The Impact of Screening Participation on Modelled Mortality Benefits of a Multi-Cancer Early Detection Test by Socioeconomic Group in England

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INTRODUCTION

- Cancer burden is higher and cancer screening participation lower among individuals living in more socioeconomically deprived areas of England, contributing to worse health outcomes and shorter life expectancy
- New approaches to screening and diagnosis are needed to contribute substantially to an overall reduction in late-stage cancer diagnoses and to reduce inequalities
- Blood-based multi-cancer early detection (MCED) tests are designed to detect a shared cancer signal from a single blood sample
  - Blood-based MCED tests could make screening more accessible, given samples can be collected in a variety of convenient locations[1]
  - The clinical utility of a previously-validated MCED test[2], Galleri®, is currently being assessed in the large, pragmatic, randomised controlled trial, NHS-Galleri (NCT05611632)[3]
  - Galleri® has higher sensitivity for poor-prognosis cancers[2]; An MCED screening programme may have greater relative benefits in more deprived groups, depending on relative screening participation in these groups

OBJECTIVE

- In this modelling study, we estimated the:
  - Potential differential reductions in late-stage cancer incidence and mortality with MCED screening in groups stratified by an area-based marker of relative deprivation (the index of multiple deprivation, IMD)[4]
  - Impact of screening participation in each IMD group on these benefits

METHODS

Data

- This work uses data provided by patients and collected by the NHS as part of their care and support
- The data are collated, maintained and quality assured by the National Cancer Registration and Analysis Service (NCRAS), part of NHS England[5,6]
- NCRAS provided incidence and five-year relative survival data for 24 cancer types and one 'other' category comprising low-incidence cancers[7], based on individuals aged 50–79 years who were diagnosed with cancer between 2013 and 2018
- Crude incidence rates (per 100,000 persons) were calculated for each cancer type by stage, five-year age band, and IMD quintile
  - For ovary, cervix, uterus, and prostate cancers, the rate was adjusted by the proportion of the relevant sex in the IMD group
  - The IMD is a set of relative measures of deprivation for small areas (Lower Layer Super Output Areas) across England
  - For this model, lymphoid leukaemia, myeloid neoplasm, and plasma cell neoplasm were considered unstageable
- For each five-year age band, five-year net survival was calculated using the Pohar Perme estimator and a period approach[8]
- The analysis was censored on 5 January 2019, providing a minimum of one year of follow-up for all individuals

Interception Model

- An interception model was used to estimate stage shift and associated potential mortality benefits[9,10]
  - The interception model is a state transition model that estimates the impact of an MCED-based screening programme when added to usual care (i.e., the current screening, referral, diagnostic, and treatment practices in England)
- Starting from the number of incident cancers in usual care, the number that would have been present but not clinically diagnosed at earlier stages in the preceding years was calculated using cancer type- and stage-specific dwell time estimates
  - An exponential distribution was used to model variation between cancers of the same type
- The number of cancers intercepted at each stage was calculated based on cancer type- and stage- specific sensitivity of an MCED test[1], adjusted using isotonic regression so that test sensitivity did not decrease by stage
- Cancers that grow quickly (shorter dwell times) are more likely to be missed as the interval between tests increases, such as by missed screening appointments

Interception Model — Assumptions

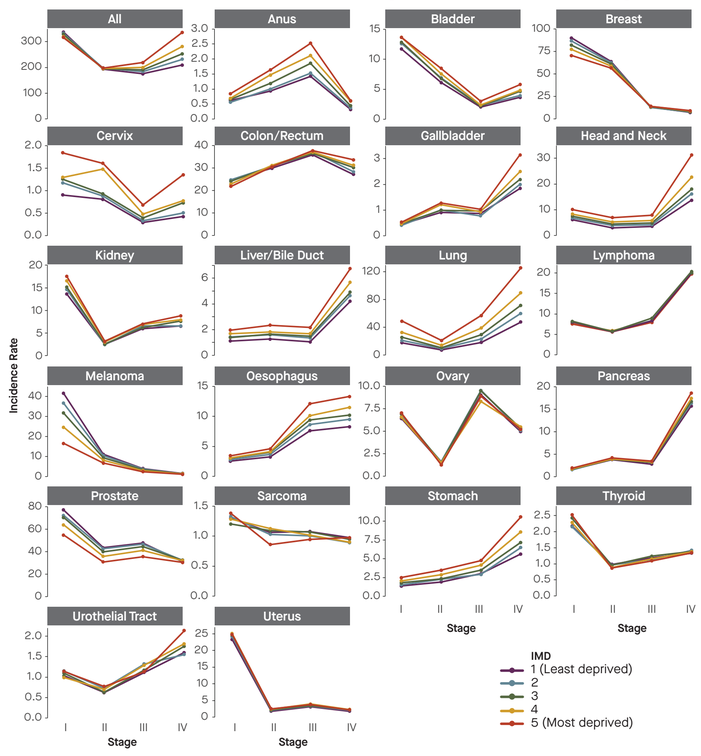
- The model made the simplifying assumption that diagnostic resolution occurred shortly after screen detection
- The model stratified the incident population by IMD group, and varied the proportion of individuals who participated in annual screening rounds
  - The model assumed everyone participated in the initial (prevalent) screening round
  - This was a simplifying assumption; real-world screening participation is usually lower in prevalent than incident screening[11]
  - The proportion of those participating in subsequent (incident) screening rounds reflected the likelihood of participation for each individual within the group, to best reflect real-world patterns of screening participation[12]
- A survival hazard ratio (HR) of three and a fast cancer dwell time for each cancer type and stage was assumed
  - The survival HR reflects a conservative assumption that cfDNA-detectable (cfDNA+) tumours carry three times the risk of cancer death than cfDNA-non-detectable (cfDNA–) tumours, based on recent findings[13]
  - There remains uncertainty regarding these assumptions; some of this may be resolved using the results of the NHS-Galleri trial and emerging evidence on cfDNA shedding
- Participation scenarios from 10–100% were modelled
  - Modelling 100% participation was required to fully understand the differential benefits between IMD groups without the confounding effect of participation

KEY RESULTS: MCED-BASED SCREENING IS LIKELY TO BENEFIT MORE DEPRIVED GROUPS THE MOST, AND UNLIKELY TO EXACERBATE EXISTING HEALTH INEQUALITIES

Cancer Incidence Rates by IMD Group

- There was an average annual cancer incidence of 1214 per 100,000 persons in 50–79 year olds in the period 2013–2018
  - Of these cancers, 1164 per 100,000 were stageable and 973 per 100,000 were staged, with 450 per 100,000 diagnosed at a late stage (III or IV)
- For all cancers combined, the most deprived IMD group had the greatest stage IV cancer incidence rate (**Figure 1**)
  - This appears to be driven by several cancer types, including anus, bladder, cervix, colon/rectum, gallbladder, head and neck, kidney, liver/bile duct, lung, oesophagus, pancreas, stomach, and urothelial tract cancers
  - For almost all cancer types, the least deprived group had the lowest incidence rates of stage IV disease

Figure 1. Crude Incidence Rate by Cancer Stage by IMD for All Cancers Combined and 21 Stageable Cancer Types Diagnosed Between 2013 and 2018 in Adults Aged 50–79 Years in England.



IMD, index of multiple deprivation

Overall Late-Stage Cancer Incidence and Mortality Reductions with MCED Screening by IMD Group

- In a 100% participation scenario, late-stage incidence was substantially reduced in all deprivation groups when MCED screening was added to usual care (**Table 1**)
  - The benefit was greater in more deprived groups
  - The most deprived group still had the greatest number of late-stage diagnoses
- Cancer mortality was consistently higher in more deprived groups under usual care, owing to the higher initial cancer burden (**Table 1**)
  - When MCED screening was added to usual care, mortality was reduced to a greater extent in more deprived groups

Table 1. Modelled Late-Stage Cancer Incidence and Mortality Rate Reduction by IMD group in an Incident Round of MCED Screening. Results are presented as the rate per 100,000 persons.

	IMD Group				
	1 (Least Deprived)	2	3	4	5 (Most Deprived)
Found Via Usual Care and MCED (%)	1107 (100)	1144 (100)	1178 (100)	1238 (100)	1348 (100)
Found Via Usual Care (%)	809 (73)	819 (72)	827 (70)	845 (68)	879 (65)
MCED Detected (%)	298 (27)	325 (28)	351 (30)	393 (32)	469 (35)
Late-Stage Diagnosis With Usual Care (%)	427 (39)	460 (40)	496 (42)	551 (45)	645 (48)
Late-Stage Diagnosis With MCED (%)	266 (24)	283 (25)	301 (26)	328 (26)	370 (27)
Reduction in Late-Stage Diagnosis With MCED (%)	160 (38)	178 (39)	195 (39)	223 (40)	274 (43)
Cancer Mortality Rate With Usual Care	358	394	430	489	594
Cancer Mortality Rate With MCED	299	329	358	407	495
Reduction in Cancer Mortality With MCED (%)	60 (17)	66 (17)	72 (17)	81 (17)	99 (17)

IMD, index of multiple deprivation; MCED, multi-cancer early detection.

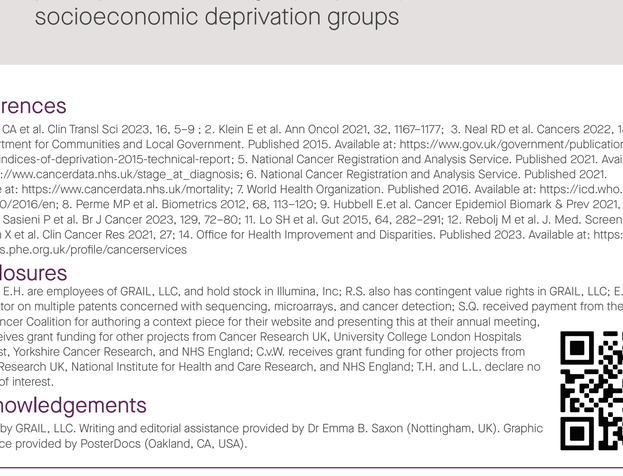
Late-Stage Cancer Incidence and Mortality Reductions with MCED Screening by Cancer Type and IMD Group

- Substantial differences in late-stage incidence and mortality reduction per 100,000 persons between most and least deprived IMD groups were noted for the following cancer types:
  - Lung cancer (incidence rate, 277 vs 93; late stage incidence reduction, 102 vs 34; mortality reduction, 29 vs 10)
  - Head and neck cancer (incidence rate, 65 vs 30; late stage incidence reduction, 30 vs 13; mortality reduction, 10 vs 5) and
  - Colon/rectum cancer (incidence rate, 137 vs 123; late stage incidence reduction, 48 vs 41; mortality reduction, 26 vs 21)
  - There was also a steep gradient in cancers shifted earlier per 100,000 persons between the most and least deprived groups for liver/bile duct (30 vs 17), oesophagus (39 vs 24), and stomach (26 vs 14) cancers, but as these cancers are less prevalent, they contributed less to the overall result
- For some cancer types (e.g., lymphoma, gallbladder, breast), late-stage incidence and mortality reduction was equivalent between most and least deprived groups
- For melanoma, thyroid, and urothelial tract cancers, there was no modelled benefit to either the most or least deprived group
  - The MCED test has low sensitivity for these cancer types in the early stages and the prevalence of thyroid and urothelial tract cancer is relatively low
  - Net survival analysis in a population of this size yielded some unreliable estimates due to small numbers, particularly for these lower-prevalence cancers

Impact of Screening Participation on the Benefits of MCED Screening by IMD Group

- The benefits of screening were attenuated by non-participation (**Figure 2**)
  - At each participation level, percentage reduction in late-stage diagnosis and cancer mortality with MCED screening was greater in more deprived groups
  - With participation rates reflecting those of current England national cancer screening programmes (60% in the most and 80% in the least deprived group[14], reductions in late-stage diagnoses and cancer mortality were greater in more deprived groups

Figure 2. Reductions in Late-Stage Cancer Diagnoses (A) and Cancer Mortality (B) per 100,000 Persons Available to be Screened, by Screening Participation Rate and IMD Group.



IMD, index of multiple deprivation; MCED, multi-cancer early detection.

CONCLUSIONS

- MCED screening is a promising intervention for the reduction of late-stage cancer diagnosis and consequent mortality
- It is unlikely to exacerbate existing health inequalities, and is a potentially powerful means of reducing socioeconomic inequalities in late-stage diagnosis, which should translate into reduced disparities in cancer mortality rates
- For the greatest possible benefit, an MCED implementation strategy should focus on enhancing equitable, informed participation, enabling equal participation across all socioeconomic deprivation groups

References

1. Clarke CA et al. Clin Transl Sci 2023, 16, 5–9 ; 2. Klein E et al. Ann Oncol 2021, 32, 1167–1177; 3. Neal RD et al. Cancers 2022, 14, 4818 4. Department for Communities and Local Government. Published 2015. Available at: https://www.gov.uk/government/publications/english-indices-of-deprivation-2015-technical-report; 5. National Cancer Registration and Analysis Service. Published 2021. Available at: https://www.cancerdata.nhs.uk/stage_at_diagnosis; 6. National Cancer Registration and Analysis Service. Published 2021. Available at: https://www.cancerdata.nhs.uk/mortality; 7. World Health Organization. Published 2016. Available at: https://icd.who.int/browse10/2016/en; 8. Perme MP et al. Biometrics 2012, 68, 113–120; 9. Hubbell E.et al. Cancer Epidemiol Biomark & Prev 2021, 30, 460; 10. Sasieni P et al. Br J Cancer 2023, 129, 72–80; 11. Lo SH et al. Gut 2015, 64, 282–291; 12. Rebolj M et al. J. Med. Screen. 2019; 13. Chen X et al. Clin Cancer Res 2021, 27; 14. Office for Health Improvement and Disparities. Published 2023. Available at: https://fingertips.phe.org.uk/profile/cancerservices

Disclosures

R.S. and E.H. are employees of GRAIL, LLC, and hold stock in Illumina, Inc; R.S. also has contingent value rights in GRAIL, LLC; E.H. is an inventor on multiple patents concerned with sequencing, microarrays, and cancer detection; S.Q. received payment from the Global Lung Cancer Coalition for authoring a context piece for their website and presenting this at their annual meeting, and receives grant funding for other projects from Cancer Research UK, University College London Hospitals NHS Trust, Yorkshire Cancer Research, and NHS England; C.v.W. receives grant funding for other projects from Cancer Research UK, National Institute for Health and Care Research, and NHS England; T.H. and L.L. declare no conflict of interest.

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