Multi-Cancer Early Detection Tests: Will they Deliver? What to Expect?

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Value in Cancer Care Summit November 15 2024

The Buzz

IN THE LAB

STAT+

Liquid biopsies could help screen for countless cancers. But who should get them?

Mercy among first to offer $949 blood test that can screen for more than 50 types of cancer

Reprints

Prevent Cancer Foundation champions introduction of Nancy Gardner Sewell Medicare Multi-Cancer Early Detection Screening Coverage Act in the House

HEALTH · PUBLIC HEALTH

Could a simple blood test detect cancer at an early—and more treatable—stage? The technology exists—and FDA approval may not be far off

Why the Buzz?

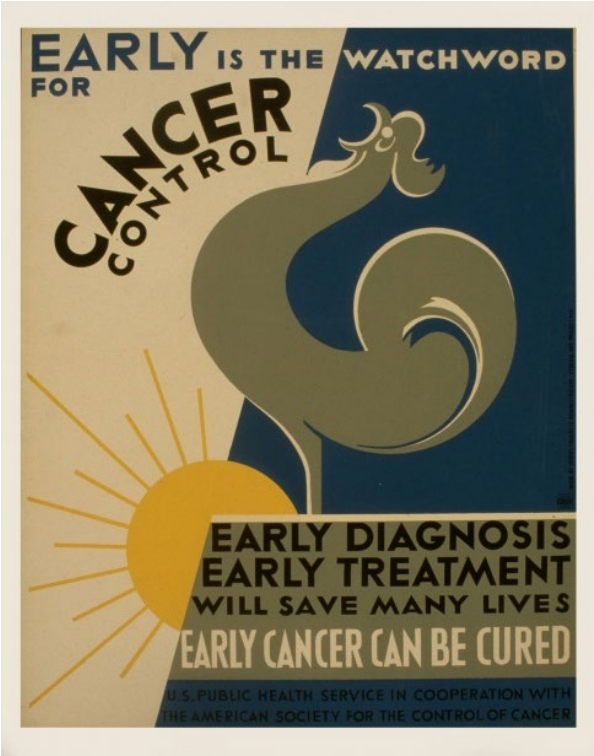
Major technology advance

Marketing

Published measures of diagnostic performance are promising

Enduring faith in the early detection solution

1960s

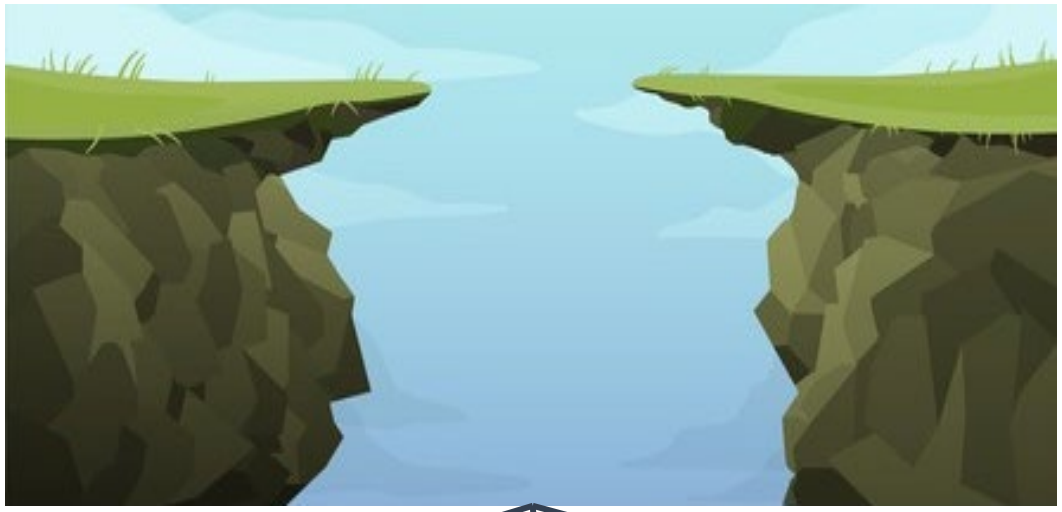


2020s

The gap between performance and outcomes

PERFORMANCE

Can the test detect the target cancer/s? What is the accuracy?



OUTCOMES

Does the test reduce late-stage cancers? Does it reduce cancer deaths?

Performance of the test in people not yet diagnosed with cancer

Opportunity to detect cancer early and change its fate

Implementation of and access to the test and downstream care

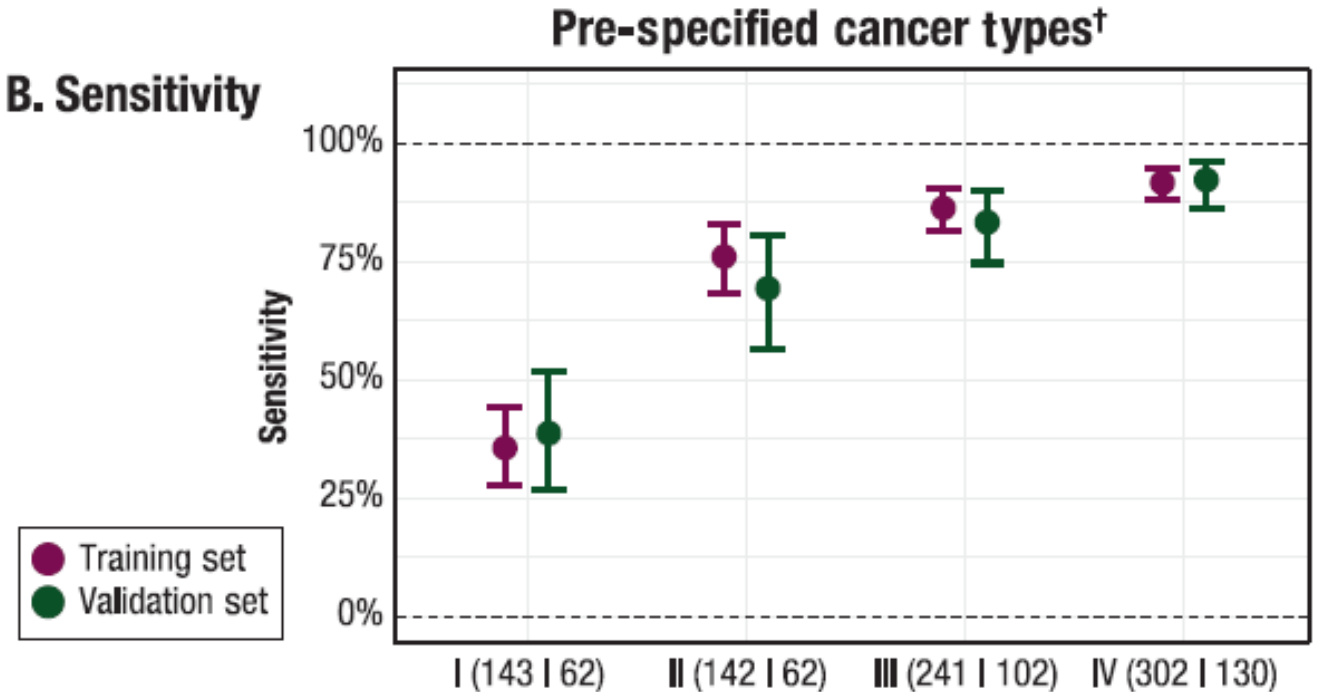
Sensitivity: A primary measure of performance

Likelihood a test will be positive if the cancer is there

Different versions of sensitivity

A.	Sensitivity to detect <u>known</u> cases	*Established first and common in early studies of test performance*
B.	Sensitivity to detect cases <u>before</u> diagnosis	*Much harder to assess* but likely lower than A*

Sensitivity for one test in known cases



Sensitivity by stage
(overall 67.3% for 12 cancers)

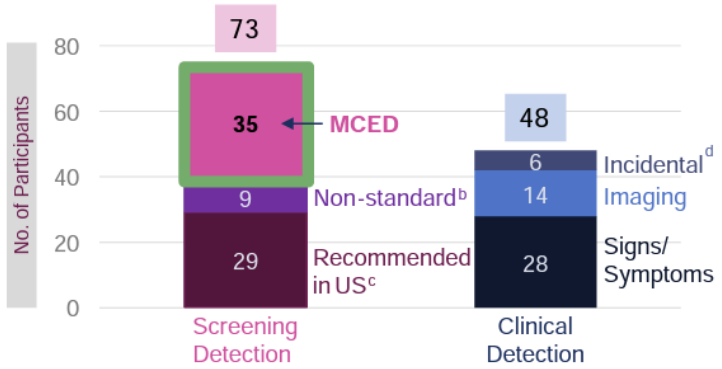
Liu et al Annals of Oncology 2020 for Grail test

Sensitivity in people not yet diagnosed

Cancers Identified Within One Year of MCED Testing

Participants with Cancers Detected by Either Screening or Clinical Findings

121 participants had a cancer diagnosis within 1 year



- 35/121 (29%) had cancer diagnosed and positive MCED
  - 2/35 had cancer detected by the MCED test but work-up began before results were disclosed

MCED, multi-cancer early detection.
[a]Based on participants with cancer status assessment at the end of the study.
[b]3 thyroid and 6 melanoma.
[c]Breast, cervical, colorectal, lung, and prostate cancer.
[d]1 incidental radiology finding, 1 incidental finding on routine physical exam, 2 changed lab values, 1 surveillance of prior cancer, 1 follow-up after MGUS diagnosis.

PARIS 2022 ESMO congress

Deb Schrag, MD, MPH

Sensitivity* under screening (overall 29% for 12 cancers)

Considerably less than sensitivity in known cases

This is to be expected

Schrag et al ESMO 2022 and Lancet 2023 for Grail test

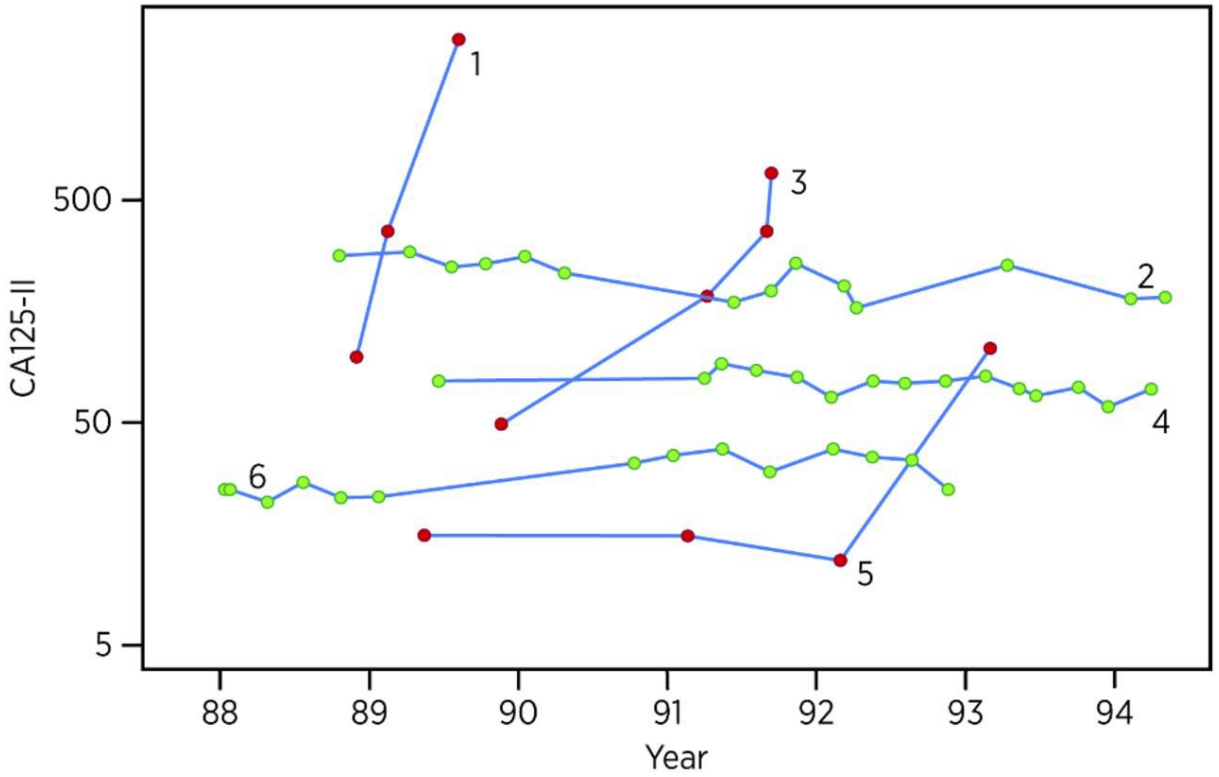
We might think we have a sensitive test…

Biomarkers and Strategies for Early Detection of Ovarian Cancer

Robert C. Bast Jr, Zhen Lu, Chae Young Han, Karen H. Lu, Karen S. Anderson, Charles W. Drescher, and Steven J. Skates

DOI: 10.1158/1055-9965.EPI-20-1057 Published December 2020

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION



- *Blue – ovarian cancer cases*
- *Green – non-cancer controls*

- *ROCA algorithm based on individual CA125 trajectories*
  - *Approximate sensitivity in people not yet diagnosed:* ***86%***

Menon et al JCO 2015

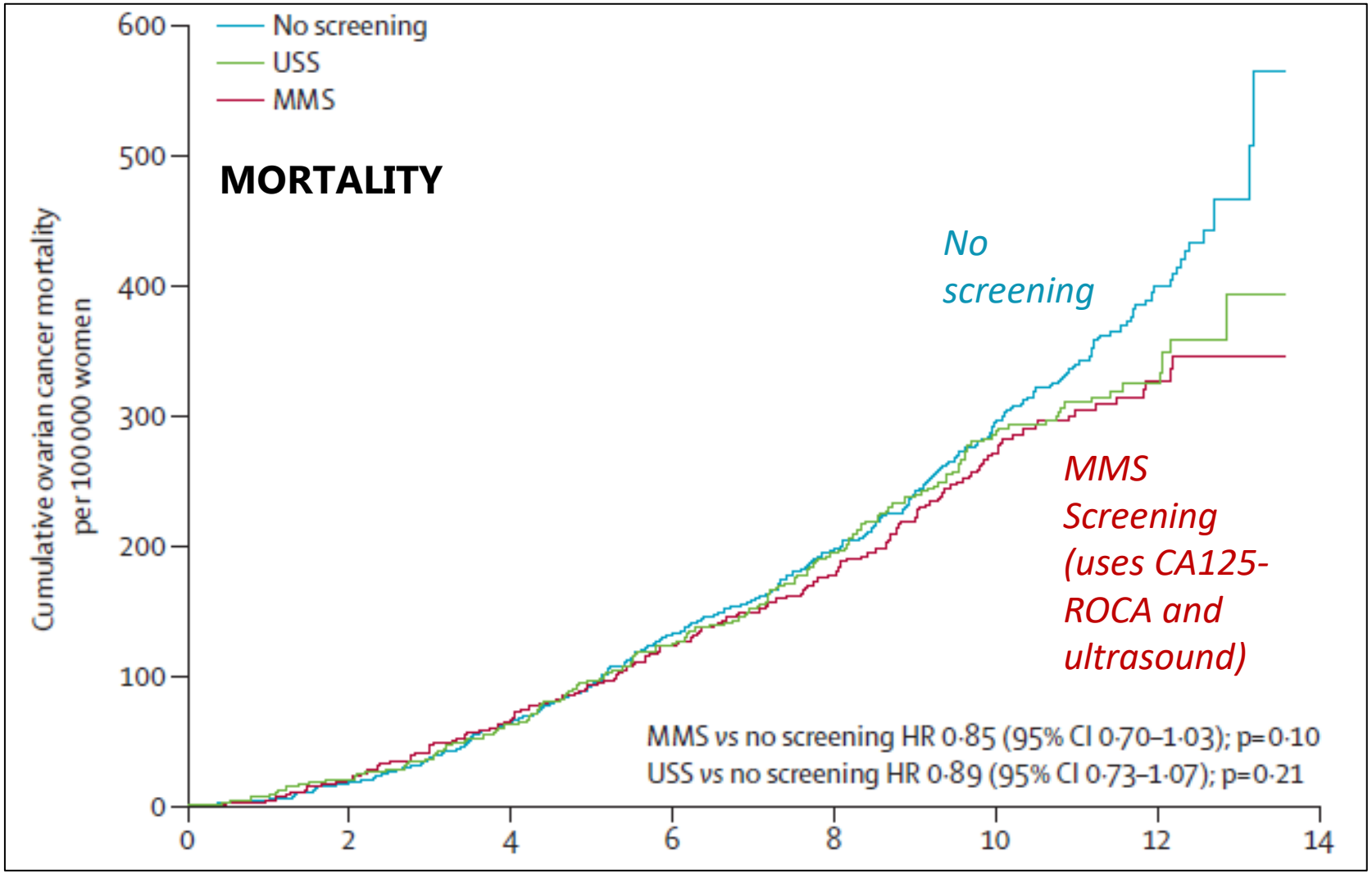
But it might not deliver

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

Jacobs et al, Lancet, 2017

UKCTOCS ovarian cancer screening trial

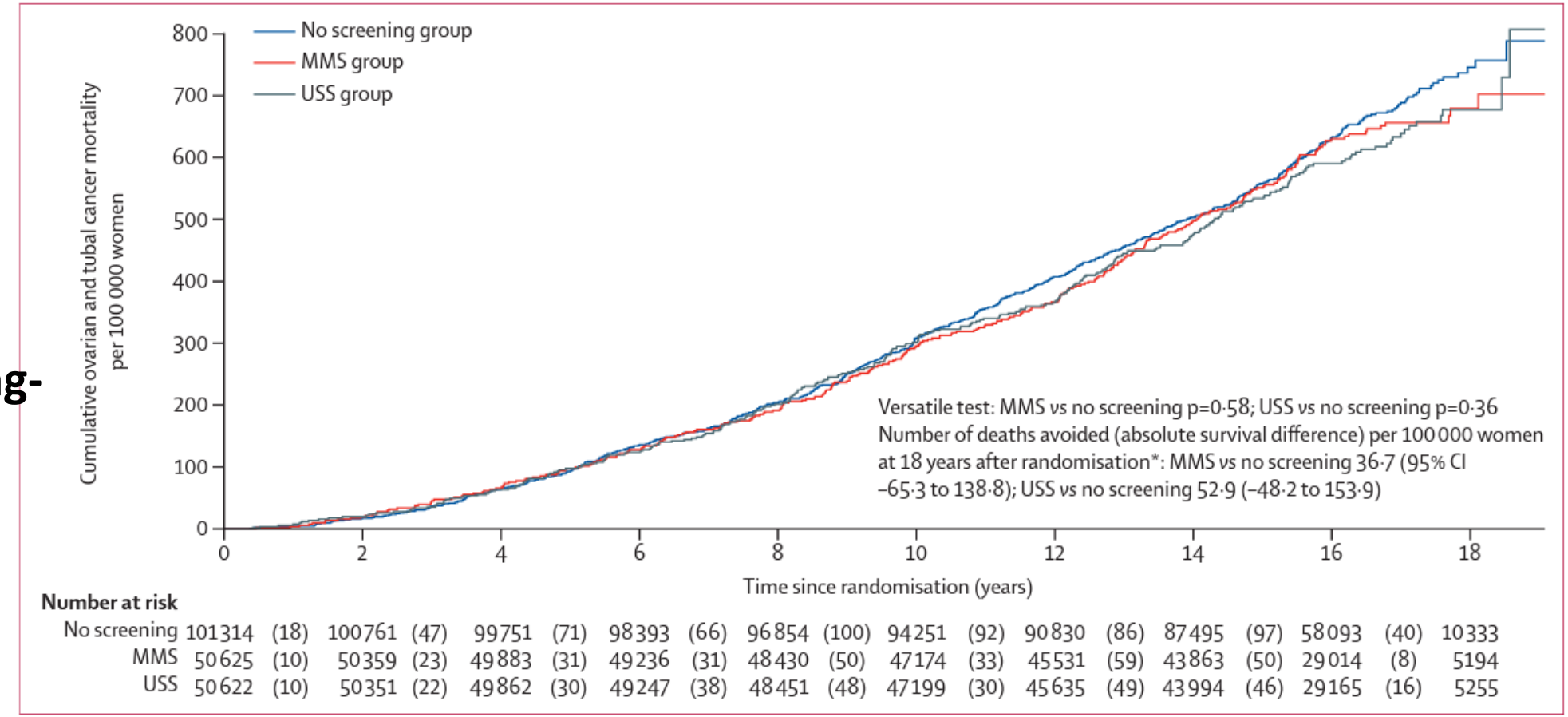
Primary report: Non-significant 15% mortality reduction on MMS (ROCA) arm



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 Raikou, Jatinderpal K Kalsi, Robert Woolas, Ranjit Manchanda, Rupali Arora, Laura Casey, Anne Dawnay, Stephen Dobbs, Simon Leeson, Tim Mould, Mourad W Seif, Aarti Sharma, Karin Williamson, Yiling Liu, Lesley Fallowfield, Alistair J McGuire, Stuart Campbell, Steven J Skates, Ian J Jacobs, Mahesh Parmar

No mortality reduction on long-term follow-up



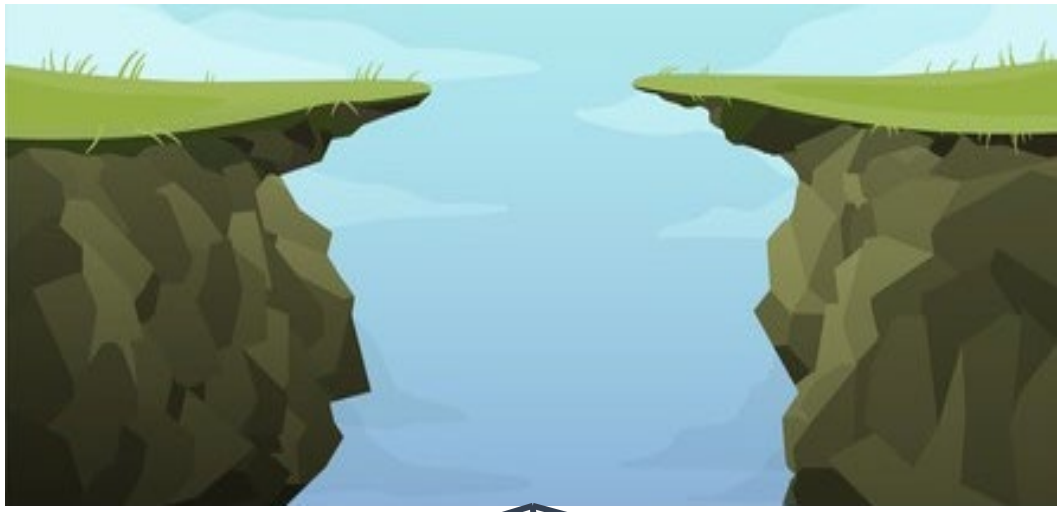
Number at risk

No screening	101314	(18)	100761	(47)	99751	(71)	98393	(66)	96854	(100)	94251	(92)	90830	(86)	87495	(97)	58093	(40)	10333
MMS	50625	(10)	50359	(23)	49883	(31)	49236	(31)	48430	(50)	47174	(33)	45531	(59)	43863	(50)	29014	(8)	5194
USS	50622	(10)	50351	(22)	49862	(30)	49247	(38)	48451	(48)	47199	(30)	45635	(49)	43994	(46)	29165	(16)	5255

The gap between performance and outcomes

PERFORMANCE

Can the test detect the cancer?
What is the accuracy?



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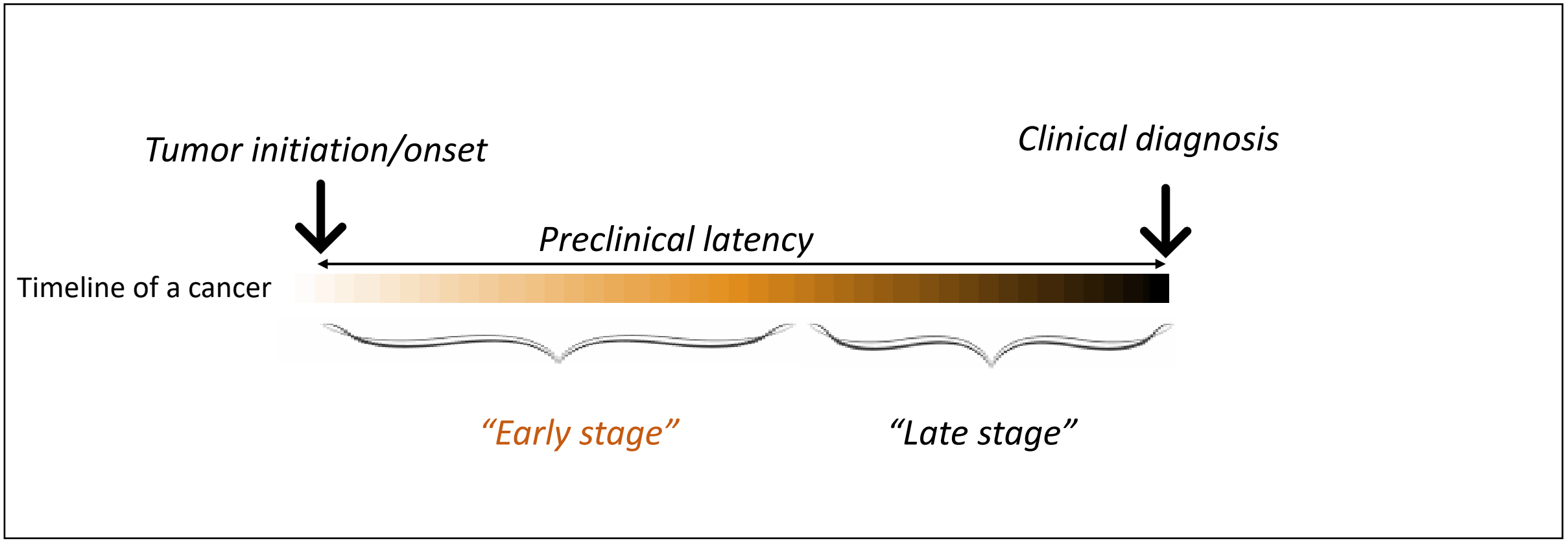
Opportunity to detect cancer early and change its fate

Implementation of and access to the test and downstream care

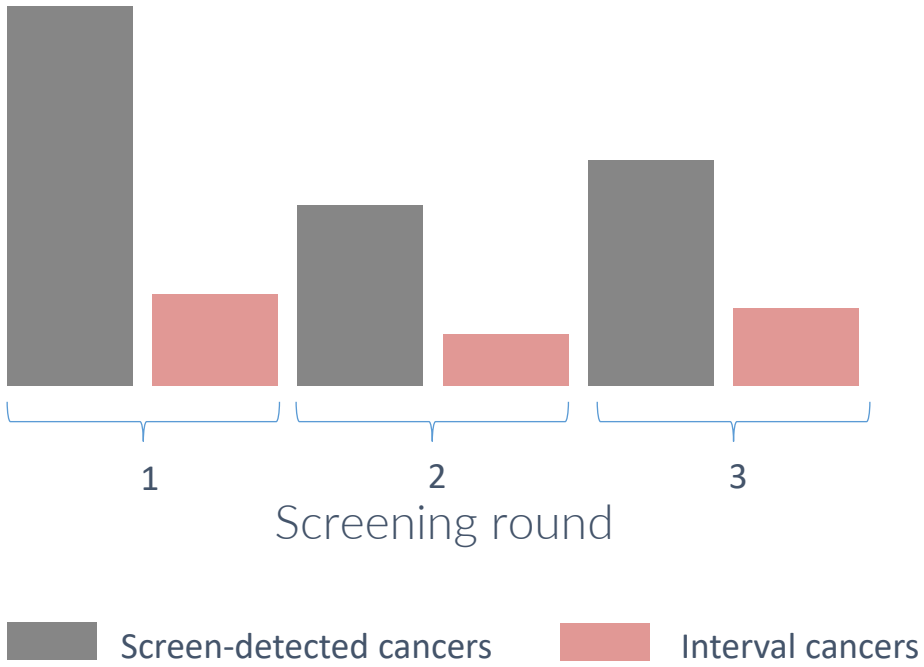
Opportunity for interception



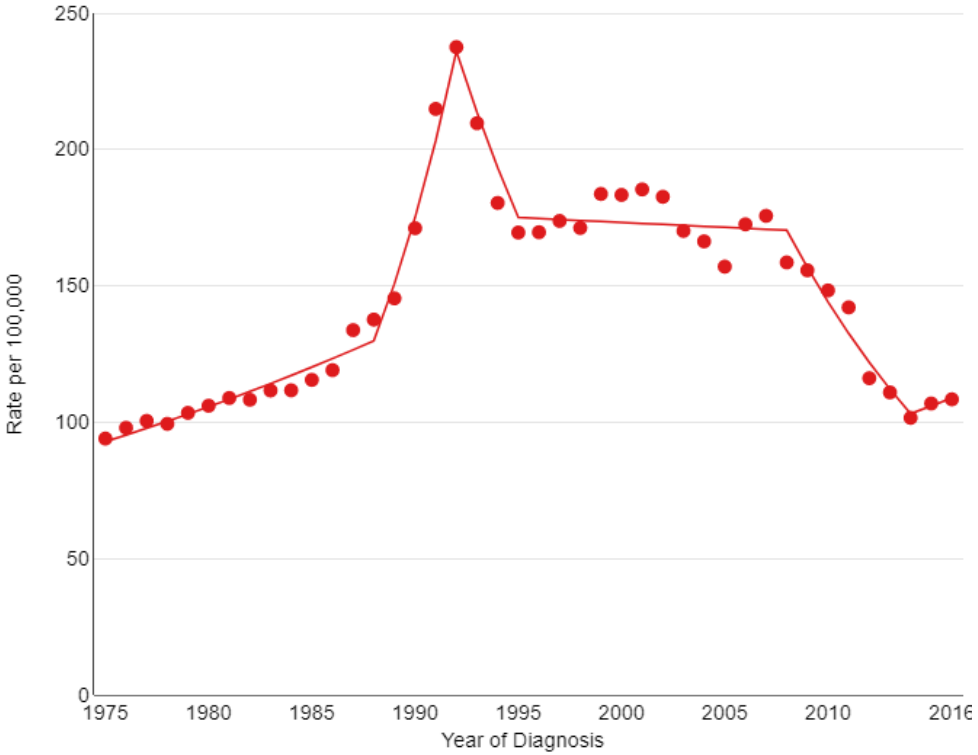
How do we learn about opportunity?

From studying changes in disease incidence under screening

Incidence at and between screens in trials



Population patterns under screening



Created by https://seer.cancer.gov/explorer on Wed Jan 22 2020.

Different cancers – varying preclinical latencies

Prostate	7-14 years	Different estimation methods US population data
Colorectal	3.5-5 years	Different estimation models Combination of data sources
Lung	4 years	One model/estimation method Data from PLCO/NLST
Breast	3.5-6.5 years	Different methods, cal. periods Screening trials and BCSC data

Platinum Priority – Prostate Cancer
Editorial by Allison S. Glass, Matthew R. Cooperberg and Peter R. Carroll on pp. 753–755 of this issue

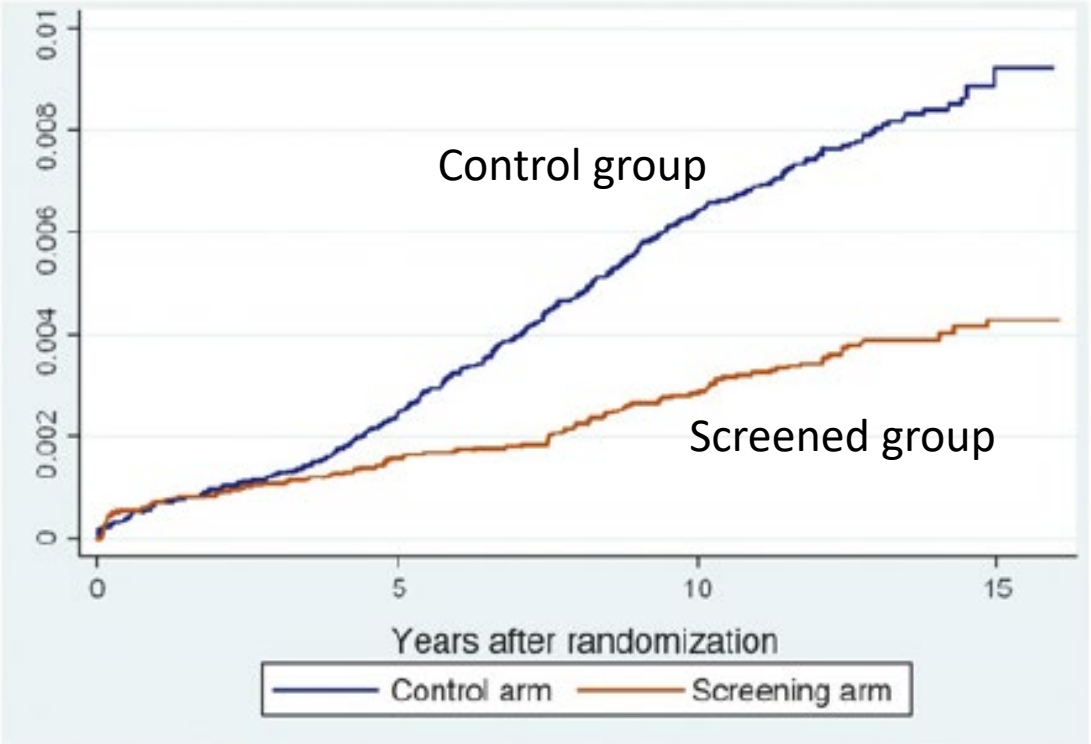
Screening for Prostate Cancer Decreases the Risk of Developing Metastatic Disease: Findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC)

Late-stage incidence reduced by **50%** in the screen group

Due to long opportunity despite modest sensitivity (20 - 30%)

Led to a **20%** reduction in cancer death rate

Late-stage cancer incidence



Schroder et al Eur Urol 2017

So what explains the ovarian cancer results?

Preclinical latency in ovarian cancer is much shorter

Lack of opportunity for early detection could explain trial results

Analysis	Cancer	Mean sojourn time (y)
Primary	All	2.08 (1.75, 2.51)
Secondary	HGSC	1.85 (1.44, 2.33)
	non-HGSC	8.23 (5.75, 11.10)

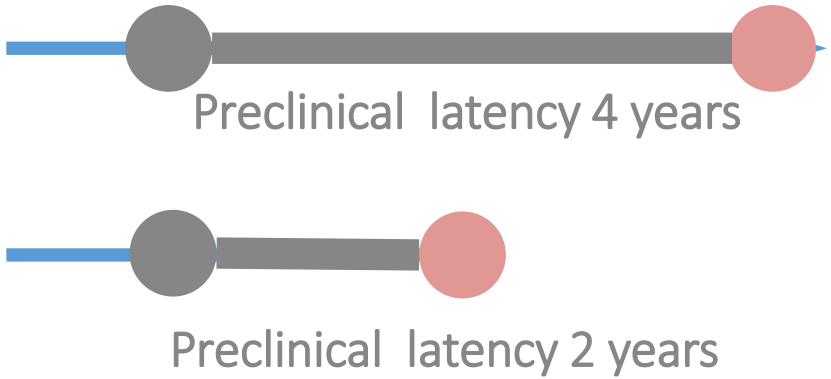
HGSC: high-grade serous carcinoma

Ryser, Lange, Menon, Etzioni, in press

What about cancers without screening programs?

We really don’t know the opportunity for detecting these cancers early

- We can be optimistic and assume long preclinical latency
- We can be pessimistic and assume short preclinical latency



Expected reduction in late-stage diagnoses over five years

40-50%

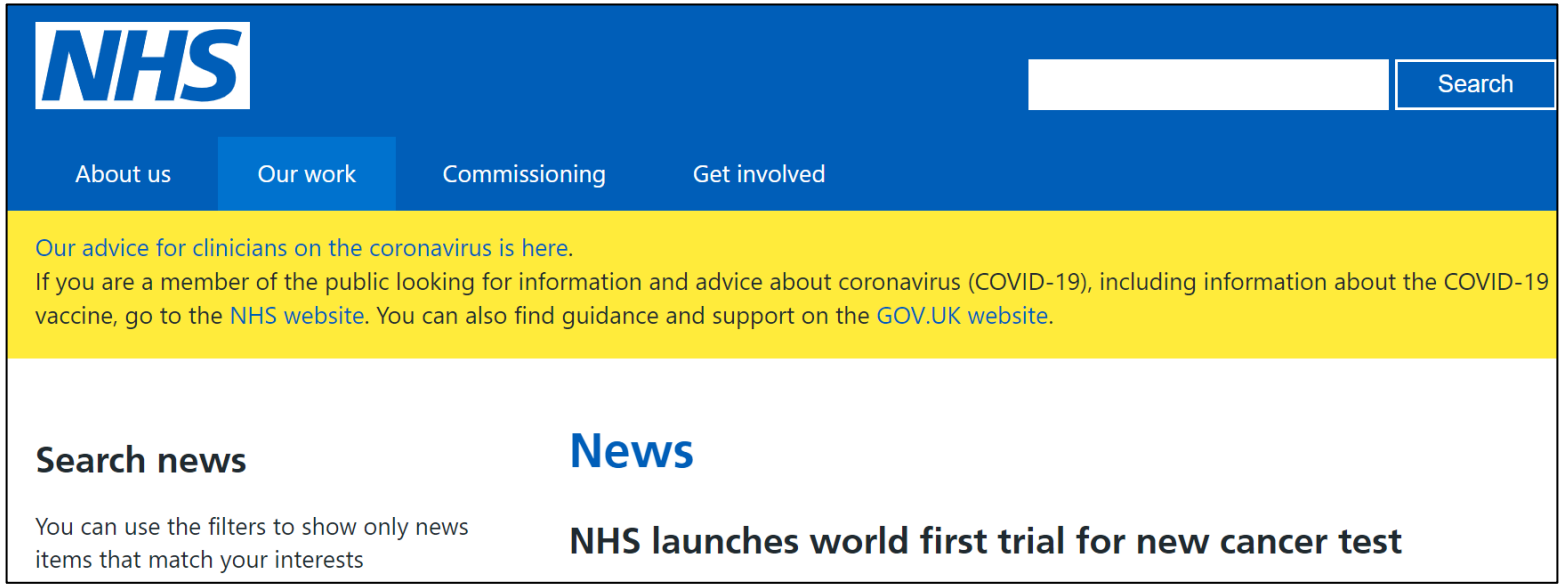
10-20%

RESEARCH ARTICLE | APRIL 11 2024

Projecting the Impact of Multi-Cancer Early Detection on Late-Stage Incidence Using Multi-State Disease Modeling

Jane M. Lange ; Kemal Caglar Gogebakan ; Roman Gulati ; Ruth Etzioni

A trial studying this is under way in the UK



Initial results of the study are expected by 2023 and, if successful, the NHS in England plans to extend the rollout to a further one million people in 2024 and 2025.

The NHS-Galleri study is a Randomised Control Trial (RCT) – meaning that half the participants will have their blood sample screened with the Galleri test right away and the other half will have their sample stored and may be tested in the future. This will allow scientists to compare the stage at which cancer is detected between the two groups.

What is a good enough late-stage reduction?

The New Y

Sunday, August 31, 2025

Galleri Trial Lowers Late-St

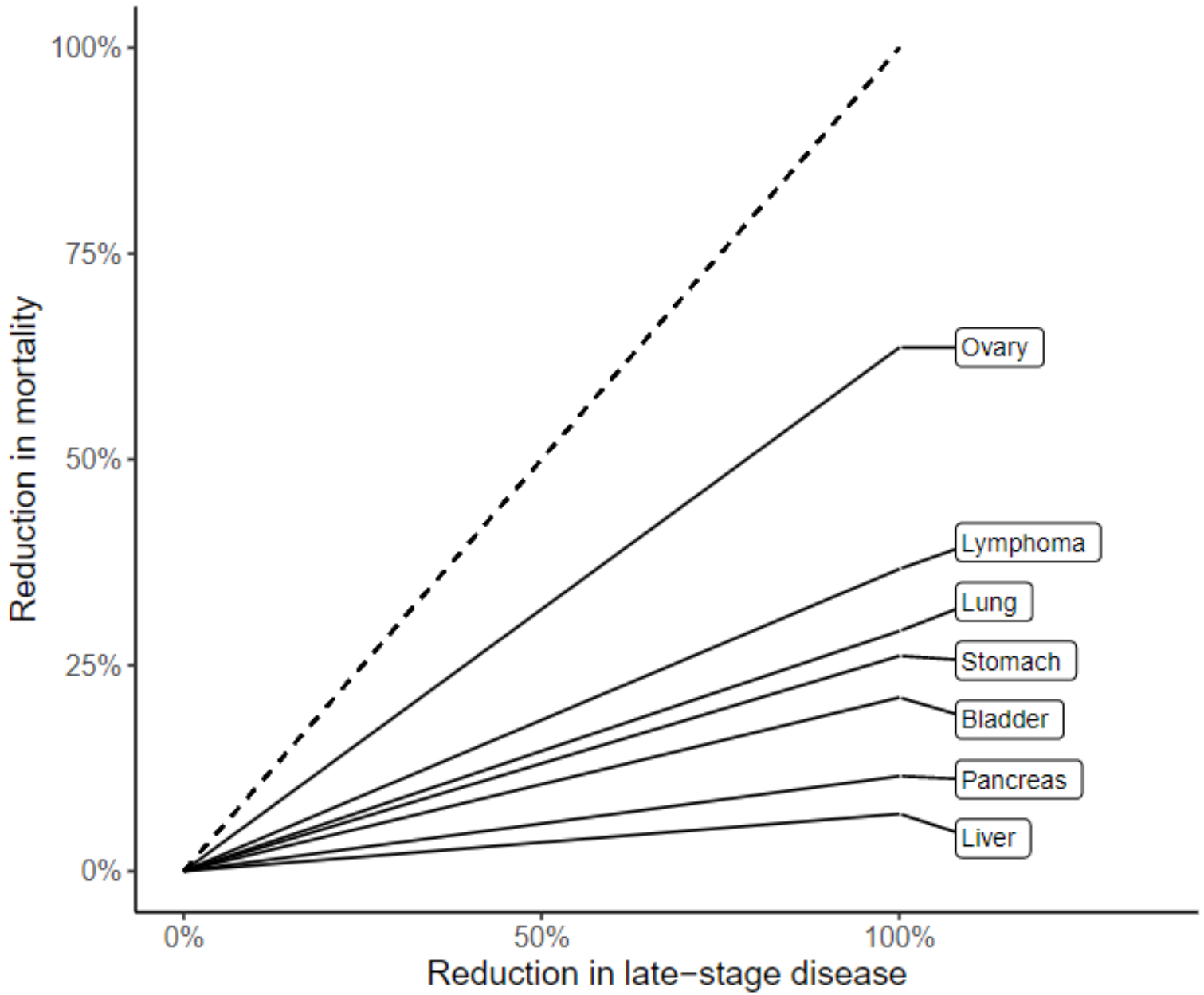
The NHS-Galleri Trial of multi-cancer early detection screening in diagnosis of late-stage cancers in a landmark study Friday. reported a 14 percent drop

Ren
foll
imp

NHS
Galleri Trial

A given late-stage reduction means different things for different cancers

Same reduction in late stage: variable expected reduction in mortality aross cancers



Owens L et al CEBP 2022

Why worry?

Poor evidence base leading to suboptimal or harmful medical decisions

Marketing and misinformation capitalizing on belief in early detection

Focus on positive outcomes disregarding downsides of screening

Marketing and misinformation

Marketing and misinformation

- If MCED is as effective for these cancers as it has been in the best case for cancer with existing screening tests (30% mortality reduction)
- Then 62% of deaths will occur in these cancers!

How accurate is the Galleri blood test?

Depending on the test, traditional screening tests have a false-positive rate of 10% to 40%. Galleri has a 0.5% false-positive rate, which means it's highly accurate.

"It finds 51.5% of cancers," points out Dr. Klein. "If you look at the 12 cancers that account for two-thirds of all deaths in the U.S., it actually finds 67% of those."

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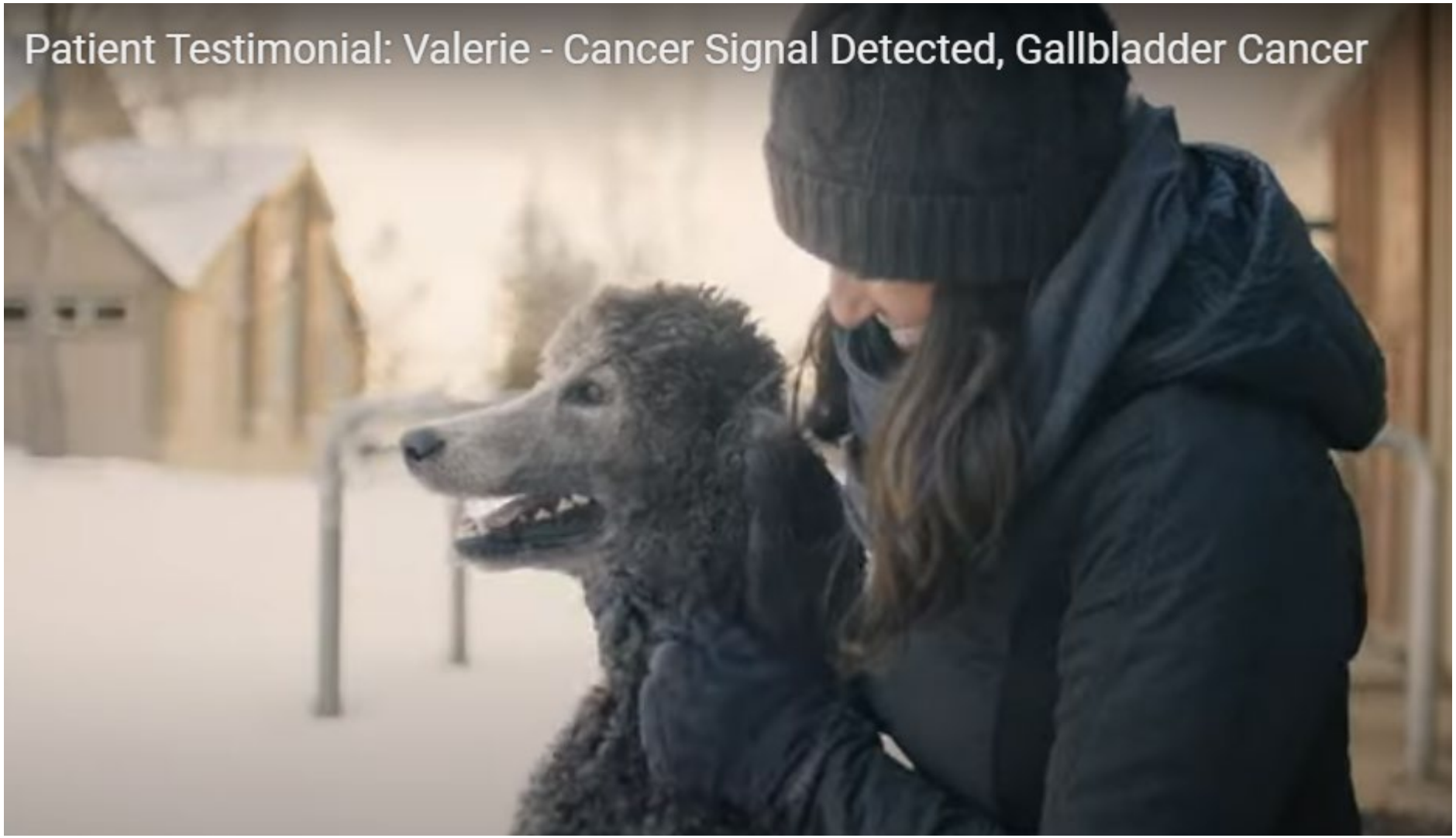
CONSERVATIVE

"It finds 51.5% of cancers," points out Dr. Klein. "If you look at the 12 cancers that account for two-thirds of all deaths in the U.S., it actually finds 67% of those."

OUT OF POSITIVE TESTS HOW MANY FOUND TO HAVE CANCER

IN PEOPLE KNOWN TO HAVE CANCER NOT IN THE SCREENING POPULATION

Focus on positive



How do you solve a problem like incidentalomas?

We know certain facts about incidentalomas. We know what they are: incidentally discovered masses or lesions, detected by computed tomography (CT), magnetic resonance imaging (MRI), or other imaging examinations performed for an unrelated reason.[1] We know why incidentalomas are increasing: The number of CT exams performed in the United States has increased geometrically over the decades, rising from 3 million annually in 1980 to close to 80 million annually currently, along with remarkable improvement in spatial and contrast resolution on newer-generation CT scanning equipment.[2] We know that up to 70% of persons undergoing screening CT colonography have at least one detectable incidentaloma.[3] We know incidentalomas are found in 34% of hemodynamically stable blunt trauma patients.[4] We know that 35% of patients undergoing CT for thoracolumbar blunt trauma injuries harbor incidentalomas.[5] We know that nodular incidentalomas are found in at least 25% of patients undergoing chest CT.[6] We know that incidentalomas occur in at least 40% of abdominal and pelvic CT exams obtained for research purposes.[7] We know incidentalomas are present in 49% of patients undergoing aortoiliac CT angiography prior to aortic valve repair.[8] We know that incidentalomas are found in up to 50% of the lungs on CT exams of the chest, up to 15% in the kidneys and liver on abdominal CTs, and up to 67% in the thyroid gland on neck ultrasound exams.[9] And we know that the chance that an incidentaloma found in any of these exams could represent a lethal carcinoma is < 1%.[9]

https://appliedradiology.com/articles/how-do-you-solve-a-problem-like-incidentalomas

Who's Afraid of Early Cancer Detection?

Grail seeks FDA approval for its Galleri test, which can detect tumors long before symptoms develop. But critics worry that the costs are too high.

What's wrong with this headline?

Who's Afraid of Early Cancer Detection?

Grail seeks FDA approval for its Galleri test, which can detect tumors long before symptoms develop. But critics worry that the costs are too high.

We actually do not know yet that the test can detect cancers long before symptoms develop

These studies have not yet been done

It's not just about the costs though these are likely to be high

Many other concerns!

- *Diagnostic odysseys*
- *Misinterpretation of negative results*
- *Incidental findings*
- *Quality of life*

The (formidable) task ahead

In cancer, early detection tests are recommended when we have reliable evidence that benefits outweigh harms

We are very far from having this evidence for MCED

What we need now

A. **Educate** patients, providers, and the public about why early detection is not always a slam dunk
B. **Understand** that it not just about the test – testing is just the first step in a process – access and implementation are critical
C. **Recognize** that access to testing is meaningless without access to the next steps including appropriate treatment

Thank you

- Lukas Owens
- Roman Gulati
- Yibai Zhao
- Noel Weiss
- Jane Lange
- Kemal Gogebakan
- Yingye Zheng
- Ziding Feng
- Early Detection Research Network
- Cancer Screening Research Network

Rosalie and Harold Rea Brown chair at Fred Hutch

CEDAR at the Knight Cancer Institute

NCI's Cancer Intervention and Surveillance Modeling Network

NCI R35 Modeling and Analytics for Novel Cancer Diagnostics