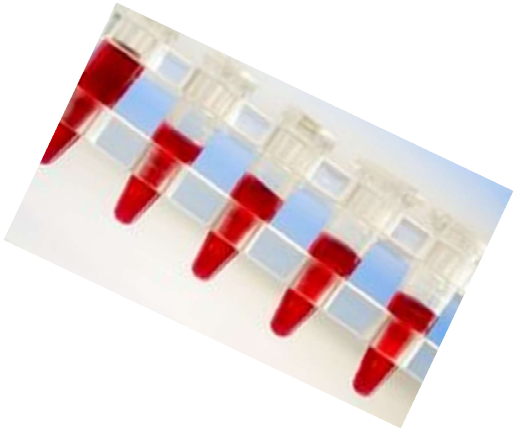
Now that we can walk are we ready to run?

From single-cancer screening to multi-cancer early detection

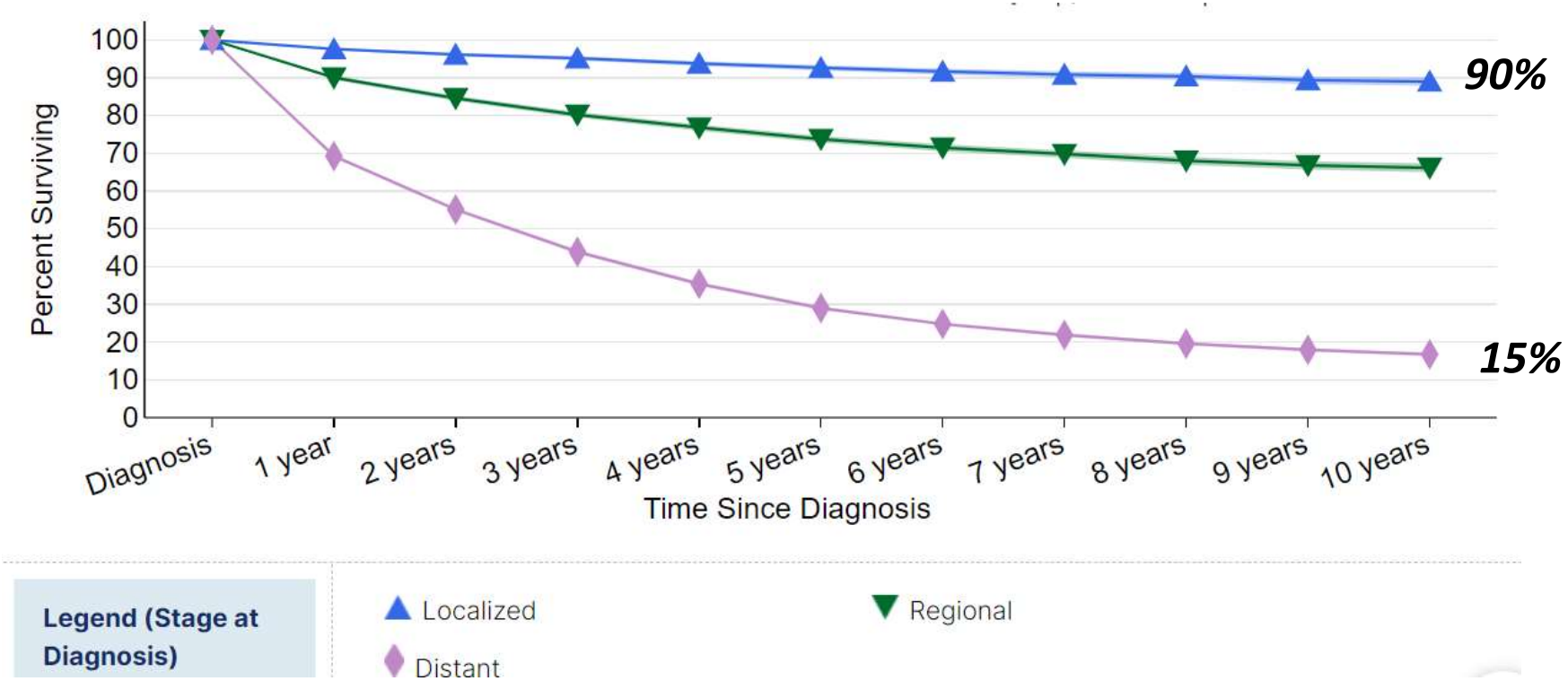
Ruth Etzioni PhD
Fred Hutchinson Cancer Research Center
And
CEDAR at the Knight Cancer Institute



Disclosures

- Dr Etzioni has consulted for Grail in the past
- Dr Etzioni holds shares in Seno Medical

Ovarian cancer - a poster child for early detection



Flashback: A biomarker for ovarian cancer

- CA-125 is a protein that is encoded by the MUC16 gene
- Discovered as marker for ovarian cancer in the **early 1980s**
- Initially detected using a murine monoclonal antibody OC125

Reactivity of a Monoclonal Antibody with Human Ovarian Carcinoma

ROBERT C. BAST, JR., MARYELLEN FEENEY, HERBERT LAZARUS, LEE M. NADLER, ROBERT B. COLVIN, and ROBERT C. KNAPP, *Sidney Farber Cancer Institute,*

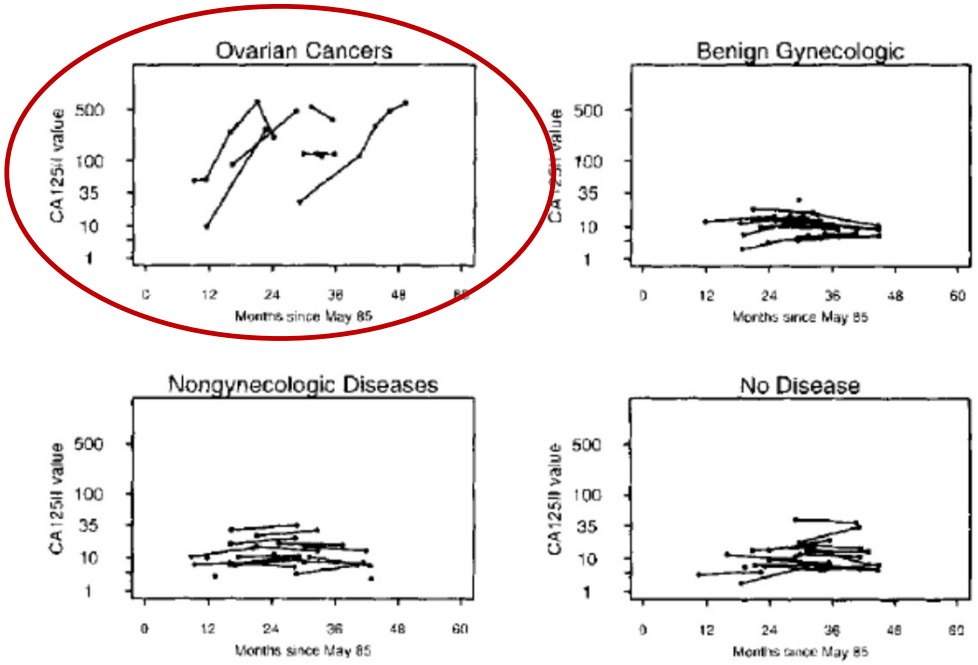
Journal of Clinical Investigation 1981

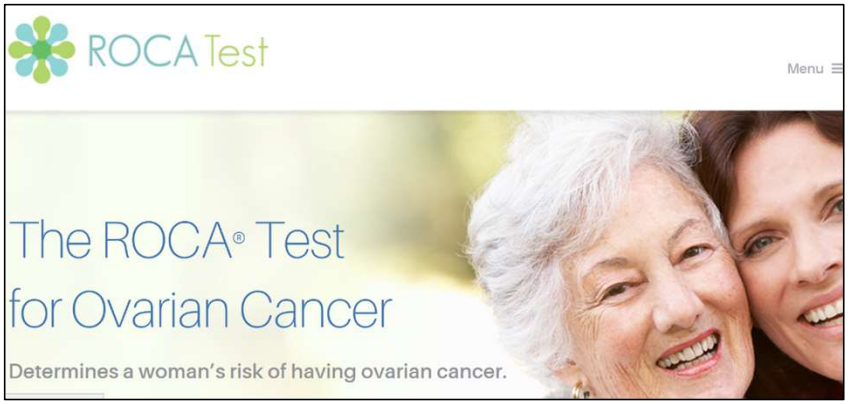
ABSTRACT A murine monoclonal antibody (OC125) has been developed that reacts with each of six epithelial ovarian carcinoma cell lines and with cryopreserved tumor tissue from 12 of 20 ovarian cancer patients. By contrast, the antibody does not bind to a variety of nonmalignant tissues, including adult and fetal ovary. OC125 reacts with only 1 of 14 cell lines derived from nonovarian neoplasms and has failed to react with cryostat sections from 12 nonovarian carcinomas.

Toward an Optimal Algorithm for Ovarian Cancer Screening with Longitudinal Tumor Markers

Steven J. Skates, Ph.D., Feng-Ji Xu, M.D.,† Yin-Hua Yu, M.D.,†*
*Kerstin Sjövall, M.D., Ph.D.,‡ Nina Einhorn, M.D., Ph.D.,‡ YuChiao Chang, Ph.D.,**
*Robert C. Bast, Jr., M.D.,† and Robert C. Knapp, M.D.**

Cancer 1995





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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening

Usha Menon, Andy Ryan, Jatinderpal Kalsi, Aleksandra Gentry-Maharaj, Anne Dawnay, Mariam Habib, Sophia Apostolidou, Naveena Singh, Elizabeth Benjamin, Matthew Burnell, Susan Davies, Aarti Sharma, Richard Gunu, Keith Godfrey, Alberto Lopes, David Oram, Jonathan Herod, Karin Williamson, Mourad W. Seif, Howard Jenkins, Tim Mould, Robert Woolas, John B. Murdoch, Stephen Dobbs, Nazar N. Amso, Simon Leeson, Derek Cruickshank, Ian Scott, Lesley Fallowfield, Martin Widschwendter, Karina Reynolds, Alistair McGuire, Stuart Campbell, Mahesh Parmar, Steven J. Skates, and Ian Jacobs

MMS sensitivity was 85.8%

MMS specificity was 99.8%

3.8 unnecessary surgeries per cancer detected

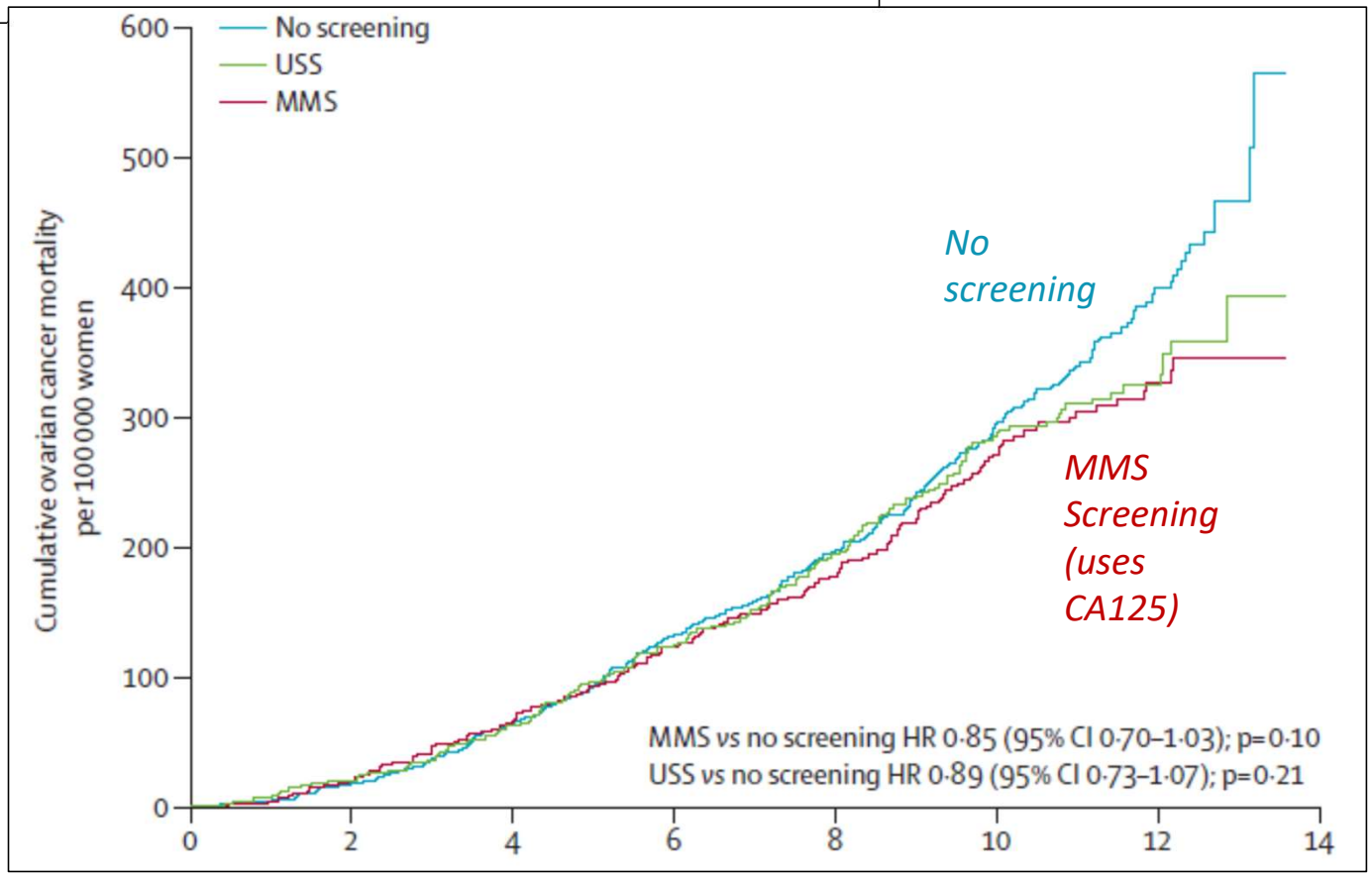
- UKCTOCS trial started in 2001: N=202,000
- 2 screen arms **MMS** used ROCA to triage to ultrasound
  USS used ultrasound only

Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Jacobs et al, Lancet, 2017

MORTALITY

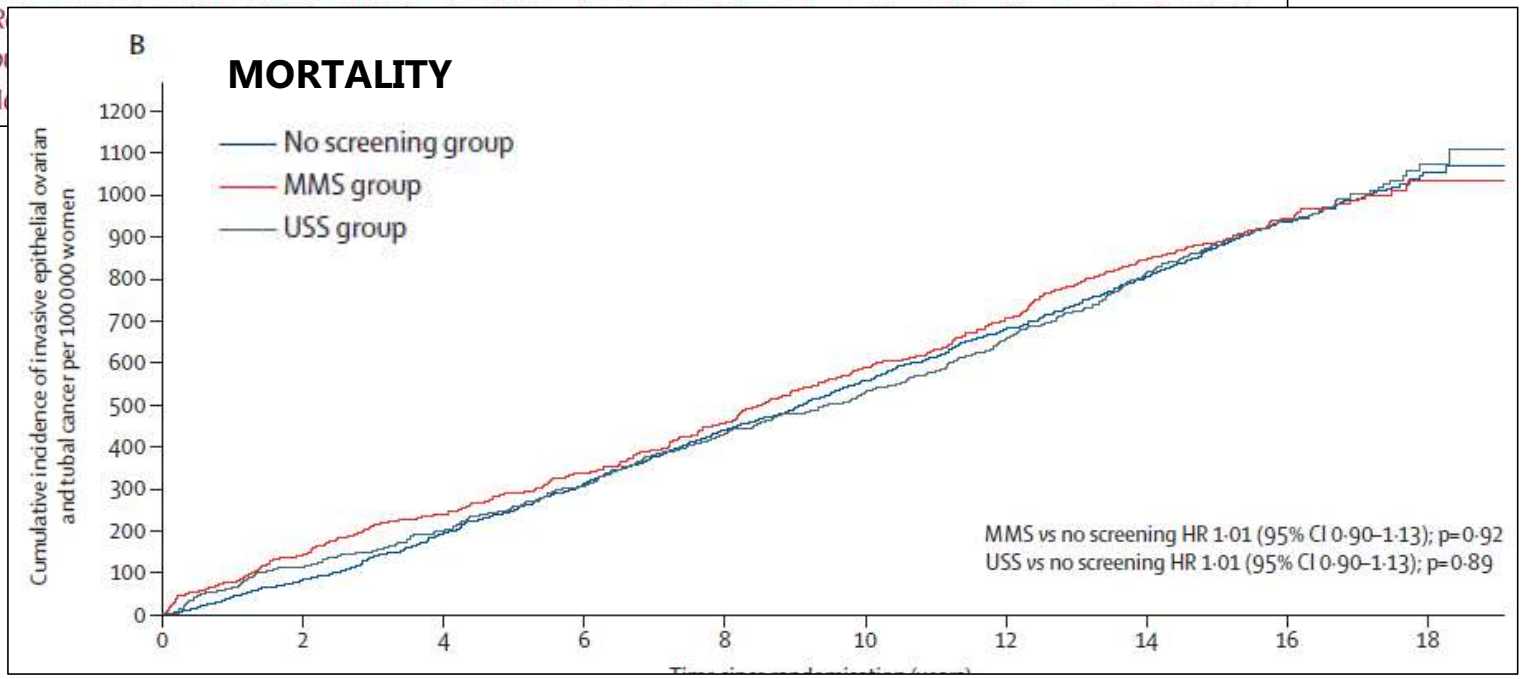
15% mortality reduction on MMS arm (p=0.1)



Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Usha Menon, Aleksandra Gentry-Maharaj, Matthew Burnell, Naveena Singh, Andy Ryan, Chloe Karpinskyj, Giulia Carlino, Julie Taylor, Susan K Massingham, Maria R... Simon Leeson, Tim Mould, Mo... Steven J Skates, Ian J Jacobs, M...

Lancet, May 2021



Early detection at a crossroads

Medscape Saturday, May 15, 2021

Disappointment: Screening for Ovarian Cancer Does Not Cut Deaths

ScienceDaily®

A large-scale randomised trial of annual screening for ovarian cancer, led by UCL researchers, did not succeed in reducing deaths from the disease, despite one of the screening methods tested detecting cancers earlier.

PRECISION ONCOLOGY NEWS

Multi-Cancer Molecular Screening Assays Primed for Clinical Implementation in 2021

Jan 11, 2021 | Molika Ashford

GRAIL

Galleri™

Thrive.
AN EXACT SCIENCES COMPANY

freenome

Spot the pattern, **treat the cancer.**

DELFI

Tests differ in their algorithms and outputs

	GRAIL **Galleri** Liu Ann Onc 2020	**DELFI** Cristiano Nature 2019	**THRIVE** **DETECT-A** Lennon Science 2020
Number of cancers	Up to **50 cancers** Sensitivity assessed for 12	**7 cancers**	Latest prospective study identified cancer in **10 organs**
Features	cfDNA methylation patterns	cfDNA fragment size distributions cfDNA mutations	cfDNA mutations Protein biomarkers
Output	**Cancer indicator** **Tissue of origin**	**Cancer indicator** **Tissue of origin**	**Cancer indicator** (Whole-body PET-CT for tissue of origin)

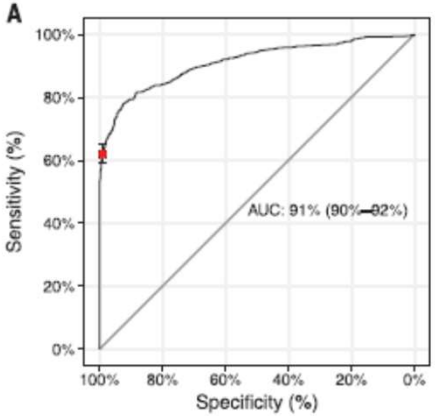
What we know about the new tests
1. They can find cancer when we know it is there

(With high specificity)

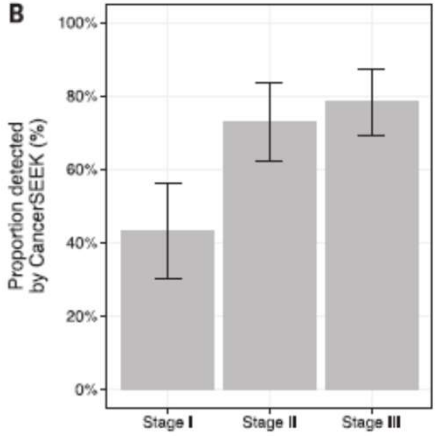
CANCER

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

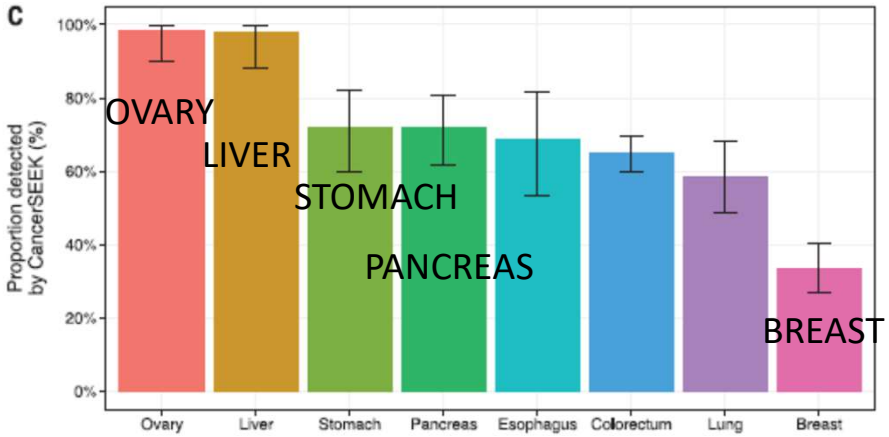
Cohen *et al.*, *Science* **359**, 926–930 (2018)



Overall discrimination



Sensitivity by stage

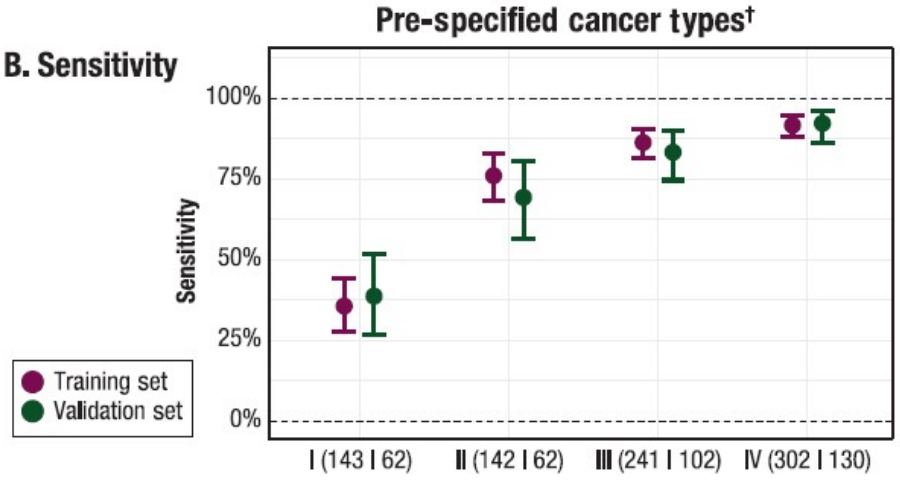


Sensitivity by cancer

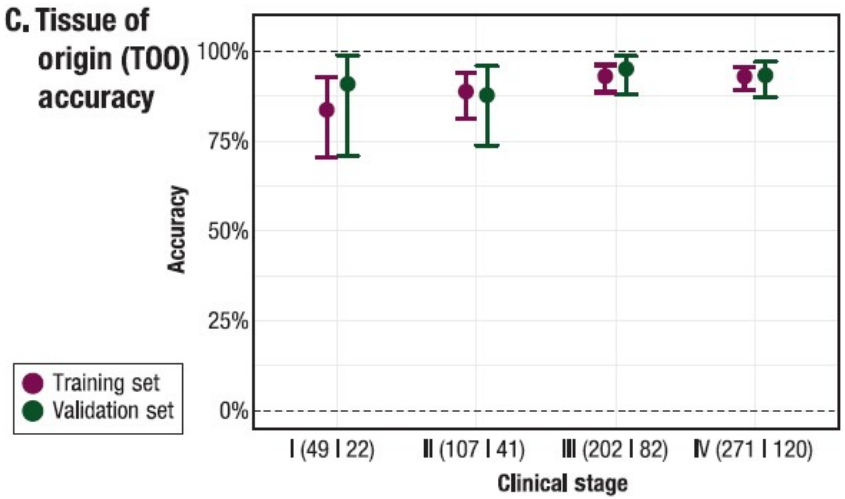
Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA

Annals of Oncology, 2020

M. C. Liu[1†], G. R. Oxnard[2†], E. A. Klein[3], C. Swanton[4,5], M. V. Seiden[6*] & on behalf of the CCGA Consortium[‡]



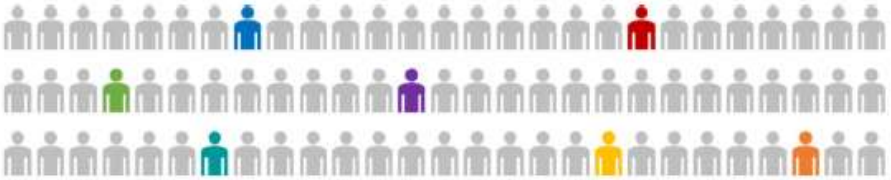
Sensitivity by stage



Fraction correctly localized by stage

What we know about the new tests
2. They are highly specific

- A highly specific test has a **low false-positive rate**
- This is important in cancer screening because the majority of persons tested do not have cancer



High specificity means low:

$$\frac{\text{False positives}}{\text{True positives}}$$

$$\frac{\text{Unnecessary biopsies}}{\text{Cancers detected}}$$

But policy is driven by outcomes

PERFORMANCE

- Sensitivity
- Specificity

OUTCOMES

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

From performance to outcomes: three drivers

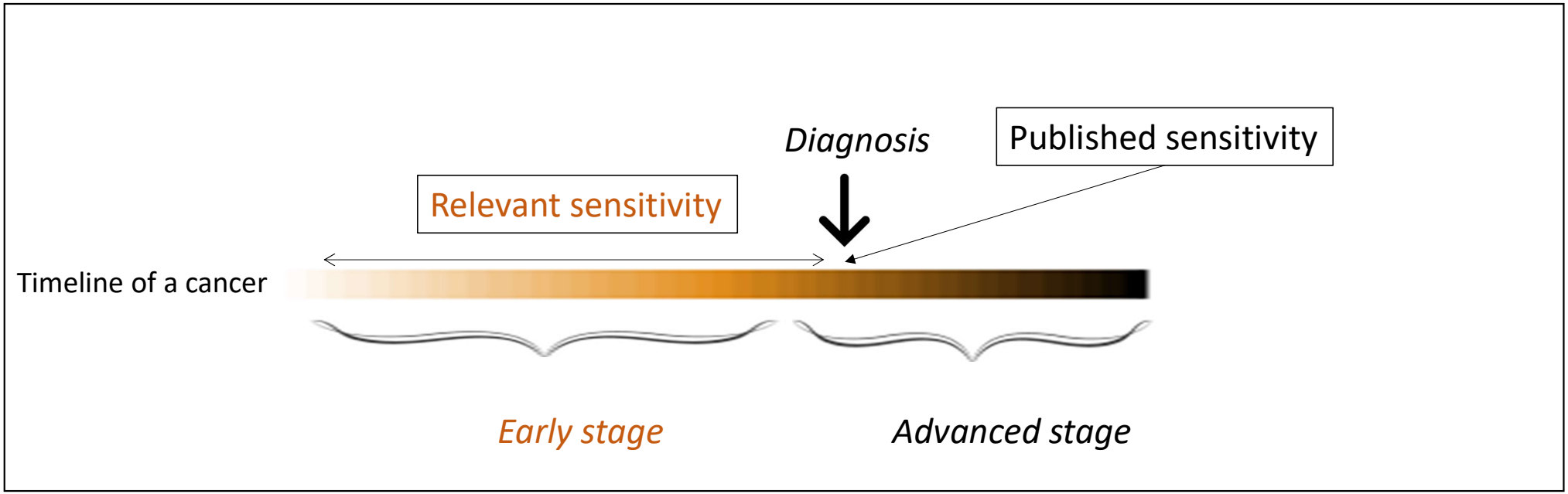
PERFORMANCE

OUTCOMES

1. **Sensitivity** to detect latent disease
2. **Opportunity** to detect early latent disease
3. **Curability** of early* disease

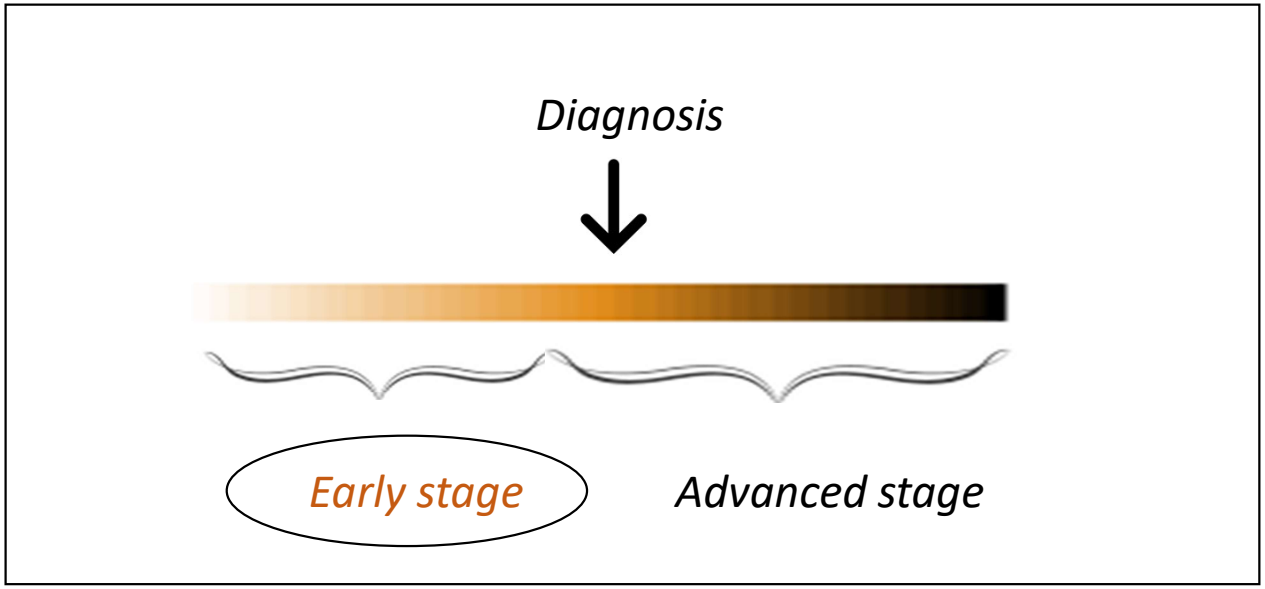
From performance to outcomes

1. Sensitivity to detect latent disease



- Published sensitivities relate to time of (non-screen) diagnosis not before
- Required: ability to readily and accurately confirm presence of disease

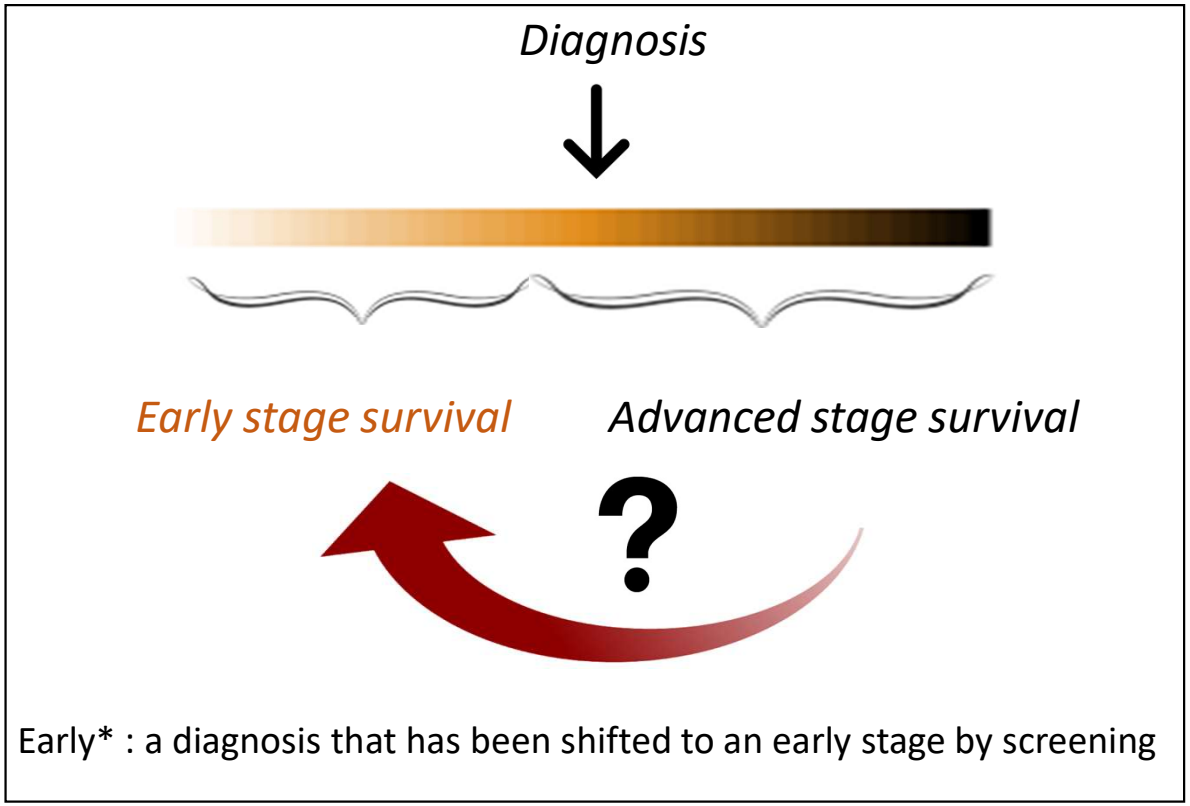
From performance to outcomes
2. Opportunity to detect early latent disease



- Published studies tell us nothing about the duration of early-stage disease
- Varies across cancers; not easy to identify without data from screened cohorts

From performance to outcomes

3. Curability of early* disease



Early* : a diagnosis that has been shifted to an early stage by screening

From performance to outcomes: three drivers

PERFORMANCE

OUTCOMES

1. **Sensitivity** to detect latent disease
2. **Opportunity** to detect early latent disease
3. **Curability** of early* disease

What did we learn from the ovarian trial?

Sensitivity of MMS to detect latent disease

Estimated sensitivity close to 85% based on CA125 and ultrasound imaging of the ovaries. But early Type II (aggressive) tumors begin in the ***Fallopian tubes***

Opportunity to detect early latent disease

In MMS arm incidence of stage IV reduced by almost ***25%***

But incidence of stage II+IV reduced by only ***10%***

Curability of early disease*

Despite ***10%*** *reduction in stage III+IV incidence,* ***no difference*** *in disease-specific mortality*

How can we learn about whether performance of multi-cancer tests will translate to outcomes?

Screening trials

- Least do-able, most informative but rarely the final word

Prospective screening studies

- More do-able, less informative, no control group

Modeling analyses

- Subject to information gaps and make many assumptions
- Can give ballpark predictions

Sensitivity? Opportunity? Curability?

A prospective study

CANCER

Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention

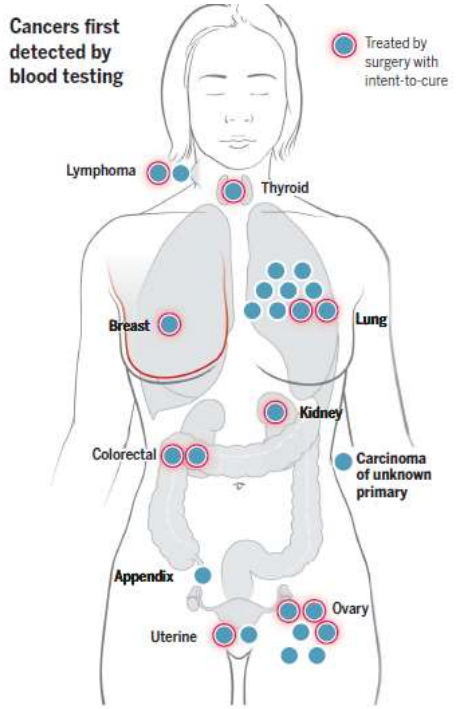
- 10,000 women given DETECT-A test
- Two positive tests followed by PET-CT

26 cancers detected by the test

24 additional cancers by standard screening

46 cancers diagnosed by neither approach

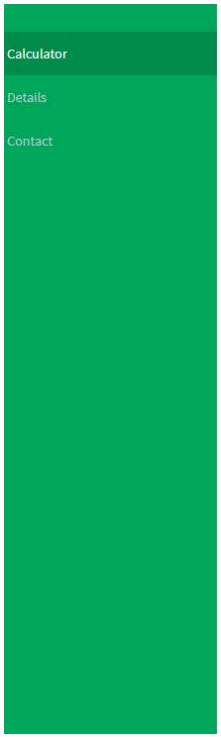
127 positives recommended imaging



Sensitivity? Opportunity? Curability?

Lennon *et al.*, *Science* **369**, 49 (2020)

A modeling study



Expected harms and benefits of multi-cancer early detection tests

This calculator provides a transparent computational framework for translating the diagnostic performance of a multi-cancer test to clinically relevant outcomes.

Outcomes of single-occasion testing performed at age 50, 60, or 70 for 100,000 persons with specified sex and race category are generated given test characteristics specified by the user and estimates of disease prevalence and disease-specific mortality in the United States. A user can specify test characteristics for detecting specific cancers, the associated mortality reduction for cancers detected by the test, and which cancers to include in the test's target set.

See the Details tab for more information and th

Population characteristics

Sex: Female

Race category: All races

Screening age: 50 years

Test characteristics

Test specificity: 0.99

Configure multi-cancer test

http://mced-calculator.fredhutch.org

Test characteristics

Test specificity:

0.99

Configure multi-cancer test

Site	Sensitivity	Localization	Reduction
Lung and Bronchus	0.67	0.9	0.1
Colon and Rectum	0.67	0.9	0.1
Ovary	0.67	0.9	0.1
Pancreas	0.67	0.9	0.1
Urinary Bladder	0.67	0.9	0.1

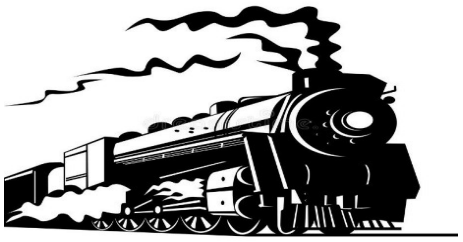
er 100,000 persons

Count
1038
403
24

Expected outcomes per 100,000 persons

Outcome	Count
Exposed to unnecessary confirmation	1038
Cancers detected	403
Cancer deaths prevented	24

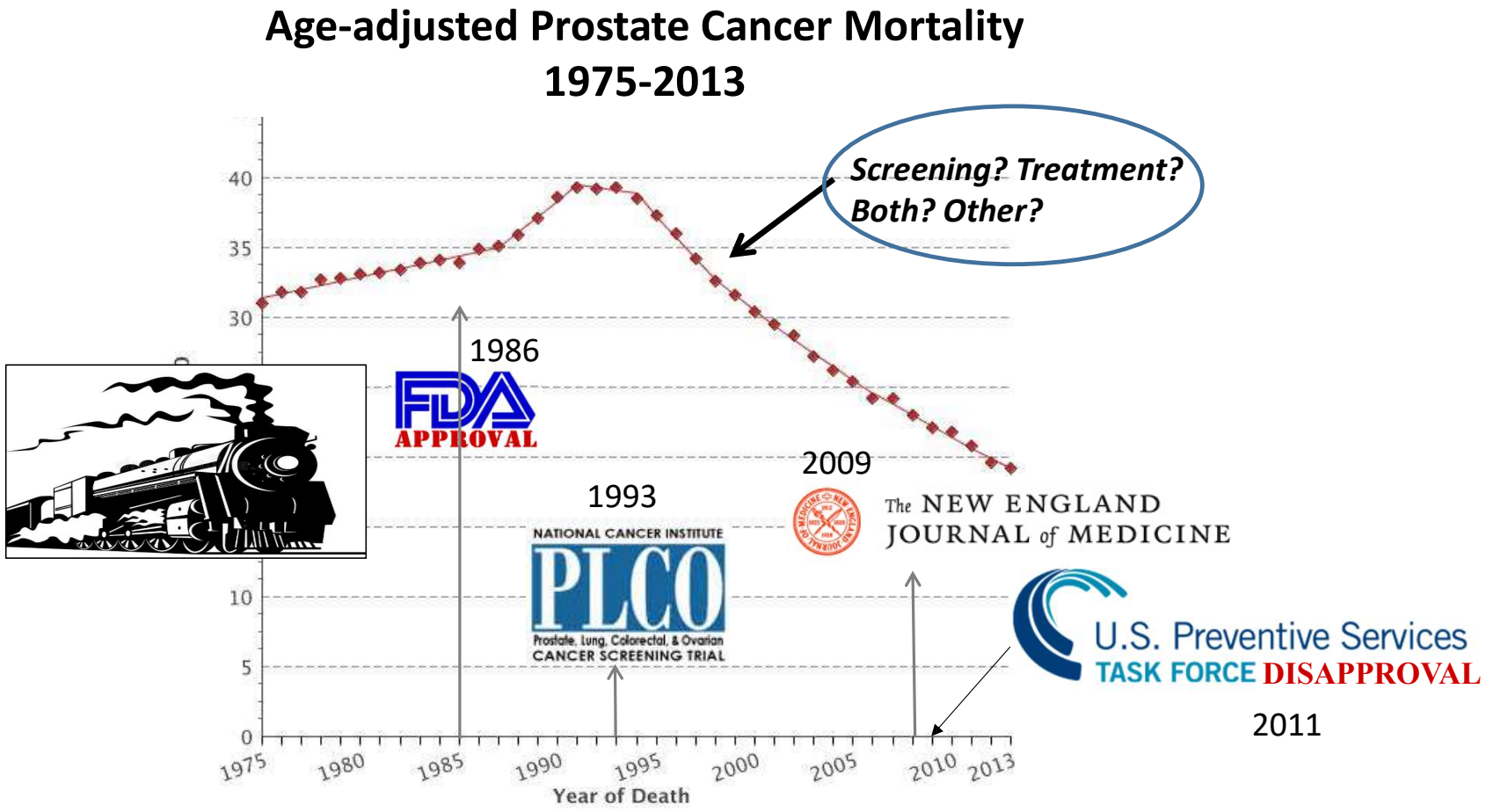
Jiao et al, "**A Quantitative Framework to Study Potential Benefits and Harms of Multi-cancer Early Detection Testing**" revised for CEBP

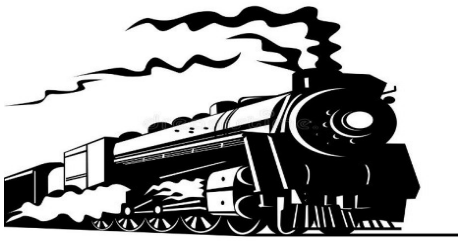


Wrap-up

- Multi-cancer early detection is a **critically important technology advance**
  - Complexities of early detection are as present as ever
- Expect **few exposed to unnecessary biopsy** per versus cancer detected
  - More complex confirmation process: **how should this be done?**
- Tests will likely detect some cancers that we do not currently screen for
  - Unclear from current data **whether their fate will be altered**
- Heed timing and message of the **ovarian cancer screening** story
  - Learn also from the **prostate cancer story**

PSA and prostate cancer screening





Take action

- Multi-cancer early detection is a critically important advance
- Expect few exposed to unnecessary biopsy per versus cancer detected
  - More complex confirmation process: how should this be done?
- Tests will likely detect some cancers that we do not currently screen for
  - Unclear at this point whether their fate will be altered
- Heed timing and message of the ovarian cancer screening story
  - Learn also from the prostate cancer story

Strongly urge the development of a data resource to track utilization and outcomes of these tests while we await further results regarding harm, benefit and cost

Thank you!

- **Boshen Jiao**
- **Roman Gulati**
- Noel Weiss
- Scott Ramsey
- Tina Clarke-Dur
- Earl Hubbell
- Christos Patriotis

Rosalie and Harold Rea Brown chair at Fred Hutch

CEDAR at the Knight Cancer Institute

NCI's Cancer Intervention and Surveillance Modeling Network

See http://mced-calculator.fredhutch.org *for our new multi-cancer test calculator that permits configuration of a multi-cancer test and projection of select outcomes*