Evaluating the Clinical Utility of Multi-Cancer Early Detection (MCED) Tests:

Envisioning A Path Forward

A REPORT FROM

The Multicancer Early Detection Consortium

Clinical Utility Working Group

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Executive Summary

Cancer is the second-leading cause of death in the United States (2021)[1] and causes 1 in 4 deaths in the UK (2019).[2] Early detection and treatment has been a key to reducing cancer mortality. Yet early detection of many cancers remains elusive. Recommended population screening modalities are only available in the US and UK for a few of the more common cancers: breast, colon, lung, cervical, and in some circumstances in the US, prostate. Taken together, these cancers represent less than half of all new cases of cancer diagnosed each year in the US.[3] Effective screening tools for additional cancer types could foster continued progress in reducing cancer mortality. Multi-cancer early detection (MCED) tests represent a possible set of tools to expand the range of early cancer detection.

This paper is intended inform providers, guideline developers, regulators payers and other decision-makers who will need to make judgments about the benefits and risks of MCED testing in the context of substantial uncertainty. While MCEDs also hold promise for diagnostic use in symptomatic patients, the focus here is screening. The paper provides an overview of the limitations of currently available cancer screening tests, the promise of MCEDs for cancers without established screening tests, the current state of MCED test development, the evolving evidence landscape for use of MCEDs in cancer screening, and the shape of clinical evidence needed for further development.

MCEDs are (primarily) blood-based tests able to detect the presence of multiple cancer types through identification and analysis of circulating tumor cells, cell-free DNA, proteins, and other markers.[4] Many tests are currently in development. Published validation studies display tests having a range of test designs and performance characteristics, varying abilities to predict tissue of origin, and large variation in the extent to which tests have been trained and validated. The most developed of these tests thus far have been designed for very high true negative rates (high specificity) with the tradeoff that many true positives are missed (variable sensitivity by cancer type). This design represents an inversion of the conventional guideline-directed, single-cancer screening paradigm, where screening tests have very high sensitivity but also relatively lower specificity.

Despite their variable sensitivities for individual cancer types, MCEDs have the potential to detect many cancers at one time. Individual cancer types are relatively uncommon in an asymptomatic adult population, while cancer in the aggregate is much more common. By casting a wide net for cancers of many types, MCEDs reduce the number of individuals needed to be screened to identify a true positive, increasing the overall probability of finding cancer in screening populations. While MCED testing is still nascent, and few clinical utility studies demonstrating benefit to patients have been completed, the technology and its potential uses are evolving rapidly. Some tests are already available commercially and—considering the immediacy of the continuing public health impact of cancer—some health systems are already exploring integration of MCED cancer screening into clinical practice alongside guideline-directed single-cancer screening.

Therefore, rapid evaluation of clinical utility is needed. Yet randomized controlled trials (RCTs) with mortality endpoints, which are the gold standard for assessing new screening tests, can take decades and many thousands of patients to yield results. In the interim, MCED tests are likely to evolve rapidly, diminishing the relevance of trial results. There is also potentially significant opportunity cost in deferring adoption of screening tools that could reduce cancer mortality. One notable exception is a UK-based MCED screening trial has been able to rapidly recruit 140,000 patients through the National

Health Service to assess an intermediate endpoint (stage shift) relatively quickly – within three to four years of randomization – followed by longer-term assessment of cancer-specific mortality.[5] Although it evaluates only one test among many, the trial demonstrates the possibility of rapid recruitment of large populations within large, integrated health systems and points the way towards one use of intermediate endpoints.

Given this rapidly evolving landscape, even as longer-term RCTs with mortality endpoints are being developed, we argue for a collaboratively pursued, parallel strategy for more rapid evidence development. This evidence generation strategy, or clinical utility framework, would articulate a plan of studies, including randomized trials with intermediate or surrogate outcome measures, observational studies, real world data collection and modeling, capable of providing a rational basis for decision-making while insights into mortality benefits gradually emerge. Although the recommended studies would not produce the traditional level of certainty that inform single-cancer screening recommendations, they would contribute to a growing body of knowledge, maturing on a continuum, that would provide for increasing confidence in decision-making as results accumulate.

The MCED Consortium has made progress toward developing this clinical utility framework. The Consortium is a non-profit organization with a mission to reduce the burden of cancer by evaluating how MCED technologies may improve cancer detection, treatment, and care to benefit all people.[6] The framework is being developed by the MCED Consortium's Clinical Utility Workgroup, which is comprised of experts representing academic researchers with expertise in cancer screening, regulatory experts, payer organizations, diagnostics companies, and others with a shared interest in assuring high-quality evidence is accessible to decision-makers as quickly as possible.

In this paper we preview key methodologic strategies we believe must be adopted for successful evidence development. We aim to build support for this approach, to help set expectations for future studies to inform clinical and policy decisions, and to take a first step in preparing stakeholders for a coordinated effort in evidence generation.

The framework is informed by the perspectives described above and several additional key principles. Underlying each of these concepts is the recognition that generating more certain evidence requires more time and more patients. The potential harms of early adoption must be carefully balanced against the potential harms of failing to detect cancers that may be more amenable to effective therapy. Key principles for the forthcoming framework include the following.

- MCED tests are designed on the principle that all tumors have shared biological features, with a common set of cellular products accessible through the circulatory system. This biology allows for the detection of a cellular signature associated with many different types of cancer. As such, MCED tests are intended to be used and evaluated as a single, integrated test; not as a panel of individual cancer screening tests. Variations in natural histories of, and treatment options for, individual cancer types may create the need in some circumstances to evaluate MCEDs on a cancer-by-cancer basis (or even by subtypes of a given tissue of origin). The clinical utility framework considers the circumstances where cancer-specific analysis and reporting may be needed while maintaining the fundamental principle that MCEDs function as a single test.
- Development and use of intermediate and surrogate endpoints likely to correlate with effectiveness of MCEDs in screening will be necessary to support nearer-term evaluation of

MCEDs. Such endpoints should be judiciously chosen and standardized in their use so that comparisons can be made across studies, facilitating more rapid learning. At this time, a key candidate measure is an increase in detected incidence of early-stage cancers with a corresponding decrease in detected late-stage cancers (stage shift). Other useful tools might include assessment of the proliferative rate of detected tumors as determined by gene expression profiling and possibly the pathological grade of tumors. Proliferative rate is indicative of tumor aggressiveness, which is frequently correlated with tumor lethality. There may also be a similar relationship between pathological grade and lethality. These assessments may therefore provide insights about the impact of MCED screening tests on preferential detection of potentially lethal cancer types vs. possible overdiagnosis of indolent cancers. In addition, a more conventional endpoint in oncology trials, time-to-progression, might serve as a useful surrogate for mortality.

- If and when MCED tests are adopted for screening, it will be crucial to employ strategies for ongoing learning about test performance and associated outcomes that can complement data generated from screening RCTs and other studies. Plans for the development and use of real-world data (RWD) to generate real-world evidence (RWE) integrated meaningfully with other studies are therefore a central focus of the emerging framework. One key priority is to standardize data elements (e.g., data collected on patient characteristics, clinical confirmation procedures and pathology, MCED test screening characteristics, etc.) and definitions used to assure comparability between datasets. Furthermore, policy mechanisms to promote broad collection of these standardized data elements are essential.
- Evidence generation is viewed as a continuum over which study questions, study designs, and study outcomes will evolve. Although a continuum, the pathway for evidence generation will not be strictly linear. Improvements to testing technology are expected and will be accounted for. Results from completed studies will inform rethinking of other, ongoing work, and offer insights into the design of future products and future studies.
- Cooperation and collaboration of many stakeholders is needed for successful near- and intermediate-term evaluation of MCED screening. For example, this is necessary in the context of standards for clinical validation data and reporting needed to inform clinical utility study designs. The Consortium will seek alignment with others working in this area, notably the US FDA and BLOODPAC. Likewise, cooperation and alignment on collection of RWD must be sought from health systems, employers and other organizations that initiate MCED testing. In these and other ways, a community of stakeholders must be engaged and mobilized.

Introduction

Cancer is the second-leading cause of death in the United States (2021)[7] and causes 1 in 4 deaths in the UK (2019).[8] Effective prevention, detection, and treatment have been key strategies for achieving reductions in disease-specific mortality for some cancers over the past two decades,[9] yet early detection of many cancers remains elusive. In 2018 in England, almost half (45.5%) of cancers with known stage at diagnosis were diagnosed in stages 3 or 4.[10] Population screening modalities are only formally recommended for a few of the more common cancers: breast, colon, cervical, lung (for individuals with elevated risk in the US and soon to be introduced in the UK), and prostate (in some cases in the US, but not in the UK). Taken together, these cancers represent less than half of all new cases of cancer diagnosed each year in the US.[11] This is true, in part, because the high cost and methodologic feasibility of evaluating screening modalities for individual cancer types is not practicable for low-prevalence cancers.[12] Earlier detection and treatment may improve mortality for some of these cancers and, if more cancers are cured, may reduce per-cancer medical costs for cancer care, which were estimated to be $157.7 billion in the US in 2020.[13] For continued progress on early detection, diagnosis, and treatment of cancer, expanded screening tools to identify less common cancers are needed, along with efficient methods to evaluate the clinical validity and utility of emerging tests. Recent advances in blood-based screening tests have led to the development of multiple cancer early detection (MCED) tests which may offer a pathway to population screening and detection of cancers for which no screening tests currently exit.

MCEDs are blood-based tests able to detect the presence of multiple cancer types through identification and analysis of circulating tumor cells, cell-free DNA, proteins, and other markers.[14] Aggregating many cancer types into one blood-based test platform for screening represents a fundamentally different testing paradigm with many potential advantages, including non-invasiveness and ease of use that may promote adherence to recommended screening protocols. In addition, leveraging the aggregate prevalence of many cancers increases the likelihood of identifying cancer (of some type) through the process of screening. Nevertheless, there are significant challenges to designing studies that evaluate the benefits and harms of MCED screening, and there is not yet an established cancer screening paradigm for this class of tests. Moreover, given that several MCED tests of varying designs are in development, study results for one type of MCED test may not be assumed to stand in for others. Given varying test performance characteristics, inclusivity of different cancer types, and the variety of subtypes and natural histories for each cancer, increased detection could lead to unnecessary treatment of non-lethal cancers (sometimes called “overdiagnosis”) and lethal cancers could still progress too quickly to be caught in the screening window.

From a methodologic perspective, the gold standard approach to assessing potential benefits and harms of new screening modalities is to conduct large, randomized studies measuring long-term patient outcomes, including disease-specific mortality endpoints, before introduction into widespread use. Expectations for these studies by guideline developers such as the US Preventive Services Task Force (USPSTF) and the UK National Screening Committee (UKNSC) are high. Yet the evaluations are so lengthy, the ultimate results may not be relevant to rapidly evolving technologies. Meanwhile, cancer mortality will amass even as knowledge of screening benefits and harms may come too slowly to guide patients and providers in the interim. For MCEDs, the availability of laboratory developed tests (LDTs) (which in the US can bypass Food and Drug Administration review procedures) means that patients and providers who desire it will be able to access testing for their own purposes. The need is urgent,

therefore, for near-term evaluations to be done even as large, long-term studies are planned. Accordingly, while acknowledging the need for RCTs with mortality endpoints, the MCED Consortium supports a strategy of multiple parallel studies and ongoing data collection for evaluation of the benefits, risks, and costs of MCED screening.

For this reason, the Clinical Utility Workgroup of the MCED Consortium has developed this white paper to review the current landscape for MCED tests and suggest a framework of clinical utility studies that would provide reasonable confidence of the risks and benefits of using MCED tests in cancer screening. The ultimate framework would envision an evidence base in the short, intermediate and long terms to evaluate MCED tests for cancer screening now and, as they evolve over time. The MCED Consortium is a non-profit organization with a mission to reduce the burden of cancer by evaluating how MCED technologies may improve cancer detection, treatment, and care to benefit all people.[15] The Clinical Utility working group is comprised of experts representing academic researchers, payer organizations, and diagnostics companies having a shared interest in assuring high-quality information is accessible to decision-makers as expediently as possible.

The focus of this white paper is on MCEDs that test blood for screening asymptomatic adults. Yet liquid biopsy is emerging as a flexible approach to detecting cancers in other contexts.[16] Sample media may include blood, urine, saliva, or cerebrospinal fluid. Analysis may focus on single or multiple cancer types for diagnosis, treatment response, relapse monitoring, or other purposes. Multi-cancer tests will therefore also likely be used for diagnosis of symptomatic patients and other purposes in various body fluids. The Clinical Utility Workgroup will address diagnostic use of MCEDs in a separate paper.

Our target audience is clinical and health policy decision makers in the US and UK, including US primary care clinicians and payers. By describing current available evidence and anticipating a pathway and rationale for future clinical studies, we can help to set reasonable expectations for available evidence and outcomes over time. The future framework would then further inform decision-maker expectations while providing a road map for test developers as they consider how to design studies intended to inform these decision-makers.

Role for MCEDs, Potential Benefits, and Possible Harms

Limitations of Current Screening Modalities

Successful treatment of most cancers relies on detection prior to the onset of metastatic disease, when treatment may alter the natural history of the cancer, possibly for a cure, extend survival, improve quality of life and/or control symptoms. Various entities in the US and UK (e.g., the USPSTF; American Cancer Society, ACS; UKNSC; Cancer Research UK, CRUK) recommend screening for common cancers (breast by mammography, cervical by Pap smear, colorectal by colonoscopy or non-invasive stool-based testing), and in the US and in England also lung by low-dose CT imaging of high-risk people who formerly or currently smoke). Prostate cancer screening is not recommended in the UK and is only used in certain circumstances in the US.[17] The recommendations are based on evidence that when employed appropriately these tests reduce cancer mortality.[18] Their use highlights the power of screening to detect non-metastatic cancer types amenable to cure, and in some cases (cervical CIS and colonic adenomas) allowing identification and removal of precancerous lesions.

Nevertheless, the current guideline-directed screening programs suffer from many limitations. The cancer types covered by these programs only comprise approximately 38% of the entire cancer mortality burden in the US in 2022[19] and 18% in the UK in 2020.[20] Hence, there are no organized screening programs for cancer types that contribute in aggregate to the majority of all cancer deaths, including those, for example, of the pancreas, liver, esophagus, and ovary. These four cancers are typically diagnosed at a late stage in most patients; hence their prognosis is generally poor. In aggregate these four cancers accounted for approximately 18% of cancer deaths in the US in 2022 and almost 17% in the UK in 2020.[21,22] Despite the benefits that accrue from screening programs, more than 600,000 people a year nevertheless die of cancer in the US, over 378,500 of these for which there are currently no recommended population screening tests. The cancer types currently included in organized screening represent those that are the most common (except for cervical cancer, which was a common cancer 70 years ago when cytology screening became established). Screening strategies for breast, colon, prostate, and lung cancer all benefit from the practicality of imaging or direct access to tissue (with tolerable morbidity for surgical excision) or tumor derived DNA and blood-containing samples (fecal). The absence of some or all of these qualities, in addition to lower prevalence, may partially explain why there has been greater emphasis on developing new screening technologies for cancers with established screening recommendations rather than bringing novel cancer types into the fold.

Finally, while adherence to screening guidelines varies by cancer type and by population subgroup, adherence rates for these screening modalities are often suboptimal. In the US between 2000 and 2015, overall uptake for cervical screening was 81.3%; for breast cancer screening was 71.7%, and for colorectal screening was 63.4%.[23] Uptake of National Health Service (NHS) cancer screening programs in England in 2019-2020 was 72.2% for cervical screening[24] and 69.1% for breast screening,[25] while from 2012 to 2015 it was 57.9% for colorectal screening.[26] Sociodemographic patterns of uptake can be complex. In the US, for example, non-Hispanic Black women have higher uptake of mammography than white women (69.7 vs 65.8%), while other ethnic groups all have lower coverage (e.g., 60.9% in Hispanic women). Nevertheless, uptake is consistently negatively correlated with economic disadvantage. For example, colorectal cancer screening uptake is consistently lower in areas of greater deprivation in England, and women in these areas are less likely to take part in breast, cervical and colorectal cancer screening. [27,28] Year-over-year declines were seen for colon cancer screening uptake in the UK between 2010 and 2015, and the declines were socially graded: for the most and the least deprived area-level socio-economic deprivation quintiles, uptake was 43% vs 57%; for the most and the least area-based ethnic diversity quintiles, uptake was 41% vs 56%; and for men and women, uptake was 47% vs 56%.[29] Similarly, Americans having higher education, higher income and health insurance are more likely to have had a recent breast, cervical and colorectal cancer screening.[30] In the US, lung cancer screening has been consistently low, with use of low-dose computed tomography (LDCT) in eligible persons under 10%.[31] In addition, over time adherence to repeated screenings declines for both serial single cancer screens and for screening across multiple sites (i.e., breast, cervical and colon).[32,33] Even individuals who follow current guidelines are substantially more likely to be diagnosed during their lifetime with a non-screened cancer than those for which they were screened.[34]

To foster continued gains in population-level reductions in cancer mortality, additional or potentially improved approaches to screening are needed to identify more cancers earlier and improve access and adherence to screening. Because of their ability to screen for multiple cancer types simultaneously and conveniently, MCEDs may be promising for overcoming these challenges.

Potential of MCED Test to Address Unmet Need in Screening

Unlike the single-cancer screening modalities noted above, MCED tests are designed to detect multiple cancer types simultaneously. MCED tests potentially combine several advantages which, ultimately, can lead to improved public health: 1) the ability to detect cancer types currently lacking routine screening modalities, including rare forms for which screening modalities are unlikely ever to be developed individually; 2) aggregation of many individual cancer types, leading to a relatively low number of asymptomatic individuals needed to be screened before finding some type of cancer ; 3) for many MCEDs, multi-cancer detection with high specificity, meaning a high rate of true negative findings; 4) multi-cancer detection in a single, easily used, minimally invasive modality.

MCEDs measure cancer-derived biomarkers in body fluids, such as blood or urine, making the screening procedure for individuals generally less invasive and easier to accomplish, possibly becoming part of routine primary care visits. This simplicity may help to promote better adherence to future screening guidelines if patients have access to testing through insurance coverage (in the US) or provision through the NHS (in the UK). Some MCEDs can also provide insights on tumor biology (e.g., mutations) that may be informative for guiding treatment. MCED tests have the potential to detect cancer earlier than it would otherwise be detected symptomatically or incidentally. If so, MCED testing could facilitate earlier initiation of treatment, when a cancer may be more amenable to treatment, leading to improved outcomes.

By increasing the numbers and variety of cancer types detected through a single screening modality, the number of individuals needed to be screened to find a cancer (NNS, or number needed to screen) tends to be lower for MCEDs than for single-cancer modalities.[35] For example, using a test with theoretically perfect performance characteristics, the NNS to find one esophageal cancer among average Americans aged 50 to 80 is 1,000, whereas to find any cancer the NNS is only 33).[36] In effect, screening with an MCED has a greater likelihood that some type of cancer will be detected as compared to single-cancer modalities. This is a direct consequence of the fact that the prevalence of a single cancer in an asymptomatic average risk population is very low, while the combined prevalence of all cancers (aggregate prevalence) is higher.[37] Currently MCED false positive rates can be high (e.g., ref. 38) and the sensitivity of detecting early-stage cancers is still often less than that for detecting late-stage cancer (e.g. ref. 39). Nevertheless, the possibility of leveraging aggregate prevalence and reducing NNS for multi-cancer screening is suggestive of enormous potential for MCEDs to significantly improve the efficiency and cost-effectiveness of cancer screening.[40]

As noted, many MCEDs are currently being developed to achieve low false positive rates (high specificity).[41,42,43,44,45] While guideline-based single cancer tests can be highly sensitive in detecting cancer (high true positive rates), the false positive rates can be very high, leading to a significant number of recalled patients for further evaluation. Some proportion of this recalled cancer-free group will potentially undergo unnecessary invasive diagnostic procedures. MCEDs with low false positive rates would thus potentially be associated with reduced unnecessary recall and follow-up. The tradeoff is that MCED tests have limited sensitivity for some cancer types and would therefore also miss opportunities for detection. Even so, given that feasible screening modalities are lacking for most cancers, even a test with suboptimal sensitivity may be an improvement over nothing if downstaged tumors have better outcomes and unnecessary recall is infrequent. With continued innovation and improvement, the potential of MCEDs to address the unmet needs of current guideline-directed screening may be

possible. (For information on how providers should consider and interpret MCED statistical sensitivity and specificity data within the clinical context, see the MCED Consortium Care Delivery Workgroup white paper.[46])

Clinical Utility and Limitations of Randomized Trials for Evaluation

"Clinical utility" refers to a diagnostic or screening test that is useful to change the management of a patient for improvement of net health outcomes.[47,48,49] A screening or diagnostic test does not have inherent utility; rather, utility is conditioned on the outcomes of specific therapeutic or other management decisions made based on the test result. [50]

The gold standard approach to evaluating the clinical utility of a cancer screening test in asymptomatic individuals is to conduct a large randomized clinical trial (RCT) with disease-specific mortality from the target cancer as the primary outcome measure.[51,52] The main advantage of RCTs is to mitigate biases (such as lead time, length time, and selection biases) that alternative designs may not fully address. In addition, an RCT powered to assess a reduction in cancer mortality assures that the intended use of a screening modality can ultimately result in lives saved or significantly prolonged through treatment of the cancer earlier in its natural history. Another advantage of conducting an RCT with a mortality endpoint is that the findings are widely seen as unassailable. Lacking supporting evidence from an RCT, a test may be judged to be unproven and face considerable downstream challenges to clinical adoption and payment. It is fair to say that "it takes a village" to move from evidence to policy. Favorable findings from an RCT can open the gates to implementation.

This high bar for evidence comes at a high cost. The decision to launch a prospective RCT of cancer screening means an enormous commitment of time and resources to answer a narrow question (i.e., does a particular screening protocol result in a more favorable outcome measured by a lower rate of disease-specific mortality compared with no screening, or screening with an alternative screening test). An RCT with a cancer mortality endpoint typically requires a large sample size to have adequate power, long durations of time for planning, enrollment, multiple rounds of screening, and an extended period of follow-up to measure outcomes and report results. Time from planning to study completion is commonly measured in decades. This timeline leads to many challenges. Long enrollment periods can lead to significant washout of the intervention effect when screening rounds end for initial enrollees and follow-up ensues while new enrollees begin screening. RCTs can underestimate the true benefit of the intervention due to practical design compromises allowing study durations shorter than a lifetime of screening and follow-up. Over time, failure to adhere to the randomization assignment (when individuals in the experimental group do not attend and individuals in the control group receive the intervention outside of the trial) can significantly erode statistical power and prolong follow-up. Moreover, interpretation of the results of lengthy trials can be confounded by changes in practice patterns, adoption of new therapies, and improvements in testing technologies arising during the study. For these reasons, relying on a single, decisive RCT to determine the value of a screening test many years after it is launched can be seen as unwisely "putting all the eggs in one basket." Doing so delays acquisition of new knowledge and can discourage investigations to explore contemporaneous questions the ongoing trial was not designed to answer.

Looking retrospectively, it is difficult to identify a prevention/early detection RCT that ultimately met all its goals. In the end, the protocol may be judged as effective for some but not others in the target population, as was the case with single-view, biennial mammography screening in women ages 40-49 in

the breast cancer screening RCTs.[53] Or we may find the protocol was flawed, as we saw in the early trials for lung cancer screening by chest x-ray.[54] For many years afterward, the lack of efficacy of lung cancer screening was considered settled science—all lung cancer screening, not only screening by chest x-ray—despite the serious defects of trial design.[55] In another example, results of two ovarian cancer screening trials (the ovarian arm of the PLCO [N = 78,216] and the United Kingdom Collaborative Trial of Ovarian Cancer Screening Trial [UKCTOCS, N = 202,638]) were not published until 18 and 20 years after initial randomization.[56,57] The findings from both studies, which showed no reduction in ovarian cancer mortality, were important but not timely. Similarly, mortality outcomes for prostate cancer screening, and the revised guidelines recommending against its use in the general US population (which were later reversed back to a recommendation for shared decision making), did not become available to patients and providers until approximately 30 years after general PSA screening began to be adopted. The delays in initiating and completing these studies poorly served patients and providers. Meanwhile, the full PLCO trial cost $454 million (in 2011 dollars; $617 million in 2023 dollars).[58,59]

While all clinical study designs have strengths and pitfalls, this brief review of long-term RCT limitations suggests that we should energetically pursue near- and intermediate-term studies of MCED use in cancer screening—both because of the promise of MCEDs to reduce overall cancer mortality, and because their ease-of-use may promote rapid adoption.[60] Studies parallel to RCTs are often discouraged out of concerns regarding redundancy or undermining ongoing trials. Nevertheless, such investigations are needed, first, as a hedge against potential RCT defects that threaten the ability to measure intended outcomes. Second, and at least as important, for some decision-makers the development of early evidence (observational and randomized with intermediate or surrogate endpoints) may prove sufficient to introduce MCED testing earlier than would be possible if we relied entirely on the eventual availability of RCT/mortality results. At this time, however, the UKNSC requires mortality reduction for the introduction of new screening programs. Finally, as a practical matter, if RCTs with mortality endpoints are assumed to be the only path forward, investment for test development is likely to flee and a unique opportunity to expand cancer screening and reduce cancer mortality will be lost.

Accordingly, nearer-term alternative evidence strategies are needed to evaluate MCED in a manner that compliments and informs emerging trial designs and that evolves as evidence accrues. The needed evidence framework will be the subject of a separate white paper. This discussion has provided our rationale for creating an investigational pathway for MCEDs to inform decision-making while mortality-based RCTs are planned and carried out.

Potential Harms of MCED Screening and Early Adoption

Because of the relative rarity of individual cancers, for all screening modalities statistically speaking there is a low likelihood that any single participant will benefit from routine cancer screening while any harms associated with testing will accrue mainly to otherwise healthy people across multiple screening intervals.[61,62] MCEDs can increase the overall likelihood of detecting cancers and therefore potentially increase the likelihood of both benefits and harms in a screening population. The degree to which increased benefits and harms are experienced could depend on the specific combination of cancer types included in the MCED and on the performance characteristics achieved. Recognized potential harms of screening and their relevance to MCED testing is reviewed here.

Overdiagnosis

Some cancer types are more likely to grow and metastasize before they can be detected in a given screening interval while slower-growing tumors (some proportion of which are indolent) are more likely to be detected.[63] The detection of a cancer that is either non-progressive or is detected by screening shortly before the patient dies from other causes is commonly described as *overdiagnosis*. In either case, the diagnosis may lead to unnecessary treatment and may cause significant harm. Since MCED testing with blood is minimally invasive, it may be feasible to use a shorter screening interval than conventionally used for single-cancer screens, making it more likely to find and treat both lethal cancers and indolent cancers. Early data suggests that some MCED detection technology may preferentially detect consequential cancers.[64,65] If so, it would help to mitigate concerns related to overdiagnosis. However, more work is needed to characterize this phenomenon and its implications in practice. The assessment of the proliferative rate of each detected tumor in screening studies could provide insight on early detection rates of consequential cancers.

Positive Screening Test Follow-up and Correct Tumor Localization

A positive screening test commonly requires follow-up to determine if the initial finding was true or false. This may entail additional testing, short-term surveillance, or possibly an invasive procedure. The patient may experience harms from procedures or from the screening test itself if follow-up ultimately yields a negative finding. Patients may experience emotional harm from this experience. Many MCED tests are tuned to have a low false positive rate, which can reduce this concern.

Relatedly, an issue with all MCED tests that predict tissue of origin (TOO) is the risk of not consistently and accurately identifying the TOO associated with a positive cancer signal. This challenge pertains regardless of the mode by which TOO is predicted. A positive but indeterminate finding could trigger a diagnostic odyssey for some patients.[66] Such a diagnostic odyssey might involve more extensive investigation, added potential for incidental findings, and possible emotional distress for patients. This could be a challenge particularly in individuals with a positive MCED result that proves to be a false positive after completion of a diagnostic evaluation. Moreover, concern over this risk can become a barrier to adoption for some US payers or for the NHS, where resources are constrained.

Different MCED tests set forth different modes by which TOO is identified. One MCED test, which determines TOO from methylation patterns, reported promising data (in a conference paper, not yet published) as part of the PATHFINDER study.[67] In this report, 39 participants with a cancer signal detected by two versions of the same MCED test, including those with true positive and false positive results, were studied. Diagnostic evaluations were consistent with cancer signal origin in 30/39 (77%) cases. Diagnostic resolution was achieved in 32/39 (82%) participants after initial evaluation, while 7/39 (18%) required additional workup. This report provides an encouraging recent snapshot of test technology that continues to evolve.

Another test in development addresses TOO localization using a different strategy by performing diagnostic positron emission tomography-computed tomography scanning [PET-CT] without a predicted TOO for each positive test result (DETECT-A study).[68] This approach in the DETECT-A study correctly localized all MCED-detected cancers for those individuals who's positive MCED result proved to be a true positive. Other tests in development may offer different strategies for tumor localization.

Guideline-based protocols are needed for the range of findings that will derive from MCEDs, and evaluation needed of adherence to these recommendations.

False Negative Findings

Although false negative test results are not usually considered a harm of screening, there has always been concern that if symptoms subsequently arise, the negative test result might deter seeking a consultation. Since some MCEDs include cancer types for which guideline-directed screening already exists, the absence of a positive signal for these cancers may give the individual a false sense of confidence that the guideline-directed screening test is not needed, or that a consultation is not needed if symptoms appear. Whether a negative MCED test results in inappropriate reassurance and reduced adherence with standard of care screening is not known at this time, and it will be important to measure such effects as MCEDs are evaluated. Clinical validation data published to date for many MCEDs exhibit a range of sensitivities across individual cancers, many below 80%. Therefore, when MCED tests are used for screening, some cancers may often be missed. Patient and provider education strategies will be needed to ensure appropriate interpretation of results and encourage continued guideline-directed screening. Engagement with a patient interested in an MCED test may create an opportunity to engage and educate them about a comprehensive suite of recommended cancer screening tests and health promotion.

Early Adoption

While early adoption is not a harm by itself, and may be beneficial for many individuals, as noted earlier, harm to patients can come from the failure to gather meaningful evidence in an efficient and timely fashion. In the UK system, there may also be economic impacts on the NHS, even if it has not yet adopted MCED testing, if significant numbers of patients access MCED tests privately and then seek further testing or reassurance from NHS providers.

Other Risks

Other risks worth noting are not directly caused by MCED screening itself but may be a consequence of the research practices or the legal frameworks under which care is delivered. In research, racial and ethnic diversity in test populations for MCED validation and utility clinical studies is crucial to assuring tests perform well across subgroups and that any benefits seen can accrue equally across populations.[69] To do otherwise may exacerbate inequities in health outcomes. Additionally, in the US health system, a positive finding of cancer by an MCED test may be deemed a “pre-existing condition,” even if the individual is not symptomatic. Under US law, health insurance benefits cannot be denied or excluded due to pre-existing conditions, however this prohibition does not apply to other forms of insurance such as life, disability, or long-term care. Even so, we are not aware of cases of insurance denials based on MCED results.

Current MCED Development and Evaluation

As noted, MCED tests measure biological signals that are the hallmarks of cancer in body fluids such as blood and urine.[70] While mutational analysis of tumor DNA may produce results limited to specific sites of origin, cancer tumors share a common biology; numerous biomarkers amenable to evaluation are

common to a broad range of cancers and are readily accessible in the circulatory system, enabling multi-cancer detection.[71] Circulating tumor cells, cell fragments, or cell-free DNA shed by tumors may be analyzed for telltale changes in DNA or RNA sequences or other structural abnormalities, cancer-specific tumor mutations, patterns of DNA methylation (indicative of changes in gene expression) or fragmentation patterns. Antibodies or other immune-related cells may be targeted. Levels of protein biomarkers may be analyzed. Levels of circulating tumor cells or other cell products may also be informative (e.g., for assessing the clinical significance of detected cancer).[72] Tests under development use one or more of these parameters, the results of which are sometimes interpreted by machine learning algorithms, to detect the presence of cancer. Depending on the test, a wide range in numbers and types of cancers may be detected. For some tests, the cancer TOO may also be predicted. Researchers continue to seek new approaches and additional biological signals that may indicate the presence and site of origin of cancer.

As of this writing (August 2023), at least 10 MCED blood tests were found to be in various stages of clinical validation for purposes of adult cancer screening.[73,74,75,76,77,78,79,80,81,82,83] Any of the analytes noted above may be combined in a single test to produce a cancer signature or signal, and analytical capabilities or methods for each analyte may vary among tests. Accordingly, differences in the target biomarkers, analytical platforms, and algorithms used to process results lead to differing between-test performance characteristics for each cancer detected. For tests capable of identifying TOO, the frequency of correct identification varies between cancer types and between tests.

Before studies of efficacy and clinical utility can be justified, a screening or diagnostic test must be shown to identify a condition of interest with well validated performance characteristics (clinical validity). Early clinical validity is often determined through case-control studies in which blood (or other types of) samples from patients with and without cancer are analyzed. The samples are typically post-diagnosis (taken before initiation of treatment), sourced from biorepositories or from current known cases at medical centers and other sources. Once the assay is “trained” to detect cancer (i.e., developing a classification algorithm and cutoff points), then the test is “locked” to further changes and evaluated in a separate, independent set of samples to determine performance characteristics (e.g., sensitivity, specificity, positive predictive value, negative predictive value). While case-control designs with post-diagnosis samples are economical and timely for initial test refinement and validation, they tend to exaggerate screening test performance in the intended use population.[84] Among other challenges for these studies, the proportion of cancer cases to non-cancer controls is highly enriched, thus not representative of intended use. For a more accurate understanding of test performance, clinical validity should be assessed in prospective studies conducted in populations of asymptomatic, intended use populations—the individuals for whom the test would be used in practice.

For the ten tests noted above, only three of the studies published were prospective interventional studies conducted in large screening populations.[85,86,87] Of these three, two were not designed with clinical validation as the primary objective.[88,89] Results of another large prospective longitudinal study, not yet published but available as a conference paper, was designed to assess clinical pathways (numbers and types of procedures and time required to achieve diagnostic resolution following a positive test result) as primary outcomes with clinical validation test characteristics as secondary outcomes.[90] Two of the published studies conducted validation in patients with and without cancer enrolled on a post-diagnosis basis with independent validation sets.[91, 92] The remainder of the studies constituted earlier phases of discovery with more preliminary assessments of performance. Given the

variability of studies done, resulting test performance characteristics cannot be meaningfully compared across different MCED tests. Note also that while tests are locked for a given study, at the conclusion of the study a test may be unlocked and refined based on the results, then re-locked for another study. Accordingly, the results for the same test may not be comparable across sequential studies unless the researchers have designed the studies to allow comparison of test versions.

All told, the MCED tests reviewed here vary greatly in their level of development. However, at least one has advanced to the threshold of clinical utility studies and has initiated a clinical trial with the NHS in the UK. The trial enrolled an extraordinary 140,000 patients in a one-year period.[93] This achievement was facilitated by the centralized care delivery and data infrastructure of the NHS—advantages the US health care system lacks. Even so, large integrated regional health systems in the US have been able to serve as platforms for reasonably large screening studies of MCEDs.[94,95]

So far, however, trials have focused on a single MCED test even as multiple tests are available, and more are in development. Again, due to the differing between-test detection abilities, mortality outcomes of the trials would need to compare death rates that were relevant to each of the cancers detected by each test. Furthermore, MCED technology will be evolving. Platform trials (where several interventions can be evaluated simultaneously against a common control group, with the ability to add new interventions and update the control group throughout the trial[96]) may be helpful in dealing with the development of new tests and with revisions to existing tests. It is unclear whether such trials will be able to adapt as rapidly and frequently as the test technologies evolve. However, the National Cancer Institute (NCI) has proposed an adaptive platform trial that would include early stopping rules to discontinue study arms with outdated tests, transparent processes for adding new study arms, and concurrent observational studies to independently validate candidate MCED tests for inclusion.[97]

While these efforts continue, complementary evidence generation is needed. Creating a portfolio of systematic assessment of the benefits and risks of MCED tests will require sustained collaboration across a range of experts and stakeholders, including test developers, clinicians, health systems, researchers, funders and others, with engagement of crucial decision-makers such as the UKNSC and US FDA.

Overview to Elements of a Clinical Utility Framework

A clinical utility framework for MCED screening will describe an interconnected chain of data collection strategies and study designs (both observational and randomized) that can support judicious clinical and policy decision-making. With the goal of timely evidence development, the framework will suggest the use of certain intermediate and surrogate endpoints and recommend approaches to confirm their relationship to long-term outcomes. Robust clinical validation should be a prerequisite for advancement to clinical utility studies. For this reason, a clinical utility framework may provide some guidelines for demonstration of clinical performance. While a full and detailed account of the framework will be undertaken in a separate paper, in this section we review some key aspects of study design and take initial positions on how these must be integrated into the clinical utility framework we envision.

Aggregate vs. Single-Cancer Evaluation

Blood-based MCED testing is founded on the commonality of cellular products across tumors and their accessibility through the circulatory system. Hence, MCEDs are intended to be used and evaluated as an integrated single-test screening modality that can detect multiple cancer types, not as a panel of

multiple different cancer screening tests. As such, the clinical utility of the test would be demonstrated by an aggregate decrease in late-stage cancers and eventually a reduction in cancer-related mortality. As noted above, the opportunity for improved population outcomes is enhanced by the ability of these tests to identify cancers for which current standard screening tests do not exist, taking into account the potential risks of overdiagnosis and harms from following-up positive test results.

Yet this framework for evaluating the clinical utility of MCED screening raises concerns. Each of the cancer types identified by MCED tests has its own natural history, optimal screening window, and ability to be treated that varies by stage of detection, tumor grade and molecular type, and other factors. These sorts of differences are evident even within cancer types having the same TOO. These types of concerns have shaped the current guideline-directed screening modalities; they do not share the same target populations or screening intervals. These challenges are compounded with MCED screening, where evaluation in the aggregate could average out subgroup (between-cancer type) differences in benefit and harm, minimizing larger risks and concealing both large and negligible benefits for individual cancer types targeted by the test. Even with high-quality TOO estimates, the complexity of diagnostic workup following an MCED test has only been assessed for one test.[98] Even supposing a demonstrated improvement in an aggregate outcome such as stage shift or overall survival, it cannot be taken for granted that patients ultimately diagnosed with specific cancers, or diverse subgroups based on race, ethnicity, tumor genetics, co-morbidities, and other characteristics, would benefit equally, i.e., have a similar ratio of benefits to harms. (See research study recommendations from the MCED Consortium Health Equity Workgroup.[99]) This is an area of need for data-gathering.

That said, it is worthwhile to note that the issue of heterogeneity in the benefits and risks of subpopulations within a screened group is also a feature of currently recommended cancer screening tests. For example, mammography does not perform as well in women with significant mammographic breast density.[100,101] Some tumors are harder to image than others even in the non-dense breast. Some tumors have immunochemical/histological features that are more challenging to treat (for example, triple negative breast cancers) and they occur with roughly twice the frequency in Black women vs. white women.[102,103] Screening guidelines vary in recommended screening intervals because some guideline developers are more focused on harms than benefits (and vice-versa), but it is also known that sojourn time varies with age groups. Most individuals undergoing breast cancer screening are unaware of these variables or the fact that a positive finding could have a broad range of implications (not unlike individuals undergoing MCED screening). Ideally performance would be uniform across populations. Yet despite this heterogeneity, breast cancer screening programs still prevent many thousands of deaths each year due to early detection, while not all subgroups of screened women are found to have similar increased detection at early stages or reduced cancer-related mortality.[104] The individual tumor outcomes are important, but if the test delivers an overall aggregate benefit based on the cancers that are not covered by the current guideline-directed screening strategies, this would still represent an overall benefit to screened patients since it demonstrates an advantage above and beyond the currently recommended screening options. The advantage would be all-the-more evident if MCEDs were additionally shown to catch interval (between-screen) cases of colorectal, breast, lung, and cervical cancers, or cases in individuals who are non-adherent to guideline-directed screening.

Even so, it would still be valuable over time to learn more about the benefits and risks in patient subgroups, and this applies equally well to breast cancer screening and MCED testing with heterogeneity in the outcomes for individual cancer subgroups. This does not preclude the need to generate evidence

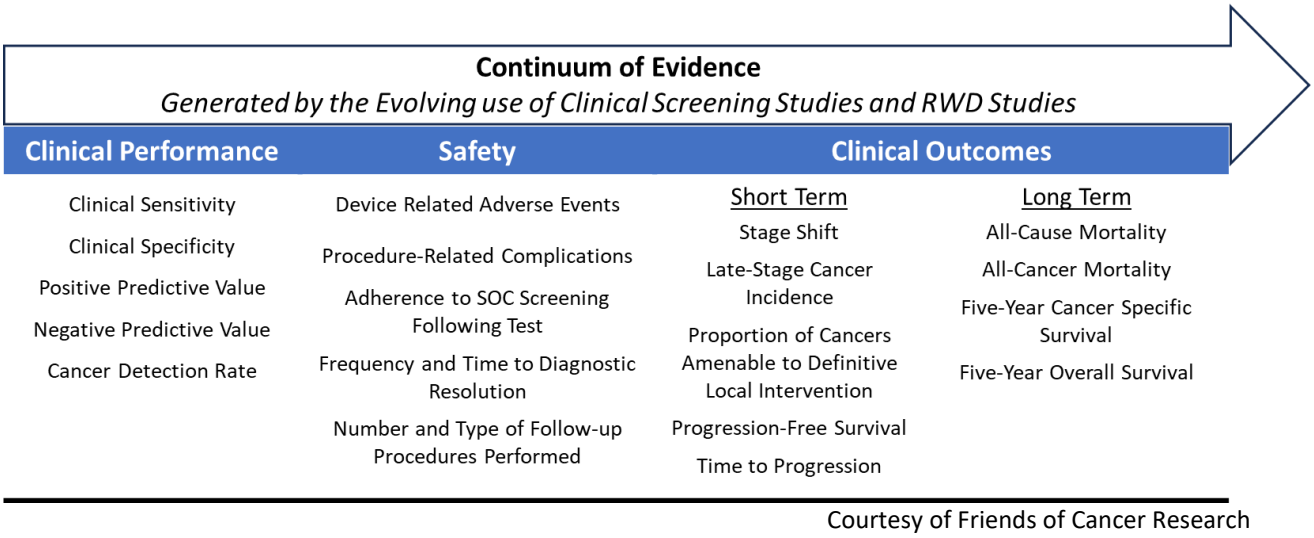
on the outcomes for individual cancers. Over time, additional evidence on cancer-specific outcomes and positive predictive values would be likely to improve the use of MCEDs by refining target populations (which initially are broadly conceived), screening intervals (initially perhaps chosen more for convenience in clinical practice than as an optimized screening strategy), or the cancer types included in testing. This type of evidence can also bolster the information available to clinicians counseling patients on MCED screening. Accordingly, at least one major US health plan advises MCED test developers to include in their evidence submissions significant cancer-specific information, including TOO-specific recommendations for clinical pathways to follow a positive test result.[105] This type of laborious cancer-specific data collection may be facilitated in the near term through efficient use of real-world evidence (described in more detail below). Also, for chain-of-evidence studies designed to make an indirect case for clinical utility, cancer-specific test performance specifications and other data are necessary (as in the previously noted payer guidelines).

Ultimately, the goal of evaluation should be to assess the value of MCED as a single test administered periodically to screen for cancer in a general screening population. A framework for clinical utility should consider carefully the circumstances under which evaluations should be made by subgroup or cancer type, seeking to build an evidence base that can rely on more streamlined studies as it matures.

Continuum of Evidence

The MCED Consortium sees evidence generation for MCEDs as layered and progressive, maturing on a continuum as MCED technologies evolve. An evidence framework should build successively on case-control studies, return of results studies, clinical utility studies, and RCTs before, or in parallel with, assessment of mortality endpoints (Figure 1). Clinical studies and data reporting for MCED tests should be well designed, planned, and coordinated and provide evidence with consistent measurement standards across successive research milestones. These should include measures to sufficiently evaluate clinical test performance, safety implications, and short-term/long-term clinical outcomes and psychological outcomes to assess potential harms associated with false positive/negative MCED test results.[106]

Figure 1. Continuum of Evidence



Courtesy of Friends of Cancer Research

Use of intermediate/surrogate outcome measures

There has been much interest in designing randomized trials using outcome measures for which changes or manifestations are evident and measurable earlier than cancer-specific mortality to assess the value of screening strategies. These are often called surrogate or intermediate outcome measures. Here we will use the term "intermediate outcome" to denote outcome measures that the patient personally experiences, such as stage of disease, grade and subtype of disease. By contrast, surrogates are measures that are not directly experienced by the patient, such as biomarkers or genetic signatures, which are related to the state of disease or other relevant outcomes (especially mortality). Intermediate and surrogate outcomes can also be used as a means of stating that the cancer-specific mortality is unlikely to be improved – i.e. as means of assessing a potential lack of benefit/futility.

Currently, the test of an intermediate or surrogate outcome to predict mortality is best evaluated retrospectively with the findings from RCTs of cancer screening. For example, the principal benefit of mammography screening is reducing the incidence rate of advanced breast cancer; researchers established a correlation between reduction of late-stage disease and eventual mortality reduction through retrospective analysis of screening trials.[107] However, this type of retrospective analysis is not yet feasible for MCED screening trials. Information from other trials may nevertheless be informative. A group of UK and US investigators are currently conducting a review to associate various intermediate and surrogate outcomes with mortality outcomes from approximately 50 trials of cancer screening conducted to date. When complete, this review should provide significant insight on the best use of surrogate and intermediate outcomes. Until then, other forms of reasoning are needed. The MCED consortium's clinical utility framework will therefore consider alternative modes of validation for intermediate and surrogate endpoints, with focus especially on the utility of shifts in stage-specific incidence, and the use of selected biomarkers and gene expression profiling, briefly outlined below. Below we outline these and other possible intermediate endpoints to be considered more fully in the forthcoming clinical utility framework. In addition, a more conventional endpoint in oncology trials,

time-to-progression, might serve as a useful surrogate for mortality. It is not described below due to its familiarity, but it may also play an important role in the forthcoming framework.

Stage specific incidence outcome measures

Early-stage cancers (i.e., cancers detected early in the natural history of progression) are more successfully treated and cured in almost every organ site and tumor subtype. Therefore, one of the most compelling intermediate outcomes for cancer screening involves so-called "stage shift," or the increased incidence of diagnosis of a particular cancer type at an early stage, *accompanied by a matched decreased incidence of diagnosis of that cancer type at a late stage.* While intuitively attractive, stage shift is subject to biases that must be accounted for by researchers. If a cancer is detected early, before the clinical presentation of signs and symptoms, then the starting point for measurement is moved back in time. This shift (called lead time bias) makes survival time seem longer, even if early detection makes no difference to when the patient dies. Length time bias arises from the differences between slower progressing cancers and faster ones. Since the window of detection is shorter for faster moving cancers, slower progressing cancers tend to be over-sampled in the screening process. The screen-detected cohort is thus biased toward slower progressors with intrinsically better outcomes, which can artificially inflate measurements of survival outcomes.

While some modeling studies have been done to estimate the impact on mortality when earlier diagnosis is achieved,[108] no direct assessment of clinical utility has yet been published. As noted above, a large RCT of one MCED test was initiated in 2021 in the UK NHS.[109] This trial of 140,000 persons receiving three annual screens will measure as a primary endpoint the reduction in late-stage cancer, which should be available in 2024. A secondary endpoint is to compare cancer-specific mortality in the intervention and control arms using a retrospective nested analysis, followed by data on cancer mortality in late 2026. In the longer term, a large-scale trial with mortality as an endpoint is currently in the early stages of planning by the NCI and hopefully will produce important results in the US, but a readout of results cannot be expected for at least a decade following initiation, and likely much longer.

Outcomes Related to Treatability and Treatment of MCED-Detected Cancer

Another potential intermediate outcome (noted in Figure 1 above) is proportion of detected cancer amenable to treatment with curative intent. This outcome is related to stage shift in that while late-stage cancer is generally treated palliatively (non-curatively), early-stage, localized cancer is often considered more amenable to resection, radiation, or other treatments intended to cure the underlying condition. Hence, a higher proportion of treatment-amenable cancers detected with MCED screening as compared to the proportion arising from standard of care screening care may be an indicator of *effective* earlier detection. Not only was that cancer detected earlier, but the evident stage shift potentially benefited the treatment decisions.

The potential impact of this decision-making (i.e., decisions for treatment with curative intent) can then be followed longitudinally, leading to milestones that can serve as additional intermediate endpoints. For example, measurement could be made of the proportion of patients who remained cancer-free after one year following MCED early detection and treatment with curative intent. While achieving this milestone is no guarantee that the patient will remain cancer-free, comparison to outcomes from a standard of care screening group diagnosed with the same types of cancer may reveal a difference in recurrence rates. If so, this would represent a clear benefit to early-treated patients. Differences in

recurrence patterns could continue to be tracked for these cohorts, illuminating any benefit in time-to-relapse and, other benefits such as quality-of-life.

When cancer screening leads to improvements in mortality or other clinical benefits, these benefits are the direct result of the success of cancer-directed interventions that follow the detection of cancer. These proposed intermediate endpoints may enable an early assessment of the potential of a screening program to ultimately reduce cancer morbidity and mortality.

Pathological Grade of Cancer

Pathological grade of cancers has been proposed as an important measurement in screening trials. While the relationship between earlier detection of high-grade cancer types and reduction of mortality is not established, in theory, early detection of higher-grade cancers provides improved detection of consequential cancer types with higher mortality risk. If early detection of higher-grade cancer were accompanied by relatively fewer findings of lower grade cancers (which harbor more of the indolent lesions) this could be interpreted as improved specificity. But if, instead, the number of lower grade cancers detected is roughly equal or greater than the count of high-grade tumors, it would reflect poorer specificity. If higher grade cancers can be detected *early enough* to be more easily and effectively treated, the detection of these cancers may improve mortality, but would certainly improve treatment-related morbidity. These critical conditional statements must be addressed by any proposed study design short of RCT with mortality endpoints. This proposition is complicated further because the relationship of grade with prognosis is cancer-site specific, thus any inferences using grade (and the consequent potential impact on mortality) may have to be made at the individual cancer-site level, rather than across cancers. Ovarian serous carcinomas, for example, can be thought of as two distinctly different diseases classified by low versus high grade, now with known molecular mechanistic differences in addition to known mortality risk differences. Alternatively, pathological grade may be useful to assess a lack of potential benefit (futility) criteria at the individual cancer level rather than a criterion to claim success for an MCED. The potential usefulness of this endpoint in MCED screening trials and steps needed to establish confidence in its use will be assessed by the Clinical Utility Workgroup as it considers pathways to recommend for the clinical utility framework.

Biomarkers and gene expression signatures

Early gene expression signatures have proved useful in predicting recurrences and response to therapy largely by converting the subjective nature of the pathologist's interpretation to a more objective and reproducible method. The proliferative rate of tumors is a key characteristic separating indolent versus aggressive disease in many cancer types (more proliferative lesions are more aggressive). Given the power of gene expression assays to predict outcomes in the context of optimal therapy, and the utility of high-density data sets for ongoing discovery, the framework will consider the value of including *more than standard of care* cancer genotype/phenotype analysis in screening studies. Characterizing proliferative rate and other characteristics of detected tumors would help to establish the frequency with which consequential cancers are found early through MCED screening and allow for prediction of patients most likely to benefit.

The Role of Modeling

Modeling is the development of "mathematical frameworks that facilitate estimation of the consequences of health care decisions."[110] These frameworks are particularly useful when linking evidence along a causal chain, when direct evidence of the effect of an intervention (such as the use of a clinical test) on an outcome is lacking. Generally, a decision analytic model is developed for this purpose. Test performance data from validation studies is combined with disease prevalence and epidemiologic data, as well as treatment outcomes from clinical trials, to model a specific clinical scenario of test use with predicted outcomes.[111] Models may be used for exploring and communicating results of clinical as well as policy decisions where budget constraints and value assessment may be important considerations for the introduction of a new technology. Decision models may be especially useful for illuminating aspects of clinical utility; they have been used by the USPSTF to assess the benefits and harms of specific interventions, including screening.[112]

While many models have been developed for the risks and benefits of single-cancer screening, models for MCED screening have only recently been emerging. To date, modeling has employed published test validation data and known cancer epidemiology (e.g., cancer-specific incidence rates from the NCI Surveillance, Epidemiology, and End Results [SEER] database) to assess potential reductions in mortality and possible cost savings associated with earlier detection and treatment of cancer.[113,114] Modeling has also exposed limitations and challenges of using stage shift as an endpoint.[115] In the latter case, modelers found that the expected mortality reduction for a given stage shift varies significantly depending on cancer- and stage-specific survival distributions. Even when stage shift was substantial, some cancer types exhibited limited potential for mortality improvement. Modelers have also worked to characterize the downstream consequences of MCED screening, especially harms from unnecessary confirmation tests balanced against tests' putative benefits.[116,117]

While these early efforts to develop models for MCED benefit, risk, and cost have helped to generate insights, models are only as good as the data supporting them.[118] Robust clinical study data on benefits and risks of MCED screening, including cancer detection rates by cancer type and stage, the diagnostic paths taken for true positives and false-positive cases, and cancer treatment outcomes, among other information, is needed both from randomized trials and real-world data to create more opportunity for robust modeling.[119,120] Specific strategies should be envisioned to leverage ongoing studies and to plan a sequence of future studies that will most efficiently map together for efficient and effective use of models. The planned framework will therefore consider the role of modeling in the planned evidence timeline, seeking a coordinated and efficient approach to leveraging emerging study data in models.

The Role of Real-World Data and Real-World Evidence in the Evaluation of MCED Tests

As MCED tests are adopted for screening, it will be crucial to employ strategies for ongoing learning about test performance and associated outcomes that can augment data generated from screening RCTs and other studies. These real-world data (RWD) will also allow exploration and a form of assessment of the pathway from a positive screening test to a full diagnosis for MCEDs. As tests become available for widespread use, collecting data from routine practice is also likely to provide information across demographic subgroups and be more representative of the target population than individual clinical studies of whatever size. For these reasons, plans for the development and use of RWD to generate real-

world evidence (RWE) integrated meaningfully with other studies will be a central focus of the framework.

While RWD is currently often collected and used to update clinical practice guidelines, and it has now also started to be collected on the use of MCEDs by early adopting health systems, the process of doing so is not efficient or well-coordinated. For RWE to become an important source of information, significant prospective planning is needed, mirroring much of what is done in the planning of an RCT. The planned framework will provide insight and recommendations on key questions that can be informed using RWD, potential data sources, data quality attributes, and necessary metrics for evaluation of MCED tests.[121]

With an evolving environment for MCED technology and cancer intervention, evidentiary milestones will be defined to provide preliminary indicators of success, for example a reduction of advanced stage disease. While intermediate outcome measures are unlikely to provide the full body of evidence needed to assess the value of a screening test, defining key measures that can be evaluated early in development of MCED tests will allow stop/go decisions regarding individual tests or versions of them. Alignment on priority or "core" measures that should be generated and made available for all MCED tests would assist advanced planning for data collection efforts, ensure optimal and constant evaluation of different tests over time, and ultimately improve public confidence and utilization of MCED tests.

Defining a cohesive approach to longitudinal data generation would also help identify sources of data that may be sufficient for generating evidence based on clinical practice (e.g. RWE). Examples include health systems, research networks, payer databases and clinical registries. Furthermore, identifying specific data elements upfront that need to be collected to perform the necessary analyses involved in determining clinical utility of individual MCED tests will help ensure optimal data collection and quality.

Several efforts have developed concrete suggestions about study designs that can be used in parallel with randomized trials to advance our understanding of the benefits and harms of MCEDs. Friends of Cancer Research has suggested that cross-sectional, case control, and cohort studies have roles to play where RWD, and in these cases, observational data, can complement randomized clinical trials.[122] Etzioni, et al. (2021) [123] also urges a coordinated effort to collect data while certain MCEDs are being disseminated so that these tests and their outcomes can provide data to assist in the evaluation of the way in which these tests are employed, and the clinical paths taken by persons tested, with their follow up information and outcomes.

While there are places for both cross-sectional and case-control data, a rigorously defined series of cohort studies has the most potential to complement clinical trials. In some cases, it is possible such data may be sufficient for regulatory decision-making to move products to the market. To further specify the optimal study design (or designs) recommended to complement ongoing trials, we will draw from both the Friends of Cancer Research and Etzioni work to define the study questions or hypotheses, the eligible population, the data needed from these designs, and the data sources.

Conclusions and Next Steps

MCED testing represents a promising approach to expanding the range of cancer screening beyond the scope of current guideline-directed screening, allowing for earlier detection of consequential cancers, and thereby improving treatment outcomes for many patients. In so doing, the substantial social and

economic impacts of cancer may be alleviated significantly. While MCED testing is still nascent, the technology and potential uses are evolving rapidly; some tests are already available commercially. It is therefore urgent that clinical evidence illuminating the benefits and risks of MCED screening be developed as rapidly as possible, even while taking care to be methodical.

The MCED Consortium and its Clinical Utility Workgroup are committed to facilitating the needed evidence generation by framing recommendations for a program of clinical evidence development that can be implemented in the near term to guide clinical and policy decision-making, even as long-term RCTs are planned and initiated. The MCED Consortium recognizes the importance of conducting large RCTs with mortality endpoints to increase confidence in cancer screening via MCED testing, and strongly encourages all stakeholders, including test developers, patients, clinical systems and federal agencies to collaborate in the development and implementation of such trials. Simultaneously, we recognize the immediacy of the continuing public health impact of cancers of all types, most of which lack screening modalities, and consequently also the desire of some early adopting health systems to explore integration of MCED screening into clinical practice. We would urge these providers to assure patients undergoing MCED testing understand what is known and not known about the benefits and risks of MCED screening, and the continuing importance of guideline-directed cancer screening.

Given that some health systems are even now exploring MCED adoption for screening, we have an opportunity to foster collaborative efforts for evidence-based adoption, which would include prospective studies and RWE from the clinical use of MCED tests. The systematic collection of RWD to complement clinical trials is a critical aspect of near-term evaluation of MCEDs for screening and will be a key focus of the planned clinical utility framework. The framework will develop standard definitions of RWD & RWE; promote efforts to ensure the collection a set of core data elements from patients undergoing MCED testing; develop collaborative strategies to promote cooperation across test developers, health systems, payers, clinicians, and others; and create a framework for learning from clinical experience through data collection—to move MCEDs forward in the context of sensible clinical practice.

Collaborative strategies will be needed in other ways, also. For example, designing clinical utility studies requires high-quality information on MCED performance from validation studies. Agreed minimal standards are needed for reporting of MCED validation and efficacy (e.g., specifying the ways in which stages may or may not be combined when reporting detection of cancers by stage). To address this need, the Workgroup will review existing efforts for data standardization and reporting (e.g., BLOODPAC; the US FDA) and collaborate to ensure alignment.

Identifying appropriate intermediate and surrogate outcomes is another critical—and challenging—component of a near-term evidence strategy. Such outcomes would provide a reasoned and evidence-based confidence for assessment of MCED screening benefits in a timely fashion. The planned framework will consider multiple alternatives, including stage shift. Consistent and careful use of this measure will facilitate comparisons to the current NHS trial and other ongoing studies. While not definitive evidence of benefit at this time, evaluation strategies for assessing the utility of the outcome measure will be considered.

The pathway to efficient and effective evidence generation for clinical utility will require coordination and cooperation across many health care entities, and adaptive use of a growing body of evidence

across time. The MCED Consortium is committed to fostering these cooperative relationships and forging this pathway in the hope of alleviating the substantial burden of cancer mortality.

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