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Short Communication

Performance of a targeted methylation-based multi-cancer early detection test by race and ethnicity

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ABSTRACT

Disparities in cancer screening and outcomes based on factors such as sex, socioeconomic status, and race and ethnicity in the United States are well documented. A blood-based multi-cancer early detection (MCED) test that detects a shared cancer signal across multiple cancer types and also predicts the cancer signal origin was developed and validated in the Circulating Cell-free Genome Atlas study (CCGA; NCT02889978). CCGA is a prospective, multicenter, case-control, observational study with longitudinal follow-up (overall $N = 15{,}254$). In this pre-specified, exploratory, descriptive analysis, test performance was evaluated among racial and ethnic groups.

Overall, 4077 participants comprised the independent validation set with confirmed cancer status (cancer: $n = 2823$; non-cancer: $n = 1254$). Participants were stratified into the following racial/ethnic groups: Black (non-Hispanic), Hispanic (all races), Other (non-Hispanic), Other/unknown and White (non-Hispanic). Cancer and non-cancer participants were predominantly White ($n = 2316$, 82.0% and $n = 996$, 79.4%, respectively). Across groups, specificity for cancer signal detection ranged from 98.1% [$n = 103$; 95% CI: 93.2–99.5%] to 100% [$n = 85$; 95% CI: 95.7–100.0%]. The sensitivity for cancer signal detection across groups ranged from 43.9% [$n = 57$; 95% CI: 31.8–56.7%] to 63.0% [$n = 192$; 95% CI: 56.0–69.5%] and generally increased with clinical stage.

The MCED test had consistently high specificity and similar sensitivity across racial and ethnic groups, though results are limited by sample size for some groups. Results support the broad applicability of this MCED test and clinical implementation on a population scale as a complement to standard screening.

1. Introduction

Advancements in cancer screening may help reduce disparities and improve cancer outcomes across historically disadvantaged racial and ethnic groups.(Zavala et al., 2021; Cancer Disparities - National Cancer Institute, 2022) Screening assays using patterns of DNA methylation as cancer biomarkers are one promising tool.(van der Pol and Mouliere, 2019; Roy and Tiirikainen, 2020) As some evidence suggests DNA methylation patterns may differ between racial and ethnic sub-populations,(Zhang et al., 2011; Pinzon Cortes and El-Osta, 2021) care must be taken to confirm consistent performance of novel screening technologies across the general population.

A multi-cancer early detection (MCED) test (Galleri®) that analyzes methylation patterns in plasma cell-free DNA can detect a shared cancer signal across multiple cancer types and predict the cancer signal origin (CSO) from a single blood draw. This MCED test employs a targeted

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methylation sequencing assay and machine learning classifiers.(Liu et al., 2020) Independent clinical validation of this MCED test occurred in the Circulating Cell-free Genome Atlas third substudy (CCGA; NCT02889978), with the test demonstrating high specificity (99.5%) and accuracy of CSO prediction (88.7% for the top CSO in true positives) while detecting a cancer signal across diverse cancers (>50 types).(Klein et al., 2021) The objective of this pre-specified descriptive analysis was to evaluate the performance of the MCED test across racial and ethnic groups in the third CCGA substudy.

2. Methods

2.1. Study design and participants

CCGA is a prospective, multicenter, case-control, observational study with longitudinal follow-up that was divided into three pre-specified substudies (Supplemental Methods). This analysis is based on the third and final substudy. Sample collection and processing, data collection, and classification of cancer signal detection are described in Supplemental Methods.

2.2. Inclusion and exclusion criteria

Participants eligible for enrollment in the cancer arm included US adults ≥20 years old diagnosed with cancer and/or who were scheduled to undergo biopsy and/or surgical resection for known or highly suspected malignancy (see also Supplemental Methods). Non-cancer participants were screened at participating centers and were required to have their non-cancer status confirmed at least one year post blood draw, either by review of the medical records at the clinical site or by participant self-reported outcomes reported through a phone call. Cancer and non-cancer participant groups were stratified by race and ethnicity as: Black (non-Hispanic), Hispanic (all races), Other (non-Hispanic) (including but not limited to Asian, Native Hawaiian, Pacific Islander, American Indian, Alaska Native), Other/unknown, and White (non-Hispanic). Participants were required to provide written informed consent. The study was approved by the Institutional Review Board or an independent ethics committee at each participating trial site and was conducted in accordance with the International Conference on Harmonization for Good Clinical Practice guidelines and the Declaration of Helsinki.

2.3. Measurement of test performance

MCED test performance metrics for cancer signal detection included specificity (the proportion of participants with a negative test [no cancer signal detected] result among non-cancer participants) and sensitivity (the proportion of participants with a positive test [cancer signal detected] result among all cancer participants in the analysis set), as described previously.(Klein et al., 2021) Sensitivity and specificity for the MCED test were stratified by racial and ethnic groups. Accuracy of CSO prediction by cancer type and stage, stratified by race and ethnicity, was not part of this pre-specified analysis. The sensitivity with which a cancer signal was detected for 12 individual pre-specified cancer types (anus, bladder, colon/rectum, esophagus, head and neck, liver/bile duct, lung, lymphoma, ovary, pancreas, plasma cell neoplasm, and stomach) was assessed by racial and ethnic groups. These 12 cancer types are a subset of the >50 cancer types with a shared cancer signal detected by the screening test and account for approximately two-thirds of cancer-related mortality in the USA(American Cancer Society. Cancer Facts and Figures, 2021); they were selected based on the results from the first CCGA sub-study and Surveillance, Epidemiology, and End Results mortality data.(Liu et al., 2020; Surveillance, Epidemiology, and End Results (SEER) Program, 2022)

To assess whether differences in the distribution of cancer types and cancer stages within each group impacted the observed group-specific sensitivity, expected sensitivity values were calculated post hoc for each group using the cancer type- and stage-specific sensitivity rates reported in the overall CCGA3 population(Klein et al., 2021) multiplied by the total counts of each cancer type and stage combination for each racial and ethnic group. Expected sensitivity represents the sensitivity if test performance for each cancer type and stage was the same across racial and ethnic groups, and the only difference was the distribution of cancer types and stages between groups.

2.4. Statistical analysis

The Confirmed Status Analysis Set (all analyzable participants in the third CCGA substudy who were confirmed as either a cancer participant or a non-cancer participant at year-one follow-up) was evaluated. This pre-specified exploratory analysis was not powered to detect statistical differences in sensitivity and specificity between racial and ethnic groups, so no formal statistical tests were conducted. Descriptive statistics are reported. Unless otherwise stated, 95% confidence intervals (CIs) for test performance measures (sensitivity, specificity) were calculated using the Wilson (score) method. Wilson confidence intervals were chosen due to having better coverage rates for small sample sizes while not being over-conservative.(Erdoğan and Gülhan, 2016) All analyses were carried out using R software, version 3.6.0.

3. Results

3.1. Participant disposition

A total of 5309 participants were included in the third and final CCGA validation substudy (enrolled as cancer, $n = 3237$; enrolled as non-cancer, $n = 2069$; retrospectively failing eligibility, $n = 3$). Of these, 4077 (cancer, $n = 2823$; non-cancer with non-cancer status confirmed at year one, $n = 1254$) were included in the Confirmed Status Analysis Set (Supplemental Table 1, Supplemental Table 2).

3.2. Participant demographics and baseline characteristics

Demographics and baseline characteristics were mostly consistent between cancer and non-cancer participant groups (Table 1). Mean (SD) age was 60.6 (12.4) years and 55.4% of participants were female (with a higher percentage in the non-cancer versus cancer group). In the cancer group, most participants (54.9%) had stage I/II cancer. Both cancer and non-cancer groups were predominantly White (non-Hispanic) (82.0% and 79.4%, respectively).

3.3. Test performance: Specificity

Specificity for cancer signal detection was 99.5% [$n = 1254$; 95% CI: 99.0–99.8%](Klein et al., 2021) and was similar across all racial and ethnic groups, with overlapping 95% confidence intervals. Specificity was 100% for the Black (non-Hispanic) [$n = 85$; 95% CI: 95.7–100.0%], Other (non-Hispanic) [$n = 33$; 95% CI: 89.6–100.0%], and Other/Unknown [$n = 37$; 95% CI: 90.6–100.0%] groups, 98.1% [$n = 103$; 95% CI: 93.2–99.5%] for the Hispanic (all races) group, and 99.6% [$n = 996$; 95% CI: 99.0–99.8%] for the White (non-Hispanic) group.

3.4. Test performance: Sensitivity

3.4.1. Observed sensitivity

Overall sensitivity for cancer signal detection for the MCED test in the whole population was 51.5% [$n = 2823$; 95% CI: 49.6–53.3%](Klein et al., 2021) (Fig. 1a). When broken down by racial and ethnic groups, sensitivity ranged from 43.9% [$n = 57$; 95% CI: 31.8–56.7%] within the Other (non-Hispanic) group to 63.0% [$n = 192$; 95% CI: 56.0–69.5%] within the Hispanic (all races) group (Fig. 1a).

For all racial and ethnic groups, sensitivity increased with clinical

Table 1
Participant demographics and baseline characteristics.

		Cancer (*N* = 2823)	Non-cancer (*N* = 1254)	Total (*N* = 4077)
Age (years)	Mean (SD)	62.6 (11.8)	56.2 (12.6)	60.6 (12.4)
Gender	Female	1394 (49.4%)	864 (68.9%)	2258 (55.4%)
Race and ethnicity	American Indian or Alaska native	8 (0.3%)	7 (0.6%)	15 (0.4%)
	Asian, native Hawaiian or Pacific islander	49 (1.7%)	26 (2.1%)	75 (1.8%)
	Black, non-Hispanic	193 (6.8%)	85 (6.8%)	278 (6.8%)
	Hispanic	192 (6.8%)	103 (8.2%)	295 (7.2%)
	Other	65 (2.3%)	37 (3.0%)	102 (2.5%)
	White, non-Hispanic	2316 (82.0%)	996 (79.4%)	3312 (81.2%)
Family history Of Cancer	Yes	2254 (79.8%)	1014 (80.9%)	3268 (80.2%)
	No	493 (17.5%)	210 (16.7%)	703 (17.2%)
	Not sure	76 (2.7%)	30 (2.4%)	106 (2.6%)
Clinical Cancer Stage	I	849 (30.1%)	NA	849 (20.8%)
	II	703 (24.9%)	NA	703 (17.2%)
	III	566 (20.0%)	NA	566 (13.9%)
	IV	618 (21.9%)	NA	618 (15.2%)
	Not expected to be staged[a]	67 (2.4%)	NA	67 (1.6%)
	Missing	20 (0.7%)	NA	20 (0.5%)

AJCC, American Joint Committee on Cancer; NA, not applicable; SD, standard deviation.

[a] Includes cancers that do not have a staging classification per AJCC criteria such as myeloid neoplasm and lymphoid leukemia.

stage, with minor exceptions for stage IV in two groups [Other (non-Hispanic) and Other/Unknown] with small sample sizes (Fig. 1b). Stage II sensitivity among the Hispanic group (68.4% [n = 38; 95% CI: 52.5–80.9%]) was notably higher than the stage II sensitivity of other groups, such as White (non-Hispanic) (38.3% [n = 582; 95% CI: 34.5–42.3%]) and Black (non-Hispanic) (41.4% [n = 58; 95% CI: 29.6–54.2%]) (Fig. 1b).

Sensitivity of cancer signal detection was determined within each racial and ethnic group for the 12 pre-specified cancers that together account for approximately two-thirds of annual US cancer deaths. (American Cancer Society. Cancer Facts and Figures, 2021) Results were similar across racial and ethnic groups, with 95% CIs for each group overlapping the overall sensitivity for each cancer, apart for some groups with extremely small sample sizes (Supplemental Fig. 1). Specifically, for lung cancer, sensitivity was lower in the Other (non-Hispanic) group (33.3% [n = 9; 95% CI: 12.1–64.6%]) compared to the rest of the groups. For ovarian cancer, the test did not detect any of the three cases in the Black (non-Hispanic) group, but did detect most or all of the cases in the other racial and ethnic groups (Supplemental Fig. 1).

3.4.2. Post-hoc analysis: Assessing the effect of cancer type and stage on sensitivity (expected sensitivity)

In order to assess the effect of the distribution of cancer types and stages on group-specific sensitivity, expected sensitivity values were calculated for each group assuming test performance for any given cancer type and stage was identical between groups. There was minimal change in sensitivity when comparing observed to expected values (Fig. 1a), indicating that residual variation between groups may be due to differences in the distribution of cancer types and stages.

4. Discussion

In this pre-specified subanalysis of the large-scale CCGA3 clinical validation study, the MCED test demonstrated consistently high specificity even when results were assessed by race or ethnicity. As this is a descriptive analysis, direct comparisons between racial and ethnic groups were limited, but of note, the 95% CIs were generally consistent with sensitivities being similar to the overall sensitivity reported previously.(Klein et al., 2021) A pattern of increasing sensitivity with progressively higher clinical stage was also seen, similar to previous reporting.(Klein et al., 2021) Sensitivity was similar among racial and ethnic groups in most of the 12 pre-specified cancers that together account for nearly two-thirds of annual US cancer deaths.(American Cancer Society. Cancer Facts and Figures, 2021)

A numerically higher average sensitivity and stage II sensitivity were observed in the Hispanic group, which could be explained by the presence in that group of cancer types and stages that were more readily detectable by the MCED test or by differential test performance between groups for specific cancer types and stages. Additionally, some differences in MCED test sensitivity across racial and ethnic groups may be due to factors beyond cancer type and stage, including heterogeneity in the distribution of histological cancer subtypes across groups, as has been reported elsewhere.(Islami et al., 2019; Kong et al., 2020)

To evaluate some of these possibilities, a post hoc analysis was performed to assess the impact of the distribution of cancer types and clinical stages within each group on group-specific sensitivity. The observed sensitivity within each group was compared to the sensitivity expected to be measured if test performance for each cancer type and stage was the same across racial and ethnic groups (by using the cancer type- and stage-specific sensitivity rates reported in the overall CCGA3 population). This comparison yielded a similar pattern to the original analysis, i.e., similar sensitivity across racial and ethnic groups, but higher sensitivity in the Hispanic group. This suggests that some of the remaining difference between groups may be explained by unequal distribution of cancer types and stages between groups (i.e., the higher stage II sensitivity in the Hispanic group could be due to the presence of a greater proportion of certain cancer types more detectable by the MCED test and not superior test performance for the Hispanic group).

Higher rates of cancer detection achieved by advances in screening may help address racial and ethnic disparities in cancer outcomes, including mortality, through the diagnosis of cancer at earlier stages. Models of late-stage cancer diagnosis interception strongly suggest that diagnosis of cancers at an earlier stage before metastasis could result in significant mortality benefits.(Clarke et al., 2020; Hubbell et al., 2021; Clarke et al., 2022) One such study showed consistent relative mortality benefits across racial and ethnic groups in hypothetical scenarios of stage IV cancers being diagnosed instead at stages I-III.(Clarke et al., 2022)

There are several limitations to the present analysis. First, the analysis was not powered to detect statistical differences between racial and ethnic groups. While CCGA3 was a large-scale validation study, about 80% of the sample population was non-Hispanic White. Due in large part to resulting small sample sizes and unequal variances of some groups, formal statistical testing of the underlying hypothesis was limited. While larger datasets are needed to adequately compare MCED test performance across subpopulations, this initial analysis finds no strong evidence of deviations in test sensitivity in any group. Second, the distribution of cancer types and stages in this analysis may not reflect the overall distribution in the adult population since participants were not selected for enrollment based on cancer type or stage nor to reflect the demography of the larger population. Third, while the impact of the distribution of cancer type and stage was evaluated in a post hoc analysis of MCED test sensitivity, small sample sizes precluded this analysis for individual cancers. Fourth, the potential impact of additional factors beyond cancer type and stage on MCED test performance was beyond the scope of this study but may be explored in future studies. Finally, this

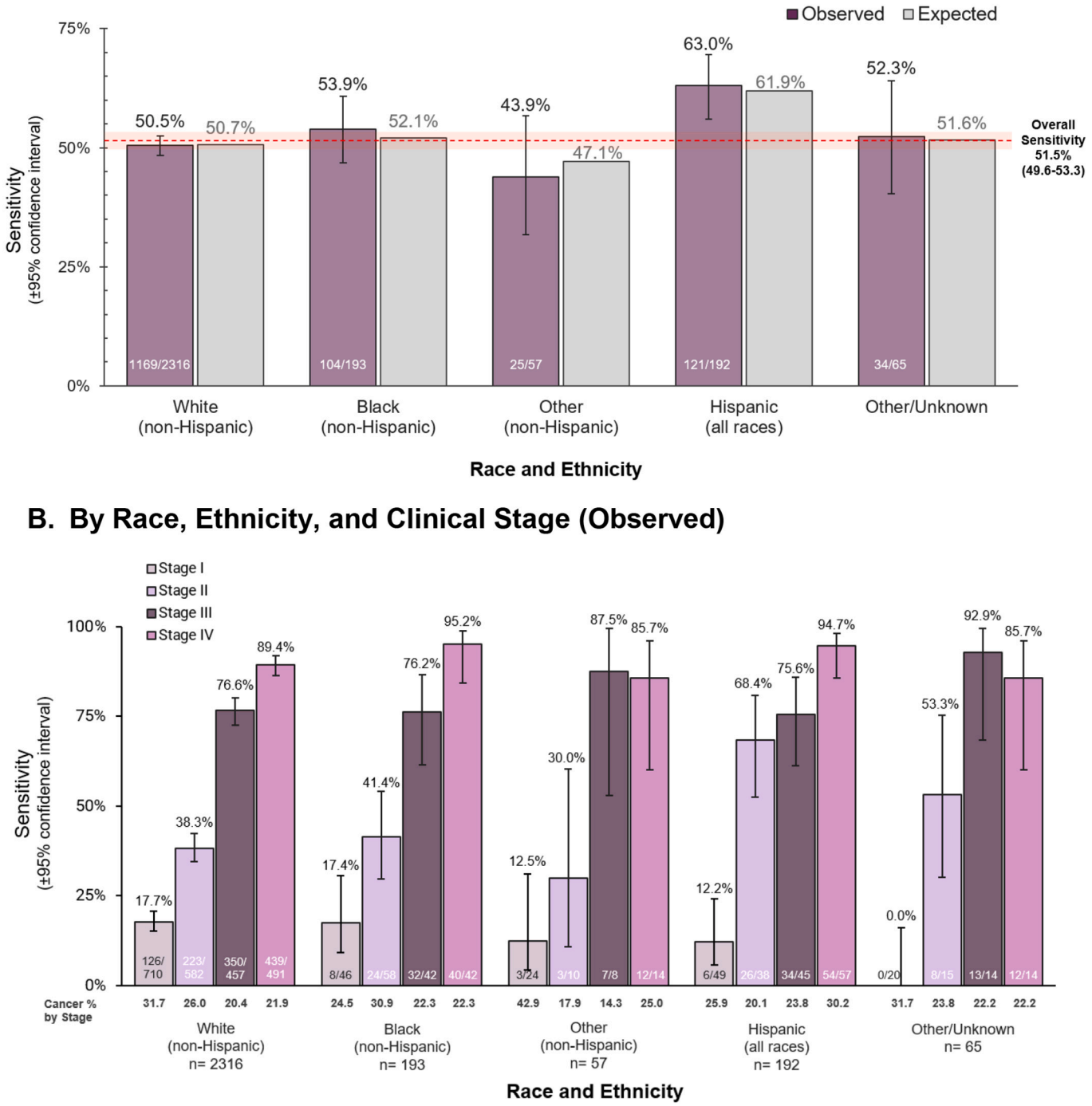

Fig. 1. Sensitivity of the Multi-Cancer Early Detection Test. (A) The horizontal dotted red line indicates the overall sensitivity for all racial and ethnic groups combined, as reported in (Klein et al., 2021) and the 95% confidence interval is represented by the red shading surrounding the dotted red line. Purple bars represent observed sensitivity for each group. Gray bars represent the sensitivity expected if test performance for each cancer type and stage was the same across racial and ethnic groups and the only difference was the distribution of cancer types and stages between groups. Expected sensitivity values were calculated using the cancer type- and stage-specific sensitivity rates multiplied by the marginal total counts of each cancer type-stage combination for each racial and ethnic group. Two-sided 95% Wilson confidence intervals were calculated. (B) Clinical stage was assigned by the treating physician or a certified cancer registry professional according to the American Joint Committee on Cancer (AJCC) Staging Manual (7th or 8th edition). Two-sided 95% Wilson confidence intervals were calculated.

analysis was performed in a case-control study with known cancer status of participants. Participants in neither arm were from an asymptomatic screening population, which is the relevant population for a cancer screening test. However, further studies in asymptomatic intended-use screening populations are completed or ongoing, including PATHFINDER (NCT04241796), PATHFINDER2 (NCT05155605), and NHS Galleri (ISRCTN 91431511).(Schrag et al., 2022)

5. Conclusion

Taken together, this descriptive analysis demonstrates that this targeted methylation-based MCED test detected a shared cancer signal across a broad range of cancers with consistently high specificity and sensitivity, generalizable across racial and ethnic populations. Combined with the primary results of the CCGA study, including high CSO prediction accuracy,(Liu et al., 2020; Klein et al., 2021) these findings suggest broad applicability of this MCED test. Larger studies that include an asymptomatic screening population with a broader range of diversity are ongoing to better inform clinical implementation of the MCED test on a population scale.

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Conflict of Interest Disclosures

SS, MT, BCC, GC, and HY have no conflicts to disclose; WHT serves as Site PI/SC for Pfizer, Alnylam, Applied Therapeutics, SalubrisBio, 3Live, BioCardia Inc., Bristol Meyers Squibb, serves in an consulting/advising role for Sequana Medical, Cardiol Therapeutics, Genomics plc, Zehna Therapeutics, Renovacor, Whiteswell, Boston Scientific, and receives honoraria or consulting fees from Springer Nature, American Board of Internal Medicine; JC has served as a consultant for IngenioRX/Anthem; EH is a full-time employee of GRAIL, LLC and owns stock in Illumina, Inc.; KNK is a full-time employee of GRAIL, LLC and owns stock in Illumina, Inc.; LRR has received grants from Bayer, BTG, Boston Scientific, Exact Sciences, FujiFilm Medical Sciences, Gilead Sciences, GlycoTest, RedHill, Target PharmaSolutions, and serves in a consulting/advising role for Bayer, AstraZeneca, Eisai, Exact Sciences, Gilead Sciences, Global Life Science Consulting, GRAIL, LLC, Hepion, MedEd Design, Medscape, Novartis Venture Fund, QED, RedHill, and The Lynx Group. C.S. recieved grant support from AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Pfizer, Roche-Ventana, Invitae (previously Archer Dx Inc), and Ono Pharmaceutical; is an AstraZeneca Advisory Board member and Chief Investigator for the AZ MeRmaiD 1 and 2 clinical trials and is also Co-Chief Investigator of the NHS Galleri trial funded by GRAIL and a paid member of GRAIL's Scientific Advisory Board (SAB); received consultant fees from Achilles Therapeutics (also SAB member), Bicycle Therapeutics (also a SAB member), Genentech, Medicxi, Roche Innovation Centre – Shanghai, Metabomed, and the Sarah Cannon Research Institute; received honoraria from Amgen, AstraZeneca, Pfizer, Novartis, GlaxoSmithKline, MSD, Bristol Myers Squibb, Illumina, and Roche-Ventana; had stock options in Apogen Biotechnologies and GRAIL until June 2021, and currently has stock options in Epic Bioscience, Bicycle Therapeutics, and Achilles Therapeutics; and is a co-founder of Achilles Therapeutics; holds patents relating to assay technology to detect tumour recurrence (PCT/GB2017/053289), targeting neoantigens (PCT/EP2016/059401), identifying patent response to immune checkpoint blockade (PCT/EP2016/071471), determining HLA LOH (PCT/GB2018/052004), predicting survival rates of patients with cancer (PCT/GB2020/050221), and identifying patients who respond to cancer treatment (PCT/GB2018/051912); holds US patent relating to detecting tumour mutations (PCT/US2017/28013), methods for lung cancer detection (US20190106751A1); and holds both a European and US patent related to identifying insertion/deletion mutation targets (PCT/GB2018/051892). C.S. is a Royal Society Napier Research Professor (RSRP\R\210001) and has received funding from the Francis Crick Institute that receives its core funding from Cancer Research UK (CC2041), the UK Medical Research Council (CC2041), and the Wellcome Trust (CC2041); Cancer Research UK (TRACERx [C11496/A17786], PEACE [C416/A21999], and CRUK Cancer Immunotherapy Catalyst Network); Cancer Research UK Lung Cancer Centre of Excellence (C11496/A30025); the Rosetrees Trust, Butterfield and Stoneygate Trusts; NovoNordisk Foundation (ID16584); Royal Society Professorship Enhancement Award (RP/EA/180007); National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre; the Cancer Research UK-University College London Centre; Experimental Cancer Medicine Centre; the Breast Cancer Research Foundation (US) (BCRF-22-157); Cancer Research UK Early Detection and Diagnosis Primer Award (Grant EDDPMA-Nov21/100034); The Mark Foundation for Cancer Research Aspire Award (Grant 21-029-ASP); Stand Up To Cancer-LUNGevity American Lung Association Lung Cancer Interception Dream Team Translational Research Grant (Grant Number: SU2C-AACR-DT23-17); and an ERC Advanced Grant (PROTEUS) from the European Research Council under the European Union's Horizon 2020 research and innovation programme (grant agreement no. 835297).

Data availability

Summary data tables and individual participant-level data, excluding protected health information, required to generate all figures and tables may be shared upon request.

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Appendix A. Supplementary data

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