Multi-Cancer Early Detection Tests for Cancer Screening

A Call for Consensus on Benefit-Risk Assessment

Network for Excellence in Health Innovation

About This Paper

This paper discusses parameters for assessment of the benefit-risk profile of multi-cancer early detection (MCED) tests that are currently in development and under evaluation in clinical studies. These MCED tests are intended for use as cancer-screening tests among adults deemed to be at elevated risk for cancer.

MCED tests are novel medical devices that present an unprecedented opportunity to change the paradigm for cancer screening. Starting in the Fall of 2020 and into the Spring of 2021, NEHI reached out to several experts in oncology practice, biostatistics, epidemiology, regulatory practice and MCED test development and, through a series of interviews and facilitated discussion panels, sought perspectives on appropriate benefit-risk review of MCED devices. NEHI is deeply grateful to the experts who contributed their insights to this paper. The views expressed in this paper are solely the responsibility of NEHI.

GRAIL, LLC. and Thrive, an Exact Sciences Company, provided support for this project.

About NEHI: Network for Excellence in Health Innovation

NEHI is a national nonprofit, nonpartisan organization composed of stakeholders from across all key sectors of health and health care. Its mission is to advance innovations that improve health, enhance the quality of health care, and achieve greater value for the money spent. NEHI consults with its broad membership, and conducts independent, objective research and convenings, to accelerate these innovations and bring about changes within health care and in public policy.

Acknowledgements

NEHI is grateful to the following panel of experts whose advice and suggestions inform this white paper:

» **Chetan Bettegowda, MD**
Jennison and Novak Families Professor of Neurosurgery
Johns Hopkins Medicine
» **Seema Singh Bhan, KD**
Senior Vice President, Public Policy & External Affairs
Thrive, an Exact Sciences Company
» **Deepshikha Bhandari, MBA**
Vice President, Regulatory Affairs
Grail LLC
» **Adam H. Buchanan, MS, MPH, LCGC**
Director
Geisinger Genomic Medicine Institute
» **Eric Fung, MD, PhD**
Vice President of Clinical Development
Grail LLC
» **Janice Hogan, JD**
Partner
Hogan Lovells LLP
» **Eric Klein, MD**
Chairman, Glickman Urological & Kidney Institute, Taussig Cancer Institute
Cleveland Clinic
» **Paul Limburg, MD**
Chief Medical Officer for Screening
Exact Sciences
Gastroenterologist
Mayo Clinic
» **Azra Raza, MD**
Chan Soon-Shiong Professor of Medicine
Director of the MDS Center
Columbia University

NEHI is solely responsible for the content of this white paper and for the recommendations made herein.

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Executive Summary

The emerging multi-cancer early detection (MCED) tests
Blood samples taken from patients have long been used to detect disease. Due to advances in genomics and artificial intelligence, blood tests can now feasibly detect signals of cancer such as genetic mutations or DNA methylation patterns, that are common in more than one type of cancer. This achievement now makes screening for multiple cancers possible with a single initial blood test and a set of related analytical services.

Blood tests, often described as multi-cancer early detection (MCED) tests, are now in active development that encompass detection of an initial signal (positive or negative) for cancer that is based on analysis of blood-borne "analytes," such as DNA, that may be shed into the blood by a tumor. When an initial signal is positive for cancer, further analysis is conducted to determine the source of the cancer, (i.e., localize the cancer), providing patients and clinicians information that may suggest further testing to diagnose a cancer. This second step may or may not be based on further analysis of the blood-borne analytes, depending on the technology and services offered by the MCED test developer.

MCED tests could prove particularly attractive for uptake among patients who do not present with any apparent signs of cancer but may have a specific identified risk, such as a family history of cancer. Some MCED tests are entering health care systems in the U.S. and abroad under such specialized conditions.

MCED tests and cancer screening
MCED tests under active development for the U.S. health care system are also designed for use in cancer screening. Cancer screening is typically defined as testing for cancer among a much larger group of patients who do not present any signs of cancers, (i.e., "asymptomatic" patients) and who are at average risk. The U.S. Food and Drug Administration (FDA) regulates medical devices for cancer screening on this basis and evaluates screening devices to assure their safe use among patients and for acceptable levels of accuracy, (i.e., the devices' clinical validity).

Adoption of MCED tests for cancer screening could have a profound impact on future health care practice. MCED testing could be deployed at a large scale, since these tests begin with a simple blood sample that can be taken during routine preventive health care interactions. Research conducted to date has also shown that MCED tests can detect signals for more types of cancer than the handful of cancers currently detected through stanrdard of care (SOC) screening recommended for U.S. adults (screening for breast cancer and colorectal cancer with mammography and colonoscopy, for example). Thus, adoption of MCED testing for cancer screening could lead to earlier detection of cancer types that otherwise often go undetected until patients present with symptoms, a point at which many cancers are more difficult to treat than they would be if detected earlier. Cancer types responsible for 50 percent or more of annual diagnoses of cancer are not subject to current SOC screening.[1]

MCED screening deployed at a scale equal to or better than the scale of current SOC screening will likely result in clinicians referring more asymptomatic patients for cancer diagnosis. This trend could result in "stage shifts" in cancer diagnosis and treatment, particularly for cancer types not subject to current screening. At the same time, and as with all cancer screening tests, MCED testing will result in some initial positive test results that prove false upon further

testing or diagnosis. Patients who receive a false positive result from MCED testing may be referred to potentially harmful and unnecessary diagnostic procedures. MCED tests now in development may mitigate this risk of "diagnostic odyssey" in at least three ways. First, the MCED test may be designed to optimize for a low rate of overall false positive findings from detection of blood-borne analytes. Second, the analytical services for localizing cancer (the second step in MCED testing described above) may further mitigate the odds that a false positive result will be reported from the completed MCED test. Finally, developers of the tests now in active development have stipulated that their MCED tests will be intended for a use that complements continued SOC screening. The MCED tests now in development, and likely to be evaluated by the FDA, will not be intended to replace the recommended use of mammography, colonoscopy, lung cancer screening, and other standard cancer screening modalities.

MCEDs create an unprecedented opportunity and an unprecedented challenge

All in all, emerging MCED tests represent both an unprecedented opportunity for improving public health, and an unprecedented challenge for appropriate regulatory review. Current practices in cancer preventive medicine and in medical device regulation are necessarily based on SOC screening that is entirely centered around single-cancer detection. Consensus is needed among practitioners, patients, and the regulatory community to establish an appropriate approach to the evaluation of MCED tests that addresses their unique features and capabilities. A pragmatic approach should begin with a thoughtful categorization of the potential benefits and risks of widespread MCED testing that will allow for comparing benefits and risks across multiple types of cancers.

The core challenge: assessing benefits and risks of new information on a patient's cancer status never available before now

Since MCED results can be generated from a blood sample taken during routine primary care, the physical administration of the MCED test seems likely to be as safe as blood draws taken for standard lab panels administered in primary health care. FDA review of MCEDs will focus more heavily on the benefits and risks of MCED test results from the standpoint of their power to detect cancer, the impact on patient care and patient behavior from MCED test results (true and false findings that are positive or negative), and the impact on public health. The novel questions for FDA review include:

- How to evaluate MCED test results, positive or negative, as they pertain to cancers otherwise subject to current, SOC screening (For example: how MCED results should be interpreted alongside results from conventional screening);
- How to evaluate MCED test results as they pertain to cancers for which there are no current standards for accuracy of detection, (i.e., most cancer types), and
- How to weigh the benefits of cancers successfully detected by MCED screening against potential risks posed by use of the tests among patients who otherwise present with no signs of cancer.

Potential risks are most often defined as risks of unnecessary and potentially harmful diagnostic follow-up

False negative test results from any screening test (for cancer or non-cancerous conditions) are a risk for patients, although a risk that can be mitigated by clinician and patient education and cautious interpretation of test results. The more tangible and often-cited risk from cancer screening is the risk triggered when a patient receives a positive finding from their cancer screening. These patients may be recommended for immediate follow-up with further testing

and diagnostic procedures. An initial, false positive screening result may expose a patient to unnecessary follow-up procedures, including those that pose risks to patient health.

Consensus is needed on the extent to which MCED utilization (blood testing and related modes of analysis) should mitigate patient risks while improving cancer detection

Since cancer screening is intended ordinarily for patients who are asymptomatic, the prevalence of cancer detected by screening is expected to be low. For this reason, a low rate of false positive findings from MCED testing will be especially important, particularly as many types of cancer that are not routinely screened today are also rare or low prevalence cancers. Developers of MCED tests now in development have declared that high test specificity, that is test specificity that yields low rates of false positive findings, should be seen as a core goal for MCED test design and for demonstration in clinical studies. High specificity should serve to avert false positive findings that might otherwise send patients into diagnostic procedures that are unnecessary or could be harmful. However, design-for-specificity may result in lower test sensitivity and false negative findings. Benefit-risk evaluation of MCEDs should factor active mitigation of false negative findings (through stipulations on clinician and patient education and counseling, for example), and the overall contribution of the MCED test to generating greater detection of cancers—a higher positive predictive value (PPV) of screening—into a final overall assessment.

Consensus is needed on the extent that "downstream" risks from diagnostic procedures should be attributed to the initial MCED test

It is important to note that an MCED test does not diagnose cancer. As noted earlier, an initial, positive signal from the MCED tests now in development will trigger analysis to localize the cancer signal. The clinical judgment and experience of the patient's clinicians will influence whether and how the patient is referred into an actual diagnostic pathway. This judgment may include the clinicians' assessment of results from SOC screening that may be pertinent at the time. Notwithstanding all this, NEHI found that expert views differ on how much risk from "downstream" diagnosis should be attributed to MCED testing, and how to weight this attribution against the value of increased cancer detection made possible by the MCED, particularly for detection of cancers for which no SOC screening is currently available in routine medical practice.

Consensus is needed on appropriate weighting of the benefits from screening cancers that are not typically screened today because screening is not cost effective with current methods

While cancer screening (MCED or otherwise) presents risks to patients, many types of cancers are not routinely screened for today because of their low prevalence, and not necessarily because of screening risks. Screening often is not cost effective because the number of asymptomatic patients needed to screen to find patients with cancer is prohibitively high. However, many of these low prevalence cancers are still deadly if allowed to progress and may be amenable to successful treatment if diagnosed at an early stage. As tests based on blood samples that could be administered during standard preventive medicine care, MCEDs may represent a widely accessible way to screen multiple types of cancer that are not otherwise feasible or cost effective to screen through single-cancer screening programs.

Consensus is needed to weight the impact of MCED testing on cancer detection and early diagnosis at the population level

Even at relatively high rates of test specificity (low rates of false positives), MCEDs may have a positive impact on the PPV of cancer screening because detection of common cancer signals

detects an aggregate prevalence of multiple cancer types. This concept of early detection of the aggregate prevalence of cancers was raised in a seminal paper by the late Dr. David Ahlquist of the Mayo Clinic and is a central issue for benefit-risk assessment of MCEDs now in development and those that will follow in coming months[2]. Current clinical thinking, public health practice, and regulatory review is necessarily built on assumptions from review of single-cancer screening. Detection of cancers at an aggregate level could increase overall detection of cancers across multiple cancer types, thus improving the Cancer Detection Rate (CDR) of cancer screening. Changes in CDR are a meaningful metric of cancer care at the population level and should be a meaningful parameter for MCED benefit-risk assessment. The novelty of cancer detection at the aggregate level is a major reason why thoughtful consensus on MCED evaluation needs to be developed in the oncology community and among regulators.

In sum, MCED benefit-risk assessment encompasses greater complexity than assessment of single cancer, SOC screening

The novel nature of MCED screening requires regulatory thinking that considers the multiple testing and diagnostic pathways that patients may face, across multiple types of cancers, all starting with a single test result.

This NEHI white paper recommends that the process begin with a thoughtful categorization of the potential benefits and potential risks that MCED screening may generate for patients. The paper outlines four general categories: clinical benefits, clinical risks, benefits from the potential impact of MCED screening on patient screening behavior and adherence, and potential risks to patient screening and adherence behavior.

The best interest of patients will be served if test developers, the FDA, and the oncology community collaborate to develop standards or guidelines to evaluate the benefit-risk of MCEDs that clearly follow multiple categories of potential benefits and risks. Closer engagement is needed among key players in this emerging field. Collaborators should come together in one or multiple complementary forums to determine a pragmatic assessment framework and how it can be operationalized to assess the many MCED screening tests that will likely emerge in coming years.

Recommendations

The FDA and the oncology community face a complex series of decisions in assessing benefits and risks of MCED screening tests. The agency often looks for advice and counsel from clinical practitioners and from patients in assessing medical device benefit and risk in outreach that is consistent with FDA statute, guidance, and practice. In the case of MCEDs, the advice of both will be especially important inputs given the novel nature of MCED screening. At the same time, the FDA has confronted issues of complex benefit-risk assessment of devices in the past, and this experience may provide guidance for construction of an MCED review structure. To these ends, NEHI recommends several next steps for the FDA and the oncology community.

Acknowledge the need for a unique benefit-risk review structure appropriate for multi-cancer screening

The FDA and the broader oncology community should acknowledge the need for a review structure for MCED benefit-risk assessment that is consistent with, and otherwise conforms to, existing FDA guidance on medical device benefit-risk assessment.

Unlike assessment of single-cancer screening devices, the MCED review structure must consider that an MCED test is a single test that detects signals from multiple cancer types. It is not a composite of multiple individual cancer detection tests, and the review structure must be capable of assessing numerous categories of benefit and risk across many cancer types, including multiple potential pathways of diagnostic follow-up and treatment, all based on the initial MCED signal and on the MCED test's capability for localizing an initial positive signal of cancer.

An MCED-specific review structure should be designed for suitability in assessing MCED tests currently in development and what is expected to be a continuing series of multi-cancer detection tests that will be developed in the future thanks to continuing advances in assay technology, biomarker development, artificial intelligence, and other advanced analytical techniques.

There are multiple ways in which a review structure for MCED screening can be constructed, but in NEHI's view the process must start with an acknowledgement that such a review structure is needed. Once again, the novel nature of MCED screening, its great potential and its undefined risks, are such that active engagement and consensus in the clinical and patient communities will be necessary. Construction of an MCED-specific review structure is an opportunity for creative partnerships among government agencies (FDA, National Institutes of Health, etc.), physician professional societies (both oncology organizations and organizations representing primary care physicians who may administer MCEDs during preventive care), cancer centers, and the patient community.

Leverage prior FDA experience to construct a matrix-style review structure appropriate to MCED screening

The FDA has taken a paradigm-shifting approach to regulation of new oncology therapies through the creation of the FDA Oncology Center of Excellence, as evidenced by acceptance of novel trial designs and clinical endpoints, and in new collaborative approaches to regulatory review enabled by the Breakthrough Therapy designation and other programs designated as Expedited Programs for Serious Conditions[3]. One result has been new approaches to regulatory review that are now leading to the first approvals of tumor-agnostic indications for some cancer therapies, based on the underlying molecular structure of some cancers[4]. In a similar manner, a new review structure for MCED screening devices should build on previous and ongoing policy development at the FDA Center for Devices and Radiological Health (CDRH), specifically policy on assessment of devices that may confer multiple levels or types of patient benefits at differing degrees of risk that may be subject to varying rates of patient risk tolerance.

One example that may be pertinent is the CDRH paradigm of benefit-risk assessment of implantable devices for weight loss. This paradigm is built on a matrix in which multiple potential adverse outcomes from a given device, further categorized by a level of severity, can be compared to different levels of durable weight loss that can be expected from devices. (For more information, please see **Appendix A**).

Build the review structure around several key parameters.

In addition to the four general categories cited above (MCED benefits and risks to patient clinical outcomes, and MCED benefits and risks to patient screening behavior), an MCED review structure should be built around several other key parameters.

- **Risk scoring formula:** A risk scoring formula should be developed and applied to the review structure. The risk scoring formula should weigh the severity and likelihood of risks across multiple diagnostic pathways that apply to cancers detectable by MCED tests, as based on the reported incidence of adverse events resulting from tests administered as part of standard diagnostic follow-up to a positive MCED test in preliminary or early feasibility studies.
- **Adverse events ranked by levels of severity:** For scoring purposes, adverse events associated with guideline-based diagnostic procedures should be grouped according to severity (e.g., all low-risk adverse events regardless of the diagnostic procedure with which they are associated). This will preserve physician autonomy in diagnostic decision-making and will allow for consistent tracking and scoring of adverse events regardless of the diagnostic procedures chosen by the physician for a given cancer signal. (See **Appendix B.**)
- **Differential consideration of MCED performance relative to detection of two groups of cancers: cancers also detected by SOC screening, and cancers not subject to SOC screening:**
    - ***Cancers subject to SOC screening***
      MCED tests are intended to complement guideline-recommended screening. As such, guidance from the oncology community will be helpful in determining how to assess MCED tests, which may be designed around goals of high rates of specificity while generating a PPV.
    - ***Cancers not subject to SOC screening***
      Guidance from the oncology community will also be important in guiding the assessment of the MCED signal as it relates to subsequent confirmation of cancers that are not subject to SOC screening. As noted throughout this paper, most types of cancer that are detectable initially by MCEDs are cancers that are not subject to SOC screening. Because no such capability has existed before, there are no well-accepted standards of test accuracy to guide evaluation of the common cancer signal returned by MCEDs, much less well-accepted standards for detection of the many cancers not subject to routine screening. For example: early detection of low prevalence cancers through single-cancer screening has been inhibited by relatively high Numbers-Needed-to-Screen, as noted above. Successful innovation to overcome this barrier has frequently been thwarted by poor specificity (i.e., high rates of false positive findings). MCED screening may create the opportunity to address both issues by generating improved detection of aggregate prevalence at a relatively high level of specificity. Because MCED tests are designed around a single cutoff point for detection of analytes that indicate an underlying cancer, the sensitivity of detection will vary depending on the type and stage of the underlying cancer. Detection of cancers at relatively low rates of sensitivity may still create a benefit that outweighs the low detection rate. Standards are needed to create a rational basis for determining an acceptable level of detection of underlying cancers as compared to detection at the aggregate level.

- **Patient preference:** Benefit and risk scoring should reflect patient preferences established in robust studies. Since novel cancer diagnostics and therapeutics are now being introduced at a rapid rate, scoring should also reflect changing patient options for diagnosis and treatment of cancers. Finally, patient preference data must include information on the preferences of adult asymptomatic patients—the patients most likely to be offered MCED testing if MCED testing is ultimately approved as a common or guideline-recommended screening intervention.
- **Benefits weighed against the risk score:** The risk score of the device will determine the magnitude of benefit that must be demonstrated by an MCED test to show a net benefit for regulatory benefit-risk assessment in pivotal trials. Benefits should be assessed across the multiple dimensions described in greater detail in this paper, including the impact of MCED screening on overall detection of cancers, the impact of earlier patient access to cancer diagnosis, and the impact on patient screening behaviors (such as improvements in adherence to screening).

Introduction

Blood tests are now in clinical trials that are designed to screen patients for multiple types of cancer with one test. This first generation of MCED tests is meant to complement single-cancer screening tests (such as mammography and colonoscopy) that are subject to clinical practice guidelines as preventive health measures for adults. (Guideline recommendations from the U.S. Preventive Services Task Force, for example). Like single-cancer screening tests, the multi-cancer tests now in development are intended for screening patients who otherwise present no signs of cancer (i.e., asymptomatic patients.) MCED tests will vary in design, detection capabilities, and the extent to which they incorporate a range of analytical services beyond initial analysis of a patient's blood sample. Current MCED tests entail one or two steps in analysis. In the first step, the MCED tests identifies molecules in the bloodstream that are indicative of cancer. This identification is made by Next Generation Sequencing (NGS) of circulating tumor DNA cells and detection of other molecules associated with cancer. If cancer is indicated, further testing (such as CT scanning or other imaging tests) may be required. Artificial Intelligence techniques, such as machine learning, may also be employed to identify the source and type of cancer detected in the patient's blood. If this second step also indicates that cancer is present, the patient's clinician may order appropriate diagnostic procedures. The type of cancer suggested by MCED findings will influence the odds that a patient will be subject to diagnostic procedures that may range from relatively unintrusive (such as imaging tests) to intrusive (such as tissue biopsies).

The MCED devices currently in clinical trials are novel medical devices. Two tests have been designated as Breakthrough Devices by the FDA, a designation that allows for expedited review of the devices because of their potential to address a serious unmet need among patients with a life-threatening condition. In the absence of a specific, fit-for-purpose regulatory framework for evaluation of multi-cancer tests, the FDA's review practice is to evaluate these novel devices using the same regulatory principles that apply to single-cancer detection tests. FDA approval of a medical device, including screening devices, depends in part upon a determination that the device will provide benefits to patients and to the public health that outweigh risks, as demonstrated in clinical trials and other competent and reliable scientific evidence. The existing framework of benefit-risk assessment of medical devices may not be suitably comprehensive for the assessment of MCEDs, given the novel nature of these devices and the potential changes in clinical practice and patient behavior that they may trigger.

A method for reviewing MCED benefits and risks, or what we refer to here as a review structure, should be based on a categorization of the multiple benefits and risks that MCED use may pose for patients. The goal of this NEHI white paper is to suggest a categorization of potential benefits and risks, and a general approach to benefit-risk assessment that will address the unique opportunities for patient health represented by MCED tests, while also addressing the unique challenges MCED tests present to evaluation and regulation.

I. Potential Benefits of MCED Tests Designed for Screening

Potential benefits of MCED screening can be defined in two categories: 1) clinical benefits to patients that occur from improved diagnosis and treatment of cancers, and 2) improvements in patient adherence to recommended cancer screening tests that might be stimulated by the availability of a blood test to detect signals from multiple types of cancer.

Clinical Benefits

Earlier detection of cancers not subject to SOC screening
Presently, standard of care (SOC) screening of U.S. adults is restricted to a handful of cancer types. Only five cancers (including lung and prostate cancer) are subject to widespread screening, of which only three (breast, cervical, and colorectal cancer) receive the highest recommendations (Grades A and B) of the U.S. Preventive Services Task Force for screening of adults, and thus are covered by health insurance as an essential health benefit[5]. Consequently, the proportion of all cancer cases initially detected by screening has been estimated at levels as low as 16 percent, due primarily to the lack of routine screening of most types of cancer[6].

Thus, a major potential benefit of MCED screening is detection of cancers that are not routinely subject to screening. Cancers detectable by a given MCED are expected to vary from one MCED product to another. However, as a class, MCED screens will generate signals of cancers for which the current screening detection rate is zero percent. Detection of cancer at the earliest possible stage of progression is potentially the most effective way to improve cancer outcomes, particularly among more aggressive cancers and cancers for which meaningful treatments are available. Most solid tumors in localized stages have well-established treatment strategies that are potentially curable. Detection of hematological malignancies in their early stages, even if pre-symptomatic, can also generate information for treatment or monitoring that holds important clinical value. Since the current sensitivity for early detection of non-screened cancers is 0 percent, any ability to detect these cancers is an important benefit, provided the tests do not generate an unacceptable rate of false positive results.

To the extent that an initial positive MCED signal leads to a confirmed cancer diagnosis at a stage earlier than the stage at which the cancer is typically diagnosed, the MCED test may contribute toward reducing the interval between cancer onset and eventual treatment, leading to the following improvements:

- Increased access to potentially curative treatment, and
- Improvement in measured outcomes of treatment, such as progression-free survival (PFS) and cancer survivorship.

Synergy with routine cancer screening
Developers of MCED tests currently in clinical trials have declared that the intended use of their MCED tests is to complement existing single-cancer screening tests, such as the cancer screenings that are recommended as SOC prevention measures by the U.S. Preventive Services Task Force.

MCED tests approved for use with this stipulation could prove synergistic with SOC screening and generate clinical benefits in the following ways:

- An additional source of information on findings generated by SOC screening, providing further indication that a cancer is not present, or further indication that a cancer may be present and that the patient may need diagnostic follow-up.
- Increased initial detection of interval cancers (i.e., cancers that progress in between cancer screening that occurs at guideline-based intervals)—an improvement in so-called "schedule sensitivity." For example, increased initial detection of interval cancers might occur if the MCED test is administered as part of blood lab work taken during a patient's annual physical or wellness visit with a primary care physician at a time different from the scheduled guideline recommended screening event. Interval breast cancers, for example, are not infrequent occurrences. They affect 12-17 percent of women receiving screening mammograms and tend to be more aggressive than screen-detected breast cancers, resulting in higher mortality risk[7,8]. MCED tests could help detect interval breast cancers that could lead to earlier diagnosis of breast cancers, and ultimately a shift in the stages at which breast cancers are diagnosed for treatment (a stage shift).

Benefits to Patient Screening Behavior and Adherence

Once again, MCED tests now in development are envisioned as tests that will complement, but not replace, guideline-recommended, single-cancer screening. Patients may react in different ways to the availability of MCEDs that will affect their adherence to single-cancer screening. For example, the relative convenience of MCEDs could make some patients less motivated to maintain adherence to single-cancer screening, a risk described in greater detail below. On the other hand, since MCED results could be delivered to patients by clinicians as part of routine wellness visits, they create more opportunity for clinicians to counsel patients on the necessity of adherence to other, recommended screening modalities. (Studies have suggested that adherence to SOC screening is positively associated with a periodic health examination, such as a routine physical scheduled with a primary care physician[9]. Clinician and patient education on appropriate use of MCEDs is also described in greater detail below.)

The benefits of improved compliance with SOC screening potentially induced by MCED screening could be categorized as follows:

- Improvements in cancer detection rates at the population level, and
- Improvements in cancer-related health disparities.

Improvements in the cancer detection rate (CDR) at the population level
MCED testing can improve CDR in two ways. First, MCED testing indicating the presence of cancer will trigger follow-up confirmatory testing and diagnosis. This will lead to a greater proportion of cancers detected that might not otherwise have been detected, or detected at later stages when prognosis is worse.

Second, a positive MCED impact on patient screening adherence rates could help address a continuing public health need by providing opportunities to counsel individuals on the need to adhere to guideline recommended screening protocols. While some rates of SOC screening have improved over the last 20 years, adherence rates are still well below national health goals. For example, the U.S. Department of Health and Human Services Healthy People 2020 goal for colorectal cancer screening was 70.5 percent, but as of 2015 adherence was approximately 60 percent of adults[10]. The breast cancer screening goal was 81.1 percent of eligible women, but only 64 percent of women reported having a mammogram within the prior 2 years[11].

Potential improvements in cancer-related disparities

Eliminating racial-ethnic health disparities has become an increasingly important goal of federal policy, and a goal that the FDA appears committed to achieving. Persistent racial and ethnic disparities in SOC cancer screening are a major reason why rates of patient adherence to cancer screening fall short of national goals. Screening data from 2019 indicates that while 42.1 percent of all eligible women completed three types of recommended SOC cancer screening (breast, cervical, and colorectal), eligible Black, Hispanic, and Asian American women were screened at lower rates: 40.9 percent, 34.0 percent, and 40.9 percent, respectively. Only 28.9 percent of all eligible men received two forms of recommended, SOC cancer screening, (colorectal and prostate), and eligible Black, Hispanic, and Asian American men were screened at even lower rates (27.2 percent, 18.6 percent, and 13.1 percent, respectively[12]).

Since MCED tests begin with blood draws that could be delivered in routine primary care, the convenience of MCED screening (as compared to single-cancer, SOC screening) could act to reduce disparities in cancer screening. This is particularly true for cancers otherwise subject to SOC screening among historically underserved patients. At the same time, some patients could choose to forgo SOC screening in the belief that MCED screening will suffice. This underscores the importance of counseling historically underserved patients, such as Black and Hispanic Americans, and the clinicians who serve them on the necessity of maintaining recommended SOC screening in addition to MCED screening.

Racial-ethnic disparities are equally persistent in the diagnosis and treatment of cancers that are not routinely screened. Unscreened cancers are frequently diagnosed among Black, Hispanic, Asian American, and American Indian patients at later stages of progression compared to diagnosis of the same cancers among white patients[13]. For example, distant pancreatic cancer (i.e., which has grown beyond the pancreas itself) is diagnosed at a rate of 8 per 100,000 Black persons, compared to 6.5 per 100,000 white persons. Here again, the relative convenience of MCED testing may contribute to improved cancer detection and a reduction of disparities in cancer care for non-white patients.

II. Potential Risks of MCED Tests Designed for Screening

Potential risks of MCED screening can also be defined in two categories: 1) clinical risks such as unnecessary or harmful diagnostic procedures that are triggered by a positive MCED test, and 2) risks to compliance with recommended cancer screening modalities.

Clinical Risks

Unnecessary and potentially harmful follow-up
False positive test results from MCEDs may trigger a cascade of follow-up diagnostic procedures that impose risks on patients. MCED test developers propose several strategies for mitigating these risks that include designing the MCED test for high specificity (thus minimizing false positive results), and through stipulations on intended use. (These are described in greater detail in Section III, below). The novel nature of MCED testing also raises the question of how much, if any, of the "downstream" risks of follow-up diagnostic procedures can be reasonably attributed to the initial MCED test (this is also discussed in greater detail below). False positive results are common among patients who adhere to recommended, single-cancer screening tests over time, thus underscoring the importance of high specificity in cancer screenings intended for large populations of patients. A study that utilized data from cancer screenings conducted between 2006 and 2015 suggested that over a ten-year period more than 50 percent of women could expect a false positive finding from annual mammography tests, while 10-12 percent of men could expect a false positive prostate-specific antigen (PSA) result indicating prostate cancer[14]. In general, risks created by an initial false positive of a screening test signal include:

- The physical and psychological burdens on patients imposed by follow-up procedures, including risks of invasive procedures that may be necessary to reach a definitive diagnosis. This includes risks of biopsies (needle biopsies, surgical biopsies, etc.)
- Economic impacts on patients and the health care system from unnecessary follow-up procedures triggered by an initial positive signal.

Overdiagnosis of cancers
MCED findings may lead to accurate diagnoses of cancers that are otherwise not considered dangerous to patients or are not considered to be "actionable" for clinical intervention. These include cancers that are deemed to be indolent cancers, such as those that are slowly growing and unlikely to require treatment, or unlikely to become a risk to a patient in their lifetime.

MCED tests currently in clinical trials for FDA approval rely on detection of blood-borne molecules of circulating tumor DNA (ctDNA) and other molecular analytes. Evidence available to date suggests that ctDNA assays are less likely to detect slow growing, encapsulated cancers, and are relatively more likely to detect cancers that are actively shedding molecular analytes into the bloodstream[15].

Cancers not detected by MCEDs
While MCED uptake may create risks triggered by false positive results, risks are created by initial false negative signals as well. These risks may be exacerbated if MCED tests are deliberately designed for high specificity (low rates of false positives), as current MCED test developers intend. Risks imposed by highly specific MCEDs can be mitigated to the extent that patients maintain compliance with existing SOC cancer screening, which is also part of the intended use that current test developers have proposed.

Risks to Patient Screening Behavior and Adherence

As noted above, the convenience of multi-cancer detection through use of a single blood test may influence patient compliance with existing, SOC cancer screening in ways that create both benefits and risks. Potential risks can be categorized as:

Patient overconfidence
MCED test results may lead to poor screening behavior among some patients. This overconfidence can result when patients receive a negative (no evidence of cancer) MCED test result. Consequently, patients may assume that compliance with recommended SOC cancer screening is unnecessary and skip recommended screenings on a guideline-based schedule. They may also become less likely to report worrisome symptoms to clinicians because they received a negative result from a prior MCED test.

As noted above, a key question in research on MCED use is the impact MCED tests will have on patient adherence to recommended SOC cancer screening. Patient access to MCED tests could positively reinforce the importance of SOC screening among some patients, but discourage compliance with SOC screening among others.

Increased volume of unnecessary diagnostic follow-up in the health care system
The greater convenience of MCED testing, and resulting uptake, may increase the volume of confirmatory testing and diagnostic procedures, resulting in an increased number of patients exposed to the risks of follow-up diagnostic pathways (e.g., risks from unnecessary biopsies).

III. Factors in Assessment of MCED Benefits and Risks

The existing FDA benefit-risk assessment framework for medical devices is relatively straightforward in concept, if often complex in practice. The framework seeks to assess 1) whether a new device confers additional patient benefits, as measured by changes in patient outcomes compared to a baseline standard set by existing devices, and 2) whether the benefits outweigh any increase in risks to patients, as compared to risks measured as changes over a baseline from existing devices and additional risks that can be attributed to use of the new device. The emerging MCED devices are novel, and there are no comparable, next generation sequencing devices to which the MCED tests can be compared precisely.

Discussions and interviews conducted by NEHI suggest that several factors should be incorporated into an MCED review structure to shape how potential benefits and risks are weighted. At least two factors (described below) are overarching. Other factors are pertinent to assessment of benefits and risks. All these factors should be considered for inclusion in an MCED-specific review structure that is consistent with the FDA's framework for benefit-risk assessment of medical devices.

Overarching Factors

There are two overarching factors for assessment of both MCED benefits and risks: design of MCED tests for high specificity, and the intended use of an MCED.

Design of the MCED for high specificity and PPV

A key factor in interpreting both benefits and risks of MCEDs is specificity of the initial MCED test signal. MCED developers have declared that their tests are designed for relatively high specificity to minimize rates of false positive signals, and yield an increase in PPV of cancer screening. The MCED tests in development are designed around a single cutoff point for the detection of molecular analytes and return one finding as to whether an underlying cancer signal is likely or unlikely. Localization of the cancer and its tissue of origin then depends upon the second step in MCED screening. MCED tests now in development subject the initial cancer signal to further confirmatory analysis through different means, such as through imaging (PET-CT scanning, for example), or through advanced computational analysis of predicative molecular signals such as tumor DNA methylation patterns.

Intended Use of the MCED

Stipulations on the intended use of MCED tests for purposes of cancer screening should act to mitigate both benefits and risks of MCED use. Since the MCED tests now in development are novel devices, there are no binding, "on label" stipulations for MCED intended use that serve as a benchmark at present. However, several stipulations of intended use seem most likely to be applied to the first set of MCED tests that gain FDA approval, as detailed below.

- **Intended use with adult patients who are asymptomatic**
  Clinicians and patients may opt to utilize MCED tests when patients have an identified risk for cancer, such as a family history of cancer, a history of smoking or exposure to environmental risks of cancers, and the like. However, for purposes of FDA approval as screening tests, the FDA-approved intended use of MCEDs may likely be for adults who reach age thresholds that are consistent with the age thresholds for existing, standard-of-care cancer screening tests.
- **Intended use as tests complementary to standard cancer screening**
  MCED test developers have declared that MCED tests in development today will be intended for use as screening that is additive or complementary to existing, guideline-recommended cancer screening modalities such as mammography and colonoscopy. While some patients may consider MCEDs as a replacement for SOC screening (a risk identified above), the FDA-labeled intended use would likely stipulate that MCEDs are not a replacement for SOC screening. Additional measures, such as an effective program of clinician and patient education, might be required for administration in conjunction with the MCED to ensure continued patient compliance with SOC screening.
- **Intended use requiring follow-up testing to work-up the initial signal**
  MCED test developers also suggest that, as products intended for use alongside SOC cancer screening, FDA-stipulated labeling on MCED tests will clarify that the tests should be followed by further confirmatory testing when the initial MCED test signal indicates that an underlying cancer may be present. A cancer signal indicated by an MCED screening is not a cancer diagnosis. When MCED screening indicates that cancer is present, the test must be followed by a confirmatory, clinically established diagnostic test, such as a blood test, imaging test, or certain endoscopic procedure. Cancer-related invasive procedures, including surgery or biopsy, are not expected to be performed as a first step based on a positive MCED result. Biopsies, surgeries, or other invasive procedures are expected only after direct visualization, palpation, or through imaging of a suspicious lesion. The expected number of patients who go on to experience an invasive procedure without leading to a cancer diagnosis should be low compared to patients referred for diagnosis and invasive procedures after positive results from single-cancer screening. This is due to the high level of test specificity (as designed for and demonstrated by test developers), and appropriate follow-up to a positive MCED test result.

Factors in Assessing MCED Benefits

Several factors will be key to assessment of MCED benefits, including the following identified by NEHI.

MCED impact on adherence to single-cancer screening and subsequent detection of cancers now subject to routine, preventive screening
MCED tests will detect cancer signals from cancers that are also targets of SOC screening, such as screening for breast cancer (mammography), colorectal cancer (colonoscopy), and lung cancer (low dose computed tomography). MCED tests now in development are intended to complement SOC screening. In effect, they will add an extra "belt and suspenders" to SOC screening. Like the MCED tests now in development, SOC screening modalities also generally call for an immediate sequence of follow-up testing (i.e., reflex testing) when an initial positive test result is found. Clinical evidence will be necessary to establish the impact of MCED screening on detection of cancers subject to routine, single-cancer screening; for example, the impact on patient adherence to SOC screening, and the impact that an additional form of cancer detection (detection by MCED) has on the overall PPV of screening and cancer detection rates.

Standards of accuracy pertinent to cancers not routinely screened
Since asymptomatic patients are not routinely screened for most cancers, there are no consensus-backed or guideline-based reference standards of accuracy for detection of these cancers. Data from some clinical studies, such as the Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial, and others may provide some context for considering standards of accuracy for MCED testing. Care must be taken to interpret these given the fact that these performance characteristics reflect a single-cancer screening modality.

As noted earlier, MCED tests developed for screening employ a single cutoff point for detection of molecular analytes associated with multiple, different cancer types, and thus generate a common cancer signal. Confirmation of the cancer signal is established by further analysis and is not based on the common cancer signal. The first step is analysis to localize the common cancer signal and identify the type of cancer that may be present. MCED tests now in development employ differing techniques for localization of cancer signals, and tests designed in the years ahead will likely use competing, alternative techniques as well. The accuracy of the final result will necessarily be a product of the accuracy of all the testing completed for the patient. The challenge for MCED review will be deriving one overall or aggregate value to patients and public health from this mix of methods.

Ideally, the assessment process should also take into account "downstream" changes or innovations in diagnostic testing for cancers that are detectable by an MCED test.
These factors may include:

- The likelihood of progression of the MCED-detectable cancers
- Developments in cancer diagnostics that may render "upstream" detection by the MCED more reliable and reduce the time-to-diagnosis for patients with cancer
- The value of intensive patient monitoring and "watchful waiting" that would not be initiated "but for" early detection from an MCED test.

Patient preference and risk tolerance

FDA guidance on benefit-risk assessment of medical devices seeks to actively incorporate patient preference information (PPI) and a consideration of patient risk tolerance[16]. The FDA Center for Devices and Radiological Health has played a leading role in the regulatory community in exploring new methods and procedures for developing PPI suitable for regulatory decision-making. The advent of multi-cancer early detection could be a major impetus for accelerating progress in this still-developing field. Two key factors include:

- **Preferences of asymptomatic patients**
  MCED tests intended for cancer screening will be administered to asymptomatic patients. Benefit-risk assessment of MCEDs requires an empirically sound assessment of the value that asymptomatic patients place on the detection of cancers that are not now subject to routine screening (in contrast to cancers such as breast cancer or colorectal cancer) in exchange for the potential risks of confirming the presence of cancer through further testing and diagnostic procedures.
- **Preferences expressed by cancer patient communities**
  One of the more challenging aspects of MCED benefit-risk assessment is a decision on whether or how to weigh the preferences of communities representing patients with diagnosed cancers or patients with known and elevated risks for cancers. Patients with active cancer diagnoses are not the intended subjects of MCEDs. Patients with confirmed cancers can be expert advocates with direct experience of the patient diagnostic journey, including first-hand knowledge of the impact of cancer screening, diagnosis and treatment on patient and family life.

Public health benefits

The FDA framework for benefit-risk assessment of medical devices includes consideration of a device's impact on public health. (Widespread MCED use could create some public health risks as well; these are categorized under "Factors in Assessing MCED Risks.")

If the benefit-risk issues identified here are resolved satisfactorily, the most significant impact on public health expected of MCED screening may well be earlier detection at population scale of multiple cancers that are not routinely screened for at present. MCED screening at population scale could lead to a positive change in overall detection of cancers in the U.S. population or among other defined patient populations, improving CDRs.

Several other influences could further define the impact on public health of both MCED benefits and risks, including:

- **Intended use population**
  The patient population targeted for MCED screening will be defined by the test's intended use. As noted above, an FDA-approvable intended use seems likely to be for adults who are asymptomatic, at age thresholds consistent with current, standard-of-care screening recommendations.
- **Patient access to and uptake of MCED screening**
  Factors that will determine patient access and uptake at the population level include:
  - Patient and clinician education, including demonstration of effective methods of education on appropriate use of the MCED, interpretation of MCED results, and the rates of adoption of effective education measures.
  - Clinician adoption: Rates of clinician adoption and prescription of MCED screening as part of overall cancer screening protocols.

Factors in Assessing MCED Risks

As noted earlier, patients will likely face minimal physical risks from administration of the MCED test because the test is initiated with a routine blood sample drawn by a phlebotomist or other medical professional. The primary risks to patients from MCED testing are the physical and psychological risks that may arise in administration of follow-up procedures that may be triggered by an initial, positive MCED signal.

The initial MCED signal vs. localization of cancer
Experts consulted by NEHI generally agreed that a distinction should be made between the initial MCED test signal (molecular signals common to multiple types of cancer) and the "second step" analysis or testing that localizes an underlying cancer. MCED products currently under review by the FDA incorporate different and proprietary approaches to confirming an initial positive MCED signal and confirmatory testing. The accuracy of the initial MCED signal and of confirmatory analysis or testing should be assessed separately.

Attributing the risks of follow-up procedures
In principle, the clinical consequences of a screening test are a key consideration in FDA assessment of the test's benefits and risks; it is not enough to review the accuracy of the test alone. In this review paradigm, "downstream" patient risks would not occur "but for" an initial signal from a screening or diagnostic device, and the test bears some responsibility for triggering the risks. At the same time, relatively high levels of inaccuracy in SOC screening tests (such as breast cancer and prostate cancer screening) have been associated with unnecessary patient risks and harms. However, this has not stopped greater adoption of SOC screening in the daily practice of medicine or FDA approval of follow-on devices for SOC screening.

Consensus around a principle of attribution for multi-cancer early detection is a central issue in creating a usable review structure for benefit-risk assessment of MCEDs. Experts consulted by NEHI differ on the extent to which the "downstream" consequences of multi-cancer screening can be reasonably attributed back "upstream" to an initial MCED test signal.

Nevertheless, in principle FDA review considers downstream procedures in assessing the overall risk profile of a cancer screening test. NEHI finds that experts have a range of viewpoints on attribution of downstream risk to cancer screening conducted "upstream." We summarize expert perspectives into three simplified viewpoints as follows:

Viewpoint I. Full attribution of risks from diagnostic follow-up to the MCED
In this view, most or all risks of diagnostic follow-up are attributed to the initial MCED screen. For example, when a false positive MCED signal results in unnecessary and potentially harmful diagnostic follow-up, risks and harms are attributed to the initial MCED test. "But for" the initial MCED test, the cascade of procedures would not have occurred. In this viewpoint, any event that occurs as a result of a positive MCED signal, even if several steps removed from the MCED test (such as a biopsy ordered after a patient underwent diagnostic imaging which was itself triggered by a positive MCED test), would still be attributed to the original MCED test result no matter how many intermediate steps occurred.

Viewpoint II. Attribution of risk to confirmatory testing, not to the MCED
In this view, only the risks from testing performed as an immediate follow-up to a positive MCED signal may be attributed to the MCED test. For example, if a positive MCED signal necessitates the need for follow-up imaging, only the risks of imaging would be attributed back to the MCED test. Some experts point out this approach is consistent with clinical practice, in which clinicians generally order imaging or other, non-invasive testing (when appropriate) before concluding that an invasive procedure, such as a surgical biopsy, is necessary. At that point, the risks of the invasive procedures are attributable to the intermediate step, such as the imaging protocol or other non-invasive testing.

Viewpoint III. Attribution of risks to the diagnostic pathway, not to the MCED
A third viewpoint is that a positive MCED test serves to put a patient in line for guideline-based follow-up, but subsequent risks of follow-up are inherent in pathways of guideline-based diagnosis. Here once again, MCED test developers point out that first generation MCED tests are designed for high specificity and low rates of false positive findings, and those non-invasive confirmatory steps (such as imaging or localization through further data analysis) will be triggered when a patient's MCED test is positive. From that point onward, the risks of patient harm are the risks of guideline-based diagnosis.

In Viewpoint I, all downstream risks are attributed to the initial MCED test. A consistent approach to attributing benefits and risks thus might also attribute all downstream patient benefits to the initial MCED test as well. In contrast, in Viewpoint II and Viewpoint III, downstream risks are attributed to either confirmatory testing (the "next step" after an MCED result) or to the diagnostic pathway that might follow a positive MCED test result. A consistent approach might require that the patient benefits of downstream testing and diagnostic procedures be attributed to the downstream procedures – not the MCED – in a similar and consistent manner, even though the MCED triggered detection of a cancer that would otherwise have gone unscreened and undetected. This is another aspect of benefit-risk assessment of multi-cancer early detection that should be resolved by consensus development. This would enable clear guidance on the attribution of downstream benefits and risks that can be incorporated into the review structure of multi-cancer early detection devices.

Factors in assessing MCED risks to public health
Our paper notes the potential benefits to public health from MCED screening above, including the potential, significant benefit that MCED screening may have on improving the cancer detection rate in patient populations if MCED tests are approved and adopted at scale. Potential offsetting risks include those identified previously, namely the potential increased volume of unnecessary diagnostic follow-up to patients receiving a false positive signal from an MCED screen. These risks may result in:

- An increased number of patients exposed to the risks of follow-up diagnostic pathways (e.g., risks from unnecessary biopsies)
- Unnecessary shifts in health care resources (reimbursements, clinical time, and attention) devoted to diagnostic follow-up, including resources diverted from higher value services
- Wider health care and health outcome disparities due to disparities in access to MCED testing
- Wider health care and health outcome disparities due to disparities in access to follow-up diagnosis

IV. Evidence Generation

As detailed above, the novel nature of MCED tests designed for cancer screening requires a new approach to benefit-risk assessment. This approach will require greater consensus on appropriate standards, including for the initial signal returned by the MCED blood assay and for the sensitivity and specificity of detection of underlying cancers after confirmatory analysis or testing of a positive MCED signal indicates the presence of cancer.

Demonstrating MCED performance, relative to new standards of review, presents its own set of challenges. Supportive evidence must link data from the initial MCED test results to data on follow-up testing of positive MCED tests, which would include data on the localization of a suspected cancer. Initial MCED test results should also be linked to data on further diagnosis, treatment, and patient outcomes to provide additional support for benefit and potential clinical utility.

A second major challenge is found in incorporating these endpoints within appropriate strategies for clinical trials, observational cohort studies and real-world evidence generation. Experts generally agree that longitudinal interventional trials are the best way to generate accurate, robust data on the performance, benefits, and risks associated with MCED tests. However, generating statistically robust evidence prospectively on the detection of most types of cancer, especially relatively low-incidence cancers, among what is likely to be the intended use population (asymptomatic patients) will require extensive patient enrollment with monitoring over an extended period. As noted above, relatively high estimates of the Number-Needed-to-Screen for low-incidence cancers is a major reason why only a handful of cancers are routinely screened.

A key decision for FDA review is a decision on the evidence it will require for evaluation before a product is approved, and evidence it will require for review in the months or years after a product is approved. MCED tests must meet safety and effectiveness requirements and provide a net benefit to patients. However, the FDA is also mandated to make approval decisions that support timely patient access to novel devices that meet a serious unmet medical need. MCED tests currently under FDA review have Breakthrough Device designations that facilitate FDA review of such products.

Recommendations of specific MCED strategies for clinical trial design and evidence generation are beyond the scope of this NEHI review. However, consultation with experts did underscore that innovative evidence strategies are likely to be needed for MCED review. Innovative approaches may combine several strategies, such as:

- Prospective interventional studies
- Comparison of MCED results among elevated-risk patients with results from testing of patients with identified risks, such as a history of smoking
- Predictive analysis of MCED results conducted in modeling of appropriately validated retrospective cancer screening
- Diagnosis and treatment data, and fit-for-purpose analysis of MCED results as assessed in real-world data
- Observational cohort studies

V. Recommendations

The novel nature of MCED tests, the opportunity for an unprecedented paradigm shift in cancer screening, and the complexities of evaluating MCED devices consistent with FDA guidance all call for development of a creative approach that leverages the existing regulatory framework but encompasses MCED-specific elements of benefit-risk assessment.

Based on discussions and interviews organized by NEHI, this paper recommends that the FDA undertake a consensus-based process to use the existing regulatory review framework as a foundation and enhance it with MCED-specific elements to define a "review structure" suitable for benefit-risk assessment of MCEDs. This review structure should enable a weighting of benefits and risks from outcomes of screening (such as follow-up diagnosis) triggered by the initial MCED signal, and be a single, overall assessment that is consistent with the FDA's framework of benefit-risk assessment of medical devices.

A high priority will be consensus on a practical standard of accuracy for MCED screening. As noted above, MCED screening will return an initial signal indicating whether cancer is or is not present; current test developers set a cut point for detection of this signal that is chosen for high specificity (low rates of false positives) to minimize unneeded and potentially harmful follow-up. Concomitant rates of sensitivity should result in a net positive addition to the rate of detection of all cancers – an aggregate CDR – resulting from use of the MCED test and should set an initial level of PPV for MCED screening.

Meanwhile, demonstrating the impact of MCED screening on detection and diagnosis of many specific cancers will require both extended periods of time and use with very large groups of patients. Many cancers that appear to be detectable by MCEDs are relatively low-incidence cancers that are typically detected at a point when they are symptomatic, or a clinical suspicion is aroused (i.e., at a late stage). Conventional, pre-approval clinical trials, sufficiently well-powered to demonstrate the sensitivity of MCED test results, would require exceptionally large patient enrollment among actively consenting patients (i.e., a high Number-Needed-To Screen). Tests would be administered under conditions that are not identical to real-world practice and require extensive patient monitoring over extended periods of time to verify patient outcomes. This raises a special challenge for the FDA, which is charged with reviewing medical devices for safety and effectiveness but is also authorized to expedite review of devices for the purpose of creating timely access to innovations for cancer patients, a goal that the FDA actively applies to review of cancer therapeutics as well. (As also noted above, the two leading products now in development for eventual FDA review were granted Breakthrough Device status by the agency).

An alternative approach would be to reach a consensus on attributing the level of "downstream" risks to patients (such as risks of intrusive and potentially harmful diagnostic follow-up), based on some composite measure of risks posed by follow-up. These risks would be quantified by current data on patient outcomes from diagnostic follow-up on those suspected to have cancer. Assessment should also give weight to patient preferences, particularly those most likely to be screened, and their assessment of the tradeoffs between gaining early detection of cancers (including cancers currently not routinely screened) and the likelihood of unnecessary and potentially harmful follow-up.

We did not discover perfectly germane models for MCED benefit-risk assessment, but some precedents can provide inspiration. FDA review of devices implanted for weight loss surgery entails consideration of the varying degrees of durable weight loss at varying degrees of risk. Individual patients may differ (and likely do differ) in evaluating the trade-offs between potential benefits and potential risks. A similar approach could be applied to an MCED review structure, albeit at a much higher level of complexity since MCEDs may detect one of many cancers. MCEDs have varying degrees of accuracy, exposing patients with a positive initial test signal to multiple pathways of diagnostic follow-up to confirm cancers, with patient risk tolerance varying depending on the likelihood of confirming specific cancers.

We recommend three actions for the FDA's consideration in concert with the oncology community.

1. **Acknowledge the need for a unique benefit-risk review approach for multi-cancer screening**
   The FDA and the broader oncology community should acknowledge the need for a review structure tailored to the unique complexities of MCED benefit-risk assessment, while still consistent with existing FDA guidance on medical device benefit-risk assessment. Unlike assessment of single-cancer screening devices, the MCED review structure must consider that an MCED test is a single test that detects signals common to multiple cancer types. It is not a composite of multiple individual cancer detection tests. It must be capable of assessing benefit and risk to patients with one of many types of cancers, as confirmed or localized through varying techniques and diagnosed, if warranted, through several potential pathways of diagnostic follow-up.

   An MCED-specific review structure should be designed for adaptability to what may prove to be rapid evolution in the field of multi-cancer early detection. This is especially true considering the continuing advances in assay technology, biomarker development, artificial intelligence, and other advanced analytical techniques. Creation of the MCED-specific review structure should also be viewed as consistent with the trend toward precision oncology and informed by the FDA experience with evaluation of molecular diagnostics.

   Active engagement and consensus in the clinical and patient communities will be necessary. Construction of an MCED-specific review is an opportunity for creative partnerships among government agencies (FDA, NIH), physician professional societies (both oncology organizations and those representing primary care physicians who may administer MCEDs during preventive care), cancer centers, the patient community, and test developers.

2. **Leverage prior FDA experience to construct a matrix-style review structure appropriate for MCED screening**
   A new review structure for MCED screening devices should build on policy development at the FDA Center for Devices and Radiological Health (CDRH) that enables assessment of devices that may confer multiple levels or types of patient benefits at differing degrees of risk, and subject to varying rates of patient risk tolerance.

   One example that may be pertinent is the CDRH paradigm of benefit-risk assessment of implantable weight loss devices, which is built on a matrix in which multiple potential adverse outcomes from a given device, further categorized by level of severity, can be compared to different levels of expected durable weight loss. (For more information, please see **Appendix A.**)

3. **Review structure considerations**
The review structure should meet the requirements of existing FDA benefit-risk assessment of medical devices. Key parameters of the review structure include the following:

- **Risk scoring formula**
A risk scoring formula should be developed and applied to the review structure. The risk scoring formula should weigh the severity and likelihood of risks across multiple diagnostic pathways that apply to cancers detectable by MCED tests. The formula should be based on the reported incidence of adverse events resulting from tests administered as part of standard diagnostic follow-up to a positive MCED test in preliminary or early feasibility studies.
- **Adverse events ranked by levels of severity**
For scoring purposes, adverse events associated with guideline-based diagnostic procedures should be grouped according to severity (i.e., all low-risk adverse events regardless of the diagnostic procedure with which they are associated). This will preserve physician autonomy in diagnostic decision-making and will allow for consistent tracking and scoring of adverse events regardless of the diagnostic procedures chosen by the physician for a given cancer signal (see **Appendix B.**)
- **Differential consideration of MCED performance relative to detection of two groups of cancers: cancers also detected by SOC screening, and cancers not subject to SOC screening**
    - **Cancers subject to SOC screening**
    MCED tests are intended to complement guideline-recommended screening. As such, guidance from the oncology community will be helpful in determining how to assess MCED tests, which may likely feature lower sensitivity but higher specificity than SOC screening.
    - **Cancers not subject to SOC screening**
    Guidance from the oncology community will also be important for the assessment of the MCED signal as it relates to subsequent confirmation of cancers that are not subject to SOC screening. As noted throughout this paper, most cancer types that are initially detectable by MCEDs are cancers that are not subject to SOC screening. Since no such capability has existed before, there are no well-accepted standards of test accuracy to guide evaluation of the common cancer signal returned by MCEDs, much less well-accepted standards for detection of the many cancers not subject to routine screening.
    For example, early detection of low prevalence cancers through single-cancer screening has been inhibited by relatively high Numbers-Needed-to-Screen, as noted above. Successful innovation to overcome this barrier has frequently been thwarted by poor specificity (i.e., high rates of false positive findings). MCED screening may create the opportunity to correct both of these issues by improving aggregate prevalence at a relatively high level of specificity. Because MCED tests are designed around a single cut-off point for detection of analytes that indicate an underlying cancer, the sensitivity of detection will vary depending on the type and stage of the underlying cancer. Detection of cancers at relatively low rates of sensitivity may still create a benefit that outweighs the low detection rate. Standards are needed to create a rational basis for detection of underlying cancers as compared to detection at the aggregate level.

- **Patient preference**
  Benefit and risk scoring should also reflect patient preferences established in robust studies. Scoring should also reflect changing patient options for diagnosis and treatment of cancers. Finally, patient preference data must include data on the preferences of asymptomatic patients, who represent the most likely subjects of MCED screening.
- **Benefits weighed against the risk score**
  The risk score of the device will determine the magnitude of net benefit that must be demonstrated by an MCED test to show a net benefit for regulatory benefit-risk assessment in pivotal trials. Benefits should be assessed across the multiple dimensions described above, including the impact of MCED screening on overall detection of cancers (an aggregate cancer detection rate), the impact on the elapsed time from screening to cancer diagnosis (time-to-diagnosis) and a path to treatment, and the impact on patient screening behaviors (such as incidental improvements in adherence to screening).

VI. Conclusion

Multi-cancer early detection (MCED) tests will change cancer screening in profound ways, starting with their capability to detect common cancer signals from one of the dozens of cancer types that are not subject to routine screening today, and are thus more likely to progress to points at which they are symptomatic and more difficult to treat successfully. Somewhat paradoxically, as cancer diagnostics and therapies become more and more precise, MCED screening that begins with detection of common cancer signals opens the possibility of cancer detection on a population-scale in a way not possible with the limited number of single-cancer screening modalities in use today.

To realize the full potential of MCED tests and their safe and effective use, MCED-specific approaches to the assessment of benefits and risks are needed. Consensus in the regulatory and clinical communities is urgently needed to achieve an appropriate and pragmatic weighting of the potential benefits of multi-cancer detection against the known risks of diagnostic follow-up, and how much diagnostic risk may be attributed to MCED screening. MCED tests are developed around single cut-off points in the detection of common cancer signals, such as circulating tumor DNA molecules; an acceptable range for MCED test sensitivity needs to be recognized. An appropriate standard for weighting the PPV of MCED screening must be recognized as well. These are complex decisions that should be made based on a viable consensus within the communities most affected – patients and clinicians – as well as in the regulatory community. A common forum to develop consensus and guide pragmatic implementation of these review standards should be created as a high priority for the FDA, the oncology community, and the cancer patient community.

Appendix A: The FDA Center for Devices and Radiological Health Paradigm of Benefit-Risk Assessment of Weight Loss Devices

Staff at the FDA's Center for Devices and Radiological Health (CDRH) originally presented a proposal for benefit-risk assessment of weight loss devices to the agency's Gastroenterology and Urology Advisory Panel in 2012[17]. The approach has been refined in discussion papers issued by the agency since that time, including a paper released by the FDA in 2019[18].

FDA-CDRH paradigm of benefit-risk assessment of weight loss devices
The benefit-risk assessment for an obesity device is made based on the safety data available from a pilot study or other human experience with the device, and serves to guide the design of the pivotal study in the pre-market approval process.

If, during the pivotal study, a device is found to demonstrate higher risk than anticipated based on pilot data, it would be expected that the device also demonstrates correspondingly greater benefit. Conversely, if a device was shown to be less risky than initially anticipated, a lower success margin would be considered acceptable.

Risk Determination
Categories of expected and unexpected events, including adverse events and follow-up procedures, are created. All events that fit into a single outcome category are intended to be of approximately equal severity/risk.

Adverse events are categorized by their relative risk based on outcome. For example, vomiting is traditionally reported as mild, moderate, or severe, but the new paradigm categorizes the severity of vomiting and groups it with other events of similar severity. Therefore, vomiting could fall into a range of categories, from treatable with over-the-counter medicines to requiring the administration of IV fluids in a hospital setting.

To make a final risk level assessment, the number of different types of harmful events that could potentially result from using the device, and the severity of each event, are determined. When multiple harmful events occur at once, the aggregated effect is the sum of all individual effects. A cascading event is considered cumulative, and simultaneous events are each counted individually.

The devices are then given an overall risk level based on the percentage of patients who experience each category of events in the year after device placement. The overall risk level for a device is based on the highest risk level for any category.

Benefit Determination
Benefit targets are based on the risk level the device was assigned. Targets for level 1 devices are loosely based on the end points used by the FDA Center for Drug Evaluation and Research (CDER) for weight loss drugs, whereas the targets for level 4 devices are roughly based on approved weight loss devices.

The expected durability of weight loss depends on the risk level of the device. A level 1 device would not be required to provide long-term weight loss; effectiveness can be evaluated after only 6 months. However, for a level 4 device, effectiveness needs to be evaluated at 3 years to ensure sustained benefit.

In addition, the panel discussed specific trial design considerations, including methods for assessing weight loss, the timing of primary end point assessment, and appropriate study controls.

The primary method for weight loss assessment was shifted to be the percentage of total body loss (%TBL) rather than the traditional measure, percentage of excess weight loss (%EWL). This change was made based on recently published literature and CDRH's use of %TBL in reporting weight loss in clinical trials. It was also felt to be a more accurate assessment of true weight loss in lower weight individuals.

Appendix B: Example Probabilistic Risk Scoring Mechanism

	Adverse Events		
Incidence	Low Severity: Nausea, vomiting, headache, itching, flushing, rash, easily controlled bleeding	Medium Severity: Bleeding requiring treatment, infection	High Severity: Perforated colon
<=1%			
1-5%			
6-10%			
>=20%			

***not an exhaustive list of events**

Endnotes

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NEHI (Network for Excellence in Health Innovation
133 Federal Street, Boston, MA 02110 | 617.225.0857
www.nehi-us.org