Multi-cancer early detection tests in bowel screening

Professor Bethany Shinkins
University of Warwick

Any views I express are my own, and not representative of the UK National Screening Committee, NICE or NIHR

What are MCEDs?

- MCEDs are minimally invasive tests (typically based on blood samples), capable of detecting multiple cancer types simultaneously.
- Often also able to predict the most likely cancer site(s)
- Typically use cfDNA ± protein biomarker patterns to identify cancer-specific signatures
- Biomarker information is often combined using machine learning or artificial intelligence methods
- Lots of different tests available using different technology, detecting different numbers of cancers

Evidence Summary

- Completed prospective studies
- Ongoing prospective studies
- Discussion of evidence gaps

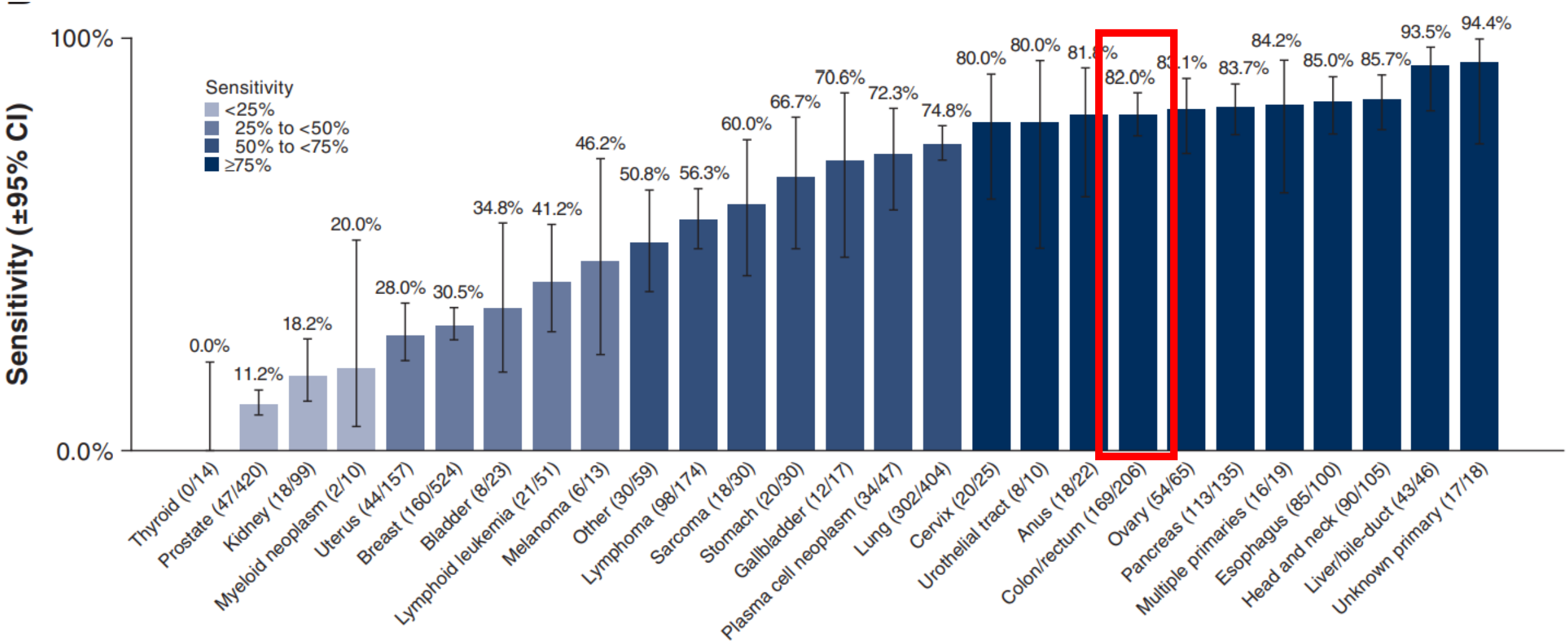
Completed Prospective Studies

Circulating Cell-free Genome Atlas study

- A prospective, multi-centre, **case control**, observational study with longitudinal follow-up
- Intervention: GRAIL Galleri Test
- Study was divided into three pre-specified sub-studies (i) discovery, (ii) training and validation with the selected and updated assay and classifiers, and (iii) clinical validation within an independent validation set with a further refined assay and classifiers optimized for screening.
- n=4,077 (cancer = 2,823; non-cancer = 1,254)

Klein, E.A., et al., 2018. Development of a comprehensive cell-free DNA (cfDNA) assay for early detection of multiple tumor types: The Circulating Cell-free Genome Atlas (CCGA) study. *J Clin Oncol*, *36*(15 Suppl), p.12021.

Circulating Cell-free Genome Atlas study



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SYMPLIFY study: Design

- Design: Multicentre, observational study (England and Wales)
- Population: 18 years or older, referred for urgent investigation for a possible gynaecological, lung, lower gastrointestinal, or upper gastrointestinal cancer or to a rapid diagnostic centre with non-specific symptoms that might be due to cancer (n=5461)
- Intervention: GRAIL Galleri MCED test (detects 50 cancers)
- Comparator: All patients were followed up until diagnostic resolution or 9 months.
- Outcome: Diagnostic accuracy for new invasive cancer cases

Nicholson, B.D., Oke, J., Virdee, P.S., Harris, D.A., O'Doherty, C., Park, J.E., Hamady, Z., Sehgal, V., Millar, A., Medley, L. and Tonner, S., 2023. Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPLIFY): a large-scale, observational cohort study. *The Lancet Oncology*.

SYMPLIFY study: Results

- 5461 as the cohort for analysis (368 with a cancer diagnosis and 5093 without a cancer diagnosis;
- Sensitivity = 70·8% (95% CI: 62·4–78·3) for n=97/137 colorectal cancers
- N=94/97 had a correct predicted cancer signal origin
- Sensitivity was greater with more advanced stage (not reported for colorectal cancer specifically, but for all cancers ranged from Stage I: 24·2% (95% CI: 16·0–34·1) to Stage IV: 95·3% (95% CI: 88·5–98·7)

Nicholson, B.D., Oke, J., Virdee, P.S., Harris, D.A., O'Doherty, C., Park, J.E., Hamady, Z., Sehgal, V., Millar, A., Medley, L. and Tonner, S., 2023. Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPLIFY): a large-scale, observational cohort study. *The Lancet Oncology*.

PATHFINDER study: Design

- Population: Adults aged ≥50. Cohort 1: elevated risk group (n=3655). Cohort 2: non-elevated risk group (n=2923). 91·7% were white.
- Intervention: GRAIL Galleri MCED Test (detects 50 cancers)
- Reference standard: End-of-study cancer-status assessment 12 months after enrolment, which included a review of electronic health records to confirm the presence or absence of cancer.
- Outcomes:
  - The number of days from test result to diagnostic resolution
  - Extent of testing for those with a +ve test result.

Schrag, D., Beer, T.M., McDonnell, C.H., Nadauld, L., Dilaveri, C.A., Reid, R., Marinac, C.R., Chung, K.C., Lopatin, M., Fung, E.T. and Klein, E.A., 2023. Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study. *The Lancet*, *402*(10409), pp.1251-1260.

PATHFINDER study: Results

- A cancer signal was detected in n=92/6621 participants:
  - 35 were true positives (38%) – 24 were in the additional-risk cohort. 2 of the 35 TPs were colorectal cancers (both stage IV)
  - 57 were false positives (62%)
- 95.5% were TNs, 86 (1.3%) were FNs and 208 (3·2%) did not have a cancer status assessment at the end of the study
- True positives had a shorter median time to diagnostic resolution (57 days [33–143]) compared with false positives (162 days [44–248])
- Most participants with a +ve had both laboratory tests and imaging. Fewer procedures were done in participants with FP results than TP results.

Schrag, D., Beer, T.M., McDonnell, C.H., Nadauld, L., Dilaveri, C.A., Reid, R., Marinac, C.R., Chung, K.C., Lopatin, M., Fung, E.T. and Klein, E.A., 2023. Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study. *The Lancet*, *402*(10409), pp.1251-1260.

DETECT-A: Study Design

- Population: n=9,911 women aged 65-75 years, no history of cancer, from a population with high adherence to standard of care screening (aimed to enrich for ovarian cancer)
- Intervention: CancerSeek MCED test (15 cancers), if positive repeat test
- Reference standard: 12 month follow-up, PET-CT for positives
- Outcomes: Accuracy of the test, number and proportion of cancers detected by site and stage, mortality, potential harms

DETECT-A: Results

- 26/96 cancers detected, sensitivity =27.1% (95% CI: 18.5-37.1%). N=2 were colorectal cancers
- Specificity: 98.9% (95% CI: 98.7 to 99.1)
- CSO data not reported

Ongoing Studies

GRAIL Galleri Test

- RCT: NHS-Galleri Trial
  - Primary objective: to demonstrate a statistically significant reduction in the incidence rate of stage III/IV cancers
- Cohort studies:
  - Pathfinder 2: Evaluating the Safety and Performance of the GRAIL Multi-Cancer Early Detection Test in an Eligible Screening Population. N=35,000. Estimated completion 2027.
  - REFLECTION: To describe signal detection and cancer detection within and across sites among participants who opt to receive Galleri® in a real world setting. Estimated completion 2026.
  - SUMMIT: 13,000 participants aged 55-77 years, from participating general practitioner (GP) practices in North Central and East London. The participants enrolled will be people who are at high-risk for lung cancer due to a significant smoking history based on validated risk scores. Estimated completion 2030.

Discussion

- Evidence of the clinical effectiveness of MCEDS in a screening context is very limited, some ongoing studies which should be published in the next few years
- So far, MCEDs positioned as complementary to current cancer screening programmes, not replacement
- No evidence as to whether a MCED should be used as part of colorectal cancer screening programme - to boost participation?
- The confirmatory diagnostic pathway is not clearly established at this time for many of the cancer types detected by the MCEDs

PREEMPT CRC study

- A prospective multi-centre observational study to validate a blood-based test for the early detection of colorectal cancer
- Population: Participants aged between 45 – 85 years who are eligible for CRC screening and scheduled for a standard-of-care screening colonoscopy. Targeting over 25,000.
- Intervention: Freenome test, combines tumour- and non-tumour signals from DNA and proteins and uses machine learning to detect CRC and advanced adenomas

https://www.freenome.com/clinical-studies/

ECLIPSE study

- A prospective, observational multi-site
- Population: expected to enrol approximately 10,000 individuals aged 45-84 who are at average risk for colorectal cancer.
- Intervention: blood-based ctDNA LUNAR-2 test to detect colorectal cancer (Guardant Health)
- Reference standard: Colonoscopy as well as one and two-year outcomes post-procedure
- Outcomes: Diagnostic accuracy

https://crweworld.com/article/news-provided-by-globenewswire/1285643/guardant-health-initiates-eclipse-pivotal-study-for-its-lunar-2-blood-test-for-colorectal-cancer-screening