Impact of MCED Screening Interval on Reduction in Late-Stage Cancer Diagnosis and Mortality

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BACKGROUND

- Cancer is one of the leading causes of death around the world, but at present, screening is only recommended for a few cancer types.[1–4]
- Multi-cancer early detection (MCED) tests screen for many cancers simultaneously.[5]
- Most cancers detectable by an MCED test are currently diagnosed at late stage and are suspected of being aggressive.[5]
- Using lung as an example of an aggressive cancer, the evidence shows that annual screening using LDCT has a favorable benefit-harm ratio, which suggests that annual screening may be favored for an MCED test.[6]
- We use an existing model of a cell-free DNA (cfDNA) MCED test to examine how annual and biennial screening intervals affect the magnitude of cancers that can be found by MCED testing.[7]

RESULTS

- Annual screening could intercept 370 cancers/year/100,000 people, reducing overall late-stage cancer diagnosis by 49% (**Table**).
- Biennial screening could intercept 292 cancers/year/100,000 people, resulting in a 39% reduction in late-stage diagnosis (**Table**).
- There is between a 31% and 49% reduction in cancer diagnosis at late-stage, depending on screening interval and tumor growth rate scenario, a non-trivial benefit versus the current practice of not using an MCED (**Table**).
- With annual screening of 100,000 people, 84 deaths would be averted within 5 years versus current practice, compared to 68 averted with biennial screening (**Table**).
  - The least favorable scenario modeled, biennial screening with fast aggressive tumor growth, results in 54 deaths averted within 5 years.
- Annual screening results in 20 more deaths averted with fast aggressive and 16 more averted with fast tumor growth rate versus biennial screening.
- As anticipated, more cancers present as interval cancers (ie, are diagnosed between screens) under faster growth rates and longer screening intervals.
- In both tumor growth rate scenarios, annual screening leads to fewer late-stage diagnoses (**Figure 3A** and **3C**) and fewer deaths (**Figure 3B** and **3D**) versus no screening and biennial screening.

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

Tumor Growth Rate	MCED Screening Interval	Cancer cfDNA Detected		PPV/ year	Diagnoses at Late-Stage (III/IV)		Deaths within 5 years[b]		
		N	% vs Annual	%	N	Benefit vs No MCED (% reduction)[c]	N	Averted vs No MCED N	Averted vs No MCED %
	None	0	-	-	409	-	392	-	-
Fast Aggressive	Biennial	219	71	47	284	31	338	54	14
	Annual	310	100	38	236	42	318	74	19
Fast	Biennial	292	79	54	248	39	324	68	17
	Annual	370	100	43	210	49	308	84	21

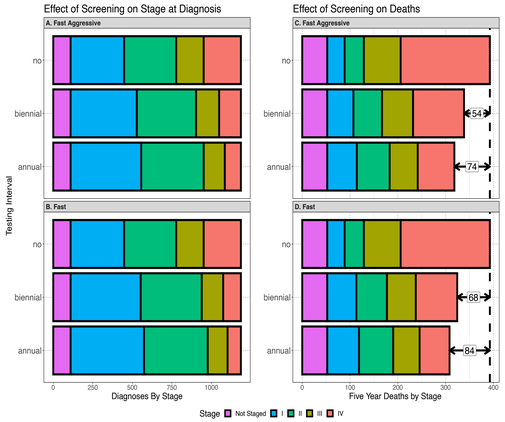
Abbreviations: cfDNA, cell-free DNA; MCED, multi-cancer early detection test; PPV, positive predictive value.

[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]Deaths within 5-years of original diagnosis (ie, in the absence of MCED screening) to account for lead time.

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

Figure 3. Effect of Screening on Stage at Diagnosis and Deaths by Growth Rate Scenario



In the top panels, stage of diagnosis **(A)** and resulting impact on deaths **(B)** in the Fast Aggressive tumor growth rate scenario with annual, biennial, or no MCED screening are shown. In the bottom panels, stage of diagnosis **(C)** and resulting impact on deaths **(D)** in the Fast tumor growth rate scenario with annual, biennial, or no MCED screening is shown. "Not staged" refers to cancers that are not expected to be staged or have non-standard staging, such as brain and leukemia.

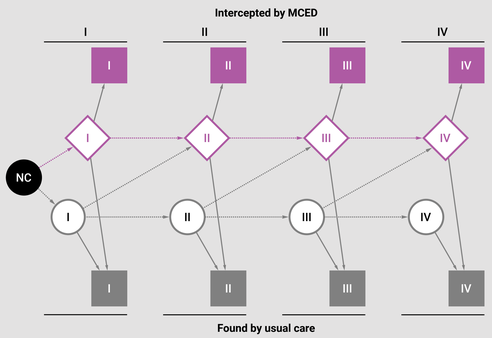
DISCUSSION

- Both annual and biennial screening demonstrated 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 to biennial screening.
  - Biennial screening, which requires fewer clinic visits, had a higher PPV.
- To put these data in the context of expected number of deaths within 5 years of diagnosis from cancers diagnosed over 100K person years (SEER database),
  - Even the least favorable scenario modeled for added MCED testing results in 54 fewer deaths over 5 years, which is comparable to eliminating the number of deaths recorded in SEER from breast (17) and colorectal (33) cancer combined.[5]
  - The most favorable scenario, with 84 averted deaths, would be more than deaths due to breast, colorectal, and pancreatic (30) cancer combined.[5]
  - The difference between deaths averted with annual versus biennial screening (~20) is comparable to all upper GI (22) or head and neck (14) cancers being eliminated as a cause of death.[5]
- Though tumor growth rates for cfDNA-shedding cancers are poorly understood, this 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.

METHODS

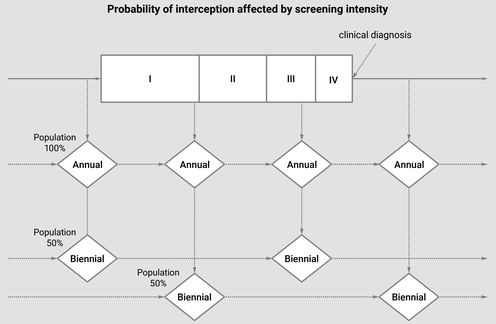
- Using US Surveillance, Epidemiology and End Results (SEER) data describing stage-specific incidence and cancer-specific survival of persons aged 50-79, published MCED performance measures, and previously published state-transition model (**Figure 1**),[7] we computed potential diagnostic yield, stage shift, and effect on mortality of annual or biennial MCED screening added to usual care.
- Extending this work to understand the influence of screening interval (annual vs biennial, **Figure 2**), we performed a sensitivity analysis for screening interval interacting with two tumor growth rate scenarios:
  - Fast scenario: grow quickly, 2-4 years dwell time in Stage I, with successive stages accelerating
  - Fast Aggressive scenario: grow very quickly, 1-2 year dwell time in Stage I with successive stages accelerating
- 1- and 2-year screening interval scenarios were modeled, as recommended in the literature.[8–12]
- Screening intensity, defined as % of patients screened per year, is 100% with annual screening, 50% with biennial screening, and 0% without an MCED test (**Figure 2**).
- We present summary statistics for performance as the expected rate in a sample of population-per-year of cancer incidence.

Figure 1. State-transition 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. 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.

Figure 2. Effect of screening intensity on stage of diagnosis



The probability that a cancer progresses without being intercepted by an MCED test is dependent on the screening intensity (ie, how often the MCED test is administered) compared to the tumor growth rate. With annual screening, 100% of patients are tested per year; with biennial screening, 50% of the population would be tested in any given year, while the other 50% would be subject to interval cancers. In this schematic, the solid top line represents a single hypothetical patient and indicates that with usual care (no MCED test) cancer would be clinically diagnosed at Stage IV. With annual screening, the cancer will be detected at Stage I. With biennial screening, there is a 50% chance of the cancer being detected at Stage I and 50% at Stage III.

References

1. US Preventive Services Task Force. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325(10):962-970. doi:10.1001/jama.2021.1117
2. US Preventive Services Task Force. Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2018;320(7):674-686. doi:10.1001/jama.2018.10897
3. US Preventive Services Task Force, Davidson KW, Barry MJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325(19):1965. doi:10.1001/jama.2021.6238
4. Siu AL, U.S. Preventive Services Task Force. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2016;164(4):279-296. doi:10.7326/M15-2886
5. Klein EA, Richards D, Cohn A, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol Off J Eur Soc Med Oncol*. Published online June 23, 2021:S0923-7534(21)02046-9. doi:10.1016/j.annonc.2021.05.806
6. de Koning HJ, Meza R, Plevritis SK, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2014;160(5):311-320. doi:10.7326/M13-2316
7. Hubbell E, Clarke CA, Aravanis AM, Berg CD. Modeled Reductions in Late-stage Cancer with a Multi-Cancer Early Detection Test. *Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol*. 2021;30(3):460-468. doi:10.1158/1055-9965.EPI-20-1134
8. Heuvelmans MA, Oudkerk M. Appropriate screening intervals in low-dose CT lung cancer screening. *Transl Lung Cancer Res*. 2018;7(3):281-287. doi:10.21037/tlcr.2018.05.08
9. Lee SJ, Zelen M. Mortality modeling of early detection programs. *Biometrics*. 2008;64(2):386-395. doi:10.1111/j.1541-0420.2007.00893.x
10. Buskermolen M, Cenin DR, Helsingen LM, et al. Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a microsimulation modelling study. *BMJ*. 2019;367:l5383. doi:10.1136/bmj.l5383
11. D'Cruz AK, Vaish R. Risk-based oral cancer screening — lessons to be learnt. *Nat Rev Clin Oncol*. 2021;18(8):471-472. doi:10.1038/s41571-021-00511-2
12. Smith RA. Screening Fundamentals. *JNCI Monogr*. 1997;1997(22):15-19. doi:10.1093/jncimono/1997.22.15

Author Disclosures

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