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Multi-Cancer Early Detection:
Hope for Future OG Cancer Detection

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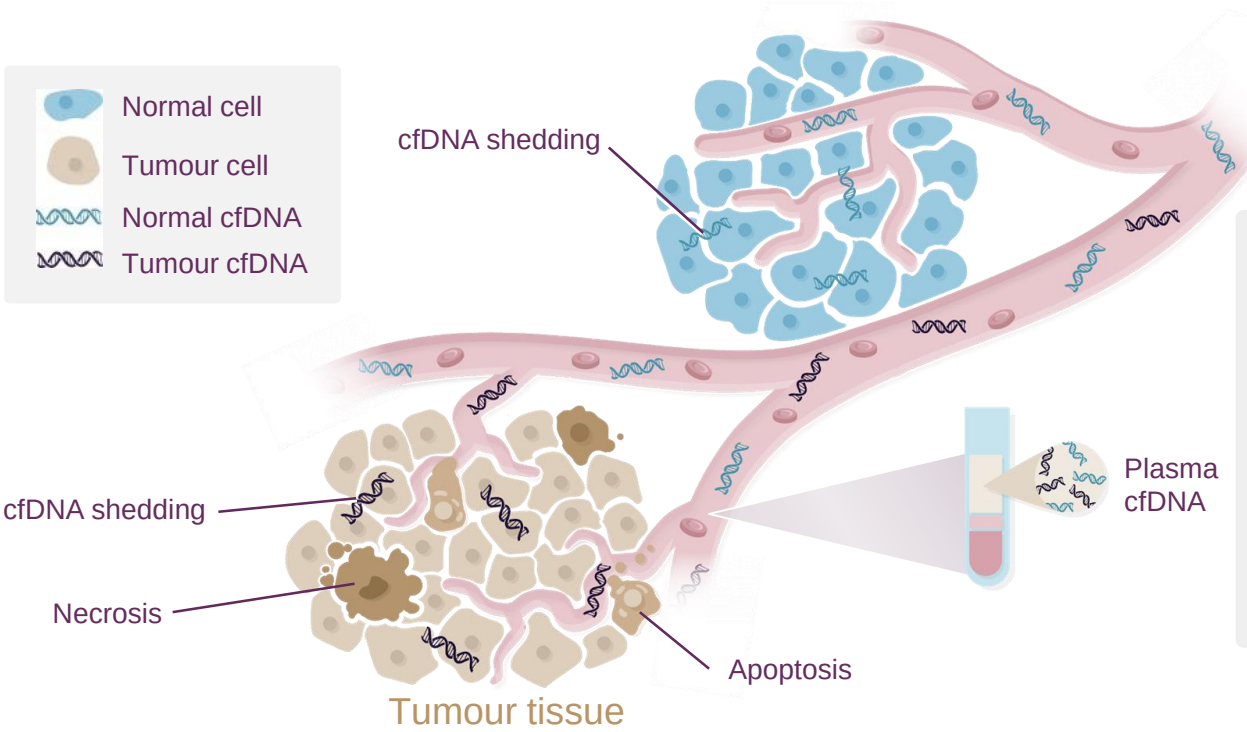
Multi-Cancer Early Detection Tests

Tumours Shed Nucleic Acids Into Blood Carrying Cancer-Specific Information[1,2]



Cancer-associated aberrations in cfDNA

- Mutations
- Chromosome alterations
- DNA methylation patterns

cfDNA, cell-free DNA.

[1]Corcoran R et al. *N Engl J Med*. 2018;379:1754-1765. [2]Thierry A et al. *Cancer Metastasis Rev*. 2016;35:347-376.

A Multi-Cancer Early Detection (MCED) Test May Decrease Cancer-Related Mortality

MCED test as a complement to existing screening

Detect many lethal cancers, including unscreened cancers, using single blood sample collected at point-of-care

Identify signal origin to direct diagnostic workup

Large-scale clinical validation

High specificity (~99%) could limit false positives and unnecessary workups

Potential for:

- More cancer cases detected through screening
- Improved patient outcomes and survival
- Decreased burden of care

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The Galleri® Test Predicts Cancer Signal Origin(s)

The Galleri® Test has 21 Possible Cancer Signal Origins:

CSO Reported	What is included
Anus	Anus
Bladder, Urothelial Tract	Bladder, Renal Pelvis, Ureter, Urethra
Bone and Soft Tissue	Skeletal muscle and other connective tissue, Vascular tissue, Bone and cartilage
Breast	Breast
Cervix	Cervix
Colon, Rectum	Colon, Rectum, Appendix
Head and Neck	Oropharynx, Hypopharynx, Nasopharynx, Larynx, Lip and oral cavity (including oral tongue), Nasal cavity, Paranasal sinuses, Major salivary glands
Kidney	Kidney
Liver, Bile Duct	Liver, Intrahepatic bile duct
Lung	Lung, Bronchus

CSO Reported	What is included
Lymphoid Lineage	Lymphoid Lineage
Melanocytic Lineage	Melanocytic Lineage
Myeloid Lineage	Myeloid Lineage
Neuroendocrine Cells of Lung or other Organs	Neuroendocrine Cells of Lung or other Organs
Ovary	Ovary, Fallopian tube, Primary peritoneum
Pancreas, Gallbladder	Pancreas, Extrahepatic bile duct, Gallbladder
Plasma Cell Lineage	Plasma Cell Lineage
Prostate	Prostate
Stomach, Oesophagus	Stomach, Oesophagus
Thyroid Gland	Thyroid Gland
Uterus	Uterus

CSO, cancer signal origin. Galleri is a registered trademark of GRAIL, LLC.

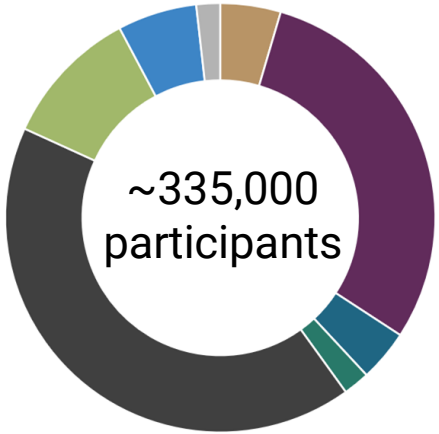
Klein E, et al. *Ann Oncol*. 2021;32(9):1167-1177. DOI: 10.1016/j.annonc.2021.05.806.

GRAIL's Clinical Development Programme

GRAIL's Clinical Development Programme

Test development, validation and implementation in population-scale studies

1	**CCGA** (n=15,254) NCT02889978	Develop and validate a cell-free DNA-based MCED test
2	**STRIVE** (n=99,481) NCT03085888	Evaluate MCED test performance in women to detect invasive cancers[a]
3	**SUMMIT** (n=13,035) NCT03934866	Validate MCED test clinically in individuals at high risk of lung cancer
4	**PATHFINDER** (n=6,662) NCT04241796	Evaluate clinical implementation and perceptions of MCED test
5	**SYMPLIFY** (n=6,242) ISRCTN 10226380	Assess MCED test in individuals with signs/symptoms of cancer
6	**NHS-Galleri** (n~140,000) ISRCTN 91431511	Assess clinical utility of MCED for population screening in the UK
7	**REFLECTION** (n~35,000) NCT05205967	Assess experience/clinical outcomes in real-world setting
8	**PATHFINDER 2** (n~20,000) NCT05155605	Evaluate MCED test performance in eligible screening population



[a]In women undergoing mammography screening.
n~ indicates approximate enrollment.
CCGA, Circulating Cell-free Genome Atlas; MCED, multi-cancer early detection.

Key Performance Features of the Multi-Cancer Early Detection Test

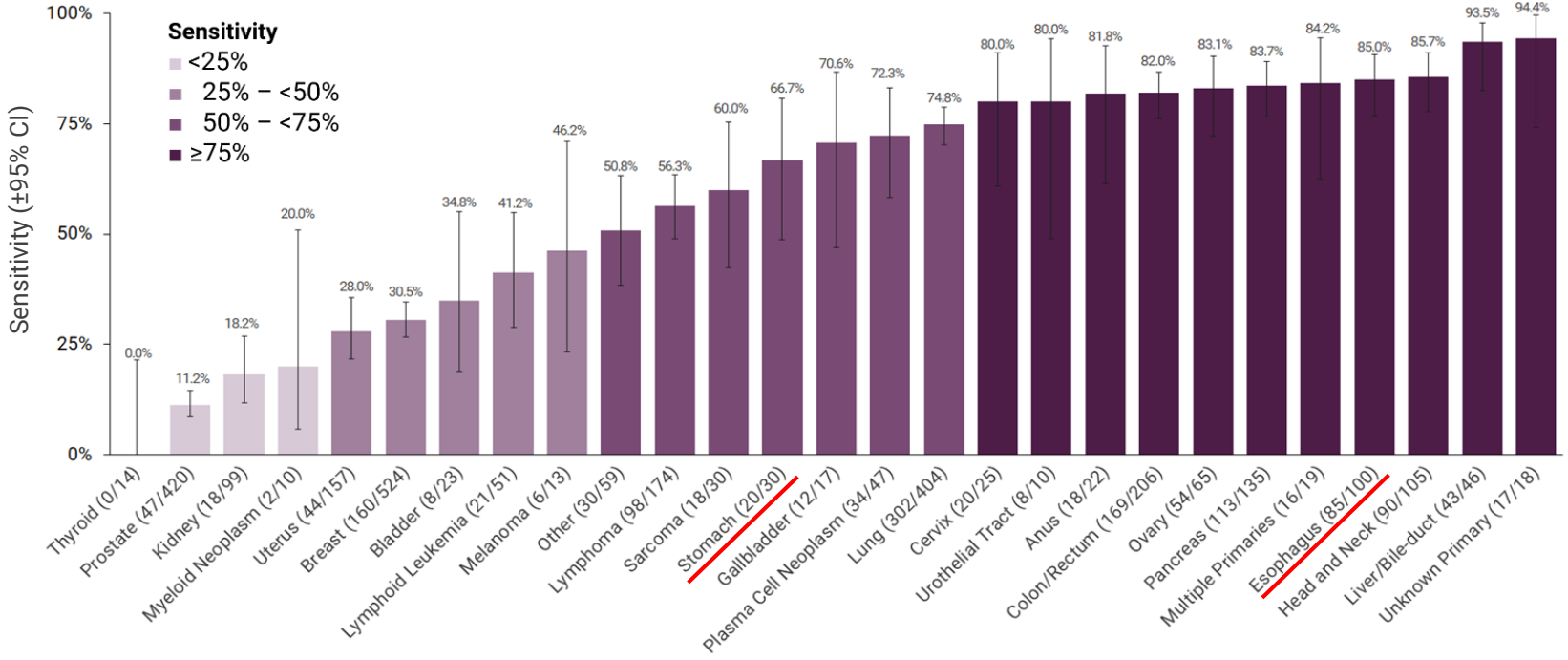
CCGA Substudy 3

Cancer Types Detected[a]	Positive Predictive Value (Adjusted[b])	False Positive Rate
>50	44%	0.5%

[a]Test detects a cancer signal shared by over 50 types of cancers.
[b]Positive predictive value was adjusted to SEER cancer incidence and stage distribution in the 50–79 y age group.
CCGA, Circulating Cell-free Genome Atlas.
Klein EA, et al. *Ann Oncol*. 2021;32(9):1167-1177. DOI: 10.1016/j.annonc.2021.05.806.

Sensitivity of Cancer Signal Detection by Cancer Class

CCGA Substudy 3



Comprises all cancer stages, including missing stage and cancer classes that do not have staging per American Joint Committee on Cancer (AJCC) staging manual.
CCGA, Circulating Cell-Free Genome Atlas; CI, confidence interval.
Klein E, et al. *Ann Oncol*. 2021;32(9):1167-1177. DOI: 10.1016/j.annonc.2021.05.806.

Key Findings From Early MCED Test

PATHFINDER Study

Early MCED Test

- MCED testing approximately doubled the number of cancers detected with standard of care screening
- ~50% of new cancers were Stage I or II
- No adverse events due to diagnostic workups after a signal detected result
- Cancer diagnostic resolution was expedient (even during COVID-19)
- Prediction of cancer origin directed clinical workup
- Invasive procedures were more common in true positives
- Early test version led to relatively few false positives (High specificity and PPV)

Supports feasibility of broad screening use

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Schrag D, et al. Presentation at European Society of Medical Oncology (ESMO) Congress 9-13 September, 2022; Paris, France.

Consistent MCED Test Performance in an Intended Use Population

Clinical Validation Study (CCGA3)[1]

0.5%	44%	89%
False positive rate	Positive predictive value (modeled)	Cancer Signal Origin accuracy[a]

Intended Use Population Study (PATHFINDER)[2]

0.5%	43%	88%
False positive rate (to date)	Positive predictive value	Cancer Signal Origin accuracy[b]

[a]Accuracy of top Cancer Signal Origin for true positive cancer participants with a Cancer Signal Detected. [b]Accuracy of top two cancer signal origin prediction for true positive patients, based on prespecified reanalysis of blood samples with Galleri test. [1]Klein E, et al. *Ann Oncol*. 2021;32(9):1167-1177. DOI: 10.1016/j.annonc.2021.05.806. [2]Schrag D, et al. Presentation at European Society of Medical Oncology (ESMO) Congress 9-13 September, 2022; Paris, France.

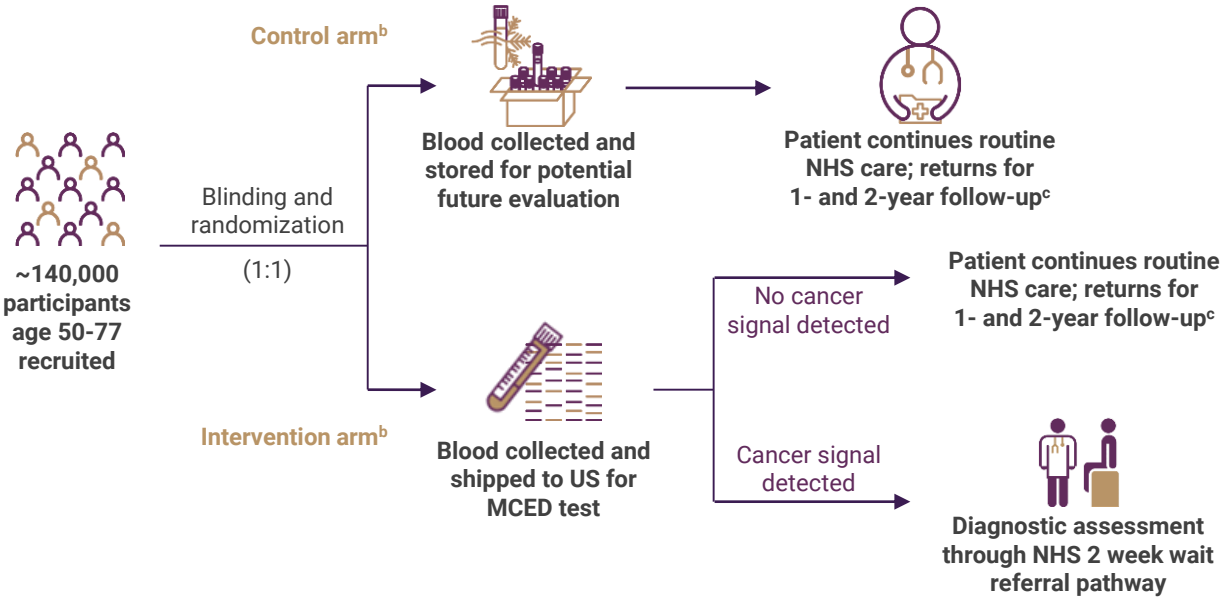
The NHS-Galleri Trial

Prospective, randomised, controlled trial to assess the clinical utility of MCED test for population screening in the UK (ISRCTN 91431511)

Study Goals

Demonstrate a significant reduction in the absolute numbers of stage III and IV cancers[a] diagnosed in the intervention arm compared with the control arm

Study Design

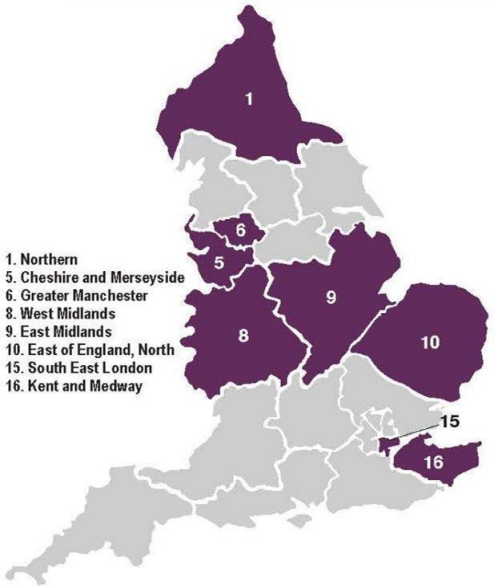


[a]The following cancer types are not routinely staged and are excluded: brain cancers, leukemias, cancers of unknown primary. [b]Unless diagnosed with cancer, participants in both arms will be asked to return for annual visits at approximately 12 and 24 months. [c]Results will not be returned to GP/patients to maintain blinding between arms.
MCED, Multi-cancer early detection.

Enrolling In Eight Regions of England

NHS-Galleri Trial

Eight Participating Cancer Alliances



Enrolment Routes

~1.5 Million
Invitations sent by NHS DigiTrials

~17,200
Invitations sent by general practices

~2,400
Recruited through open enrolment

Neal R, et al. *Cancers*. 2022; 14(19):4818. https://doi.org/10.3390/cancers14194818.

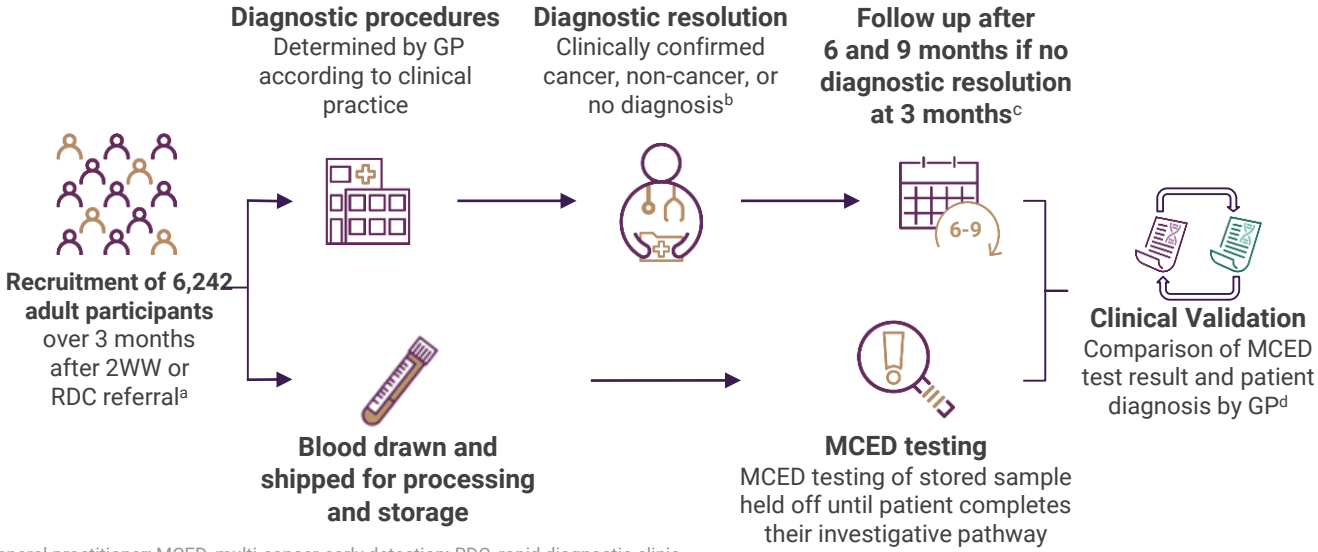
The SYMPLIFY Study

Performance evaluation of an in-vitro diagnostic device (PEIVDD) in the NHS in England and Wales (ISRCTN 10226380)

Study Goals

Evaluate performance of a MCED test for detection of cancer and prediction of CSO

Study Design



2WW, two-week-wait; CSO, cancer signal origin; GP, general practitioner; MCED, multi-cancer early detection; RDC, rapid diagnostic clinic.
[a]2WW Lung, 2WW upper gastrointestinal, 2WW lower gastrointestinal, 2WW gynae, and RDC. [b]No diagnosis defined as no diagnosis of cancer and no non-cancer condition diagnosed to explain presenting complaint. [c]Primary and secondary care electronic records collected at 12 months to capture late diagnosed cancers. [d]No individual results will be returned to the study participants or the clinicians responsible for their care.

Thank you

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