GRAIL

KING'S College LONDON

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

NHS Galleri Trial

Introducing the NHS-Galleri trial

Introduction for UK healthcare professionals

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Disclaimer and Disclosure

This deck is for exchange of medical and scientific information with UK healthcare professionals.

The content is this presentation is the confidential and proprietary information of GRAIL.

Information disclosed or discussed in this presentation is subject to obligations of confidentiality and is not to be discussed, shared or forwarded.

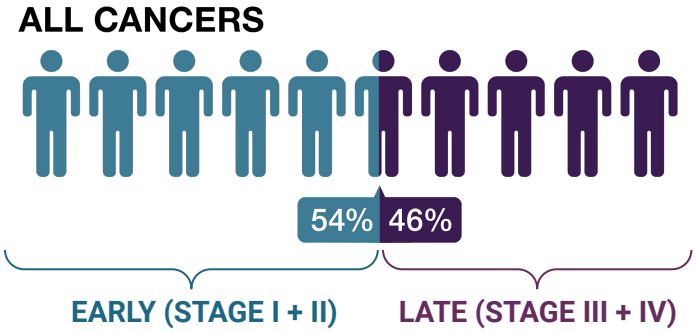
The product discussed in this presentation has a CE and a UKCA mark, and will be used within its intended use.

In the United States (US), the Galleri® test is an Investigational Device and limited by Federal (or US) law to investigational use. A description of this clinical trial is available on www.ClinicalTrials.gov, as required by US Law.

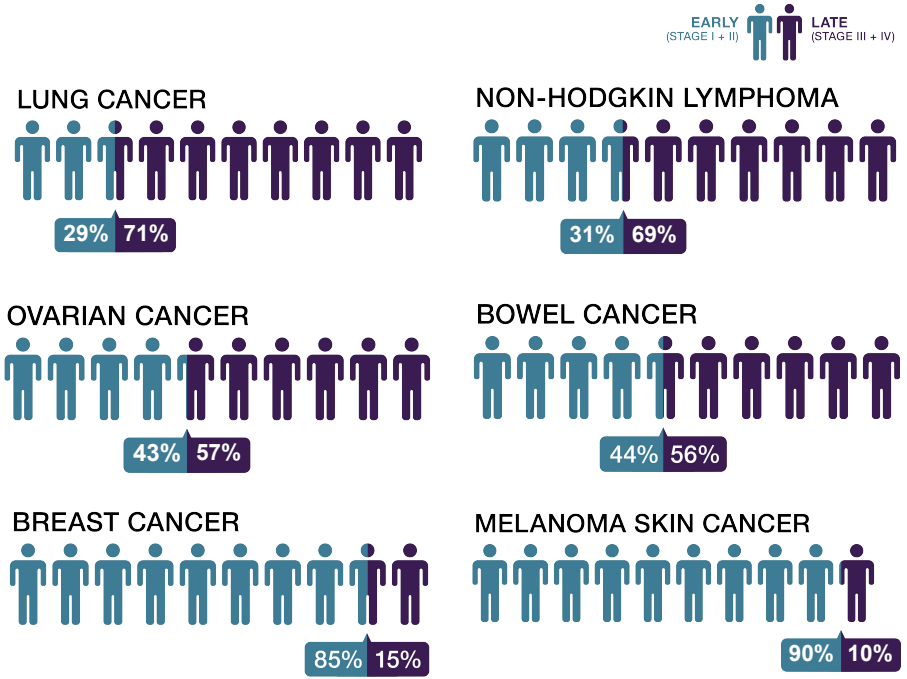
Some of the data presented are preliminary.

Many cancers are diagnosed at a late stage

Stage of cancer when diagnosed, England 2012-17[1]



NHS Long Term Plan aims to **diagnose 75% of cancers at stage I/II by 2028**[2]



[1]National Cancer Registration and Analysis Service (NCRAS). Stage breakdown by Clinical Commissioning Group (CCG) 2017. http://www.ncin.org.uk/publications/survival_by_stage. Accessed January 2023. [2]NHS England. NHS Long Term Plan. https://www.longtermplan.nhs.uk/online-version/chapter-3-further-progress-on-care-quality-and-outcomes/better-care-for-major-health-conditions/cancer. Accessed January 2023.

Three cancers are routinely screened for

Three cancers have routine screening programmes in England[1], and a targeted screening programme is being introduced for a fourth cancer[2]

Breast cancer

Offered every 3 years to women aged 50 to 70

Women >70 years old can self-refer

Cervical cancer

Offered to all women and people with a cervix aged 25 to 64

- Every 3 years for those aged 26 to 49
- Every 5 years for those aged of 50 to 64

Bowel cancer

Home test kit offered every 2 years to people aged 60 to 74

People ≧75 years old and over can request a kit

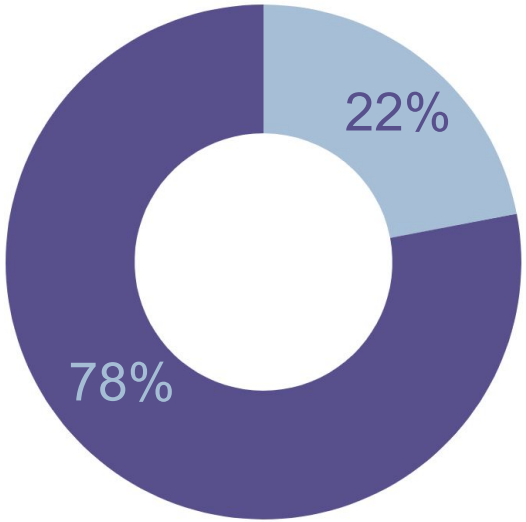
Lung cancer (recommended)

The UK National Screening Committee has recommended targeted lung cancer screening for people aged 55 to 74 at high risk of lung cancer

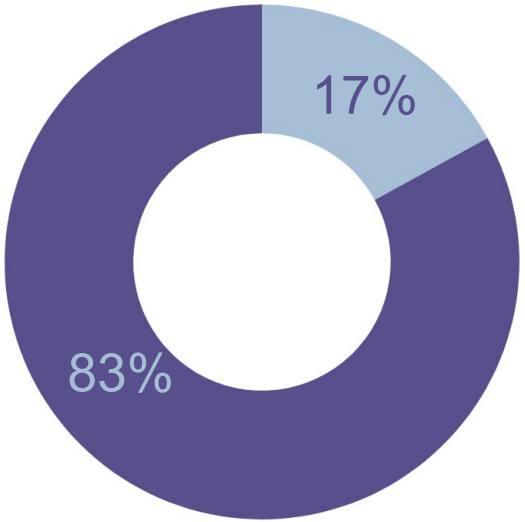
[1]NHS. NHS screening. https://www.nhs.uk/conditions/nhs-screening. Accessed February 2023.
[2]National Screening Committee (NSC). Lung cancer - UK NSC screening recommendation. https://view-health-screening-recommendations.service.gov.uk/lung-cancer. Accessed February 2023.

Cancers without a screening programme account for majority of cancer cases and deaths

Incidence[1]



Mortality[2]



Cancers with screening[a]

Cancers without screening

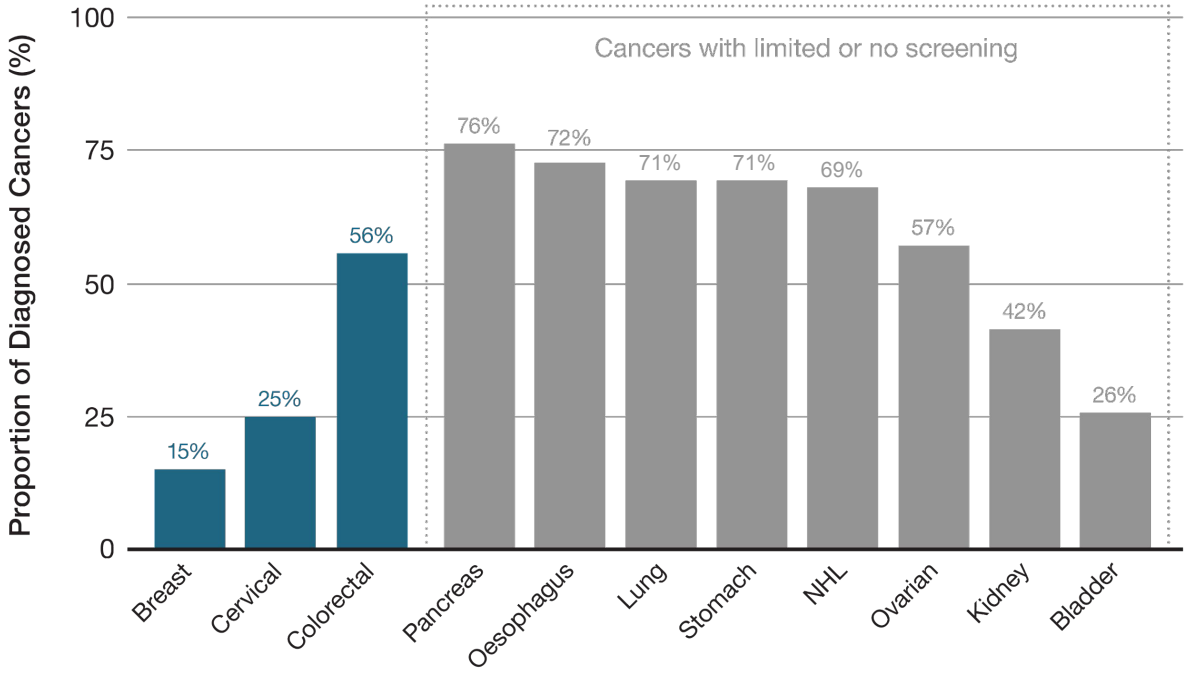
[a]Breast, bowel and cervical cancer.

[1]National Cancer Registration and Analysis Service (NCRAS). Cancer incidence and mortality for England, 2016-2020. https://www.cancerdata.nhs.uk/incidence_and_mortality. Accessed February 2023.

[2]Office for National Statistics. Mortality statistics - underlying cause, sex and age, 2016-2020. https://www.nomisweb.co.uk/query/construct/summary.asp. Accessed February 2023.

Unscreened cancers are generally detected at later stages

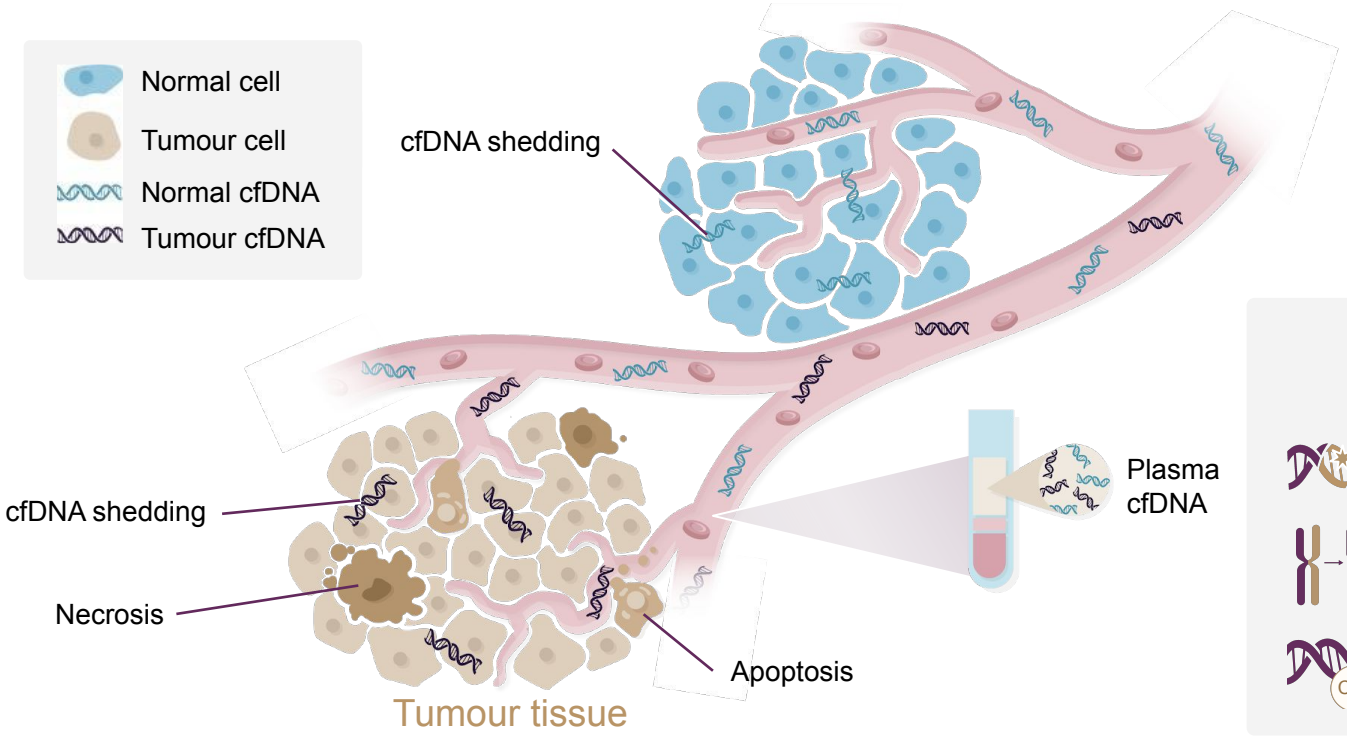
Selected cancers with regional or distant metastasis (stage III/IV) at diagnosis



The y axis shows proportion of diagnosed cancers that were staged.
NHL, Non-Hodgkin lymphoma.
National Cancer Registration and Analysis Service (NCRAS). Stage breakdown by CCG 2017. http://www.ncin.org.uk/publications/survival_by_stage. Accessed January 2023.

Multi-cancer early detection

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.

Multi-cancer early detection (MCED) tests

The NHS-Galleri trial is investigating the use of an MCED test called Galleri®

Blood sample collected

'Cancer Signal Detected' by the test

Test predicts the tissue or organ associated with the cancer signal

- The test involves taking a blood sample from a patient and analysing it using targeted methylation sequencing and machine learning.
- This process can identify abnormal DNA methylation sequences that are a signal of cancer.
- If a cancer signal is detected, the methylation patterns are examined to predict tissue type or organ associated with the cancer signal, to direct diagnostic work up.

Predicting Cancer Signal Origin(s)

The Galleri test has 21 possible Cancer Signal Origins[1]

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, Esophagus	Stomach, Esophagus
Thyroid Gland	Thyroid Gland
Uterus	Uterus

CSO, Cancer Signal Origin.

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

Test designed to complement existing cancer screening

The Galleri test does not replace existing cancer screening programmes

Detects many types of cancer that do not have screening tests

- Detects a signal shared by many different types of cancer.[1]
  - An early study reported that a cancer signal was detected across more than 50 types of cancer.
  - This includes many types of cancer that do not have screening tests.

Intended to complement existing cancer screening tests

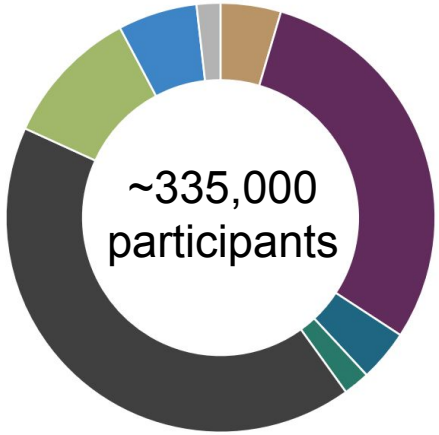
- Does not replace recommended single cancer screening tests.

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

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	Clinical validation 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) NCT05611632	Assess clinical utility of MCED for population screening in the UK
7	**REFLECTION** (n~17,000) 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]n women undergoing mammography screening.
n~ indicates approximate enrollment. Follow-up indicates end of study data post follow-up.
CCGA, Circulating Cell-free Genome Atlas; MCED, multi-cancer early detection.

The Circulating Cell-Free Genome Atlas Study (CCGA Study)

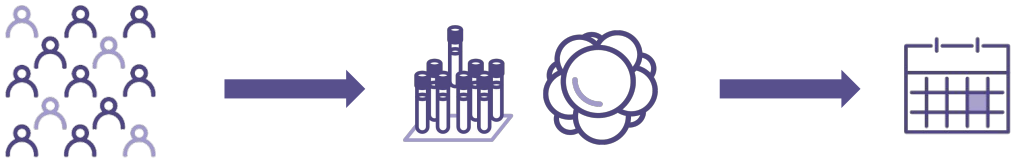
CCGA3

A prospective, multi-centre, case-control, observational study (NCT02889978)

Study goals

- Develop and validate a blood-based MCED test analysing plasma cfDNA
- Detect cancer signals across multiple cancer types and simultaneously predict their signal origin

Study design



15,254 participants with or without cancer

Fully enrolled (142 sites)

Blood samples
All participants

Tissue samples
Participants with cancer only

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

Cancer signal detection: specificity and overall sensitivity[1]

	Cancer (n=2823)	Non-cancer (n=1254)	Total (n=4077)
Test positive	1453	6	1459
Test negative	1370	1248	2618

Specificity:
99.5%
(95% CI: 99.0–99.8%)

0.5%
false positive rate

Sensitivity:
51.5%
(95% CI: 49.6–53.3%)

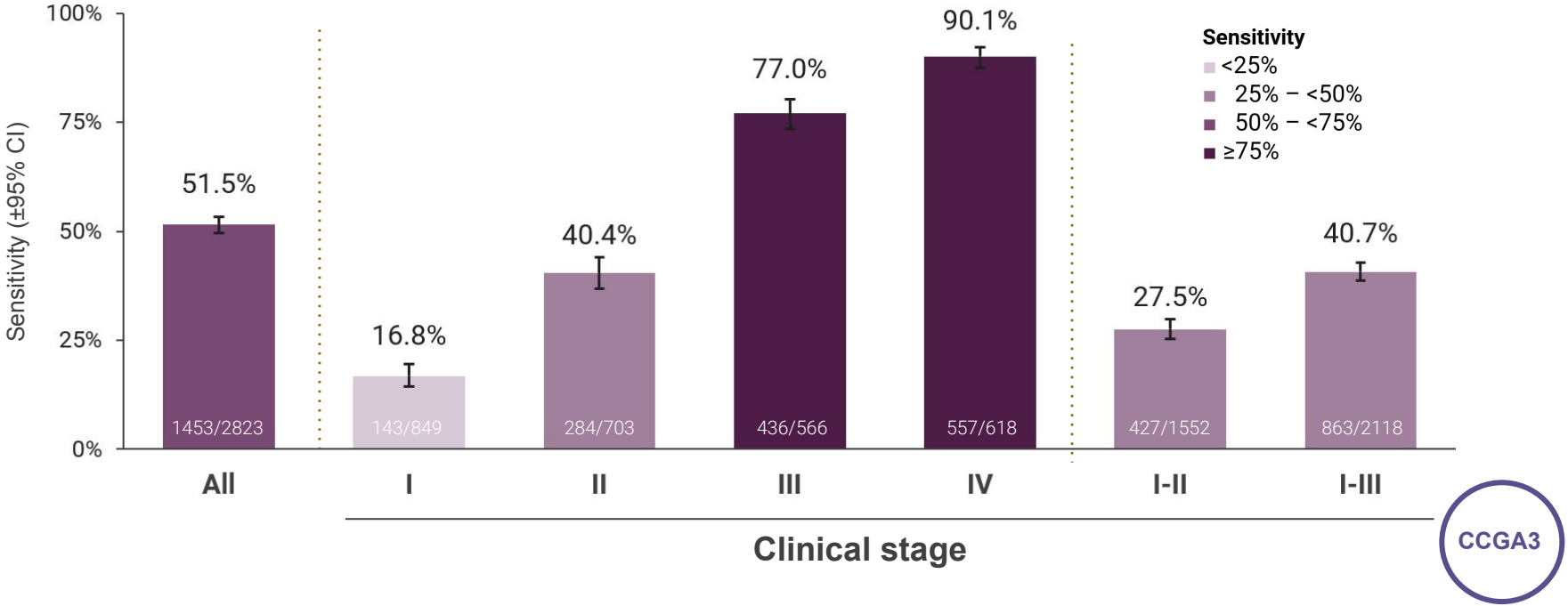
CCGA3

CI, confidence interval.

[1]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 clinical stage[1]

Sensitivity increased with increasing clinical stage



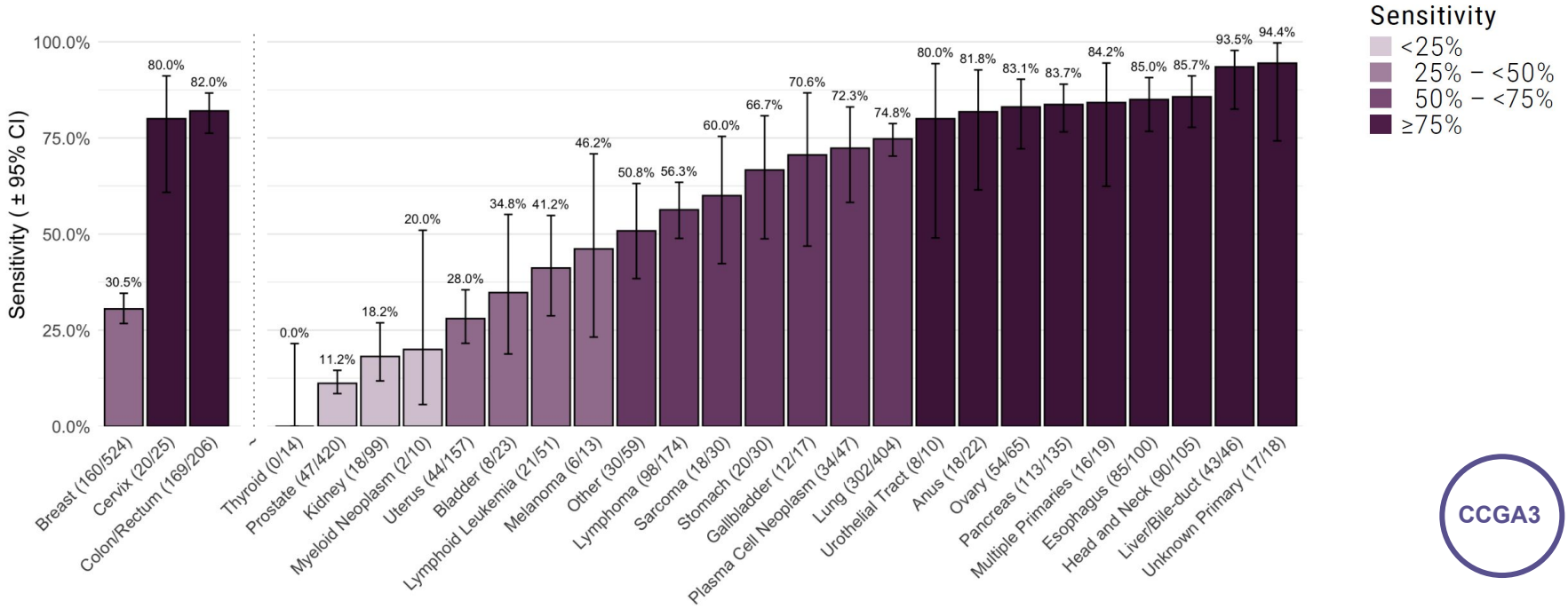
'All' comprises all cancer stages, including missing stage and cancer classes that do not have staging per American Joint Committee on Cancer (AJCC) staging manual.
CI, confidence interval.

[1]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 type[1]

Cancers with common screening options:
46.2% (95% CI: 42.7%, 49.8%)

Cancers without common screening options:
53.0% (95% CI: 50.8%, 55.1%)



CCGA3

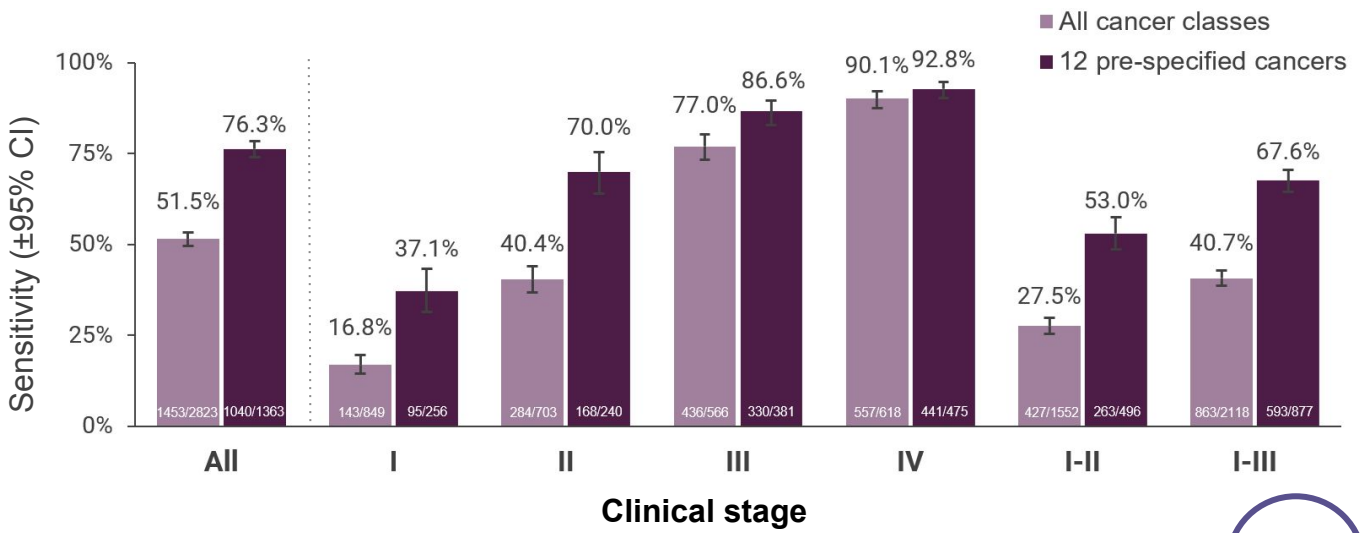
CI, confidence interval.
[1]Klein EA, et al. *Ann Oncol.* 2021;32(9):1167- 1177. DOI: 10.1016/j.annonc.2021.05.806.

Sensitivity of cancer signal detection 12 pre-specified cancers[1]

Sensitivity was higher in 12 cancers responsible for more than 60% of cancer deaths, particularly at early-stage disease

12 cancers that account for 61% of UK cancer deaths[2]

- Anus
- Bladder
- Colon/rectum
- Oesophagus
- Head and neck
- Liver/bile duct
- Lung
- Lymphoma
- Ovary
- Pancreas
- Plasma cell neoplasm
- Stomach



CCGA3

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[2]Cancer Research UK. The 20 Most Common Causes of Cancer Deaths, UK, 2018; https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/common-cancers-compared#heading-Zero. Accessed June 2021.

Consistent performance seen in clinical studies

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	Positive predictive value	Cancer Signal Origin accuracy[b]

[a]Based on tissue of origin class assigned in 96% of cases where cancer was detected. [b]Accuracy of top two Cancer Signal Origin prediction, based on prespecified reanalysis of blood samples with Galleri test.
[1]Klein EA, 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

NHS-Galleri trial objective and partners

NHS-Galleri

Objective

To demonstrate a statistically significant reduction in the incidence rate of stage III and IV cancers diagnosed in the intervention arm (blood tested with Galleri test) versus control arm (blood stored)

Partners

GRAIL

GRAIL, LLC is a company in the United States that developed the Galleri test. They have also set up a subsidiary in the UK, GRAIL Bio UK Ltd. (GRAIL). They are the main funder and organiser of the NHS-Galleri trial.

NHS

NHS England is partnering with GRAIL and will provide follow-up tests, hospital care and any treatments related to the trial.

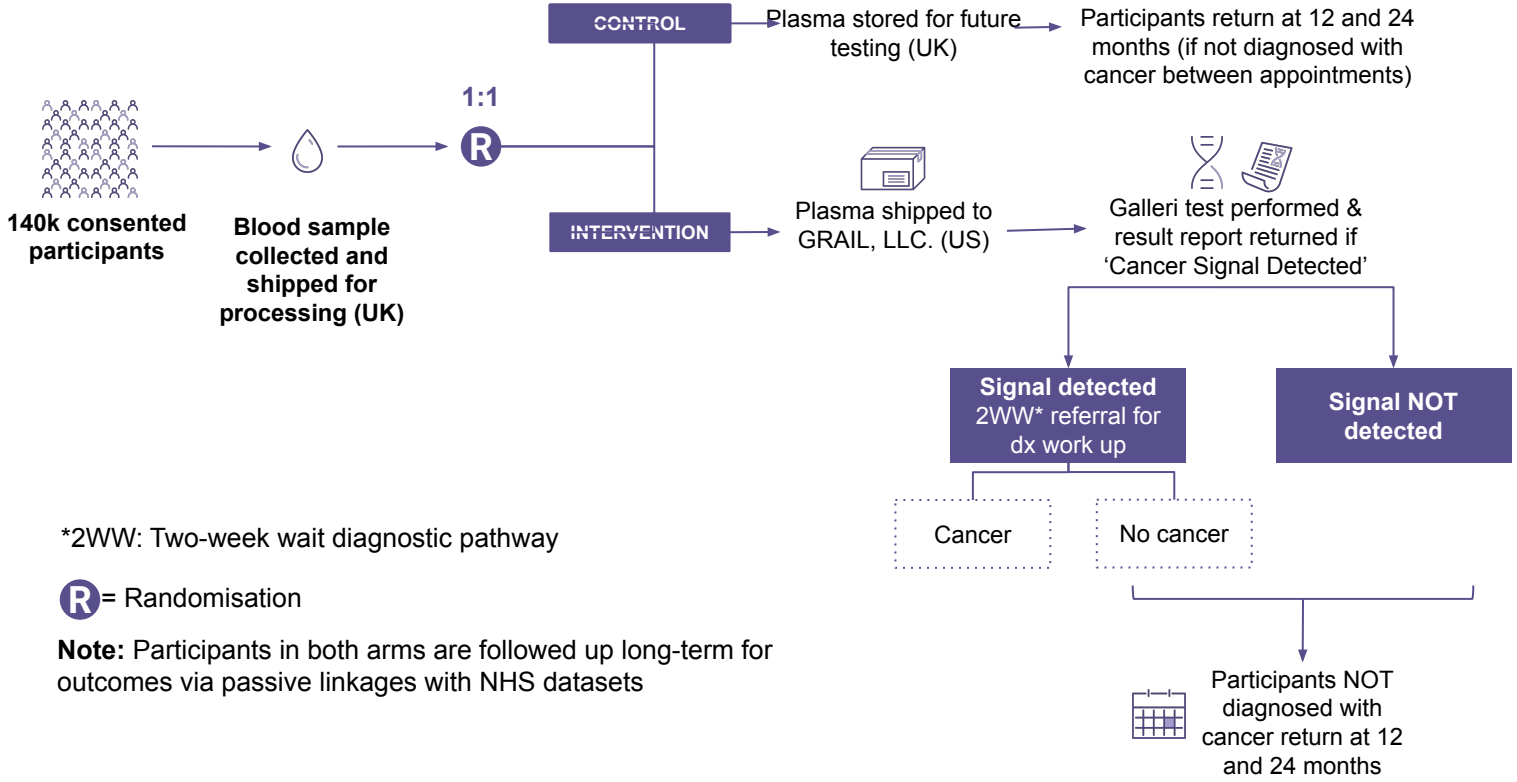
CANCER RESEARCH UK | KING'S COLLEGE LONDON CANCER PREVENTION TRIALS UNIT

The Cancer Research UK & King's College London Cancer Prevention Trials Unit, a team of cancer researchers and trial managers, coordinate the trial and will analyse the results.

NHS-Galleri trial design[1]

A prospective, randomised, double blind, controlled trial (NCT05611632)

NHS-Galleri



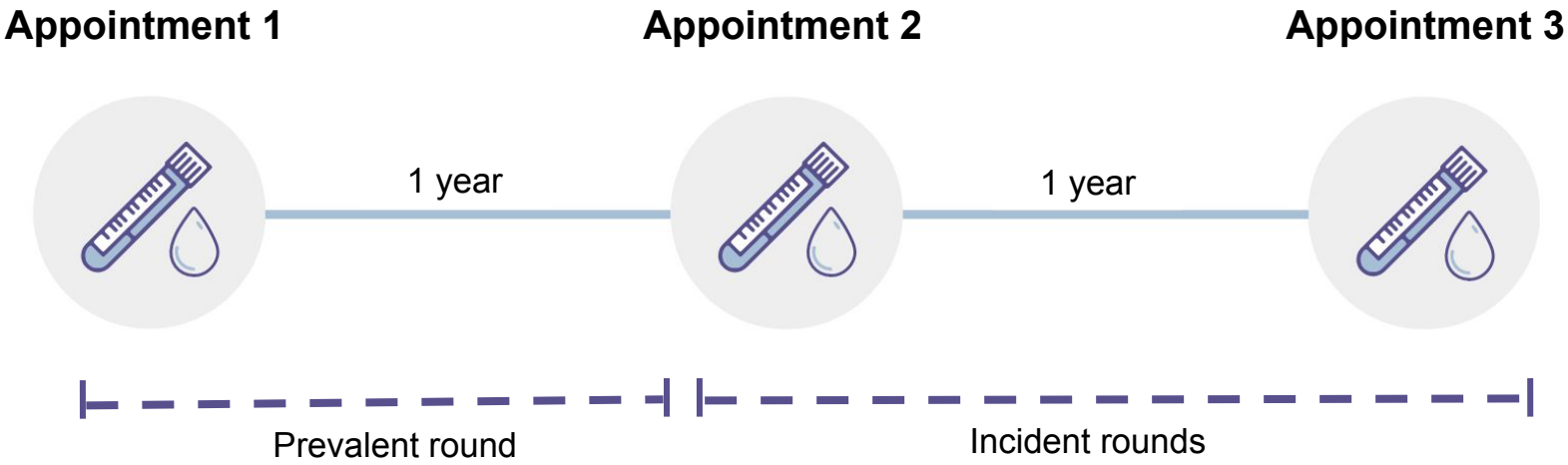
*2WW: Two-week wait diagnostic pathway

R = Randomisation

Note: Participants in both arms are followed up long-term for outcomes via passive linkages with NHS datasets

[1]Neal R, et al. *Cancers*. 2022; 14(19):4818. DOI: 10.3390/cancers14194818.

The NHS-Galleri trial is assessing an annual screening approach[1]



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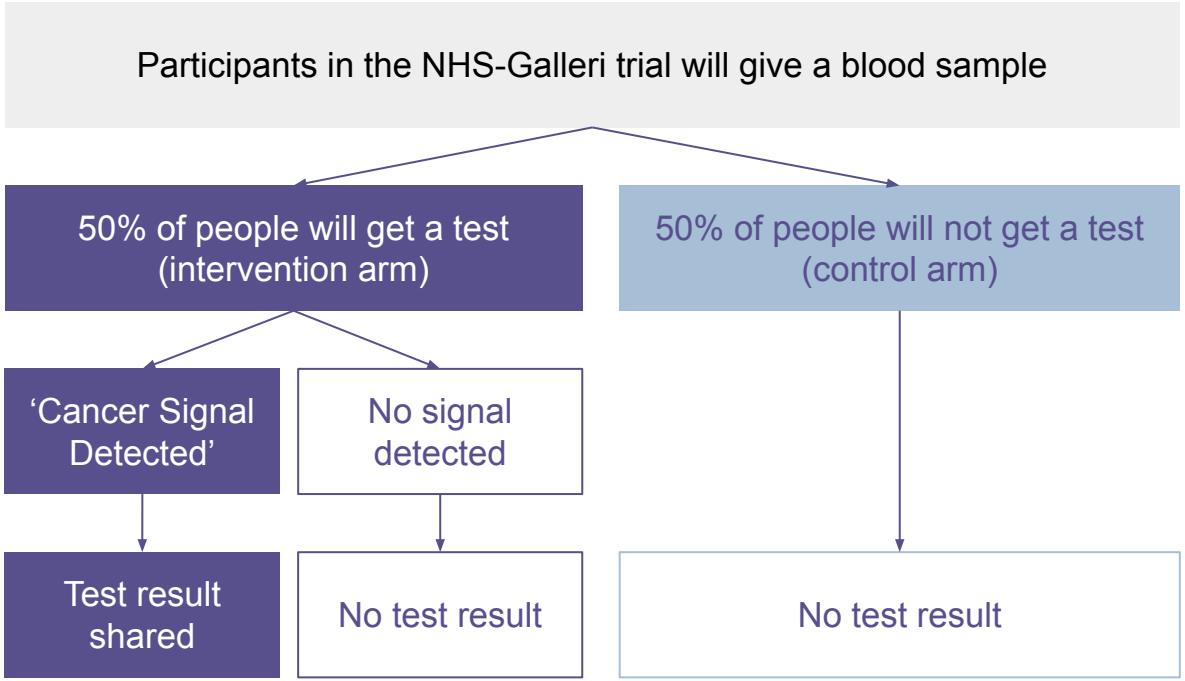
Sample collection using specialised mobile clinics

NHS-Galleri

Return of results to NHS-Galleri trial participants

NHS-Galleri

Most participants will not receive a test result



Referral of NHS-Galleri trial participants to the NHS[1]

NHS-Galleri

Referral process for trial participants with a ‘Cancer Signal Detected’ result

GRAIL labs inform trial nurses of result (copy of report shared)

Trial nurse informs participant of result by phone

Trial nurse sends follow up letter to participant and their GP

Trial nurse refers participant to appropriate two-week wait pathway via NHS e-referral system

Participant passes into NHS care

- A ‘Cancer Signal Detected’ result is not a diagnosis of cancer.
- Follow-up investigations must take place to confirm if the participant has cancer.

[1]NHS England. Guidance for NHS-Galleri trial referrals. 2021. https://future.nhs.uk/connect.ti/canc/view?objectId=119332229. Accessed April 2023.

Attending routine cancer screening appointments

NHS-Galleri

Participants in the NHS-Galleri trial are advised that it is important to continue to attend cancer screening appointments and inform their GP of any new or unusual symptoms

Potential future pilot

NHS England will decide whether to run a pilot

- If early trial data is promising, NHS England will run a pilot programme
- The pilot would offer up to 1 million tests is select areas in England from 2024

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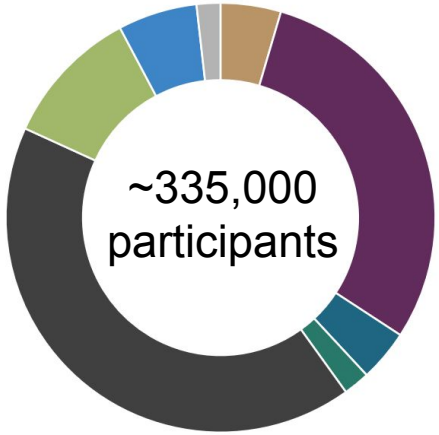

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Any questions?

Thank you

For more information, please visit:
www.nhs-galleri.org