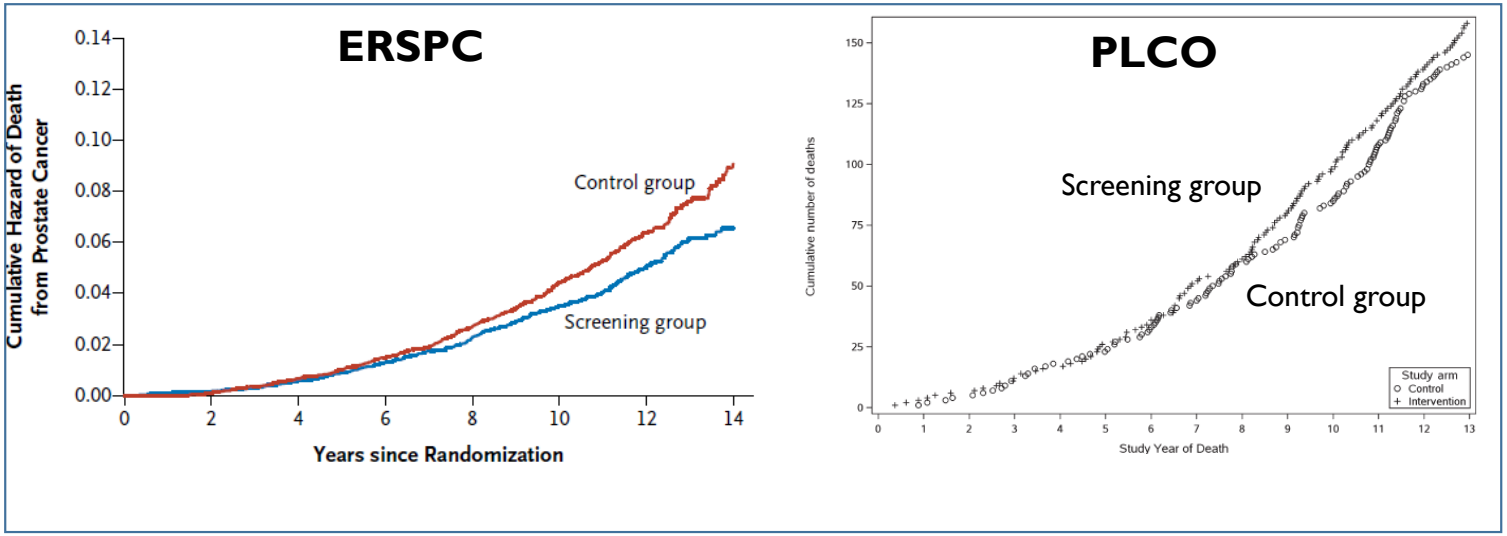


Predicted rates of change in PSA (PSA velocity) were linear and curvilinear for control and BPH subjects, respectively. Subjects with cancer demonstrated both a linear and an exponential phase of PSA velocity.. **Estimates of prostatic growth rate from changes in PSA may be useful clinically in management of men with prostate disease**.

US prostate cancer mortality



Two screening trials



	ERSPC	PLCO
Mortality rate ratio	0.79	1.09
Lives saved per 1000	1.07	–0.03

Schröder et al., N Engl J Med, 2012; Andriole et al., J Natl Cancer Inst, 2012

2012: USPSTF D Recommendation

CLINICAL GUIDELINE | Annals of Internal Medicine

Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, PhD, on behalf of the U.S. Preventive Services Task Force*

There is adequate evidence that the benefit of PSA screening and early treatment ranges from 0 to 1 **prostate cancer deaths avoided** per 1000 men screened

At the same time, **overdiagnosis and overtreatment** of prostatic tumors that will not progress to cause illness or death are frequent consequences of PSA-based screening.

The USPSTF concludes that there is moderate certainty that the **harms** of PSA-based screening for prostate cancer outweigh the **benefits**.

Moyers et al, Ann Int Med, 2012

Culture of performance

STAT[1]

Grail, a deep-pocketed startup, shows 'impressive,' if early, results for cancer blood test

By Matthew Herper[2] @matthewherper[3]

May 31, 2019

A New $500 Blood Test Could Detect Cancer Before Symptoms Develop

Victoria Forster Contributor

Pharma & Healthcare

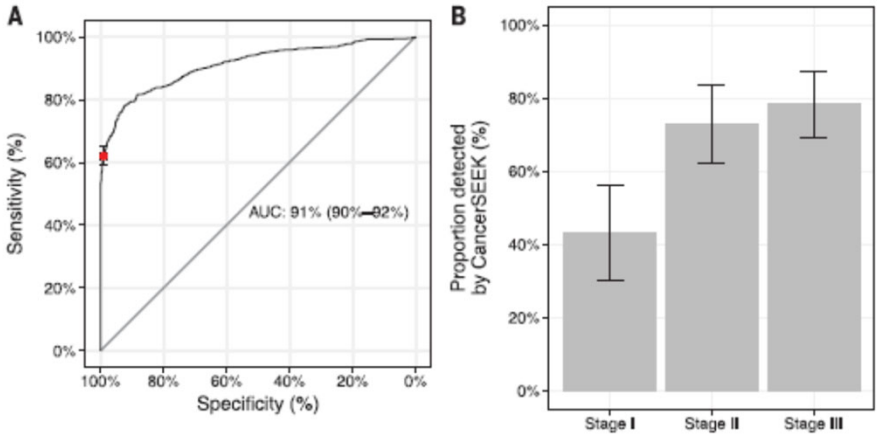
Cancer research scientist and childhood cancer survivor.

Culture of performance

CancerSEEK tests were positive in a median of 70% of the eight cancer types. The **sensitivities** ranged from 69 to 98% for the detection of five cancer types (ovary, liver, stomach, pancreas, and esophagus) for which there are no screening tests available for average-risk individuals

CANCER

Detection and localization of surgically resectable cancers with a multi-analyte blood test



From performance to **benefit**/**harm**

- Sensitivity
- Specificity
- AUC
- PPV

- **Lives saved**
- **Metastases prevented**
- **Quality of life**
- **Overdiagnosis/overtreatment**
- **Unnecessary biopsies**
- **Costs**

From performance to outcomes – EDRN phases

Preclinical Exploratory	***PHASE 1***	*Promising directions identified*
Clinical Assay and Validation	***PHASE 2***	*Clinical assay detects established disease*
Retrospective Longitudinal	***PHASE 3***	*Biomarker detects disease early before it becomes clinical and a "screen positive" rule is defined*
Prospective Screening	***PHASE 4***	*Extent and characteristics of disease detected by the test and the false referral rate are identified*
Cancer Control	***PHASE 5***	*Impact of screening on reducing the burden of disease on the population is quantified*

Sensitivity
Specificity

Benefit
(Harm)

Pepe et al JNCI 2001

From performance to outcomes – EDRN phases

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Can modeling be used here?

Sensitivity
Specificity

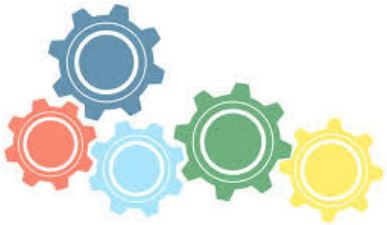
↓

Benefit
(Harm)

Pepe et al JNCI 2001

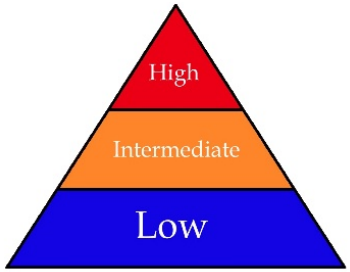
Three parts of today's presentation

Models



Biomarkers for early detection

Biomarkers for risk stratification



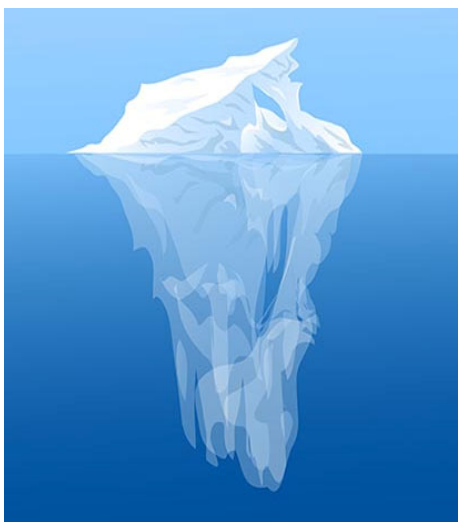
Models

Modeling is a system for thinking clearly about **cancer interventions** and how they interact with **population dynamics** and the **disease process** itself to produce **outcomes**

Natural history is key in modeling early detection

- Natural history = underlying disease process: onset, latency and progression
- Given observed incidence and screening patter)ns learn about natural history

Natural history



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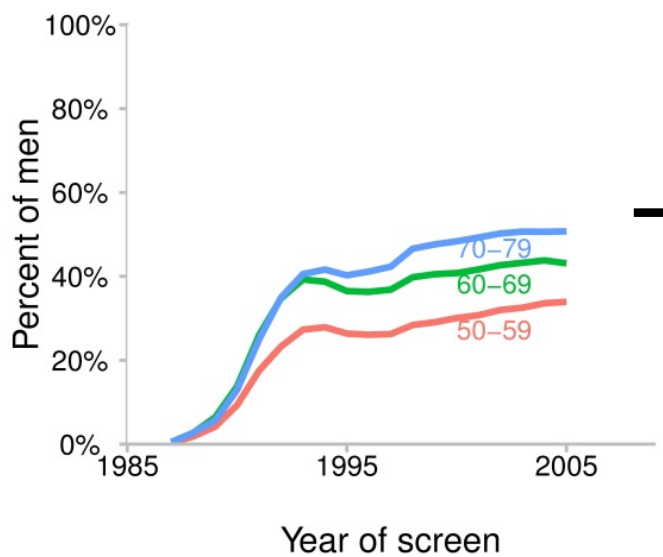
Screening (and biopsy patterns



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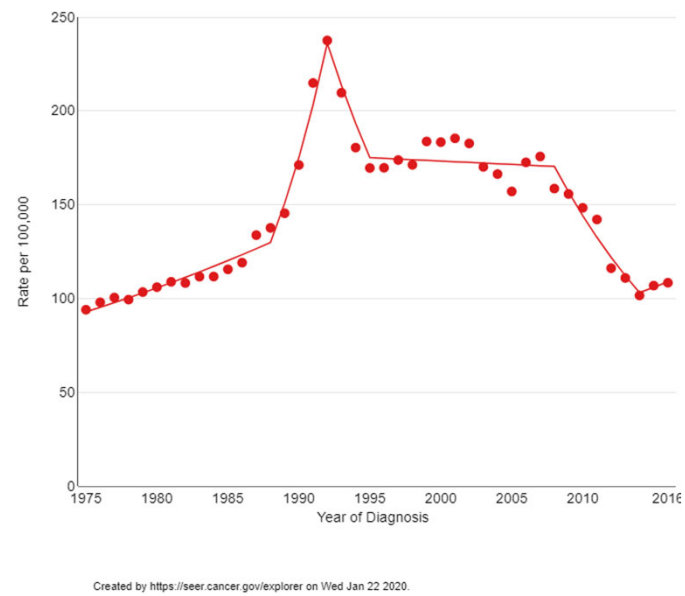
Observed incidence



Modeling early detection

Three building blocks

1. Natural history:
how does disease arise and progress without screening?

- *Learn from incidence patterns*
- *May include biomarker trajectories*
- *Major concern: identifiability*

2. Diagnostic performance:
specificity and sensitivity at each disease state

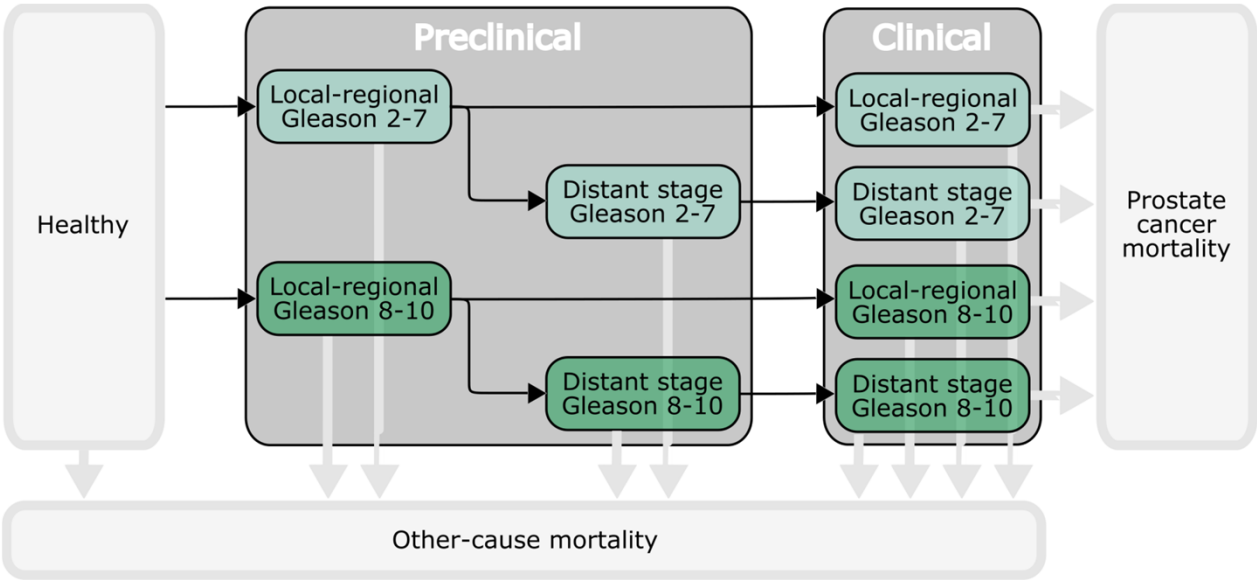
- *Affects earliness of detection, stage shift*

3. Benefit of early detection:
improvement in disease survival due to screening

- *Critically influences results*
- *Most basic model based on stage shift*
- *Other models may require calibration*

A multi-state model for prostate cancer

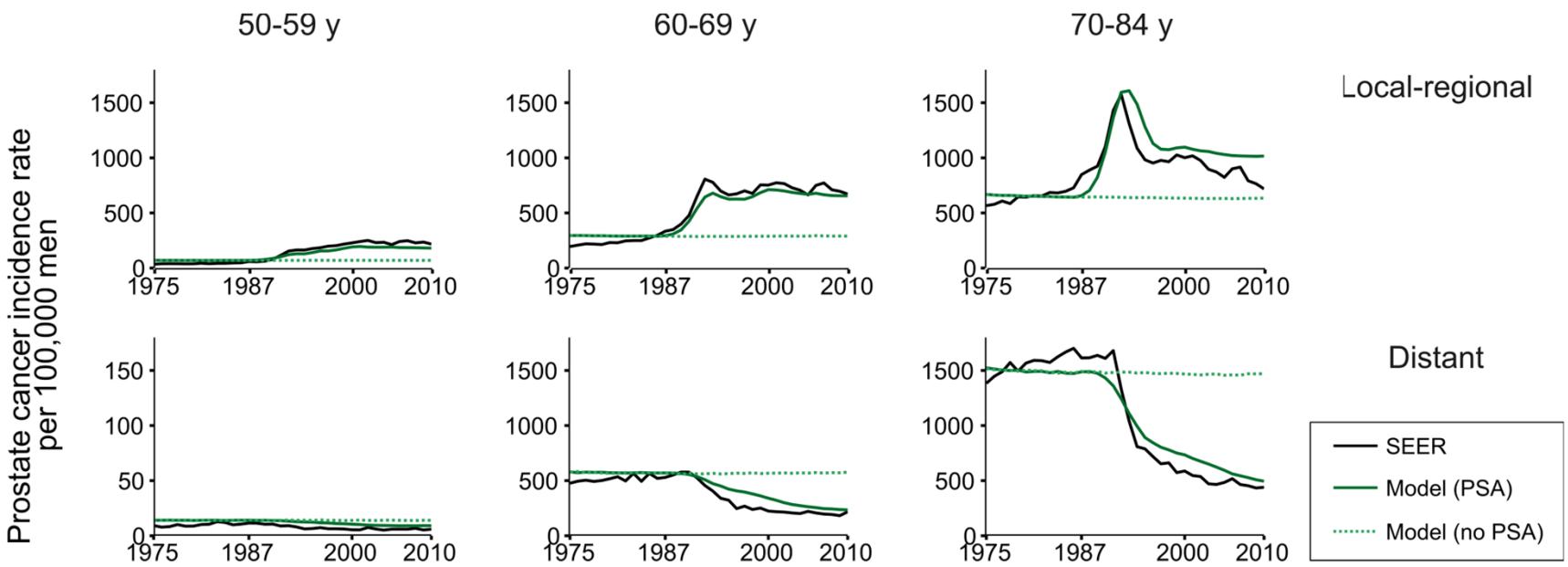
- Onset by Gleason score and progression to metastatic and clinical states
- Link between progression risks and PSA growth



Gulati et al, Biostatistics, 2010; CEBP, 2011; Ann Int Med, 2013

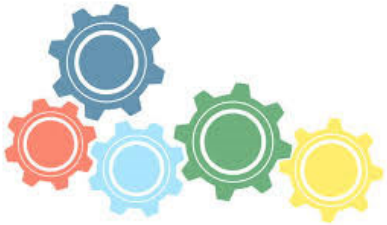
Natural history model calibrated to SEER incidence before and after dissemination of PSA screening

Model calibration to Surveillance, Epidemiology, and End Results incidence rates



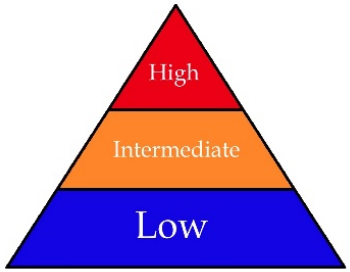
Three parts

Models



Biomarkers for early detection

Biomarkers for risk stratification



Biomarkers and models

Case 1: Building a biomarker into a (new) model

- Build biomarker into the natural history process
- Prostate model: link progression with biomarker level
- Ideal data: prospective screening data with biomarker levels

Case 2: Add a biomarker to an existing model

- Add biomarker to natural history process
- Prostate model: link biomarker with existing screening modality
- May be able to make do with cross-sectional data

Novel reflex biomarkers for prostate cancer

What are benefits/harms of reflex tests for PSA 4-10 ng/ml?

RESEARCH ARTICLE | PROSTATE CANCER

Urine *TMPRSS2:ERG* Fusion Transcript Stratifies Prostate Cancer Risk in Men with Elevated Serum PSA

Scott A. Tomlins[1], Sheila M. J. Aubin[2], Javed Siddiqui[1], Robert J. Lonigro[1,3], Laurie Sefton-Miller[1], Siobhan Miick[2], Sarah Willia...
+ See all authors and affiliations

Original Investigation

July 2016

A Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer at Initial Biopsy

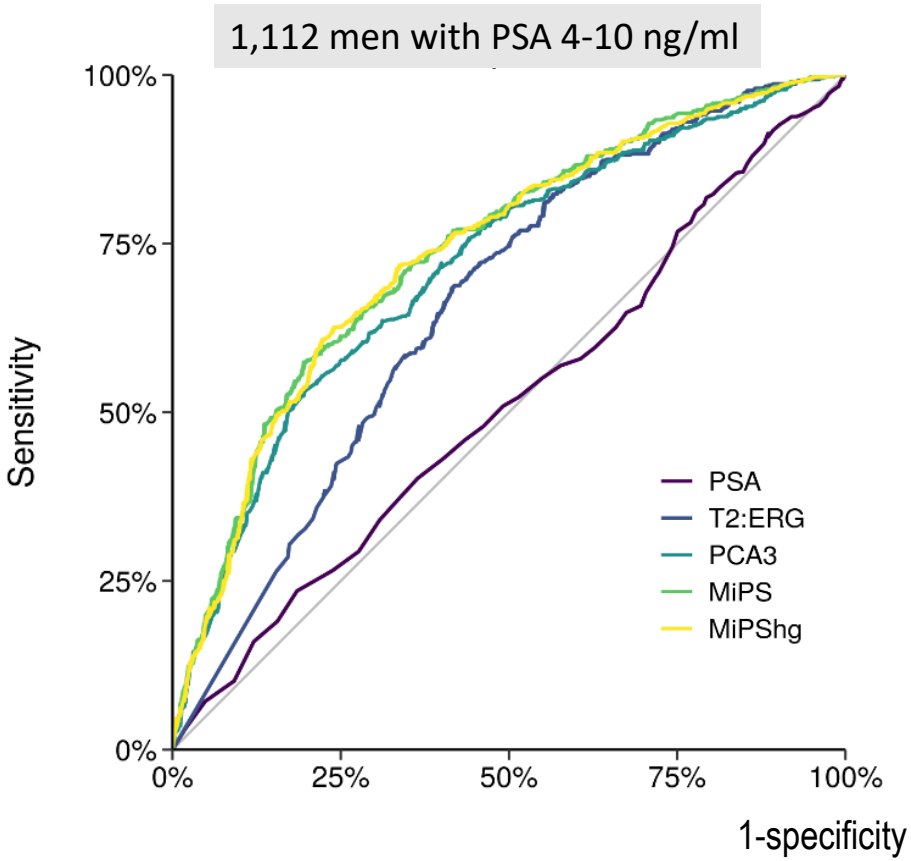
James McKiernan, MD[1]; Michael J. Donovan, PhD, MD[2]; Vince O'Neill, MD[3]; et al

Can Urinary PCA3 Supplement PSA in the Early Detection of Prostate Cancer?

John T. Wei, Ziding Feng, Alan W. Partin, Elissa Brown, Ian Thompson, Lori Sokoll, Daniel W. Chan, Yair Lotan, Adam S. Kibel, J. Erik Busby, Mohamed Bidair, Daniel W. Lin, Samir S. Taneja, Rosalia Viterbo, Aron Y. Joon, Jackie Dahlgren, Jacob Kagan, Sudhir Srivastava, and Martin G. Sanda

See accompanying editorial doi: 10.1200/JCO.2014.58.5547

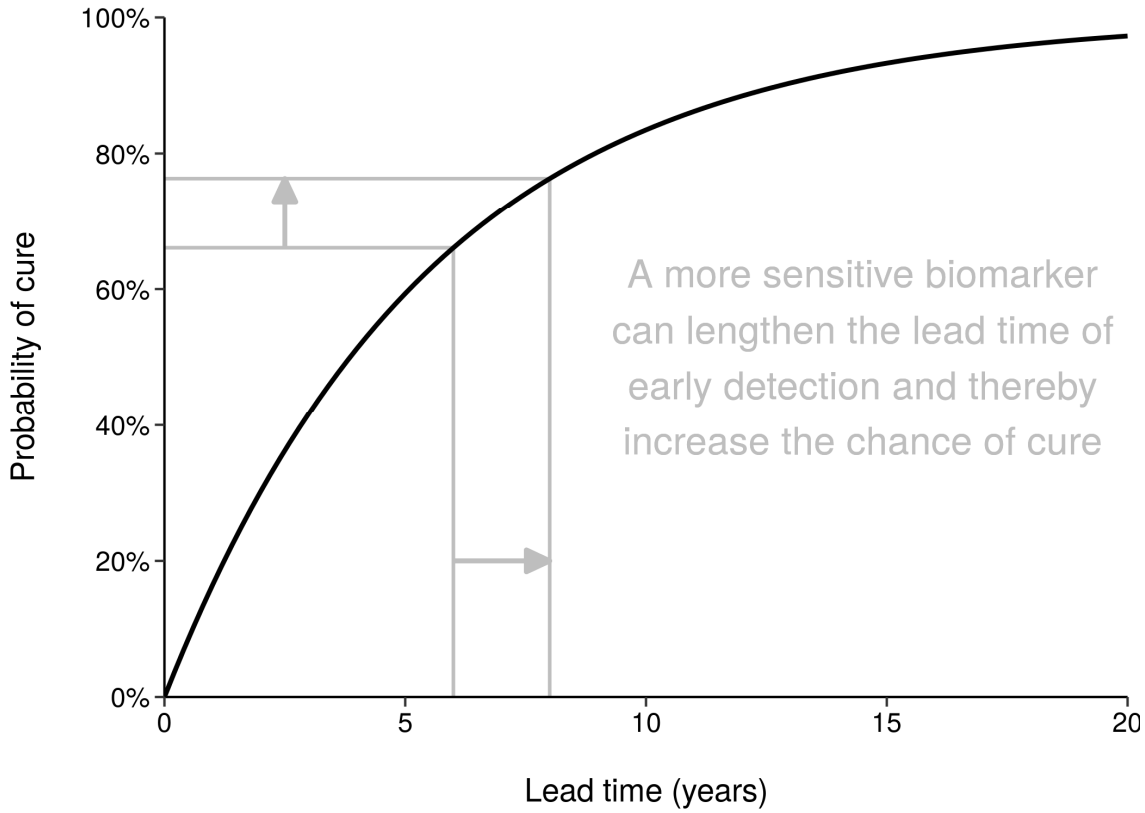
Three reflex tests added to existing model



1. Existing model:
   - Stage progression+ PSA growth
   - **Lead-time dependent cure rate**
2. Data available:
   - Biomarker measurements
   - PSA

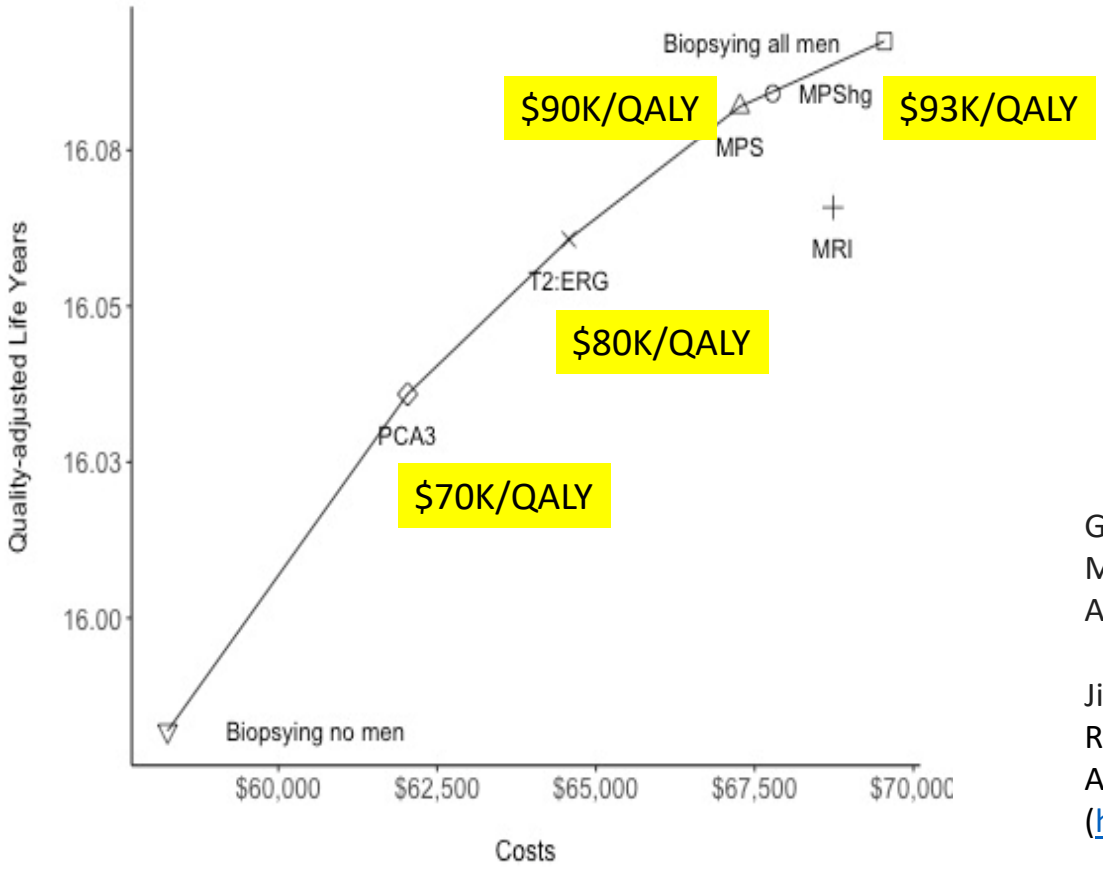
Impute new biomarker trajectories based on correlation with PSA, age and disease status

Lead-time-dependent cure rate



Results for annual screening age 55-69

Lead-time-dependent cure rate calibrated to ERSPC



Gulati et al. Overdiagnosis and Lives Saved by Reflex Testing Men With Intermediate Prostate-Specific Antigen Levels. JNCI April 2020

Jiao et al. Comparative Effectiveness and Cost-Effectiveness of Reflex Testing Men with Intermediate PSA levels: A Systematic Analysis. Under review (https://bjiao.shinyapps.io/ReflexTest_CEA/)

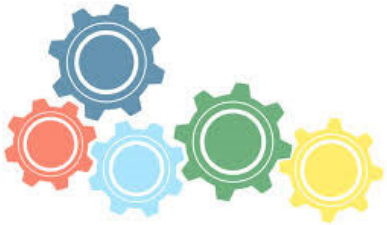
Novel biomarkers: prerequisites

1. A calibrated natural history model
2. Link between biomarker and existing model
3. Data to inform biomarker-model link
4. Concept for how the biomarker will impact survival benefit

Natural history models developed using data from cohorts or populations screened with older modalities can be valuable

Three parts

Models



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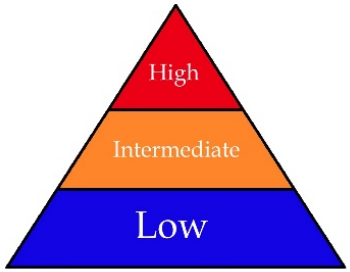


Risk stratification

Concentrate screening effort among population subgroups with highest risk of disease and potentially highest benefit in an absolute sense

Some risk stratification metrics

Demographic	Race and prostate cancer
Genetic	Germline genomic score
Acquired	Smoking and lung cancer
Precursor	Adenoma and colorectal cancer
Biomarker	PSA at age 45 and prostate cancer

How do we risk stratify early detection?

Just knowing that risk of diagnosis is higher/lower is not enough

➡ **Need to understand how disease differs across strata**

Onset	*Change ages to screen*
Progression	*Change screening interval*
Detectability	*Change screening modality*

➡ **Need to clarify objectives**

- Equity? Maximize benefit? Optimize cost effectiveness?

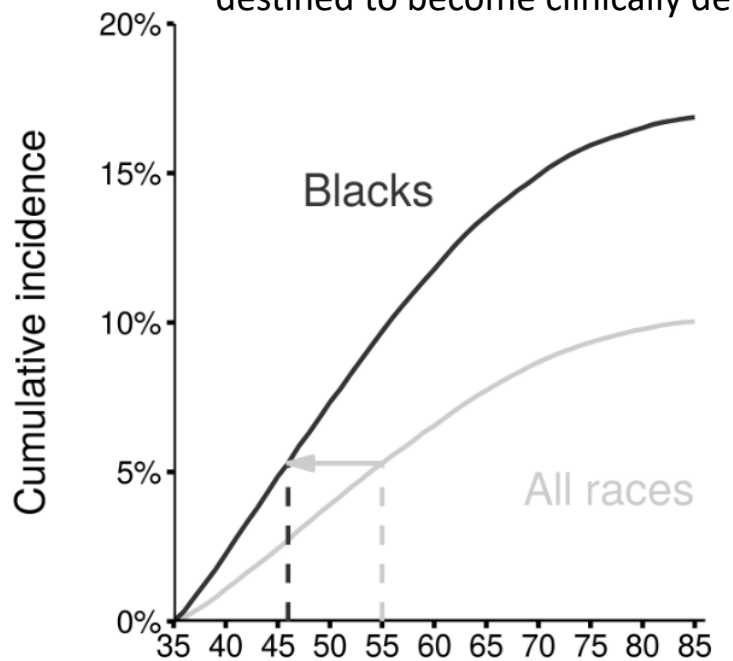
Example: Screening black men for prostate cancer

Equity objective – equal intervention for equal burden

- Black men have a **higher risk** of prostate cancer **onset**
- Incidence of latent non-overdiagnosed disease reaches level of average-risk population **ten years earlier**
- For **equity**, start screening black men **ten years earlier**

Tsodikov et al Cancer 2017; Etzioni and Nyame, JNCI 2020

Cumulative incidence of latent disease destined to become clinically detected



**Survival in the absence of screening is based on pre-PSA-era diagnoses by race*

Example: Genomic Score for prostate cancer

Identify risk-based strategies that are cost effective compared with non-stratified

Three risk strata based on Prompt PGS test

	LOW	MODERATE	HIGH
Fraction in each stratum	19%	47%	34%
Relative risk of onset	0.77	1.08	1.82

Precision screening: more intensive for high-risk, less intensive for low-risk

Hendrix et al, submitted

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Hendrix et al, submitted

Thresholding of risk can be highly impactful for both benefit and cost

Population

versus

Cost of the test for risk and the heterogeneity of risks are also important

Closing remarks

Modeling offers an important translational tool for early detection research

Areas ripe for deployment

- Targeting diagnostic performance
- Evaluating novel markers to improve existing screening tests
- Identifying and evaluating precision screening strategies
- Determining how realistic dissemination affects impact/inequity

Opportunity

- Leveraging broad range of data sources to inform models

Caution

- Understand model assumptions and their implications
- Don’t outsource modeling – build collaborative teams

Thank you!

- Roman Gulati
- Lurdes Inoue
- Jane Lange
- Nathaniel Hendrix
- Boshen Jiao
- Todd Morgan
- Yaw Nyame
- CISNET prostate cancer group