Design Considerations for Multi-Cancer Detection Assay Clinical Trials: The Cancer Screening Research Network

CSRN Statistics and Data Management Center
CSRN Coordinating and Communication Center
Fred Hutchinson Cancer Center

May 20, 2025

NCI Cancer Screening Research Network
A program of the National Cancer Institute of the National Institutes of Health

Acknowledgement

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Research reported in this presentation was supported by Division of Cancer Prevention of the National Institutes of Health under the following award numbers:

- **5UG1CA286954**
- **1UG1CA286941**
- **5UG1CA287044**
- **5UG1CA286946**
- **5UG1CA287013**
- **5UG1CA287017**
- **5UG1CA287011**
- **5UG1CA287007**
- **5UG1CA286949**

Murtha Cancer Center Research Program on behalf of the Department of Defense's ACCESS Hub's research effort reported in this presentation was supported by The Uniformed Services University of the Health Sciences award number **HU00012420063.**

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Disclosures

- Ruth Etzioni has no relevant disclosures
- Ziding Feng has institutional research contracts from Fujifilm and Exact Sciences. He was on the Scientific Advisory Committee for Guardant Health but resigned from that role after receiving the CSRN grant.
- Katherine Guthrie has no relevant disclosures
- Charles Kooperberg has no relevant disclosures

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Design of the CRSN Vanguard Feasibility Study

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May 20, 2025

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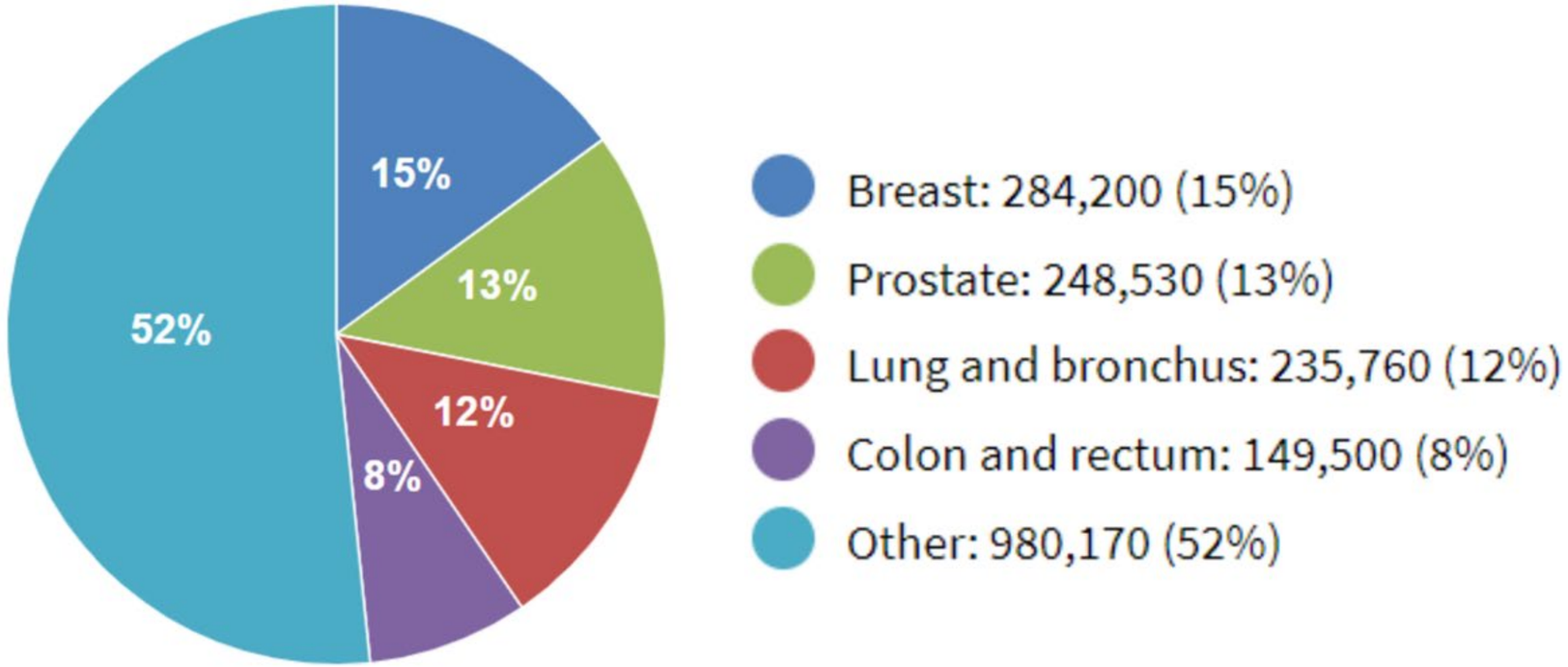
Current Screening Landscape

Cancer screening exists for common cancers

Currently, screening tests exist for only a few organ sites, but they are some of the most common cancers in the US:

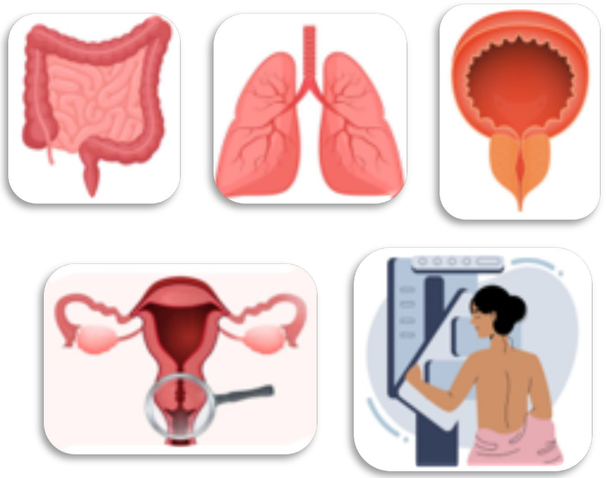


More than half of cancer deaths are at sites that have no screening tests, including highly deadly cancers like ovarian cancer and pancreatic cancer.

Current paradigm of cancer screening

Conventional cancer screening methods are:

- ✓ Organ-specific
- ✓ Aim to detect cancers at early stages
- ✓ Designed to have high sensitivity



Cancer screening tests that are recommended for use have evidence that their use saves lives, including:

- ✓ Mammography
- ✓ Pap smear
- ✓ Colonoscopy

Current paradigm – what works well

Strong evidence of **mortality reduction** through a screening program

- Actual cancer **prevention** through detection and treatment of pre-cancer with a reduction in incident cancers
  - Examples: colorectal and cervical cancer

- Cancer treatment at **early** stage, where "early" means mortality reduction
  - Examples: breast, lung, and prostate cancer

These are major 'wins' that we don't want to lose by virtue of changing the cancer screening paradigm

Current paradigm – what doesn't work well

Large burden of unscreened cancers

- Over half of cancer deaths are at organ sites that have no screening tests

Despite evidence for mortality reduction, participation in regular screening varies

- ~80% for breast and cervical cancer[1]
- Less than 70% for colorectal cancer[1]
- ~18% for lung cancer[2]

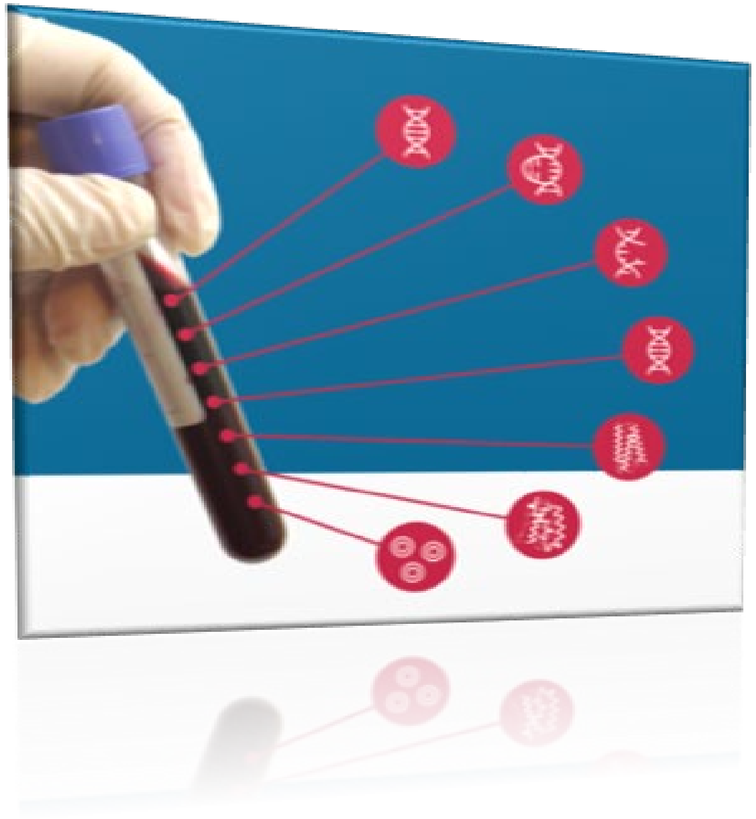
Burden of false positive screening results

- Regular screening increases probability
- Possibility of having an invasive diagnostic workup[3]

[1]Ma ZQ et al. *Prev Chronic Dis*. Apr 21, 2022;19:E22. doi:10.5888/pcd19.220063
[2]Bandi P et al. *JAMA Int Med* 2024;184(8). doi:10.1001/jamainternmed.2024.1655
[3]Croswell JM et al. *Ann Fam Med*. May-Jun 2009;7(3):212-22. doi:10.1370/afm.942
[3]Ho TH et al. *JAMA Netw Open*. Mar 1, 2022;5(3):e222440. doi:10.1001/jamanetworkopen.2022.2440

Multicancer Detection (MCD) Tests

What is a Multi-Cancer Detection (MCD) test?



- Leverages the shared biology of cancer cells of different tissues
- Measures biological signals which are shed into body fluids by cancer cells, such as:
  - DNA (e.g., methylation, fragmentation, or mutations), RNA, proteins
- Aims to screen for several cancers from different organ sites at the same time
- Two parts to an MCD test:
  - Biologic measurement of the specific signals
  - Software algorithms for determining the cut-point for a positive test and the tissue of origin (TOO)

How could MCDs improve cancer screening?

- ✓ Screening for cancer at organ sites currently without a screening test
- ✓ MCD tests *may* detect cancers which are hard to identify at an earlier stage
- ✓ MCD tests can potentially identify cancers from many different organ sites with a single test
- ✓ Since they rely on a blood draw, they may be more acceptable to people than other more invasive cancer screening tests

But… do we know <u>enough</u> about how to use MCD tests for cancer screening??

Unanswered questions: potential harms from MCD tests

- ❑ What kind/how many diagnostic tests are needed to make a cancer diagnosis?
- ❑ What happens if following a positive MCD test, you do not find a cancer?
- ❑ How many people will be subjected to unnecessary invasive procedures?
- ❑ Will people stop standard-of-care cancer screening if they get a negative MCD test?
- ❑ Will a blood test make screening more accessible or exacerbate disparities?
- ❑ Will these assays lead to overdiagnosis of indolent cancers?

Why do we need RCTs of MCD tests?

There is limited evidence supporting MCD tests for early detection

(and the evidence we have is primarily from MCD companies)

- Published MCD test sensitivities for early-stage disease vary widely across cancer types
- No evidence about impact on cancer-specific or overall mortality
- No evidence about harms of testing (e.g., over-diagnosis)
- No standards to guide primary care providers in how to follow-up an abnormal result

These are critical to understanding the true value of MCD tests for public health and their implications for health care providers and systems

The Cancer Screening Research Network (CSRN)

Overall goals of the CSRN

Design, develop, and conduct cancer screening trials and studies

- Develop trials for emerging cancer screening technologies.
- Assess clinical utility and outcomes of screening programs/biomarkers.
- Use novel risk assessment tools to individualize screening protocols.
- Evaluate effectiveness, feasibility, and scalability of screening strategies.
- Address challenges in implementing screening strategies.

Network Structure

Accrual, Enrollment, and Screening Sites (ACCESS Hubs)

- Participate in the scientific development of CSRN trials and studies, recruit participants, and conduct study protocols

Statistics and Data Management Center (SDMC)

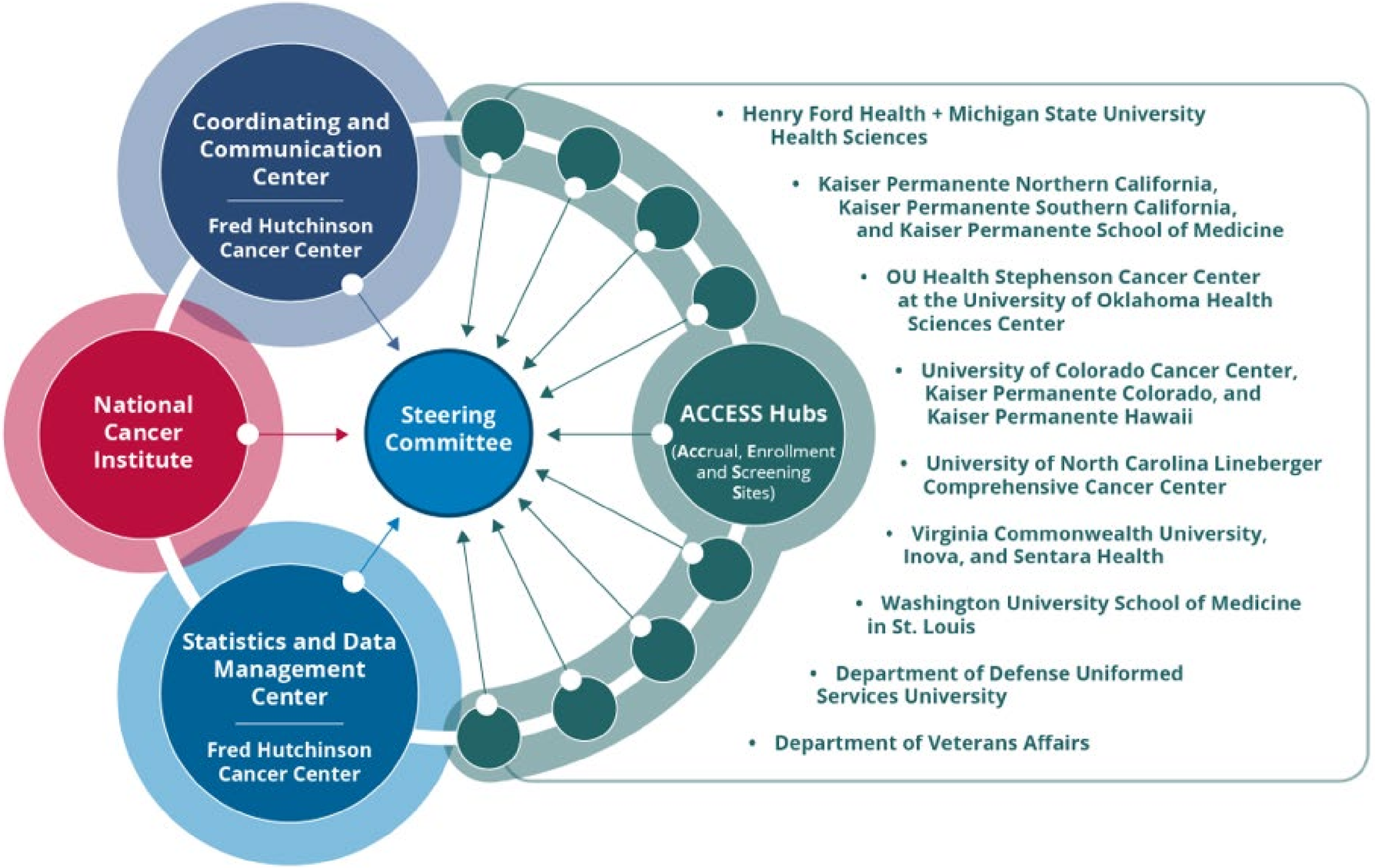
- Provides statistical expertise and centralized data management, quality control, and reporting

Coordinating and Communication Center (CCC)

- Coordinates study operations, and develops and implements communication activities

NATIONAL CANCER INSTITUTE

CANCER SCREENING RESEARCH NETWORK

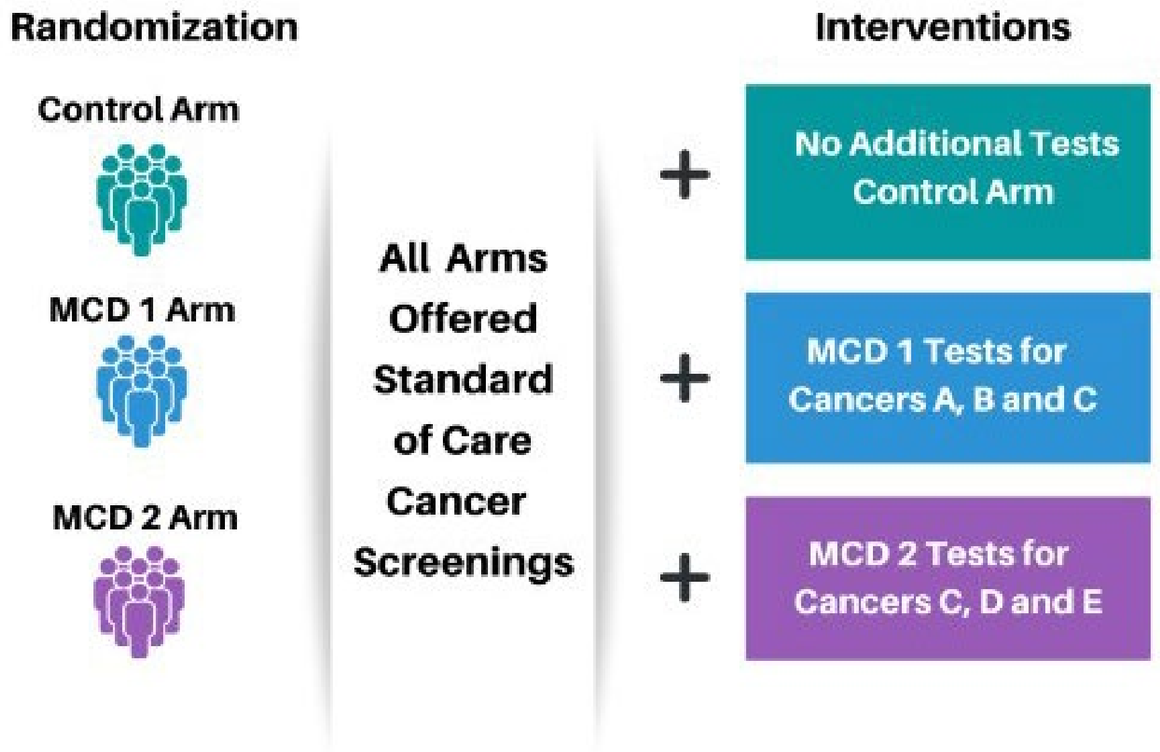


The Vanguard Study

The Vanguard Study

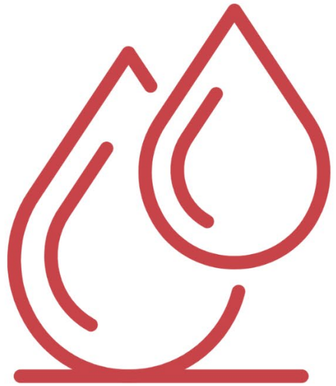
Feasibility study to inform designs of large-scale screening intervention trials

~6,000 – 8,000 participants / arm



The Vanguard Study

Testing a new way to screen for cancer



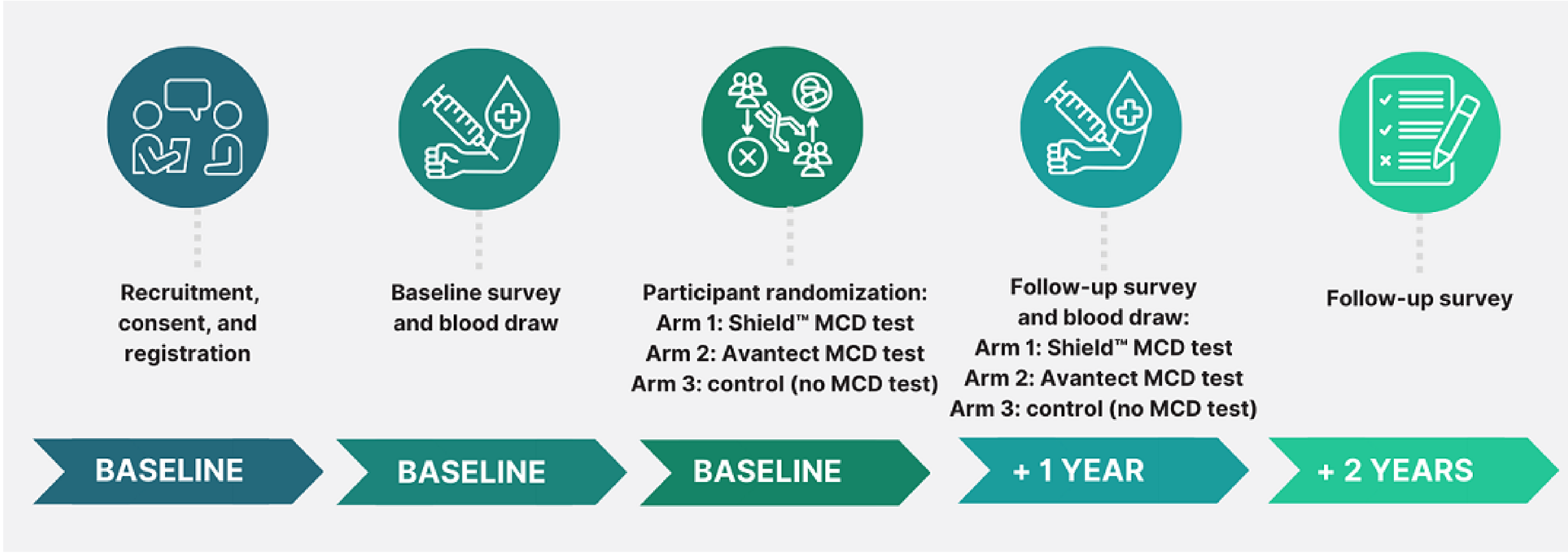
Primary Objectives (Feasibility)

- Assess the feasibility of recruitment and adherence to protocol-required baseline and follow-up data and blood collection.

- Assess the feasibility of achieving equitable enrollment of underrepresented communities.

The Vanguard Study

Study procedures



The Vanguard Study

Trial characteristics

Limited eligibility criteria

- Aged 45-75 years, without cancer in last 5 years
- Languages: English, Spanish, and Arabic

Wide variety of recruitment sites, methods and populations

- Primary care clinics
- Federally qualified health centers
- Indian Health Service sites
- Military and Veterans Affairs health clinics

Single blinding at 4 Hubs, no blinding at 5 Hubs

- Participants at blinded Hubs will only be unblinded if they receive an MCD test with abnormal result

The Vanguard Study

Diagnostic evaluations

Total of 18,000 – 24,000 participants

~4% of participants will receive abnormal/positive MCD test

- 300 – 400 participants/year undergoing diagnostic workup
- Each test result includes two potential cancer sites - “tissues of origin”
- Protocol provides guidance on diagnostic pathways for each cancer site
- More intensive data collection for diagnostic procedures and their effects
- Diagnostic workups may happen in the community

The Vanguard Study

Secondary Objectives (Feasibility)

- To assess the impact of participant blinding on willingness to participate, adherence to protocol required baseline and follow-up data, blood collection, and on rates of standard of care screening.
- To determine the timeliness of returning MCD test results to participants.
- To understand the factors contributing to lack of diagnostic resolution of an abnormal MCD test.
- To examine the effects of participant characteristics, including cancer risk factors and social determinants of health, on all aspects of feasibility.
- To estimate the proportion of participants receiving an MCD test outside of the trial.

The Vanguard Study

Secondary Objectives (Clinical Impact and Outcomes)

- To estimate the proportion of abnormal MCD tests that are diagnostically resolved, and their time to resolution.
- To compare the proportion of participants who receive standard of care screening during follow-up between the intervention and control arms.
- To assess the accuracy of tissue of origin prediction for each MCD assay.
- To estimate the incidence of complications related to diagnostic evaluation of an abnormal MCD test result.
- To assess the effect of an abnormal MCD test and diagnostic workup on anxiety and cancer worry.
- To evaluate the clinical diagnostic performance of the MCD assays.

The Vanguard Study

Exploratory Objectives

- To estimate rates of late-stage cancer, and the distribution of cancer stage.
- To estimate assay-targeted cancer-specific mortality of each MCD assay, all cancer-specific mortality, and all-cause mortality.

What's next for CSRN?

Trials for clinical utility

Subsequent trial for clinical efficacy is envisioned as a platform study

- Multiple test arms, adaptive to changing MCD landscape
- Targeted cancer-specific mortality endpoint

Design informed by the Vanguard Study results

- Do we need blinding? A control arm?
- Diagnostic workup support?

MCD testing of stored blood samples

- Assess feasibility of alternate statistical designs to reduce scale of efficacy trial
- Balance with ethical concerns about control arm testing without returning results

Are MCD tests ready for primetime?

Ziding Feng, PhD
CSRN Statistics and Data Management Center
Professor, Fred Hutchinson Cancer Center
May 20, 2025

NCI Cancer Screening Research Network
A program of the National Cancer Institute of the National Institutes of Health

Outline

- How to assess the readiness of a MCD test?
- Have MCD test development followed the established guideline?
- Benefit / Cost (harm) analysis
- Concluding remarks

Disclaimer

- My talk represents my personal opinions, does not represent the views of CSRN or NCI

- The discussions and recommendations in my talk are related to the planning and justification of large randomized trials and clinical utility assessment, not related to Vanguard Trial itself which is a feasibility study, not an efficacy/clinical utility study

How to assess the readiness of a MCD test?

- 5-Phase guideline
  - A roadmap for developing evidence to support a screening test

- BHC: Benefits and Harms Condition
  - Specify all elements of benefits and harms to be considered

5-Phase guideline for screening analog to 4-Phase guideline for therapeutic trials

Figure 2. Phases of Biomarker Development

(Pepe, et al. JNCI 2001, 93:1051-1061)

Preclinical Exploratory	***PHASE 1***	*Promising directions identified*
Clinical Assay and Validation	***PHASE 2***	*Clinical assay detects established disease*
Retrospective Longitudinal	***PHASE 3***	*Biomarker detects preclinical disease and a "screen positive" rule 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 burden of disease on population is quantified*

Most MCD test development did not have Phase-3 before moving to Phase-4

- Phase-3 could be long and expensive, and boring.

- Phase-3 is not adequate for FDA approval

- However, Phase-3 is crucial!
  - Intended asymptomatic population
  - Appropriate cutoff and sensitivity estimate for Phase 4&5
  - Final safeguard before acting on patients

Discrepancy in sensitivity (at ~99% specificity) between Phase 2 and Phase 4 studies from main MCD tests

	Phase 2	Phase 3	Phase 4
GRAIL (Galleri)	67.3% (Stage I-III) (Liu et al. Ann. Onc, 2020)	?	29% (35/121) (PATHFINDER)
Exact Sciences (CancerSEEK)	62-70% (Stage I-III) (Cohen et al. Science, 2018)	?	27% (26/96) (DETECT-A)

Having Phase 3 would avoid such surprise!

Sensitivities for Phase 2, 3, and 4 are different

Sensitivity definitions:

- Phase 2 – P(test positive on blood at time of diagnosis | clinically diagnosed cancer)
- Phase 3 – P(test positive on blood from **asymptomatic persons** | clinically diagnosed cancer **during follow up**)
- Phase 4 – P(test positive on blood from **asymptomatic persons | test detected cancer, may or may not plus** clinically diagnosed cancer during follow up)

- Observed Phase 4 sensitivity tends to be higher than Phase 3 sensitivity due to
  - Over diagnosis
  - Lead time > follow up period

Why should not skip Phase 3?

- Phase 3 provides realistic sensitivity estimate for intended population for Phase 4/5 trial planning
- Avoid premature jump to a large expensive randomized trial
- Protect patients - the last safeguard before acting on patients based on test results

Efficient way to conduct Phase 3 study

- Use existing biorepositories, e.g., PLCO, WHI, UK-Biobank, Cohorts with blood draws on persons without symptom for cancer, some later during follow up diagnosed with cancer.

- Control arm of a randomized Phase 4/5 trial, e.g., Vanguard Trial control arm will collect blood, a natural Phase 3 study

- Even if it requires your own Phase-3 study, it enables fast-track the process of Phase 4/5 study, e.g., a quick Phase 4 (PPV and stage shift) adaptive to Phase 5 trial
  → still better off

Benefits and Harms Analysis

- MCD test stakeholders have been emphasizing the high PPV of the tests, not much mentioning false negatives.

- The claim: “There is no harm from test negatives as they will be treated the same way if there is no MCD test.”

Benefit and Harm Condition (BHC)

$$p*TPR*B_{+D} - p*(1-TPR)*C_{-D} + (1-p)*(1-FPR)*B_{-N} - (1-p)*FPR*C_{+N} - C_b > 0$$

P = disease prevalence

TPR = true positive rate

FPR = false positive rate

B_{+D} = benefit of true positive

B_{-N} = benefit of true negative

C_{-D} = cost of false negative

C_{+N} = cost of false positive

C_b = cost of the test

(Ref: Pepe et al. Clin Chem 2016 May; 62(5):737-742)

More on BHC

Dropping BHC elements in benefit/harm analysis should be justified

- Potential harm from false negatives should not be ignored:
  - Forgone SOC screening
  - Delayed diagnosis due to false security
  - Relax on preventive lifestyle

- Assay cost: ~$1,000/year, likely annual cost

Will blinding eliminate the harms from false negatives?

Blinding on randomization assignment does improve the compliance to protocol in the trial

- Vanguard Trial will evaluate the feasibility and logistics of blinding to inform future large trial design

- In real world the test result is not blinded, all these harms could occur
  - A large randomized trial deploying blinding should consider this implication

Example where no harm from false negatives

Electronic Medical Record (EMR) based pancreatic ductal adenocarcinoma (PDAC) early detection strategy in newly onset diabetes patients (NOD)

- PDAC prevalence rate 0.85% in newly onset diabetes, aged 55-75, non-Hispanic Whites. Risk further enriched to 2-3% by ENDPAC (enriching new-onset diabetes for pancreatic cancer) score (based on age, HbA1c change, weight change, all from EMR).

- Strategy:
  - Use EMR to identify NOD patients and calculate ENDPAC score
  - Approach/consent high ENDPAC score patients for pancreas CT

- Low ENDPAC scores patients are NOT approached and unaware of the study

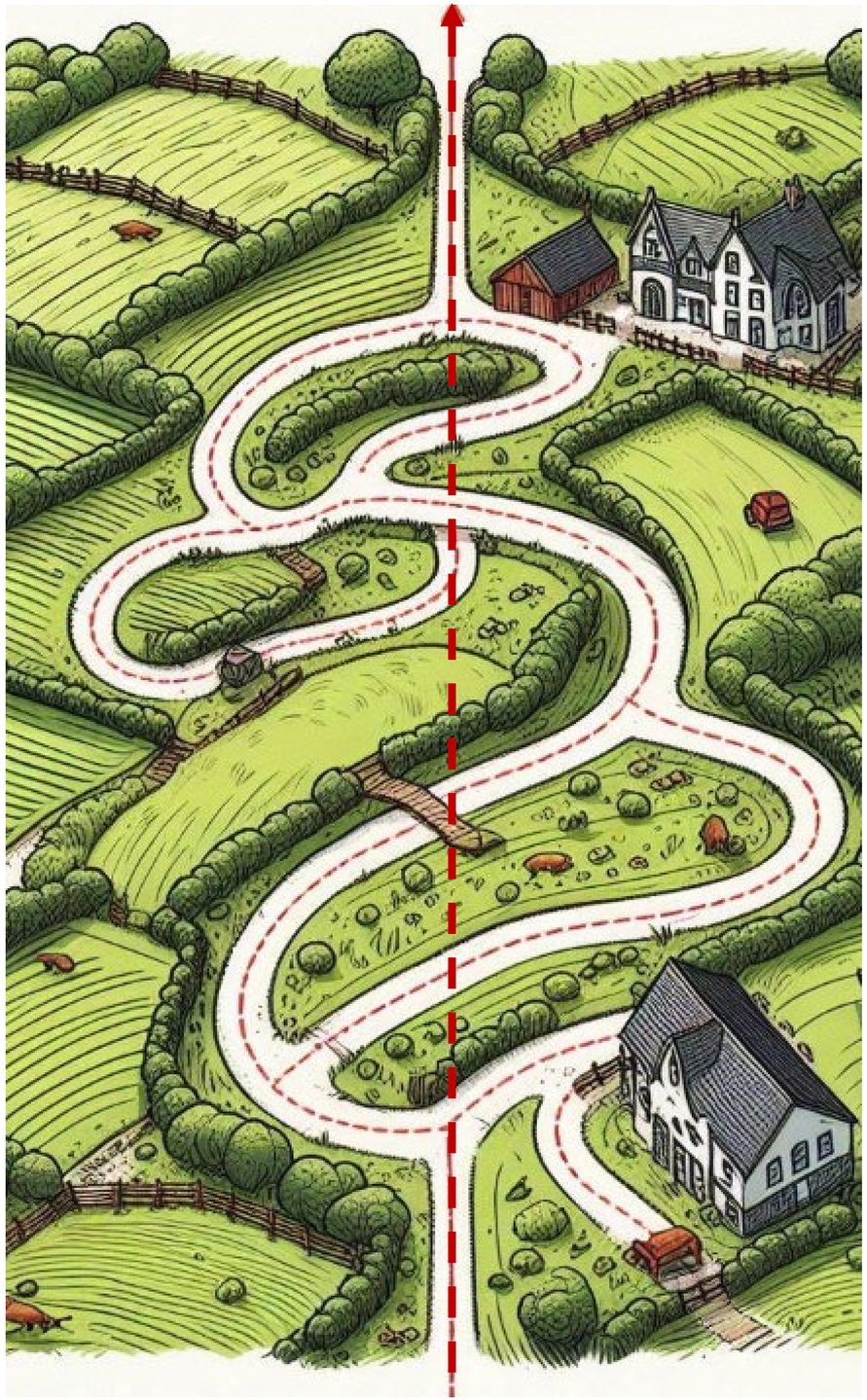
- Identification of ENDPAC score high patients has no/minimum implementation cost

- BHC reduced to $p*TPR*B_{+D} - (1-p)*FPR*C_{+N} > 0$, "How many imaging workups for one detected PDAC?"

Concluding Remarks

- Before launching a large randomized trial (Phase 4 or 5), one should have solid test performance data from Phase 3, particularly the test positive rule and the test sensitivity for asymptomatic patients

- Benefits and Harm analysis should consider all elements, including false negatives and test cost, in justifying and planning a large Phase 5 randomized trial



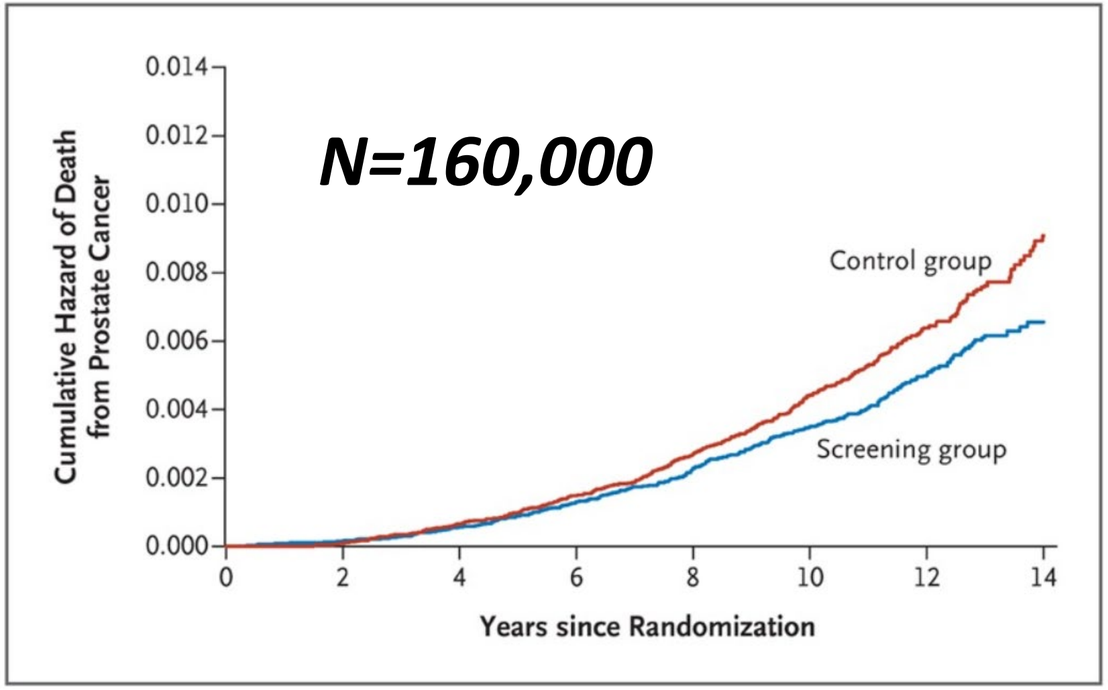
Can We Shortcut Cancer Screening Trials?

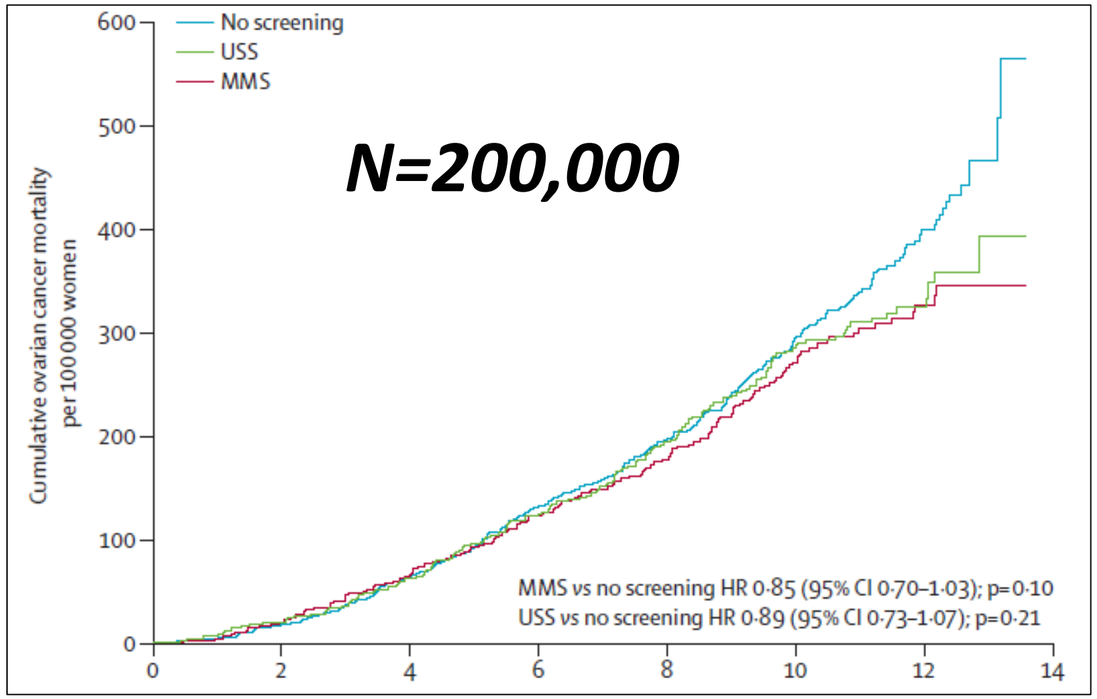
Ruth Etzioni
Fred Hutch Cancer Center
Rosalie and Harold Rea Brown Chair

Society for Clinical Trials Annual Meeting 2025
Vancouver BC

Cancer screening trials: a retrospective

- Primary endpoint: cancer-specific mortality
- Large lengthy studies due to typical rarity of this endpoint





Why disease-specific mortality?

Primary aim of cancer screening is to reduce deaths from cancer

Much work showing that alternative endpoints not reliable

- **Survival from diagnosis** subject to length and lead-time bias
  - Survival may be improved in screen arm without any in change disease mortality
- **Stage distribution** may also produce bias
  - Apparent shift toward earlier-stage diagnoses in screen arm may be an artifact of length bias or a result of overdiagnosis
- **Reduction in late-stage incidence**
  - Not seriously considered perhaps due to concerns about stage shift bias
  - Possible to reduce late stage cancers without significant reduction in mortality

Is it time for a paradigm shift?

paradigm shift noun

formal

: an important change that happens when the usual way of thinking about or doing something is replaced by a new and different way

Merriam-Webster Est. 1828

RE **You**

what is a paradigm shift

OpenAI

In the context of scientific or intellectual progress, a paradigm shift occurs when a new theory or framework emerges that challenges and replaces the established paradigm. This shift often involves a radical reevaluation of existing ideas, methodologies, and approaches. It can lead to a transformation in how problems are defined, what questions are considered relevant, and how research is conducted.

Use late-stage incidence rather than mortality?

Multicancer Early Detection Technologies: A Review Informed by Past Cancer Screening Studies FREE

Sana Raoof ; Richard J. Lee ; Kunal Jajoo; Joseph D. Mancias ; Timothy R. Rebbeck ; Steven J. Skates

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION

*Randomized control trials (RCTs) to show mortality reduction have required millions of screening-years, two-decade durations, and been susceptible to external confounding. Future RCTs with **late-stage incidence as a surrogate endpoint** could substantially reduce these challenges*

Dying To Find Out: The Cost of Time at the Dawn of the Multicancer Early Detection Era

Eric A. Klein ; Sarina Madhavan ; Tomasz M. Beer ; Chetan Bettegowda ; Minetta C. Liu ; Anne-Renee Hartman ; Allan Hackshaw

*A range of **alternative trial endpoints** have been suggested to increase the speed of clinical evaluation and translation of newer technologies like MCD into clinical practice*

Search news

You can use the filters to show only news items that match your interests

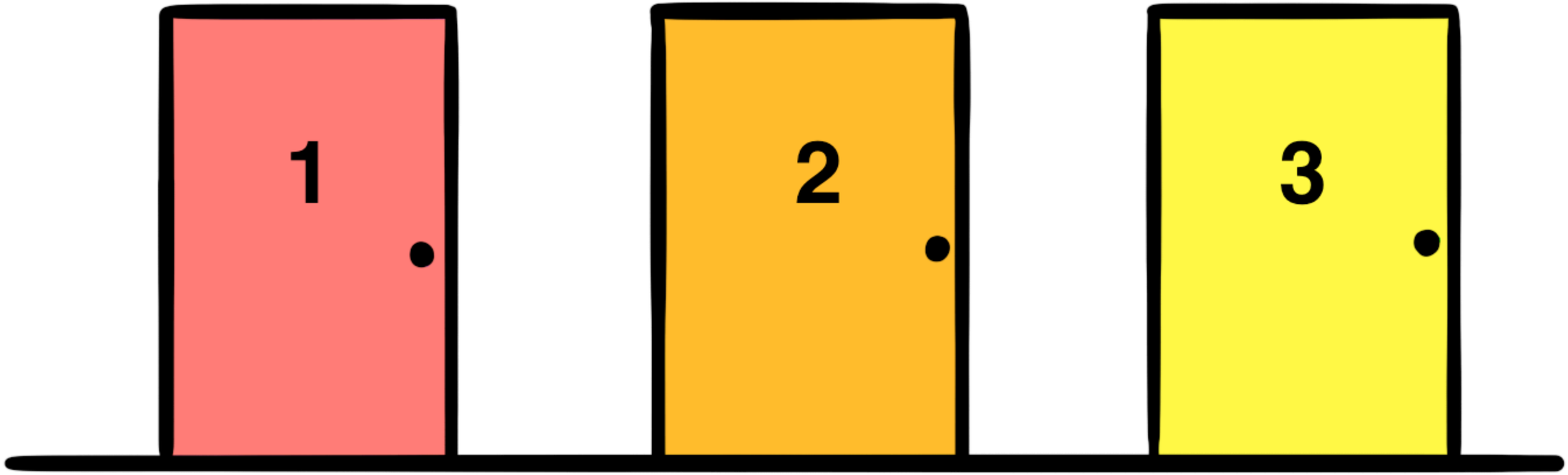
News

NHS launches world first trial for new cancer test

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.

Short-term endpoints in cancer screening trials
Surrogate, alternative, intermediate?



Surrogate
Infer mortality benefit

Intermediate
Predict mortality benefit

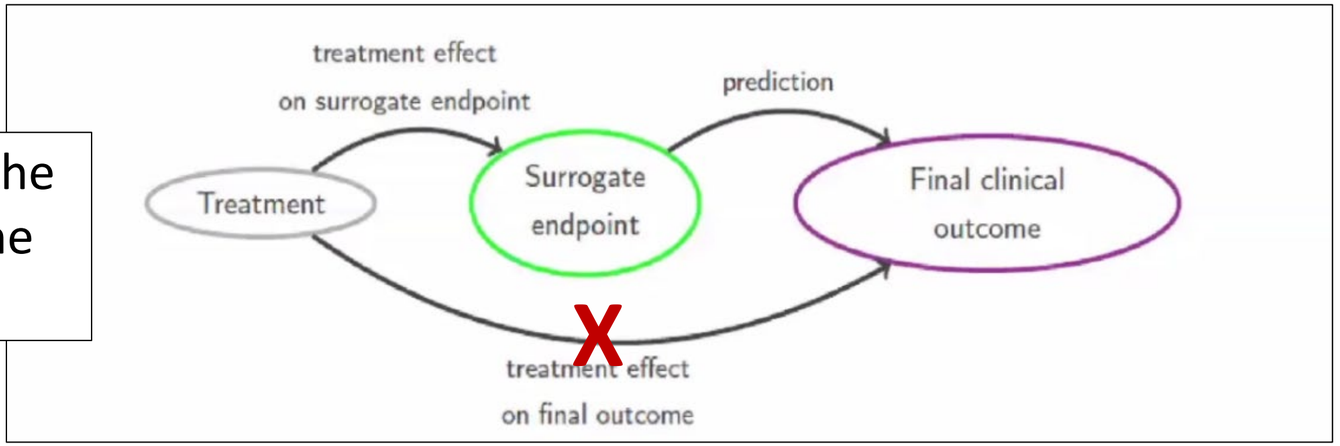
Alternative
Separate from mortality benefit

Surrogate endpoints in cancer treatment trials

If intervention “works” for surrogate can we conclude statistically it “works” for final endpoint?

Prentice: Yes if surrogate fully mediates the effect of intervention on outcome

Effect of the intervention on the outcome is via the effect of the intervention on the surrogate

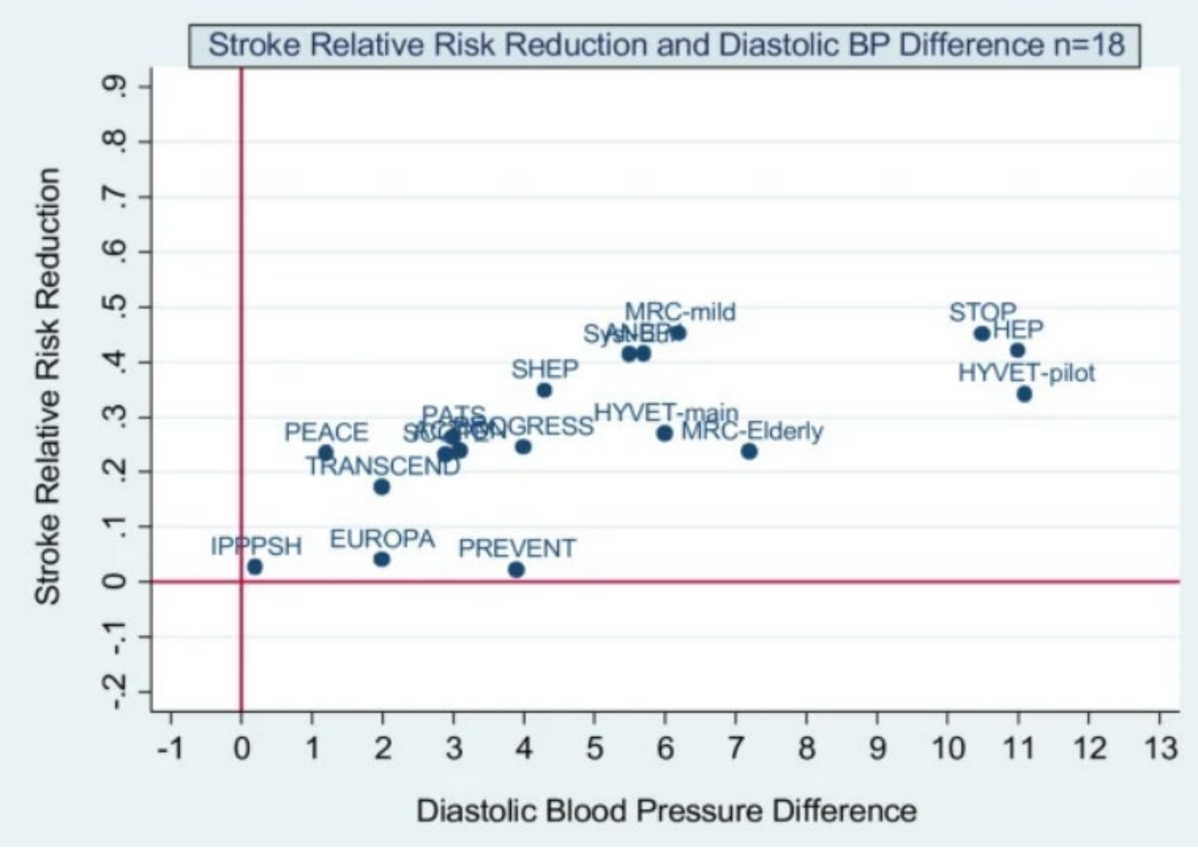


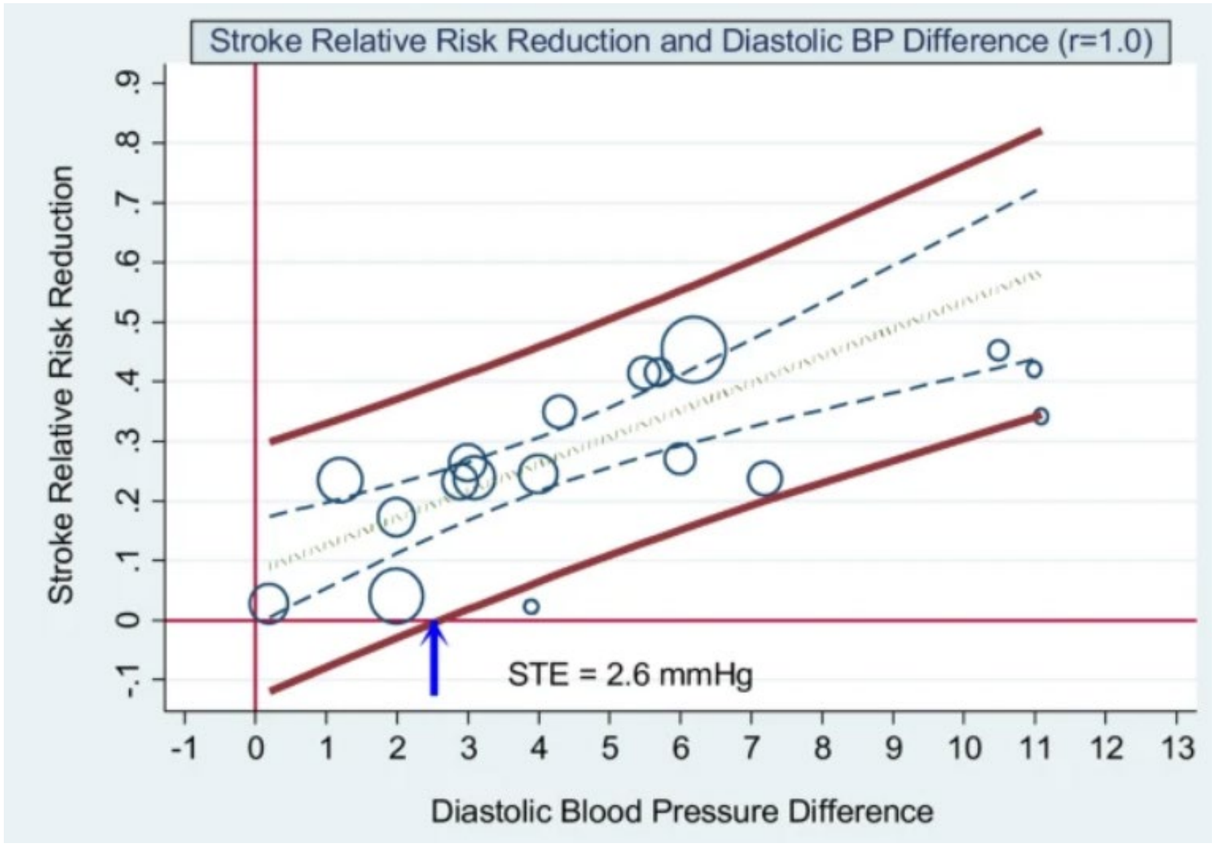
<u>Consequence of Prentice</u>

Cannot check only if surrogate is correlated with the endpoint. Rather, effect of the intervention on the surrogate must be correlated with effect of the intervention on the endpoint

Practical verification of surrogacy

Meta-regression: Across previous trials, does effect of intervention on the surrogate predict the effect of the intervention on the endpoint?





A Systematic Review and Recommendation for Reporting of Surrogate Endpoint Evaluation Using Meta-analyses

Wanling Xie, Susan Halabi, Jayne F. Tierney, Matthew R. Sydes, Laurence Collette, James J. Dignam, Marc Buyse, Christopher J. Sweeney*, Meredith M. Regan*

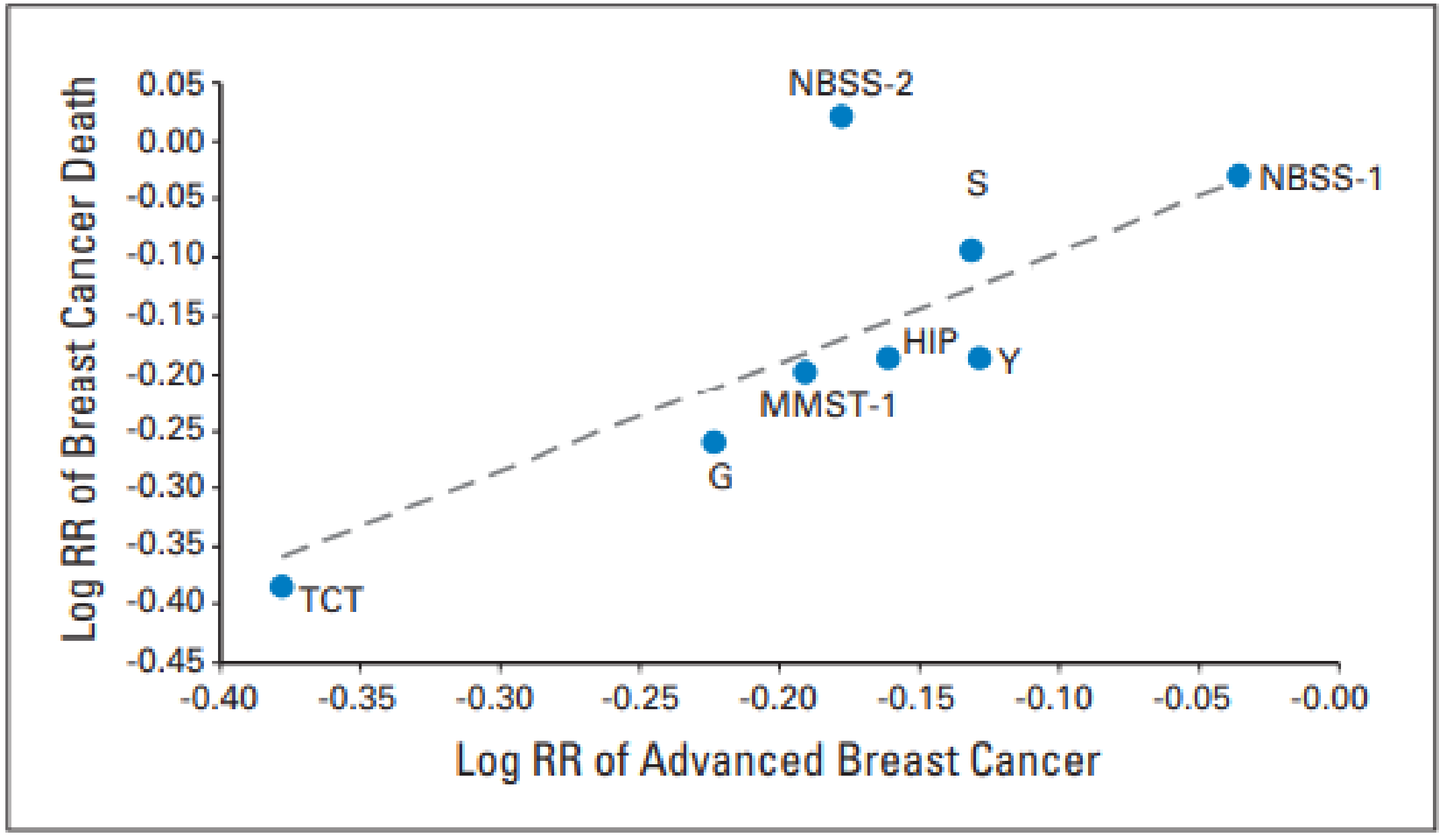
"According to the ReSEEM (Systematic Review and Recommendation for Reporting of Surrogate Endpoint Evaluation using Meta-analyses) guidelines, R^2 values ≥ 0.7 represent strong correlations (and thus suggest surrogacy), values between 0.69 and 0.5 represent moderate correlations, and values < 0.5 represent weak correlations"

What about screening trials?

A meta-regression of late-stage incidence and mortality

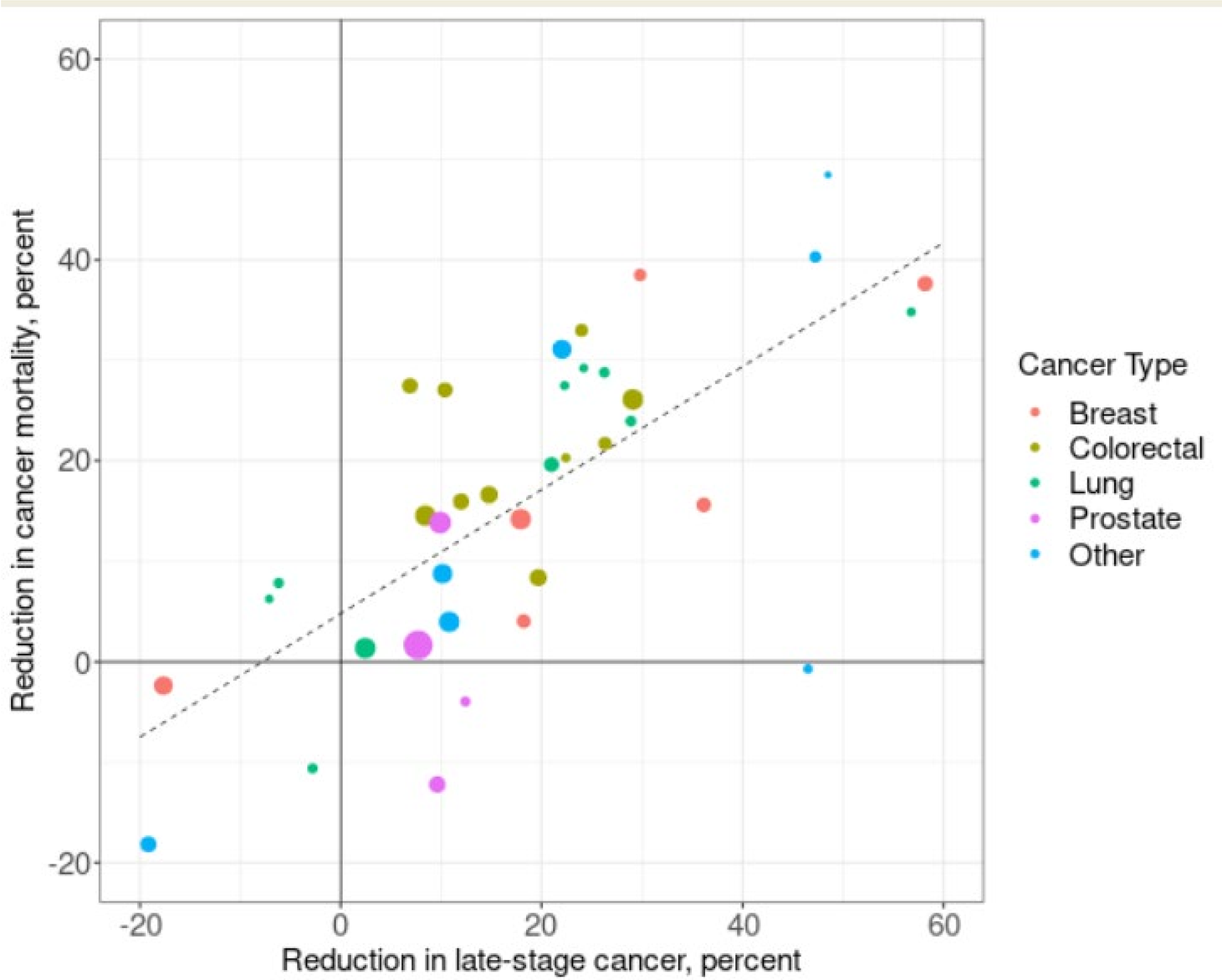
Breast cancer trials

(Autier JCO 2009)



Multiple cancers

Different results across sets of trials for different cancers



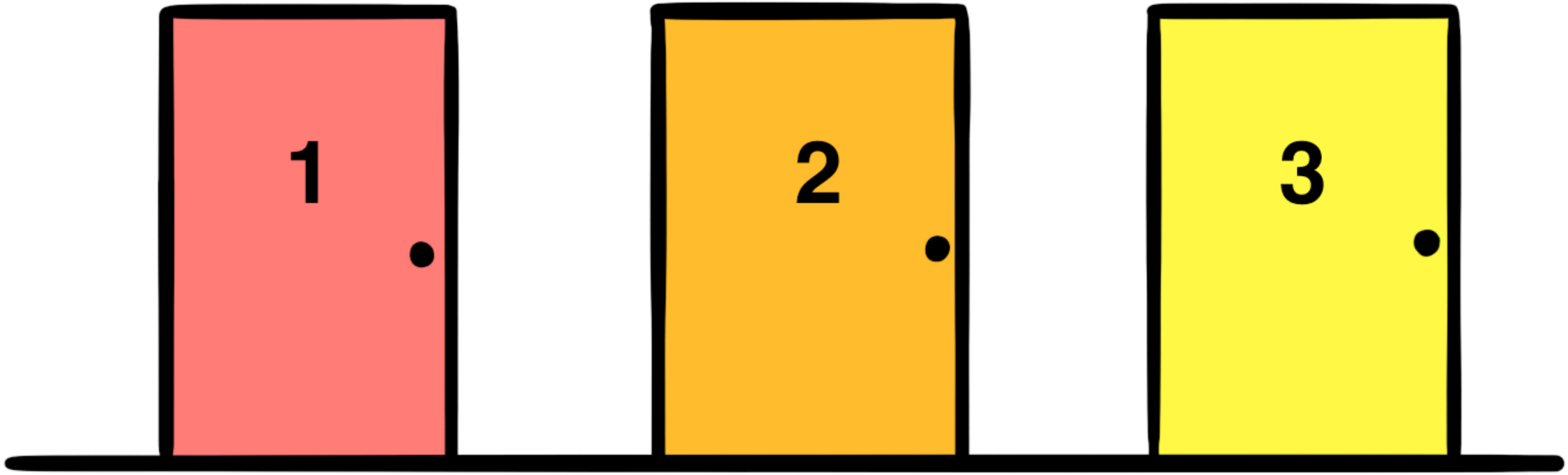
Robbins ICSN 2023, JAMA, in press

Surrogate endpoints – screening trials

- Very specific criteria for an endpoint to be a surrogate in trials
- Mostly established for treatment trials via meta-regression and some attempts in screening trials with far fewer trials
- Not possible to establish in this way for screening trials across cancers
  - Meta-regression relationships in screening trials vary across cancers
  - Relatively few trials with many differences in design and other aspects
  - In many cancers no trials at all

Unlikely that we will be able to show that late-stage incidence is adequate as a surrogate endpoint for mortality across cancers via meta-regression

Short-term endpoints in cancer screening trials
Surrogate, alternative, intermediate?



Surrogate or proxy
Infer mortality benefit

Intermediate
Predict mortality benefit

Alternative
Separate from mortality benefit

FEATURED ARTICLE

WILEY Statistics in Medicine

Five criteria for using a surrogate endpoint to predict treatment effect based on data from multiple previous trials

Stuart G. Baker

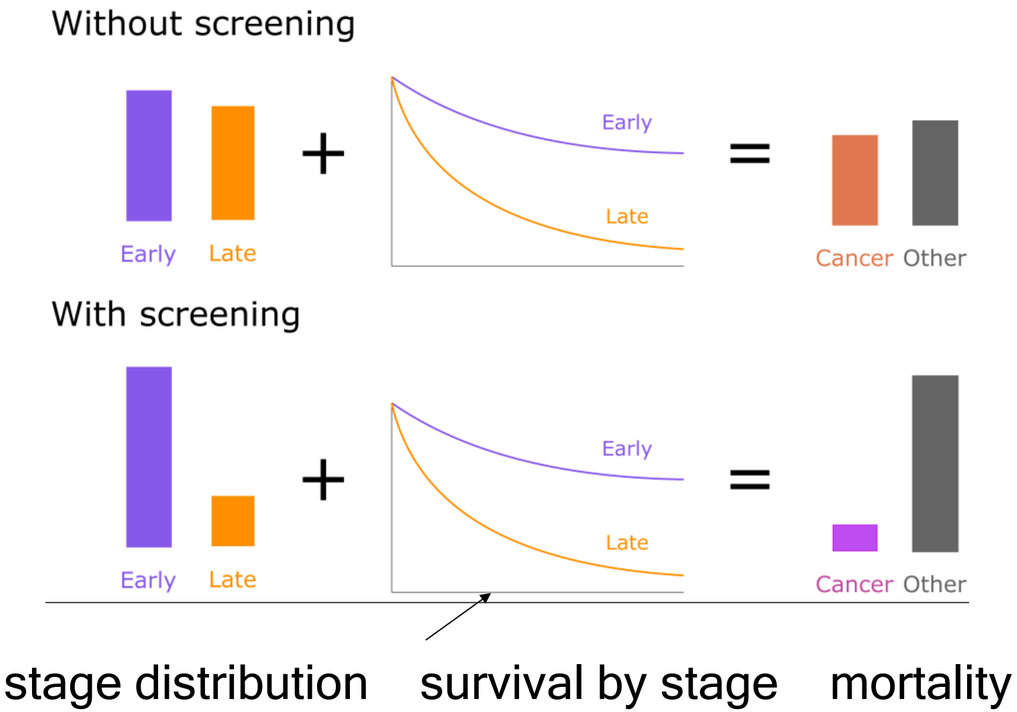
What if we have a high-correlation meta-regression? Can we use this to predict mortality endpoint in a new trial?

Baker: Only under a set of further conditions

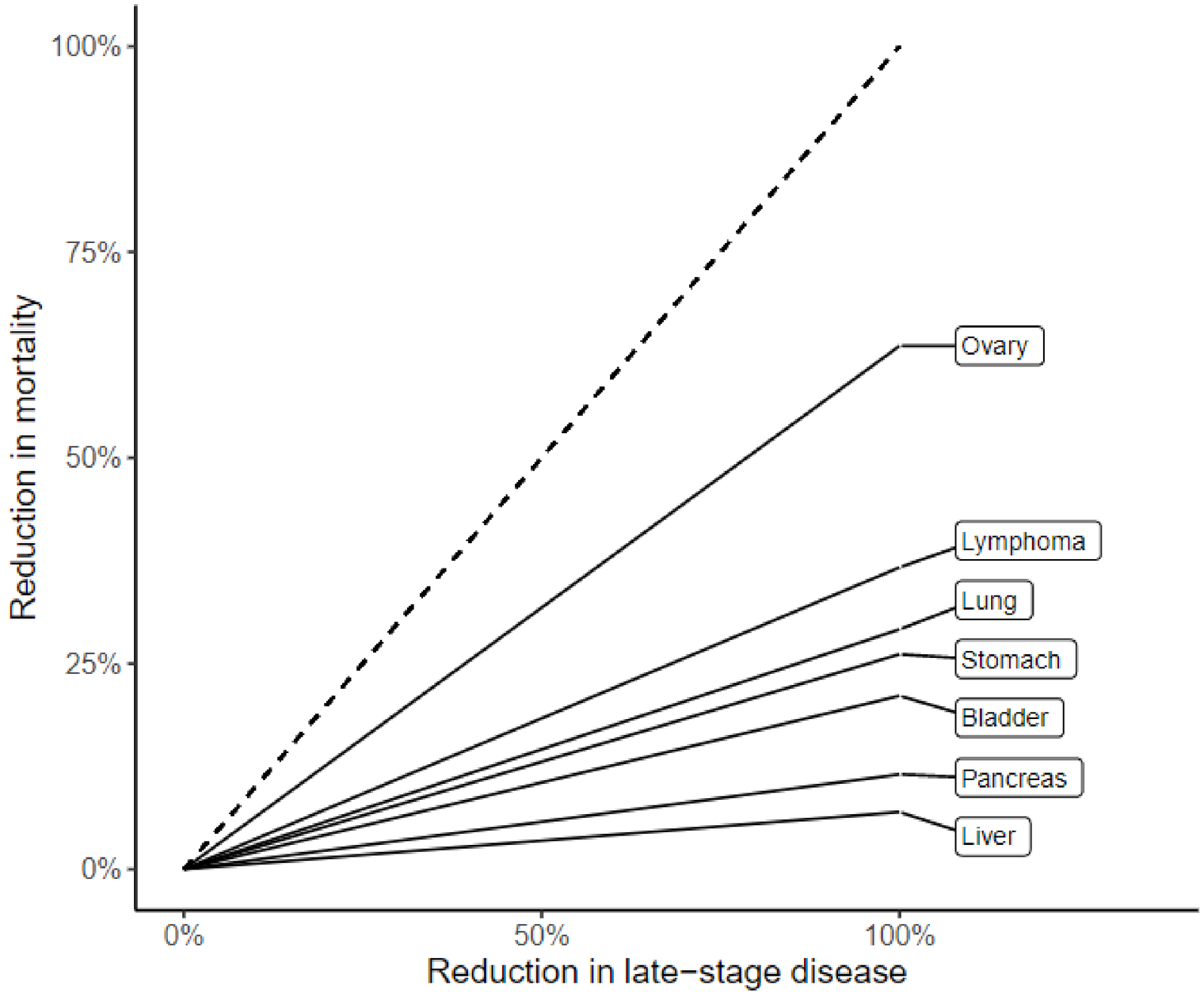
5 criteria for using a surrogate endpoint in a new trial to predict the effect of treatment on the true endpoint in the new trial. The first 2 criteria, which are easily computed from a zero-intercept linear random effects model, involve statistical considerations: an acceptable sample size multiplier and an acceptable prediction separation score. The remaining 3 criteria involve clinical and biological considerations: similarity of biological mechanisms of treatments between the new trial and previous trials, similarity of secondary treatments following the surrogate endpoint between the new trial and previous trials, and a negligible risk of harmful side effects arising after the observation of the surrogate endpoint in the new trial. These 5 criteria constitute an appropriately high bar for using a surrogate endpoint to make a definitive treatment recommendation.

Intermediate endpoints
Mechanistic alternatives to meta-regression for prediction

- If late-stage incidence is reduced by $\propto$ % what should we expect regarding mortality reduction?
- Commonly assume a stage-shift model
- Predict reduction in mortality by replacing disease survival for cases shifted out of late stage by the survival of early- stage cases
- This mechanistic model permits projections for all cancers not only those with prior trials
- Predicted reduction in mortality in steady state is proportional to but less than $\propto$ %



Mortality reduction as a function of late stage reduction ∝ for different cancers in SEER

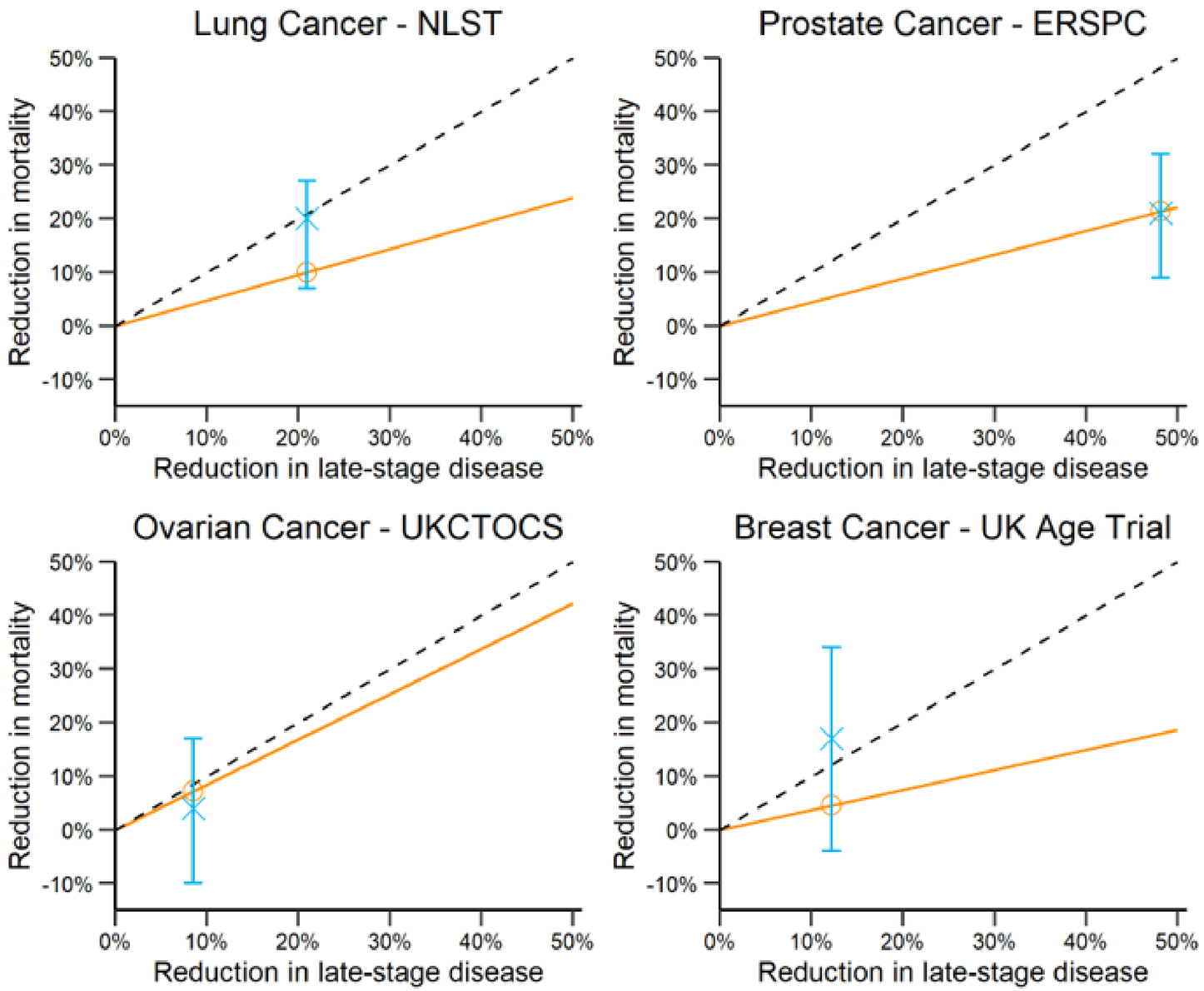


For a given reduction in late stage incidence, variable predicted reduction in mortality across cancers

Owens L et al CEBP 2022

Observed and predicted mortality reduction given late-stage reduction in four trials

x observed
o predicted



Owens et al CEBP 2022

Predicting mortality reduction given stage
Current mechanistic models have limitations

Simple stage-shift model:

1. Ignores disease subtype

2. Does not accommodate within-stage shifts

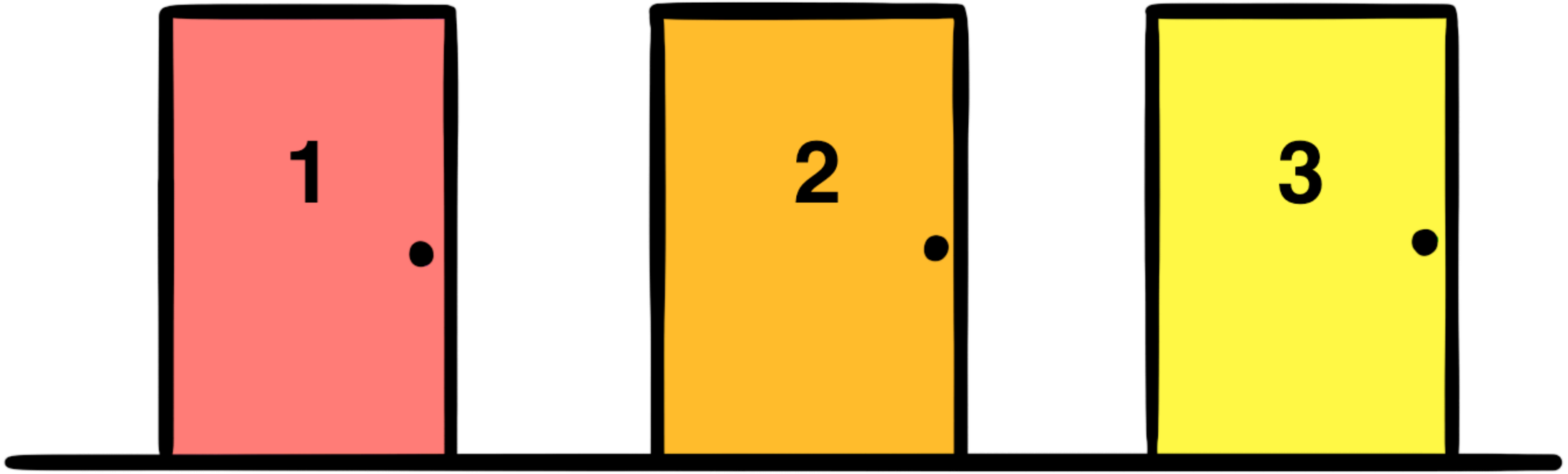
3. Will not perform as well if treatments change

4. Only projects mortality reduction concurrently with late-stage reduction

Predicting mortality reduction given stage
Current mechanistic models have limitations

Simple stage-shift model:	Some remedies:
1. Ignores disease subtype	1. Predict by subtype
2. Does not accommodate within-stage shifts	
3. Will not perform as well if treatments change	3. Incorporate novel treatments by explicitly improving stage-specific survival rates
4. Only projects mortality reduction concurrently with late-stage reduction	4. Extrapolate late-stage reduction to predict future mortality reduction

Short-term endpoints in cancer screening trials
Surrogate, alternative, intermediate?



Surrogate or proxy
Infer mortality benefit

Intermediate
Predict mortality benefit

Alternative
Separate from mortality benefit

What if it were all about late stage reduction?

Rationale

- Cancer screening is designed to **move cancer diagnosis earlier**
- From downstaging to mortality benefit requires access to effective treatments
  - Lack of effective treatment may make screening seem ineffective
  - As treatments change benefit of screening may change and trials may become outdated
  - Differing treatments between screen/control groups may bias perception of screening benefit

- *Focus on late-stage reduction as a primary endpoint; **this** is target of cancer screening*
- *In making decisions based on trial results, carefully assess treatment availability/efficacy*

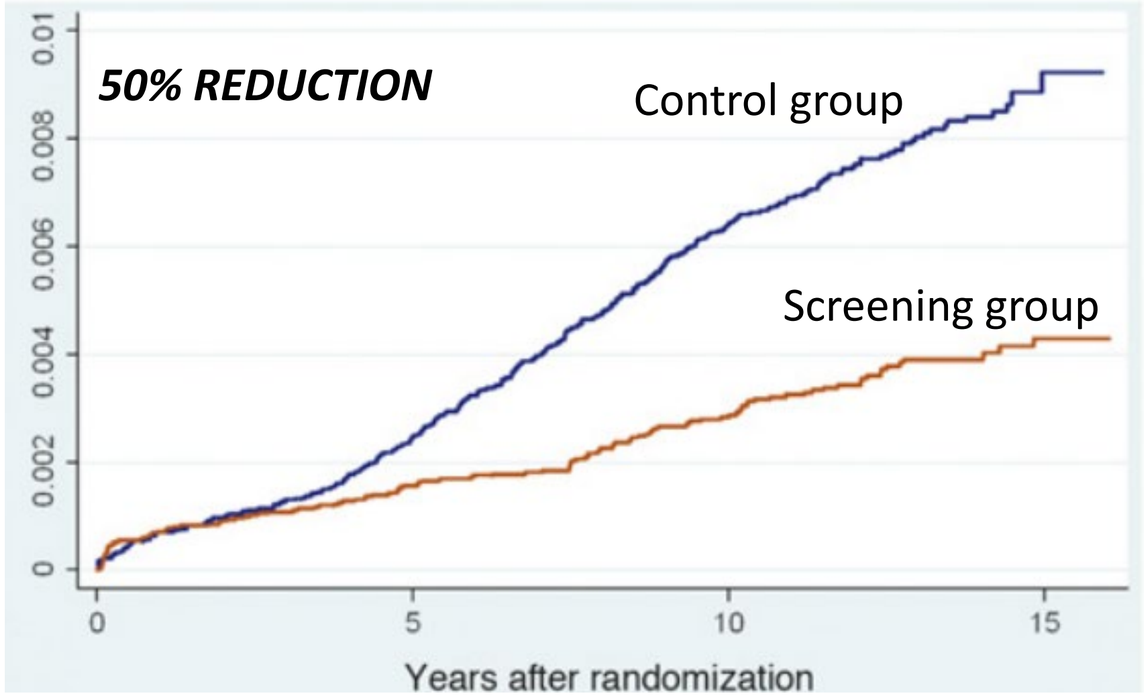
May lead to awkward conversations and serious conundrums

We have evidence that this test will detect cancer earlier but we cannot promise (at this time) that this will probably not improve your chances of surviving it

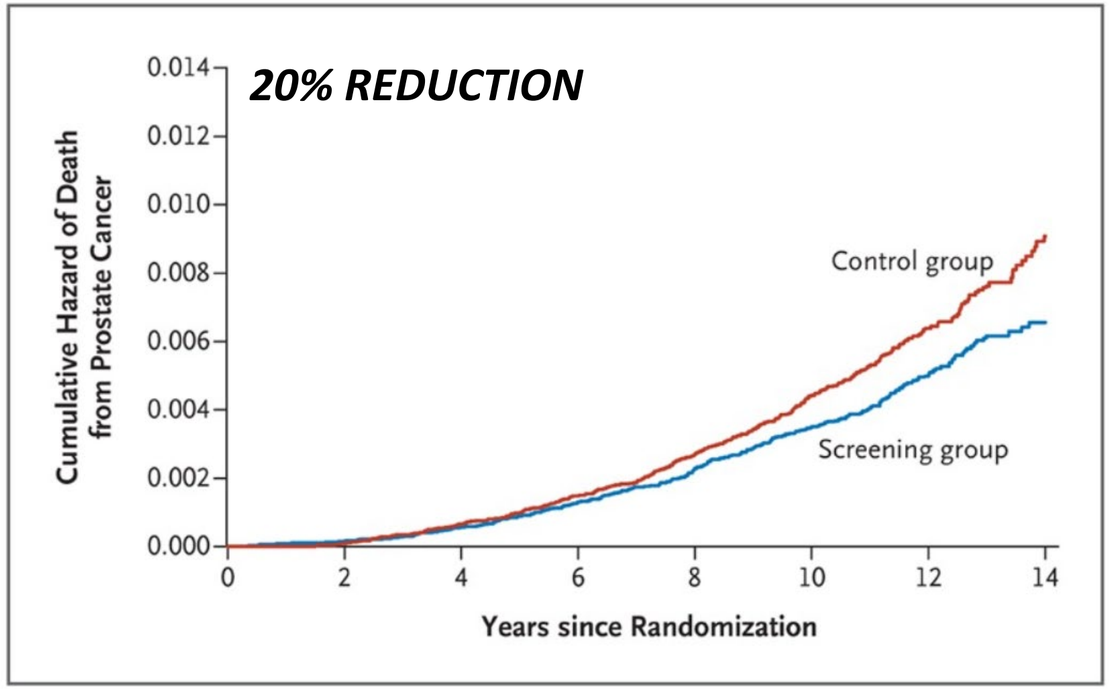
I cannot offer my patients this screening test unless they can get curative treatment if caught early!

What is an adequate late-stage reduction?
Late-stage incidence and mortality in ERSPC

Cumulative incidence late stage RR=0.5



Cumulative incidence mortality RR=0.8



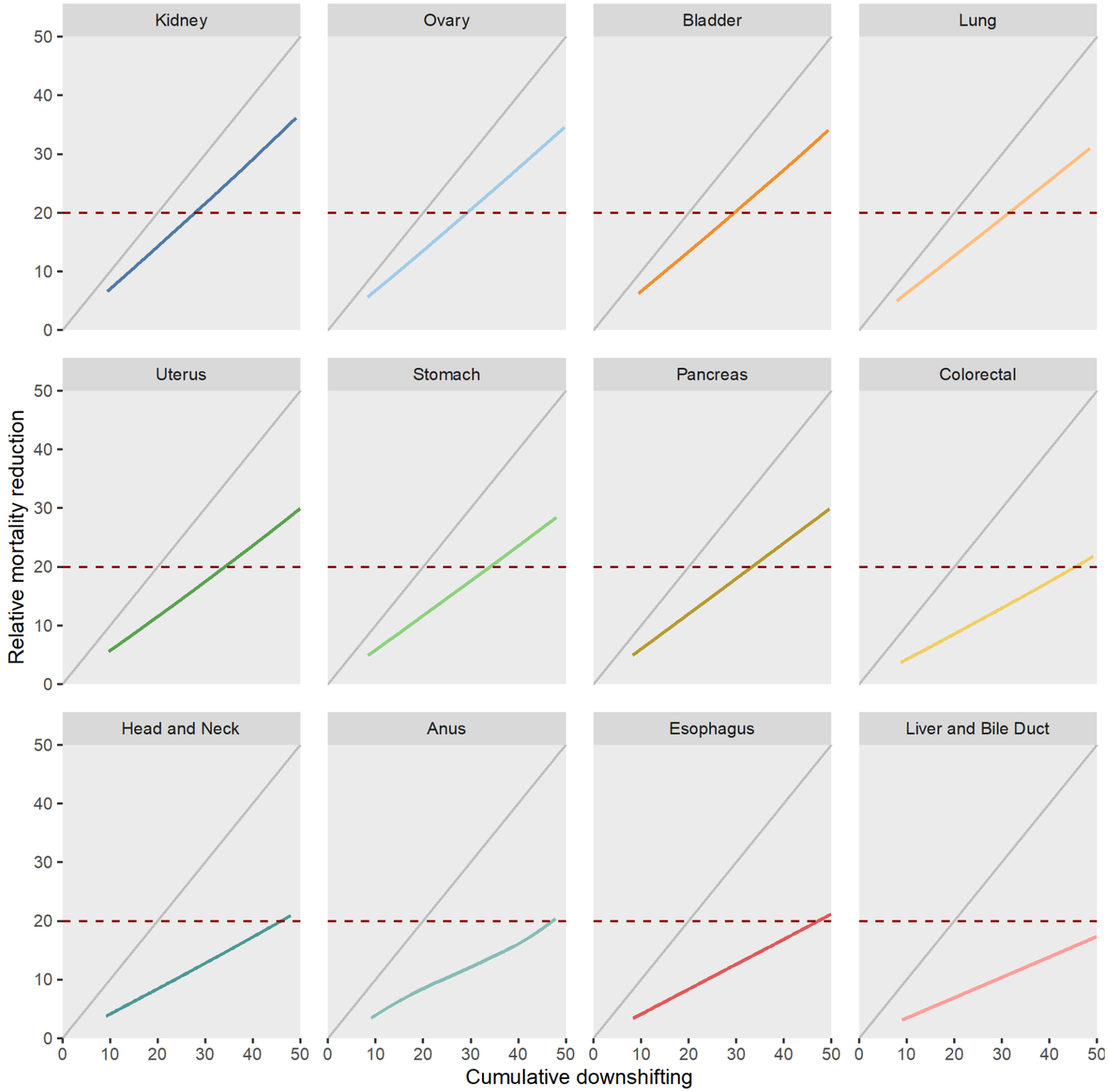
Adequate late-stage incidence reduction may differ across cancers

Figure shows percent reduction in distant-stage incidence corresponding to a 20% reduction in mortality for each cancer based on stage-shift model

Highly variable across cancers

This may not be the best way to determine thresholds for adequacy of late-stage reductions

What is an alternative?



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News

NHS launches world first trial for new cancer test

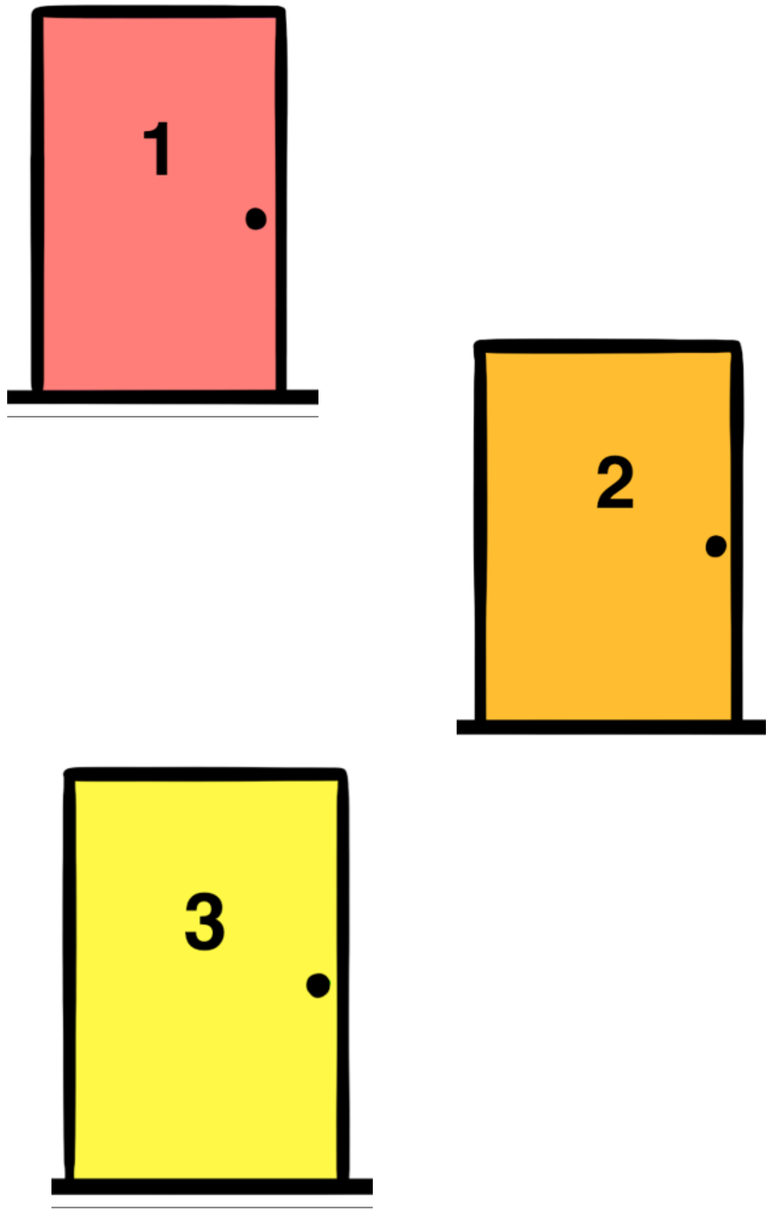
Initial results of the study are expected by 2023 and, if successful, the NHS in England plans to extend the rollout to a further one million people in 2024 and 2025.

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.

Summary

- It is easy to say that we need a paradigm shift towards shorter and more efficient screening trials
- But that does not provide a path forward that reliably identifies interventions that should be considered adequately effective
- Need to be specific about how we plan to use the short-term endpoint
- This will tell us what to do to ensure it is adequate
- On this front we have more work to do

We have not fully opened any of the three doors yet!



Thank you! Team and support

- Lukas Owens
- Roman Gulati
- Kemal Gogebakan
- Noel Weiss, UW
- Stuart Baker, NCI
- Hilary Robbins, IARC
- Jane Lange, CEDAR at KCI

Rosalie and Harold Rea Brown chair at Fred Hutch

NCI R35 Modeling and Analytics for Novel Cancer Diagnostics

NCI Cancer Screening Research Network

Discussion
A few more random thoughts

Charles Kooperberg, PhD
CSRN Statistics and Data Management Center
Professor, Fred Hutchinson Cancer Center
May 20, 2025

NCI Cancer Screening Research Network
A program of the National Cancer Institute of the National Institutes of Health

The Vanguard Study

Broad eligibility

Eligibility:

- Age, no-cancer, language
- Wide variety of recruitment sites, methods and populations

Followed by:

- Consent
- Baseline questionnaire
- Blood draw
- Randomization

The Vanguard Study

Broad eligibility

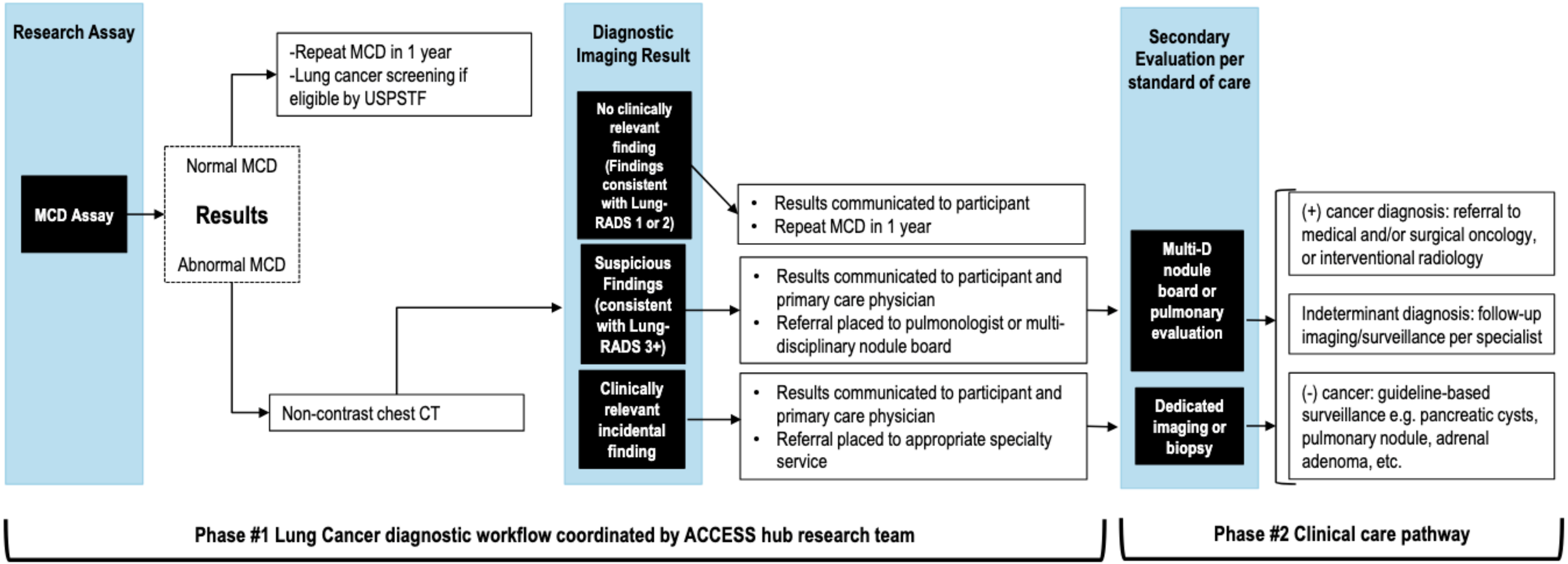
During follow-up:

- Additional blood draw after 1 year
- Annual questionnaire (incl screening history, cancer findings).
- Brief additional annual questionnaire about anxiety/worries (only for positive MCD tests, subset of other groups)

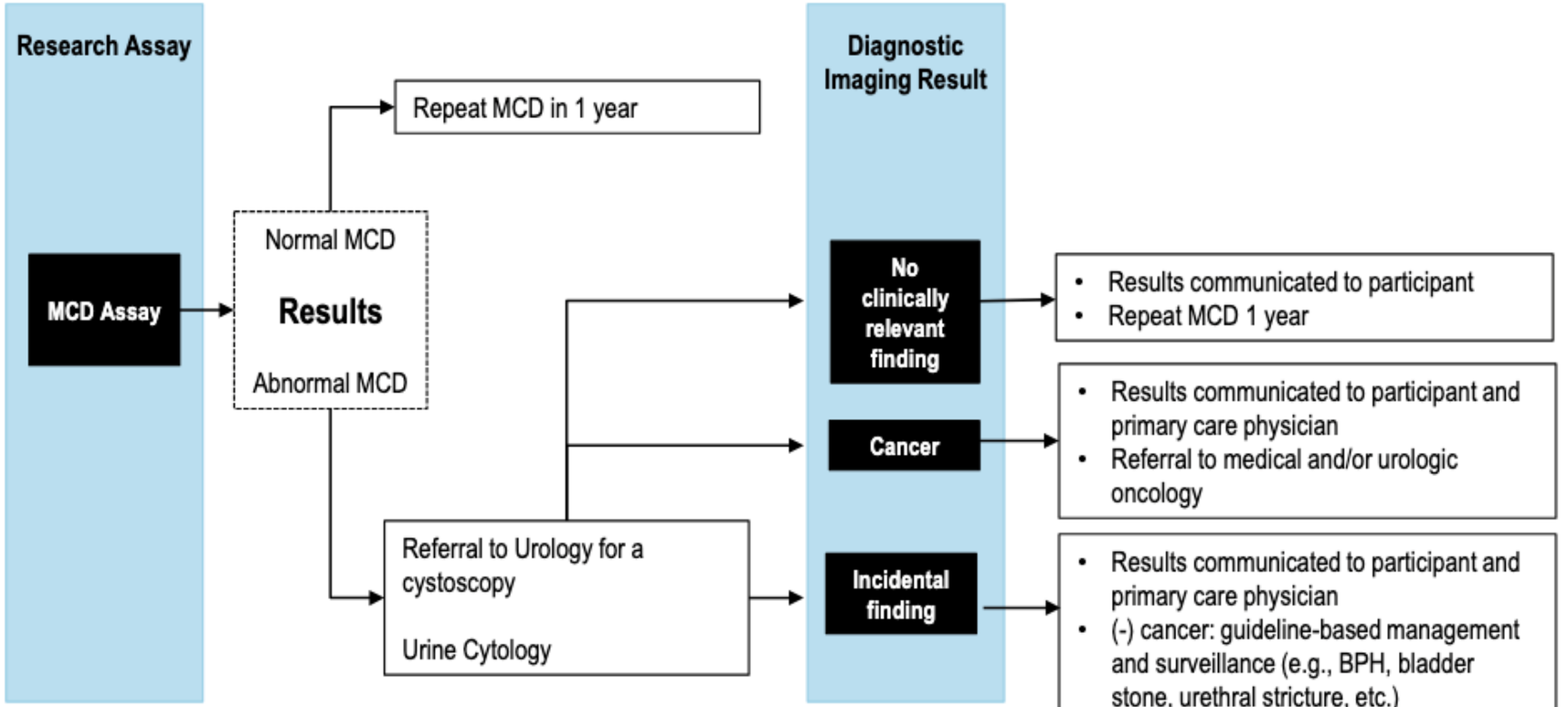
Positive MCD tests - work-up:

- Can happen anywhere (own provider, ACCESS Hub ....)
- Providing guidance (but not mandates) for diagnostic pathways balanced with intent to thoroughly and flexibly capture data on workups

Diagnostic Workflow for a Positive MCD Test (Lung TOO)



Diagnostic Workflow for a Positive MCD Test (Bladder TOO)



Phase #1 Bladder Cancer diagnostic workflow coordinated by ACCESS hub research team

The Vanguard Study

Why store additional blood

- Potential study for new tests.
- Intended Effect Analysis

Intended Effect Analysis

Key idea – compare outcomes only among screen ever-positives

Key Assumptions -

- Screening only affects cancer outcomes in screen ever-positives
- Underlying event rates in screen never-positives equal across arms (no “false reassurance effect”)
- By randomization, underlying ever-positive proportions equal across arms

IE Design

- Test control arm specimens towards end of trial (no return of results)
- Analyze primary event rate only in ever-positives across arms
- Increases power due to eliminating “noise” of events in never-positives

Katki H et al. *J Natl Cancer Inst* 2024 Apr 11;116(8):1280–1287. doi: 10.1093/jnci/djae083

IE Approach – Practical Considerations

- Practical issues affecting IE assumptions
- Possible unequal adherence with blood draw across arms (could result in unequal ever-positive groups across arms)
- Possible “loss of signal” of MCD test with delayed testing
- Ethical issues with real-time testing with or without return of results
- Testing for a “false reassurance” effect in never-positives
- Having some Hubs blinded and some unblinded will allow us to evaluate the unequal adherence and no false reassurance assumptions
- CSRN has discussed the IE approach, but there is no plan to do so

Discussion

NCI Cancer Screening Research Network

A program of the National Cancer Institute of the National Institutes of Health

Thank you

NCI Cancer Screening Research Network

A program of the National Cancer Institute
of the National Institutes of Health