Towards a Paradigm Shift for Cancer Screening Trials in the MCED Era

Peter Sasieni

Disclosure

Paid advisory roles:

- GRAIL (on-going)
- NSV (on-going)
- Roche Molecular Diagnostics (one-off)

Share ownership

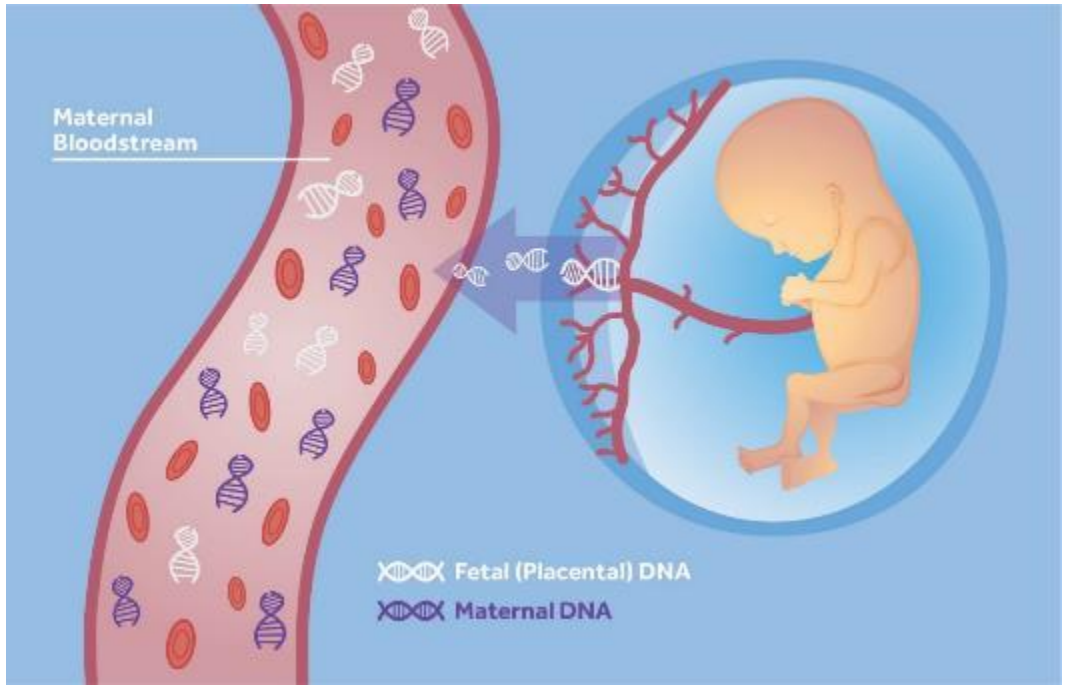
- None

The challenge – progress over the last 30 years has been depressingly slow

Multi-cancer early detection tests

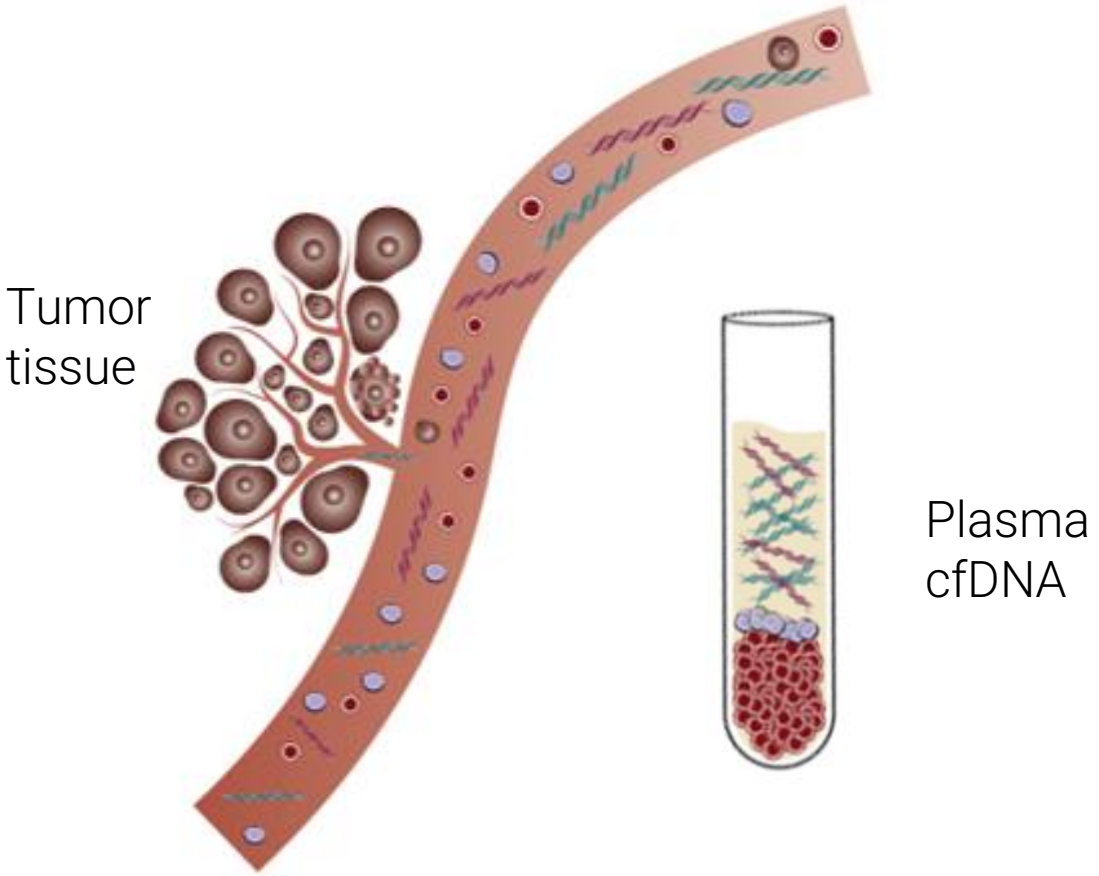
Using cutting-edge DNA technology

- Looking for cell-free DNA in blood
- Antenatal screening
  - At the end of the first trimester 12% of cfDNA in the mother's blood comes from the foetus
- Similarly, a small proportion of cfDNA in the blood of someone with cancer will come from the tumour



Multi-Cancer Early Detection (MCED) tests

A small proportion of cfDNA in the blood of someone with cancer will come from the tumour

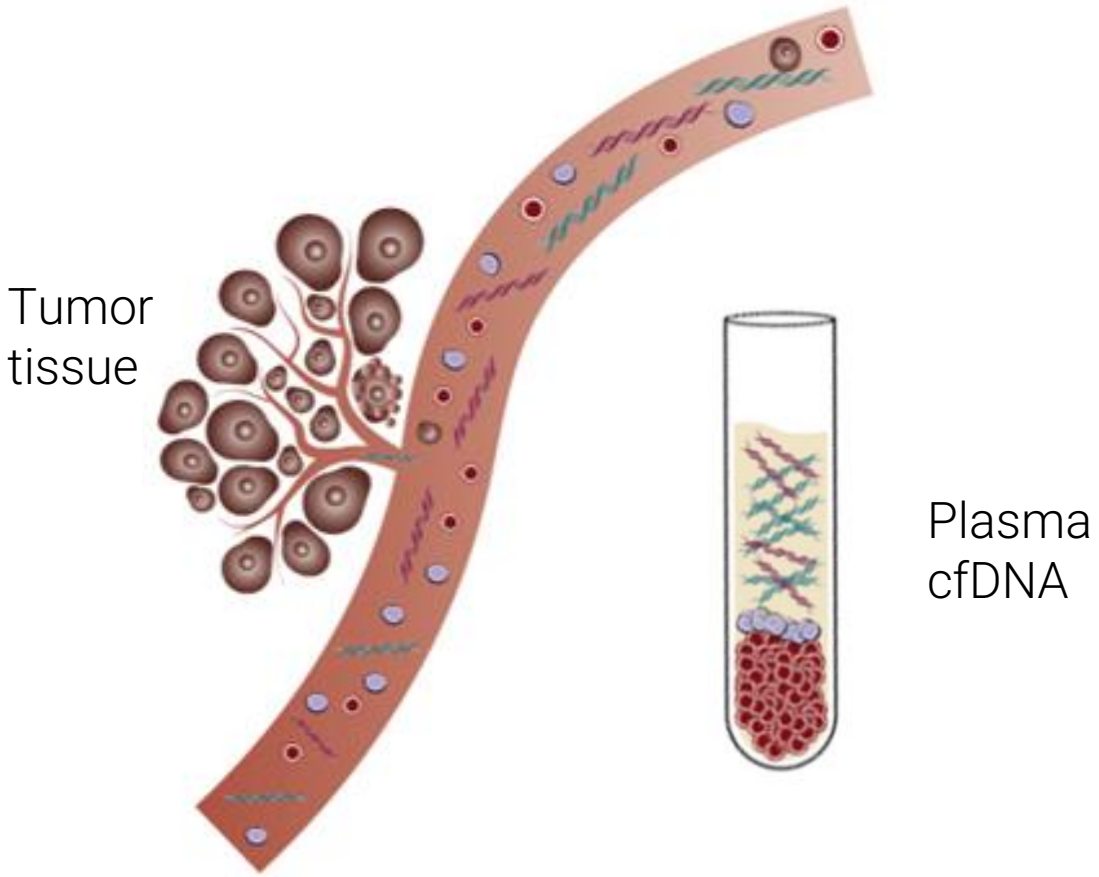


- Tumours shed nucleic acids into blood and other body fluids, carrying cancer-specific information
- Patterns in cell-free DNA (cfDNA) isolated from peripheral whole blood
- A pattern associated with cancer = ‘Cancer Signal Detected’
- A pattern associated with different organs

Figure from Liu MC, et al. *Ann Oncol*. 2020;31(6):745-759. DOI: 10.1016/j.annonc.2020.02.011.

Galleri™: a Multi-Cancer Early Detection (MCED) test

Tumours shed nucleic acids into blood and other body fluids, carrying cancer-specific information

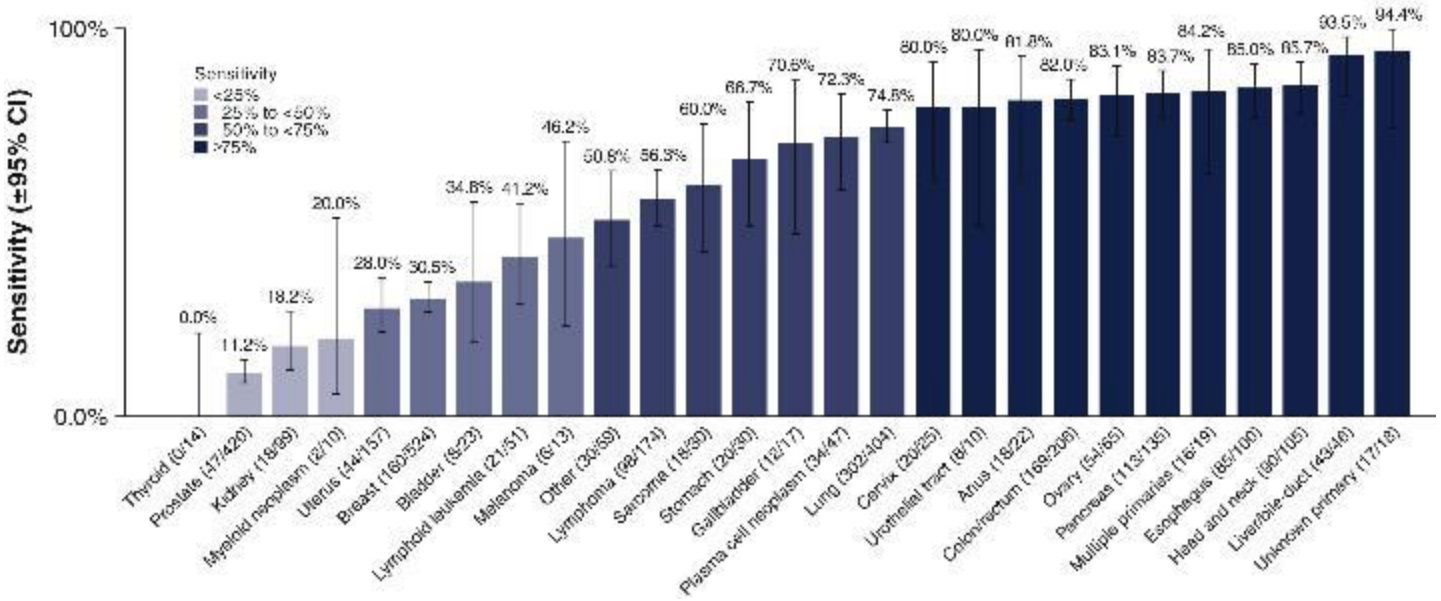


- Galleri recognises methylation patterns in cell-free DNA (cfDNA) isolated from peripheral whole blood
- A methylation pattern associated with cancer = ‘Cancer Signal Detected’
- Can detect cancer when only 0.02% of cfDNA contains variant alleles
- When a cancer signal is detected, the report will include one or two predicted ‘Cancer Signal Origin’ (CSO)

Figure from Liu MC, et al. *Ann Oncol*. 2020;31(6):745-759. DOI: 10.1016/j.annonc.2020.02.011.

CCGA3: Results

- Specificity: 99.5% (99.0-99.8%) [n=1254]
- Sensitivity: 51.5% (49.6-53.3%) [n=2823]



	All cancers	12 pre-specified
Stage I	17%	37%
Stage II	40%	70%
Stage III	77%	87%
Stage IV	90%	93%

Sensitivity by stage

12 = anus, bladder, colorectal, oesophagus, H&N, liver, lung, lymphoma, ovary, pancreas, multiple myeloma, stomach

Cancer signal of origin

- Top signal of origin correctly predicted cancer site in 89% of cases with a positive test
  - CSO was less good at:
    - Cervix (signal was often for anus or head & neck)
    - Ovary (signal often uterus)
  - Use of 2nd CSO would improve accuracy of prediction

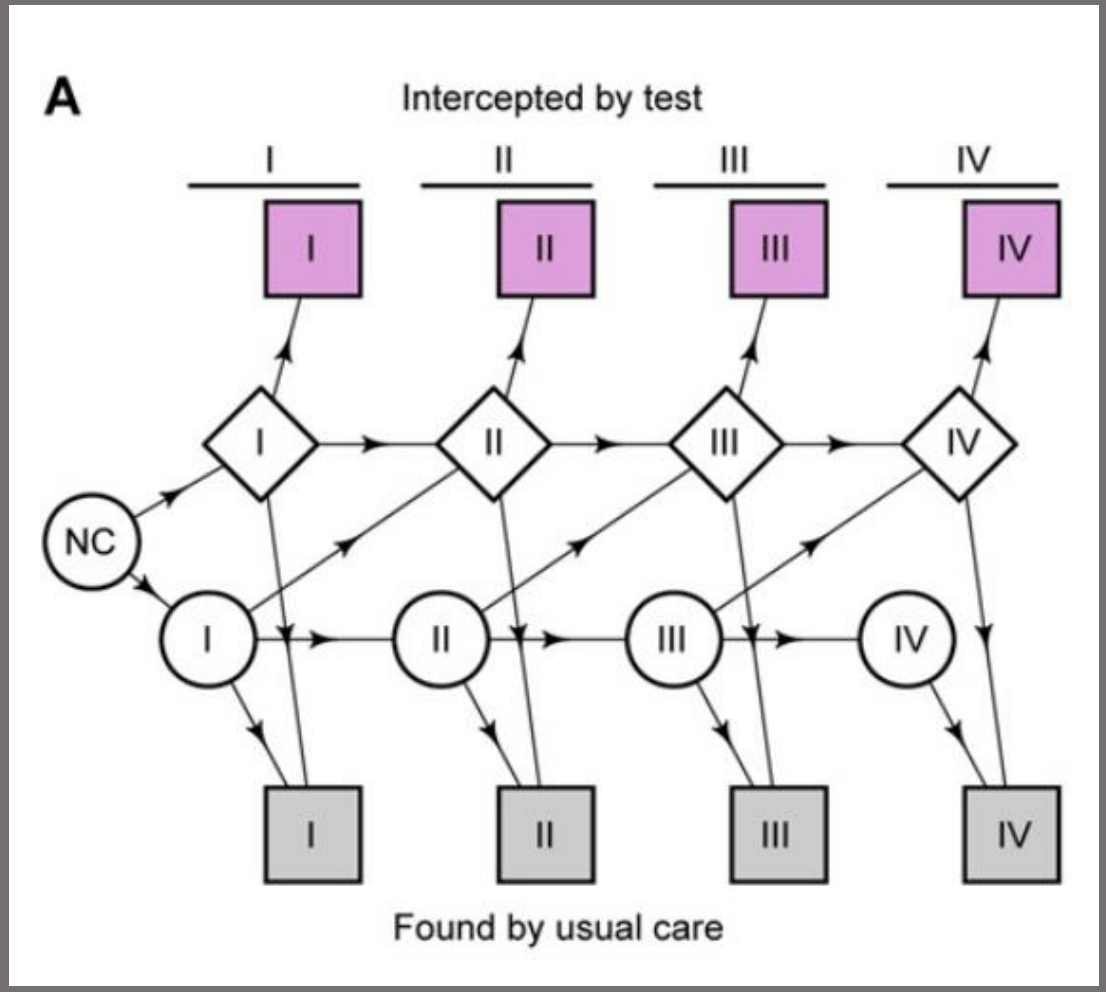
Principles for clinical trial design

Principle

In the absence of empirical evidence use modelling to determine sample size

Computer modelling what might happen

	Usual care	MCED screening	Prevented
Advanced cancers	455	275	180 (40%)
Cancer deaths (within 5 years)	396	325	71 (18%)



Principle

Take advantage of electronic health records

Unbiased ascertainment of major study outcomes (Sir Rory Collins)

- Missing data have little impact if this is unbiased with respect to allocation
- Adjudication of study outcomes adds substantial cost, but typically little gain
- Put greater reliance on comparison with the randomly-allocated control group

More Trials
@More_Trials

Principle

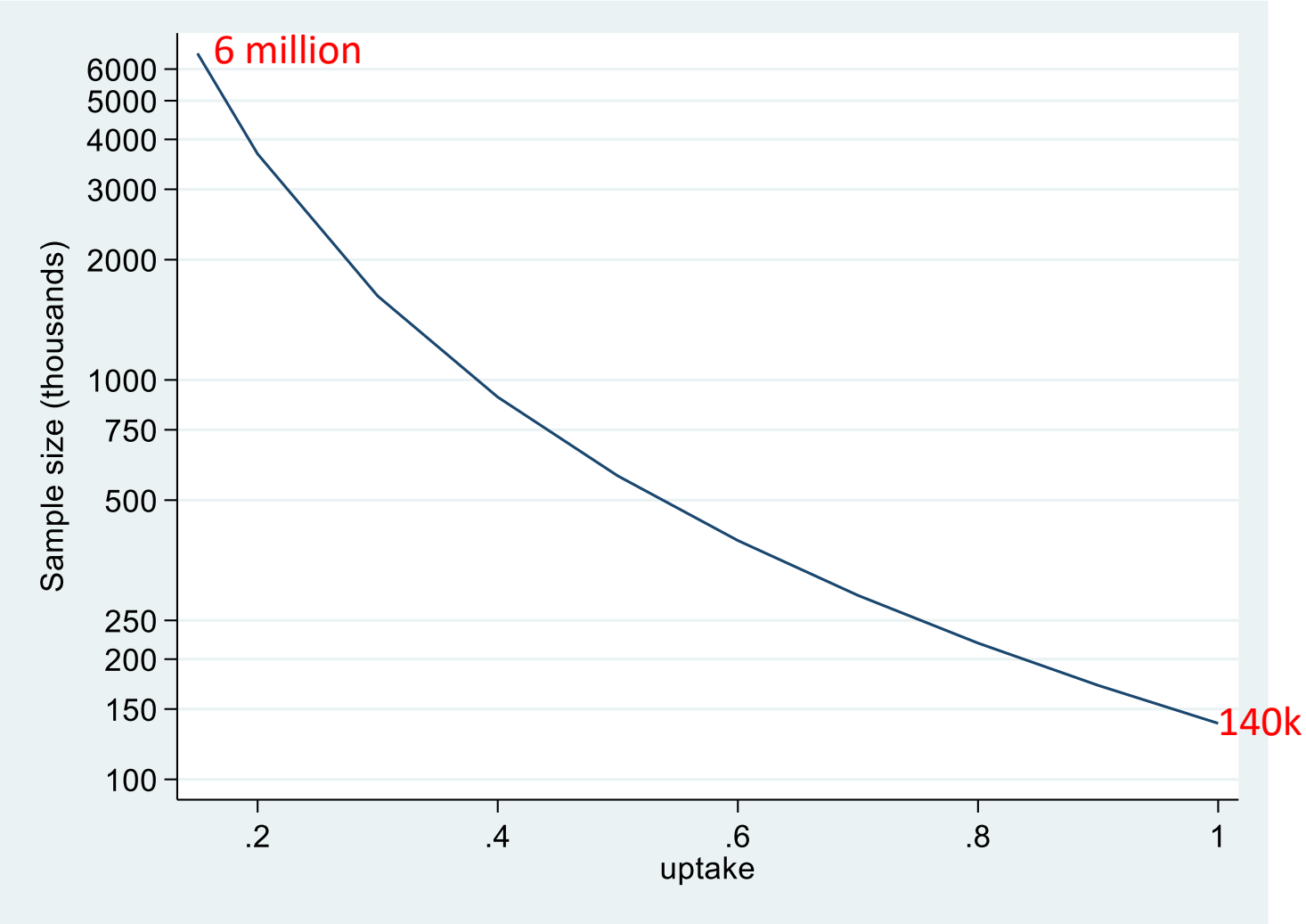
In trials of screening, it is important to consider the impact of non-compliance and contamination on the power of the trial and, where necessary, to design the trial to minimise contamination and non-compliance

Example: CAP trial of prostate screening by PSA

- Cluster Randomized Trial
- 415,357 men randomized
- 36% in the intervention group had PSA testing
- 10-15% in the control arm had PSA testing (10 years)
- Results: Deaths from prostate cancer (549 vs 647)
  - ITT (Effectiveness): RR=0.96 [95% CI: 0.85 to 1.08]
  - Efficacy: RR=0.93 [95% CI: 0.67 to 1.29]

Martin et al. JAMA 2018

Sample size as a function of screening uptake



Design considerations for cancer screening trials

Concealed vs Revealed

- Test everyone for but only tell those randomised to intervention the results of the test!
  - 100% compliance!

Test vs store

- Don’t actually test everyone in the control sample – simply store the sample for future analysis
  - More ethical than ignoring the test result?
  - Saves money

Test vs Store: Efficient Analysis

- Only look at those who die of cancer AND had a positive test result
  - Screening only makes a difference in those who test positive
  - Look at those whose samples were positive to see whether acting on the result makes a difference
- Can use the same idea to study overdiagnosis
  - Compare all cancers diagnosed during follow-up who were test positive at baseline

Number needed : MCED screening

	Advanced cancer	Cancer Mortality
Pragmatic (15% uptake)	6 million	
Randomise at clinic	140,000	300,000
Retrospective test positive		140,000

Healthy Volunteer Effect

Healthy volunteers can adversely impact on power

- UKCTOCS: Burnell et al. Trials 2011
  - Mortality: Expected 12,247; Observed 4,569; SMR 0.37
    - Year 1 mortality: SMR 0.19
  - Cancer mortality: Expected 4419; Observed 2469; SMR 0.56
  - Cancer incidence: Expected 4610; Observed 4131; SIR 0.88

  - Ovarian cancer SMR (Apr 2015) 0.58, but increasing.
  - Estimated impact on power: reduced from 80% to 54%

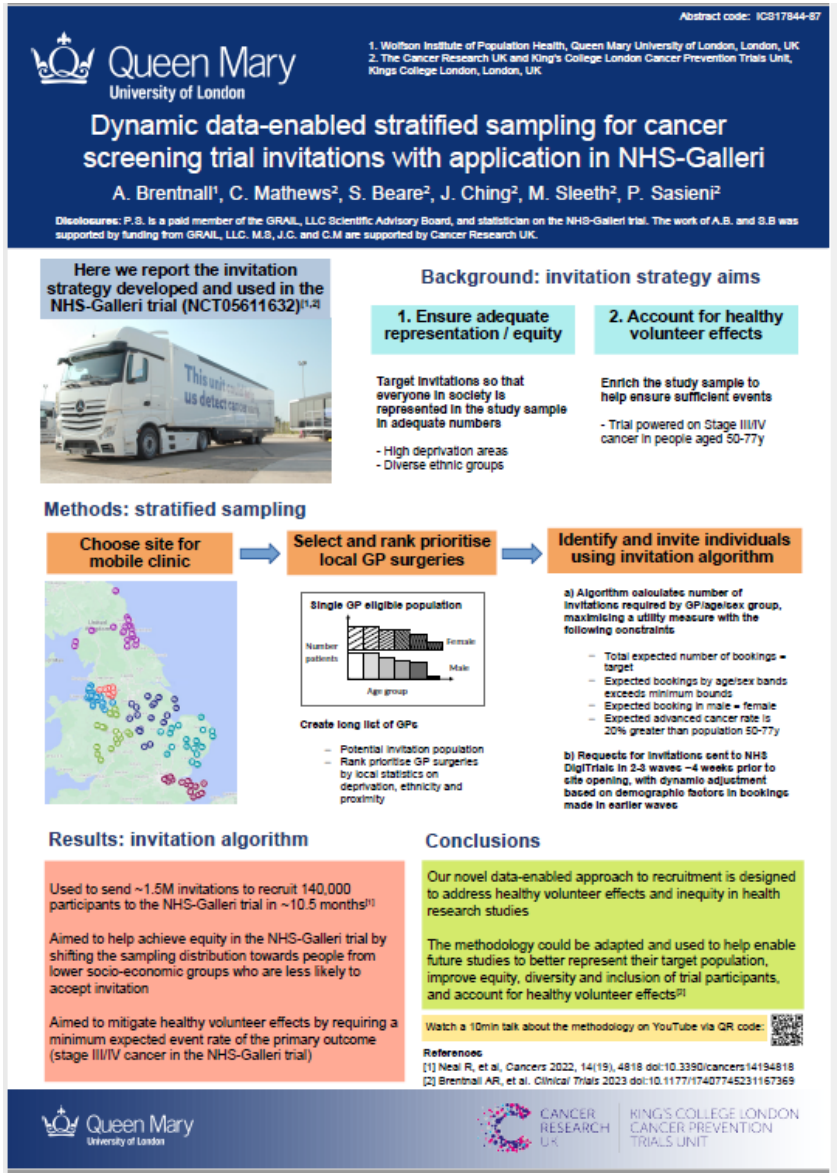
Compensating for healthy volunteers

1. Ensure representativeness in terms of SES / deprivation (since it is the biggest determinant of life-expectancy)
   - Age-standardised cancer incidence IMD 1: 690/100k
   - Age-standardised cancer incidence IMD 5: 583/100k

2. Tilt the age distribution of recruited participants towards older ages
   - Cancer mortality aged 50-59: 0.16%
   - Cancer mortality aged 70-79: 4.05%

Dynamic data-enabled stratified sampling for cancer screening trial invitations with application in NHS-Galleri

ICS17844-87



Abstract code: ICS17844-87

Queen Mary University of London

1. Wolfson Institute of Population Health, Queen Mary University of London, London, UK
2. The Cancer Research UK and King's College London Cancer Prevention Trials Unit, Kings College London, London, UK

Dynamic data-enabled stratified sampling for cancer screening trial invitations with application in NHS-Galleri

A. Brentnall[1], C. Mathews[2], S. Beare[2], J. Ching[2], M. Sleeth[2], P. Sasieni[2]

Disclosures: P.S. is a paid member of the GRAIL, LLC Scientific Advisory Board, and statistician on the NHS-Galleri trial. The work of A.B. and S.B was supported by funding from GRAIL, LLC. M.S, J.C. and C.M are supported by Cancer Research UK.

Here we report the invitation strategy developed and used in the NHS-Galleri trial (NCT05611632)[1,2]

Background: invitation strategy aims

1. Ensure adequate representation / equity

Target invitations so that everyone in society is represented in the study sample in adequate numbers

- High deprivation areas
- Diverse ethnic groups

2. Account for healthy volunteer effects

Enrich the study sample to help ensure sufficient events

- Trial powered on Stage III/IV cancer in people aged 50-77y

Methods: stratified sampling

Choose site for mobile clinic → **Select and rank prioritise local GP surgeries** → **Identify and invite individuals using invitation algorithm**

Create long list of GPs

- Potential invitation population
- Rank prioritise GP surgeries by local statistics on deprivation, ethnicity and proximity

a) Algorithm calculates number of invitations required by GP/age/sex group, maximising a utility measure with the following constraints

- Total expected number of bookings = target
- Expected bookings by age/sex bands exceeds minimum bounds
- Expected booking in male = female
- Expected advanced cancer rate is 20% greater than population 50-77y

b) Requests for invitations sent to NHS DigiTrials in 2-3 waves ~4 weeks prior to site opening, with dynamic adjustment based on demographic factors in bookings made in earlier waves

Results: invitation algorithm

Used to send ~1.5M invitations to recruit 140,000 participants to the NHS-Galleri trial in ~10.5 months[1]

Aimed to help achieve equity in the NHS-Galleri trial by shifting the sampling distribution towards people from lower socio-economic groups who are less likely to accept invitation

Aimed to mitigate healthy volunteer effects by requiring a minimum expected event rate of the primary outcome (stage III/IV cancer in the NHS-Galleri trial)

Conclusions

Our novel data-enabled approach to recruitment is designed to address healthy volunteer effects and inequity in health research studies

The methodology could be adapted and used to help enable future studies to better represent their target population, improve equity, diversity and inclusion of trial participants, and account for healthy volunteer effects[2]

Watch a 10min talk about the methodology on YouTube via QR code:

References
[1] Neal R, et al. *Cancers* 2022, 14(19), 4818 doi:10.3390/cancers14194818
[2] Brentnall AR, et al. *Clinical Trials* 2023 doi:10.1177/17407745231167369

Queen Mary University of London

CANCER RESEARCH UK | KING'S COLLEGE LONDON CANCER PREVENTION TRIALS UNIT

Primary endpoint

Cancer-specific mortality or stage III+IV incidence

Cancer-specific mortality

- Standard endpoint
- Robust
- Clear relevance to patients

- Takes a long time
- Depends on treatment
- Rarer outcome so requires larger trial

Stage III+IV incidence

- Not usually used
- Maybe be poorly recorded
- Clear relevance to patients
  - Economic advantage of avoiding late-stage disease
  - Clinical advantage of only having early stage disease even if would not have died from late stage disease

- Typically 1-5 years before death
- Independent of treatment
- More common outcome so requires smaller trial

Results from NELSON

	Lung cancer mortality	Stage III+ lung cancer incidence
Year 10 Rate ratios	0.76 (0.62-0.94)	0.71 (0.57-0.88)

de Koning et al NEJM 2020

Results from Göteborg randomized population-based prostate cancer screening trial

	Prostate cancer mortality	Advanced prostate cancer	High-risk+ prostate cancer
Year 22 Rate ratios	0.71 (0.55-0.91)	0.65 (0.50-0.86)	0.77 (0.65-0.91)

Frånlund et al. The Journal of Urology. April 2022

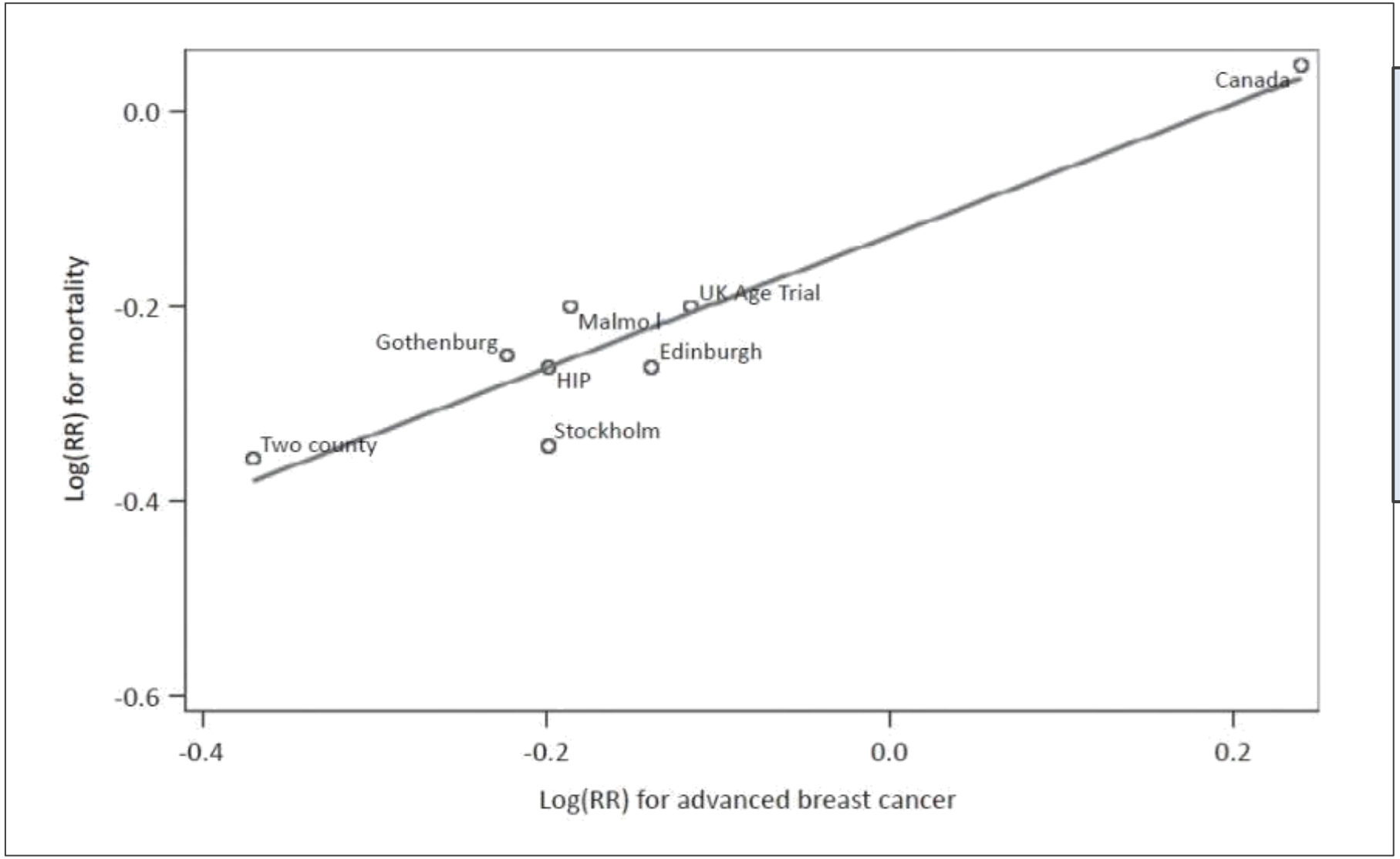
Results from UKCTOCS randomized population-based ovarian cancer screening trial

	Ovarian cancer mortality	Stage III+IV ovarian cancer
MMS vs control	0.96 (0.83-1.10)	0.89 (0.78-1.02)
USS vs control	0.94 (0.82-1.08)	1.00 (0.87-1.13)

Menon et al. Lancet. 2021

Breast cancer mortality vs incidence of advanced disease

Plot of log(RR) for mortality against log(RR) for advanced disease in breast cancer screening RCTs



The greater the reduction in risk of advanced breast cancer, the greater the mortality reduction

Tabar et al. Breast J 2015

NHS-Galleri Trial

- MCED Screening RCT
- Funding contract executed May 2021
- Achieved FPI 31st Aug 2021
- Nearly 1.5 million invites sent-out working with NHS DigiTrials
- 140k recruitment reached in July 2022 (10.5 months)
  - Representative SES diversity
  - Ethnicity ‘boost’

NHS-Galleri Trial of Multi-Cancer Early Detection: Design and Equitable Study Recruitment Tactics

ICS17779-94

ICS17779-94

NHS-Galleri Trial of Multi-Cancer Early Detection: Design and Equitable Study Recruitment Tactics

ICSN 2023
June 21-23, 2023
Turin, Italy

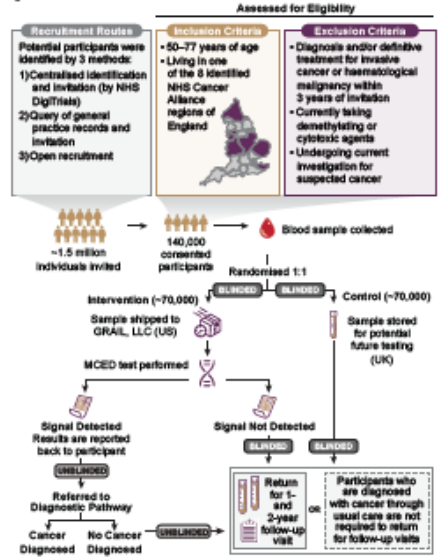
Christina A. Clarke Dur,[1] Charles Swanton,[2] Richard D. Neal,[3] Peter Johnson,[4] Nan Zhang,[5] Harpal Kumar,[6] Peter Sasieni[6]
[1]GRAIL, LLC, Menlo Park, California, USA; [2]University College London, London, UK; [3]University of Exeter, Exeter, UK; [4]NHS England, London, UK; [5]GRAIL Bio UK Ltd, subsidiary of GRAIL, LLC, London, UK; [6]King's College London, London, UK. | Corresponding author email: cclarke@grailbio.com

THE NHS-GALLERI TRIAL USED MULTIPLE ENRICHED ENROLMENT APPROACHES TO ENSURE REPRESENTATIVENESS IN STUDY RECRUITMENT, WITH THE GOAL OF ENROLLING A PARTICIPANT POPULATION REFLECTIVE OF THE GENERAL POPULATION AGED 50–77 YEARS IN ENGLAND.

Introduction: The NHS-Galleri trial (NCT05611632) is a randomised controlled trial (RCT) assessing the clinical utility of a multi-cancer early detection (MCED) test in an asymptomatic population alongside current screening programmes. The primary objective is to demonstrate a significant reduction in the incidence rate of stage III and IV cancers diagnosed in the intervention arm compared with the control arm 3–4 years after randomisation.[1]

Trial Design

Over 140,000 asymptomatic participants were enrolled in ~10.5 months by inviting ~1.5 million people aged 50–77 in select regions of England via the NHS DigiTrials service.



Participant follow-up data are accrued in routine NHS datasets.

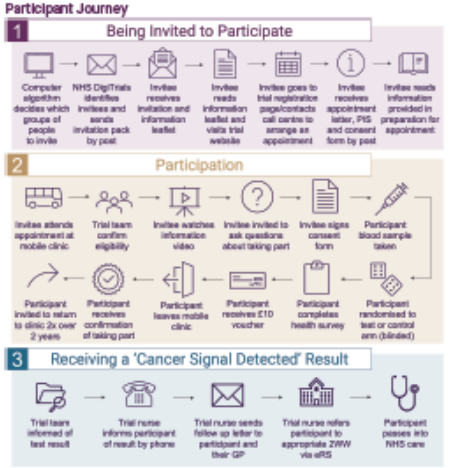
Enriched Enrolment Approaches

A variety of enriched enrolment approaches were used to recruit a representative* study population, including:

- Monitoring participant clinical and demographic factors, and dynamically adjusting invitation lists[2]
- Stationing mobile clinics in socioeconomically deprived and ethnically diverse areas
- Engaging with voluntary and community sector organisations in socioeconomically deprived and ethnically diverse communities to encourage enrolment
- Implementing measures to remove access barriers (eg, interpreters, wheelchair/step-free access)

*Defined as: including a reasonable absolute number of participants across sexes, neighbourhood-based socioeconomic groups, and major ethnic minority groups.

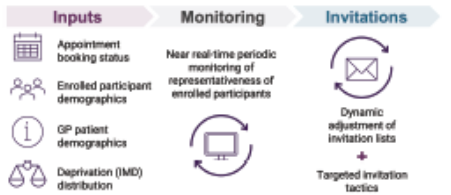
Participant Journey



2WW, two-week wait diagnostic pathway; eRS, e-referral system; GP, general practitioner; PIS, Participant Information Sheet.

Using specialised mobile clinics, peripheral blood is collected by routine venipuncture at up to three study visits one year ± six weeks apart, reflecting an annual screening approach.

Dynamic Targeting Of Invitations



The representativeness of enrolled participants compared with the general population aged 50–77 years was characterised and monitored during recruitment, and invitation lists were adjusted dynamically as needed.[2]

References: 1. Neal RD, et al. 2022. Cancers 14(18):4474. 2. Swanton C, et al. 2022. Clinical Trials.

Conclusions: The NHS-Galleri trial is the first RCT that is statistically powered to assess the clinical utility, including harms and benefits, of an MCED test alongside the standard of care. The trial aimed to enrol a representative population sample to promote health equity and to minimise 'healthy volunteer bias' observed in prior screening studies. The trial successfully used a number of enriched enrolment approaches to recruit a diverse participant group representative of the intended use population.

Disclosure: study funded by [illegible]

Primary endpoint

- Reduction in Stage III & Stage IV cancers within 3.0-4.0 years of the first blood draw
  - Provides read-out two-three years earlier than cancer-specific mortality
  - More robust than looking for an increase in early stage cancers
  - Clear relevance to patients

Sequential conditional testing

1. Test for reduction in stage III+IV cancers at 12 sites: lung, head and neck, colorectal, pancreas, myeloma/plasma cell neoplasm, liver/bile duct, stomach, oesophagus, anus, lymphoma, ovary, and bladder
2. If (and only if) $p<0.05$ (for prespecified 12), test for reduction in all stage III+IV cancers other than prostate cancers
3. If (and only if) $p<0.05$ (for all but prostate), test for reduction in all stage III+IV cancers

- Since additional testing is conditional on a significant result, there is no need to adjust p-value for multiple testing
- If anything there is a loss in power (for all cancers), but there is no gain in Type I errors

Secondary endpoint

- Reduction in cancers deaths in individuals with a cancer signal detected on their blood sample within 5.0-6.0 years of the first blood draw
  - Mortality endpoint
  - Leveraged to individuals in whom screening could make a difference
  - Only requires retrospective testing of samples from controls who die from cancer

NHS-Galleri Trial Design

Three rounds of annual screening

Provides information on both prevalent and incident screens

Passive follow-up of all participants through NHS Digital

NHS-Galleri Trial Design

Randomised controlled trial

- Necessary for robust causal inference

Concealed v revealed

- Ensures 100% compliance on first screen

Preserve blinding for most participants

- Likely to increase compliance with future screening rounds

NHS-Galleri Trial Design

140,000 volunteers aged 50-77

- Representative of the population of England

Bloods from half tested, others stored

- Control bloods permit retrospective testing to know “what would have happened”

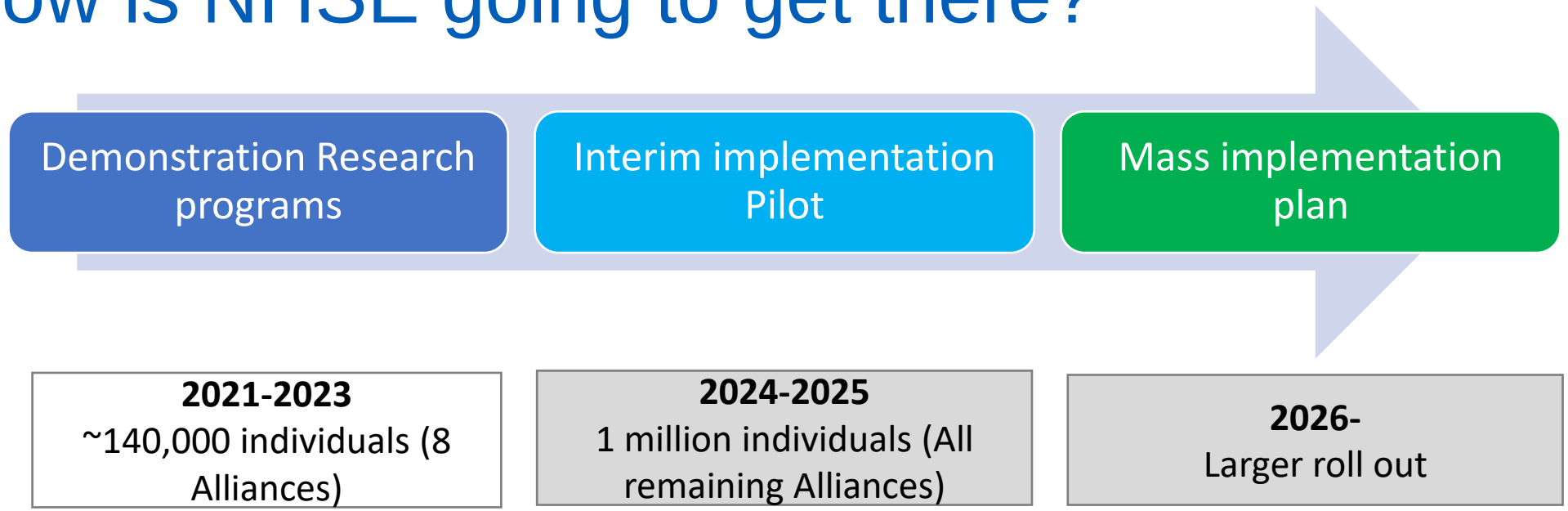
Primary endpoint: stage III+IV cancer

- Diagnoses within 3 years of last person enrolled

Vision

75% of cancer diagnoses at an early stage by 2028

How is NHSE going to get there?



Thank you