Clinical Referral to the NHS Following Multi-Cancer Early Detection Test Results from the NHS-Galleri Trial

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INTRODUCTION

- Multi-cancer early detection (MCED) tests are designed to screen for multiple cancer types with a single test[1].
  - If shown to be effective in an asymptomatic population, MCED tests could increase the proportion of cancers diagnosed early, provided they are integrated effectively into existing healthcare systems.
- One blood-based MCED test (Galleri®) can identify DNA shed by cancer cells and predicts the tissue type or organ associated with this cancer signal (Cancer Signal Origin; CSO)[2].
  - The clinical utility of this MCED test for asymptomatic population screening in combination with existing NHS cancer screening programmes is being assessed in England among individuals aged 50–79 years in the randomised, controlled NHS-Galleri trial (NCT05611632)[1].
  - The trial represents an opportunity to establish how individuals with a 'Cancer Signal Detected' (CSD) test result that includes a predicted CSO can be efficiently referred for follow-up diagnostic investigation in a national healthcare system[1], whilst maintaining as near equivalent diagnostic investigation as possible between the intervention and control arms.

OBJECTIVES

- To describe how existing NHS standard-of-care cancer pathways are being used for the referral and diagnostic investigation of participants with a CSD MCED test result in the NHS-Galleri trial.
- To highlight elements of this approach that could inform screening trial conduct in the UK and the potential implementation of MCED tests for national population screening in future.

OVERVIEW

- CSOs predicted by MCED tests are a novel clinical indicator for the referral of asymptomatic individuals into existing NHS urgent suspected cancer pathways; for referrals from the NHS-Galleri trial, adaptations to standard NHS referral models were required to:
  - Enable efficient referral of trial participants via the existing NHS e-Referral Service (e-RS) into Trusts in England, which provide secondary care services including cancer diagnostic testing;
  - Facilitate receipt of trial participants by Trusts; and
  - Support clinical decision making on participant diagnostic journeys to reinforce standard-of-care approaches.
- We identified and addressed clinician and systems-level challenges in our approach, including:
  - Clinician understanding of the MCED test, interpretation of results, and appropriate subsequent referral pathway decisions;
  - Establishing a novel point of entry into existing urgent suspected cancer pathways; and
  - Ensuring follow-up and safety netting, especially in more complex cases (e.g., two predicted CSOs).
- The trial nurses managed potential anxiety around the MCED test result among participants and supported adequate understanding of CSD test result implications, including that:
  - Follow-up diagnostic testing is required to confirm cancer;
  - False positive results can occur; and
  - A CSD test result is not predictive of future genetic cancer risk.

Disclosures

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KEY RESULTS: WE ENABLED EFFICIENT REFERRAL OF TRIAL PARTICIPANTS WITH A 'CANCER SIGNAL DETECTED' MCED TEST RESULT FOR DIAGNOSTIC INVESTIGATION IN THE NHS

Optimising Referral of Trial Participants into Secondary Care

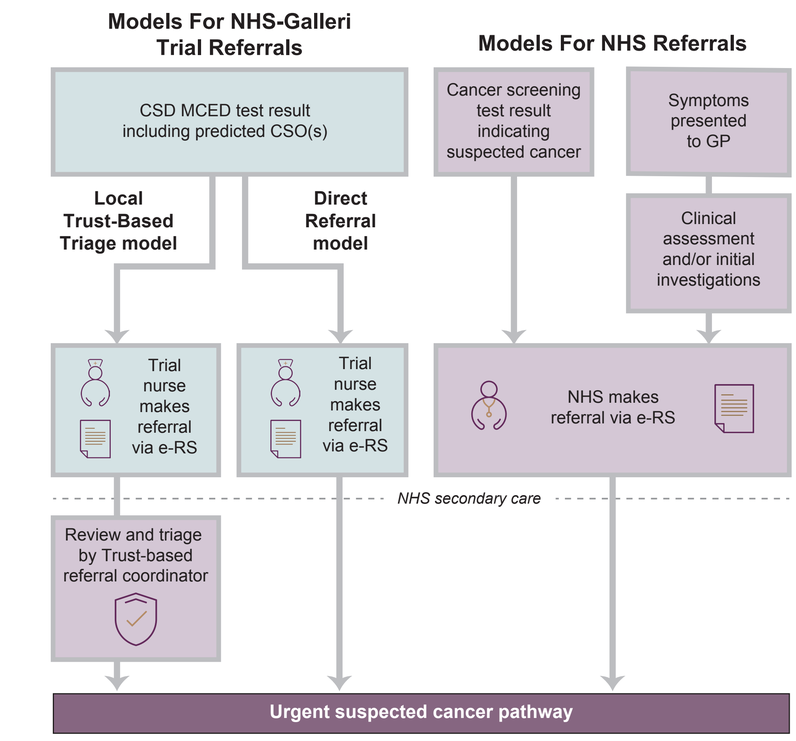
- We developed a national, standardised e-referral form to facilitate and expedite referrals of trial participants by trial nurses from a centralised hub via the e-RS to pre-specified Trusts in England for diagnostic testing.
  - The form provides the MCED test result report, including one or two predicted CSOs.
  - Unlike standard NHS referral forms, the trial referral form does not include additional healthcare information (e.g., medical history, blood results or a Summary Care Record), because the trial nurses do not have access to NHS clinical data.
  - Trial nurses are NHS employees, so they can access and make trial referrals via the e-RS.
  - Trusts can request support with understanding referrals from the trial nurses using contact details included on the form.

Facilitating Receipt of Trial Participants by Secondary Care

REFERRAL MODELS

- In collaboration with Cheshire and Merseyside and South East London Cancer Alliances, we developed and tested two models for referring participants with a CSD test result into standard-of-care cancer pathways, both currently being used in the trial (**Figure 1**).

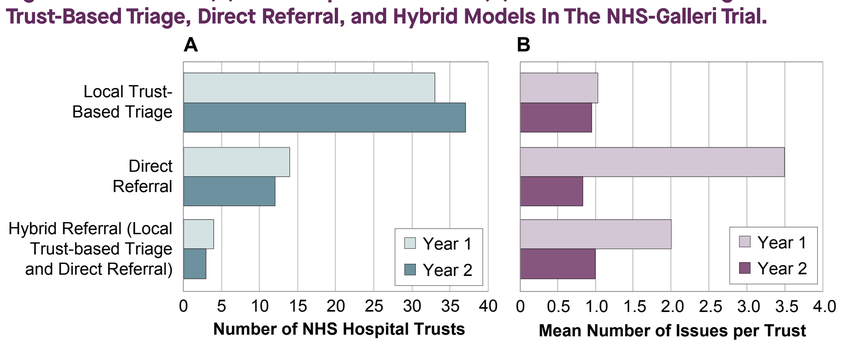
Figure 1. Referral Models Used in the NHS-Galleri Trial Compared With Standard NHS Referral.



CSD: 'Cancer Signal Detected'; CSO: Cancer Signal Origin; e-RS: NHS e-Referral Service; GP: general practitioner; MCED: multi-cancer early detection; NHS: National Health Service.

- In the Local Trust-Based Triage model, a designated Trust-based referral coordinator triages referrals made by the trial nurses and re-routes participants into the most appropriate local urgent suspected cancer pathway based on the predicted CSO(s) in the test result report, or to a non-specific symptoms (NSS) pathway, Rapid Diagnostic Centre (RDC) or pre-diagnosis service. This became the preferred model for the trial.
  - Referral coordinators have local operational knowledge of the Trust, and are thus well placed to triage referrals and refer participants into the most appropriate pathway in their locality.
  - Referral coordinators are also able to monitor each participant's diagnostic journey, which is particularly important for cases that may require referral into more than one pathway for a conclusive diagnosis.
- In the Direct Referral model, trial nurses make referrals directly into the relevant urgent suspected cancer pathway, based on the predicted CSO(s) in the test result report.
  - This model places no additional burden on Trusts relating to referral decisions; however, trial nurses have less local operational knowledge than a Trust referral coordinator and often face complexity in deciding between local pathway options.
  - Although supporting information about the trial is sent with each referral, there is an increased risk of the referral being erroneously declined; this is likely due to a lack of understanding about the trial process, given each secondary care clinician may receive few referrals from the trial, if any.
- A small number of Trusts used a hybrid model, in which most referrals were made via Local Trust-Based Triage, but Direct Referral was used for some specialties.

Figure 2. Number of (A) NHS Hospital Trusts and (B) Issues Per Trust Using Local Trust-Based Triage, Direct Referral, and Hybrid Models In The NHS-Galleri Trial.



Year one: N = 51 Trusts; year two: N = 52 Trusts. Data was collected up to 4 December 2023.

- The number of Trusts using the recommended Local Trust-Based Triage model increased from 64.7% at the end of year one to 71.2% at the end of year two (**Figure 2A**).
- There were ~3 times more referral issues (i.e., referrals not managed according to current clinical guidance) per Trust raised among Trusts using Direct Referral in the first year vs. those using Local Trust-Based Triage (**Figure 2B**).
- A major source of referral issues was a lack of awareness of the trial among clinicians at the Trusts.
- Several Trusts switched to Local Trust-Based Triage in the second year due to issues they experienced with Direct Referral in the first year.

SAFETY NETTING

Central Safety Netting	Local Trust Safety Netting
Responsibility lies with the trial team. Trial nurses deliver CSD test results by telephone; participants are briefed about what to expect once referred. Trial team contacts participants approx. every seven days after referral to ensure they have been offered an appointment for clinical assessment; participants can raise any concerns in these calls. If an appointment is not secured, the trial team escalates to the trial coordinator at the relevant Trust. Trial nurses send reconciliation emails to each Trust to ensure that the number of referrals sent matches the number received by the Trust, and check whether referrals have been made by reviewing actions recorded in the e-RS.	Trial clinical champions and Trust referral coordinators were established at each Trust, and the relevant service names, clinics, and urgent suspected cancer pathway e-RS codes were identified. Responsibility lies with named trial clinical champions at each Trust. Local clinical champions respond to any simple queries from receiving clinicians, and escalate questions relating to the referral to the trial team. Local Trust referral coordinators support trial clinical champions with these processes.

Supporting Clinical Decision Making

- Any diagnostic investigation for trial participants takes place within the NHS, and is considered to be outside of the trial.
  - Receiving Trusts are responsible for the clinical management of referred trial participants according to national[3] and local guidance for urgent suspected cancer referrals.
- We broadly matched all CSO options resulting from a CSD test result to existing adult NHS urgent suspected cancer pathways (**Table 1**), using advice and clinical expertise from primary and secondary healthcare professionals external to the trial.
  - This map is intended to help trial nurses and Trust referral coordinators refer participants to the most appropriate urgent suspected cancer pathway in the absence of any symptoms.
  - The downstream diagnostic pathway for referrals from the trial are thus the same as for referrals from standard points of entry in the NHS, minimising deviation from standard-of-care practices and additional burden on secondary care.
  - The national target in England for urgent suspected cancer referrals is applied to referrals from the trial, to ensure urgency and timeliness in the diagnostic investigation of referrals.

Table 1. Map of CSOs to Existing Standard-of-Care Urgent Suspected Cancer Pathways.

CSO(s)	Urgent suspected cancer pathway
Anus; Colon, Rectum	Lower gastrointestinal
Bladder, Urothelial Tract; Kidney; Prostate	Urology
Bone and Soft Tissue	Sarcoma
Breast	Breast
Cervix; Ovary; Uterus	Gynaecological
Head and Neck; Thyroid Gland	Head and neck
Liver, Bile Duct; Pancreas, Gallbladder; Stomach; Oesophagus	Upper gastrointestinal
Lung	Lung
Lymphoid Lineage; Myeloid Lineage; Plasma Cell Lineage	Haematology
Melanocytic Lineage	Skin
Neuroendocrine Cells of Lung or Other Organs	Lung/Other; a referral may be made to a local neuroendocrine multidisciplinary Trust, if available

CSO: Cancer Signal Origin.

- We developed a guidance document for clinicians to support the interpretation of existing standard-of-care practice following a CSD test result during the NHS-Galleri trial.
  - This document emphasises the use of existing national and local guidelines, clinical judgement, and clinician–patient decision making.
  - It includes extensive frequently asked questions on managing referrals and the trial in general.
  - The document captures key learnings and safety information from Trust experiences of managing trial referrals based on outcomes from frequent clinical meetings between trial team representatives and NHS England.
- The trial team works closely with Cancer Alliances and Trusts to ensure best practice is shared rapidly (e.g., via intranet toolkits, briefing documents and webinars).

CONCLUSIONS

- Our innovative approach enabled referral of participants with a CSD test result from a large, randomised controlled trial into appropriate existing urgent suspected cancer pathways across NHS Hospital Trusts in England.
  - This process was designed to be simple and low-burden for secondary care, and places no additional direct workload burden on primary care.
  - Participants with a CSD test result are expected to receive diagnostic investigation broadly in line with the current standard-of-care and national targets in England[3,4].
  - We hope insights from our work could help accelerate screening trial conduct in the UK, and support the implementation of MCED population screening programmes in future.

References

1. Klein, E.; .Madhavan, S.; Beer, T.M.; et al., A. Dying To Find Out: The Cost of Time at the Dawn of the Multicancer Early Detection Era. *Cancer Epidemiol Biomarkers Prev.* 2023, 32(8), 1003–1010. 2. Schrag, D.; Beer, T.M.; McDonnell, C.H.; et al., Blood-Based Tests for Multicancer Early Detection (PATHFINDER): A Prospective Cohort Study. *The Lancet* 2023, 402, 1251–1260. 3. Suspected Cancer: Recognition and Referral NICE Guideline [Ng12]. Available online: https://www.nice.org.uk/guidance/ng12 (accessed 21 March 2024). 4. NHS England Faster Diagnosis. Available online: https://www.england.nhs.uk/cancer/faster-diagnosis/ (accessed on 21 March 2024).

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