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ORIGINAL ARTICLE

The impact of multicancer early detection tests on cancer stage shift: A 10-year microsimulation model

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Abstract

Introduction: Early detection of cancer improves survival following diagnosis. However, routine screening is limited to a few cancer types. Multicancer early detection (MCED) tests could revolutionize cancer screening by simultaneously detecting multiple cancer types. This study evaluates the potential impact of an MCED test on stage shift in the US general population.

Methods: A microsimulation model of 14 solid tumor cancer types that account for nearly 80% of cancer incidence and mortality was developed. The model was calibrated to reproduce annual incidence rates reported in the Surveillance, Epidemiology, and End Results database. Cancer diagnosis could arise from standard-of-care procedures or annual MCED testing. MCED sensitivities were derived from a large, multicenter, prospective, case control study. Ten-year disease progression was simulated for 5 million US adults aged 50 to 84 years. The primary outcome was stage shift resulting from MCED testing.

Results: Over 10 years, supplemental MCED testing led to a 10% increase in Stage I diagnoses, 20% increase in Stage II diagnoses, 34% increase in Stage III diagnoses, and 45% decrease in Stage IV diagnoses, relative to the standard of care alone. The largest absolute reductions in Stage IV diagnoses were in lung (400 vs. 765 per 100,000), colorectal (96 vs. 236), and pancreatic (89 vs. 211) cancer. The largest relative reductions were in cervical (83%), liver (74%), and colorectal (59%) cancer.

Conclusion: MCED testing has the potential to substantially reduce late-stage cancer diagnoses, improve outcomes across multiple cancer types, and address a critical gap in screening.

KEYWORDS
liquid biopsy, early detection of cancer, cancer screening test, cancer staging, cancer or tumor staging

INTRODUCTION

Cancer is the second-leading cause of death in the United States.[1] In 19 states, cancer has surpassed heart disease as the leading cause of death.[2] An estimated 2 million new cancer diagnoses were made in 2024 alone, with 600,000 people dying from the disease.[1] The economic burden of cancer was estimated to be $209 billion in 2020 and is expected to continue to rise in parallel with the growing cancer burden among the aging US population, as well as the adoption of newer, more expensive treatments into the standard of care (SoC).[3]

Early detection of cancer could reduce cancer-related mortality by averting progression to late-stage cancer and metastasis, which is associated with lower likelihood of cure and survival.[4] However, approximately half of cancer cases in the United States are detected at an advanced stage.[5] Currently, routine screening is recommended for only four cancers (i.e., breast, cervical, colorectal, and lung) by the US Preventive Services Taskforce,[6] with approximately 70% of new cancer cases being associated with cancer types with no available screening tests.[1]

A promising revolutionary approach to enhance the early detection of cancer is multicancer early detection (MCED) tests. These blood-based tests have the ability to screen for multiple cancer types simultaneously, thereby addressing the current limitations of type-specific cancer screening tests. Several new MCED tests are being evaluated. For instance, results from the Detecting cancers Earlier Through Elective Mutation-based Blood Collection and Testing study, the first large, prospective, interventional clinical trial of an MCED test, found that all patients diagnosed and treated for Stage I and II cancer remained cancer-free after the median follow-up of 4.4 years.[7,8] More recently, the Ascertaining Serial Cancer patients to Enable New Diagnostic 2 study, a large, multicenter, prospective, case control study had a specificity of 98.5% and a sensitivity of 50.9% across 21 cancer types.[9]

Despite the promise of MCED tests, real-world data on their long-term effectiveness will not be available for many years. In the interim, simulation modeling is a useful tool for predicting the impact of these tests on cancer diagnosis patterns. In particular, overdiagnosis—the detection of cancers that would not have resulted in symptoms or harm—has been a longstanding concern around some cancer screening programs because it contributes to unnecessary treatments and patient anxiety. Modeling can estimate overdiagnosis rates caused by MCED testing to address these concerns.

The objective of this study was to evaluate the potential impact of an MCED test on cancer detection in the US general population. We developed a microsimulation model of 14 cancer types with the primary outcome of stage shift—the downward shift in cancer stage at the point of diagnosis, relative to the SoC—resulting from the supplemental use of an MCED test.

MATERIALS AND METHODS

We developed the Simulation Model for MCED (SiMCED), a continuous-time, discrete-event microsimulation model of 14 solid tumor cancer types: breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, kidney, liver, lung, ovarian, pancreatic, prostate, and urinary bladder. These cancer types were selected based on the following reasons. First, they collectively account for nearly 80% of all incident cancers.[10] Second, the model includes only cancer types that can be detected by the MCED test. Third, health states in SiMCED are based on the American Joint Committee on Cancer's I through IV staging system for solid tumor cancer types; therefore, common blood-based cancers like leukemia, lymphoma, and myeloma were excluded because of incompatibility with the model structure. SiMCED simulates individuals as they develop cancer and progress through Stages I to IV. Diagnosis of cancer can arise from SoC procedures or MCED testing. Epidemiological data inputs were obtained from the Surveillance, Epidemiology, and End Results database.[10]

Simulated cohort

The simulated cohort consisted of 5 million US adults aged 50 to 84 years (born 1931–1965) without a cancer diagnosis. The composition of sex, race, and single year of age was consistent with that of the US population in 2015.[11] This starting year was selected to allow for comparison against observed 5-year trends in cancer diagnosis. For each individual, a lifespan was estimated from all-cause mortality life tables.[12]

Natural history

A simulated individual can develop only one cancer type in their lifetime. Second primary and recurrent cancers are not modeled for the following reasons. First, they have markedly different pathogenesis and care processes that make them incompatible with the model structure. Second, the MCED test is not targeted toward individuals who have already had a cancer diagnosis and are undergoing surveillance for additional cancers. For each cancer type, the time to oncogenesis follows an exponential distribution with a rate specific to the individual's sex, race, and age. The cancer type with the

earliest time of oncogenesis before the time of death is the cancer type that the individual develops. In the absence of a diagnosis, cancer progresses according to cancer type– and stage-specific dwell times synthesized from published literature and expert surveys (Table 1).[13,14] The actual dwell time experienced by an individual follows an exponential distribution with a rate given by the base case value for their cancer type and stage.

Unobserved incidence

Population-level cancer registries report observed cancer cases but do not characterize the volume of undiagnosed disease. Therefore, the prevalence and total incidence of cancer may be much higher than what is observed in registries. A backwards induction approach was developed to estimate the unobserved cancer burden.[15,16] Using the rationale that cancer is a progressive disease in which a case of late-stage cancer must have existed at an earlier time point as a case of early-stage cancer, Stage IV cases were backtracked to Stages I through III based on dwell times. From this, we estimated the unobserved cancer prevalence and incidence for each combination of cancer type, cancer stage, sex, race, and age.

Cancer diagnosis

Diagnosis under the SoC encompasses existing routine screening procedures, incidental detection, and symptomatic presentation. Diagnosis was assumed to occur immediately upon advancement to Stage IV cancer because of the high likelihood of having symptoms requiring medical care. In all other stages, the time to SoC diagnosis follows an exponential distribution with a rate specific to the cancer type and stage, as well as the individual's sex, race, and age. MCED testing was modeled as a supplemental screening approach with cancer type– and stage-specific sensitivities derived from a case control study.[9] In the base case, the MCED test was administered annually at the beginning of each calendar year to individuals aged 50 to 84 years, with the assumption of 100% uptake (i.e., the proportion of the cohort who will take the MCED test at all) and 100% adherence (i.e., the probability of an individual accepting the MCED test each time it is offered). It is unclear what impact, if any, MCED testing will have on real-world SoC screening uptake and adherence. Nevertheless, the MCED test is intended to supplement—not replace—existing screening practices. For these reasons, we hypothesized that the introduction of MCED testing would have no effect on SoC screening. Scenarios with decreased rates of SoC diagnosis were not explored.

TABLE 1 Cancer type– and stage-specific dwell times (in years) in the absence of a diagnosis.

Cancer type	Stage I	Stage II	Stage III	Stage IV
Breast	3	2	1	0.5
Cervical	4	2.5	1	0.75
Colorectal	1	1.5	1.25	0.75
Endometrial	3.5	2.25	1	0.5
Esophageal	2	1.5	1	1
Gastric	0.75	1	1	0.5
Head and neck	2.5	1.5	1.25	0.5
Kidney	4	2	1	0.5
Liver	2	1	0.5	0.5
Lung	2	1.5	1	1
Ovarian	2	1.25	0.75	0.5
Pancreatic	1	1	0.75	0.5
Prostate	7	5	3	1.5
Urinary bladder	5.5	5.5	4.5	1

Model calibration

For each cancer type, we used the outputs from the unobserved incidence methodology as initial estimates for the time to oncogenesis, the initial prevalence by stage, and the time to SoC diagnosis by stage. These parameters were subsequently calibrated at the cancer type and stage level. The calibration target was annual incidence rates of diagnosis averaged over calendar years 2015 to 2021.[10] Calibration was performed on an open cohort version of the model where individuals aged <50 years were also initialized and "entered" the model when they attained 50 years of age. Thus, the model replicates population dynamics that may influence cancer diagnosis rates over the calibration period. Figure S7 compares final model outputs against Surveillance, Epidemiology, and End Results–reported incidence.

Model analysis

The model was run twice, once without MCED ("SoC") and once with MCED ("SoC + MCED"). In each instance, we recorded incident diagnoses by cancer type and stage over a time horizon of 10 years. The main result was stage shift due to the supplemental use of an MCED test. We report all incidences as rates per an initial closed cohort size of 100,000.

Scenario analyses

To evaluate the robustness and sensitivity of our model assumptions and conclusions, we simulated various scenarios (described in detail in Table S4). First, we replaced annual testing with biennial and triennial testing. Second, we investigated imperfect uptake and adherence levels of 90%, 70%, and 50%. The lower bound of 50% is below real-world adherence to noninvasive laboratory tests for

cancer detection, such as those for colorectal cancer.[17–19] Third, we modeled reduced MCED sensitivities by applying a discount factor of 80% to account for potentially lower effectiveness in a real-world setting. Fourth, we varied the dwell times in Table 1 by ±25% to model different speeds of progression. Unobserved incidence was not included separately in the scenario analysis. The unobserved incidence methodology derives initial estimates for several model parameters based on dwell times, but they are ultimately adjusted via calibration to be compatible with the model's initial population and incidence of diagnosed cancer over the calibration period. Therefore, the effect of updating unobserved incidence based on lower or higher dwell times will be "masked" by calibration, and only the effect of the dwell times will be observed. Fifth, using the base case setup, results for longer time horizons of 20 and 50 years were generated. Last, we simulated a scenario with one-time MCED testing in year 1 to isolate the effect of a single MCED test over a 10-year period.

RESULTS

Over the 10-year horizon, supplemental testing with an annual MCED test resulted in a 10% increase (3364 vs 3068 cases per 100,000) in Stage I diagnoses, 20% increase (2491 vs 2079) in Stage II diagnoses, and 34% increase (1896 vs 1414) in Stage III diagnoses, relative to the SoC alone; in contrast, Stage IV diagnoses decreased by 45% (1159 vs 2108) (Figure 1A). The cumulative number of diagnoses was 8669 under the SoC, and 8910 when supplemented by MCED testing, equating to a modest increase of 2.8% (241 per 100,000). Of these 241 additional diagnoses, 82 were made in individuals who died from non–cancer-related causes under the SoC after their counterfactual time of MCED diagnosis, and 159 were in individuals who were eventually diagnosed under the SoC after the first 10 years. Figure 1B depicts the flow of individuals from their stage at diagnosis under the SoC to their stage at diagnosis when SoC is supplemented with MCED testing.

Table 2 lists the 10-year reductions in Stage IV incidence by cancer type. The cancer types with the highest absolute reduction were, in order, lung (400 vs 765), colorectal (96 vs 236), and pancreatic (89 vs 211). The cancer types with the highest relative reduction were cervical (83%), liver (74%), and colorectal (59%). Stage IV reduction across all cancers increased from 45% to 50% when breast and prostate cancer—for which MCED sensitivities are low—were excluded. Stage IV reduction was higher for cancer types with recommended screening (51%) than for those without recommended screening (39%). The equivalent tables for Stages I, II, and III (Tables S1-3) can be found in the Supplementary Material. Figure 2 describes 10-year stage shift stratified by cancer type, showing the relatively low amount of stage shift from late- to early-stage diagnoses for breast cancer, and the low amount of overall stage shift for prostate cancer.

Figure 3 presents temporal differences in stage shift. Stage shift was more pronounced in the first year of MCED testing—where the relative increase in Stages I, II, and III were 13%, 32%, and 70%, respectively—than in subsequent years, due to the higher initial number of undetected cancer cases. However, the relative reduction in Stage IV diagnoses is stable within 42% to 45% over the 10-year horizon.

Table 3 summarizes the findings from the scenario analyses, where MCED testing interval, MCED uptake and adherence, MCED sensitivities, and cancer dwell times were varied within clinically plausible ranges. Overall, testing interval had the greatest impact on Stage IV reduction. Longer testing intervals were associated with decreased Stage IV reduction, which dropped steeply from 45% in the base case with annual testing (10 total screens over 10 years) to 28% with biennial testing (five total screens) (Figure S1A) and 22% with triennial testing (four total screens) (Figure S1B). Reducing MCED uptake and adherence to 90% produced a modest change in results, achieving a 41% Stage IV reduction in both scenarios. Reducing uptake and adherence to 70% produced Stage IV reductions of 32% and 33%, respectively. Reducing uptake and adherence to 50% produced Stage IV reductions of 23% and 24%,

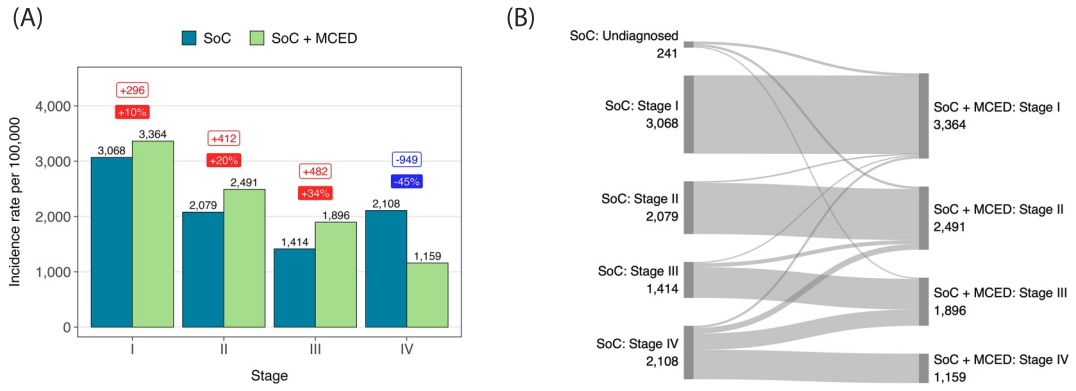

FIGURE 1 (A) 10-year stage shift. In the base case, the assumptions were annual MCED testing with 100% uptake and adherence. (B) 10-year individual-level stage shift flows. Numbers are counts of individuals per 100,000. Note that "SoC: Undiagnosed" does not depict all undiagnosed cases, only those that are undiagnosed in the "SoC" scenario but become diagnosed in the "SoC + MCED" scenario within the 10-year time horizon. MCED, multicancer early detection; SoC, standard of care.

TABLE 2 Reduction in 10-year stage IV incidence by cancer type (per 100,000).

Cancer type	SoC	SoC + MCED	Absolute change	Relative change
Breast	106	53	−53	−50%
Cervical	12	2	−10	−83%
Colorectal	236	96	−140	−59%
Endometrial	39	22	−17	−44%
Esophageal	49	26	−23	−47%
Gastric	79	32	−47	−59%
Head and neck	172	112	−60	−35%
Kidney	74	55	−19	−26%
Liver	66	17	−49	−74%
Lung	765	400	−365	−48%
Ovarian	50	34	−16	−32%
Pancreatic	211	89	−122	−58%
Prostate	202	197	−5	−2%
Urinary bladder	47	24	−23	−49%
Total	2108	1159	−949	−45%
Total excluding breast and prostate cancer	1800	909	−891	−50%
Total for cancer types with recommended screening	1119	551	−568	−51%
Total for cancer types without recommended screening	989	608	−381	−39%

In the base case, the assumptions were annual MCED testing with 100% uptake and adherence.

Abbreviations: MCED, multicancer early detection; SoC, standard of care.

respectively. Applying a discount factor of 80% to MCED sensitivities caused Stage IV reduction to drop to 37%.

As expected, the scenario with slower dwell times had better Stage IV reduction (48%) compared to the base case because of greater chances of MCED detection when a cancer progresses more slowly (Figure S2A). Conversely, the scenario with faster dwell times had worse Stage IV reduction (41%) because of reduced opportunities for MCED detection with a faster progressing cancer (Figure S2B). There was a notable difference in the relative change in Stage III incidence: 27% with slower dwell times versus 42% with faster dwell times.

When the time horizon was extended to 20 years, Stage IV reduction remained at 45% (Figure S3A). With a 50-year horizon, Stage IV reduction decreased to 41% (Figure S3B), suggesting that the greatest stage shift benefit is realized early—within the first 20 years after the introduction of the MCED test. In the scenario with one-time MCED testing in year 1, Stage IV reduction dropped drastically to 7%, whereas Stages I through III increased by only 1% to 5% (Figure S4).

DISCUSSION

The findings from this study suggest that blood-based MCED tests have the potential to improve early cancer detection. As MCED is an emerging technology, data on its effectiveness in the real world will not be available until several years after its implementation; therefore, we used a simulation model to evaluate its potential effectiveness. Our study demonstrates that incorporating an annual MCED test into the SoC could lead to substantial downstaging of cancer stage at diagnosis over a 10-year period, with a notable reduction in Stage IV diagnoses. These findings have strong clinical implications because earlier stage diagnosis is associated with improved survival.[4]

Our study adds to the growing body of knowledge on the downstream impact of MCED testing. Hubbell et al. developed a state-transition model for 18 cancer types. For an open cohort of US adults aged 50 to 79 years, they estimated reductions in late-stage incidence between 177 (43%) and 220 (54%) per 100,000 after 1 year of MCED testing.[20] Tafazzoli et al. observed increases in Stages I and II diagnoses of 3192 and 2021 per 100,000, and decreases in Stages III and IV diagnoses of 1136 and 3704 per 100,000.[21] Sasieni et al. estimated reduction in lifetime late-stage diagnoses was between 5468 (40%) and 7032 (50%) per 100,000.[22] Most recently, Lange et al. developed a model of 12 cancer types that was parameterized to emulate an MCED trial to project outcomes beyond the trial period. The reduction in late-stage incidence was 21% to 43% after three screens and 34% to 55% after seven screens.[23] Although our findings complement these studies, the key strength of our model is its ability to estimate overdiagnosis as a direct consequence of MCED testing arising naturally from the MCED sensitivities. This is in contrast to Tafazzoli et al., who treated the overdiagnosis rate as a model parameter.[21] Our results indicate that the increase in total diagnoses was only 2.8% with the addition of MCED testing, suggesting that overdiagnosis may not be an issue with this technology. This is a critical finding because it mitigates concerns that MCED testing could lead to a surge in unnecessary cancer diagnoses and treatment. Additionally, this analysis includes a comprehensive scenario analysis to examine the effect of different testing intervals, uptake rates, and adherence levels.

Another key finding of our study is the potential 45% reduction in 10-year Stage IV cancer incidence due to annual MCED testing with 100% uptake and adherence. Stage IV cancer is associated with poorer prognosis, higher treatment costs, and lower quality of life; thus, MCED testing may significantly alleviate the clinical and economic burden of cancer. Our breakdown of Stage IV reductions by cancer type further emphasizes the clinical utility of MCED testing as the cancer types that had the largest absolute reductions (i.e., lung, colorectal, and pancreatic) are among the most aggressive cancer types with the poorest survival rates. Of note, we observed a 34% increase in Stage III diagnoses with MCED. The observed increase in Stage III diagnoses is due to the relatively low MCED sensitivities in Stages I to II and relatively high sensitivities in Stage III, causing downstaging cases from Stage IV to III to outnumber those from Stage III to I and II. Interestingly, Stage IV reduction was greater for

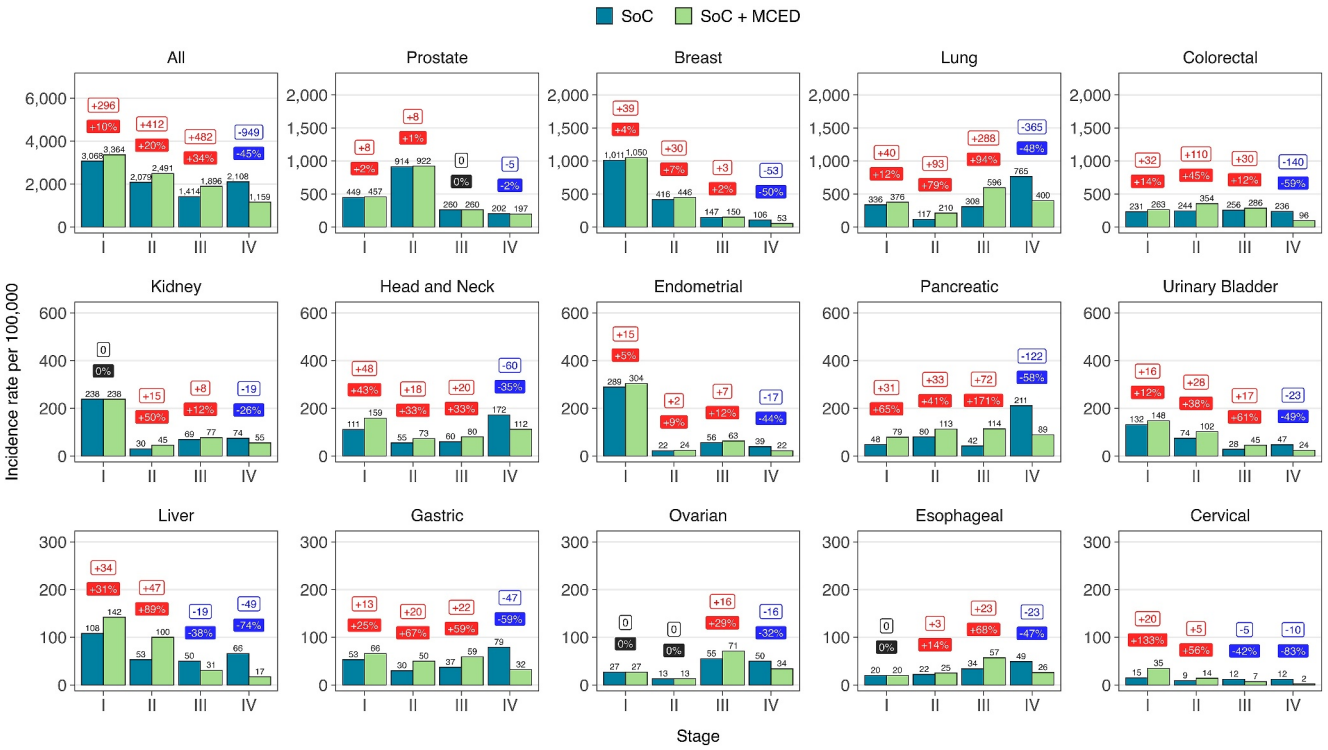

FIGURE 2 10-year stage shift by cancer type, ordered by total incidence. In the base case, the assumptions were annual MCED testing with 100% uptake and adherence. MCED, multicancer early detection; SoC, standard of care.

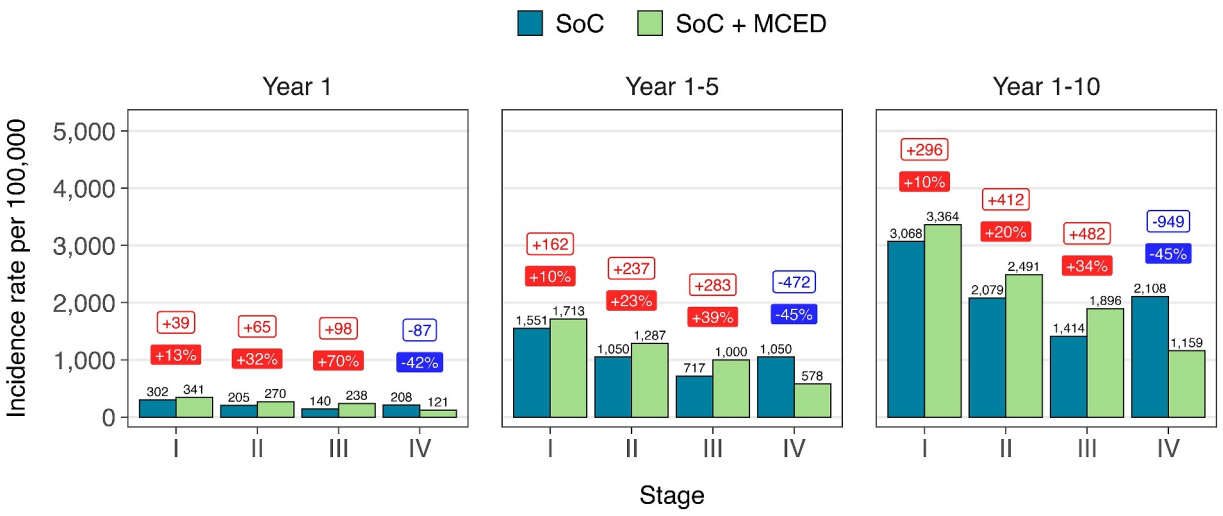

FIGURE 3 10-year stage shift by time window. In the base case, the assumptions were annual MCED testing with 100% uptake and adherence. MCED, multicancer early detection; SoC, standard of care.

cancer types with recommended screening than for those without. This suggests that MCED testing could be effective for boosting stage shift when used to supplement routine screening, while being the driver of stage shift for cancer types without screening tests.

In our scenario analysis, testing interval had the greatest impact on Stage IV reduction. Biennial and triennial testing produced approximately half of the Stage IV reduction achieved by annual testing. One-time MCED testing at the beginning of the 10-year period produced a modest Stage IV reduction of only 7%. These results indicate that frequent testing is an important factor affecting the real-world effectiveness of MCED. Our study also explored the impact of varying levels of uptake and adherence. Even under scenarios where annual uptake and adherence were reduced to 50%, MCED testing still resulted in a 23% to 24% Stage IV reduction. While this is a positive outcome, it underscores the importance of public health initiatives—such as public awareness campaigns,

TABLE 3 Reduction in 10-year Stage IV incidence by scenario (per 100,000).

Scenario name	SoC	SoC + MCED	Absolute change	Relative change
Base case				
	2108	1159	−949	−45%
MCED testing interval				
Biennial	2108	1515	−593	−28%
Triennial	2108	1640	−468	−22%
MCED uptake				
90%	2108	1253	−855	−41%
70%	2108	1440	−668	−32%
50%	2108	1633	−475	−23%
MCED adherence				
90%	2108	1241	−867	−41%
70%	2108	1414	−694	−33%
50%	2108	1598	−510	−24%
MCED sensitivities discounting				
80%	2108	1334	−774	−37%
Dwell times				
Slower	2113	1091	−1022	−48%
Faster	2132	1262	−870	−41%
Time horizon				
20 years	3912	2170	−1742	−45%
50 years	5406	3177	−2229	−41%
One-time MCED testing				
	2108	1967	−141	−7%

Abbreviations: MCED, multicancer early detection; SoC, standard of care.

education on the benefits of early cancer detection, and efforts to reduce disparities in access to screening—to promote widespread adoption and consistent use of MCED tests.

We recognize several limitations of this research. First, there is uncertainty around epidemiological parameters, such as dwell times and unobserved incidence. However, we demonstrated the robustness of our conclusions to variations in dwell times. A second source of uncertainty is the performance of the MCED test in the real world, which may be much lower than what was estimated in the case control study.[9] We addressed this uncertainty by simulating a scenario with sensitivity discounting, finding the stage shift benefit to be reduced but not insignificant. A third limitation is related to model structure. Routine screening for the four US Preventive Services Taskforce-recommended cancers is not modeled explicitly but captured implicitly via diagnosis rates. Crucially, these rates are assumed to remain the same after the introduction of an MCED test. Although it is plausible that the availability of an MCED test may cause individuals to forgo routine screening or to reduce their screening frequency, the MCED test was intended to supplement—not replace—SoC screening; therefore, scenarios with decreased rates of SoC diagnosis were not explored. Fourth, our model does not allow individuals to develop more than one cancer type in their lifetime, although the MCED test is capable of detecting second primary or recurrent cases. Therefore, the true stage benefit of MCED testing may be underestimated in this analysis. Finally, because this analysis is tailored to the US population, these results may not extend to other regions where MCED testing might be introduced.

There are several promising avenues for future work. Most importantly, the mortality benefit attributable to stage shift needs to be quantified. Given the strong link between earlier-stage diagnosis and improved survival, it is likely that MCED testing will result in survival gains, though this remains to be demonstrated in long-term, real-world studies. One crucial consideration in the estimation of mortality benefit is improving survival over time. MCED testing should be modeled in the context of continual improvements in cancer care that enhance the value of early detection. Second, the economic impact and cost-effectiveness of MCED testing is also left to future research. It is currently unclear how stage shift will impact health care costs in both the short and long term. Last, several model extensions can be considered. If data on altered routine screening patterns due to the availability of MCED become available, these behaviors can be incorporated into the model. Subgroup analysis can be performed to identify populations where MCED testing may be particularly effective, or that may derive heightened benefit because of lack of access to routine screening. A true open cohort model incorporating population aging and immigration can be developed to provide accurate forecasts of MCED testing outcomes at the population level. The setting of the analysis can be extended to other countries and regions that are considering the adoption of MCED.

CONCLUSION

Our study shows that MCED testing has the potential to substantially reduce Stage IV cancer incidence, particularly for cancer types that lack routine screening programs. Although further research is needed to validate these findings in real-world settings, our results suggest that MCED testing could transform cancer diagnosis and improve patient outcomes across a broad range of cancer types.

AUTHOR CONTRIBUTIONS

Jagpreet Chhatwal: Conceptualization; formal analysis; methodology; investigation; supervision; project administration; writing—review and editing; validation; funding acquisition; resources; writing—original draft. **Jade Xiao**: Formal analysis; data curation; visualization; writing—original draft; methodology; writing—review and editing; validation; software. **Andrew K. ElHabr**: Software; validation; methodology; writing—review and editing; writing—original draft; visualization; formal analysis; data curation. **Christopher Tyson**:

Conceptualization; data curation; writing—review and editing; methodology; resources. **Xiting Cao**: Conceptualization; data curation; writing—review and editing; project administration; supervision; methodology; investigation; resources. **Sana Raoof**: Writing—review and editing. **A. Mark Fendrick**: Writing—review and editing. **A. Burak Ozbay**: Writing—review and editing. **Paul Limburg**: Writing—review and editing. **Tomasz M. Beer**: Writing—review and editing. **Andrew Briggs**: Writing—review and editing. **Ashish A. Deshmukh**: Writing—review and editing

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CONFLICT OF INTEREST STATEMENT

Jagpreet Chhatwal has ownership in Value Analytics Labs. Christopher Tyson, Xiting Cao, A. Burak Ozbay, Paul Limburg, and Tomasz M. Beer are employees of Exact Sciences. Sana Raoof is a consultant for GRAIL, Exact Sciences, the American Cancer Society, and C the Signs. A. Mark Fendrick directs the University of Michigan Center for Value-Based Insurance Design; he reports providing consulting services to AbbVie, CareFirst Blue Cross Blue Shield, Centivo, Clover Health, Community Oncology Association, Covered California, Elektra Health, EmblemHealth, Employee Benefit Research Institute, Exact Sciences, GRAIL, Health[at]Scale Technologies, HealthCorum, MedZed Inc., Merck and Company, Mother Goose Health, Phathom Pharmaceuticals, Proton Intelligence, Inc., Sempre Health, Silver Fern Healthcare, US Department of Defense, Virginia Center for Health Innovation, Wellth, Yale-New Haven Health System; he reports receiving research support from the Agency for Healthcare Research and Quality, West Health Policy Center, Arnold Ventures, National Pharmaceutical Council, Patient-Centered Outcomes Research Institute, Pharmaceutical Research and Manufacturers of America, the Robert Wood Johnson Foundation, the state of Michigan, and the Centers for Medicare and Medicaid Services; serves as coeditor for the *American Journal of Managed Care*; and maintains a partnership at VBID Health. Andrew Briggs has consulting or advisory roles at AstraZeneca, Ipsen, Idorsia, Sanofi, Pfizer, Novartis, Rhythm Therapeutics, BMS GmbH & Co KG, Gilead Sciences, Teofarma, Astellas Pharma, Takeda, Bipi. Ashish A. Deshmukh is a consultant for Merck Inc. and Value Analytics Labs. Sana Raoof and Ashish A. Deshmukh received consulting fees from Value Analytics Labs. No additional conflicts of interest were reported by the rest of the authors.

DATA AVAILABILITY STATEMENT

All data generated by the simulation model are made available in the manuscript. Model code is unable to be shared publicly due to proprietary restrictions.

INSTITUTIONAL REVIEW BOARD STATEMENT

This study did not involve any interaction with patients, patient data, or protected health information. All data used in this research were obtained from publicly available sources, secondary datasets, or nonhuman subject activities. As such, the study was deemed not to involve human subjects as defined by the U.S. Department of Health and Human Services (45 CFR 46.102).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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