

Estimating Preclinical Detection Window, Multi-Cancer Early Detection (MCED) Test Sensitivity, and Episode Sensitivity in the NHS-Galleri Trial Using the Incidence Method

Earl Hubbell, PhD¹; Alpa V. Patel, PhD²; Christina A. Clarke, PhD, MPH¹; James Dai, PhD¹; Wei Liang, PhD³; Rebecca Smittenaar, PhD³; Charles Swanton, MBPhD⁴; Peter Sasieni, PhD⁵
¹GRAIL, Inc., Sunnyvale, California, USA; ²American Cancer Society, Atlanta, Georgia, USA; ³GRAIL Bio UK Ltd., London, UK; ⁴Francis Crick Institute and University College London Hospitals, London, UK; ⁵Wolfson Institute of Population Health, Queen Mary University of London, London, UK

INTRODUCTION

- NHS-Galleri, an interventional, randomized controlled trial of an MCED cancer screening blood test with 3 annual screening rounds, provides information about the natural history of cancer interacting with MCED detection
- Several seemingly simple questions about the NHS-Galleri trial results include:
 - “What is the test sensitivity by stage in NHS-Galleri?”
 - “What is the episode sensitivity by stage in NHS-Galleri?”
 - “What is the detection window (lead time) in NHS-Galleri?”
- These questions are difficult to answer² because intervention has changed observations of:
 - When** cancers are diagnosed
 - At which stage** they are diagnosed
 - Changed cancer incidence** from potentially overdiagnosed cancers or early detection
- The **incidence method**^{3–5} consists of comparing the incidence of test-negative cancers in the intervention arm to the expected incidence of cancers (as estimated by the incidence of cancers in the control arm)
 - Because cancers diagnosed in test-negative participants are not altered in time or stage, and are not overdiagnosed by whatever test is being performed, this provides valid (although limited, see Methods) estimates
- We can therefore use the incidence method to estimate MCED test performance conditional on stage as well as time

OBJECTIVES

- Here, we examine the natural history of cancer interacting with MCED screening, inferring parameters including estimated length of the preclinical detectable window, as well as test sensitivity and 12-month episode sensitivity (incidence rounds)
 - Similar parameters were previously examined in the American Cancer Society (ACS) Cancer Prevention Study 3 (CPS-3) cohort and biobank⁶
- In this post-hoc analysis of NHS-Galleri, we assess these parameters using the incidence method, which complements those obtained from non-interventional biobank studies

ESTIMATED DETECTION WINDOWS ARE LONGER THAN 1 YEAR, COMPATIBLE WITH ANNUAL SCREENING

CANCERS SHEDDING CIRCULATING TUMOR DNA EVOLVE RAPIDLY

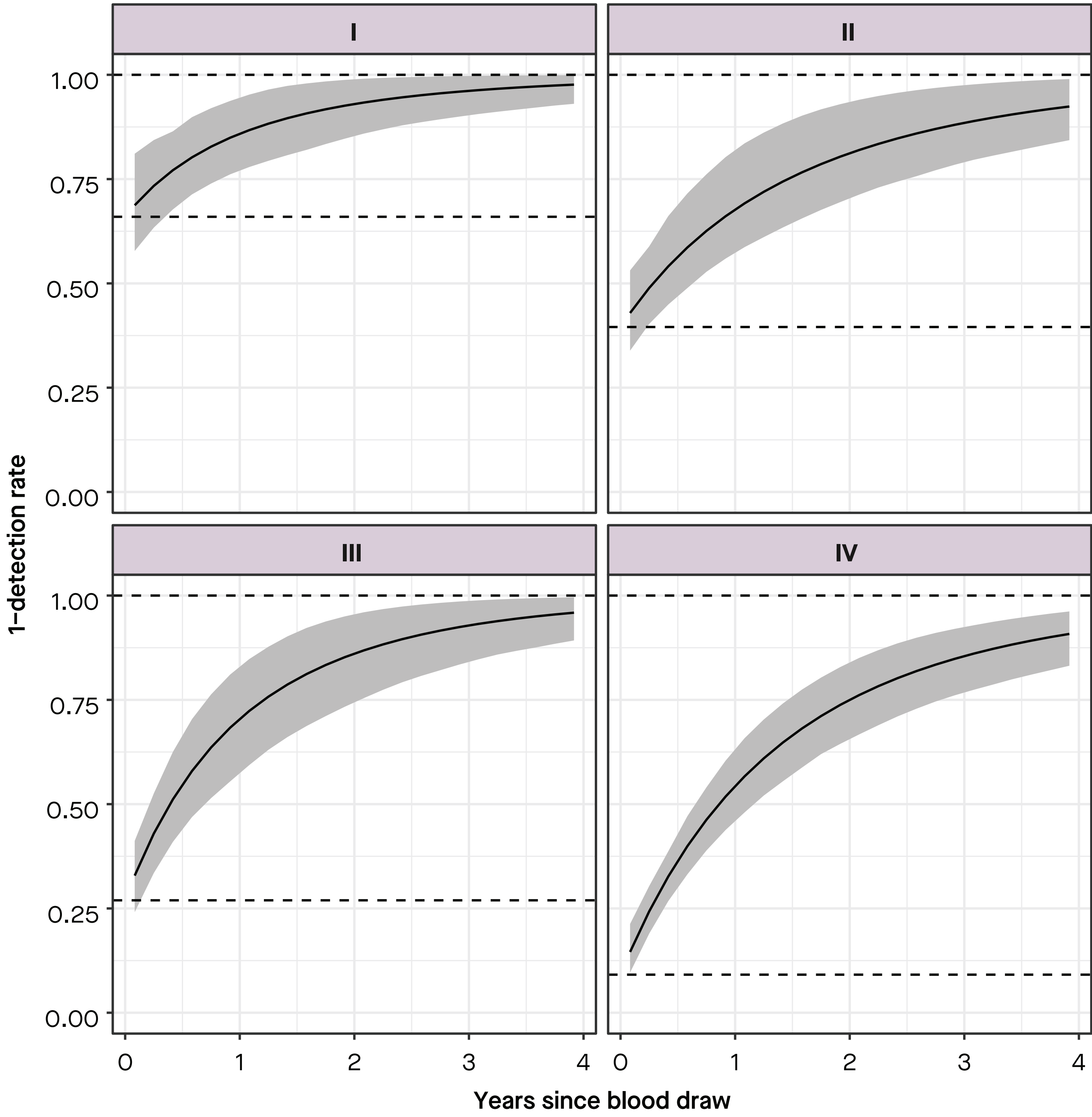


Figure 1. Posterior Estimates for (Non-) Detection Rate by Time Since Blood Draw Conditional on Stage at Original Clinical Diagnosis.

Solid line is the median posterior estimate for non-detection rate over time; ribbon is 95% point-wise credible interval. The horizontal dashed line at the y-intercept indicates the non-detection rate (the relative incidence of test-negative compared to total cancer incidence), which corresponds to test sensitivity as would be seen in a case-control study (Supporting Table 2) (1 – detection rate = non-detection rate). These plots are aggregated over a prespecified set of individually fit 12 cancer types responsible for >60% of cancer deaths.^{*1,7} Inferred detection window is shown in Supporting Table 1. Integrated over 1 year, the estimated episode sensitivity is shown in Supporting Table 3.

Changes in cancer detection are visible within even a 1-year period

- By fitting a model using the incidence method, we obtain 3 clinically relevant estimates (shown in aggregate in Figure 1 and in Supporting Tables 1–3):
 - Test sensitivity that would be seen in a case-control study by stage, which is estimated by (1 – y-intercept)

- Average detection window, which corresponds to the natural timescale over which the exponential curve for detection changes
 - Proportion of cancers detected over a selected screening period, such as 12 months as seen in the NHS-Galleri trial
- By integrating the posterior, episode sensitivity rates can be estimated for different screening intervals

METHODS

- What’s the essential insight?
 - True Positive/Total = 1 – Test-Negative/Total
 - Note we do not observe “Total” directly because it is affected by intervention
 - We can note this as a realization of (incidence – interval cancer rate)/incidence
 - This is implemented as
 - Control ~ Incidence
 - Interval cancer ~ function(Incidence)
 - Because neither the control arm cancers nor interval cancers are altered in time or stage, they allow estimation of statistics conditional on stage
- Technical modeling details
 - Following the analysis done for the ACS CPS-3 biobank,⁶ we treat non-detection rate over time as an exponential model with an intercept representing the non-detection rate at time zero, and a timescale depending on the cancer type and stage (Figure S1)
 - Detection rate at time zero is constrained to be non-decreasing by stage within each cancer
 - Observed counts in 2-month intervals are modeled as Poisson given the underlying rate of cancer in the population and the non-detection rate
 - No prior case-control information is used when fitting the model, unlike the prior (ACS CPS-3 biobank) analysis
 - The Stan programming language is used to fit a hierarchical model for parameters using Rstan⁸
 - Because cancer signals are increasing over time on a timescale of years, we can treat each blood draw as a sweep of detectable cancers, so all 3 rounds of NHS-Galleri are modeled as time-since-blood draw
- Technical limitations
 - The y-intercept estimates the detection rate when blood draw and original clinical diagnosis occur simultaneously, corresponding to the test sensitivity in a case-control study where cases are ascertained through clinical diagnosis. This differs from estimates of preclinical sensitivity, including cases at a stage before clinical diagnosis, as might be estimated from a three- or five-stage natural history model

- Episode sensitivity per stage as estimated by “the detection method,” consisting of dividing test-positives by stage by the total observed by stage, is a biased estimate of underlying episode sensitivity.² It can be larger or smaller than the unbiased episode sensitivity from “the incidence method” depending on the effect of intervention on stage
- In general, this technique measures the ability to move cancers from clinical detection to detection through screening, stratified by the original clinical stage at diagnosis. It cannot estimate any sensitivity estimates including unobserved stages, such as would be obtained by a natural history model that involves extra assumptions

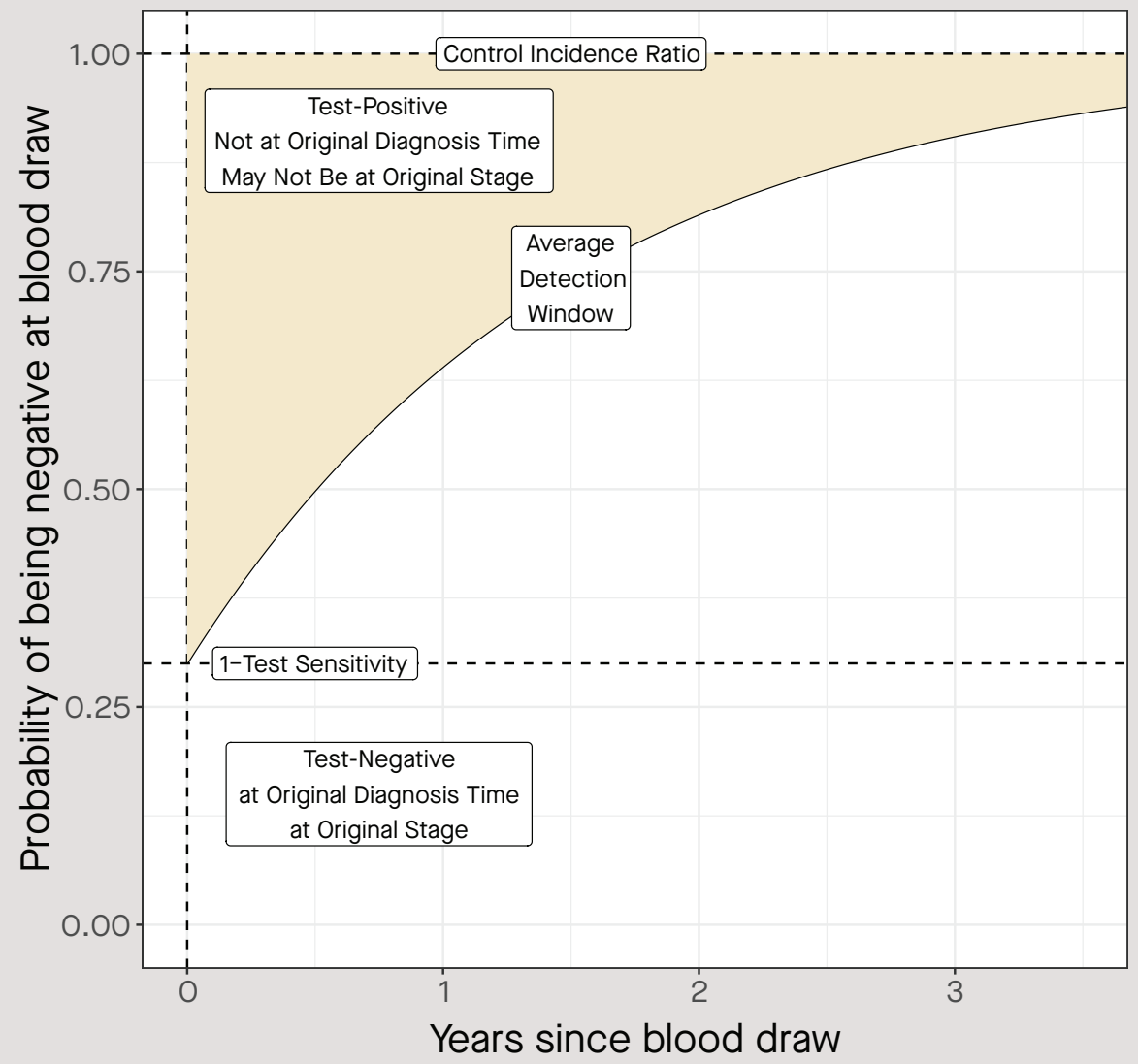


Figure S1. Non-Detection Rate Over Time for Theoretical One-Time Intervention. This figure shows the general structure of the incidence method applied to a study. Test-positives (shaded) are shown at the original diagnosis time in the future, which cannot be observed directly. Test-negatives (white) are shown at the original diagnosis time, which can be observed. The probability of being test-negative at blood draw for a cancer diagnosed in the future is determined by a ratio to the control incidence (here, illustrated with perfect data with no noise). The average detection window is noted as the average original diagnosis time among test-positives, inferred from the curve of non-detection.

SUPPORTING DATA

Supporting Table 1: Estimated Detection Window by Stage.
Note: Intervals for early stages are generally wider due to increased uncertainty. This detection window is the total preclinical detectable phase, but cannot be divided into time spent in stages using this method. Prespecified 12 cancer types* only included.

Statistic	Stage	Mean (95% CI)
Detection Window	I	1.49 (0.58–2.86)
Detection Window	II	1.80 (0.87–2.88)
Detection Window	III	1.24 (0.66–2.09)
Detection Window	IV	1.69 (1.16–2.42)

Supporting Table 2: Estimated Test Sensitivity. Sensitivity when blood draw is at the same time as clinical diagnosis, hence stage is the same as clinical diagnosis. This estimate is comparable to that obtained from case-control studies where the same is true. Prespecified 12 cancer types* only included.

Statistic	Stage	Mean (95% CI)
Test Sensitivity	I	0.34 (0.19–0.47)
Test Sensitivity	II	0.60 (0.49–0.70)
Test Sensitivity	III	0.73 (0.62–0.82)
Test Sensitivity	IV	0.90 (0.83–0.96)

Supporting Table 3: Estimated 12-Month Episode Sensitivity Stratified by Original Stage at Clinical Diagnosis. Proportion of cancers detected by MCED screening in a 12-month screening interval; incidence rounds. Prespecified 12 cancer types* only included.

Statistic	Stage	Mean (95% CI)
Episode Sensitivity (12 month)	I	0.22 (0.13–0.31)
Episode Sensitivity (12 month)	II	0.44 (0.32–0.53)
Episode Sensitivity (12 month)	III	0.47 (0.36–0.57)
Episode Sensitivity (12 month)	IV	0.65 (0.59–0.71)

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CONCLUSIONS

- Similar to prior biobank study analysis, estimated detection windows for late-stage cancers are longer than 1 year
- Test sensitivity is higher than episode sensitivity, as expected when detection rates change over time
- These results are compatible with annual screening; however, this method allows computation of the episode sensitivity at shorter or longer screening intervals
- Using a simple method without many assumptions, we uncover important natural history parameters of cancer relating to the MCED test from the NHS-Galleri trial
 - This method avoids issues with potential overdiagnosis, cancers coming from outside the follow-up window, or changes in stage
- Further follow-up time and data will continue to improve estimation of parameters

*Prespecified set of 12 cancer types responsible for >60% of cancer deaths; includes cancer of the anus, bladder, colon/rectum, head and neck, liver/bile-duct, lung, lymphoma, esophagus, ovary, pancreas, plasma cell neoplasm (myeloma), and stomach.^{1,7}

Disclosures

EH, JD, CAC, WL, and RS are current employees of GRAIL, Inc., with equity in the company. EH also holds multiple patents for MCED with GRAIL, Inc., pending and issued. AVP reports no conflicts of interest. CS acknowledges grant support from Invitae (previously Archer Dx Inc - collaboration in minimal residual disease sequencing technologies) and Personalis. He is Co-Chief Investigator of the NHS-Galleri trial funded by GRAIL and is a paid member of GRAIL’s Scientific Advisory Board. CS is a paid board member for Novartis from March 2026; a paid board member for Bicycle Therapeutics and is also Chair of Bicycle Therapeutics Clinical Advisory Group. He has received or receives consultant or advisory fees from Genentech and China Innovation Centre of Roche (CICoR) - Shanghai; Medixi Ventures; Relay Therapeutics (SAB member); Saga Diagnostics (SAB member); and Sarah Cannon Research Institute. He has received consultancy, advisory fees or honoraria from AstraZeneca (uncompensated), Pfizer, and Achilles Therapeutics. CS has equity and or stock options in Bicycle Therapeutics, Novartis, Relay Therapeutics, and Saga Diagnostics. He has previously held stock and was co-founder of Achilles Therapeutics. CS declares a patent application for methods to lung cancer (PCT/US2017/028013); targeting neoantigens (PCT/EP2016/059401); identifying patient response to immune checkpoint blockade (PCT/EP2016/071471); methods for lung cancer detection (US20190106751A1); identifying patients who respond to cancer treatment (PCT/GB2018/051912); determining HLA LOH (PCT/GB2018/052004); predicting survival rates of patients with cancer (PCT/GB2020/050221); methods and systems for tumour monitoring (PCT/EP2022/077987); analysis of HLA alleles transcriptional deregulation (PCT/EP2023/059039); technique for detecting minimum residual disease (PCT/EP2023/065074); and relating to the use of plasma proteomics for risk prediction of lung cancer (PCT/EP2025/086701). CS is an inventor on a European patent application (PCT/GB2017/053289) relating to assay technology to detect tumour recurrence. This patent has been licensed to a commercial entity and under their terms of employment CS is due a revenue share of any revenue generated from such licence(s). PS has consulting/advisory roles with GRAIL Bio UK, Ltd and MEDIAN Technologies (Inst), and has received research funding from GRAIL Bio UK, Ltd. (Inst) and Merck (Inst).

