Agenda/Speakers

Intro to Multi-cancer Early Detection (MCED)
Anuraag Kansal, PhD

National health system and payer perspectives
Maarten IJzerman, PhD

MCED and the value flower
Laura Housman, MPH, MBA, DrPH Candidate

Modeling the impacts of MCED
Jaime Caro, MDCM, FRCPC, FACP

GRAIL

Exploring Unmet Needs in Cancer Screening and the Value of Multi-Cancer Early Detection Testing

Anuraag Kansal, PhD
Sr Director, HEOR
GRAIL, LLC

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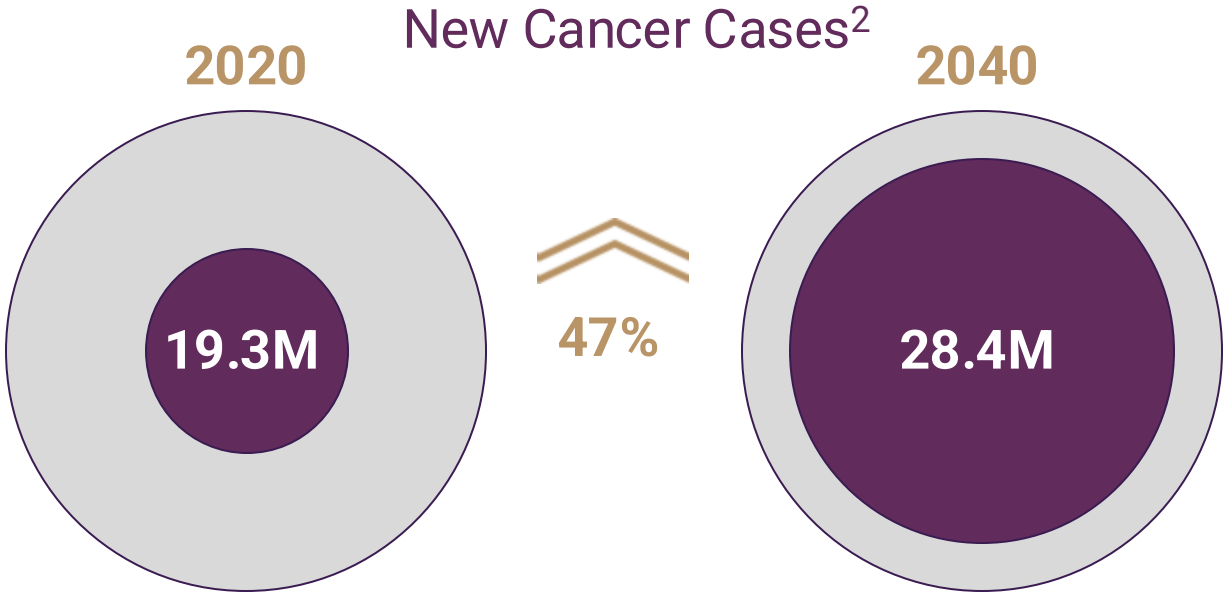
Globally, Cancer Cases Are On the Rise

Annual ASIRs for all cancers combined increased between 2007 and 2017 in 123 countries[1]



The largest increase was in the middle Sociodemographic Index countries (52% increase). Changing age structure, population growth, and changing ASIRs contributed 24%, 10%, and 18%, respectively[1]

ASIR, age-standardized incidence rate.

[1]Fitzmaurice C et al. *JAMA Oncol.* 2019;5:1749-1768. [2]Sung H et al. *CA Cancer J Clin.* 2021;71:209-249.

The staggering human and economic toll from cancer

8.7M
Years of lost life[1]

One of the leading causes of death in the US[2] with more than 600,000 deaths expected in 2022[3]; $94.4B in lost earnings associated with cancer mortality

$207B
Annual cost of cancer[4]

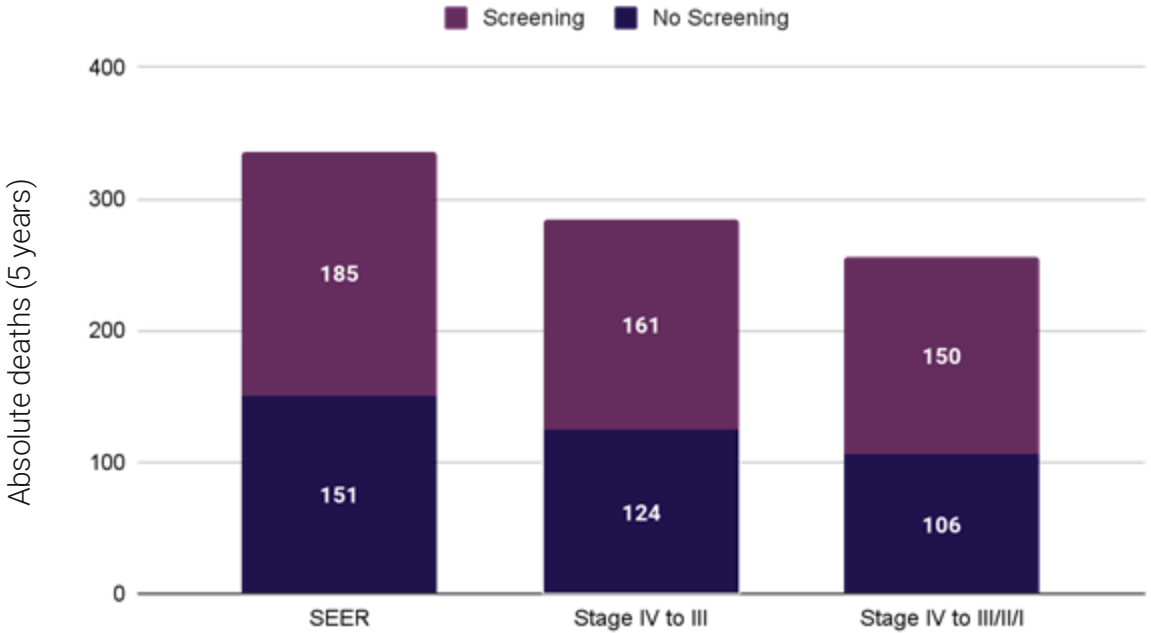
Total estimated US direct healthcare costs in 2020

$1.3T
Economic burden[1,5]

The majority is due to cancers without recommended screening programs

US, United States.
1. Islami F, et al. JAMA Oncol. 2019;5:e191460. 2. https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm. 3. Siegel R, et al. CA Cancer J Clin. 2022;72:7-33.3.https://seer.cancer.gov/statfacts/html/all.html. 4. Mariotto et al. (2020) Cancer Epi Biom Prev 29:1304. 5. Based on willingness to pay of $150,000.

Stage IV cancers represent 18% of cancers, but 48% of mortality



Estimated 5-year cancer-related deaths under hypothetical stage shift scenarios among US persons ages 50-79, with attention to recommended screening status of cancer types. Total cancer-related deaths expected in hypothetical cohort of 100,000 persons with characteristics similar to the SEER18 population ages 50-79 during the years 2006-2015. "SEER" refers to real SEER population. "Stage IV to III refers to the scenario under which all stage IV cancer has outcomes similar to stage III. "Stage IV to III/II/I" refers to scenario under which one third of stage IV cancers were diagnosed at stage III, one third diagnosed at stage II and one third diagnosed at stage I. "Screening" refers to cancer types with USPSTF-recommended screening programs (lung, colorectal, and breast)

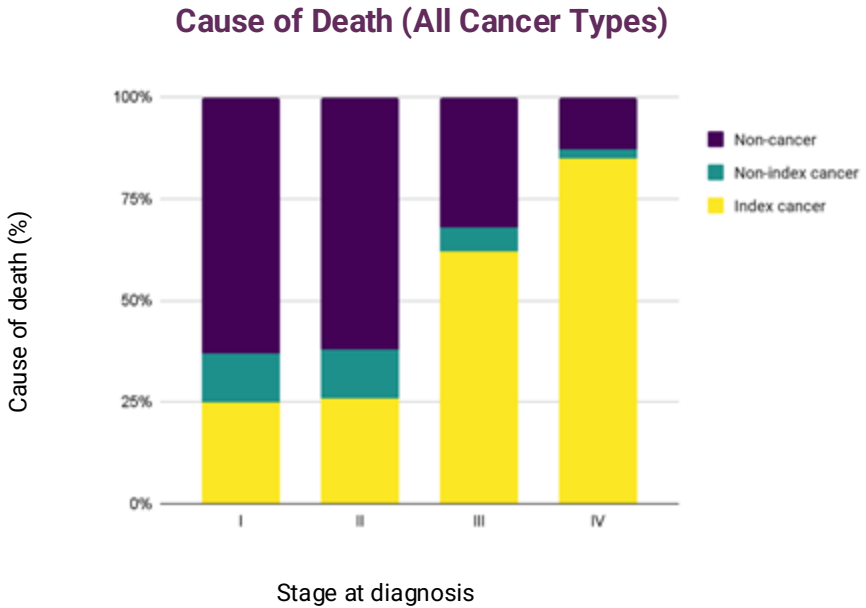
Clarke et al. Cancer Epidemiol Biomarkers Prev 2020;29:895–902

Detect Cancer Early, When it can be Cured

Early-Stage Cancer Usually Is Not Fatal, But Late-Stage Cancer Usually Is

27%
of patients diagnosed at stage I-II
died from their index cancer

85%
of patients diagnosed at stage IV
died from their index cancer



Chang ET, et al. Cancer Causes Control. 2024. https://doi.org/10.1007/s10552-023-01842-4.

US-GA-2400456

The Problem of Cancer Death is Due Mostly to Unscreened Cancers

>70%

Cancer deaths result from cancers without recommended screening[1]

86%

Of cancers are not found through recommended screening[2]

~4x

Increased survival rate when diagnosed **EARLY**[3*]

* "Early/Localized" includes invasive localized tumors that have not spread beyond organ of origin, "Late/Metastasized" includes invasive cancers that have metastasized beyond the organ of origin to other parts of the body.
[1]Estimated deaths per year in 2020 from American Cancer Society Cancer Facts and Figures 2020. Available at www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/cancer-facts-and-figures-2020.pdf. [2] NORC at the University of Chicago. Only 14% of diagnosed cancers are detected by screening with a recommended screening test. [3] Based on five year survival rate. Data on file from Surveillance, Epidemiology, and End Results (SEER) 18 Regs Research Data, Nov 2018 Submission. Includes persons aged 50 – 79 diagnosed 2006-2015.

Approaches to Cancer Screening With Liquid Biopsies

- Detect driver cancer gene mutations in plasma cfDNA

- Combined analyses (circulating proteins and cancer-associated mutations in plasma)
- Identify tissue- and/or cancer-specific epigenetic changes
- Find differences in genome-wide fragmentation patterns of tumor/ nontumor cfDNA

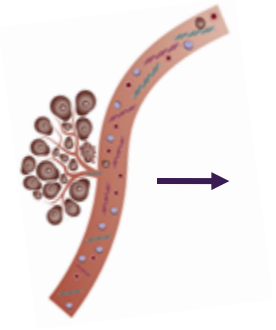
- Methylation-based assay that detects various cancers spanning disease stages and tissue-of-origin identification

cfDNA, cell-free DNA; DNA, deoxyribonucleic acid.

Ignatiadis M et al. *Nat Rev Clin Oncol*. 2021;18(5):297-312. DOI: 10.1038/s41571-020-00457-x.

GRAIL's Multi-Cancer Early Detection Test is Based on a Single Blood Draw

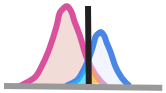
The GRAIL test is an adjunct to standard of care screening methods and is not a replacement for existing cancer screening tests



Tumor sheds cfDNA[a] fragments into bloodstream

Blood plasma isolated (contains cfDNA fragments)

Targeted methylation analysis of cfDNA



1st ML[b] classifier

Cancer signal detected (+)

No cancer signal detected (-)

With high specificity and PPV

2nd ML classifier

Cancer signal origin (CSO) predicted

The MCED test does not detect all cancers and should be used in addition to routine cancer screening tests recommended by a healthcare provider.

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[a] cfDNA, cell-free DNA
[b] ML, machine learning
Adapted from Liu MC, et al. *Ann Oncol.* 2020;31(6):745-759. DOI:10.1016/j.annonc.2020.02.011.

Companies in the Early Detection Cancer Screening Landscape

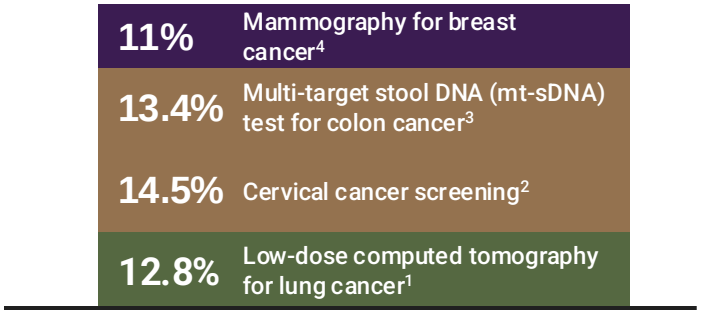
Commercially-Available SCED

Notes: Not exhaustive list of companies

The Solution is Not More Single Cancer Screening Tests

Screening 60-79-year-old female smokers with 4 single-cancer tests has a **cumulative**

43% false positive rate (FPR)*



*Assumes eligibility for all 4 tests.

Screening the same patients with the Galleri MCED test (>50 cancer types)

<1% FPR (FPR)*

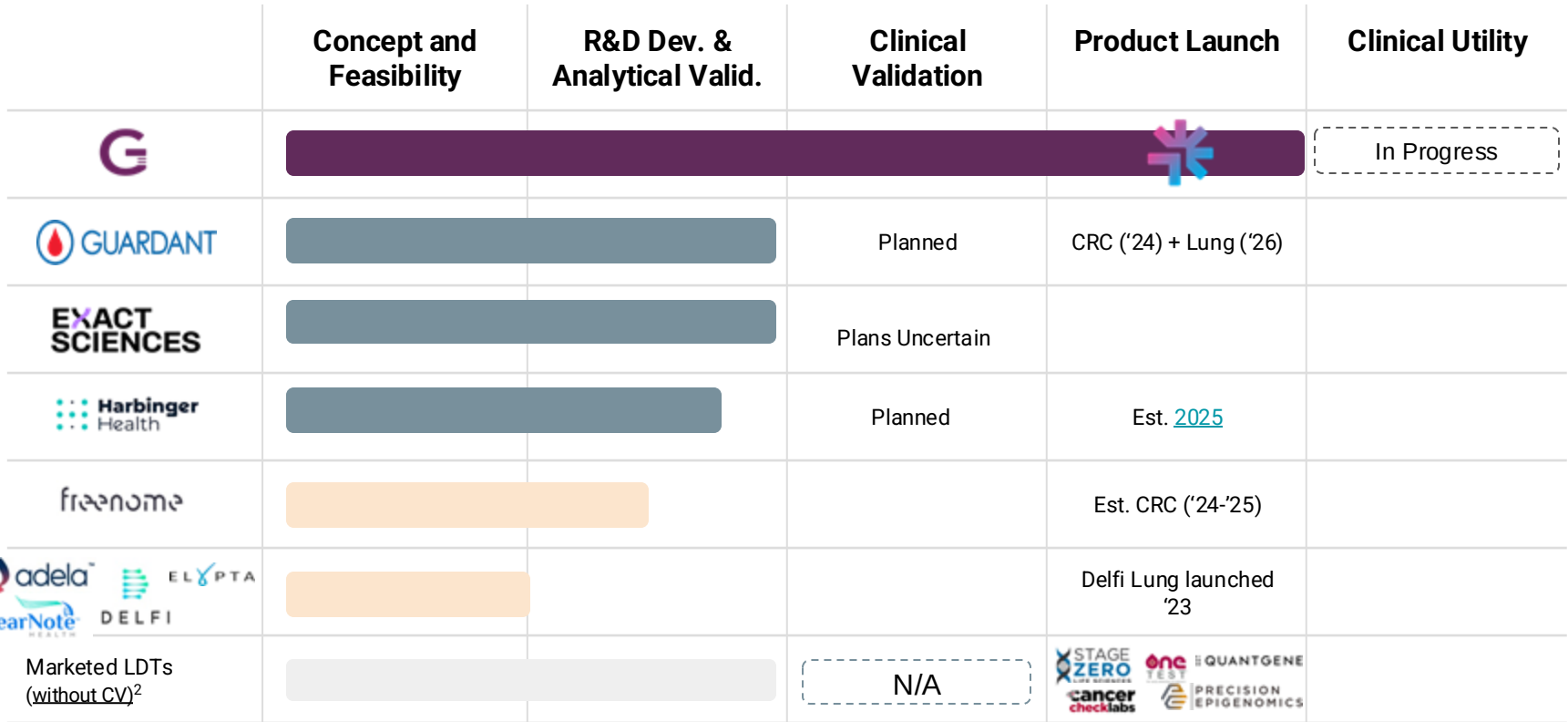
*Assumes eligibility for all 4 tests.

31% **The cumulative FPR for male smokers aged 60-79**

A false positive result in any screening modality would require follow-up testing or interventions – GRAIL could improve the efficiency of cancer diagnosis and care by eliminating unnecessary follow-up testing and streamlining the process

1. Pinsky PF, et al. Ann Intern Med. 2015;162:485-491. 2. Kim, et al. JAMA. 2018;320(7):706-714. 3. US Food and Drug Administration PMA P130017: FDA summary of safety and effectiveness data. August 11, 2014. Accessed March 21, 2020. 4. Lehman CD, et al. Radiology. 2017;283:49-58. Data on file GA_2021_005 .5. Wolf, et al. CA Cancer J Clin. 2010;60:70-98.

State of the Science (US)



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Note: [1] ClearNote - Formerly Bluestar Genomics. [2] Commercially available MCED LDTs in the US. MCEDs in the US (does not include MCEDs in ex-US). Not an exhaustive list of MCEDs in development.
Disclaimer: All anticipated development timelines are from external sources and do not represent an GRAIL's assessment of program progress.

Galleri test performance in clinical validation and intended use studies

CCGA3
Clinical Validation Study[1,2]

0.5%	44%	89%
False-positive rate	Positive predictive value (modeled)	Cancer signal origin accuracy[1,2]

PATHFINDER
Confirmatory Intended Use Population Study[3]

0.5%	43%	88%
False-positive rate	Positive predictive value	Cancer signal origin accuracy*

1. Based on tissue of origin class assigned in 96% of cases where cancer was detected accuracy of top Cancer Signal Origin for true positive cancer participants with a Cancer Signal Detected., 2. Klein EA et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. Ann Oncol. 2021;32(9):1167-1177. doi: 10.1016/j.annonc.2021.05.806., 3. Schrag D et al. Blood-bassed tests for multicancer early detection (PATHFINDER): a prospective cohort study. Lancet. 2023;402:1251-60.*Accuracy of top two cancer signal origin prediction for true positive patients, Based on prespecified reanalysis of blood samples with Galleri test.

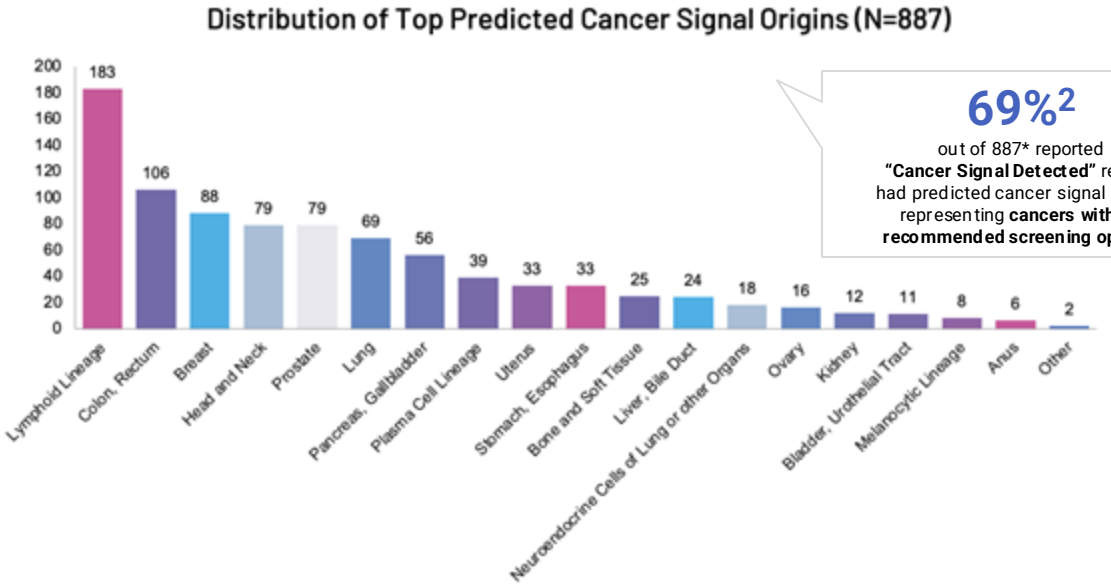
Real-world Galleri test performance is as expected and consistent with that in prior clinical studies, with 100,000+ tests completed and 7,100+ prescribing physicians across the US†

Cancer Signal Detection Rate as expected for an intended use population**

0.95%[1]

of test results
were Cancer Signal Detected

The top* cancer signal origins reported represent a variety of cancer types



69%[2]
out of 887* reported **"Cancer Signal Detected"** results had predicted cancer signal origins representing **cancers without recommended screening options**

†As of June 12, 2023.
*Limited to the top predicted Cancer Signal Origin cases. A subset of confirmed cancers included stage I and II cancers, including anus, chronic lymphocytic leukemia, colon, esophagus, hepatoma, Hodgkin's lymphoma, multiple myeloma, non-small cell lung, pancreas, prostate, rectum, tonsil, tongue, uterus.
**Real-world CSDR was comparable to expected CSDR modeled from SEER and the prospective, return-of-results PATHFINDER study cancer signal detection rate.[3]

Source: [1]Westgate et al. Journal of Clinical Oncology 2023 41:16_suppl, 10519-10519; [2]Data on file GA-2022-0078. [3]Schrag D, Beer TM, McDonnell CH, et al. Lancet. 2023;402(10409):1251-1260. doi: 10.1016/S0140-6736(23)01700-2.

National Health System and Payer Perspectives

Maarten IJzerman, PhD

Erasmus School of Health Policy & Management

Multi-cancer early detection: A health systems perspective

Maarten J. IJzerman, PhD
University of Melbourne, Melbourne, Australia
Erasmus University Rotterdam, the Netherlands

Acknowledgments: Mussab Fagery, Hadi Khorshidi, Stephen Wong, Özge Karanfil, Lotte de

With

Erasmus University Rotterdam

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Conflicts of interest

- I do not receive an honorarium nor compensation of other expenses for participating in this panel

- I do not have any other conflicts of interest to declare

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Multi-Cancer Early Detection (MCED)

- MCEDs analysing methylations and mutations in cfDNA, miRNA and/or cancer proteins
  - Ability to identify Tissue of Origin (TOO)
- Designed with fixed false-positive rate to avoid cumulative false-positives
- Improved outcomes through stage shift, i.e. earlier detection a-symptomatic
  - Alternatively, TOO in CUPs

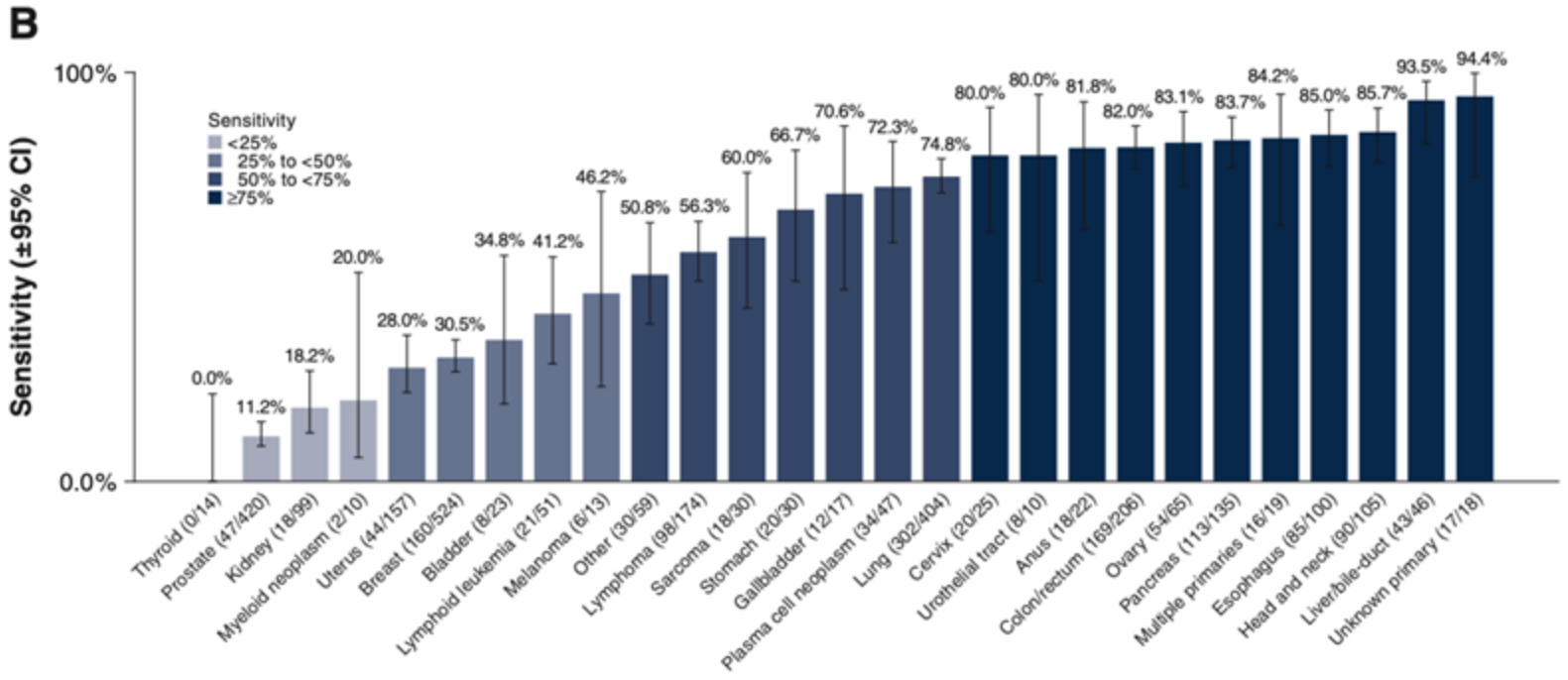
- **Where to use MCEDs and add value?** (de With *et al*, 2023)
  - Over the counter ⛔
  - Population screening ✅, but unlikely for all cancers due low prevalence
  - Primary care ✅, possible for ruling out, yet symptomatic in advanced stage
  - Hospital ⛔

MCEDs

Test name (first author)	CancerSEEK (Cohen et al., 2018)	Pantum/EDIM (Grimm et al., 2013)	PanSeer (Chen et al., 2020)	Galleri (Klein et al., 2021)
Company name (country)	Exact Science (USA)	RMDM Diagnostics/ Zyagnum AG (Germany)	Singlera Genomics (USA)	GRAIL (USA)
Biological signal	Mutations and protein markers	Apo10 and TKTL1 in monocytes	DNA methylation	cfDNA methylation
Age range, years	17-93	19-85	35-85	>20
% women	51%	46%	34%	55%
Number of cancer types	8	3	5	>50
Sensitivity (number with cancer)*	62% (1,005)	97% (213)	95% (98)	52% (2823)
Tumor of origin accuracy	83%	-	-	89%
FPR*	0.9% (812)	4.0% (74)	3.9% (207)	0.5% (1,254)

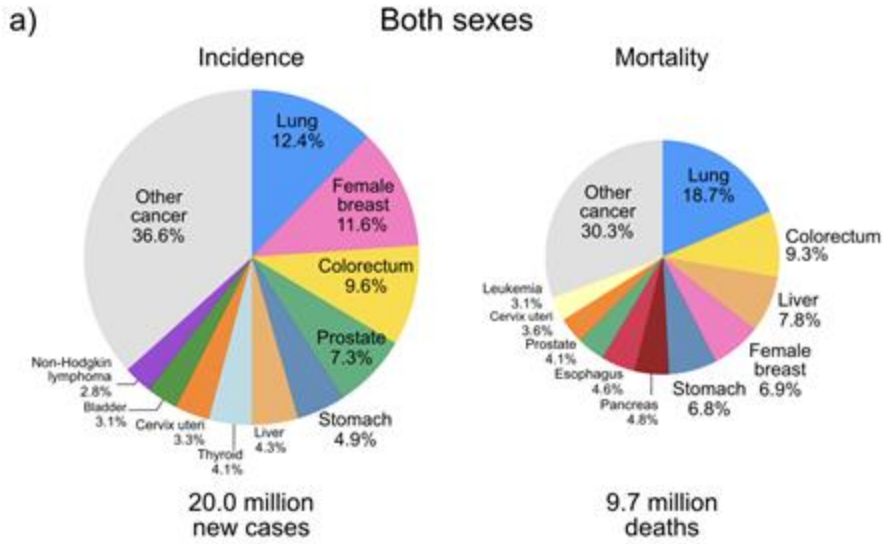
Adapted from: Hackshaw *et al*,

Initial validation results (Galleri™)



Klein *et al*. Annals Oncology,

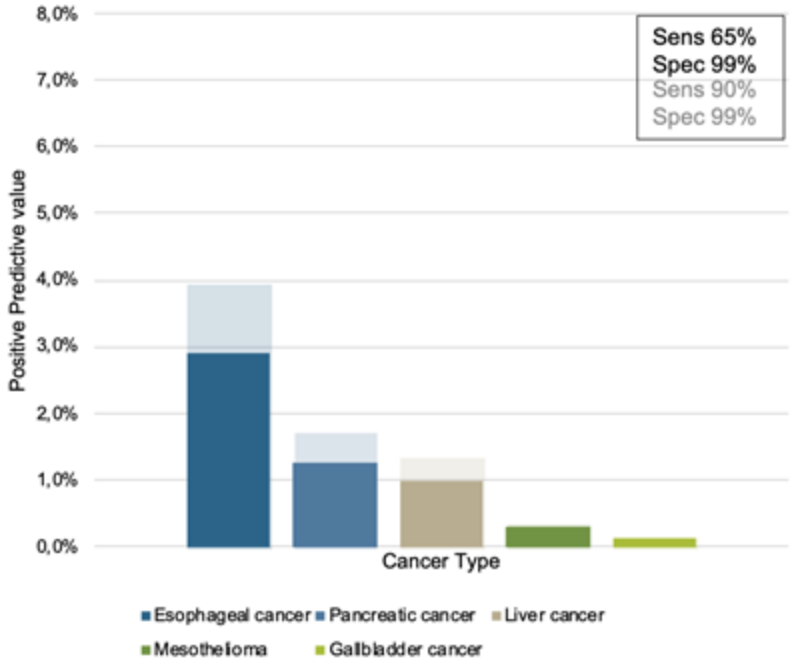
Deadly cancers (mortality vs. 5-year survival)

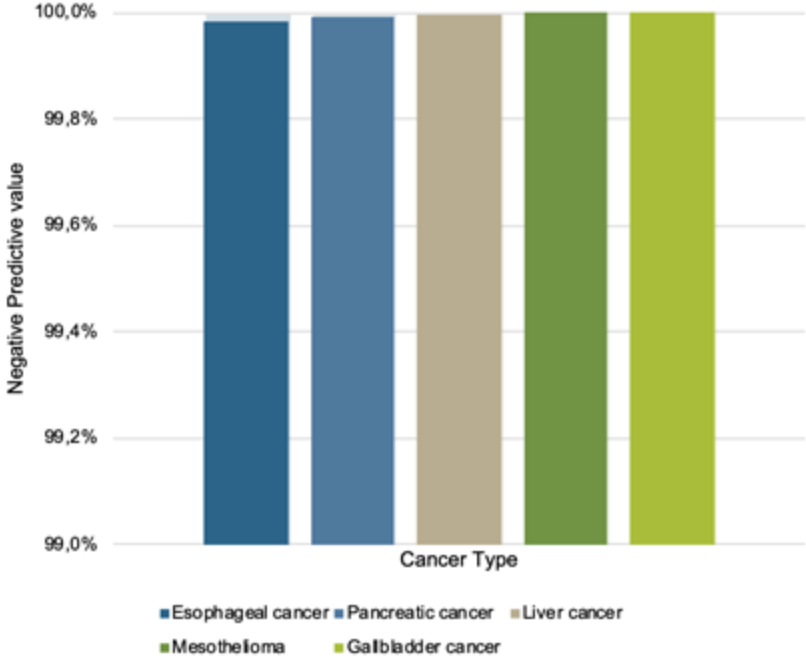


Bray et al, 2024

Source: Cancer Australia

A needle in a haystack?





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Utility of screening multiple diseases?

- Low-dose CT screening for LC, COPD, CVD (Behr *et al*, Eur Radiology, 2022)
  - Population sharing the same risk factors
  - Probability of concurrent presence of diseases (e.g. probability CVD+LC)
  - Clinical utility of detection is different for LC, CVD, COPD

Table 2 Headroom analysis outcomes for a screening population of current and former smokers between 50 and 75 years old

				Incremental MAC (€ per screened individual)	
		Incremental disease management costs (€ per screened individual)	Effectiveness gap (incremental QALY per screened individual)	WTP: €20 k/ QALY	WTP: €80 k/ QALY
Diseases screened*	Patients with disease				
LC + CVD + COPD	155,966	− 14	0.048	971	3,844
LC + CVD	136,752	− 12	0.044	895	3,546
LC + COPD	43,666	− 37	0.009	230	809
LC	13,262	− 37	0.004	113	341

Cancer screening and participation rates

Tumor	Eligible population	A$ per screen	Policy	Participation rates
Breast cancer	3,590,050	A$ 59	50-74, once in 2 years	
Colorectal cancer	6,090,980	A$ 65	50-74, once in 2 years	
Cervical Cancer	6,859,061	A$ 35	25-74, once in 5 years	
Lung Cancer	580,000	A$ 299	To commence 2025	

1 A$ = 0.65 US$

MCED test approximately A$1,500 (US$ 949)

Lung cancer screening for people aged 50-70, no symptoms and at least 30 pack-years

BreastScreen AUSTRALIA
A joint Australian, State and Territory Government Program

NATIONAL BOWELCANCER SCREENING PROGRAM

NATIONAL CERVICAL SCREENING PROGRAM
A joint Australian, State and Territory Government Program

Cancer screening and participation rates

Tumor	Eligible population	A$ per screen	Policy	Participation rates
Breast cancer	3,590,050	A$ 59	50-74, once in 2 years	47.5%
Colorectal cancer	6,090,980	A$ 65	50-74, once in 2 years	40.9%
Cervical Cancer	6,859,061	A$ 35	25-74, once in 5 years	62.4%
Lung Cancer	580,000	A$ 299	To commence 2025	60%

1 A$ = 0.65 US$

MCED test approximately A$1,500 (US$ 949)

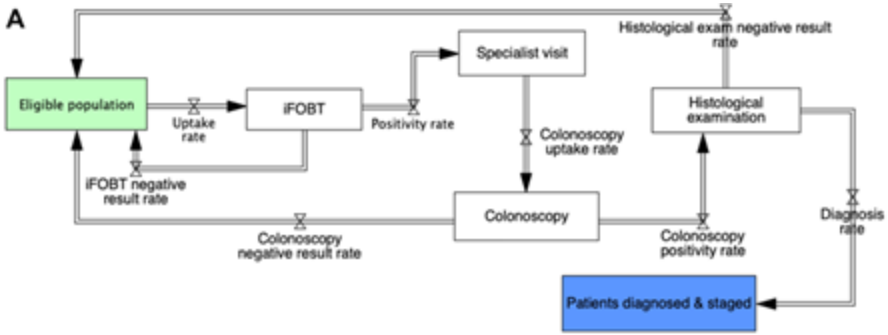
Lung cancer screening for people aged 50-70, no symptoms and at least 30 pack-years

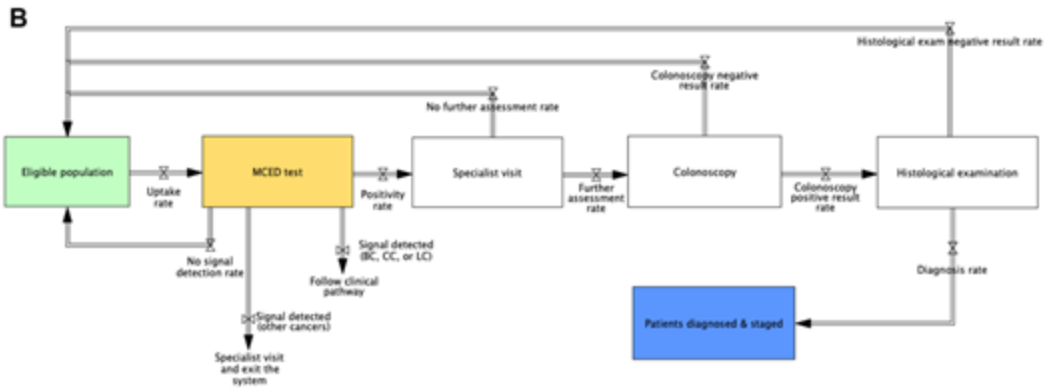
BreastScreen AUSTRALIA
A joint Australian, State and Territory Government Program

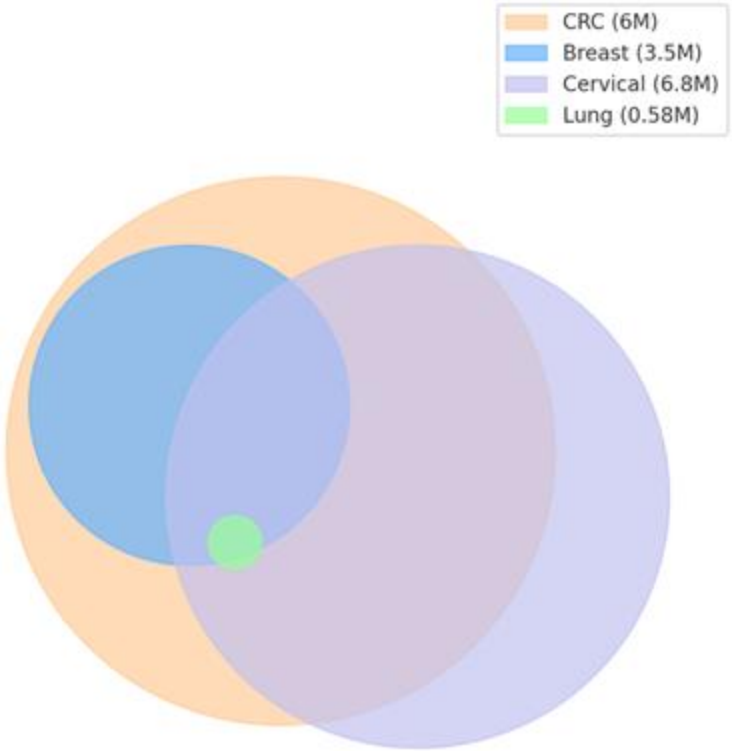
NATIONAL BOWELCANCER SCREENING PROGRAM

NATIONAL CERVICAL SCREENING PROGRAM
A joint Australian, State and Territory Government Program

Complementing SoC screening
non-participants and overlapping target populations

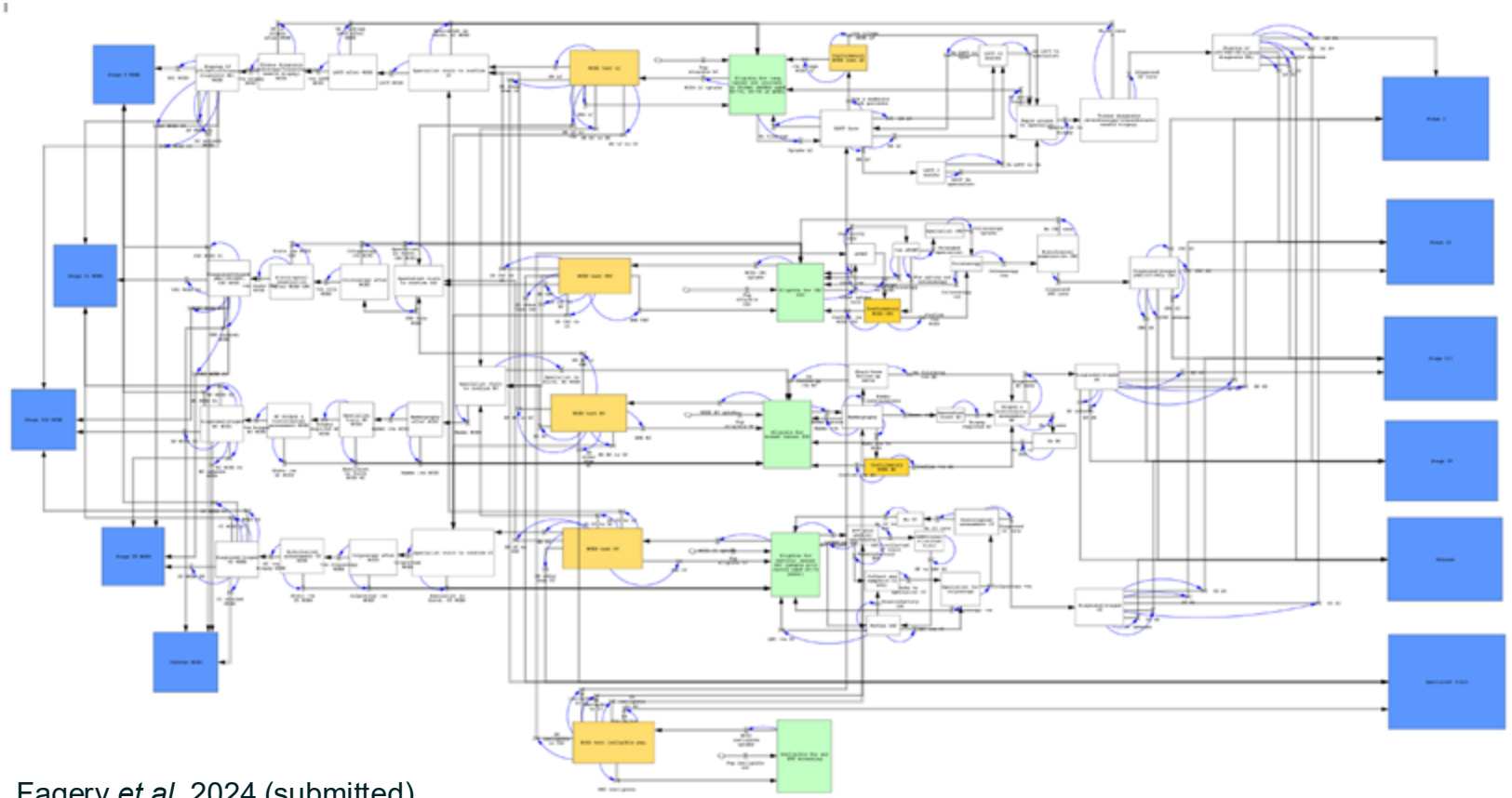






Fagery *et al*, Pharmacoeconomics Open, 2024

A systems dynamics approach



Fagery *et al*, 2024 (submitted)

Results for varying uptake rates

1 A$ = 0.65 US$

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Conclusions

- MCED targeting non-participants, assuming 25% uptake of MCED
  - Aggregate detection rate increases from 18.5% to 21.3% (+729 patients)
  - 400k A$ / early detected case
  - Population budget impact is 2,9 billion A$
    - Total cost of cancer care approximately 10 billion A$

Points for discussion

- Utility and improved outcomes in high volume cancers only?
- SOC participation rates are low, why not increase participation?
- Is offering MCED testing an incentive for SoC screening non-participation?
- Will non-participants adhere to MCED if not opting for SOC screening?
- Overdiagnosis (non-lethal cancers); value of knowing remains controversial

Literature

- De With, L de, Multi-Cancer Early Detection Tests: The Holy GRAIL or a Mirage in Future Cancer Control? Presented European Cancer Summit, November 2023, Brussels, Belgium
- Fagery M, et al Integrating Multi-Cancer Early Detection (MCED) Tests with Standard Cancer Screening: System Dynamics Model Development and Feasibility Testing. Pharmacoeconomics Open, October 2024 (online)
- Hubbell, E., et al., Modeled Reductions in Late-stage Cancer with a Multi-Cancer Early Detection Test. Cancer Epidemiol Biomarkers Prev, 2021. 30(3): p. 460-468.
- Tafazzoli, A., et al., The Potential Value-Based Price of a Multi-Cancer Early Detection Genomic Blood Test to Complement Current Single Cancer Screening in the USA. Pharmacoeconomics, 2022. 40(11): p. 1107-1117.
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- Lavaze, P et al., Combined population genomic screening for three high-risk conditions in Australia: a modelling study. eLancet, December 2023
- Behr CM et al., Can we increase efficiency of CT lung cancer screening by combining with CVD and COPD screening? Results of an early economic evaluation. European Radiology, 2022, May;32(5):3067-3075

MCED and the Value Flowers

Laura Housman, MPH, MBA

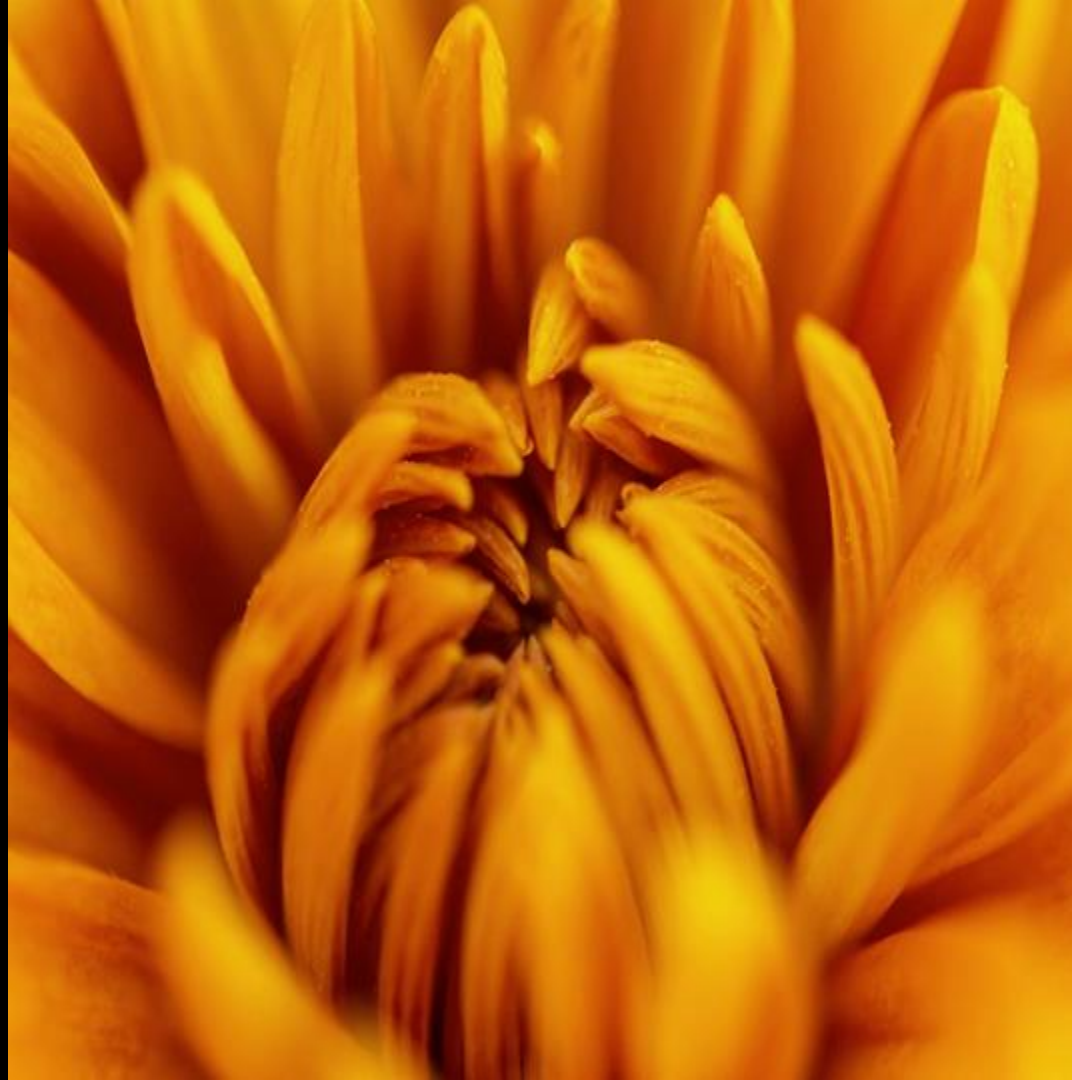
Better health happens when we connect.

CAPTURING THE IMPACT OF EARLY CANCER DETECTION USING THE ISPOR VALUE FLOWER

ISPOR EU

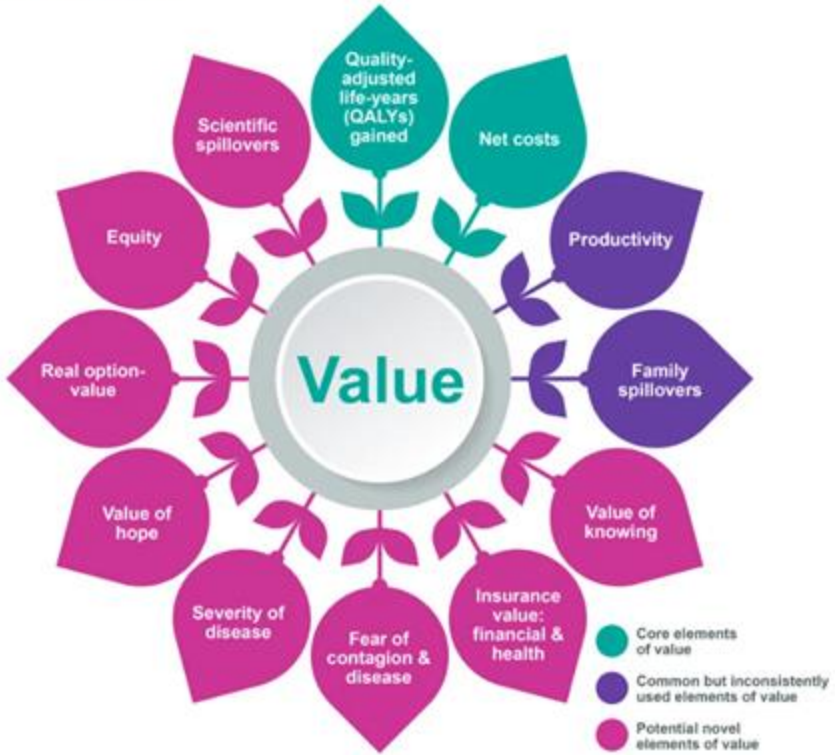
Tuesday, November 19, 2024

Avalere Health™



The Value Flower:

Towards a more holistic understanding of drug value and innovation



Source: ISPOR

Avalere Health

Nearly 70% of the ISPOR Value Flower represents novel elements of value.

Can early detection of cancer demonstrate enough value to move some of these novel elements to be considered core?

Potential First Focus Areas of Value Demonstration

Build upon existing studies; expand knowledge base and utility

Value of knowing

Negative test results from MCED tests provide potential value to patients in terms of emotional and psychological benefits.(ISPOR 2023)

Regardless of income level or race/ethnicity, a negative MCED test result provides additional value to the US general population beyond traditional clinical benefits, has positive impacts on psychological /emotional health, and could promote adherence to or increase preventive healthcare. (ISPOR 2024)

Equity in care

Racial/ethnic minorities and those of low to mid income anticipated greater positive impacts, specifically to preventive health behaviors with a negative MCED result. (ISPOR 2024)

Real option value

Assessing and capturing the additional consumer value associated with earlier detection (or non-detection) while not double-counting the value from a payer perspective when determining reimbursement.

What is the opportunity cost of not screening? Or, of screening with existing methodologies with lower sensitivity rates?

Avalere Health™

We partner with changemakers to navigate the complex healthcare ecosystem and bring innovation to the hands of those who can benefit from it.

Together, we can make **better health happen**.

Modeling the Impacts of MCED

Jaime Caro, MDCM, FRCPC, FACP

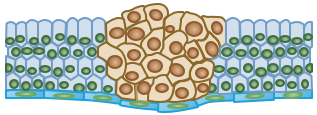
The value of a multi-cancer early detection genomic blood test: methodological considerations

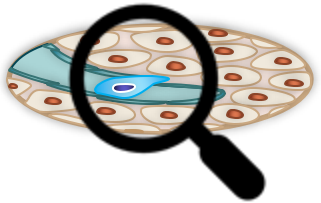
J. Jaime Caro MDCM FRCPC FACP

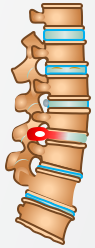
Prof (adj), Epidemiology and biostatistics, McGill U, Montreal, Canada
Prof in practice, Health Policy, LSE, London, UK
Prof (Hon), Saw Swee Hock School of Public Health, NUS, Singapore
Chief Scientist, Evidera

The world leader in serving science

Screening for cancer

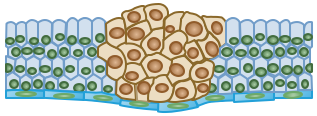


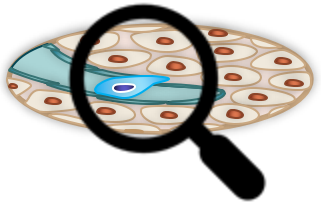




- Longer survival
- Less invasive treatment
- Lower costs
- A negative test also has value
  - Reassurance
- And more

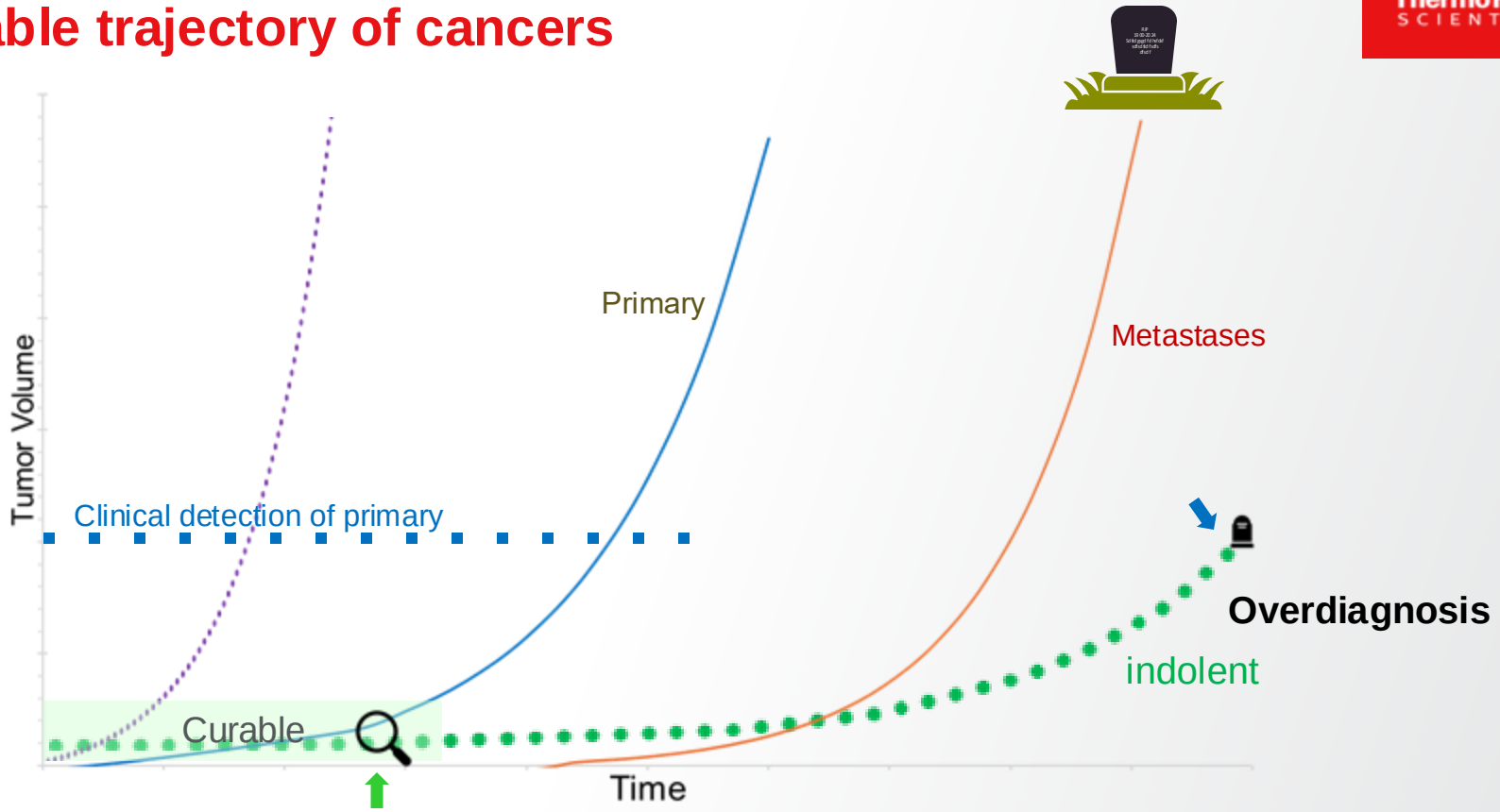
Screening for cancer





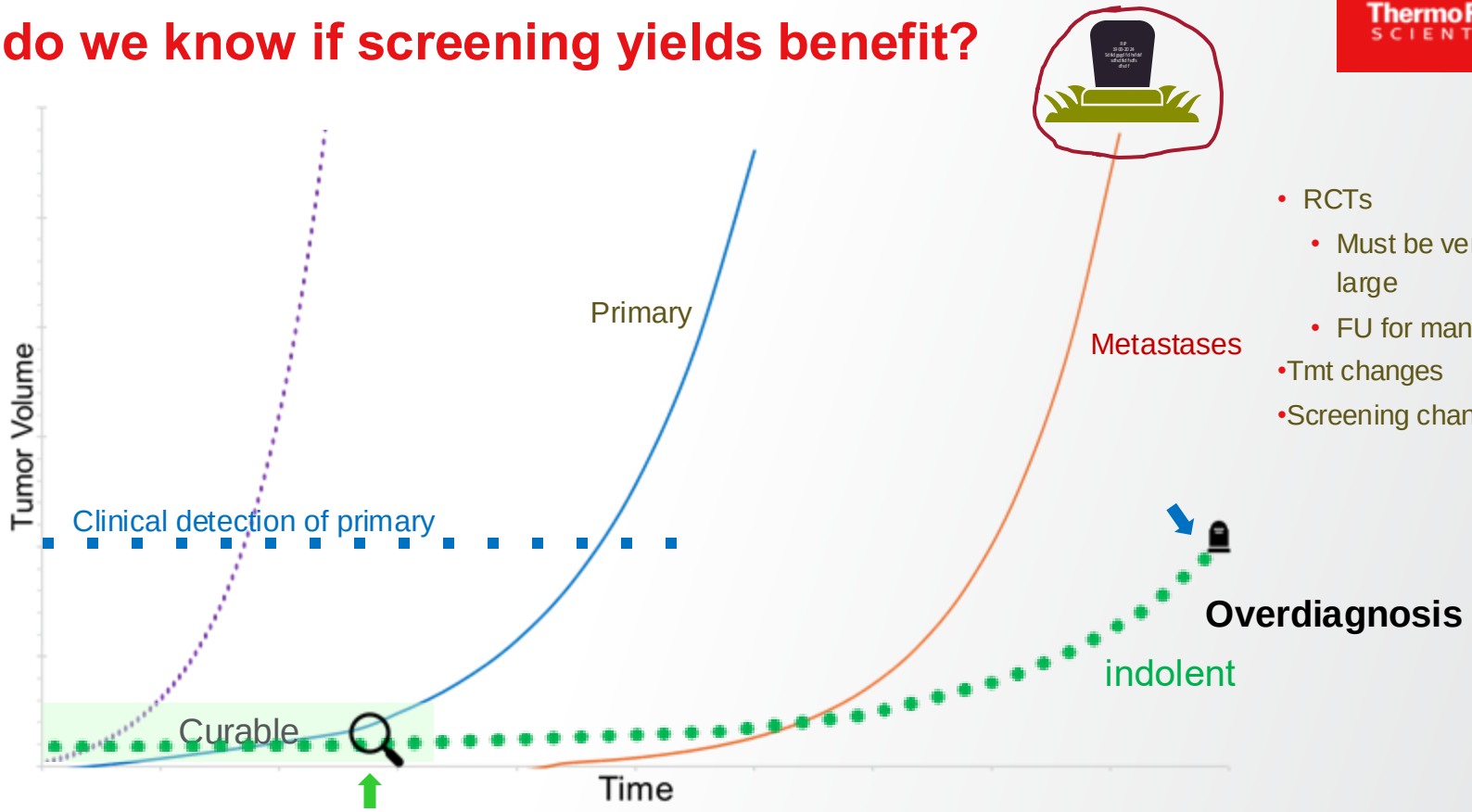
- ✓ 1. Early detectability of the cancer
- ✓ 2. Accurate screen test (Se, Sp, PPV, NPV)
- ✓ 3. Availability of effective treatment
- ✓ 4. Better probability of cure if intervening earlier
- ? 5. Aggressive trajectory if undetected early (but not too aggressive…)

Variable trajectory of cancers



Lin RS, Plevritis SK. Comparing the benefits of screening for breast cancer and lung cancer using a novel natural history model. Cancer Causes Control 2012; 23:175–185

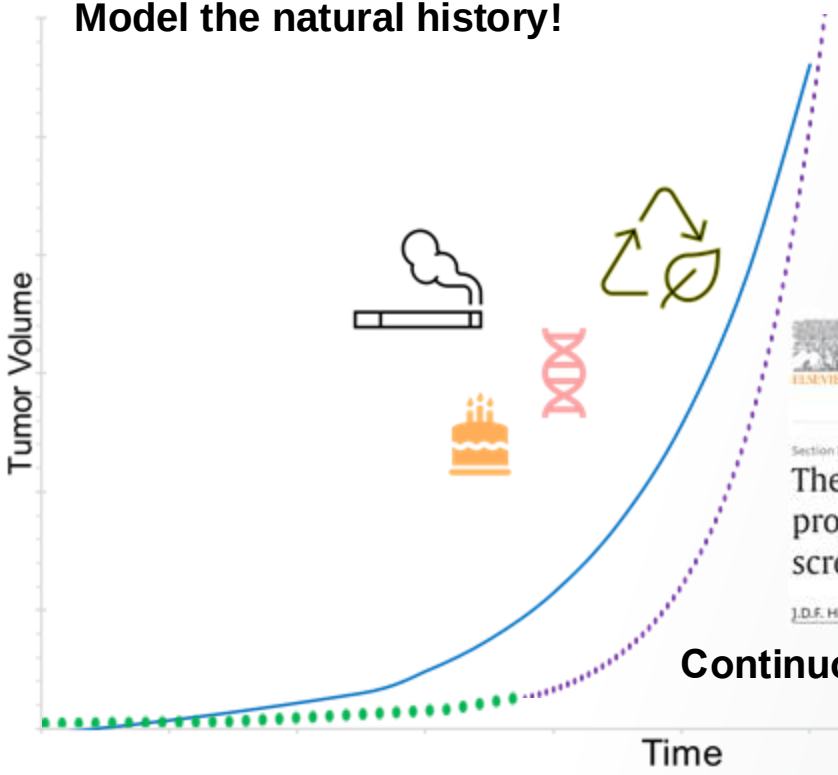
How do we know if screening yields benefit?



- RCTs
  - Must be very large
  - FU for many yrs
- Tmt changes
- Screening changes

How do we know if screening yields benefit?

Model the natural history!



CAN*TROL: a computer model for designing national cancer control strategies.

Eddy DM

Bulletin du Cancer. 01 Jan 1987, 74(3):323-332
PMID: 3620737

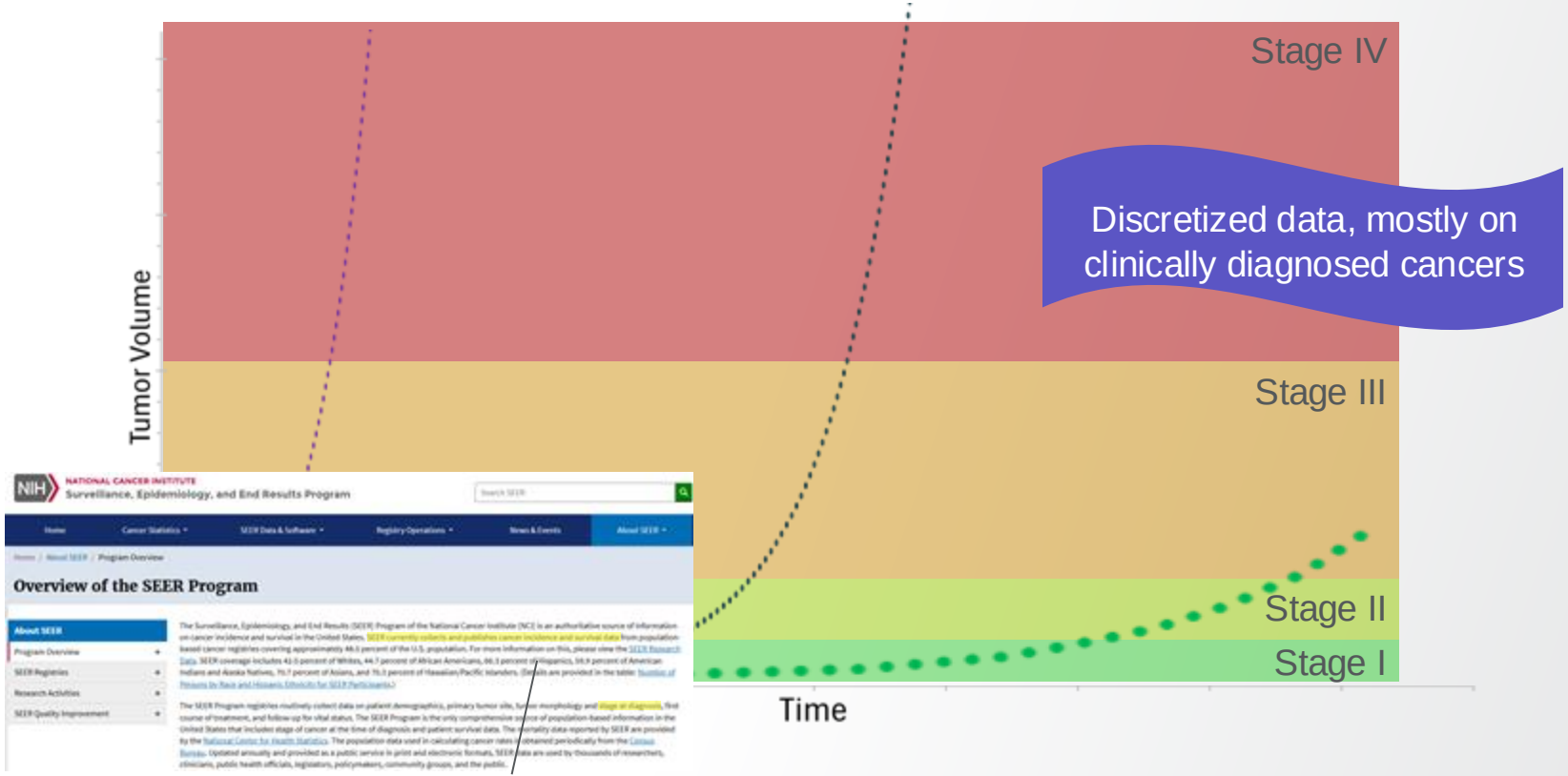
The MISCAN simulation program for the evaluation of screening for disease

J.D.F. Habbema, G.J. van Oortmarssen, J.Th.N. Lubbe, P.J. van der Maas

Modeling the natural history of a cancer is very difficult!

Continuous, even if variable, process

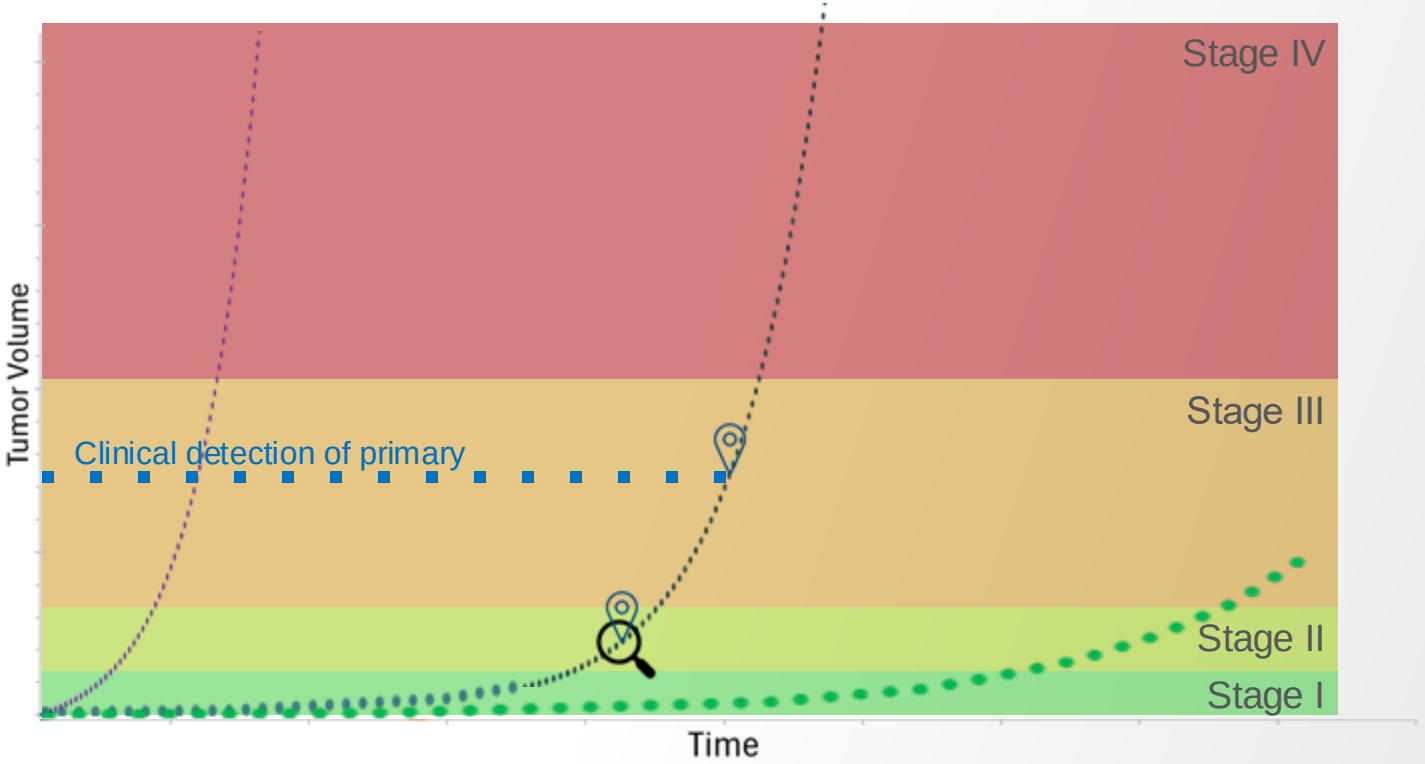
How do we know if screening yields benefit?



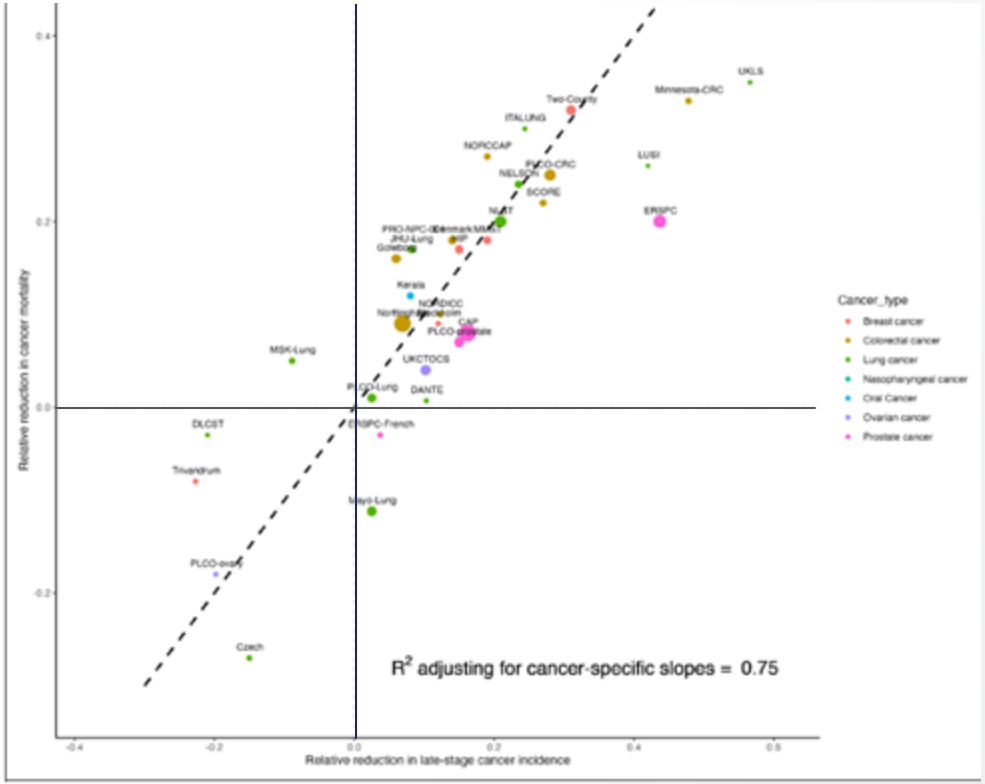
SEER collects … cancer incidence and survival data…and stage at diagnosis

https://seer.cancer.gov/about/overview.html

How do we know if screening yields benefit?

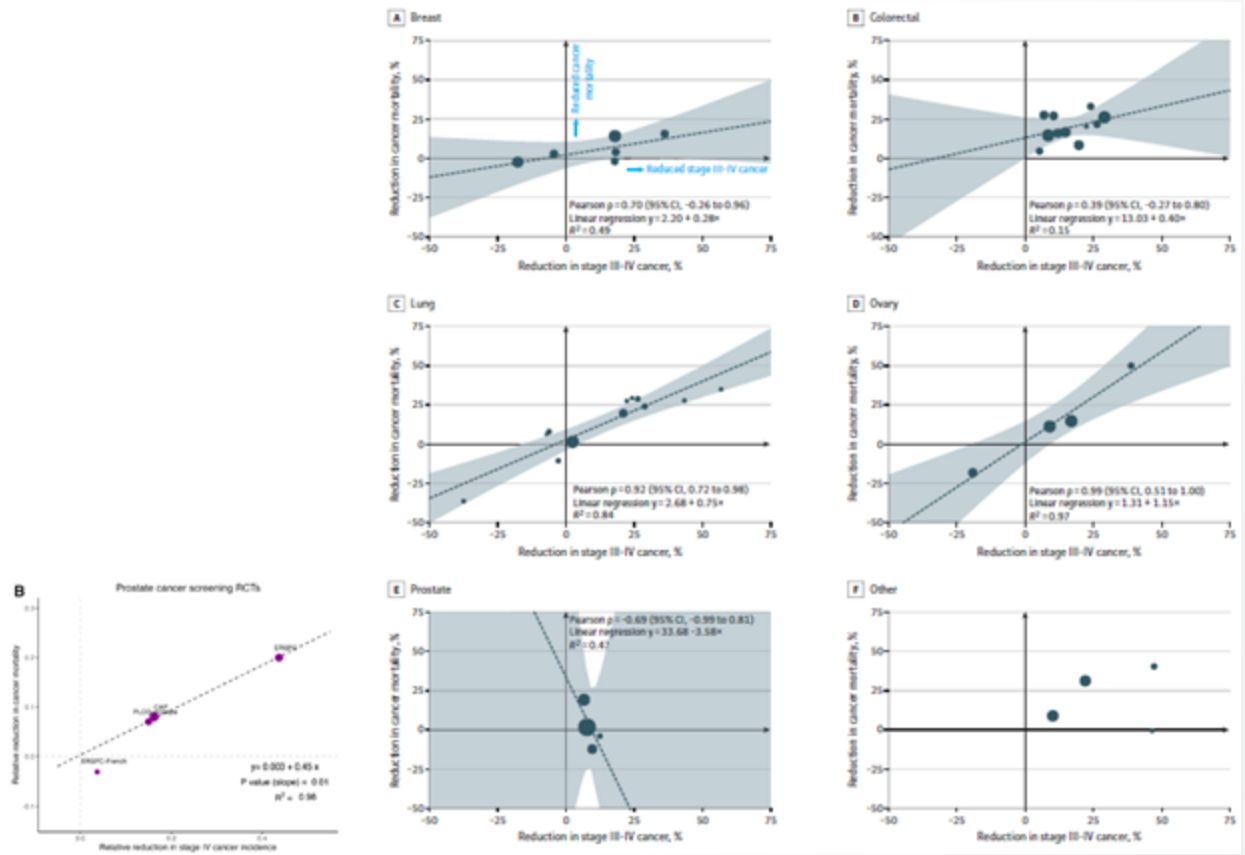


Does stage shift predict mortality reduction?



Dai JY, Georg Luebeck E, Chang ET, Clarke CA, Hubbell EA, Zhang N, Duffy SW. Strong association between reduction of late-stage cancers and reduction of cancer-specific mortality in meta-regression of randomized screening trials across multiple cancer types. Journal of Medical Screening. 2024:1-12

Does stage shift predict mortality reduction?



Why the difference?

- Length of follow-up considered
- Definition of “late-stage”
- Inclusion of non-randomized studies

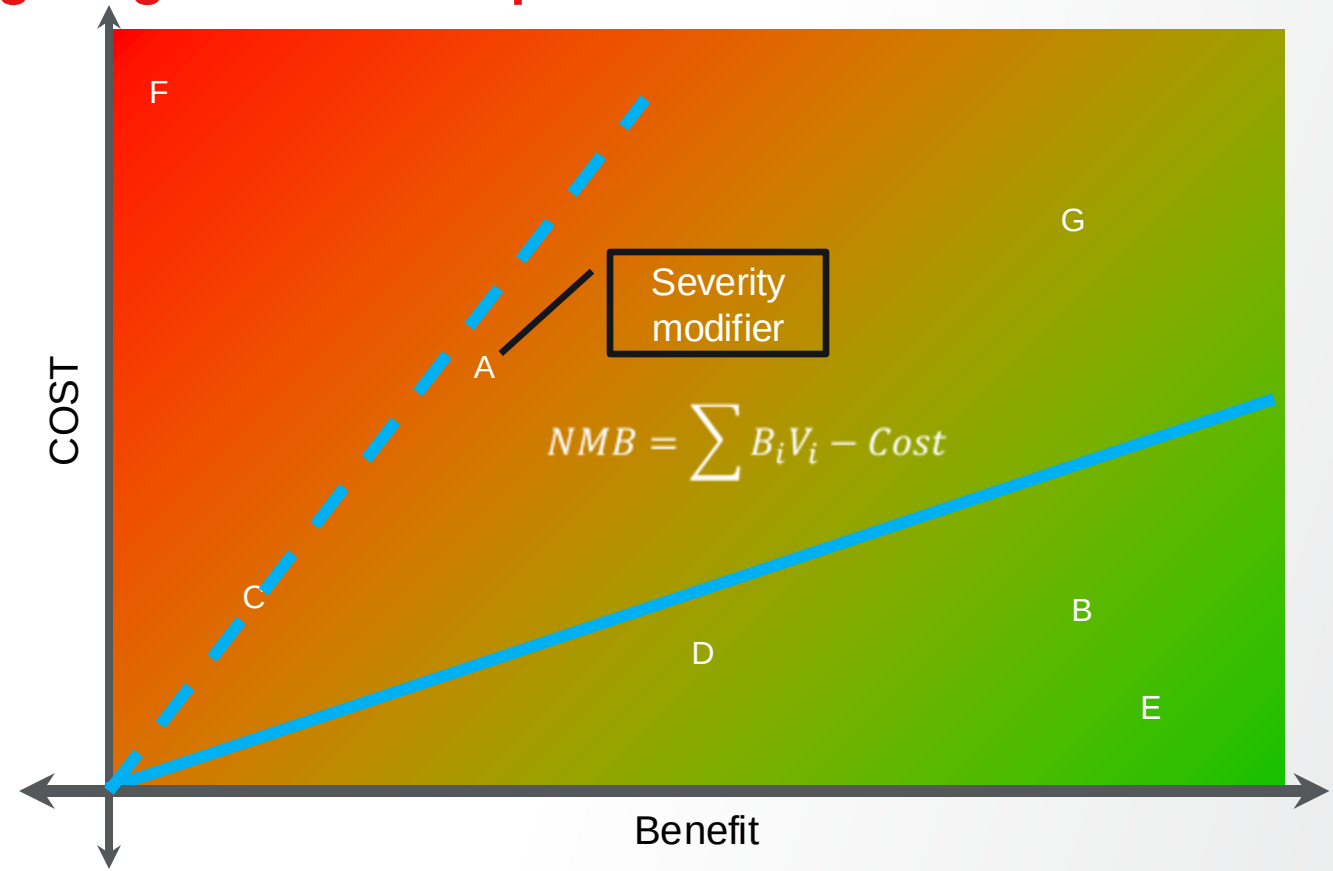
Feng X, Zahed H, Onwuka J, Callister ME, Johansson M, Etzioni R, Robbins HA. Cancer stage compared with mortality as end points in randomized clinical trials of cancer screening: a systematic review and meta-analysis. JAMA 2024;331:1910-17

What about the downside?

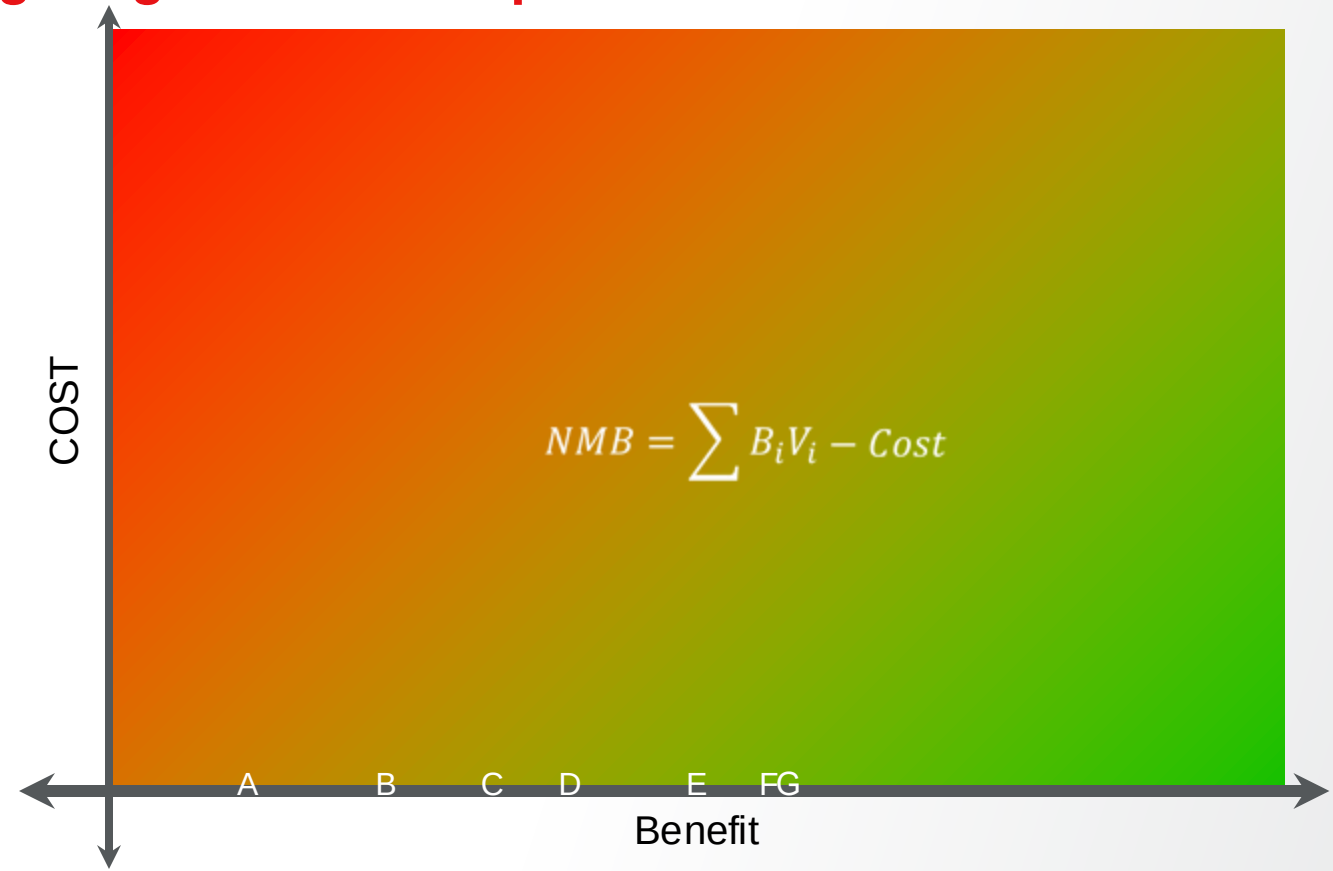
- Overdiagnosis
- False positives
  - Unnecessary work-up
  - Complications of work-up
  - Anxiety
  - Costs
  - Decreased willingness to continue screening
- False negatives
  - Delayed diagnosis
  - Inappropriate reassurance
  - Failure to seek care if symptoms develop
  - Incorrect assessment of risk
  - No change in risky behaviours

Modeling screening for cancer is complex and requires many assumptions and extrapolations!

Aggregating across multiple indications



Aggregating across multiple indications



Factors other than stage

BJC

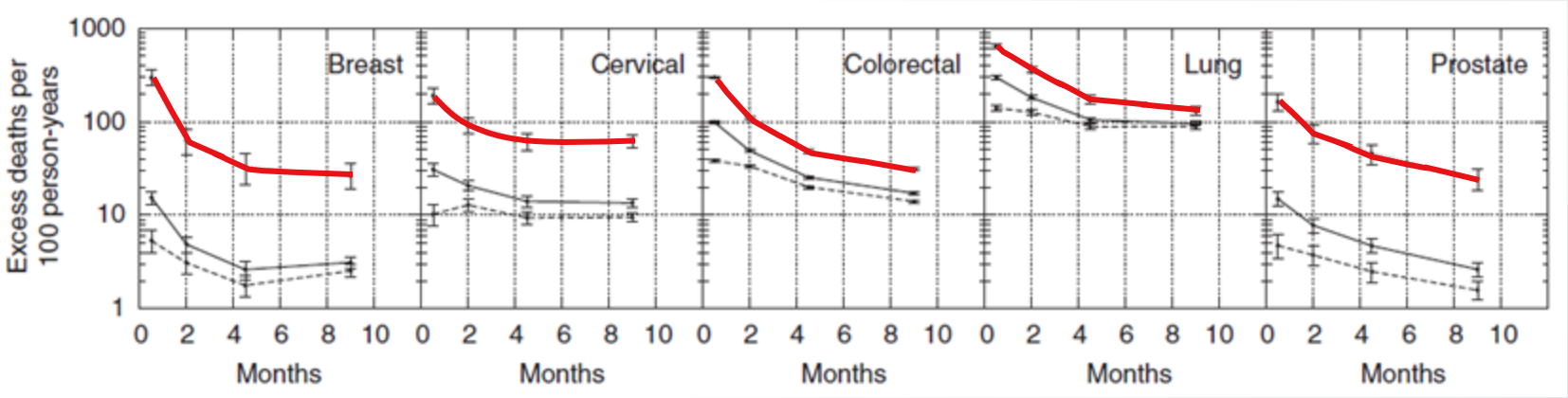
British Journal of Cancer (2013) 109, 2027–2034 | doi: 10.1038/bjc.2013.569

Keywords: diagnosis; pathways; referral; survival; emergency; route

Emergency presentation of cancer and short-term mortality

S McPhail*[,1], L Elliss-Brookes[1], J Shelton[1], A Ives[2], M Greenslade[2], S Vernon[3], E J A Morris[4] and M Richards[5]

"In summary, EP is a strongly predictive leading indicator of
short-term mortality following cancer diagnosis."



McPhail S et al. Emergency presentation of cancer and short-term mortality. British J Cancer 2013;109: 2027–34.

Conclusion

- Screening for cancer “makes sense”, but
- Demonstrating it reduces mortality is difficult
  - Trials need to be very large
  - Long duration
- Modeling is required to inform timely decisions
- Simulating the trajectory of screened cancers is also very difficult
  - Evidence is mainly from clinically diagnosed cancers
  - Cancer is a continuous process, but data are discretized
  - Relations may not apply or require modification
  - If there are indolent cancers, clinical data won’t encompass them
- There are some downsides to screening that need to be modeled
- MCED introduces additional considerations.

Thank you

GRAIL

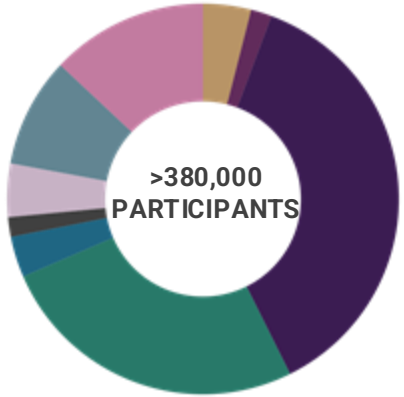
Questions?

Appendix

GRAIL Clinical Development Program

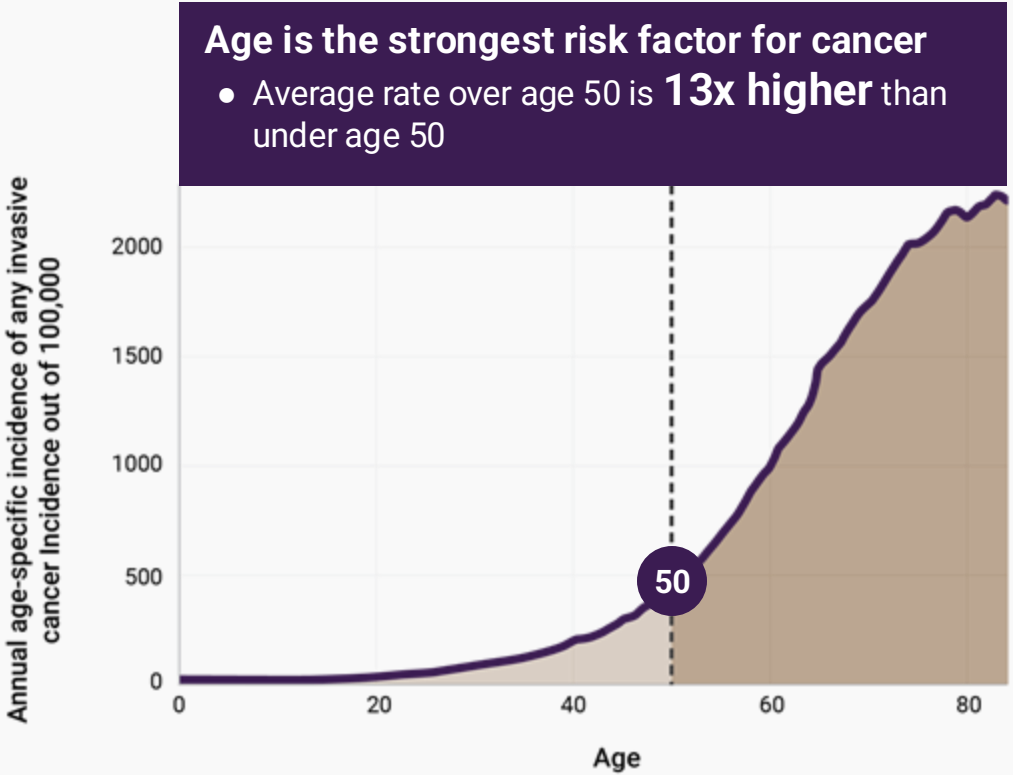
Test Development, Validation, and Implementation in Population-Scale Studies

1	**CCGA** (n=15,254)	**Develop and validate a cell-free DNA-based MCED test** *Enrollment: complete, published*	*Annals of Oncology* and *Cancer Cell* 2020-2023
2	**PATHFINDER** (n=6,662)	**Evaluate clinical implementation and perceptions of MCED test** *Enrollment: complete, published*	*The Lancet* 2023
3	**SYMPLIFY** (n=6,242)	**Assess MCED test in individuals with signs/symptoms of cancer** *Enrollment: complete, published*	*Lancet Oncology* 2023
4	**NHS-GALLERI** (n≈142,321)	**Assess clinical utility of MCED for population screening in the UK** *Enrollment: complete*	
5	**STRIVE** (n=99,481)	**Evaluate MCED test performance in women to detect invasive cancers**[a] *Enrollment: complete*	
6	**SUMMIT** (n=13,035)	**Clinical validation in individuals at high risk of lung cancer** *Enrollment: complete*	
7	**REFLECTION** (n≈17,000)	**Assess experience/clinical outcomes in real-world setting** *Enrollment: ongoing*	
8	**PATHFINDER 2** (n≈35,000)	**Evaluate MCED test performance in eligible screening population** *Enrollment: completed*	
9	**REACH** (n≈50,000)	**Understand health equity impact of Galleri in a Medicare population** *Enrollment: ongoing*	



[a]In women undergoing mammography screening. [b]Study not yet available at clinicaltrials.gov.
n≈ indicates approximate enrollment.
CCGA, Circulating Cell-free Genome Atlas; DNA, deoxyribonucleic acid; MCED, multi-cancer early detection; UK, United Kingdom.

Age is the strongest risk factor for cancer



Other risk factors include:

- Current smoking or time since quitting
- Personal history of cancer
- Family history of cancer
- Higher body mass index

Patel AV, et al. Key risk factors for the relative and absolute 5-year risk of cancer to enhance cancer screening and prevention. Cancer. 2022;128(19):3502-3515. doi: 10.1002/cncr.34396.Data: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database Incidence - SEER Research Limited-Field Data, 21 Registries, Nov 2020 Sub (2000-2018) - Linked To County Attributes -Time Dependent (1990-2018) Income/Rurality, 1969-2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission. Risk Factor Data on file: American Cancer Society Cancer Prevention Studies II/III

Desirable characteristics of a multi-cancer early detection test[1-3]

Screens for many of the deadliest cancers

…that lack recommended screening today

High positive predictive value and a low false-positive rate

…to limit unnecessary workups

Predicts the origin of the cancer signal

…to help guide diagnostic work-up

Supported by large-scale clinical studies in the intended-use population

1 Hackshaw A, et al. Cancer Cell. 2022;40(2):109-113. 2 Jamshidi A, et al. Cancer Cell. 2022; 40:1537-49. 3 Ahlquist DA. NPJ Precis Oncol. 2018;2:23.

The Circulating Cell-Free Genome Atlas (CCGA): >15K Participant Case-Control Study

Prospective, multicenter, case-control, observational study with longitudinal follow-up

Study Goals

- **Develop and validate a blood-based MCED test analyzing plasma cell-free DNA (cfDNA)**
- Detect shared cancer signal across multiple cancer types & simultaneously predict their signal origin

Study Design

15,254 participants with/without cancer

142 sites in the US and Canada

Blood samples
all participants

Tissue samples
cancer only

Follow-up for 5 years
(vital status, cancer status)

cfDNA, cell-free DNA; MCED, multi-cancer early detection test.

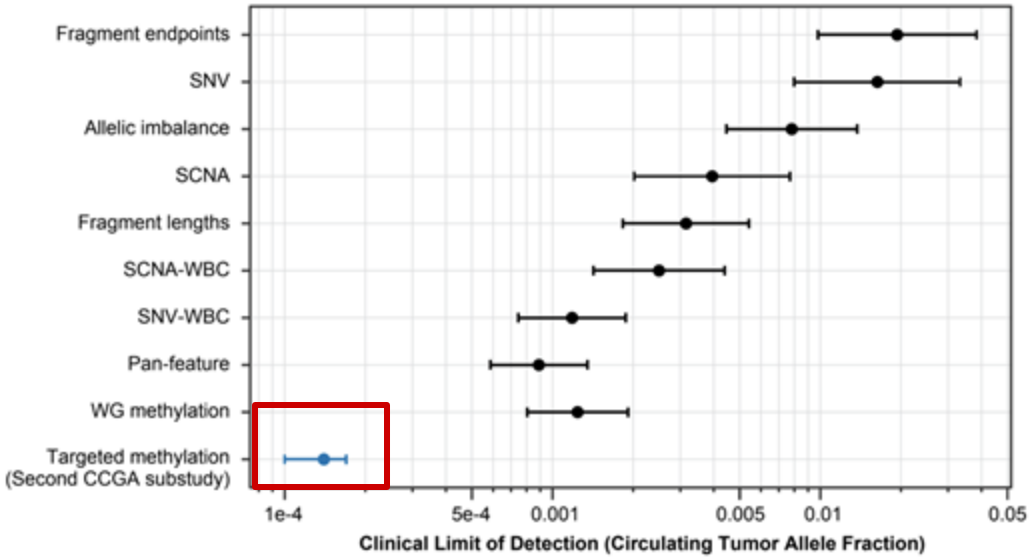
Klein E, et al. *Ann Oncol*. 2021;32(9):1167-1177. DOI: 10.1016/j.annonc.2021.05.806.

Methylation Pattern is a Powerful, Shared Cancer Signal

Blinded performance on ~1000 participants for three parallel assays

Whole genome methylation had

- Similar or better detection performance vs. 8 other classifiers
- With significantly better (80%+) CSO accuracy
- Postulated room for improvement using targeted sequencing
  - Validated in CCGA2



*clinical LoD: circulating tumor fraction amount at which the probability of detecting a cancer case is 50%

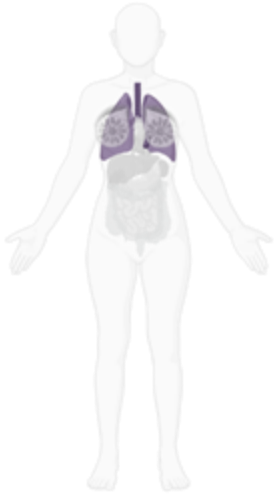
Jamshidi A, Liu MC, Klein EA, et al. Evaluation of cell-free DNA approaches for multi-cancer early detection. Cancer Cell. 2022;40(12):1537-1549.e12. doi: 10.1016/j.ccell.2022.10.022.

Diagnostic Resolution was Achieved by CSO-Directed Evaluation in 78% of Participants

An analysis of PATHFINDER study results for participants with a cancer signal detected by MCED testing

78%

PARTICIPANTS ACHIEVING DIAGNOSTIC RESOLUTION BY CSO-DIRECTED INITIAL EVALUATION (25/32)



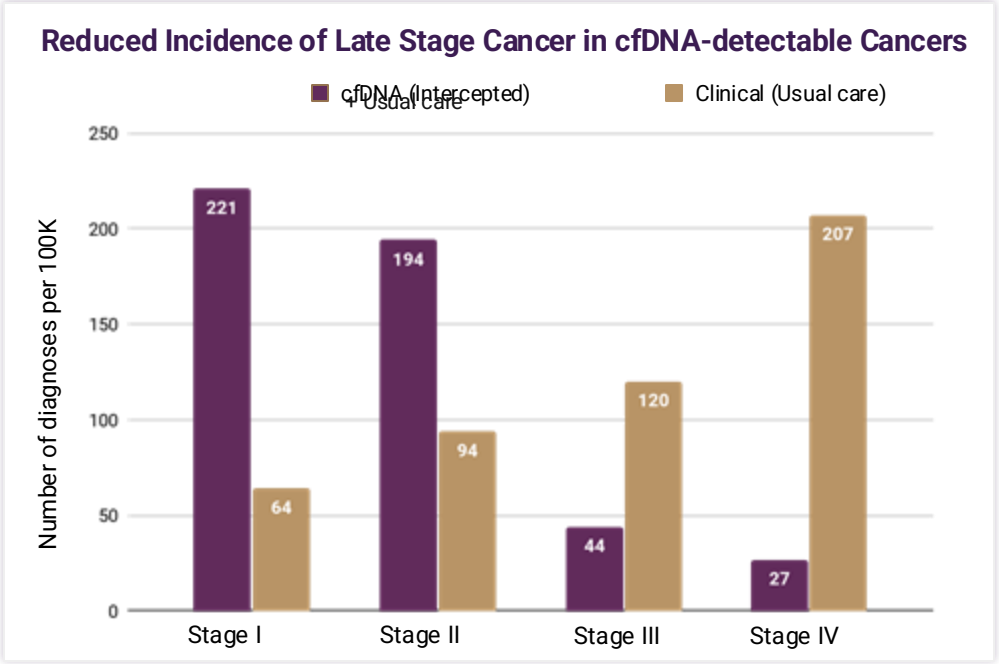
CSO, cancer signal origin.

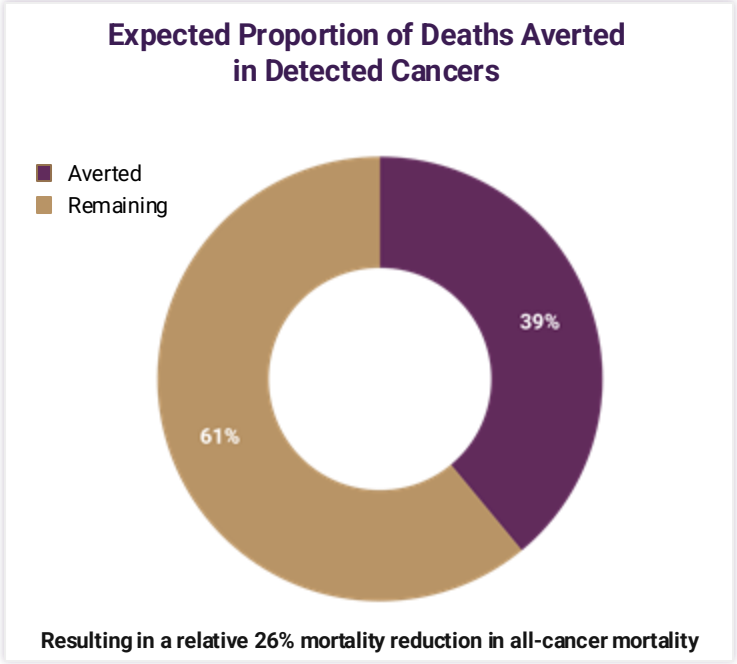
[a]Initial diagnostic evaluation/workup is defined as any diagnostic procedure conducted prior to diagnostic resolution or prior to a time interval of 3 months or longer without any workup.

Klein EA et al. Clinical Evaluation of Cancer Signal Origin (CSO) Prediction and Diagnostic Resolution Following Multi-Cancer Early Detection Testing Poster presented at ASCO Annual Meeting. June 2-6, 2023.

GRAIL

Early Cancer Detection Goal: Reduce the Incidence of Late Stage Cancer





Based on modeled data of GRAIL's MCED test in elevated risk population age 50–79 years. cf-DNA detectable cancers represent 68 percent

Hubbell E et al. *Cancer Epidemiol Biomarkers Prev.* 2021;30:460-468. cfDNA, cell-free DNA; K, thousand; MCED, multi-cancer early detection; SEER, Surveillance, Epidemiology, and End Results. Based on data from SEER18 (2006-2017) in the United States, all cancer incidence. Adding the GRAIL's MCED test to usual care (based on modeled data). Assumes long-term screening results with optimized screening interval.

GRAIL

**Usual care represents real-world cancer diagnostic processes including screening, incidental detection, and symptomatic workup.

Cancer Signal Detected Results

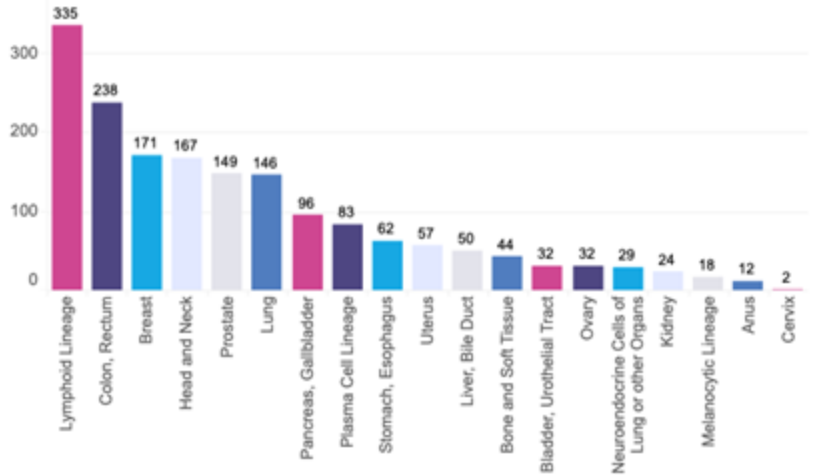
Galleri experience through the first 200,000 tests in clinical practice

68%

out of 1747 reported **“Cancer Signal Detected”** results had predicted cancer signal origins representing **cancers without recommended screening options**

The top* cancer signal origins reported represent a variety of cancer types

Distribution of Top Predicted Cancer Signal Origins (N=1747)



Galleri is a screening test and does not diagnose cancer. Diagnostic testing is needed to confirm cancer. If a cancer signal is detected, Galleri can predict the tissue type or organ associated with the signal to help healthcare providers determine next steps. The Galleri test does not detect a signal for all cancers and not all cancers can be detected in the blood. False positive and false negative results do occur.

*Out of 1747 Cancer Signal Detected cases, 623 had one Cancer Signal Origin (CSO) reported and 1124 had two CSOs reported. This representation is limited to the top predicted Cancer Signal Origin cases. Data on file GA-2022-0078

Early Real-World Experience With Repeat MCED Testing in 5,794 individuals

Cancers diagnosed after repeat testing were **mostly early stage and without screening options**

Of the 6 confirmed cancers with known stage, 1 was stage 0, 4 were stage I, and 1 was stage IV

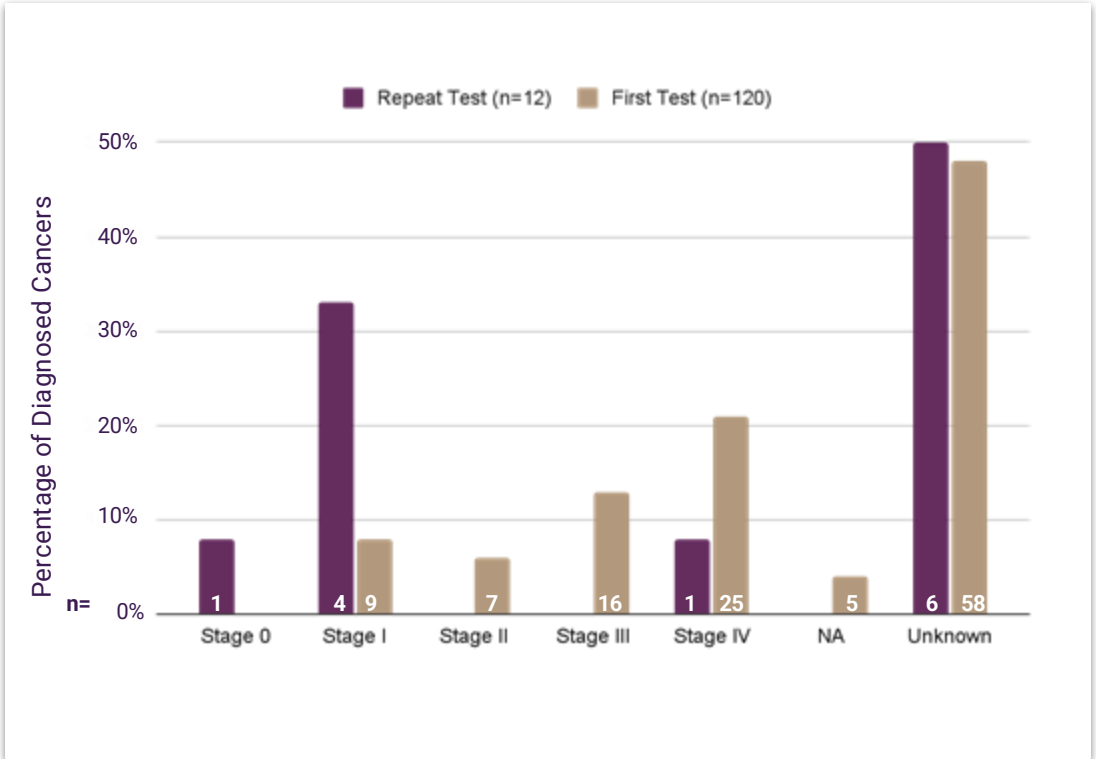
Cancer signal origin accuracy was 100% and helps direct diagnostic workup

Annual testing **may improve early detection of multiple cancer types**, including those currently **without** USPSTF-recommended screening

Abrams R, et al. Early Real-World Experience With Repeat Multi-Cancer Early Detection (MCED) Testing, Presented at American Association for Cancer Research (AACR) Annual Meeting April 5-10, 2024. San Diego, CA

Reduced Percentage of Stage IV Diagnoses With Repeat Testing

Repeat testing may improve early detection of multiple cancer types, including those currently without USPSTF-recommended screening[a,b]



[a]N values shown at bottom of each column. [b]NA, not applicable or no AJCC/Rai stage expected. Patients for whom the practice has not reported cancer staging are captured as Unknown.

Abrams R, et al. Early Real-World Experience With Repeat Multi-Cancer Early Detection (MCED) Testing, Presented at American Association for Cancer Research (AACR) Annual Meeting April 5-10, 2024. San Diego, CA

Important Safety Information

The Galleri test is recommended for use in adults with an elevated risk for cancer, such as those aged 50 or older. The Galleri test does not detect all cancers and should be used in addition to routine cancer screening tests recommended by a healthcare provider. Galleri is intended to detect cancer signals and predict where in the body the cancer signal is located. Use of Galleri is not recommended in individuals who are pregnant, 21 years old or younger, or undergoing active cancer treatment.

Results should be interpreted by a healthcare provider in the context of medical history, clinical signs and symptoms. A test result of No Cancer Signal Detected does not rule out cancer. A test result of Cancer Signal Detected"requires confirmatory diagnostic evaluation by medically established procedures (e.g. imaging) to confirm cancer.

If cancer is not confirmed with further testing, it could mean that cancer is not present or testing was insufficient to detect cancer, including due to the cancer being located in a different part of the body. False-positive (a cancer signal detected when cancer is not present) and false-negative (a cancer signal not detected when cancer is present) test results do occur. **Rx only.**

Laboratory / Test Information

The GRAIL clinical laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and accredited by the College of American Pathologists. The Galleri test was developed, and its performance characteristics were determined by GRAIL. The Galleri test has not been cleared or approved by the Food and Drug Administration. GRAIL's clinical laboratory is regulated under CLIA to perform high-complexity testing. The Galleri test is intended for clinical purposes.