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Assessment of the impact of multi-cancer early detection test screening intervals on late-stage cancer at diagnosis and mortality using a state-transition model

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Abstract

Objective Multi-cancer early detection (MCED) tests are novel technologies that detect cancer signals from a broad set of cancer types using a single blood sample. The objective of this study was to estimate the effect of screening with an MCED test at different intervals on cancer stage at diagnosis and mortality endpoints.

Design The current model is based on a previously published state-transition model that estimated the outcomes of a screening programme using an MCED test when added to usual care for persons aged 50–79. Herein, we expand this analysis to model the time of cancer diagnosis and patient mortality with MCED screening undertaken using different screening schedules. Screening intervals between 6 months and 3 years, with emphasis on annual and biennial screening, were investigated for two sets of tumour growth rate scenarios: 'fast (dwell time=2–4 years in stage I) and 'fast aggressive' (dwell time=1–2 years in stage I), with decreasing dwell times for successive stages.

Setting Inputs for the model include (1) published MCED performance measures from a large case-control study by cancer type and stage at diagnosis and (2) Surveillance, Epidemiology and End Results (SEER) data describing stage-specific incidence and cancer-specific survival for persons aged 50–79 in the US for all cancer incidence.

Outcome measures We used the following outcome measures: diagnostic yield, stage shift, and mortality.

Results Annual screening under the fast tumour growth scenario was associated with more favourable diagnostic yield. There were 370 more cancer signals detected/year/100,000 people screened, 49% fewer late-stage diagnoses, and 21% fewer deaths within 5 years than usual care. Biennial screening had a similar, but less substantial, impact (292 more cancer signals detected/year/100,000 people screened; 39% fewer late-stage diagnoses, and 17% fewer deaths within 5 years than usual care). Annual screening prevented more deaths within 5 years than biennial screening for the fast tumour growth scenario. However, biennial screening had a higher positive predictive value (54% vs 43%); it was also more efficient per 100,000 tests in preventing deaths within 5 years (132 vs 84), but prevented fewer deaths per year.

Conclusion Adding MCED test screening to usual care at any interval could improve patient outcomes. Annual MCED test screening provided more overall benefit than biennial screening. Modelling the sensitivity of outcomes to different MCED screening intervals can inform timescales for investigation in trials.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ In the absence of real-world evidence regarding multi-cancer early detection (MCED) screening intervals, modelling is required to investigate potential screening intervals of new MCED screening tests.
⇒ This study used performance estimates from a published case-control study and outcomes from the Surveillance, Epidemiology, and End Results (SEER) database, a widely used database for modelling studies.
⇒ Varied estimates of dwell time duration were used to model the heterogeneity of cancer and to explore the potential effect of screening interval on cancer detection and subsequent mortality, enabling the assessment of different types of cancer.
⇒ Estimates of changes in cancer mortality are made under several ideal assumptions and so represent the upper bounds of potential benefits of MCED cancer screening.
⇒ Model output is limited by the population cancer data used, in this case the SEER18 database, which contains data from only 14 US states.

INTRODUCTION

Cancer is one of the leading causes of death around the world.[1] At present, widespread single-cancer screening is only recommended for a few cancer types, such as breast, bowel, and cervical cancer.[2 3] These screenings have been effective in lowering cancer-specific mortality,[4 5] but can also be associated with high false-positive rates, overdiagnosis, and disparities in adherence.[6–9] The remaining cancers are detected by a variety of means in usual care, typically symptomatic detection.

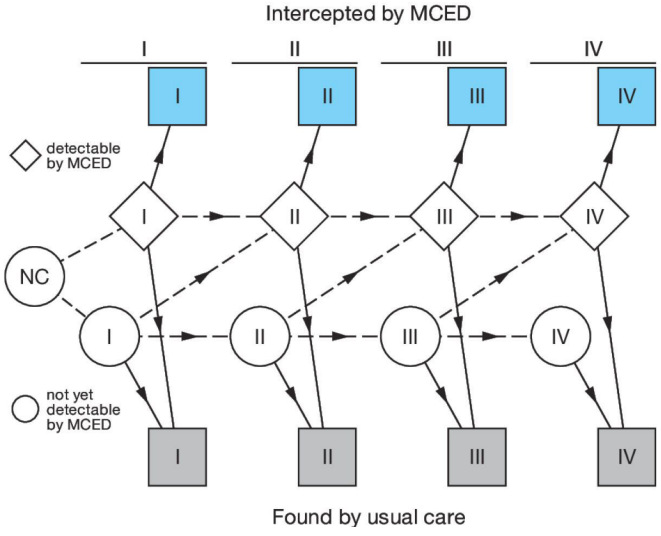

Figure 1 Interception model schematic. Cancer progression is shown in this figure as advancement from No Cancer (NC) to stage I through IV cancer from left to right. Shapes represent cancer states (○ undetectable by MCED at that stage, ♦ detectable by MCED at that stage, • diagnosed at that stage). Dashed lines indicate unobserved transitions between stages, solid lines indicate the path to diagnosis at each stage.

Multi-cancer early detection (MCED) tests are innovative new technologies that screen for a broad set of cancer types with a single blood sample.[10 11] There are several MCED tests currently under development that utilise a variety of different analytes to detect a cancer signal.[12] Cell-free DNA (cfDNA) is one such analyte that can be shed by tumours into the bloodstream and can carry cancer-specific signals.[13 14] By analysing circulating cfDNA, in combination with machine learning, an MCED test (Galleri; GRAIL, Inc., Menlo Park, CA) has been developed to detect this shared cancer signal with high specificity.[10] MCED tests can complement, though not replace, existing single-cancer screenings, as well as expand categories of screenable cancers.[11] Owing to their high specificity, MCED tests are unlikely to significantly increase the overall rate of false positives already seen with accepted single-cancer screening modalities. However, practical strategies for cancer screening using cfDNA, including the interval of screening tests, remain to be determined.

Most guideline-based single-cancer screenings are conducted every 1–5 years, depending on various factors, including the cancer growth rate.[2 15–19] By detecting precancerous lesions, some single-cancer screenings have the potential to reduce cancer incidence and can be performed at longer intervals based on the precancerous lesion growth rate.[20 21] By comparison, some tests, such as low-dose computed tomography screening for lung cancer, detect invasive cancer signals and typically need to be conducted relatively frequently to most effectively detect cancer in early stages to reduce mortality.[22] The degree by which a population-level cancer screening programme contributes to overdiagnosis depends on the sensitivity of the test to indolent cancers, the incidence of slow-growing cancers in the population, and the upper age of screening. Selecting an optimal screening interval must balance the possibility of improved and prolonged life due to earlier cancer detection against false positive test results and overdiagnosis, which could lead to unnecessary testing and treatment.[23]

The relative newness of MCED tests means that there is little longitudinal clinical data on optimal testing frequency. Filling this evidence gap is challenging because MCED screens do not individually test for single cancer types, but rather many cancers simultaneously. Thus, screening intervals must be developed to maximise the benefits across individuals who may develop a range of cancer types with different clinical features and growth rates, rather than optimising for a single cancer type. This poses a unique challenge to the implementation of an MCED screening programme for the general population. Insights into the potential influence of different screening intervals on the harms and benefits of real-world implementation of MCED testing may inform the design and interpretation of appropriate clinical trials.

To provide insight into how the screening interval might impact patient outcomes with MCED testing, we performed an analysis using a previously published screening interval model utilising MCED test characteristics from a recently published report[10] and population cancer data from the US Surveillance, Epidemiology and End Results (SEER) programme for cancer types detectable by the MCED test. In the absence of real-world evidence regarding MCED screening intervals, state-transition modelling analyses are critical to inform the selection of appropriate investigational timescales for effective screening trials.

METHODS

Model input

The current model is based on a previously published state-transition model (figure 1) that estimated the outcomes of a screening programme using an MCED test when added to usual care for persons aged 50–79.[24] Herein, we expand this analysis to model the time of cancer diagnosis and patient mortality with MCED screening undertaken using different screening schedules. As cancers progress from stage I to IV, they are more likely to be detectable by MCED and to be found by current clinical diagnostic mechanisms, although MCEDs have the potential to intercept more types of cancer at earlier stages than usual care (current clinical practice with no MCED test).[24] Inputs for the model include: (1) published performance measures from a large case-control study by stage at diagnosis for the cancer types reported by a cfDNA-based MCED test[10] (online supplemental figure S1) and (2) Surveillance, Epidemiology and End Results (SEER) data describing stage-specific incidence and cancer-specific survival for persons aged

50–79 in the US for all cancer incidence (online supplemental figure S2 and S3).[25] From the SEER programme (SEER Datasets and Software, RRID:SCR_003293), we obtained crude incidence and cancer-specific survival rates for all persons aged 50–79 when diagnosed with invasive primary cancer in one of 18 regions from 14 US states covering 28% of the US population from 2006 to 2015 and followed for vital status up to 31 December 2018 (online supplemental figure S2 and S3). This time period was chosen to provide adequate sample size and follow-up for cancer survival across a range of cancers, and because uniform American Joint Committee on Cancer (AJCC) sixth edition staging was available across the entire time period (categorised as I, II, III, IV, and unknown). The 50–79 year age range was selected to overlap with existing cancer screening efforts and recommendations as well as to minimise competing risks of non-cancer related deaths among persons aged ≥80 years of age. We modelled cancer types that may be affected by the MCED test in organ-specific groups matching the sensitivity data in Klein *et al*, including anus, bladder, breast, cervix, colon/rectum, oesophagus, gallbladder, head and neck, kidney, liver/bile-duct, lung, lymphoid leukaemia, lymphoma, melanoma, myeloid neoplasm, plasma cell neoplasm, ovary, pancreas, prostate, sarcoma, stomach, thyroid, urothelial tract, and uterus, as well as a residual group of cancers referred to as 'Other'. Definitions of International Classification of Diseases (ICD) O-3 site and histologic groupings for cancer types used to specify SEER data for this analysis are detailed in online supplemental table S1) and Hubbell *et al*.[24] SEER*Stat software (version 8.3.8) was used for all SEER calculations.

Model assumptions

This is a numerical integration model with assumptions, such as that cancers at later stages have shorter dwell times (online supplemental table S2, online supplemental table S3**,** and Hubbell *et al* supplementary data).[24] In this analysis, we model cancer detection as it reflects the requirement that a cancer case is shedding detectable circulating tumour DNA (ctDNA), and that the measured sensitivity reflects the fraction of cases shedding this biological signal. We assume that if a cancer is not shedding detectable ctDNA, it will not do so until it progresses to the next stage of cancer; and that once a cancer sheds detectable ctDNA, it will continue to do so until it is treated or the patient dies. The impact of early cancer detection by MCED on mortality was modelled by substituting the hazard of death appropriate for the stage at which clinical diagnosis would have occurred in the absence of screening with the hazard of death appropriate for the earlier stage at screen-detection (accounting for lead time). Shifts in hazards were calculated for each cancer type and stage separately and then combined to estimate the overall impact of MCED screening on mortality. False positives occur at a rate depending on the number of tests performed, and do not depend on the number of cancer types modelled or tested for. This model is used to project for stable, long-term performance of the test.

As is standard practice in models of disease screening, we consider a perfectly compliant population in which there is 100% screening uptake followed by 100% adherence with recommended diagnostic work-up and treatment, with no loss to follow-up.[9 20 26–28] This model also assumes 100% accuracy of and adherence to confirmatory testing initiated by a positive test result using either MCED or recommended screening as a part of usual care. This assumption, although not real-world, is intended to separate the performance of confirmation testing, which is not part of this work, from initial screening effectiveness, which is the focus of the current work. The goal of this analysis is to model the maximal benefits to those people who participate in the screening programme as recommended.

Analyses

In previous modelling work,[24] we performed a sensitivity analysis for an annual screening interval interacting with three hypothetical tumour growth rate scenarios. These scenarios varied in the length of the preclinical sojourn time, divided into dwell time within each clinical stage before progressing to the next. In the present analysis, we examine the effects of screening at different intervals within the two most rapid tumour growth rate scenarios from our previous study: the 'fast' and 'fast aggressive' scenarios (online supplemental table S1 and S2). In the 'fast' scenario, the range of mean dwell times across cancer types is 2–4 years in Stage I. In the 'fast aggressive' scenario the range of mean dwell times across cancer types is 1–2 years in stage I. In each scenario, successive stages are assumed to have shorter mean dwell times.

Annual and biennial screening intervals were modelled for most analyses, though 6 month intervals from 0–3 years were examined and are shown for some figures. Screening intensity, defined as the percentage of patients screened per year, is 100% with annual screening, 50% with biennial screening, and 0% without an MCED test (figure 2). With biennial screening, the 50% of patients not screened in a given year would be subject to an increased probability of interval cancers. Interval cancers are cancers that are diagnosed between a negative cancer screen and the next scheduled screening test.[29 30] The probability that a cancer progresses without being intercepted by an MCED test is dependent on the screening interval relative to the tumour growth rate. In the schematic shown in figure 2, the solid top line represents a single hypothetical patient who has a cancer that would be clinically diagnosed at stage IV with usual care (no MCED testing). The top dashed line represents a hypothetical patient who has a screen-detectable stage I cancer with a dwell time of 12 months; the cancer will therefore be detected at stage I with annual screening. With biennial screening, there is a 50% chance of the cancer being detected at stage I and 50% chance of it being detected at stage III.

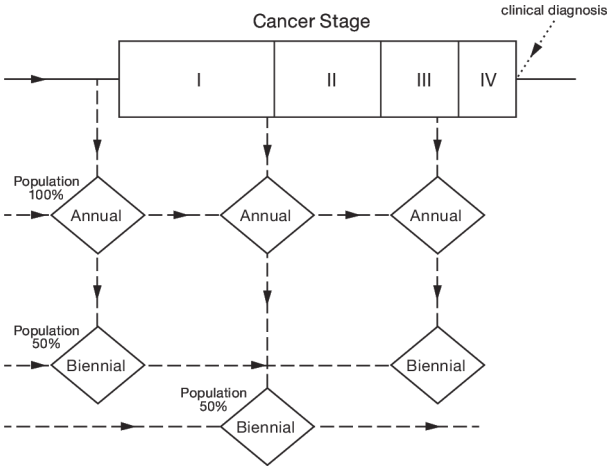

Figure 2 Effect of screening intensity on stage of diagnosis. The top line (solid) represents usual care (without MCED testing) for a single hypothetical patient who would receive a clinical cancer diagnosis at stage IV and the size of the boxes reflects the hypothetical dwell time at each stage. In this hypothetical scenario, annual population testing would result in detection of this cancer at stage I and biennial population testing would result in 50% of such individuals detected at stage I and 50% at stage III. This illustrates one particular case; the model from figure 1 computes the effect over all cases.

We report descriptive statistics for potential diagnostic yield, stage shift, and effect on cancer-specific mortality in this model after adding MCED screening at various intervals to usual care. Differences in 5-year cancer-specific survival (measured from when the cancer would have been diagnosed in the absence of MCED screening), which are strong predictors of differences in cancer-specific mortality in a cancer type, are a standard metric for benefit.[31]

The data that support the findings of this study are available in the online supplemental information and online supplemental figures S1-S3, as well as the supplementary material of Hubbell *et al*.[24]

Patient and public involvement

Patients and/or the public were not involved in the design, analyses, or reporting of this study. Patient advocacy partners at the American Cancer Society and Friends of Cancer Research will be invited to advise on the best messaging and format that will be of greatest use to communicate this research to patients.

RESULTS

In this model, adding annual MCED test screening under the fast growth scenario could intercept 370 cancers/year/100,000 people aged 50–79 and lead to a 49% reduction in late-stage (stage III and IV) cancer diagnoses. This could result in 84 deaths averted, which is 21% of all the deaths that would occur within 5 years of diagnosis with usual care only (table 1 and figure 3).

Biennial MCED test screening was able to shift stage at diagnosis and avert deaths, but not as effectively as annual screening (table 1, figures 3 and 4). The least favourable scenario shown, biennial screening with fast aggressive tumour growth, results in 54 deaths averted annually (14% reduction) compared with usual care (table 1 and figure 3). Compared with annual screening, biennial screening has a higher positive predictive value and is more efficient, as it prevents more deaths per 100,000

Table 1 Reductions in estimated late-stage cancer diagnoses and deaths by adding annual or biennial MCED to standard care*

		Hypothetical tumour growth rate scenario			
		Fast aggressive		Fast	
MCED screening interval	**None (usual care)**	**Biennial**	**Annual**	**Biennial**	**Annual**
Cancer cfDNA detected, N	0	219	310	292	370
PPV, %	–	47	38	54	43
MCED tests/year	–	50,000	100,000	50,000	100,000
FP/year due to MCED, %†	–	0.25	0.5	0.25	0.5
Diagnoses at late-stage (III/IV), N	409	284	236	248	210
Reduction vs usual care, %‡	–	31	42	39	49
Deaths within 5 years§, N	392	338	318	324	308
Deaths averted vs usual care, N (%)	–	54 (14)	74 (19)	68 (17)	84 (21)

*Performance is based on cancer incidence when screening 100K individuals. With annual screening, 100% of patients are tested per year; with biennial screening, 50% of the population would be tested in any given year.
†Annual false positive rate due to MCED testing intensity.
‡% of patients diagnosed at an earlier stage with each screening interval and tumour growth rate scenario vs current care with no MCED.
§All cancers diagnosed in 1 year and followed for deaths within 5 years of original diagnosis (ie, in the absence of MCED screening) to account for lead time.
cfDNA, cell-free DNA; FP, false positive; MCED, multi-cancer early detection test; PPV, positive predictive value.

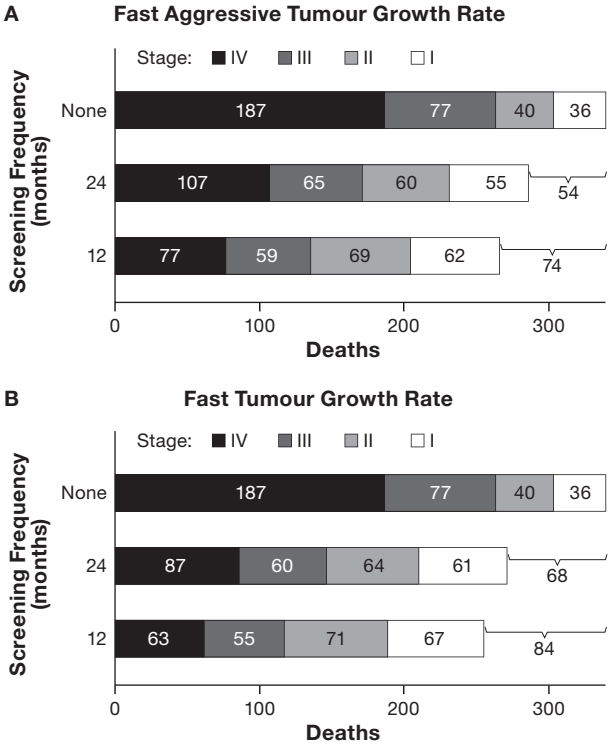

Figure 3 Effect of likely screening intervals on averted deaths by growth rate scenario. (A) The number of deaths by stage in the Fast Aggressive tumour growth rate scenario with annual, biennial, or no MCED screening are shown. The number of deaths averted vs no MCED testing are shown at the top of each bar. (B) The same information with a Fast tumour growth rate scenario is shown.

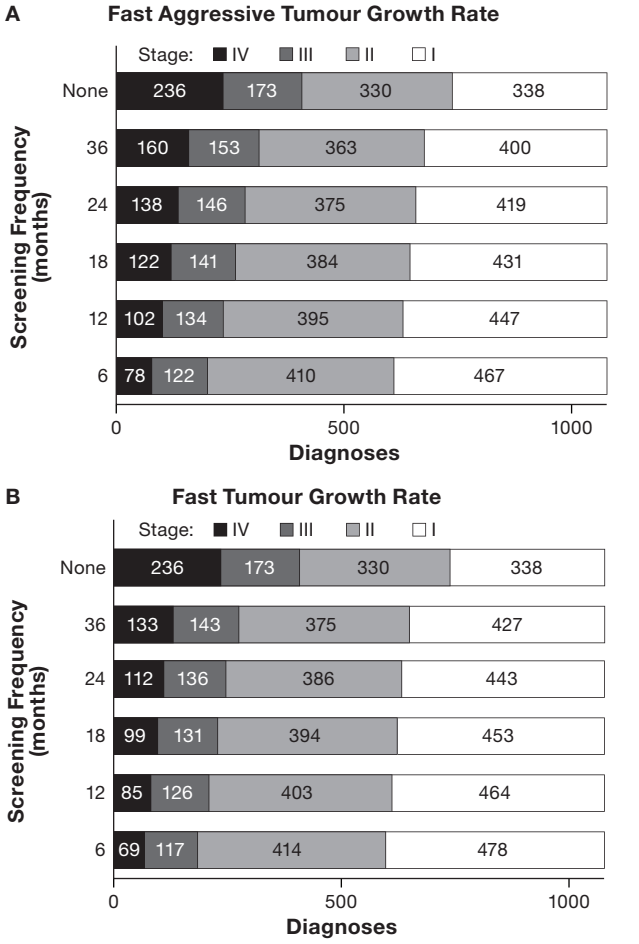

Figure 4 Stage at diagnosis with 6 month to 3 year screening intervals. (A) Shows the stage of cancer at diagnosis in the Fast Aggressive tumour growth rate scenario. (B) Shows the same for the Fast tumour growth rate scenario.

tests administered table 1). This is due to false positives only arising in those individuals tested each year, and therefore biennial screening results in a lower false positive rate per year of testing.

Looking at a broad spectrum of screening intervals, from every 6 months to every 3 years, the model shows incremental increases in the percentage of cancers diagnosed at early stage (stage I and II) with more frequent MCED testing (figure 4). All screening intervals had more favourable early-stage diagnosis rates than usual care alone. There was a larger impact on stage shift with the fast tumour growth rate vs tumours with fast aggressive growth.

As anticipated, more cancers present as interval cancers (ie, are diagnosed between screens) under faster growth rates and with longer screening intervals. In both tumour growth rate scenarios, annual screening leads to fewer deaths (figure 3) vs no MCED screening and biennial MCED screening.

These results were compared with the number of deaths within 5 years of diagnosis – that is, died before reaching cancer survivor status – from various cancers diagnosed over 100,000 person-years in the SEER database using the age range and timeframe of the model. Given that 392 individuals would be diagnosed each year with an aggressive cancer that would kill them within 5 years, earlier diagnosis through biennial MCED screening could have averted 54 (14%) of these deaths (table 1). Annual MCED screening would have resulted in 84 (21%) fewer deaths under the most favourable MCED scenario (table 1).

DISCUSSION

Based on the performance characteristics from a case-control study, both annual and biennial screening with an MCED test have the potential to intercept 31–49% of cancers at stage I-II that would otherwise present at stage III-IV. Of these, approximately equal numbers would be detected at stage I and at stage II (14% stage I, 16% stage II to 23% stage I, 26% stage II). Annual screening was associated with more favourable diagnostic yield, stage shift, and mortality when compared with biennial screening. Biennial screening, which requires fewer clinic visits, had a higher positive predictive value (PPV) and was more efficient per test. The screening interval is a component of guidelines already in practice within the US, such as annual lung cancer screening for current or former smokers aged 50 to 80 with at least a 20-pack-year

smoking history, developed using both real-world evidence and modelling.[2 9] In the absence of sufficient real-world evidence regarding MCED screening intervals, modelling is required to select screening intervals that would then be investigated in clinical trials.

Our estimates of changes in cancer mortality are made under several ideal assumptions and so represent the upper bounds of potential benefits of MCED cancer screening. We modelled individuals who are 100% compliant with MCED screening (at a specified frequency) to estimate the benefit in those who follow the recommended screening schedule, which is standard practice for this type of modelling.[25 30 31] Likewise, we assume 100% accuracy of confirmatory tests initiated by a positive cancer screening result. Real-world rates of adherence to recommended screening schedules and diagnostic follow-up will vary and result in a lower population benefit. Individuals may also elect against recommendations and warnings otherwise to substitute MCED screening for recommended single-cancer screening, thereby constraining potential mortality benefits. We assume that stage-specific cancer survival does not differ between MCED-positive and MCED-negative tumours; however, survival prediction is complex.[32] We further assume that a reduction of late-stage cancer incidence would have an impact on mortality due to detection at an earlier stage, which is contested in the literature.[33 34] Due to these necessary modelling assumptions, real-world benefits are likely to be less than those estimated in the model.

Commonly cited possible harms of cancer screening with MCED tests include false positive results and potential for overdiagnosis. In the case-control study utilised in our model, the specificity of the MCED test was 99.5%.[10] With annual population screening and a lifetime of screening, this would translate to approximately 15% of those screened having a referral for suspected cancer with no cancer found. Even doubling this false positive rate to 99%, similar to the specificity observed in a prospective clinical study (99.1%),[35] only results in a lifetime risk of 30% (online supplemental figure S4 and S5). This compares favourably with both standard-of-care screening and symptomatic referrals.[36 37] While overdiagnosis with disease screening is often related to the upper age of screening, there is no consistent trend of overdiagnosis with differing screening intervals.[38–41] Additionally, this MCED test detects fewer early-stage breast and prostate cancers detected by standard-of-care screening, which may reflect a significant number of low-aggressive or overdiagnosed cancer cases that are unlikely to shed ctDNA.[42 43] Cancer detection using cfDNA analysis may preferentially detect more lethal cancers.[32] More rapidly growing and aggressive tumours tend to shed more cfDNA, and therefore are more likely to be detected by cfDNA-based MCED screening tests.[32 44 45] Thus, cfDNA-based MCED testing may be less prone to overdiagnosis of slow growing cancers. As a consequence of this likely bias towards fast growing cancers, we used rapid rates of tumour progression, recently shown to resemble those seen in analysis of biobank samples,[46 47] between stages in this model to account for the potential short duration of tumours before clinical detection.

Cancers that shed cfDNA in a limited amount at early stages, cancers that do not shed, or cancers that grow rapidly may be diagnosed at late stage by usual care in the interval between MCED tests. If shedding onset only occurs at late stage, cancers may be found earlier by an MCED test, but still in a late stage where curative treatment is less likely to be possible. It is therefore necessary to model across cancer types and stages to account for these variations rather than using an average estimate of performance. Even current performance numbers provide an opportunity to reduce late-stage cancer incidence (online supplemental figure S6). Because standard-of-care screening can identify early-stage cancers that MCED tests are less likely to detect, the incidence of malignant cancers that progressed from more indolent lesions may increase among individuals who replace single-cancer screening with MCED screening alone. To minimise this potential harm, MCED screening is intended to be performed in addition to the United States Preventive Services Task Force (USPSTF) guideline-recommended screening practices, which were assumed to occur as part of our model. If an MCED test fails to detect a tumour, a false negative, it may be identified during routine single-cancer screening or symptomatically.

Our model had to use performance estimates from a published case-control study,[10] as sufficiently large prospective or interventional studies are still underway and have not yielded updated performance metrics. Performance may vary in the intended-use, average-risk population as compared with what was used for this model's inputs. The purpose of this model was to evaluate how sensitive the projected mortality benefits of MCED screening are to differing schedules of screening. Our modelling followed standard practice by assuming ideal screening practice, including screening adherence and diagnostic follow-up, in order to isolate the impact of screening schedules from other factors that would otherwise influence screening effectiveness. Limitations of the population cancer data used in our model, in this case the SEER18 database, such as containing only US data, can affect the model output. Geographic areas included in these SEER data have higher poverty, unemployment rate, and percentage of urban dwellers and lower educational attainment vs non-SEER areas;[48] however, it is a widely-used US database for these types of studies. Small proportions of missing or unknown data regarding cancer site, histology, or stage at diagnosis also represent a limitation. These analyses are limited to the 50–79 year-old population used in previous models,[24 49] which overlap with most screening guidelines.[2 3] Future analyses looking at optimal screening intensity by more detailed age groupings (eg, 40–50, 50–60, 60–70) could be informative.

While we have modelled cancer natural history with a standard stage-transition model, cancers may have complex properties not explicitly modelled here. Not all cancers will progress sequentially through stages I to IV and some may skip stages. For example, some fraction of cancer cases may become metastatic early, and transition from stage I to stage IV. In particular, certain histological subtypes may be more or less aggressive than average and thus impact estimations of cancer stage shifting or mortality effects due to MCED screening. Complex distributions of dwell times are also possible. These extensions are out of scope for this study. Additionally, dwell time estimates for cfDNA-shedding cancer cases are not known; however, the scale of overall time is similar to that in existing models (eg, lung cancer).[26] While clinical trials and prospective studies will generate evidence to calibrate the screening interval model, here we show the impact of a range of assumptions based on the known natural history of tumours. Although tumour growth rates for cfDNA-shedding cancers are incompletely understood, our analysis and recent studies suggest that a 3 year screening interval may be too long and allow excessive interval cancers. In a prospective cohort study of the MCED test using blood samples collected from participants diagnosed with cancer within 3 years of blood draw, a cancer signal was detected up to 3 years before diagnosis, with the test positive rate increasing progressively with shorter preclinical timescales.[46] Retroactive assessment of plasma samples in two large prospective biobank studies suggests that preclinical detectability of cancer signals resembles the tumour growth rates examined here.[47] Additionally, while the shortest interval of 6 months would have the greatest impact on mortality, this benefit may be outweighed by the cost and procedural burden on healthcare providers and patients. The effect of screening saturates as fewer newly detectable cancers arise in the interval between screens, leading to a maximum number of lives that can be saved.[24] Even continuous MCED screening cannot find cancers that do not shed significant levels of ctDNA by the time of clinical diagnosis. The results of the present analysis suggest that although the annual and biennial intervals between these two extremes are expected to have noticeable differences in expected mortality, they may be optimal for the design of future MCED screening programmes.

Our study used varied estimates of dwell time duration to model the heterogeneity of cancer and to explore the potential effect of screening interval on cancer detection and subsequent mortality. As real-world evidence becomes available, we can interrogate MCED test screening recommendations more thoroughly. For example, our dwell time duration estimates can be assessed against this evidence to infer which best approximates real-world cancer biology, calibrating the model. In previous screening settings, calibrated models were strong surrogates for cancer biology and allowed strategic exploration of harm/benefit associated with different screening intervals and likely harm/benefit before choosing one to test in the real world.[50–53]

CONCLUSION

In conclusion, annual MCED screening has a lifetime risk of false positive results comparable to the status quo of single-cancer screening and is predicted to result in downstaging of diagnosed cancers under a variety of hypothetical scenarios, including fast and aggressive tumour growth. Biennial screening was shown to be more efficient in terms of PPV, but with a noticeable decrease in potential reductions in late stage diagnoses due to fewer people screened. The optimal choice of screening interval will depend on assessments of real-world cancer survival and the costs of confirmatory testing after MCED screening. However, both annual and biennial MCED screening intervals have the potential to avert deaths associated with late-stage cancers when used in addition to current guideline-based cancer screening.

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Contributors BR: Investigation and methodology, and writing (review and editing). CAC: Study conceptualisation, data curation, formal analyses, methodology, validation, visualisation, and writing (original draft preparation, review, and editing). EH: Guarantor, study conceptualisation, data curation, formal analyses, investigation and methodology, validation, visualisation, and writing (original draft preparation, review, and editing). PS: Study conceptualisation, investigation and methodology, and writing (original draft preparation, review, and editing).

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Competing interests BR is a paid member of GRAIL Bio UK Clinical Advisory Board. CAC is employed by GRAIL, Inc, with equity. EH is employed by GRAIL, Inc, with equity; owns stock in Illumina, Inc; has multiple patents in the field of cancer detection pending to GRAIL, Inc. PS is a paid member of the Scientific Advisory Board for GRAIL, Inc, no equity.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Ethics approval was not applicable to the research conducted in this study due to the use of existing and publicly available datasets.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. The data that supports the findings of this study are available in the Supplementary Information and Figures S1-S3, as well as the supplementary material of Hubbell et al.[24]

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