Dying To Find Out: The Cost of Time at the Dawn of the Multicancer Early Detection Era

Eric A. Klein[1], Sarina Madhavan[2], Tomasz M. Beer[3], Chetan Bettegowda[4], Minetta C. Liu[5], Anne-Renee Hartman[6], and Allan Hackshaw[7]

ABSTRACT

Cancer is a significant burden worldwide that adversely impacts life expectancy, quality of life, health care costs, and workforce productivity. Although currently recommended screening tests for individual cancers reduce mortality, they detect only a minority of all cancers and sacrifice specificity for high sensitivity, resulting in a high cumulative rate of false positives. Blood-based multicancer early detection tests (MCED) based on next-generation sequencing (NGS) and other technologies hold promise for broadening the number of cancer types detected in screened populations and hope for reducing cancer mortality. The promise of this new technology to improve cancer detection rates and make screening more efficient at the population level demands the development of novel trial designs that accelerate clinical adoption. Carefully designed clinical trials are needed to address these issues.

The Public Health Burden of Cancer

Cancer is a leading cause of death globally and the most common cause of death in high-income countries. Cancer incidence is expected to rise by almost 50% (to ∼28 million new cases annually) over the next 20 years because of population growth, aging, and increased environmental exposures due to climate change (1). The American Cancer Society (ACS) estimates 1.9 million new cancer cases and more than 600,000 deaths in the United States in 2022 (2). Most cancers that result in death are diagnosed at a late stage, often requiring aggressive treatments and, in an era of molecular profiling and targeted therapies, expensive drugs. In 2017, estimated U.S. cancer healthcare spending reached $161.2 billion; productivity loss from morbidity $30.3 billion; and premature mortality, $150.7 billion, totaling 1.8% of gross domestic product (https://canceratlas.cancer.org/taking-action/economic-burden/). More effective methods of screening could have a significant impact in ameliorating these trends.

Limitations of Current Approaches to Early Detection

Despite several decades of research and significant financial investments, only four cancers have screening tests that have been shown to reduce mortality in a cost-effective fashion (breast, colon, lung, and cervical; https://canceratlas.cancer.org/taking-action/economic-burden/; https://uspreventiveservicestaskforce.org.) Their use highlights the power of screening to detect and treat precancerous lesions (cervical carcinoma *in situ* and colonic adenomas) and nonmetastatic cancers that are amenable to curable interventions. However, these four cancers account for only 25% to 30% of all cancer deaths among those recommended for screening, highlighting the limited potential of the narrowly focused current tests to provide further reductions in population-level cancer mortality.

The current paradigm also has several other limitations. First, current screening methods are limited by suboptimal adherence. The NCI reports that for 2019 only 76.4% of women ages 50 to 74 years had a mammogram within the past 2 years (NCI Cancer Trends Progress Report. https://progressreport.cancer.gov/detection/breast_cancer), while for 2018, the ACS reports that cervical cancer screening plateaued at 84%, colorectal cancer screening adherence reached only 66%, and use of low-dose CT (LDCT) in smokers remained at 5% to 6% (3). Adherence to repeated screenings declines over each screening round (4, 5), and campaigns to increase uptake have shown only modest impact over long time periods (6). There are multiple reasons for nonadherence, including anxiety following previous false-positive results or perceived reassurance over not having cancer following prior negative results. It may also be challenging for both providers and patients to stay current with knowledge about recommended screening, such as age-based recommendations that are updated in real time [for example, the recent change in United States Preventative Services Task Force (USPSTF) recommendation to start colorectal cancer screening at age 45 instead of age 50] or identifying those at high risk because of family history or known risk allele carriers. Furthermore, individuals who are screened have a higher lifetime risk of being diagnosed with a nonscreened cancer than the cancer they were screened for (7).

Structural barriers to adherence also exist (5), including the need for attendance at a medical facility for most current screening tests [apart from stool-based tests for colorectal cancer and self-sampling for human papillomavirus (HPV) DNA for cervical cancer] and presents special barriers for underinsured and remote populations. This requirement is also subject to disruption by external forces such as the COVID-19 pandemic, where screening for all cancers dropped precipitously as access was restricted and disproportionally affected medically underserved groups (8). Compared with existing screening

[1]GRAIL, Inc, and Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio. [2]Harvard Medical and Business School, Boston Massachusetts. [3]Exact Sciences Corporation and OHSU Knight Cancer Institute, Portland, Oregon. [4]Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, Maryland. [5]Natera. Inc and Mayo Clinic, Austin, Texas. [6]Adela, Inc, Foster City, California. [7]Cancer Research UK and UCL Cancer Trials Centre, University College London, London, United Kingdom.

Corresponding Author: Eric A. Klein, Glickman Urological and Kidney Institute, Desk Q10, 9500 Euclid Avenue, Cleveland, OH 44122. Phone: 216-849-7415; E-mail: kleine@ccf.org

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tests, an MCED test based on a blood draw which requires no special patient preparation and can be accomplished quickly during a short visit to a provider has the potential to improve both adherence and access.

Genomic Approaches to Early Cancer Detection

Recent advances in genomic technology and machine learning have led to the development of blood-based cell-free DNA (cfDNA) and multianalyte multicancer detection tests (MCED) that have the potential to address many of the shortcomings of the current paradigm. Conceptually MCEDs are based on targeting somatic genetic mutations characteristic of specific cancers, cancer-associated proteins, and/or a shared cancer signal common to multiple cancer types (9–11). The existence of a shared signal was inferred by studies reporting the detection of nonfetal aneuploid DNA in maternal blood from women undergoing noninvasive prenatal testing. These studies revealed the presence of clinically unsuspected asymptomatic cancers in individuals at low risk (women under 40) and detected a wide spectrum of solid, lymphoid, and hematologic tumors (Supplementary Table S1; refs. 12–16). This shared cancer signal is defined by a variety of molecular targets including DNA fragmentation, mutations, methylation patterns, and protein biomarkers (9, 10, 17, 18).

By exploiting these cancer-specific genetic and epigenetic analytes measurable in cfDNA, MCEDs can detect multiple cancer types from a single blood draw, and both case–control and prospective studies have shown that MCED tests can detect a wide range of malignancies (9–11, 17). Detection of multiple types by a single test could make screening more efficient and more cost-effective by aggregating cumulative prevalence and incidence across all cancer types, resulting in more cases detected and increasing positive predictive value (PPV; refs. 9, 20), which reached > 40% in one large study of asymptomatic patients in the intended use population (21). Using MCED tests could be especially useful for detecting low incidence cancers for which organized screening programs do not exist or are unlikely to be feasible (**Fig. 1**; ref. 19). There are ongoing and planned studies including randomized trials in asymptomatic screening populations that will help answer these questions.

MCED-based testing paradigms also show promise to reduce harms associated with false-positive results. Current single-cancer tests are calibrated for high sensitivity but typically have false-positive rates of 5% to 15% per screening episode, leading to an estimated 8 million false-positive results per year in the United States (20) and substantial cumulative false-positive rates as high as 50% over 10 years of repeated testing (22). On the other hand, MCEDs are intentionally calibrated for very low false-positive rates (9, 10) and as such the potential for harms may be reduced. For example, in the ovarian cancer screening arm of the prostate, lung, colorectal, and ovarian (PLCO) Cancer Screening Trial, more women without cancer than had cancer underwent surgery and there was a 15% complication rate among these women (23). In contrast, results from two prospective return-of-results studies in intended use populations suggest that invasive procedures are rare in the evaluation of false positive MCED results (21, 24).

Modern Screening Trials Need Redesigning

Definitive evidence on the efficacy of cancer screening (or lack thereof) has traditionally required randomized trials demonstrating a reduction in cancer-specific mortality. Challenges associated with traditional trials include the need for a large sample size, long duration,

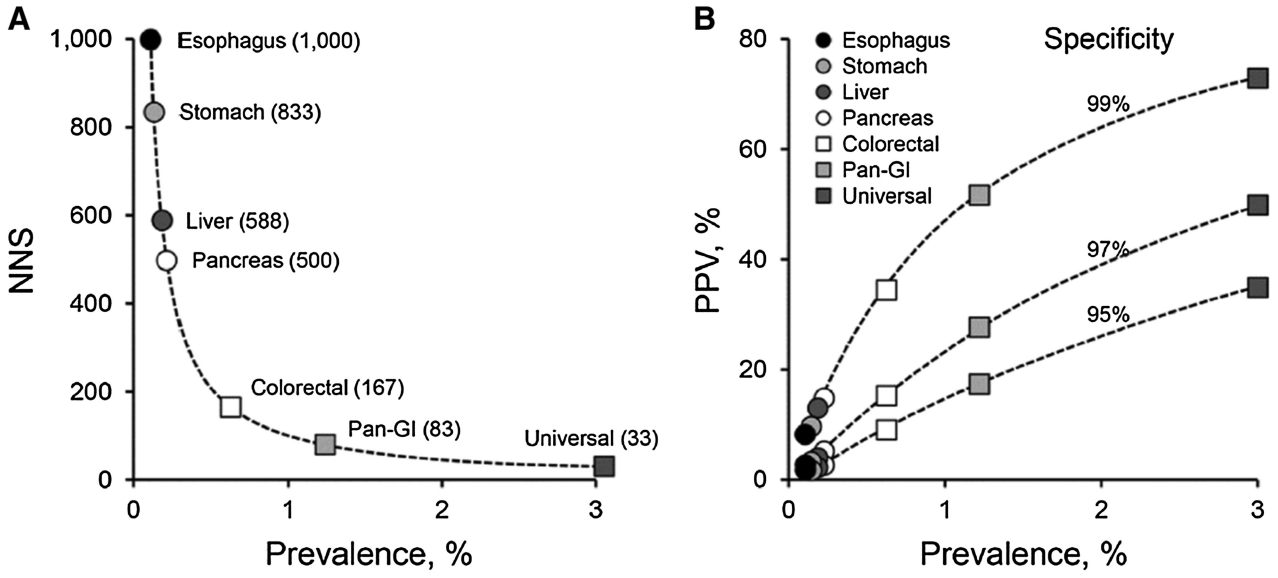

Figure 1.

Impact of cancer prevalence on screening efficiencies. **A,** Exponential relationship between cancer prevalence and the number of patients needed to be screened to detect a single-cancer (NNS). Estimated NNS is plotted for cancers at individual gastrointestinal organs (only colorectal screening is currently practiced), for combined gastrointestinal cancers (Pan-GI), and for all cancer types in aggregate (Universal). For this illustration, detection sensitivities of 100% were assumed in calculations of NNS. **B,** Influence of cancer prevalence on positive predictive value (PPV) at various specificities. Originally published by Nature Publishing Group as Ahlquist DA. Universal cancer screening: revolutionary, rational, and realizable. NPJ Precis Oncol. 2018 Oct 29;2:23 (ref. 23) and used according to NPG's policy for Open Access articles (https://support.nature.com/en/support/solutions/articles/6000217050-use-of-an-open-access-figure-or-table).

high cost, and long latency for reporting results. Two completed trials highlight these challenges. The PLCO Cancer Screening Trial (23) and the United Kingdom Collaborative Trial of Ovarian Cancer Screening Trial (UKCTOCS; ref. 25) included 78,216 and 202,638 women at average risk of ovarian cancer, respectively, randomized to ovarian cancer screening versus standard of care. Final results of these trials were not published until 18 and 20 years after initial randomization, and both trials were negative. The negative results of PSA-based prostate cancer screening in PLCO (26) were not publicly invalidated (because of the belated recognition of a drop-in rate exceeding 90% in the control arm) until 23 years after initial randomization (27). The overall cost of PLCO alone was $454 million in 2011 dollars, equivalent to $562 million in 2022 (28).

Requiring large trials with mortality endpoints for newer screening modalities such as MCEDs places a heavy burden on their development and refinement, especially given the high number of cancer deaths still occurring under current screening recommendations. Such a burden delays the realization of their potential benefits and in some cases preclude the development of promising technologies altogether. In the same way that modern drug trials are being redesigned to fit with modern therapies (e.g., basket and umbrella trials), cancer screening trials also need a major reconsideration with regards to endpoints, design, and analyses to keep up with rapidly advancing technology. The rapidly changing nature of MCED technologies means that if trials take many years, the technologies could be obsolete by the time the trials are completed.

Endpoints

A range of alternative trial endpoints have been suggested to increase the speed of clinical evaluation and translation of newer technologies like MCED into clinical practice. These include reduction in late-stage cancer incidence, candidacy for curative interventions at diagnosis, overall cancer detection rate, reduced treatment morbidity for early-stage cancers, increased treatment response rates, improved quality of life during and after treatment, utilization rates, and rates of metastatic recurrence (29–31). Focusing on asymptomatic cancers as an endpoint might also be of interest because cancer screening is generally aimed at asymptomatic patients. Even those with advanced stage disease who are diagnosed when asymptomatic could benefit by having fewer ancillary procedures (e.g., fewer bowel, biliary, or kidney obstructions). However, reliably defining, quantifying, and attributing "asymptomatic cancers" may be challenging, especially among smokers who often have chronic symptomatic conditions.

Consensus on which endpoints are regarded as being the most clinically useful could be used to design trials that test the efficacy of MCED at a fraction of the time and cost of trials powered for mortality. Some federally funded screening trials have already adopted this approach, including the ongoing Tomosynthesis Mammographic Imaging Screening Trial (TMIST) breast cancer screening trial (NCT03233191), where the primary endpoint is reduction in the incidence of late-stage disease, so designed because of the length of time needed to use mortality as an endpoint (32). The concept of using alternative endpoints is simple: a negative signal would likely portend no mortality benefit to those screened and the trial could be stopped; positive signals could serve as the basis for conditional approval and early adoption pending subsequent mortality outcomes and real-world evidence of efficacy. The latter tactic would mimic many existing accelerated oncology drug approvals based on progression-free survival (PFS) rates while awaiting post-marketing data on overall survival (OS).

Observations from screening trials for breast, colorectal, and lung cancer provide evidence supporting the use of reduction in the incidence late-stage cancer as a relevant surrogate for mortality (**Table 1**). For example, while a meta-analysis of nine randomized controlled trials (RCT) of mammography reported an overall mortality benefit of 22%, the trials that reduced advanced stage disease by ≥ 20% showed an even greater (28%) reduction in mortality for those invited, corresponding to a 40% reduction in those who actually participated in screening (33). Furthermore, reductions in advanced stage disease in these trials accounted for two-thirds of the benefit from screening (34).

Another alternative endpoint to consider is time to diagnosis, which includes patient interval (time from when bodily changes and/or first symptoms are noticed to presentation to a health care professional), diagnostic interval (date from first presentation to a health care professional to diagnosis), and referral interval (date from referral to being seen in specialist care). If delayed, these intervals are associated with more advanced-stage at diagnosis, worse survival, and greater disease and treatment-related morbidity. Although the quality of existing studies on this issue is variable, one review concluded that a shorter time to diagnosis is associated with earlier-stage diagnosis and improved survival and quality of life for a broad range of cancers including bladder, breast, colorectal, head and neck, melanoma, pancreatic, prostate, and testicular (35). There is a need for a robust discussion of these considerations in the screening community at large for the field to move forward.

Design

One large scale trial using an alternative endpoint has already completed accrual (36). The National Health Service (NHS)-Galleri

Table 1. Notable studies that demonstrate a change in late-stage incidence preceding mortality reduction.

Cancer type	Intervention, additional studies	Relationship between reduction in late-stage incidence and mortality
Breast	Mammography: Meta-analysis Tabar et al. (33) Meta-analysis Autier et al. (47)	Both studies demonstrate that late-stage reduction is correlated with mortality reduction but leads to underestimation of the mortality effect.
Bowel	FOBT: Nottingham (47) Flexible sigmoidoscopy: PLCO (47) UK flexible sigmoidoscopy trial (47)	FOBT: There was a reduction in total incidence, a nonsignificant reduction in late-stage incidence but a larger and statistically significant reduction in mortality from colorectal cancer. Flexible sigmoidoscopy: Accurate prediction of mortality based on incidence reduction was demonstrated
Lung	LDCT: NELSON (47)	Reduced mortality was preceded by stage shift

Abbreviation: FOBT, fecal occult blood test.

trial randomized participants 1:1 to an intervention (blood tested by MCED) or control (blood stored) arm. Participants in the intervention arm with a cancer signal detected have results returned and are referred for urgent investigations and potential treatment; while remaining participants in both arms stay blinded and return for their next visit. Participants are encouraged to continue other NHS cancer screening programs and seek help for new or unusual symptoms. The primary objective of this study is to demonstrate a statistically significant reduction in the incidence rate of advanced stage (III and IV) cancers diagnosed in the intervention versus control arm 3 to 4 years after randomization, with an initial readout on reduction in stage IV cancers at 1 year after the initial blood draw. Eligibility includes those in the general population ages 50 to 77 years at least 3 years without cancer diagnosis or treatment and not currently undergoing investigation for suspected cancer. The trial reached full accrual of 140,000 participants in 10 months, a pace that far exceeds prior traditionally designed trials.

An alternative proposed trial design is a nested randomized controlled trial powered for cancer mortality (31). Blood would be collected from all participants but analyzed only for (and with results returned) to those randomized to the screening-arm, such that cancer mortality remains the primary endpoint. Both groups would be followed for mortality but blood from the controls would only be assayed in those who developed cancer or died, along with a random proportion of all other controls to confirm that screen-positive rates were similar between groups. The main advantage of this trial design is that it keeps cancer mortality as the primary endpoint (in line with previous cancer trials) but enables a substantial reduction in the number of participants needed, with resultant reduced cost, and fewer deaths required than the traditional design. This approach might also serve as a nested analysis within a design based on one of the alternative endpoints, with appropriate power calculations. Some of the main concepts of the nested design have been used before to evaluate noncancer screening tests (37, 38). Potential limitations to this design include (i) whether participants change their behaviors following a test result (including negative tests), thus influencing their risk of cancer and (ii) if there was more nonadherence to testing in the control-arm than the screened arm, which might lead to fewer observed cancer deaths than expected among those with a known blood test result in the controls. Neither of these situations would be captured in the nested design but could be explored using modeling and sensitivity analyses (31).

Analysis

All randomized trials evaluating a new cancer screening test have so far compared an endpoint (e.g., cancer-specific mortality) among all participants in each arm. Because the target has been a specific cancer type, this approach has been easy to understand and claims about screening efficacy are only associated with that particular cancer. However, MCED tests target multiple cancer types. One view is that all cancer types should be analyzed together (e.g., aggregate cancer mortality, or aggregate late-stage cancer incidence). This makes it easier to power the trial without being overly large, and it also reflects what MCED tests primarily detect: cancer signals, regardless of cancer type. However, an alternative view is that MCED test performance should be evaluated for each cancer type separately, and screening efficacy claims should only be made where there has been satisfactory evidence for a particular type(s). But even in a relatively large trial, several cancer types would each have too few participants to produce any reliable estimates of screening performance using cancer mortality or alternative endpoints.

Thinking about the effects of new interventions on single-cancer types has been standard practice in oncology therapeutics for decades, in which a new cancer drug must be evaluated in separate trials (usually randomized) before a drug license and clinical guidelines are changed. However, the advent of modern tumor agnostic therapies has changed this paradigm, for which there is a direct analogy with MCED test evaluation. Molecular testing research has found an increasing number of new markers and mutations that define small disease subtypes. This has led to tumor agnostic drugs that target the marker rather than the cancer type, such as entrectinib and larotrectinib for patients with neurotrophic tyrosine receptor kinase (NTRK) fusion–positive tumors (https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc). The pivotal clinical trials have included multiple cancer types, several of which have < 10 cases. Regulatory and market access approvals have been based on all cancer types combined without the requirement to show efficacy for each type, which would be difficult given the very small patient numbers in each group. A similar approach could be applied to MCED tests, using Bayesian statistical methods to explore whether test performance is agnostic to different tumor types. Other forms of analyses could be based on grouping cancer types together. For example, those with and without current recommended screening; those with low incidence; or those with low shedding tumors. However, any of these would increase the trial size compared to using aggregate measures.

Can modeling mortality help inform trial design?

Mathematical models could be used to project reduction in, for example, late-stage disease and mortality outcomes from new screening trials. "Natural history" models of screening have been used both to plan screening trials and to extrapolate trial results to population-based screening programs (39). Such models are accurate only to the extent that there are robust data that accurately reflect dwell time in each stage for each cancer and which accurately predict both stage and mortality outcomes (40). A key question is whether modelling can be useful to illustrate whether MCED tests are effective in reducing mortality or to quantify the potential effect sizes on traditional and alternative endpoints.

Hubbell constructed a model for the effect of a MCED able to detect multiple different cancer types (41). In this analysis, similar to standard CISNET models (https://cisnet.cancer.gov/), stageable cancers are modeled as passing through four stages in the preclinical state and may be found in one of those stages if screening is successful. Each cancer type is modeled independently, as the performance of the MCED, the potential aggressiveness of tumor growth rates, as well as the potential mortality effect from being found at a given stage depends on the particular cancer and stage. These individual cancers modeled in parallel are then aggregated to summary statistics across all cancers. Cancers that are not stageable are assumed to be unaffected by screening.

The primary scenario examined is one of long-term screening in an eligible population ages 50 to 79 years, estimating the typical outcomes from a stable screening program per year of screening. Given this model, estimates of reduction in late-stage (III and IV) incidence were predicted, reaching up to 78% reduction for annual screening depending on cancer growth scenarios. Similar to Owens and colleagues (ref. 42; as discussed subsequently), this reduction in late stage does not translate one-for-one into mortality reduction. For those cancer cases found with the MCED, the mortality reduction in 5-year survival

(accounting for lead time) could reach 39%. As not all cancer cases can be found before clinical diagnosis, when aggregated with those not found, this results in a potential 26% reduction in mortality, averting or delaying 104 deaths per 100 thousand people per year. Under a variety of sensitivity analysis, this ranged from 19% to 26% of all cancer mortality.

This model shows the potential upside of MCED screening as a complement, taking into account the different characteristics of different cancers and the different prognosis of each stage in each cancer. This large potential to affect a significant fraction of all remaining cancer mortality is larger than for any single-cancer screening program and underscores the urgent need to resolve questions of MCED utility. Note that under this model, if no stage shift is achieved, no mortality improvement can be achieved, suggesting a natural endpoint for studies of MCED screening.

Owens argues that reduction in late-stage disease may not be suitable as a primary endpoint for a screening trial because predictions of mortality reduction based on this endpoint are unreliable (42). This conclusion was based on an analysis using a model for single cancers with only two stage categories, late (III/IV) and early (I/II). The analysis used four screening trials: National Lung Screening Trial (NLST; lung, low-dose CT vs. chest X-ray; ref. 43), European Randomized Screening for Prostate Cancer Trial (ERSPC; prostate – PSA blood test vs. no screening; ref. 44), UKCTOCS (Ovarian, multimodal with CA125 & ultrasound vs. ultrasound only vs. no screening; ref. 25), and the UK Age trial (breast, mammography vs. no screening; ref. 45). The selected trials provided mixed evidence for and against the suitability of late-stage incidence reduction as a good proxy for mortality.

This paper illustrates how model design choices influence outcomes of natural history models, emphasizing the need for suitable model design from the start. An important consideration includes the granularity of stages or states of disease progression used in the natural history model. Using a model with only two disease stages, early and late, may lead to greater error than a model structure with four or more stages (e.g., stages I–IV in tumor–node–metastasis; TNM system). This would impact predictions when the key distinction for survival outcomes is not solely between late and early-stages. The importance of these assumptions will vary by cancer type due to both distributions of stages at diagnosis and survival differences between stages. **Figure 2** shows the variation in 5-year survival for a selection of cancer types stratified by four categories of stage. Some cancers, such as colorectal, breast, and pancreas/gallbladder, show a pattern that could be captured by two categories. However, the figure also shows that lung, ovarian, and esophageal cancer survival are not well described by two categories as there are substantial differences between stages III and IV, and within early-stage disease between I and II.

This discussion highlights how assumptions inherent specific to each model affects predicted outcomes and how that may influence assumptions underlying trial design. These issues need careful

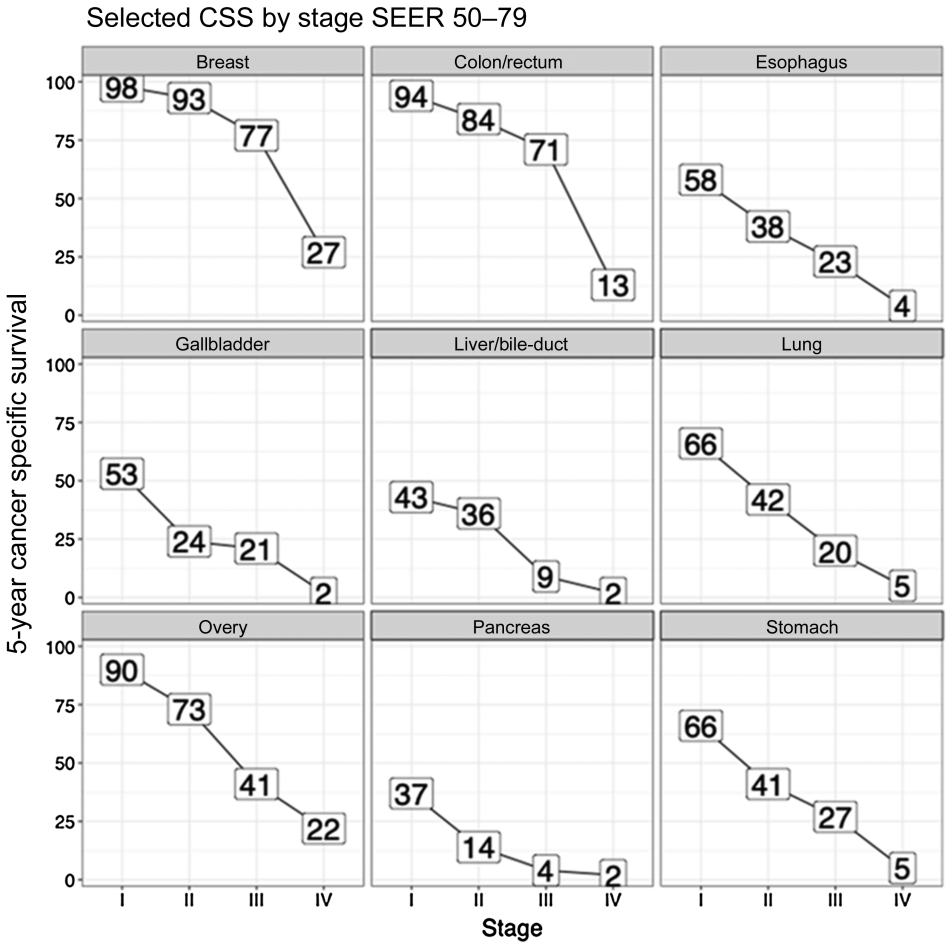

Figure 2.
Survival by stage for multiple cancer types. Source: SEER Program. SEER Program SEER Stat Database: Mortality - all COD, aggregated with state, total U.S. (1969–2016) <Katrina/Rita Population Adjustment>, NCI, DCCPS, Surveillance Research Program, released December 2018. Underlying mortality data provided by NCHS (www.cdc.gov/nchs). SEER Program. Available from: www.seer.cancer.gov.

consideration before trials are initiated. Although it is true that that stage shift does not directly imply mortality reduction (nor does it imply a linear relationship if one exists), given that mortality endpoints may not be reached for 15 years, stage shift can be used as a necessary interim endpoint to gate decisions on continuing MCED-based screening trials in their early years. If stage shift is not observed then it's unlikely that a mortality benefit will result, and the most important shift to observe is a reduction in late-stage disease without an increase in early-stage disease to avoid over diagnosis.

Challenges with Multicancer Early Detection Care Delivery

There are multiple challenges associated with implementing, maintaining, and monitoring widespread MCED testing. Careful consideration and planning will be needed to decide where blood samples are taken, by whom and who and how results are reported. Taking blood samples is likely to be done in primary care or community settings, hopefully improving access and equity especially among underserved and medically disadvantaged populations and those living in rural areas, as no special on-site processing is required. However, medical practitioners ordering MCEDs will need training to understand cancer screening and MCED performance and its consequences to deliver the screening program, answer queries from the public, explain MCED test results, and facilitate diagnostic evaluations in those needing one.

The cost of an MCED test will depend not only on the assay cost itself but how the program is delivered and where. Cost-effectiveness analyses will need to include the cost of the test, diagnostic investigations, and cancer treatments, as well as the costs of running the program. The expected reduction in late-stage disease incidence with repeated screening rounds should reduce total treatment costs. Although modeling studies suggest a marked decrease in cost per cancer found with the addition of MCED testing to standard screening (20), countries with health systems funded by the government will likely be faced with an expensive screening program, while others such as in the United States need to consider insurance coverage and find ways to include underinsured individuals. High test costs could lead to lower adherence and exacerbate existing healthcare inequities. It is also possible that cancer-specific mortality outcomes may become difficult to evaluate if control arm participants adopt screening following a "positive signal" for late-stage cancer. In this eventuality, alternative endpoints could still be used to judge whether MCED testing adds value.

All screening tests, including MCEDs, come with potential harms. Test positives from an MCED may have more diagnostic complexity than one from a traditional single-cancer screen when imaging is negative because it would not be possible to target a biopsy to definitively determine the nature of an observed abnormality. Diagnostic false positives after an MCED test could represent inadequate work-up to find a cancer that is truly present, cancer that is too small to be detected by current diagnostic and imaging tests or be a real false positive. Natural history studies with longitudinal follow-up, including the Detecting Cancers Earlier Through Elective Mutation-Based Blood Collection and Testing (DETECT-A; ref. 24) study and Circulating Cell Genome Atlas Study (CCGA; ref. 9) will be needed to define this issue in more detail and determine what percentage of patients fall into each category.

Another potential issue is whether easier access to MCED tests leads to less adherence to current guideline recommended screening. Early interventional data with prospective use of MCED tests suggests that this does not happen. In one study of 10,000 women who were screened by an MCED, adherence to mammography screening guidelines was preserved in 99%, and in a second MCED study where test results were returned to participants a minimal effect on planned screening behavior was reported (21, 24). The ideal frequency of testing is as yet unknown and remains to be determined.

Finally, as for current cancer screening tests, there is the risk of over detection of nonlethal cancers (over diagnosis), and this may vary according to cancer type. However, the biological nature of MCED tests (on the basis of the shedding of tumor fragments) suggest that the use of ctDNA as a principal analyte may favor detection of cancers with lethal potential over clinically insignificant ones. Indeed, a large MCED case–control study observed that while detected cancers had survival outcomes equivalent to Surveillance Epidemiology and End Results (SEER) observations, those not detected had better than expected outcomes for all stages (46). If confirmed this test feature would minimize risks of over diagnosis. All these potential harms are quantifiable and prospective data on their occurrence and magnitude would be easily compiled during a prospective trial of MCED-based screening.

Conclusion

The limited potential of the current screening paradigm to further reduce cancer burden at the population level and the significant cost and time needed for new drug and diagnostic test development raise important questions about how to incorporate emerging liquid biopsy–based screening technologies into clinical care. A recent economic analysis concluded that MCED testing over 5 years could result in more than 23 million life-years gained (LYG, assuming 0.18 life year gained per MCED tested individual), which substantially exceeds the estimated LYG from current screening for lung, breast, colorectal, and cervical cancers combined (47). Even if this figure is discounted for quality and implementation challenges, the scale of the potential impact of MCED is significant.

Before widespread MCED testing can be implemented, several issues will need to be resolved. Reliable and robust cost-effectiveness modeling will be essential to comprehensively evaluate the costs and benefits of MCED tests and screening programs associated with them and inform pricing and reimbursement decisions by manufacturers and payers. If randomized trials fail to show sufficient benefit in average risk populations, an evaluation of MCEDs in populations with elevated risk of cancer may be considered. Using traditional designs for cancer screening tests when evaluating MCED tests mean that results and implementation into routine practice would take many years. More efficient randomized trials, possibly with alternative primary endpoints to complement cancer mortality are required so that populations can benefit sooner if such tests are shown to be effective. Longer term follow-up can provide confirmatory evidence when clinical benefit is initially established through accelerated mechanisms. Additional research should include stratification by populations at risk, examination of adherence rates and impact on screening performance, determining screening intervals, and refining stratification into cancer types with different survival patterns. There should also be improved understanding of cfDNA kinetics and identifying best practices for diagnostic workups.

In conclusion, MCED tests represent a paradigm shift in how cancer can be detected and managed at a population level, with the potential

for significant benefits that would be accessible to more people than with current screening policies. Reliable evidence generated by randomized and interventional studies conducted in a timely fashion are urgently needed.

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