BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-086648
Article Type:	Original research
Date Submitted by the Author:	19-Mar-2024
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Keywords:	Clinical Decision-Making, Mass Screening, REGISTRIES

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Sensitivity of reductions in late-stage cancer and mortality to screening interval choice in a multi-cancer early detection state-transition model

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Keywords: early detection of cancer; cancer screening; computer simulation; clinical decision-making; registry data

Manuscript Notes:

Abstract: 283 (of 300)

Main text: 3508 (no limit)

Figures/Tables: 4/1 (of 5)

References: 56

Supplementary Files: 1

ABSTRACT

Objective

To estimate the effect of different multi-cancer early detection (MCED) screening 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 program 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 tumor growth rate scenarios.

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 USA for all cancer incidence.

Outcome measures

Diagnostic yield, stage shift, and mortality.

Results

Annual screening under the fast tumor growth scenario was associated with more favorable diagnostic yield (370 more cancer signals detected/year/100,000 people screened), stage shift (49% fewer late-stage diagnoses), and mortality (21% fewer deaths within five years) than usual care. Biennial screening had a similar, but less substantial, impact. Annual screening prevented more deaths than biennial screening, but biennial screening had a higher positive predictive value and was more efficient (ie, prevented more deaths per 100,000 tests).

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. Modeling 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 MCED screening intervals, modeling is required to investigate potential screening intervals of new MCED screening tests.
- This study uses reliable datasets, including performance estimates from a published case-control study and outcomes from the Surveillance, Epidemiology, and End Results (SEER) database, a widely used database for modeling studies.
- Varied estimates of dwell time duration were used to model the heterogeneity of cancer and 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 only US data.

BACKGROUND

Cancer is one of the leading causes of death around the world (1). At present, wide-spread 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 be also 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.

Multi-cancer early detection (MCED) tests are innovative new technologies that utilize cancer biology to screen for a broad set of cancer types with a single blood sample (10, 11). Tumors can shed cell-free DNA (cfDNA), which often carries cancer-specific signals, into the bloodstream (12, 13). By analyzing circulating cfDNA, in combination with machine learning, an MCED test (Galleri®; GRAIL, LLC, Menlo Park, CA) has been developed to detect this shared cancer signal with high specificity (10). This test can complement existing single-cancer screenings, as well as expand the category of screenable cancers (11). The high specificity of this test decreases the likelihood of false positives and the subsequent extraneous triage and diagnostic testing.

Most guideline-based single-cancer screenings are conducted every one to five years, depending on various factors, including the cancer growth rate (2, 14-18). 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 (19). By detecting precancerous lesions, some single-cancer screenings have the potential to reduce cancer prevalence, but also increase the likelihood of detecting lesions that would never develop into fatal cancer (20). By comparison, some tests detect invasive cancer signals and typically need to be conducted relatively frequently to most effectively detect cancer in early stages.

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 maximize the benefits for the greatest number of people, rather than optimizing for a single cancer type. This poses a unique challenge to the implementation of an MCED screening program 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 utilizing MCED test characteristics from a recently published report (10) and population cancer data from the US Surveillance, Epidemiology and End Results (SEER) program. In the absence of real-world evidence regarding MCED screening intervals, state-transition modeling 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 program using an MCED test when added to usual care for persons aged 50-79 (21). 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, though MCEDs have the potential to intercept more types of cancer at earlier stages than usual care (current clinical practice with no MCED test) (21). Inputs for the model include 1) published MCED performance measures from a large case-control study by cancer type and stage at diagnosis (10) (**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 USA for all cancer incidence (**Figures S2-S3**) (22). From the SEER program (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 2006 to 2015 and followed for vital status through December 31, 2018 (**Figures S2-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 AJCC 6th edition staging was available across the entire time period (categorized 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 minimize competing risks of non-cancer–related deaths among persons aged ≥80 years of age. ICD-O-3-defined site and histologic groupings for cancer types are detailed in Hubbell et al (21). SEER*Stat software (version 8.3.8) was used for all SEER calculations.

Model Assumptions

This is a numerical integration model with assumptions that include cancers at later stages have shorter dwell times (**Table S1, Table S2,** and Hubbell et al. supplementary data (21)). In this analysis, we model cancer detection as it reflects the requirement that a cancer case is shedding detectable 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. This model is used to project for stable, long-term performance of the test. As is standard practice in models of disease screening programs, 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, 23-26). 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 program as recommended.

Analyses

In previous modeling work (21), we performed a sensitivity analysis for an annual screening interval interacting with three hypothetical tumor 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 tumor growth rate scenarios from our previous study: the “fast” and “fast aggressive” scenarios (**Tables 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 modeled for most analyses, though 6-month intervals from 0 to 3 years were examined and are shown for some figures. Screening intensity, defined as 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 (27, 28). The probability that a cancer progresses without being intercepted by an MCED test is dependent on the screening interval relative to the tumor 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.

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 (29).

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 (21).

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**).

Table 1. Reductions in Estimated Late-Stage Cancer Diagnoses and Deaths by Adding Annual or Biennial MCED to Standard Care[a]

		Hypothetical Tumor 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	-	50000	100000	50000	100000
FP due to MCED, %[b]	-	0.25	0.5	0.25	0.5

Diagnoses at Late-Stage (III/IV) , N	**409**	**284**	**236**	**248**	**210**
Reduction vs Usual Care, %[c]	**-**	**31**	**42**	**39**	**49**
Deaths Within 5 years[d], N	**392**	**338**	**318**	**324**	**308**
Deaths Averted vs Usual Care, N (%)	**-**	**54 (14)**	**74 (19)**	**68 (17)**	**84 (21)**

Abbreviations: cfDNA, cell-free DNA; FP, false positive; MCED, multi-cancer early detection test; PPV, positive predictive value.

[a]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.

[b]Annual false positive rate due to MCED testing intensity.

[c]% of patients diagnosed at an earlier stage with each screening interval and tumor growth rate scenario versus current care with no MCED.

[d]All cancers diagnosed in one year and followed for deaths within 5 years of original diagnosis (ie, in the absence of MCED screening) to account for lead time.

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 favorable scenario shown, biennial screening with fast aggressive tumor 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 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 six months to every three 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

favorable early-stage diagnosis rates than usual care alone. There was a larger impact on stage shift with the fast tumor growth rate versus tumors with fast aggressive growth.

Shifting cancers to early stages at diagnosis has a resulting impact on deaths within five years of diagnosis. Two common screening intervals, annual and biennial, result in fewer deaths than usual care alone (**Figure 3**). As anticipated, more cancers present as interval cancers (ie, are diagnosed between screens) under faster growth rates and with longer screening intervals. In both tumor growth rate scenarios, annual screening leads to fewer deaths (**Figure 3**) versus no MCED screening and biennial MCED screening.

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 a large fraction of all cancers before they reach late stage, when survival is worse. Annual screening was associated with more favorable diagnostic yield, stage shift, and mortality when compared with biennial screening. Biennial screening, which requires fewer clinic visits, had a higher PPV and was more efficient per test. 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 modeling (2, 9). In the absence of sufficient real-world evidence regarding MCED screening intervals, modeling is required to select screening intervals that would then be investigated in clinical trials and real-world evidence.

To put our MCED test modeling results in context, we compared them to the number of deaths within five years of diagnosis from various cancers diagnosed over 100,000 person-years in the SEER database using the age range and timeframe of the model. Of people currently diagnosed with aggressive cancer each year, 54 fewer of them would die within five years (of when their cancer would have been diagnosed with usual care) with biennial screening. This is comparable to eliminating all deaths from breast (17 deaths) and colorectal (33 deaths) cancer combined

(22). The 84 fewer deaths under the most favorable MCED scenario is more than the total deaths within five years of diagnosis in SEER from breast, colorectal, and pancreatic (30 deaths) cancer combined (22). The 20 fewer deaths with annual versus biennial screening is comparable to all upper gastrointestinal tract (22 deaths) or head and neck (14 deaths) cancers being eliminated as a cause of death (22).

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 modeled 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 modeling (22, 28, 29). 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. We assume that stage-specific cancer survival does not differ between MCED-positive and MCED-negative tumors; however, survival prediction is complex (30). 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 (31). Due to these necessary modeling assumptions, the benefits of MCED screening on mortality in clinical practice may vary from those this model estimated.

Commonly cited possible harms of cancer screening with MCED tests include false positive results and potential for overdiagnosis. In the case-control study utilized 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%) (32), only results in a lifetime risk of 30% (**Figures S4-S5**). This compares favorably with both standard-of-care screening and symptomatic referrals (33, 34). 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 (35-38). 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 (39, 40). Cancer detection using cfDNA analysis may preferentially detect more lethal cancers (30). More rapidly growing and aggressive tumors tend to shed more cfDNA, and therefore are more likely to be detected by cfDNA-based MCED screening tests (30, 41, 42). 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 tumor progression, recently shown to resemble those seen in analysis of biobank samples (43, 44), between stages in this model to account for the potential short duration of tumors before clinical detection.

MCED screens are intended to complement existing screening programs; therefore, if an MCED test fails to detect a tumor, it may be identified during routine single-cancer screening or symptomatically. There is a potential risk if MCED tests are inappropriately used instead of, rather than in addition to, standard screening. When used appropriately alongside routine screening, individuals with a negative MCED test are not worse off. Physicians may also take this interaction as an opportunity to emphasize the value of existing screening and reinforce appropriate care. A potential benefit is the pre-symptomatic detection of many cancer types for which no recommended screening exists.

This analysis was done in the absence of randomized clinical evidence and focused on potential deaths averted, but healthcare systems may want to incorporate cost calculations into their decision-making process. While health economic considerations are outside the scope of this analysis, MCED screening interval could be an important consideration in the calculation of willingness-to-pay thresholds across countries and healthcare systems looking to develop an MCED screening program (45). In some populations, effective cancer screening as a part of usual care has been hampered by socioeconomic barriers (46-48). This analysis shows that an MCED test that can detect a shared cancer signal across more than 50 cancer types with one blood sample (10) may detect cancer earlier than current usual care. MCED tests, therefore,

have the potential to greatly impact care for social groups with relatively poor uptake of current screening programs who often present with cancer at late stage. A screening program that specifically targets those at greatest risk and concentrates on removing barriers and creating enablers for cancer screening could help reduce inequalities in cancer mortality (49).

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 to what was used for this model's inputs. The purpose of this model was to evaluate the sensitivity of MCED screening to differing schedules of screening following usual practice by modeling the sensitivity under the assumption of ideal practice, including screening adherence and diagnostic follow-up. 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 urban dwellers and lower educational attainment versus non-SEER areas (50); 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 (21, 51), 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. Screening individuals aged 75-79 (or those with otherwise reduced life-expectancy) may be considered less cost-effective or not to have a favorable benefit:harms ratio (52).

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. Complex distributions of dwell times are also possible. These extensions are out of scope for this paper. 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) (23). 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 tumors. These data indicate that a 6-month screening interval would be too short, and a 3-year interval too long. This modeling result aligns with preliminary evidence from 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 test positive rate increasing progressively with shorter preclinical timescales (43). Retroactive assessment of plasma samples in two large prospective biobank studies suggests that preclinical detectability of cancer signals resembles the tumor growth rates examined here (44). Though tumor growth rates for cfDNA-shedding cancers are poorly understood, the present analysis suggests that annual and biennial intervals are expected to have noticeable differences in expected mortality, which should be considered in the design of MCED screening programs.

This current study uses varied estimates of dwell time duration to model the heterogeneity of cancer and explore the potential effect of screening interval on cancer detection and subsequent mortality. As real-world evidence becomes available, we can interrogate MCED tests 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 (53-56).

In conclusion, given the extremely low false positive rate of an MCED test, annual screening has an acceptable lifetime risk, and there is a noticeable reduction in potential performance from staggering annual to biennial screening. However, even at a suboptimal interval, addition of an MCED test complements current guideline-based cancer screenings.

Acknowledgements:

We acknowledge Neva West, PhD (NeuroWest Solutions, Seattle, WA) and Prescott Medical Communications Group (Chicago, IL) for medical writing, editorial, and administrative support that was funded by GRAIL, LLC. This work was previously presented at European Society for Medical Oncology (ESMO) 16-21 September 2021 (57).

Funding support:

Analysis supported by GRAIL, LLC, Menlo Park, CA

Competing Interests:

Brian Rous: paid member of GRAIL Bio UK Clinical Advisory Board

Christina A. Clarke: employed by GRAIL, LLC with equity

Earl Hubbell: employed by GRAIL, LLC with equity; owns stock in Illumina, Inc; has multiple patents in the field of cancer detection pending to GRAIL, LLC

Peter Sasieni: paid member of the Scientific Advisory Board for GRAIL, LLC; no equity

Author Contributions:

Brian Rous: Investigation and methodology, and writing (review and editing). **Christina A. Clarke**: Study conceptualization, data curation, formal analyses, methodology, validation, visualization, and writing (original draft preparation, review, and editing). **Earl Hubbell:** Study conceptualization, data curation, formal analyses, investigation and methodology, validation, visualization, and writing (original draft preparation, review, and editing). **Peter Sasieni:** Study conceptualization, investigation and methodology, and writing (original draft preparation, review, and editing).

Data Availability Statement:

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 (21).

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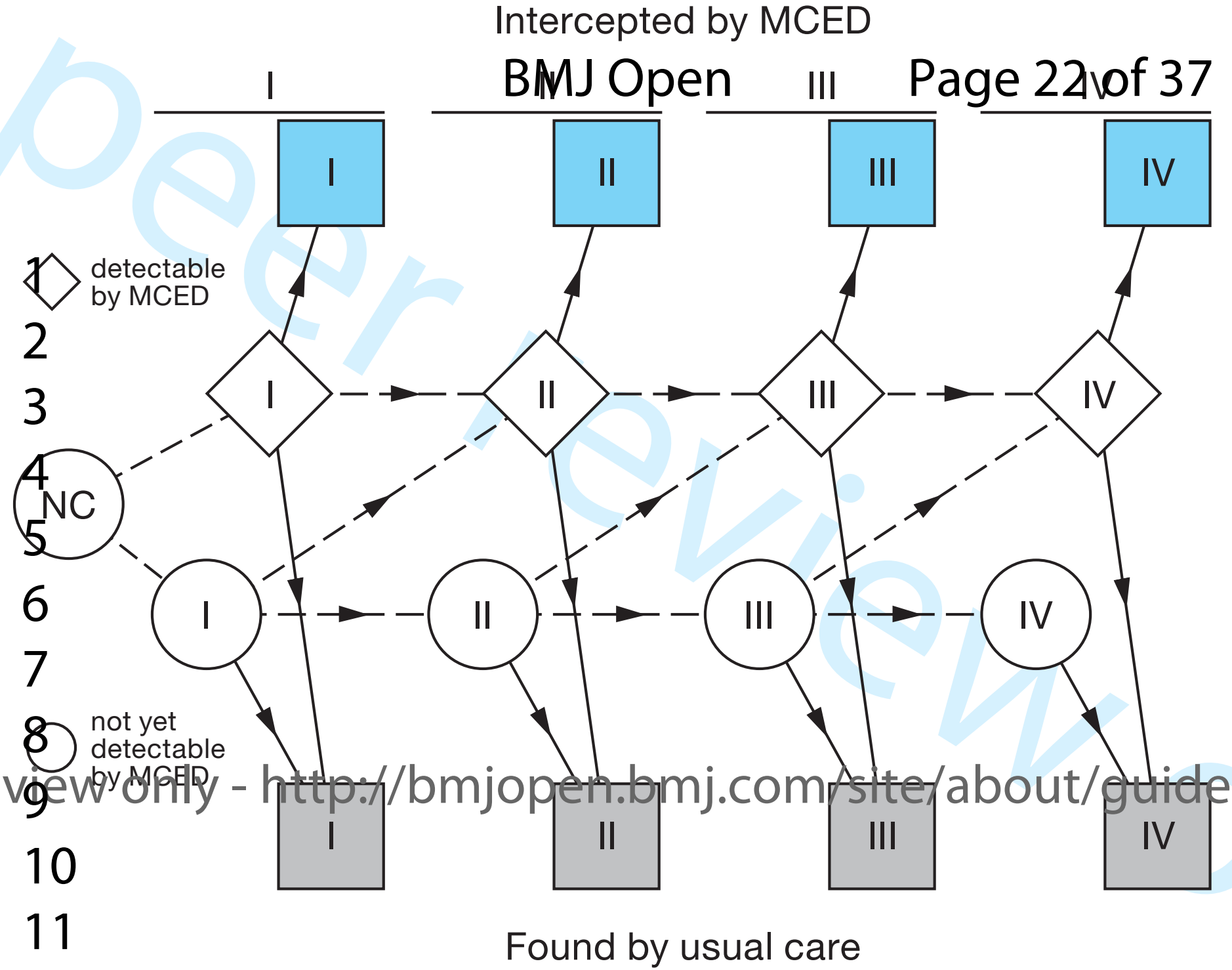
FIGURES LEGENDS

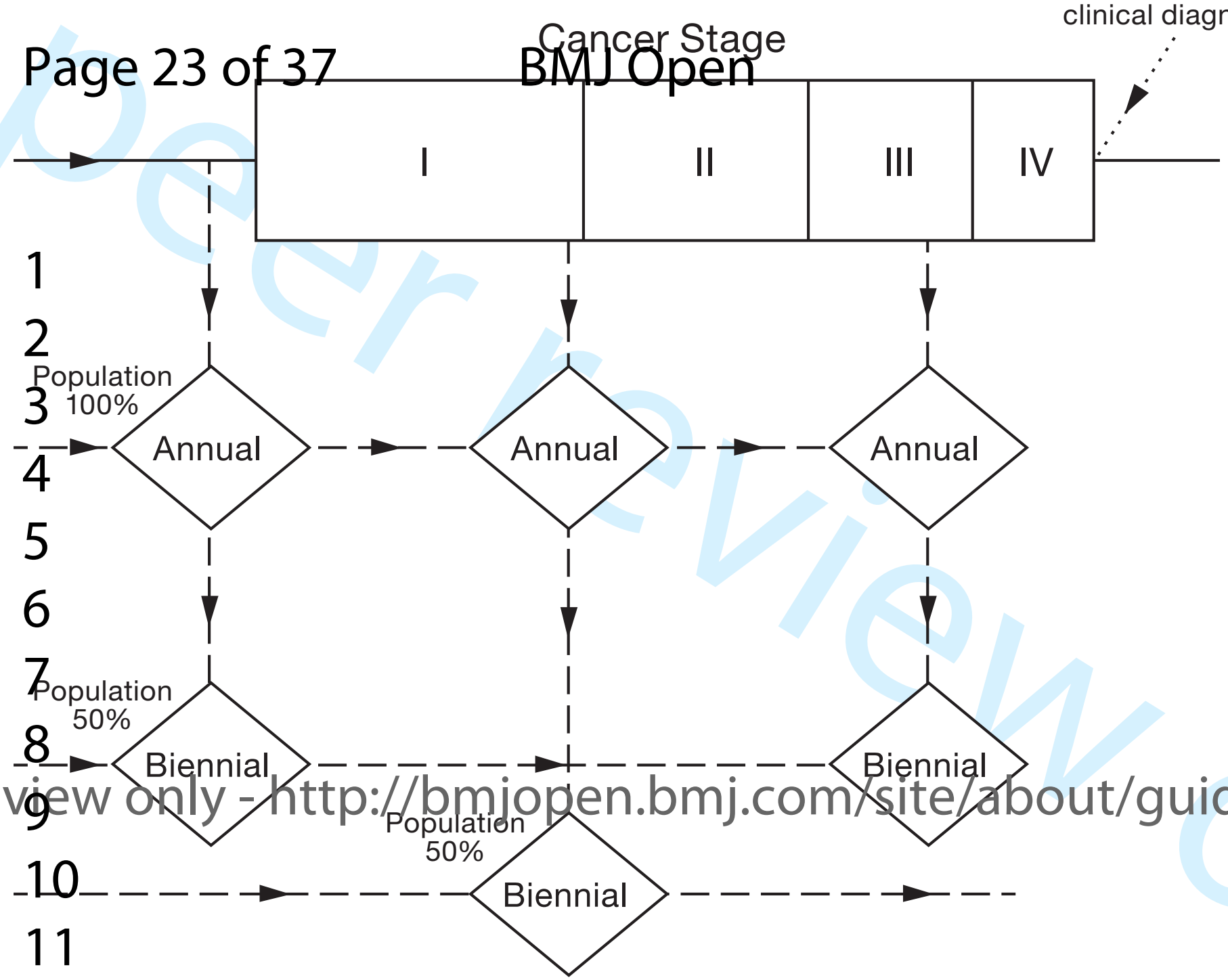
Figure 1. Interception model schematic. Cancer progression is shown in this figure as advancement from No Cancer (NC) to Stage I through IV cancer from left to right. Shapes represent cancer states (○ undetectable by MCED at that stage, ♦ detectable by MCED at that stage, • diagnosed at that stage).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

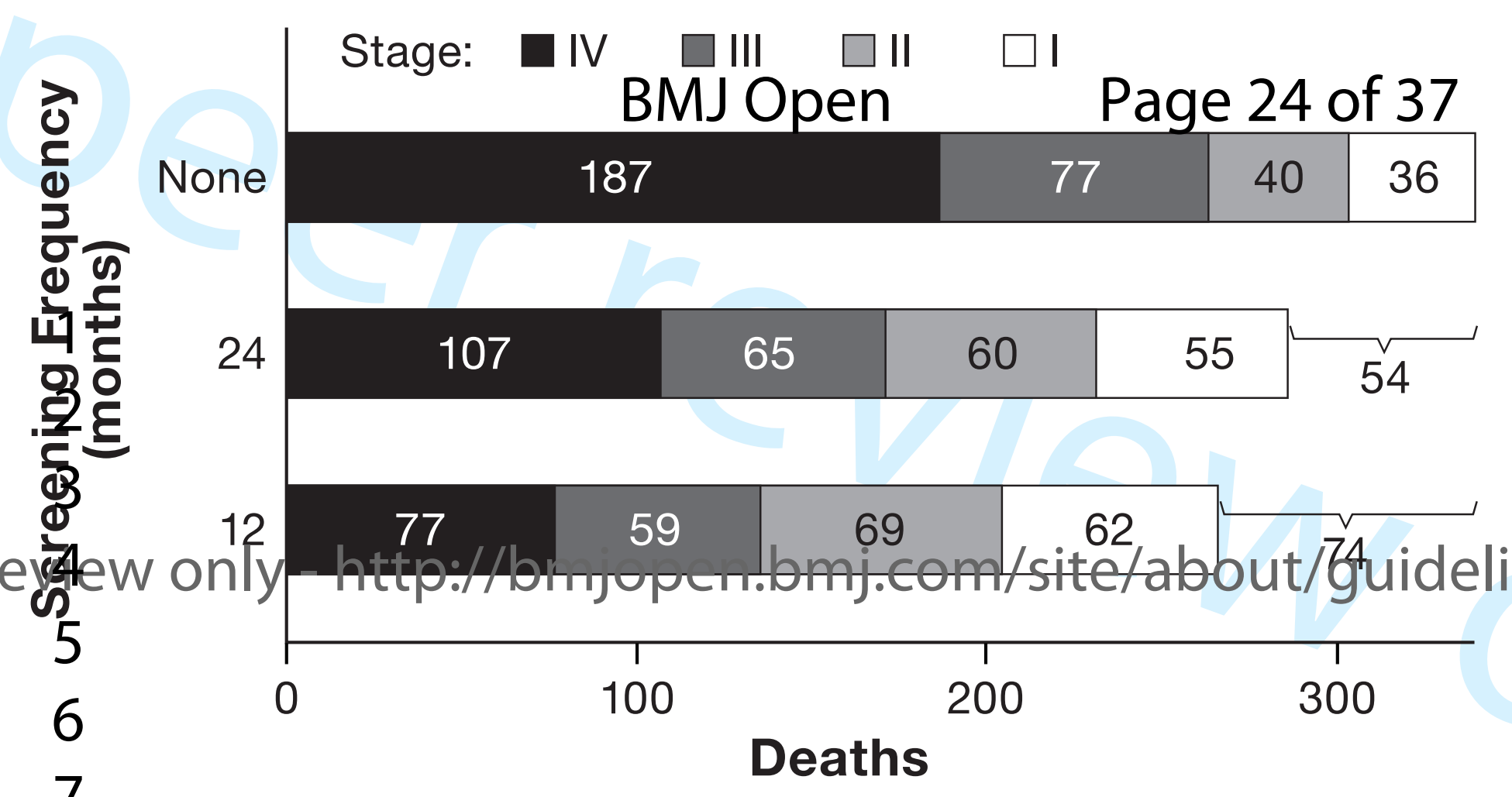
Figure 2. Effect of screening intensity on stage of diagnosis. Top line (solid) represents usual care (without MCED testing) for a single hypothetical patient who would receive a clinical cancer diagnosis at Stage IV and the size of the boxes reflects the hypothetical dwell time at each stage. In this 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.

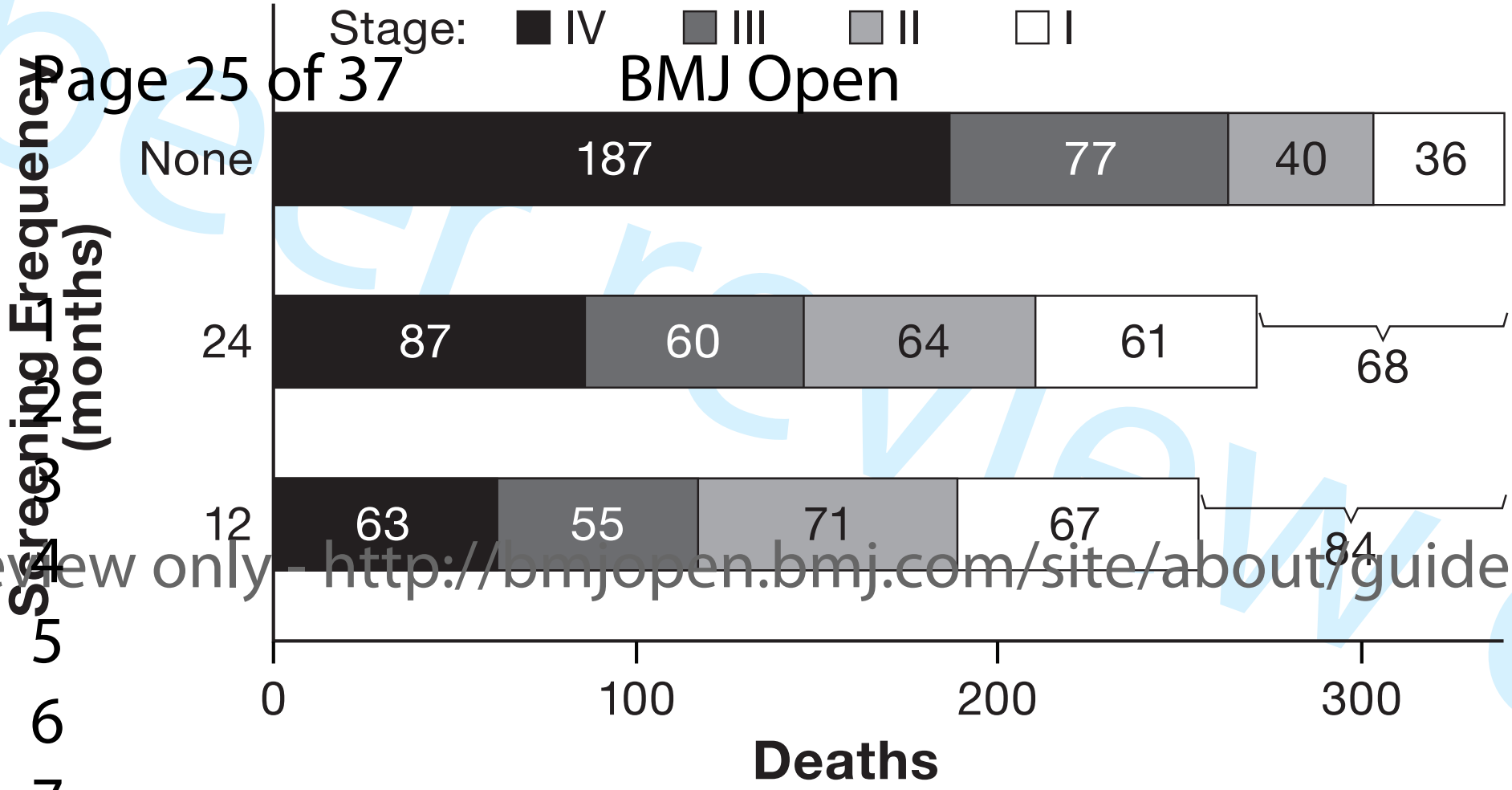
Figure 3. Effect of likely screening intervals on averted deaths by growth rate scenario. In the top panel, the number of deaths by stage in the Fast Aggressive tumor growth rate scenario with annual, biennial, or no MCED screening are shown. The number of deaths averted versus no MCED testing are shown at the top of each bar. In the bottom panel, the same information with a Fast tumor growth rate scenario is shown.

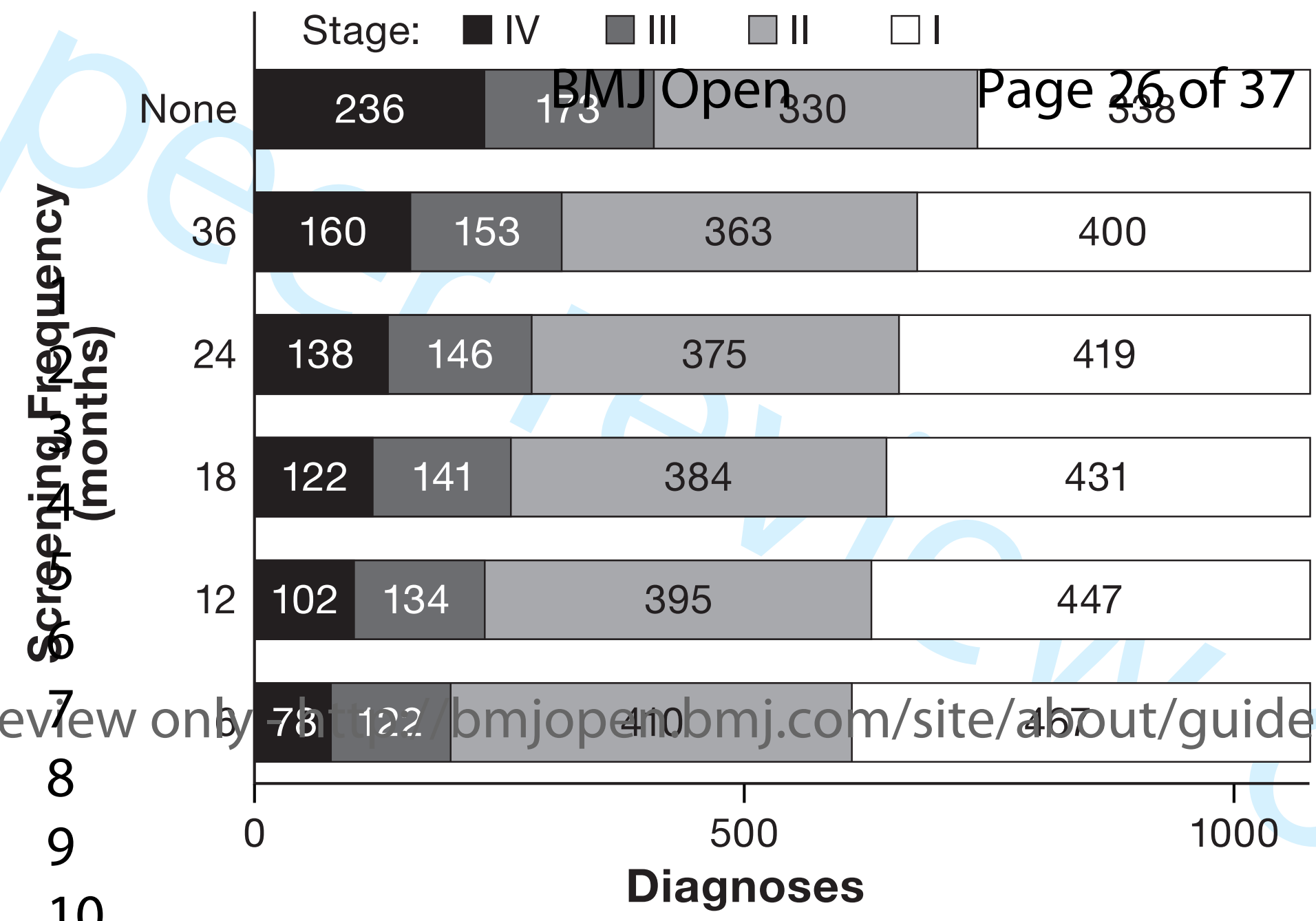
Figure 4. Stage at diagnosis with 6-month to 3-year screening intervals. Panel A shows the stage of cancer at diagnosis in the Fast Aggressive tumor growth rate scenario. Panel B shows the same for the Fast tumor growth rate scenario.

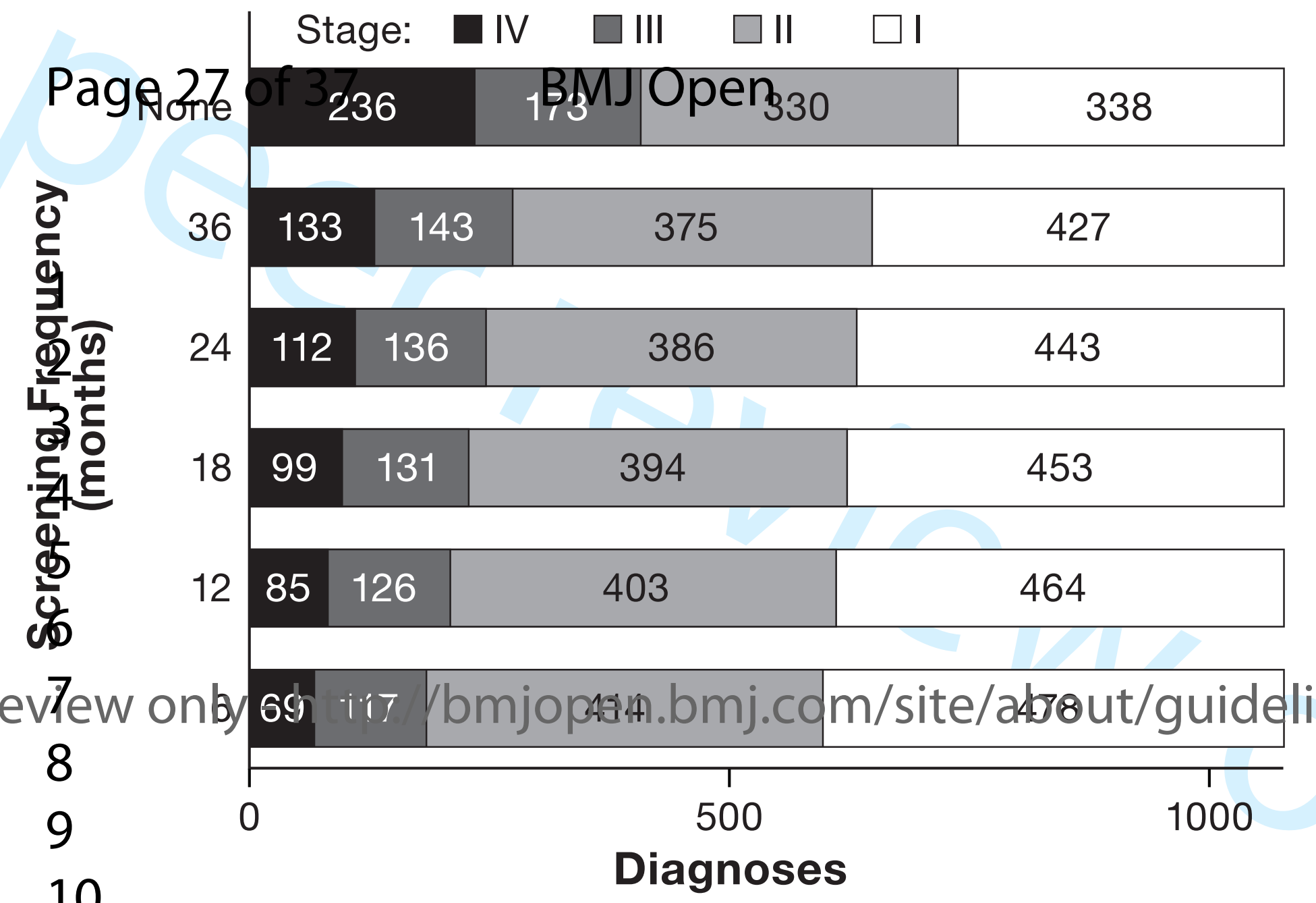












Title: **Sensitivity of reductions in late-stage cancer and mortality to screening interval choice in a multi cancer early detection state-transition model**

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SUPPLEMENTAL DATA

The data that supports the findings of this study are available here [https://github.com/grailbio-publications/Sasieni_Screening_Interval]

Table S1. Classification of Cancer Sites by Growth Pattern

dwell_group	cancer
A	Anus, Colon/Rectum, Esophagus, Lung
B	Cervix, Uterus, Head and Neck, *Lymphoid Leukemia*, Lymphoma, *Plasma Cell Neoplasm*, Ovary
C	Kidney, Liver/Bile-duct, Pancreas, Gallbladder, Prostate, Stomach, Sarcoma, Thyroid
D	Bladder, Urothelial Tract, Breast, Melanoma, *Myeloid Neoplasm*, Other

Italics indicate hematologic malignancies that are "Not Staged" in the SEER database. While the code has them assigned to the dwell groups indicated, they are not used in the modeling for this analysis.

Table S2. Dwell Times Per Cancer Stage and Growth Scenario (Years)

dwell_group	scenario	Stage			
		I	II	III	IV
A	**Fast**	2	1	0.5	0.5
A	**AggFast**	1.5	0.75	0.5	0.25
B	**Fast**	4	2	1	1
B	**AggFast**	1.5	0.75	0.5	0.25
C	**Fast**	2	1	1	0.5
C	**AggFast**	1	0.5	0.25	0.25

D	**Fast**	4	2	1	1
D	**AggFast**	2	1	0.5	0.5

Figure S1: Estimated test sensitivity for cancer type by stage based on Klein et al (1). Sensitivity is expected to be non-decreasing by stage: weighted isotonic regression is used to estimate sensitivity consistent with this constraint. Note that sensitivity in this model represents the fraction of cancers shedding detectable amounts of tumor DNA, not an independent chance of detection for each blood draw. Cancers shedding at stage I (detectable at stage I) are expected to remain detectable at later stages. Note that as any cancer case can only be expected to be found once, cases found at stage I cannot then be found again at a later stage. This accounting identity is used in the state-transition model to avoid overestimating performance.

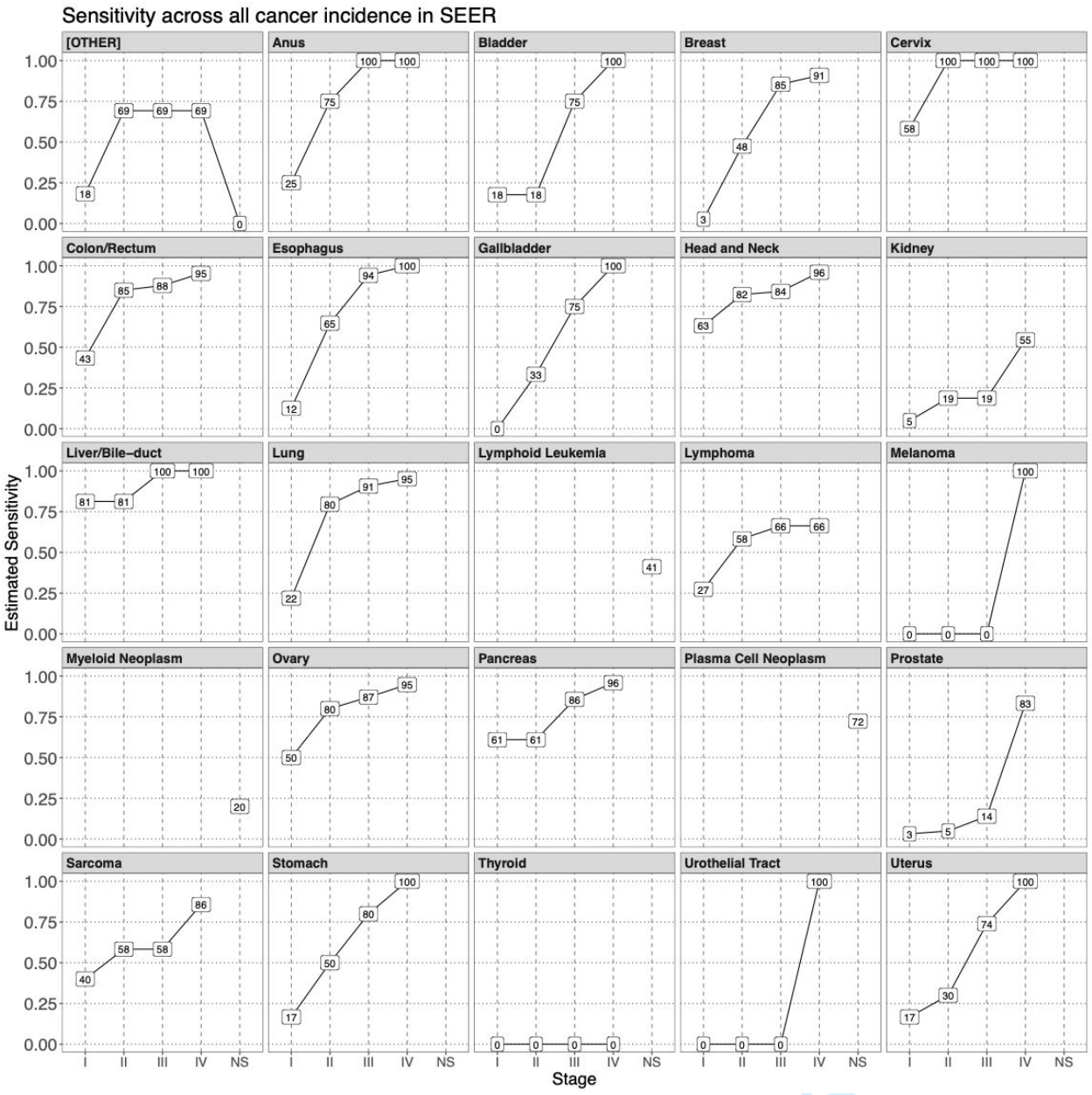


Figure S2: Cancer incidence in the Surveillance, Epidemiology, and End Results (SEER) database, ages 50-79. This is one of the inputs for the interception model and determines yearly cancer incidence expected in a typical year of individuals in this age range. Missing/unknown stage for stageable cancers is imputed into a stage using the ratios of observed cancer stages for each cancer. This covers all cancer incidence in the SEER database.

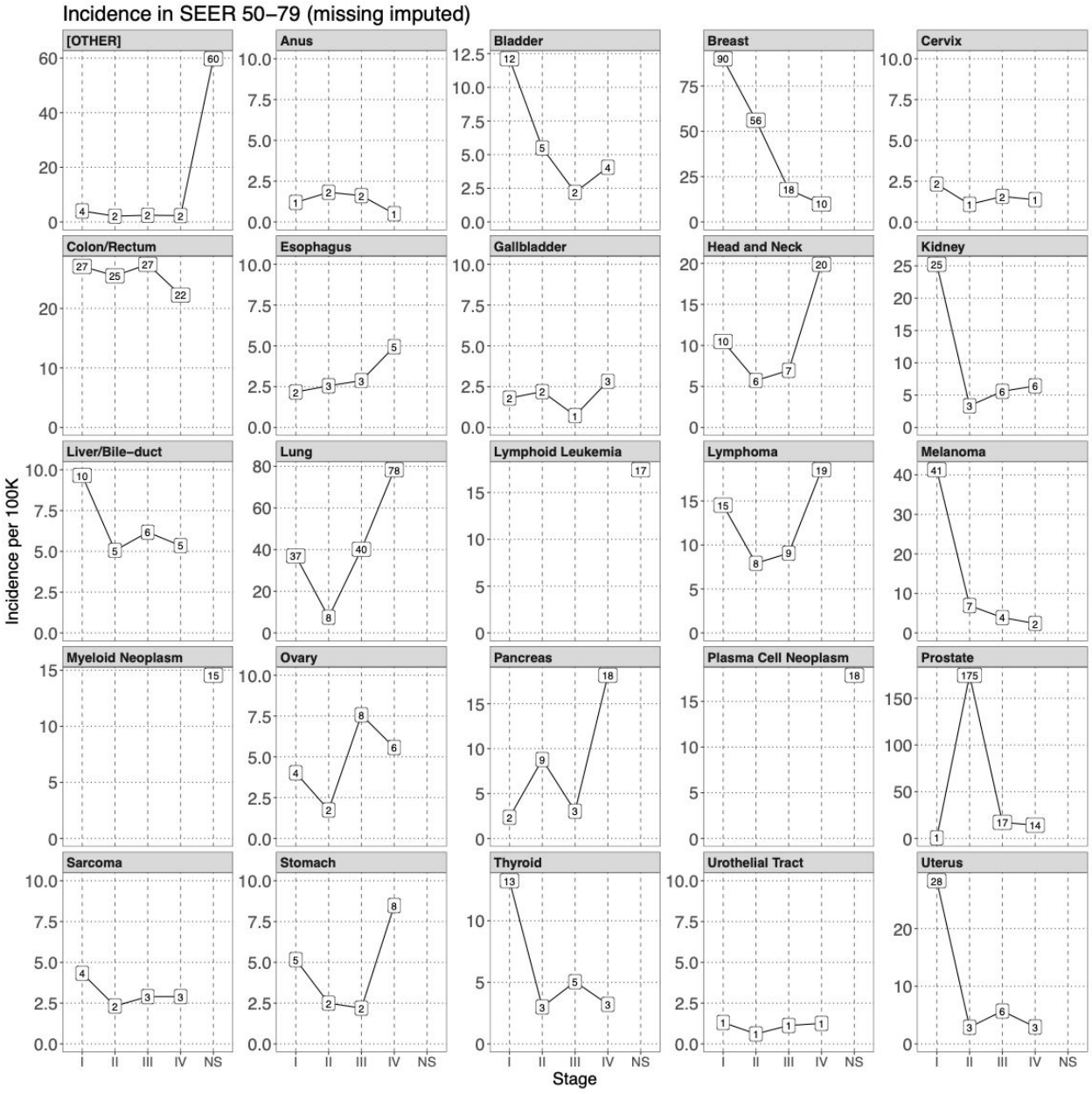


Figure S3: 5-year survival estimates from SEER. Another input metric for the model, the 5-year survival for cancer types modeled, broken out by stage. This is used as a simple metric for improvements in survival by stage.

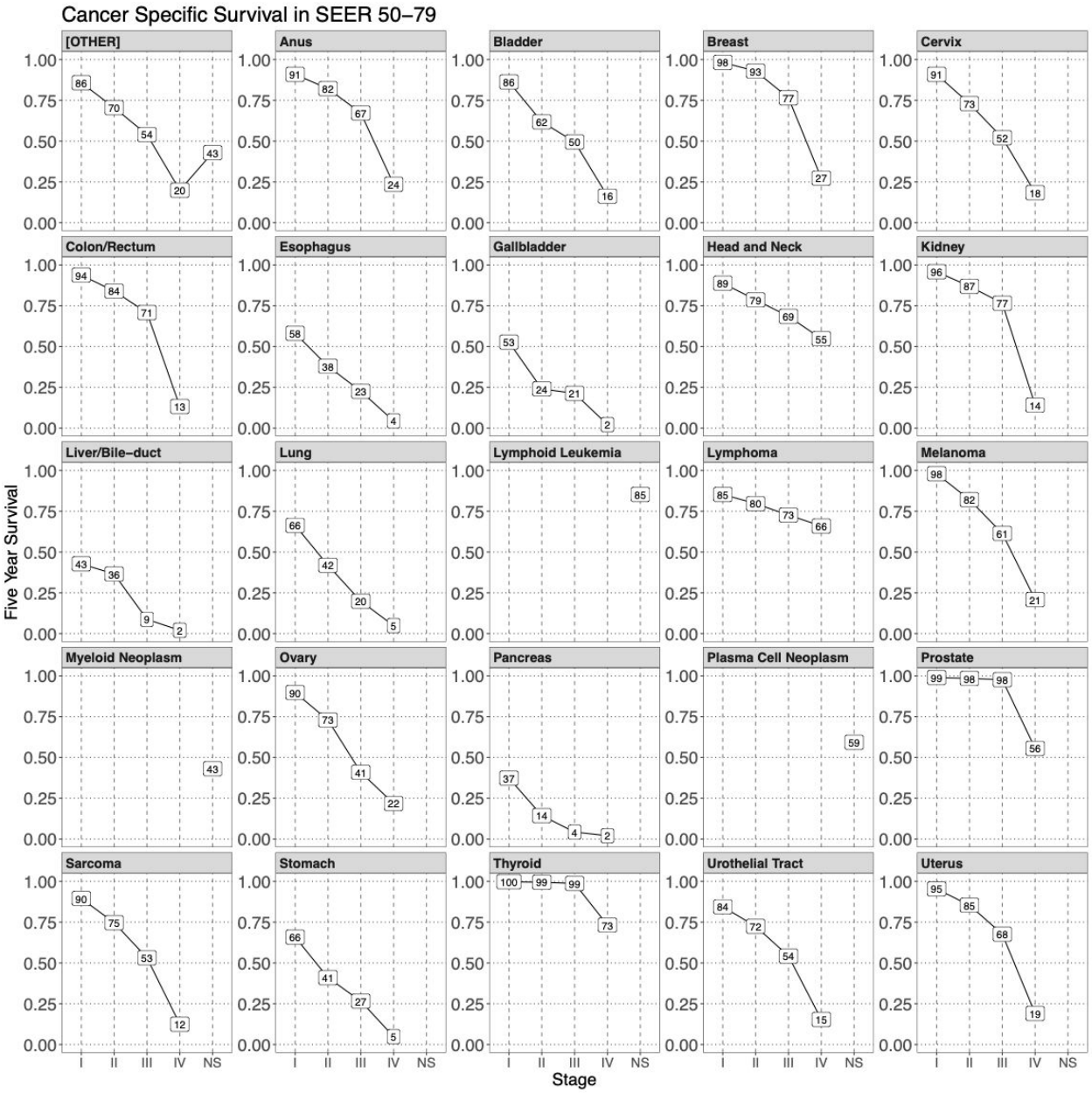


Figure S4: Cumulative odds of at least one false positive by years of annual screening at differing rates. For a given false positive rate (0.5, 1, 10%), the cumulative odds are computed by estimating the rate at which no false positives occur and subtracting from 1. MCED specificity is high; therefore, false positive rates are expected to be <1%. 10% is plotted here as a comparator for typical screening tests with a 90% specificity.

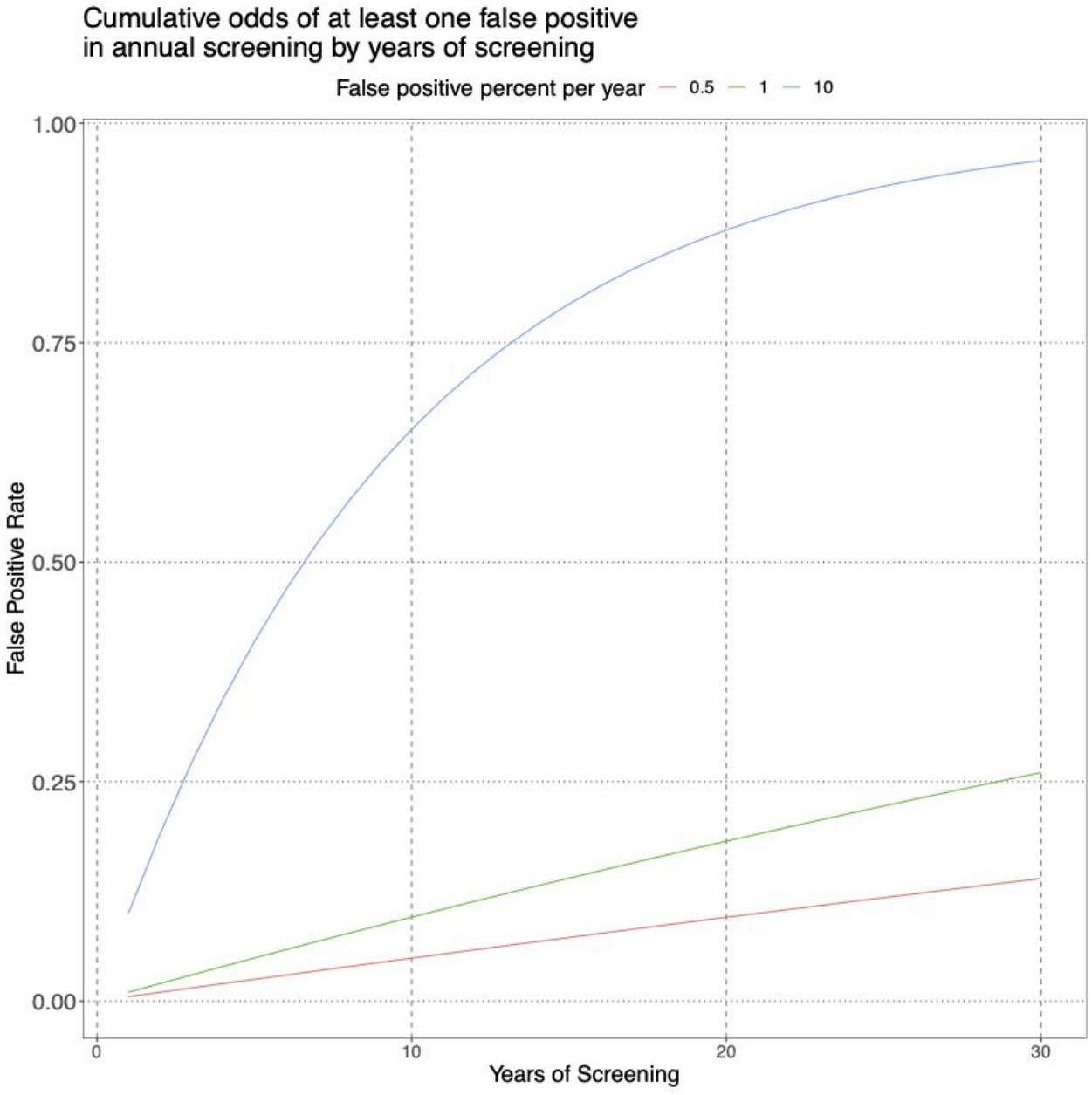
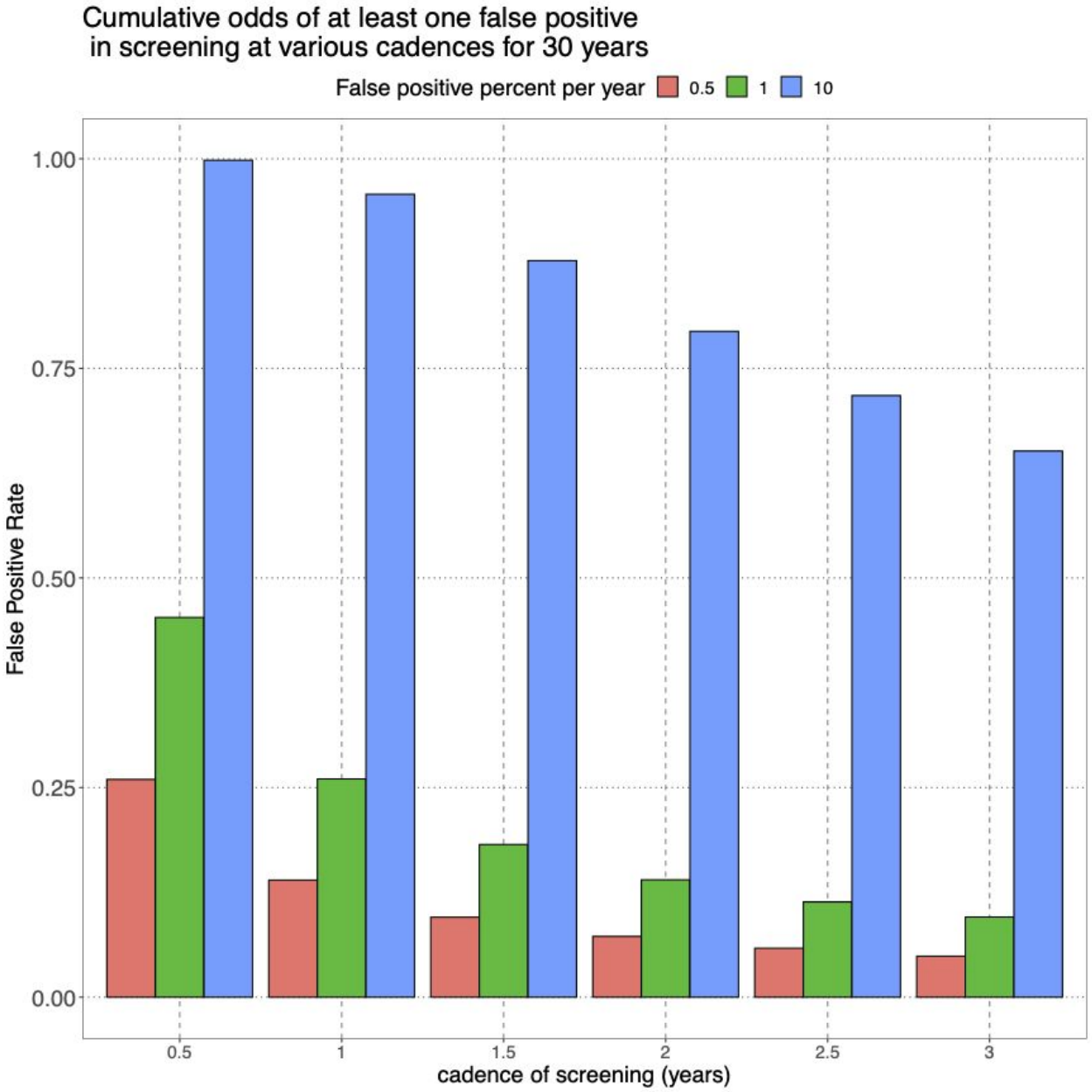


Figure S5: Cadence of screening affects absolute false positive rate expected in 30 years of screening. For each cadence of screening (6 months to 3 years), the expected rate of individuals receiving at least one false positive are shown, contrasting MCED-type false positive rates (0.5, 1%) with false positive rates from a typical screening assay (10%). Note that even 6-month screening intervals for MCED tests produce fewer false positives than 3-year screening intervals for a typical screening assay.



SUPPLEMENTAL INFORMATION

Brief description of the interception model

The interception model is designed to quickly estimate the steady-state behavior of a screening program. It takes into account the cancer incidence per year and the stage at clinical diagnosis, the detectability of cancer at each stage (probability of shedding detectable material), and an input of estimated dwell time spent in each stage.

Essentially, at a steady state, cancers detected at a given stage must a) be shedding cell-free DNA (cfDNA), b) have been missed by any prior screening, and c) not been found by usual care. The interception model estimates the odds of each of these cases given the inputs and then outputs the distribution of stage at diagnosis after an MCED test has been added to usual care. This revised stage distribution is then used to estimate the differential effect on 5-year survival as a quick estimate of mortality benefit.

There are several relevant consequences of this model to drive intuition. First, even daily screening will not find all cancer cases (not all cases shed detectable DNA). Second, dwell times are only relevant for cases that shed DNA - the duration of time spent not shedding DNA does not affect any output of the model. This subset of cancers may grow at a different rate than the set of all tumors, including non-shedding cases found by imaging. Third, the odds of being missed by a screening event depend on dwell times and the cadence of screening - faster dwell times and lower screening cadence both increase the odds of missing a detectable cancer case. Finally, we are not tracking year-by-year a fixed population aged 50-79 years; we are estimating an average year of steady-state screening in this mixed population. For instance, we are sampling the year 2025 in a screening program, rather than tracking an individual from the year 2023 to 2053. Extensive details can be found in the Hubbell et al publication (2).

The limited potential for overdiagnosis

Etzioni et al note that there are multiple models of analysis of overdiagnosis and distinguish two types of overdiagnosis discussed in the literature. The first involves competing risks of

immediate death during the lead time for cancers that would surface clinically if the individual had had the usual survival (3). For screening eligible populations (usually taken to have ~10 years of remaining life), this risk of overdiagnosis is limited for aggressive cancers with small amounts of lead time.

Data from the recently published TRACERx study showed an association between a lack of preoperative circulating tumor DNA (ctDNA) detection and good clinical outcomes with indolent lung adenocarcinoma (4). This and other evidence suggests that cancers not shedding ctDNA have better prognosis than expected (4,5). Further, there are strong biophysical arguments that ctDNA shedding requires growth, such as seen in the recently published study by Bredno, et al, which provides evidence that more aggressive tumors (metabolic activity) shed more cfDNA than slow-growing tumors (6).

The second type of overdiagnosis defined by Etzioni et al is detecting indolent cases with low odds of causing death within a typical lifespan (3). By definition, these cases have a long lead time and minimal growth rates; on biophysical grounds, they are unlikely to shed, and so will be heavily depleted within a few screens with any choice of screening interval, leaving only newly initiated cases. Overdiagnosis of this type will not be strongly affected by screening interval in the steady state, as only the rate of newly arising cases within a screening interval matters.

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BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-086648.R1
Article Type:	Original research
Date Submitted by the Author:	06-Nov-2024
Complete List of Authors:	Rous, Brian; Cambridge University Hospitals NHS Foundation Trust Clarke, Christina A.; Grail Inc Hubbell, Earl; Grail Inc SASIENI, PETER; Queen Mary University of London
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Health informatics, Research methods, Epidemiology
Keywords:	Clinical Decision-Making, Mass Screening, REGISTRIES

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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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Keywords: early detection of cancer; cancer screening; computer simulation; clinical decision-making; registry data

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 is 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 program 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 tumor 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 USA for all cancer incidence.

Outcome measures

Diagnostic yield, stage shift, and mortality.

Results

Annual screening under the fast tumor growth scenario was associated with more favorable diagnostic yield (370 more cancer signals detected/year/100,000 people screened), stage shift (49% fewer late-stage diagnoses), and mortality (21% fewer deaths within five 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 five years than usual care). Annual screening prevented more deaths within 5 years than biennial screening for the fast tumor growth scenario, but biennial screening had a

higher positive predictive value (54% vs 43%) and was 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. Modeling 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 MCED screening intervals, modeling is required to investigate potential screening intervals of new MCED screening tests.
- This study uses performance estimates from a published case-control study and outcomes from the Surveillance, Epidemiology, and End Results (SEER) database, a widely used database for modeling studies.
- Varied estimates of dwell time duration were used to model the heterogeneity of cancer and 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.

BACKGROUND

Cancer is one of the leading causes of death around the world.[1] At present, wide-spread 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 be also 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.

Multi-cancer early detection (MCED) tests are innovative new technologies that utilize cancer biology to screen for a broad set of cancer types with a single blood sample.[10,11] There are several MCED tests currently under development that utilize a variety of different analytes to detect a cancer signal.[12] Cell-free DNA (cfDNA) is one such analyte that can be shed by tumors into the bloodstream and can carry cancer-specific signals.[13,14] By analyzing 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] This test can complement, though not replace, existing single-cancer screenings, as well as expand categories of screenable cancers.[11] The high specificity of this test decreases the likelihood of false positives and the subsequent extraneous triage and diagnostic testing. 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 one to five 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 computerized 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] Tests for asymptomatic indolent cancers may lead to overdiagnosis, such as in the case of screening for prostate cancer.[23]

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.[24]

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 maximize the benefits across individuals who may develop a range of cancer types with different clinical features and growth rates, rather than optimizing for a single cancer type. This poses a unique challenge to the implementation of an MCED screening program 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 utilizing MCED test characteristics from a recently published report[10] and population cancer data from the US Surveillance, Epidemiology and End Results (SEER) program for cancer types detectable by the MCED test. In the absence of real-world evidence regarding MCED screening intervals, state-transition modeling 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 program using an MCED test when added to usual care for persons aged 50-79.[25] 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, though MCEDs have the potential to intercept more types of cancer at earlier stages than usual care (current clinical practice with no MCED test).[25] 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] (**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 USA for all cancer incidence (**Figures S2-S3**).[26] From the SEER program (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 through December 31, 2018 (**Figures S2-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 AJCC 6th edition staging was available across the entire time period (categorized 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 minimize 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, esophagus, gallbladder, head and neck, kidney, liver/bile-duct, lung, lymphoid leukemia, 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 ICD-O-3 site and histologic groupings for cancer types used to specify SEER data for this analysis are detailed in **Table S1** and Hubbell et al.[25] 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 (**Table S2, Table S3,** and Hubbell et al. supplementary data).[25] In this analysis, we model cancer detection as it reflects the requirement that a cancer case is

shedding detectable 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 modeled 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 modeled 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.[9,20,27–29] 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 program as recommended.

Analyses

In previous modeling work,[25] we performed a sensitivity analysis for an annual screening interval interacting with three hypothetical tumor 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 tumor growth rate scenarios from our previous

study: the “fast” and “fast aggressive” scenarios (**Tables 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 modeled for most analyses, though 6-month intervals from 0 to 3 years were examined and are shown for some figures. Screening intensity, defined as 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.[30,31] The probability that a cancer progresses without being intercepted by an MCED test is dependent on the screening interval relative to the tumor 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.

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.[32]

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.[25]

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**).

Table 1. Reductions in Estimated Late-Stage Cancer Diagnoses and Deaths by Adding Annual or Biennial MCED to Standard Care[a]

		Hypothetical Tumor 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	-	50000	100000	50000	100000
FP/year due to MCED, %[b]	-	0.25	0.5	0.25	0.5
Diagnoses at Late-Stage (III/IV), N	409	284	236	248	210
Reduction vs Usual Care, %[c]	-	31	42	39	49
Deaths Within 5 years[d], N	392	338	318	324	308

Deaths Averted vs Usual Care, N (%)	**-**	**54 (14)**	**74 (19)**	**68 (17)**	**84 (21)**

Abbreviations: cfDNA, cell-free DNA; FP, false positive; MCED, multi-cancer early detection test; PPV, positive predictive value.

[a]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.

[b]Annual false positive rate due to MCED testing intensity.

[c]% of patients diagnosed at an earlier stage with each screening interval and tumor growth rate scenario versus current care with no MCED.

[d]All cancers diagnosed in one year and followed for deaths within 5 years of original diagnosis (ie, in the absence of MCED screening) to account for lead time.

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 favorable scenario shown, biennial screening with fast aggressive tumor 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 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 six months to every three 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 favorable early-stage diagnosis rates than usual care alone. There was a larger impact on stage shift with the fast tumor growth rate versus tumors 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 tumor growth rate

scenarios, annual screening leads to fewer deaths (**Figure 3**) versus no MCED screening and biennial MCED screening.

These results were compared to the number of deaths within five years of diagnosis - i.e. 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 of these deaths (**Table 1**). This is comparable to a hypothetical perfect screening technology eliminating all deaths from breast (17 deaths) and colorectal (33 deaths) cancer combined.[26] Annual MCED screening would have resulted in 84 fewer deaths under the most favorable MCED scenario (**Table 1**). This is equivalent to more than the total deaths within five years of diagnosis in SEER from breast, colorectal, and pancreatic (30 deaths) cancer combined.[26]

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 favorable 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. 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 modeling.[2,9] In the absence of sufficient real-world evidence regarding MCED screening intervals, modeling 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 modeled 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 modeling.[26,31,32] 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. We assume that stage-specific cancer survival does not differ between MCED-positive and MCED-negative tumors; however, survival prediction is complex.[33] 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.[34,35] Due to these necessary modeling 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 utilized 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%),[36] only results in a lifetime risk of 30% (**Figures S4-S5**). This compares favorably with both standard-of-care screening and symptomatic referrals.[37,38] 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.[39–42] 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.[43,44] Cancer detection using cfDNA analysis may preferentially detect more lethal cancers.[33] More rapidly growing and aggressive tumors tend to shed more cfDNA, and therefore are more likely to be detected by

cfDNA-based MCED screening tests.[33,45,46] 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 tumor progression, recently shown to resemble those seen in analysis of biobank samples,[47,48] between stages in this model to account for the potential short duration of tumors 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 (**Figure S6**). MCED screens are intended to complement existing screening programs and not replace them; therefore, if an MCED test fails to detect a tumor, 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 to what was used for this model's inputs. The purpose of this model was to evaluate the sensitivity of MCED screening to differing schedules of screening following usual practice by modeling the sensitivity under the assumption of ideal practice, including screening adherence and diagnostic follow-up. 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 versus non-SEER areas;[49] 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,[25,50] 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. Screening individuals aged 75-79 (or those with otherwise reduced life-expectancy) may be considered less cost-effective or not to have a favorable benefit:harms ratio.[51]

While we have modeled cancer natural history with a standard stage-transition model, cancers may have complex properties not explicitly modeled 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 paper. 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).[27] 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 tumors. These data suggest that a 6-month screening interval would be too short, and a 3-year interval too long. This modeling result aligns with preliminary evidence from 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 test positive rate increasing progressively with shorter preclinical timescales.[47] Retroactive assessment of plasma samples in two large prospective biobank studies suggests that preclinical detectability of cancer signals resembles the tumor growth rates examined here.[48] Though tumor growth rates for cfDNA-shedding cancers are poorly understood, the present analysis suggests that annual and biennial intervals are expected to have noticeable

differences in expected mortality, which should be considered in the design of MCED screening programs.

This current study uses varied estimates of dwell time duration to model the heterogeneity of cancer and explore the potential effect of screening interval on cancer detection and subsequent mortality. As real-world evidence becomes available, we can interrogate MCED tests 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.[52–55]

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 tumor 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.

Acknowledgements:

We acknowledge Neva West, PhD (NeuroWest Solutions, Seattle, WA) and Prescott Medical Communications Group (Chicago, IL) for medical writing, editorial, and administrative support that was funded by GRAIL, Inc. This work was previously presented at European Society for Medical Oncology (ESMO) 16-21 September 2021.[56]

Funding support:

Analysis supported by GRAIL, Inc., Menlo Park, CA

Competing Interests:

Brian Rous: paid member of GRAIL Bio UK Clinical Advisory Board

Christina A. Clarke: employed by GRAIL, Inc. with equity

Earl Hubbell: employed by GRAIL, Inc., with equity; owns stock in Illumina, Inc; has multiple patents in the field of cancer detection pending to GRAIL, Inc.

Peter Sasieni: paid member of the Scientific Advisory Board for GRAIL, Inc., no equity

Author Contributions:

Brian Rous: Investigation and methodology, and writing (review and editing). **Christina A. Clarke**: Study conceptualization, data curation, formal analyses, methodology, validation, visualization, and writing (original draft preparation, review, and editing). **Earl Hubbell:** Guarantor, study conceptualization, data curation, formal analyses, investigation and methodology, validation, visualization, and writing (original draft preparation, review, and editing). **Peter Sasieni:** Study conceptualization, investigation and methodology, and writing (original draft preparation, review, and editing).

Data Availability Statement:

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.[25]

Ethics Approval Statement:

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

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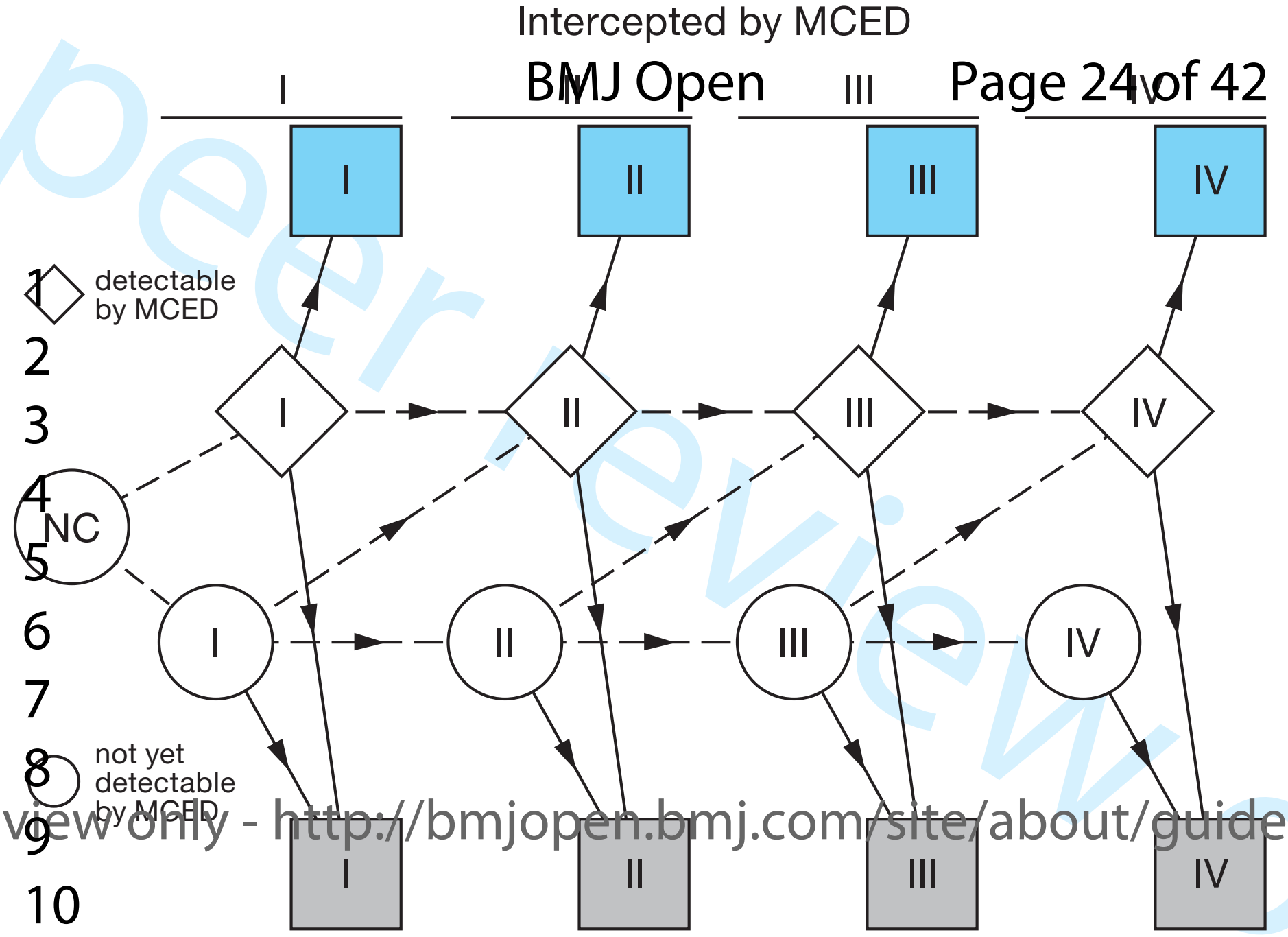
FIGURES LEGENDS

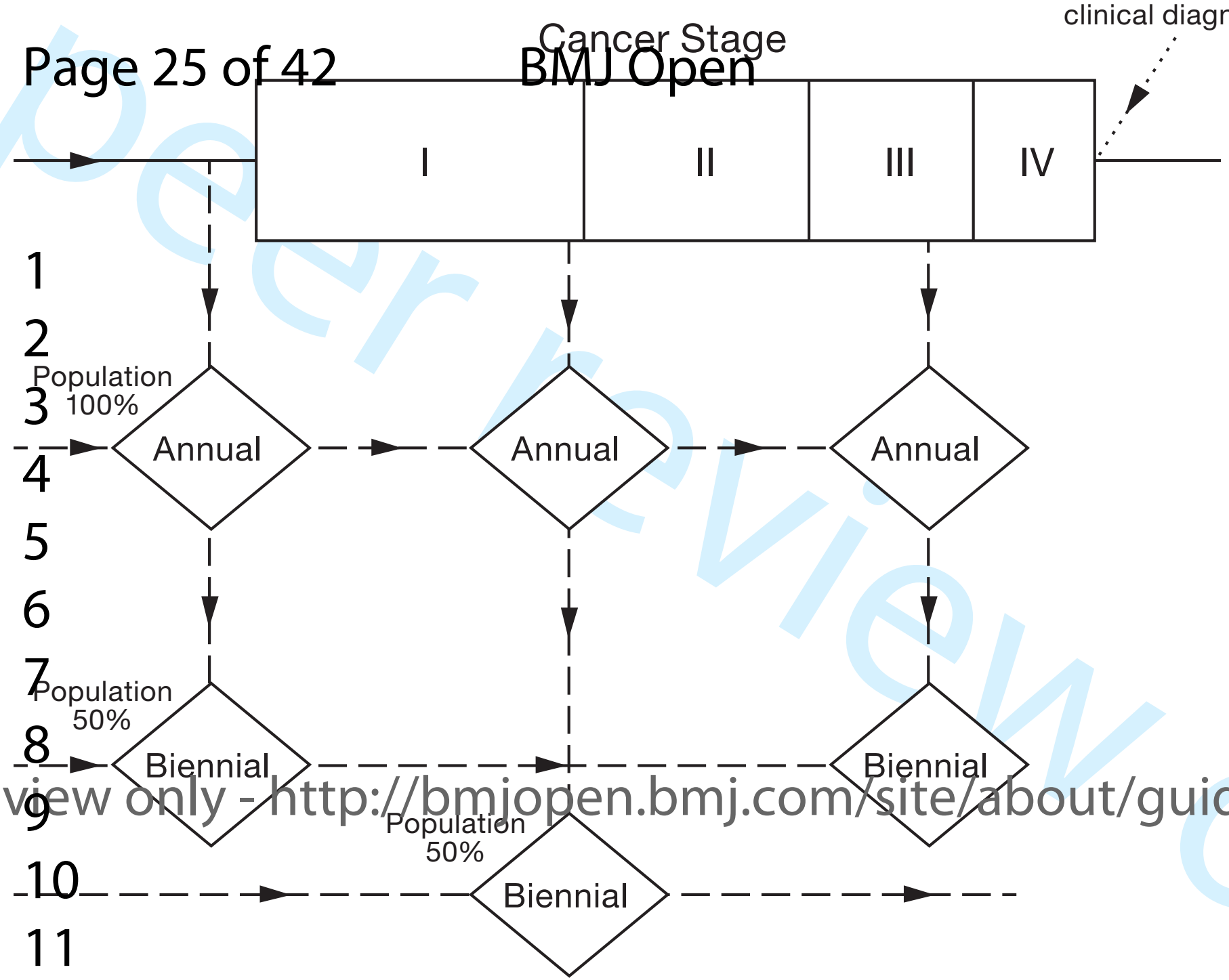
Figure 1. Interception model schematic. Cancer progression is shown in this figure as advancement from No Cancer (NC) to Stage I through IV cancer from left to right. Shapes represent cancer states (○ undetectable by MCED at that stage, ♦ detectable by MCED at that stage, • diagnosed at that stage).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

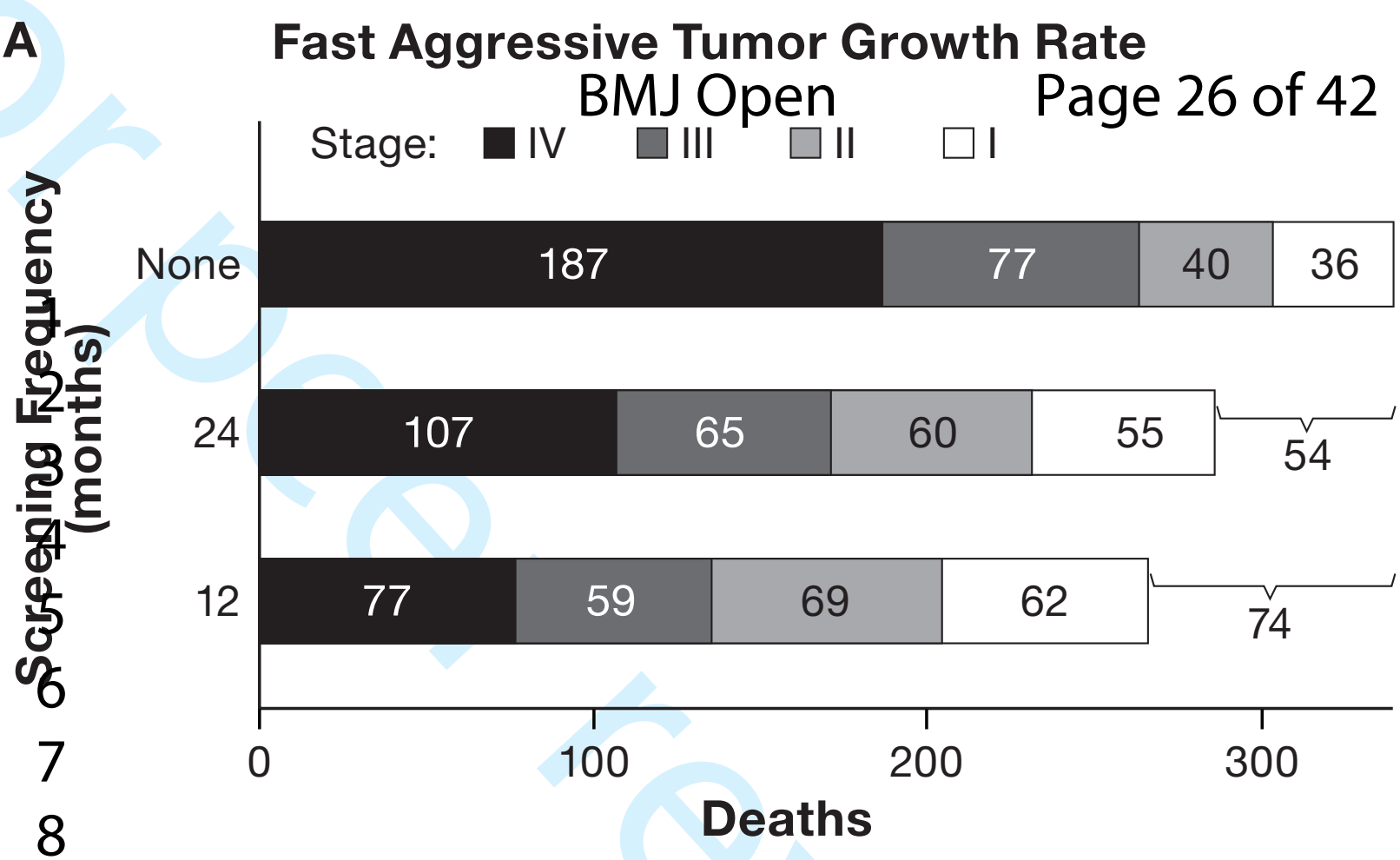
Figure 2. Effect of screening intensity on stage of diagnosis. Top line (solid) represents usual care (without MCED testing) for a single hypothetical patient who would receive a clinical cancer diagnosis at Stage IV and the size of the boxes reflects the hypothetical dwell time at each stage. In this 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.

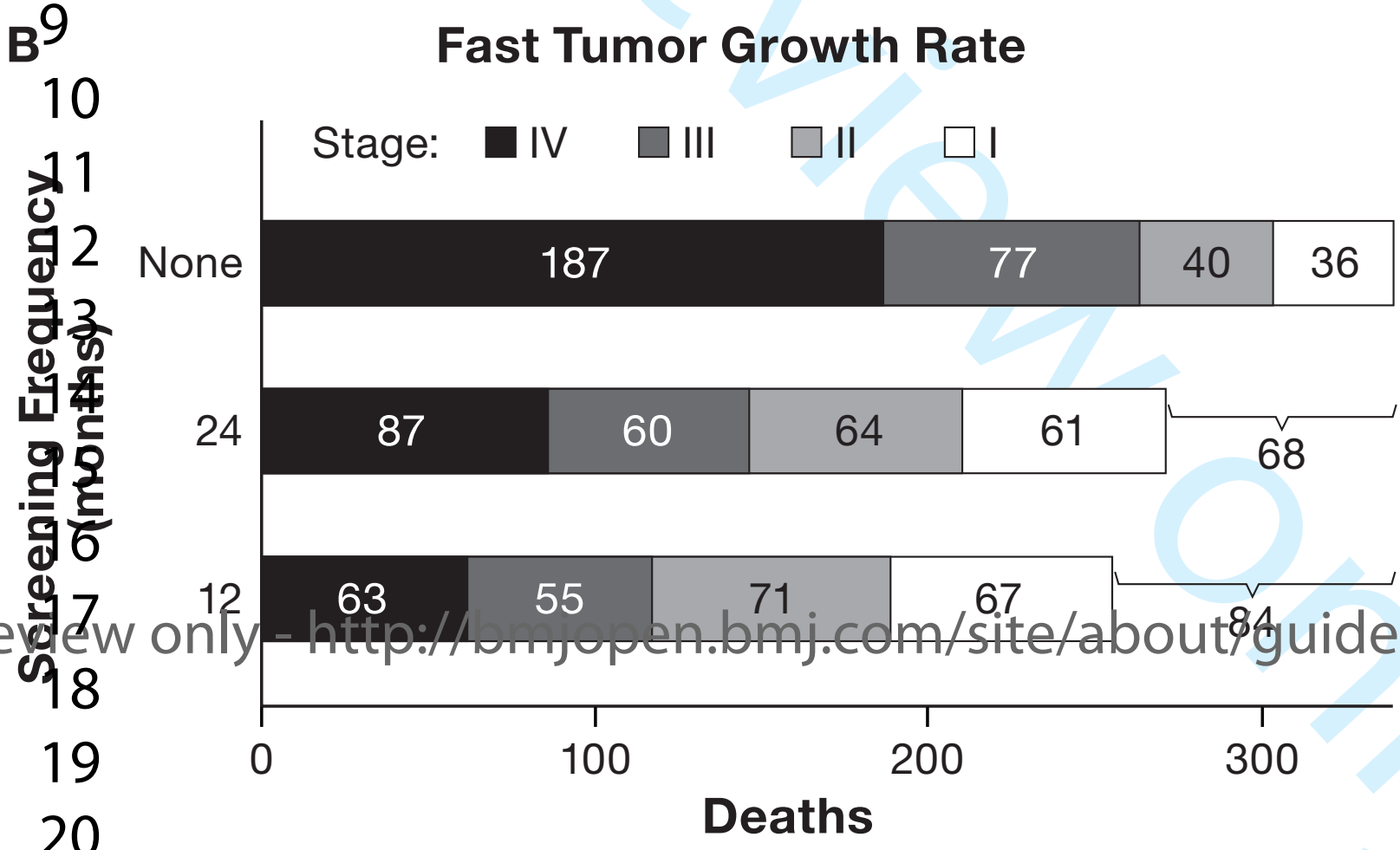
Figure 3. Effect of likely screening intervals on averted deaths by growth rate scenario. A) the number of deaths by stage in the Fast Aggressive tumor growth rate scenario with annual, biennial, or no MCED screening are shown. The number of deaths averted versus no MCED testing are shown at the top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

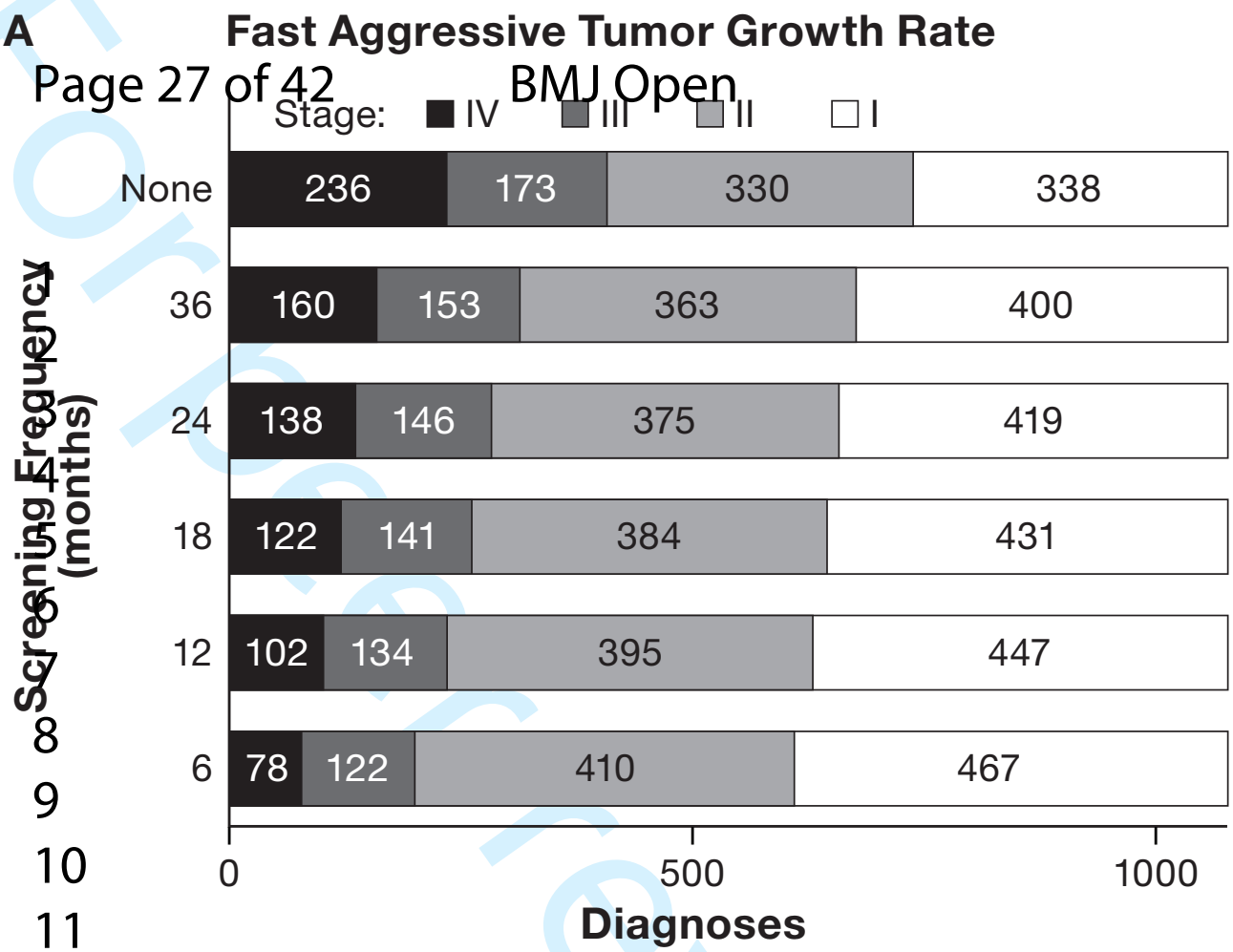
Figure 4. Stage at diagnosis with 6-month to 3-year screening intervals. A) shows the stage of cancer at diagnosis in the Fast Aggressive tumor growth rate scenario. B) shows the same for the Fast tumor growth rate scenario.

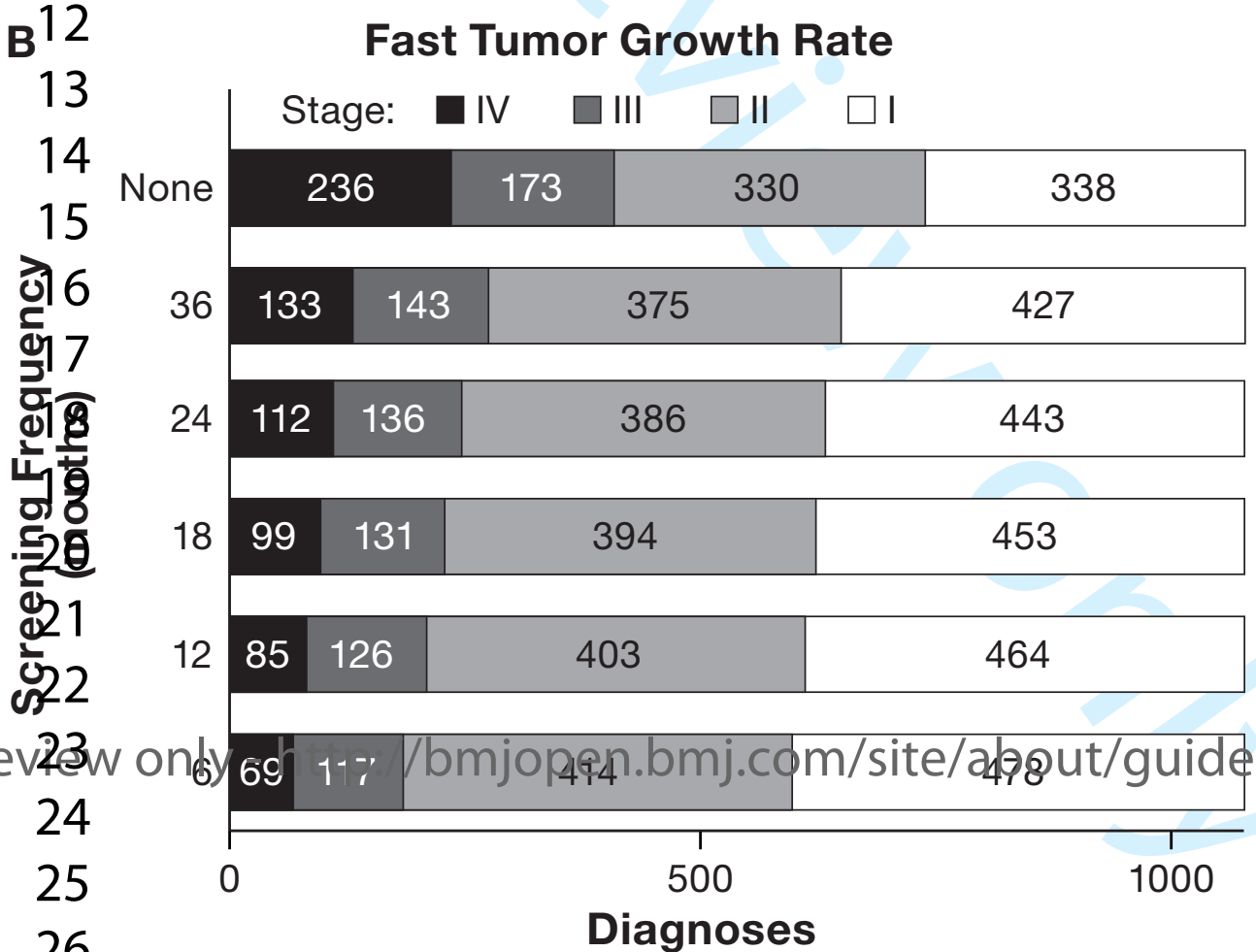












Title: **Assessment of the impact of multi-cancer early detection test screening intervals on late-stage cancer at diagnosis and mortality using a state-transition model**

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SUPPLEMENTAL DATA

The code and data that supports the findings of this study are available here [https://github.com/grailbio-publications/Sasieni_Screening_Interval]

Table S1. Definitions of Cancer Types Identified in SEER

Cancer Type	ICD-O-3 Site and Histology Code Definition
Anus	All C210-C218 excluding histology 8140, 8710-8931, 9040-9055, 9120-9342, 9580-9992; and C180-C199, C209, C260 with histology 8070-8071
Bladder	All C670-C679 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Breast	All C500-C506, C508, C509 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Cervix	All C530, C531, C538, C539 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Colon/Rectum	All C180-C199, C209, C260 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992; and C210-218 with histology 8140
Esophagus	All C150-C159 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992

Gallbladder	All C239, C240-249 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Head and Neck	All C000-C148, C300-C329 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Kidney	C649 excluding histology 8120, 8122, 8130, 8710-8931, 9040-9055, 9120-9342, 9580-9992
Liver/Bile-duct	All C220-C221 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Lung	All C340-C349 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Lymphoid Leukemia	All histology 9712, 9728, 9729, 9811-9820, 9823, 9827, 9831-9837, 9940, 9948
Lymphoma	All histology 9590-9597, 9650-9667, 9670-9671, 9673, 9675, 9678-9680, 9684, 9687-9691, 9695, 9698-9702, 9705, 9708-9709, 9714-9719, 9724-9727, 9735, 9737-9738, 9760-9761, 9764, 9826, 9838, 9970-9971
Melanoma	All histology 8720-8790
Myeloid Neoplasm	All histology 9740-9742, 9751, 9801-9809, 9840, 9860-9876, 9891-9898, 9910-9911, 9920, 9930-9939, 9941-9946, 9963-9964, 9966, 9975
Plasma Cell Neoplasm	All histology 9731-9734, 9762
Ovary	All C569, C570, C481, C482, C488 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Pancreas	All C250-C259 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Prostate	All C619 excluding 8710-8931, 9040-9055, 9120-9342, 9580-9992
Sarcoma	All histology including 8710, 8711, 8800-8931, 9040-9044, 9120-9342, 9580, 9581

Stomach	All C160-C169 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Thyroid	All C739 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Urothelial Tract	All C659, C669, C680 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992; and all C649 with histology 8120, 8122, 8130
Uterus	C540-C543, C548-C549, C559 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992

Cancer types are according to the International Classification of Diseases-Oncology, 3rd edition (ICD-O-3.1). Classifications were mapped to performance of MCED test and generally involve broad histologic categorizations (e.g., sarcoma, lymphoma, melanoma) excluded from categorizations of solid organ sites.

Table S2. Classification of Cancer Sites by Growth Pattern

dwell_group	cancer
A	Anus, Colon/Rectum, Esophagus, Lung
B	Cervix, Uterus, Head and Neck, *Lymphoid Leukemia*, Lymphoma, *Plasma Cell Neoplasm*, Ovary
C	Kidney, Liver/Bile-duct, Pancreas, Gallbladder, Prostate, Stomach, Sarcoma, Thyroid
D	Bladder, Urothelial Tract, Breast, Melanoma, *Myeloid Neoplasm*, Other

Italics indicate hematologic malignancies that are "Not Staged" in the SEER database. While the code has them assigned to the dwell groups indicated, they are not used in the modeling for this analysis.

Table S3. Dwell Times Per Cancer Stage and Growth Scenario (Years)

dwell_group	scenario	Stage			
		I	II	III	IV
A	Fast	2	1	0.5	0.5
A	AggFast	1.5	0.75	0.5	0.25
B	Fast	4	2	1	1
B	AggFast	1.5	0.75	0.5	0.25
C	Fast	2	1	1	0.5
C	AggFast	1	0.5	0.25	0.25
D	Fast	4	2	1	1
D	AggFast	2	1	0.5	0.5

Figure S1: Estimated test sensitivity for cancer type by stage based on Klein et al (1).

Sensitivity is expected to be non-decreasing by stage: weighted isotonic regression is used to estimate sensitivity consistent with this constraint. Note that sensitivity in this model represents the fraction of cancers shedding detectable amounts of tumor DNA, not an independent chance of detection for each blood draw. Cancers shedding at stage I (detectable at stage I) are expected to remain detectable at later stages. Note that as any cancer case can only be expected to be found once, cases found at stage I cannot then be found again at a later stage. This accounting identity is used in the state-transition model to avoid overestimating performance.

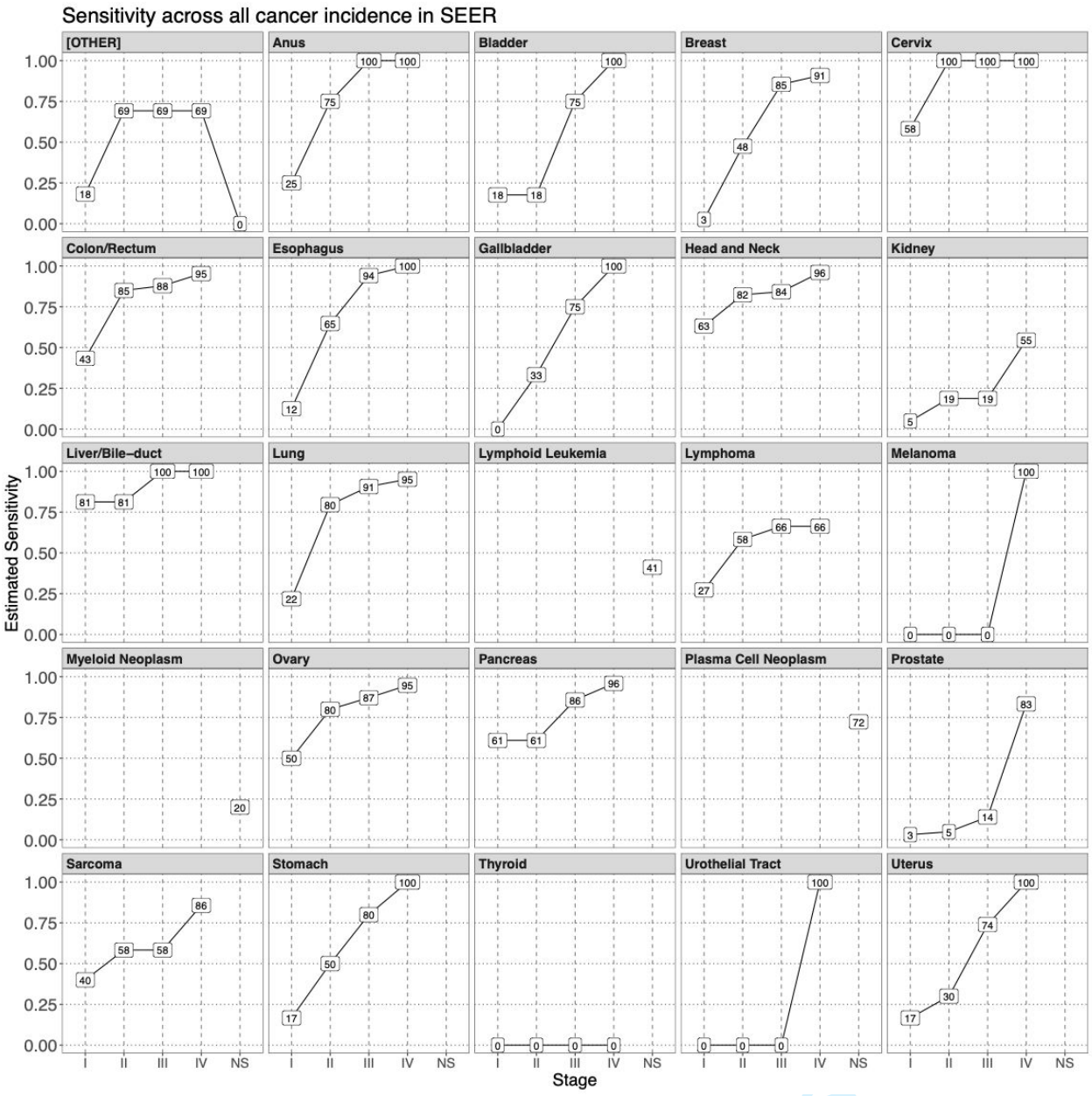


Figure S2: Cancer incidence in the Surveillance, Epidemiology, and End Results (SEER) database, ages 50-79. This is one of the inputs for the interception model and determines yearly cancer incidence expected in a typical year of individuals in this age range. Missing/unknown stage for stageable cancers is imputed into a stage using the ratios of observed cancer stages for each cancer. This covers all cancer incidence in the SEER database.

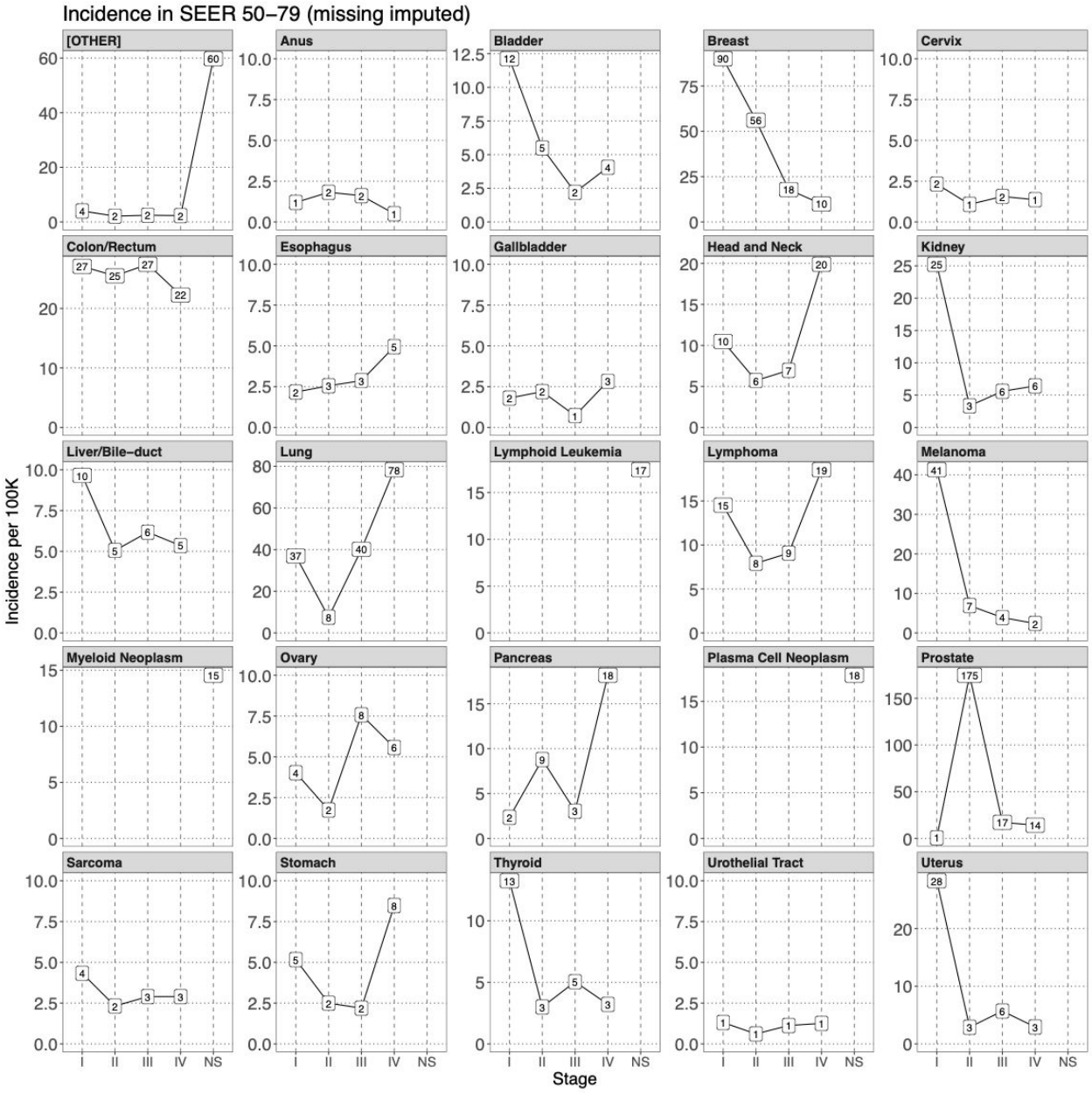


Figure S3: 5-year survival estimates from SEER. Another input metric for the model, the 5-year survival for cancer types modeled, broken out by stage. This is used as a simple metric for improvements in survival by stage.

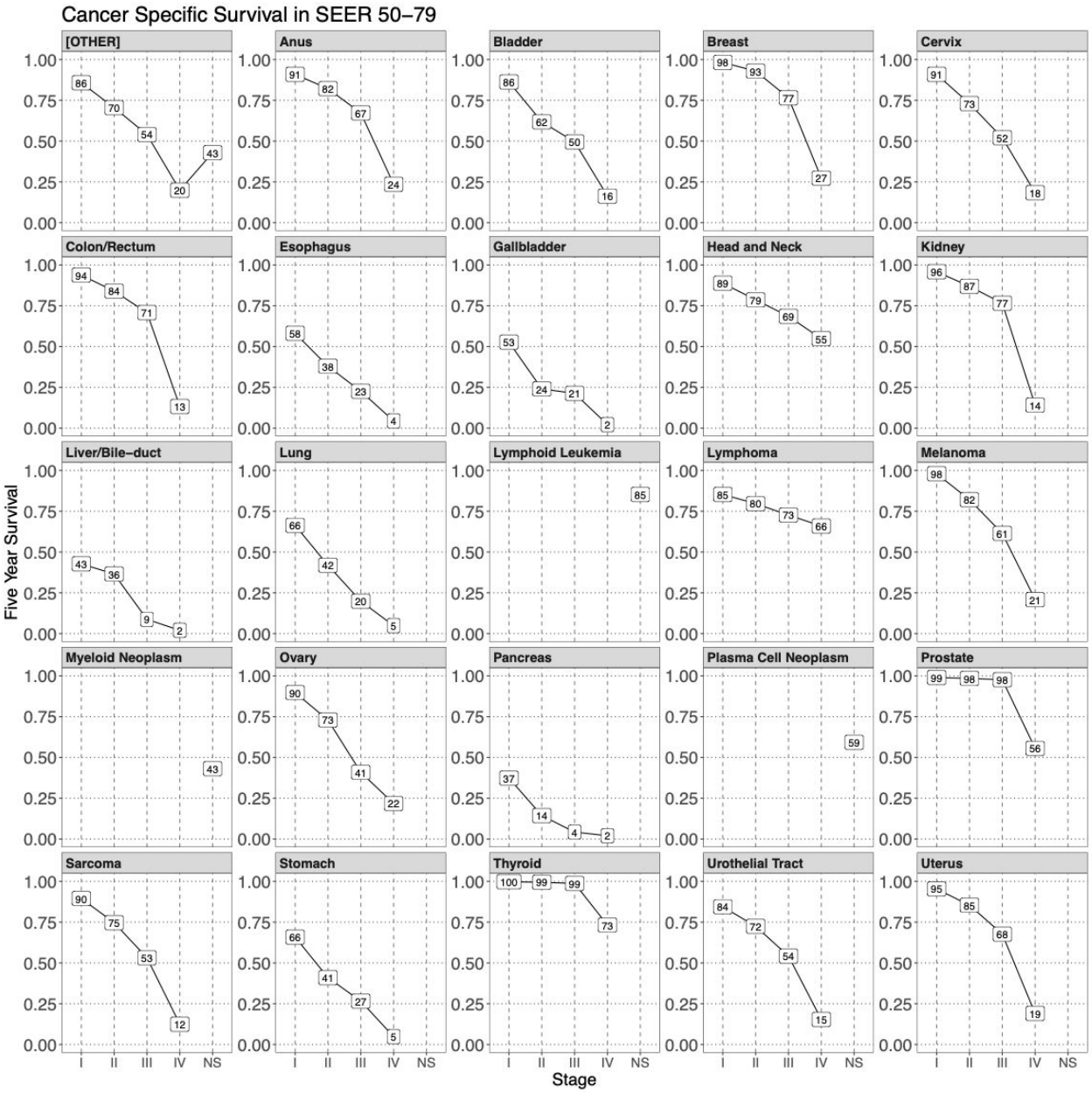


Figure S4: Cumulative odds of at least one false positive by years of annual screening at differing rates. For a given false positive rate (0.5, 1, 10%), the cumulative odds are computed by estimating the rate at which no false positives occur and subtracting from 1. MCED specificity is high; therefore, false positive rates are expected to be <1%. 10% is plotted here as a comparator for typical screening tests with 90% specificity.

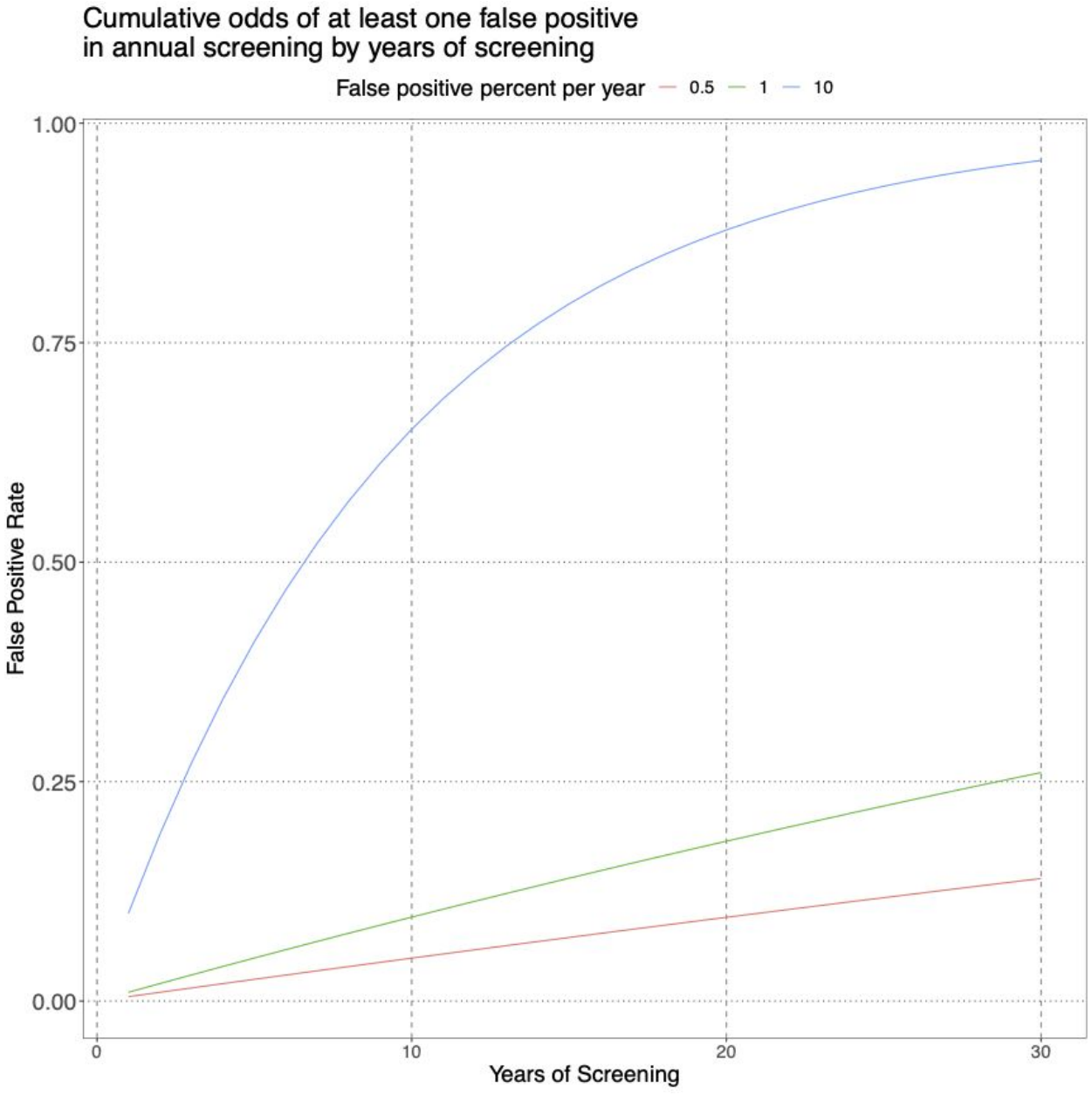


Figure S5: Cadence of screening affects absolute false positive rate expected in 30 years of screening. For each cadence of screening (6 months to 3 years), the expected rate of individuals receiving at least one false positive are shown, contrasting MCED-type false positive rates (0.5, 1%) with false positive rates from a typical screening assay (10%). Note that even 6-month screening intervals for MCED tests produce fewer false positives than 3-year screening intervals for a typical screening assay.

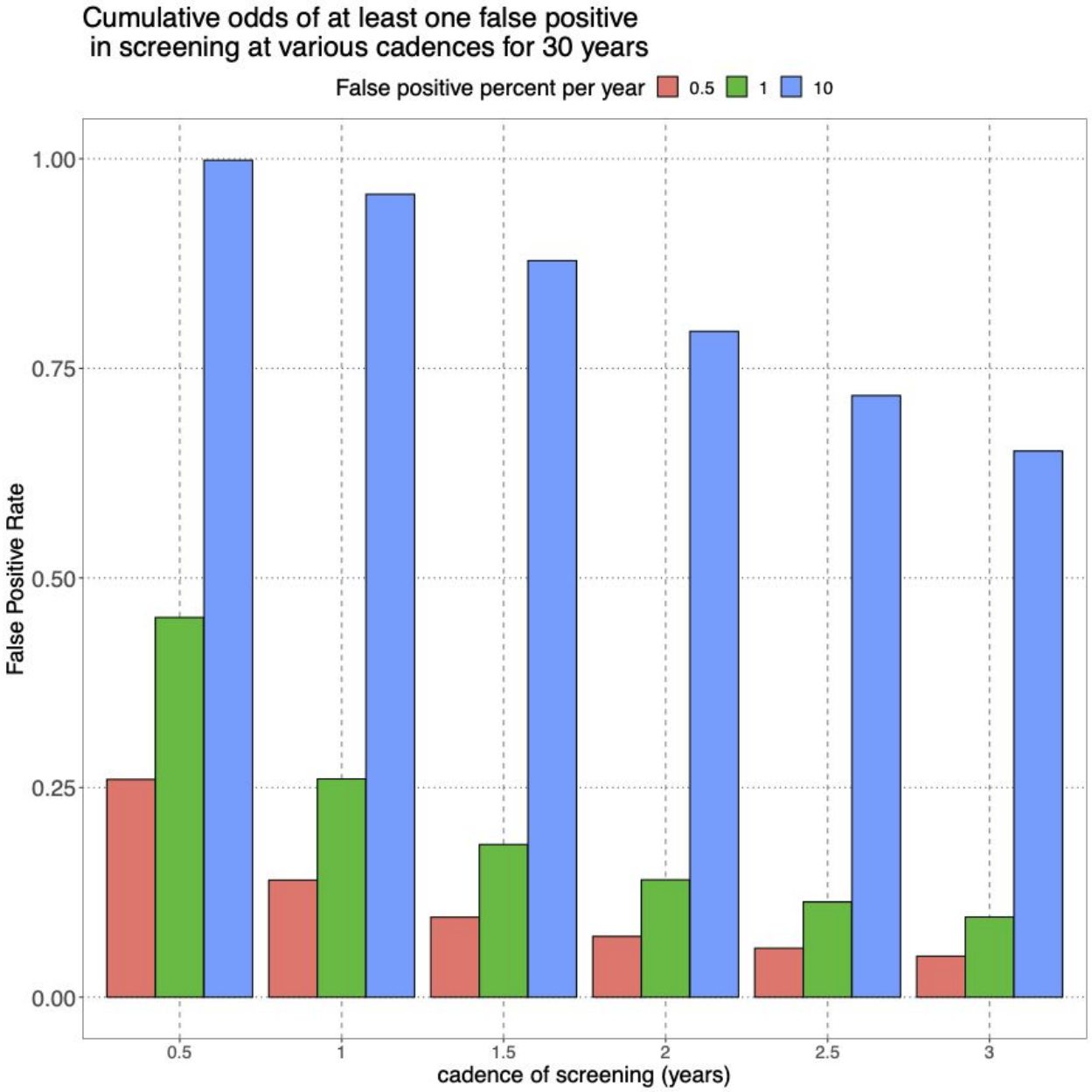
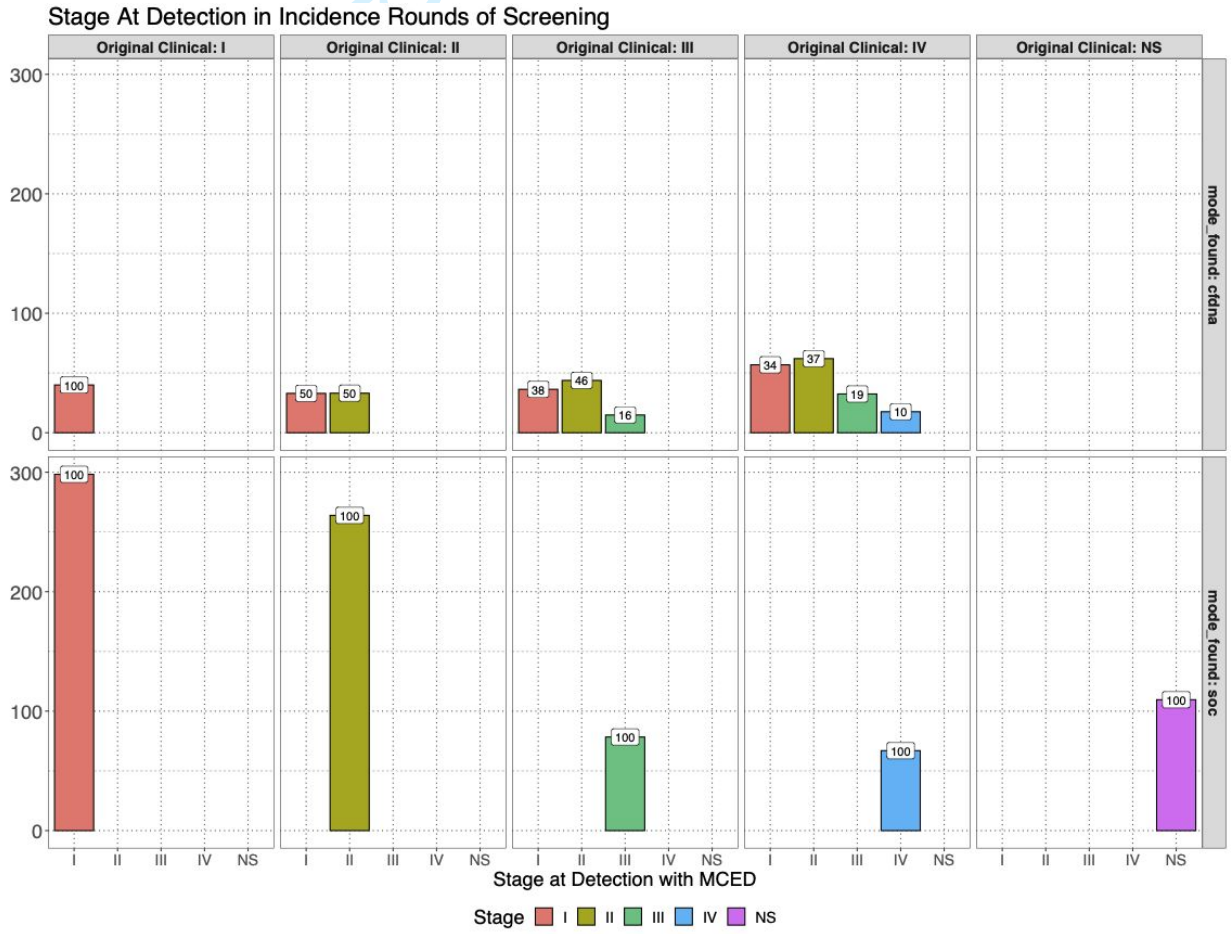


Figure S6: Effect of Screening on Stage at Diagnosis For the "Fast" tumor growth scenario and screening interval 1 year, the effect of MCED screening on stage at diagnosis is shown. Here we show the original expected clinical stage at diagnosis, as well as the stage at which such cases are detected by MCED in long-term screening. Because early detection by MCED depletes cancers that would also be detectable at late stage before that stage is reached, even though sensitivity is highest in an unscreened population for late-stage cancers. This leads to fewer cancers being found at late stage by MCED than would occur in an unscreened population. Cancers remaining to be found through usual care do not have any stage shift and represent interval cancers. Because of the depletion of late-stage cancer cases, interval cancers are mostly early stage (I & II).



SUPPLEMENTAL INFORMATION

Brief description of the interception model

The interception model is designed to quickly estimate the steady-state behavior of a screening program. It takes into account the cancer incidence per year and the stage at clinical diagnosis, the detectability of cancer at each stage (probability of shedding detectable material), and an input of estimated dwell time spent in each stage.

Essentially, at a steady state, cancers detected at a given stage must a) be shedding cell-free DNA (cfDNA), b) have been missed by any prior screening, and c) not been found by usual care. The interception model estimates the odds of each of these cases given the inputs and then outputs the distribution of stage at diagnosis after an MCED test has been added to usual care. This revised stage distribution is then used to estimate the differential effect on 5-year survival as a quick estimate of mortality benefit.

There are several relevant consequences of this model to drive intuition. First, even daily screening will not find all cancer cases (not all cases shed detectable DNA). Second, dwell times are only relevant for cases that shed DNA - the duration of time spent not shedding DNA does not affect any output of the model. This subset of cancers may grow at a different rate than the set of all tumors, including non-shedding cases found by imaging. Third, the odds of being missed by a screening event depend on dwell times and the cadence of screening - faster dwell times and lower screening cadence both increase the odds of missing a detectable cancer case. Finally, we are not tracking year-by-year a fixed population aged 50-79 years; we are estimating an average year of steady-state screening in this mixed population. For instance, we are sampling the year 2025 in a screening program, rather than tracking an individual from the year 2023 to 2053. Extensive details can be found in the Hubbell et al publication (2).

Estimation of Dwell Times

Dwell times were estimated from a group of experts as noted in Hubbell et al (2). Due to uncertainty in these opinions, sensitivity analysis was done by examining multiple scenarios.

Recent data suggests results from the fast aggressive scenario closely resembles detection rates in one biobank analysis (3). Briefly, preclinical sojourn time, defined as the total time before diagnosis of an invasive cancer in the course of usual care, was divided into dwell time per cancer type and stage. Two tumor growth scenarios were used: fast and aggressively fast. Dwell time for each cancer type and stage was approximated with an exponential distribution based on multiple previously published models (4-6). The stage at which usual care would diagnose a cancer is subject to a competing risk (discovery by usual care) and assigned a shorter dwell time distribution. Because cancer is a progressive disease, both tumor growth scenarios assumed that later stages spanned less time than earlier stages.

The limited potential for overdiagnosis

Etzioni et al note that there are multiple models of analysis of overdiagnosis and distinguish two types of overdiagnosis discussed in the literature. The first involves competing risks of immediate death during the lead time for cancers that would surface clinically if the individual had had the usual survival (7). For screening eligible populations (usually taken to have ~10 years of remaining life), this risk of overdiagnosis is limited for aggressive cancers with small amounts of lead time.

Data from the recently published TRACERx study showed an association between a lack of preoperative circulating tumor DNA (ctDNA) detection and good clinical outcomes with indolent lung adenocarcinoma (8). This and other evidence suggests that cancers not shedding ctDNA have better prognosis than expected (8, 9). Further, there are strong biophysical arguments that ctDNA shedding requires growth, such as seen in the recently published study by Bredno, et al, which provides evidence that more aggressive tumors (metabolic activity) shed more cfDNA than slow-growing tumors (10).

The second type of overdiagnosis defined by Etzioni et al is detecting indolent cases with low odds of causing death within a typical lifespan (7). By definition, these cases have a long lead time and minimal growth rates; on biophysical grounds, they are unlikely to shed, and so will be heavily depleted within a few screens with any choice of screening interval, leaving only newly

initiated cases. Overdiagnosis of this type will not be strongly affected by screening interval in the steady state, as only the rate of newly arising cases within a screening interval matter.

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BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-086648.R2
Article Type:	Original research
Date Submitted by the Author:	12-Feb-2025
Complete List of Authors:	Rous, Brian; Cambridge University Hospitals NHS Foundation Trust Clarke, Christina A.; Grail Inc Hubbell, Earl; Grail Inc SASIENI, PETER; Queen Mary University of London
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Health informatics, Research methods, Epidemiology
Keywords:	Clinical Decision-Making, Mass Screening, REGISTRIES

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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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Keywords: early detection of cancer; cancer screening; computer simulation; clinical decision-making; registry data

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 is 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 program 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 tumor 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 USA for all cancer incidence.

Outcome measures

Diagnostic yield, stage shift, and mortality.

Results

Annual screening under the fast tumor growth scenario was associated with more favorable diagnostic yield. There were (370 more cancer signals detected/year/100,000 people screened), stage shift (49% fewer late-stage diagnoses), and mortality (21% fewer deaths within five 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 five years than usual care). Annual screening prevented more deaths

within 5 years than biennial screening for the fast tumor 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. Modeling 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, modeling is required to investigate potential screening intervals of new MCED screening tests.
- This study uses performance estimates from a published case-control study and outcomes from the Surveillance, Epidemiology, and End Results (SEER) database, a widely used database for modeling studies.
- Varied estimates of dwell time duration were used to model the heterogeneity of cancer and 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, wide-spread 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 be also 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.

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 utilize a variety of different analytes to detect a cancer signal.[12] Cell-free DNA (cfDNA) is one such analyte that can be shed by tumors into the bloodstream and can carry cancer-specific signals.[13,14] By analyzing 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 one to five 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 computerized 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 program 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 maximize the benefits across individuals who may develop a range of cancer types with different clinical features and growth rates, rather than optimizing for a single cancer type. This poses a unique challenge to the implementation of an MCED screening program 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 utilizing MCED test characteristics from a recently published report[10] and population cancer data from the US Surveillance, Epidemiology and End Results (SEER) program for cancer types detectable by the MCED test. In the absence of real-world evidence regarding MCED screening intervals, state-transition modeling 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 program 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, though 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] (**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 USA for all cancer incidence (**Figures S2-S3**).[25] From the SEER program (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 through December 31, 2018 (**Figures S2-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 AJCC 6th edition staging was available across the entire time period (categorized 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 minimize 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, esophagus, gallbladder, head and neck, kidney, liver/bile-duct, lung, lymphoid leukemia, 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 ICD-O-3 site and histologic groupings for cancer types used to specify SEER data for this analysis are detailed in **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 (**Table S2, 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 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 modeled 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). Shift 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 modeled 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 program as recommended.

Analyses

In previous modeling work,[24] we performed a sensitivity analysis for an annual screening interval interacting with three hypothetical tumor 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 tumor growth rate scenarios from our previous study: the “fast” and “fast aggressive” scenarios (**Tables 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 modeled for most analyses, though 6-month intervals from 0 to 3 years were examined and are shown for some figures. Screening intensity, defined as 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 tumor 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.

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 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]

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**).

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

		Hypothetical tumor 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	-	50000	100000	50000	100000
FP/year due to MCED, %[b]	-	0.25	0.5	0.25	0.5

Diagnoses at late-stage (III/IV), N	**409**	**284**	**236**	**248**	**210**
Reduction vs usual care, %[c]	**-**	**31**	**42**	**39**	**49**
Deaths within 5 years[d], N	**392**	**338**	**318**	**324**	**308**
Deaths averted vs usual care, N (%)	**-**	**54 (14)**	**74 (19)**	**68 (17)**	**84 (21)**

Abbreviations: cfDNA, cell-free DNA; FP, false positive; MCED, multi-cancer early detection test; PPV, positive predictive value.

[a]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.

[b]Annual false positive rate due to MCED testing intensity.

[c]% of patients diagnosed at an earlier stage with each screening interval and tumor growth rate scenario versus current care with no MCED.

[d]All cancers diagnosed in one year and followed for deaths within 5 years of original diagnosis (ie, in the absence of MCED screening) to account for lead time.

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 favorable scenario shown, biennial screening with fast aggressive tumor 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 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 six months to every three 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 favorable early-stage diagnosis rates than usual care alone. There was a larger impact on stage shift with the fast tumor growth rate versus tumors 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 tumor growth rate scenarios, annual screening leads to fewer deaths (**Figure 3**) versus no MCED screening and biennial MCED screening.

These results were compared to the number of deaths within five years of diagnosis - i.e. 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 favorable 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 favorable 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. 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 modeling.[2,9] In the absence of sufficient real-world evidence regarding MCED screening intervals, modeling 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 modeled 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 modeling.[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 tumors; 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 modeling 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 utilized 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% (**Figures S4-S5**). This compares favorably 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 tumors 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 tumor 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 tumors 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 (**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 minimize this potential harm, MCED screening is intended to be performed in addition to USPSTF guideline-recommended screening practices, which were assumed to occur as part of our model. If an MCED test fails to detect a tumor, 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 to 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 modeling 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 versus 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 modeled cancer natural history with a standard stage-transition model, cancers may have complex properties not explicitly modeled 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 paper. 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 tumors. Though tumor 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 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 tumor 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 programs.

This current study uses varied estimates of dwell time duration to model the heterogeneity of cancer and explore the potential effect of screening interval on cancer detection and subsequent mortality. As real-world evidence becomes available, we can interrogate MCED tests 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]

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 tumor 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.

Acknowledgements

We acknowledge Neva West, PhD (NeuroWest Solutions, Seattle, WA) and Prescott Medical Communications Group (Chicago, IL) for medical writing, editorial, and administrative support that was funded by GRAIL, Inc. This work was previously presented at European Society for Medical Oncology (ESMO) 16-21 September 2021.[54]

Funding

This analysis was supported by GRAIL, Inc., Menlo Park, CA.

Competing interests

Brian Rous: paid member of GRAIL Bio UK Clinical Advisory Board. Christina A. Clarke: employed by GRAIL, Inc, with equity. Earl Hubbell: employed by GRAIL, Inc, with equity; owns stock in Illumina, Inc; has multiple patents in the field of cancer detection pending to GRAIL, Inc. Peter Sasieni: paid member of the Scientific Advisory Board for GRAIL, Inc, no equity.

Contributors

Brian Rous: investigation and methodology, and writing (review and editing). Christina A. Clarke: study conceptualization, data curation, formal analyses, methodology, validation, visualization, and writing (original draft preparation, review, and editing). Earl Hubbell: guarantor, study conceptualization, data curation, formal analyses, investigation and methodology, validation, visualization, and writing (original draft preparation, review, and editing). Peter Sasieni: study conceptualization, investigation and methodology, and writing (original draft preparation, review, and editing).

Data availability statement

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]

Ethics approval

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

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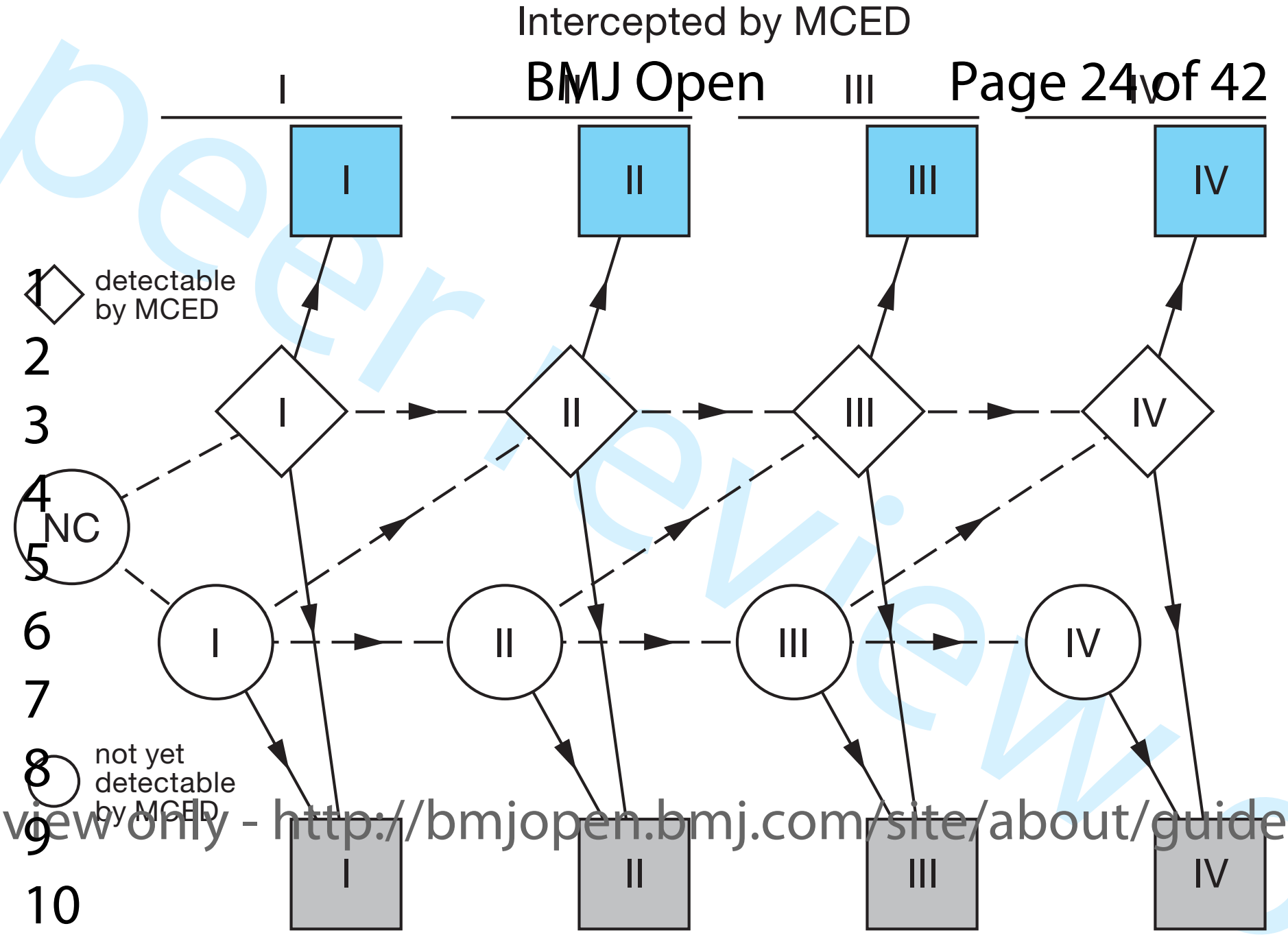
FIGURES LEGENDS

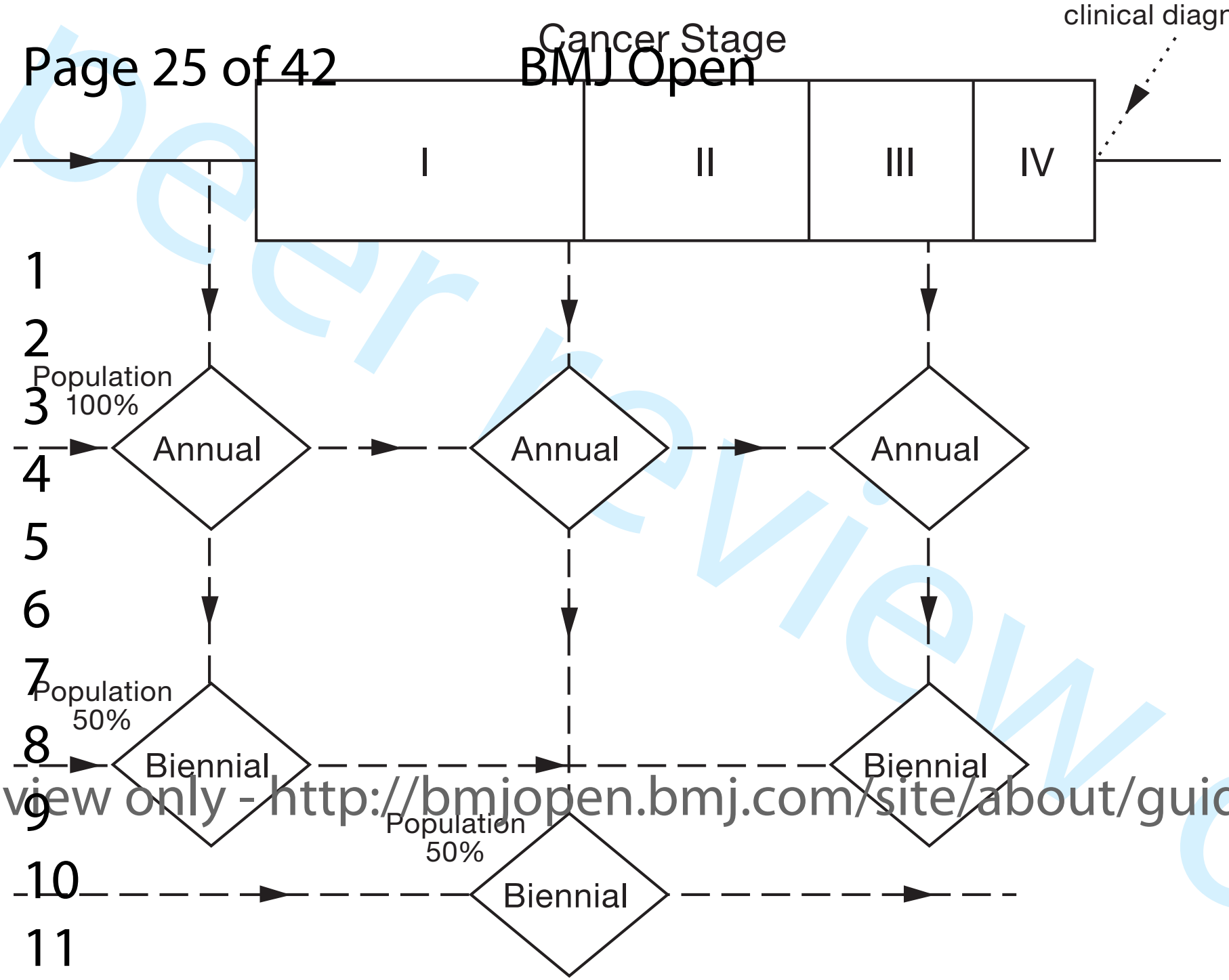
Figure 1. Interception model schematic. Cancer progression is shown in this figure as advancement from No Cancer (NC) to Stage I through IV cancer from left to right. Shapes represent cancer states (○ undetectable by MCED at that stage, ♦ detectable by MCED at that stage, • diagnosed at that stage).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

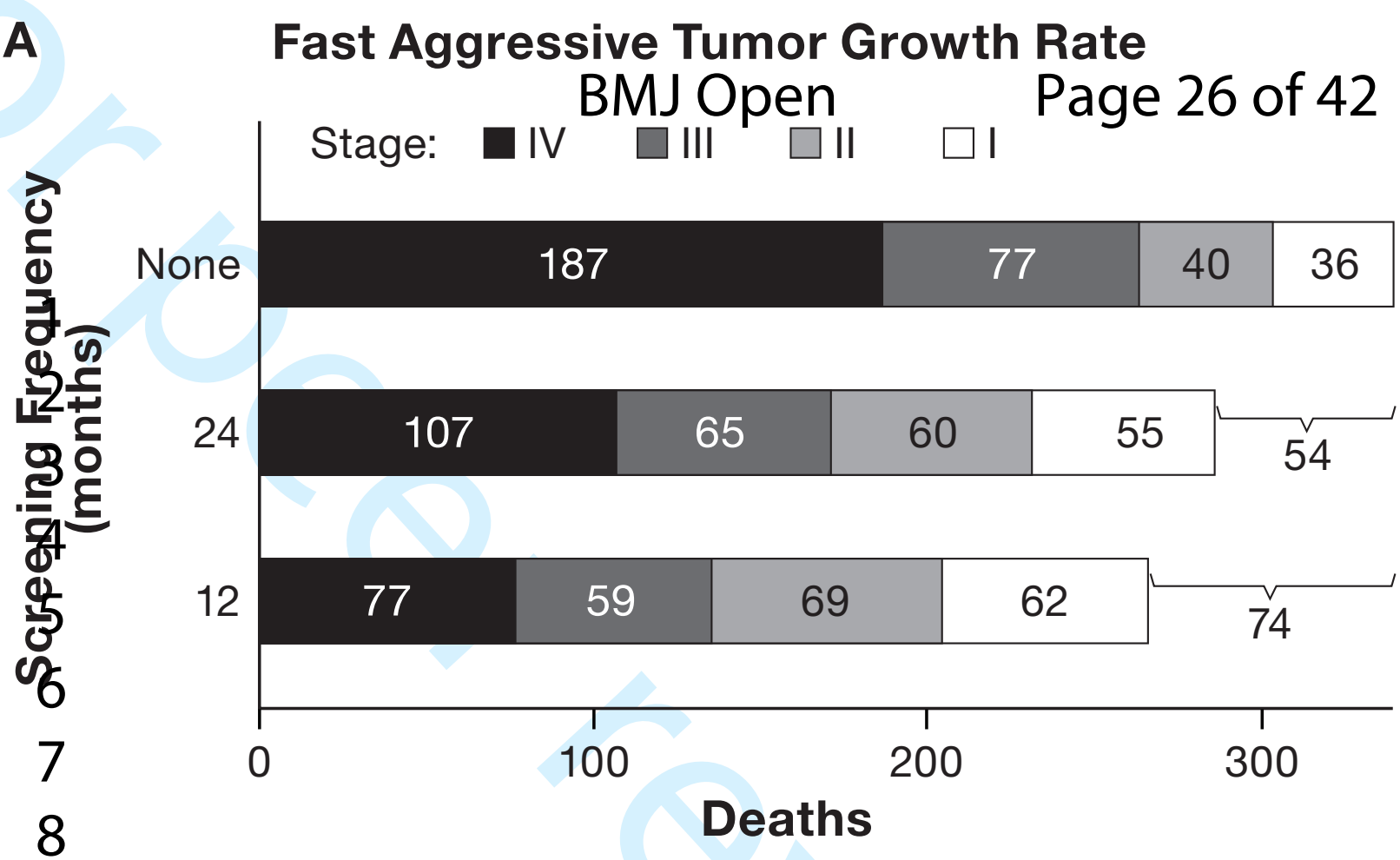
Figure 2. Effect of screening intensity on stage of diagnosis. Top line (solid) represents usual care (without MCED testing) for a single hypothetical patient who would receive a clinical cancer diagnosis at Stage IV and the size of the boxes reflects the hypothetical dwell time at each stage. In this 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.

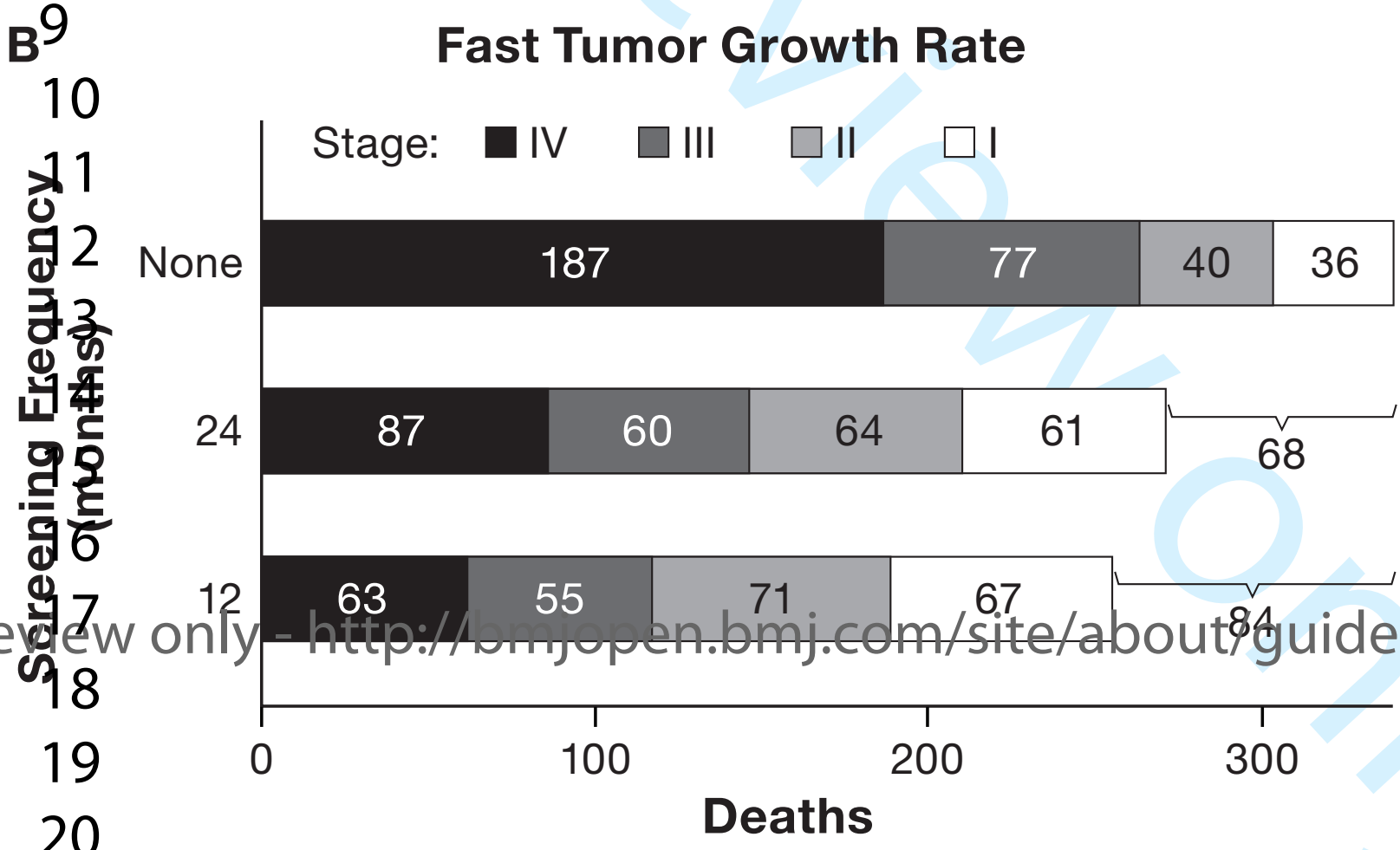
Figure 3. Effect of likely screening intervals on averted deaths by growth rate scenario. A) the number of deaths by stage in the Fast Aggressive tumor growth rate scenario with annual, biennial, or no MCED screening are shown. The number of deaths averted versus no MCED testing are shown at the top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

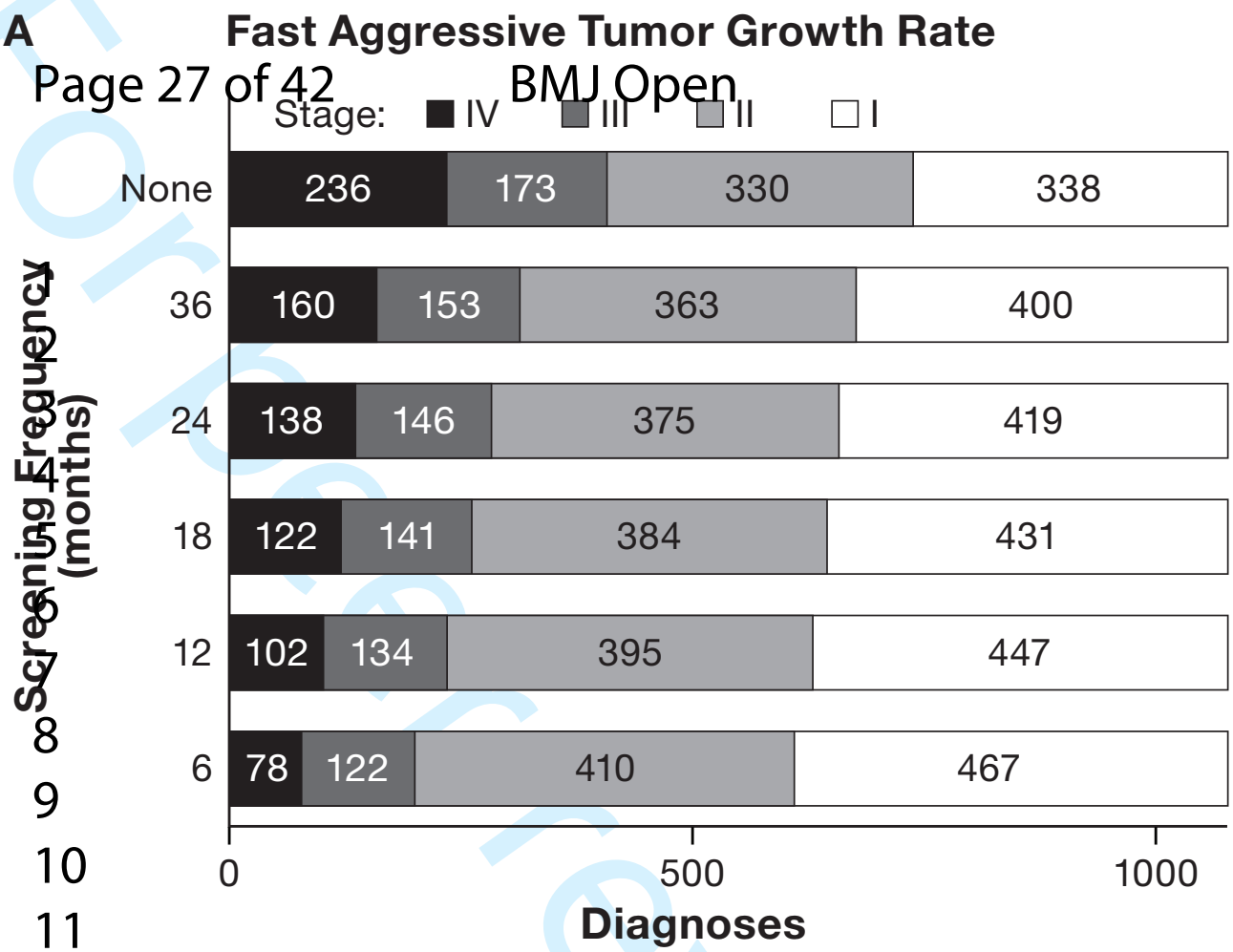
Figure 4. Stage at diagnosis with 6-month to 3-year screening intervals. A) shows the stage of cancer at diagnosis in the Fast Aggressive tumor growth rate scenario. B) shows the same for the Fast tumor growth rate scenario.

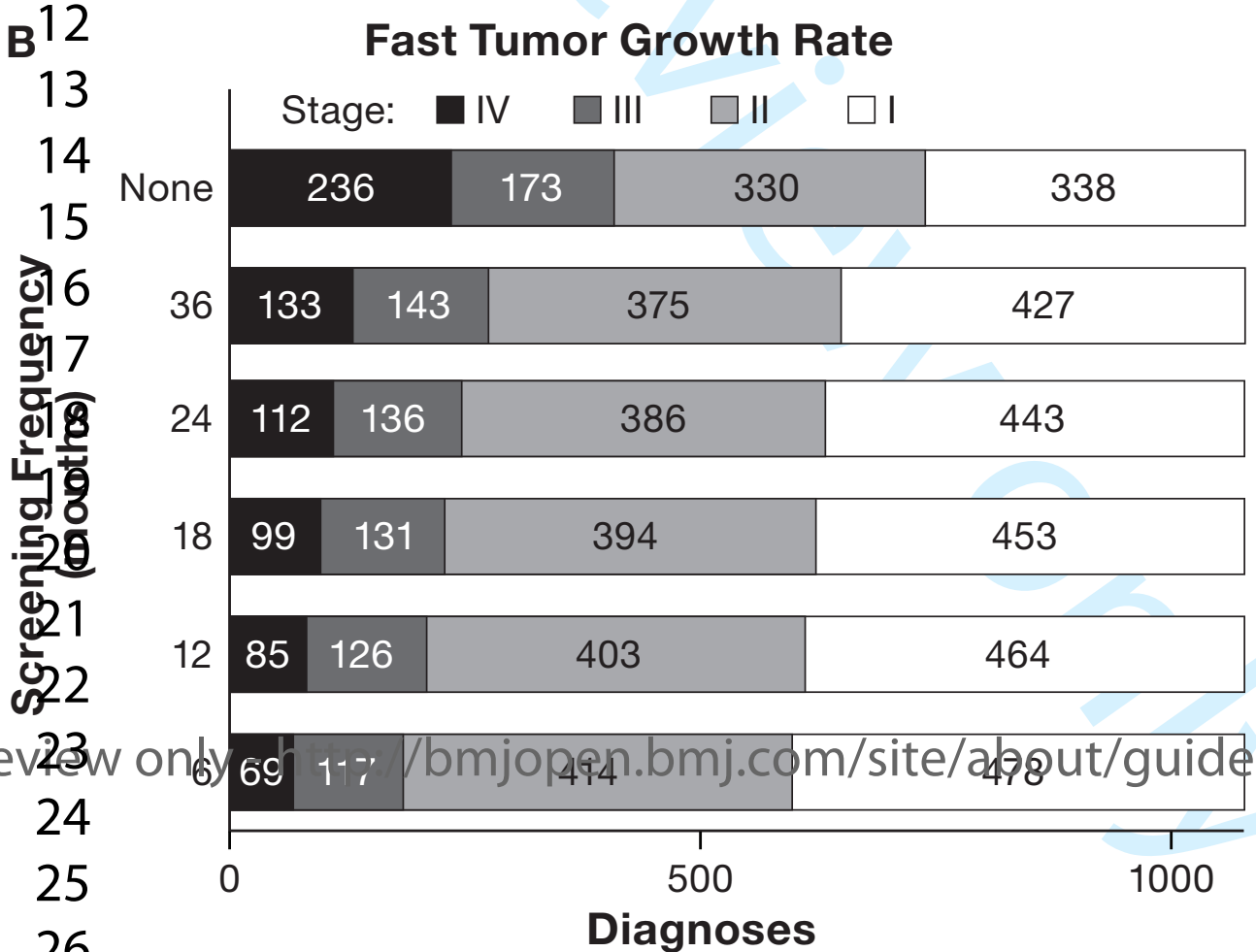












Title: **Assessment of the impact of multi-cancer early detection test screening intervals on late-stage cancer at diagnosis and mortality using a state-transition model**

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SUPPLEMENTAL DATA

The code and data that supports the findings of this study are available here [https://github.com/grailbio-publications/Sasieni_Screening_Interval]

Table S1. Definitions of Cancer Types Identified in SEER

Cancer Type	ICD-O-3 Site and Histology Code Definition
Anus	All C210-C218 excluding histology 8140, 8710-8931, 9040-9055, 9120-9342, 9580-9992; and C180-C199, C209, C260 with histology 8070-8071
Bladder	All C670-C679 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Breast	All C500-C506, C508, C509 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Cervix	All C530, C531, C538, C539 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Colon/Rectum	All C180-C199, C209, C260 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992; and C210-218 with histology 8140
Esophagus	All C150-C159 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992

Gallbladder	All C239, C240-249 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Head and Neck	All C000-C148, C300-C329 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Kidney	C649 excluding histology 8120, 8122, 8130, 8710-8931, 9040-9055, 9120-9342, 9580-9992
Liver/Bile-duct	All C220-C221 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Lung	All C340-C349 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Lymphoid Leukemia	All histology 9712, 9728, 9729, 9811-9820, 9823, 9827, 9831-9837, 9940, 9948
Lymphoma	All histology 9590-9597, 9650-9667, 9670-9671, 9673, 9675, 9678-9680, 9684, 9687-9691, 9695, 9698-9702, 9705, 9708-9709, 9714-9719, 9724-9727, 9735, 9737-9738, 9760-9761, 9764, 9826, 9838, 9970-9971
Melanoma	All histology 8720-8790
Myeloid Neoplasm	All histology 9740-9742, 9751, 9801-9809, 9840, 9860-9876, 9891-9898, 9910-9911, 9920, 9930-9939, 9941-9946, 9963-9964, 9966, 9975
Plasma Cell Neoplasm	All histology 9731-9734, 9762
Ovary	All C569, C570, C481, C482, C488 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Pancreas	All C250-C259 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Prostate	All C619 excluding 8710-8931, 9040-9055, 9120-9342, 9580-9992
Sarcoma	All histology including 8710, 8711, 8800-8931, 9040-9044, 9120-9342, 9580, 9581

Stomach	All C160-C169 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Thyroid	All C739 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992
Urothelial Tract	All C659, C669, C680 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992; and all C649 with histology 8120, 8122, 8130
Uterus	C540-C543, C548-C549, C559 excluding histology 8710-8931, 9040-9055, 9120-9342, 9580-9992

Cancer types are according to the International Classification of Diseases-Oncology, 3rd edition (ICD-O-3.1). Classifications were mapped to performance of MCED test and generally involve broad histologic categorizations (e.g., sarcoma, lymphoma, melanoma) excluded from categorizations of solid organ sites.

Table S2. Classification of Cancer Sites by Growth Pattern

dwell_group	cancer
A	Anus, Colon/Rectum, Esophagus, Lung
B	Cervix, Uterus, Head and Neck, *Lymphoid Leukemia*, Lymphoma, *Plasma Cell Neoplasm*, Ovary
C	Kidney, Liver/Bile-duct, Pancreas, Gallbladder, Prostate, Stomach, Sarcoma, Thyroid
D	Bladder, Urothelial Tract, Breast, Melanoma, *Myeloid Neoplasm*, Other

Italics indicate hematologic malignancies that are "Not Staged" in the SEER database. While the code has them assigned to the dwell groups indicated, they are not used in the modeling for this analysis.

Table S3. Dwell Times Per Cancer Stage and Growth Scenario (Years)

dwell_group	scenario	Stage			
		I	II	III	IV
A	Fast	2	1	0.5	0.5
A	AggFast	1.5	0.75	0.5	0.25
B	Fast	4	2	1	1
B	AggFast	1.5	0.75	0.5	0.25
C	Fast	2	1	1	0.5
C	AggFast	1	0.5	0.25	0.25
D	Fast	4	2	1	1
D	AggFast	2	1	0.5	0.5

Figure S1: Estimated test sensitivity for cancer type by stage based on Klein et al (1).

Sensitivity is expected to be non-decreasing by stage: weighted isotonic regression is used to estimate sensitivity consistent with this constraint. Note that sensitivity in this model represents the fraction of cancers shedding detectable amounts of tumor DNA, not an independent chance of detection for each blood draw. Cancers shedding at stage I (detectable at stage I) are expected to remain detectable at later stages. Note that as any cancer case can only be expected to be found once, cases found at stage I cannot then be found again at a later stage. This accounting identity is used in the state-transition model to avoid overestimating performance.

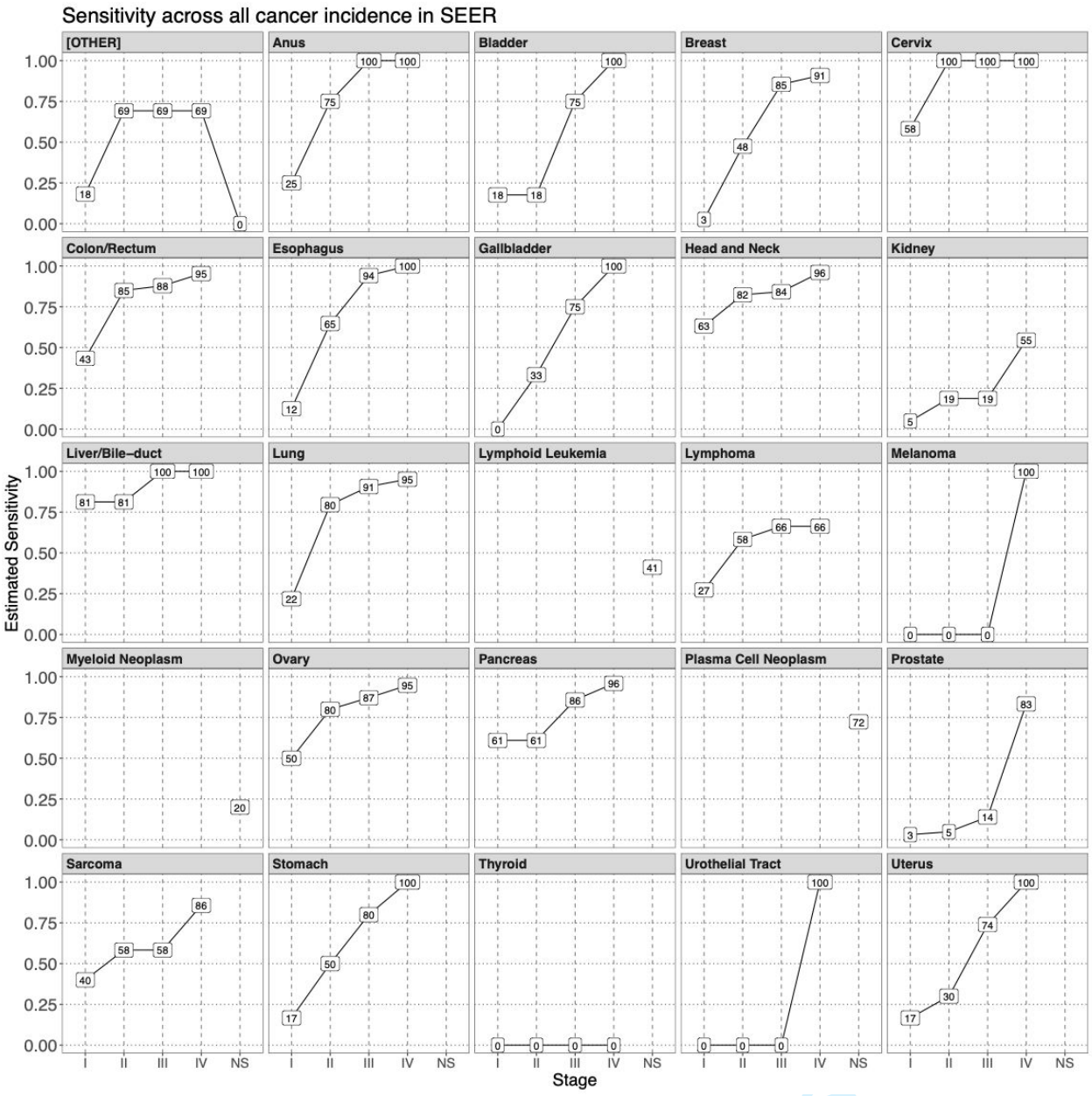


Figure S2: Cancer incidence in the Surveillance, Epidemiology, and End Results (SEER) database, ages 50-79. This is one of the inputs for the interception model and determines yearly cancer incidence expected in a typical year of individuals in this age range. Missing/unknown stage for stageable cancers is imputed into a stage using the ratios of observed cancer stages for each cancer. This covers all cancer incidence in the SEER database.

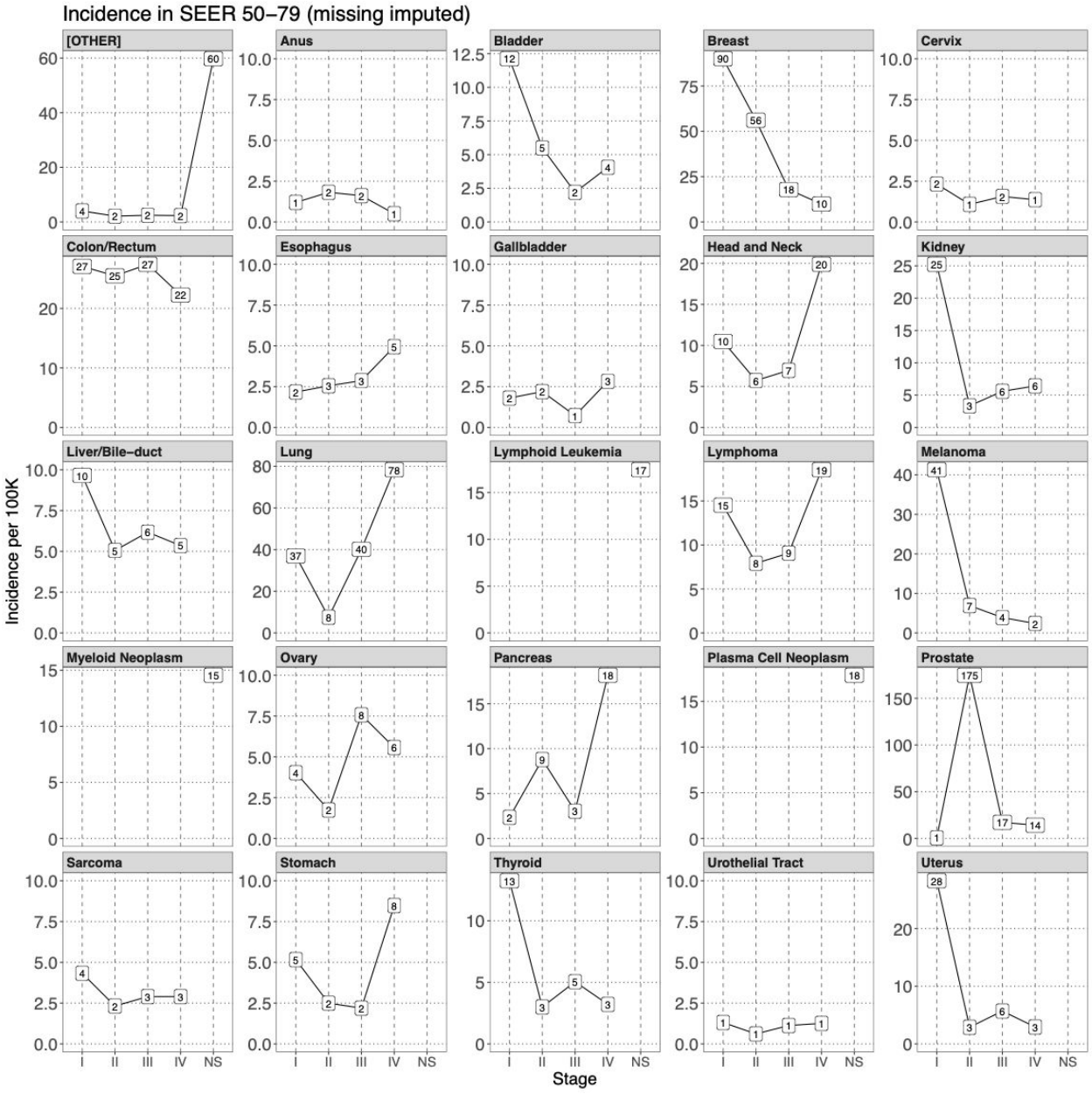


Figure S3: 5-year survival estimates from SEER. Another input metric for the model, the 5-year survival for cancer types modeled, broken out by stage. This is used as a simple metric for improvements in survival by stage.

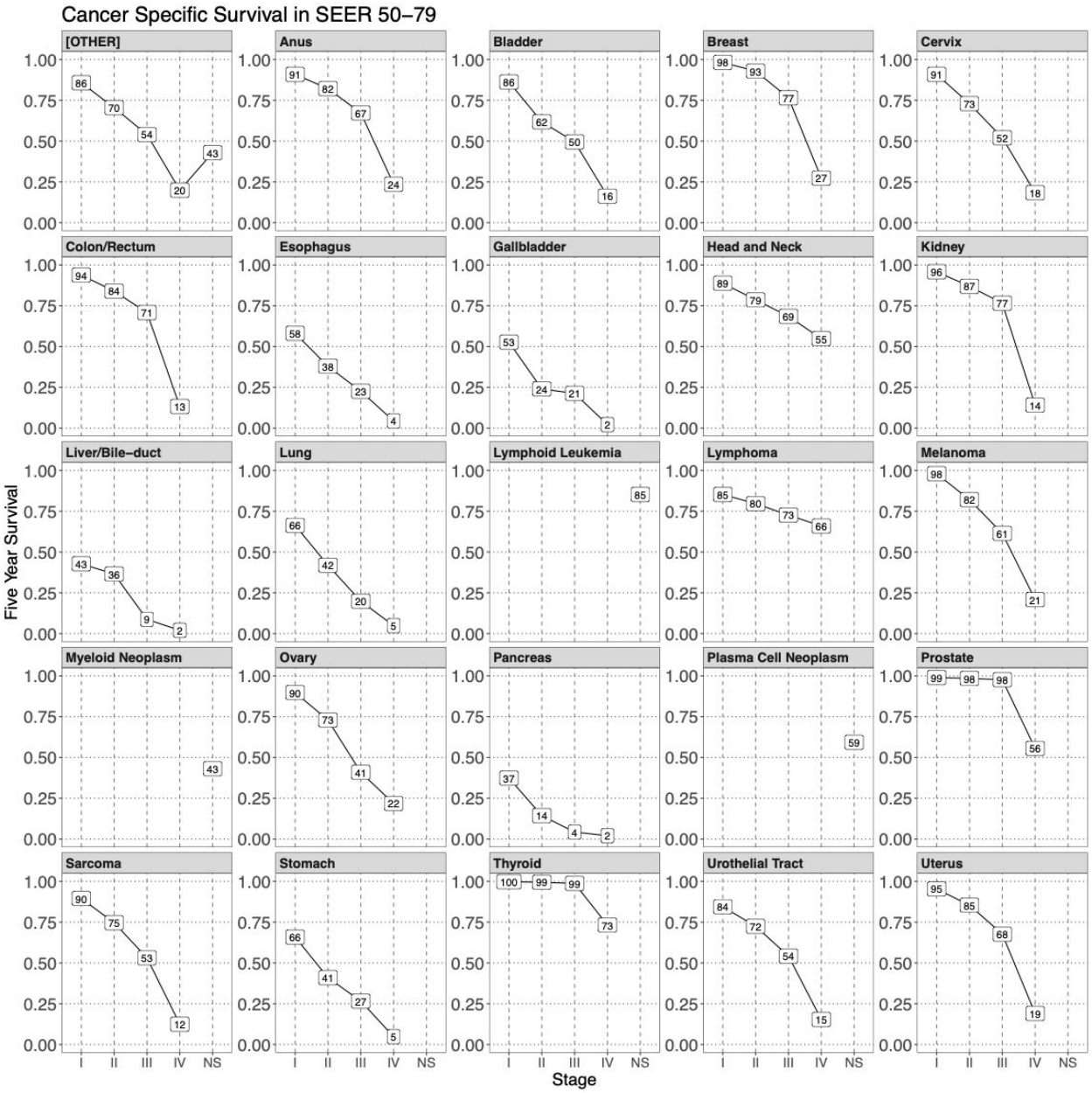


Figure S4: Cumulative odds of at least one false positive by years of annual screening at differing rates. For a given false positive rate (0.5, 1, 10%), the cumulative odds are computed by estimating the rate at which no false positives occur and subtracting from 1. MCED specificity is high; therefore, false positive rates are expected to be <1%. 10% is plotted here as a comparator for typical screening tests with 90% specificity.

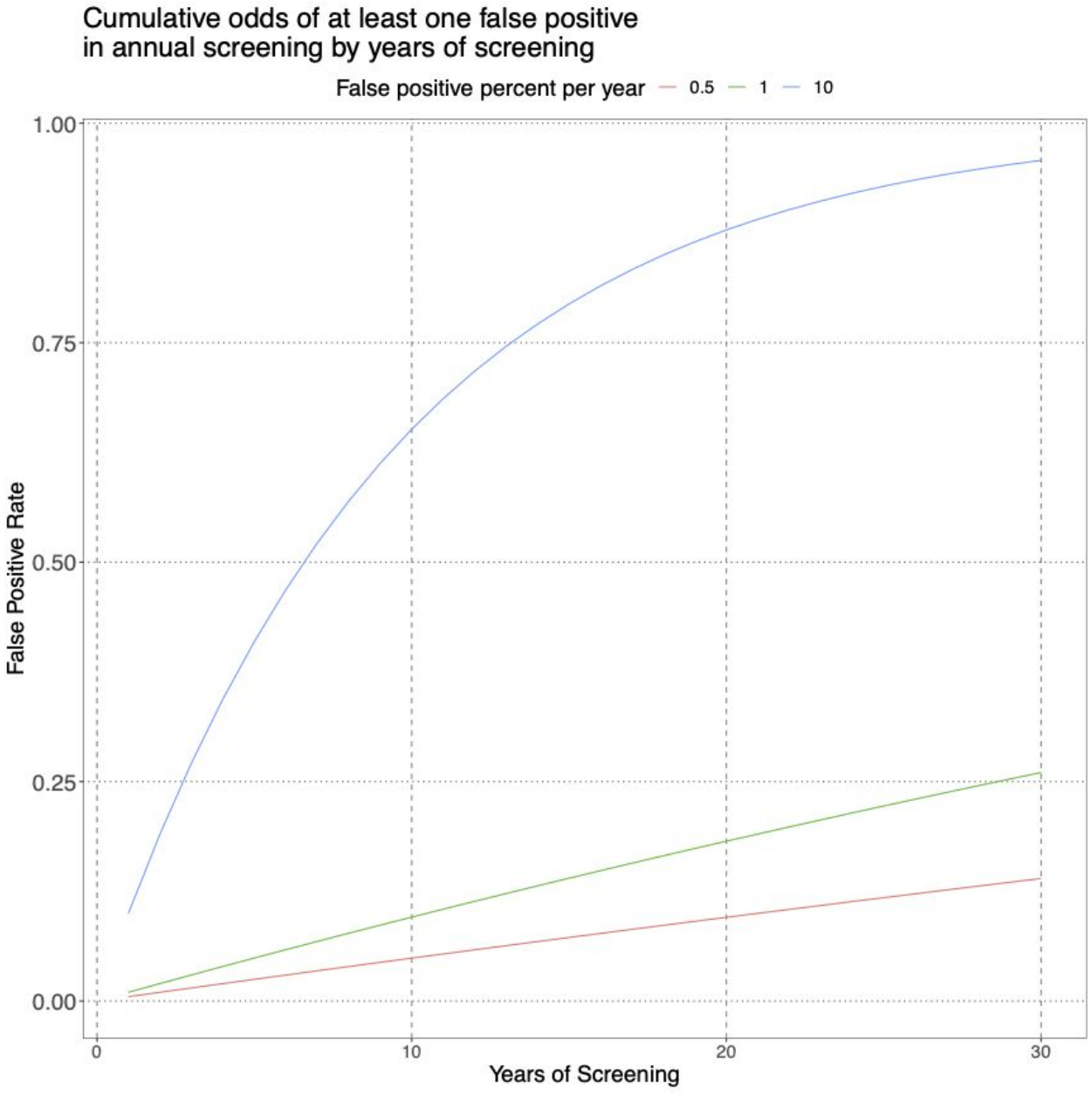


Figure S5: Cadence of screening affects absolute false positive rate expected in 30 years of screening. For each cadence of screening (6 months to 3 years), the expected rate of individuals receiving at least one false positive are shown, contrasting MCED-type false positive rates (0.5, 1%) with false positive rates from a typical screening assay (10%). Note that even 6-month screening intervals for MCED tests produce fewer false positives than 3-year screening intervals for a typical screening assay.

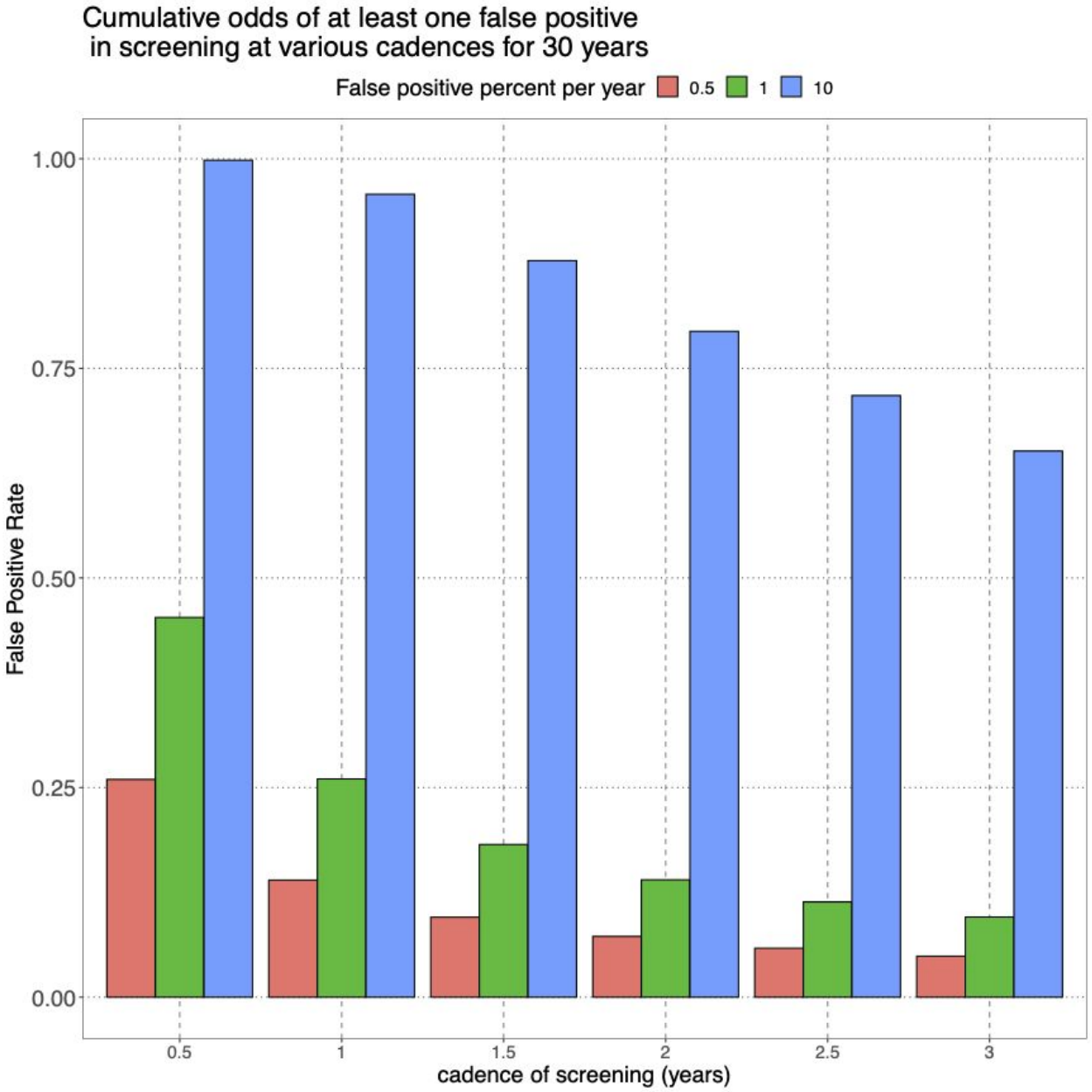
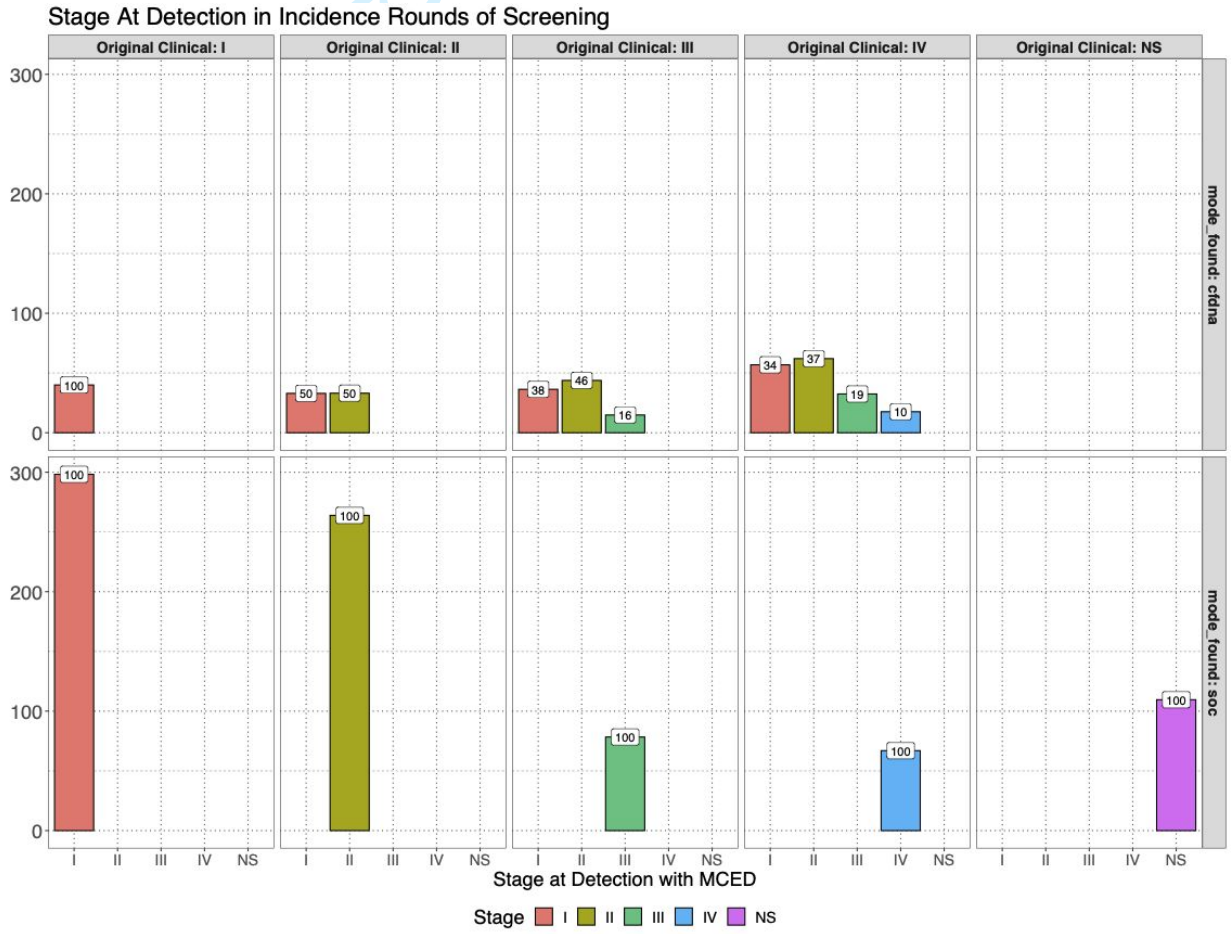


Figure S6: Effect of Screening on Stage at Diagnosis For the "Fast" tumor growth scenario and screening interval 1 year, the effect of MCED screening on stage at diagnosis is shown. Here we show the original expected clinical stage at diagnosis, as well as the stage at which such cases are detected by MCED in long-term screening. Because early detection by MCED depletes cancers that would also be detectable at late stage before that stage is reached, even though sensitivity is highest in an unscreened population for late-stage cancers. This leads to fewer cancers being found at late stage by MCED than would occur in an unscreened population. Cancers remaining to be found through usual care do not have any stage shift and represent interval cancers. Because of the depletion of late-stage cancer cases, interval cancers are mostly early stage (I & II).



SUPPLEMENTAL INFORMATION

Brief description of the interception model

The interception model is designed to quickly estimate the steady-state behavior of a screening program. It takes into account the cancer incidence per year and the stage at clinical diagnosis, the detectability of cancer at each stage (probability of shedding detectable material), and an input of estimated dwell time spent in each stage.

Essentially, at a steady state, cancers detected at a given stage must a) be shedding cell-free DNA (cfDNA), b) have been missed by any prior screening, and c) not been found by usual care. The interception model estimates the odds of each of these cases given the inputs and then outputs the distribution of stage at diagnosis after an MCED test has been added to usual care. This revised stage distribution is then used to estimate the differential effect on 5-year survival as a quick estimate of mortality benefit.

There are several relevant consequences of this model to drive intuition. First, even daily screening will not find all cancer cases (not all cases shed detectable DNA). Second, dwell times are only relevant for cases that shed DNA - the duration of time spent not shedding DNA does not affect any output of the model. This subset of cancers may grow at a different rate than the set of all tumors, including non-shedding cases found by imaging. Third, the odds of being missed by a screening event depend on dwell times and the cadence of screening - faster dwell times and lower screening cadence both increase the odds of missing a detectable cancer case. Finally, we are not tracking year-by-year a fixed population aged 50-79 years; we are estimating an average year of steady-state screening in this mixed population. For instance, we are sampling the year 2025 in a screening program, rather than tracking an individual from the year 2023 to 2053. Extensive details can be found in the Hubbell et al publication (2).

Estimation of Dwell Times

Dwell times were estimated from a group of experts as noted in Hubbell et al (2). Due to uncertainty in these opinions, sensitivity analysis was done by examining multiple scenarios.

Recent data suggests results from the fast aggressive scenario closely resembles detection rates in one biobank analysis (3). Briefly, preclinical sojourn time, defined as the total time before diagnosis of an invasive cancer in the course of usual care, was divided into dwell time per cancer type and stage. Two tumor growth scenarios were used: fast and aggressively fast. Dwell time for each cancer type and stage was approximated with an exponential distribution based on multiple previously published models (4-6). The stage at which usual care would diagnose a cancer is subject to a competing risk (discovery by usual care) and assigned a shorter dwell time distribution. Because cancer is a progressive disease, both tumor growth scenarios assumed that later stages spanned less time than earlier stages.

The limited potential for overdiagnosis

Etzioni et al note that there are multiple models of analysis of overdiagnosis and distinguish two types of overdiagnosis discussed in the literature. The first involves competing risks of immediate death during the lead time for cancers that would surface clinically if the individual had had the usual survival (7). For screening eligible populations (usually taken to have ~10 years of remaining life), this risk of overdiagnosis is limited for aggressive cancers with small amounts of lead time.

Data from the recently published TRACERx study showed an association between a lack of preoperative circulating tumor DNA (ctDNA) detection and good clinical outcomes with indolent lung adenocarcinoma (8). This and other evidence suggests that cancers not shedding ctDNA have better prognosis than expected (8, 9). Further, there are strong biophysical arguments that ctDNA shedding requires growth, such as seen in the recently published study by Bredno, et al, which provides evidence that more aggressive tumors (metabolic activity) shed more cfDNA than slow-growing tumors (10).

The second type of overdiagnosis defined by Etzioni et al is detecting indolent cases with low odds of causing death within a typical lifespan (7). By definition, these cases have a long lead time and minimal growth rates; on biophysical grounds, they are unlikely to shed, and so will be heavily depleted within a few screens with any choice of screening interval, leaving only newly

initiated cases. Overdiagnosis of this type will not be strongly affected by screening interval in the steady state, as only the rate of newly arising cases within a screening interval matter.

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