Multicancer Early Detection (MCED) Screening Guidance: A Recommended Care Pathway for Clinical Use of MCED Tests

A REPORT FROM
The Multicancer Early Detection Consortium
Care Delivery Workgroup

June 27, 2023

MCED Care Delivery Pathway: *Screening*

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Overview

The MCED Care Delivery Work Group[1] has developed the following proposed care pathway for the use of multicancer early detection (MCED) tests. MCED tests encompass a range of technologies that target multiple cancers using blood samples. When added to existing approaches to single cancer screening, these emerging technologies could provide clinicians the opportunity to identify a broad range of cancers earlier in the course of the disease, raising the potential to treat them more effectively.

These new technologies may have potential as screening devices for the population broadly or as specific tools for clinicians to help diagnose cancer in the clinical setting. As with any new diagnostic technology, concerns exist about the impact of uncertainty in test results including potential for false positives and false negatives, unnecessary and harmful care (both psychological and physical) associated with diagnostic work-up for multiple cancer sites of origin, as well as potential for increased costs and the need to measure cost effectiveness of new modalities. This paper is intended to provide guidance for providers on the potential use of MCED tests and considerations when discussing with patients.

The Work Group aims to help primary care providers understand and determine if they would like to pursue MCED tests for relevant patient populations. We are not recommending that providers use an MCED test nor are we favouring one test over the other. We also do not believe providers are obligated to offer MCED tests to patients. This resource simply highlights data points surrounding two particular MCED tests to assist providers in understanding the current development of new and emerging MCED tests. It is expected for additional MCED tests to be developed and released in the coming years.

At the present time and for the foreseeable future, MCED tests should not replace current standards of care (i.e., regular screening for average risk asymptomatic patients), but rather act as a complement to them. The Work Group's goal is to help providers understand the benefits and risks of MCED tests, and the data surrounding them, so they have the information to have educated discussions with their patients. While the Work Group makes every effort to share relevant and timely information, we recognize that new data are regularly being released and there may be lag time between publication and analyses by the Work Group. Members of the Work Group closely track published information on MCED tests and discuss as a group, relevant data points that need to be flagged and properly presented to providers. The MCED Consortium intends to make these products available on our website (https://www.mced.info/) and update them routinely to make this resource as current as practicable.

This resource is intended to walk providers and other key stakeholders through critical considerations as it relates to MCED Screening. The Work Group is developing a second resource focused on Diagnostic Confirmation (post-MCED testing), which will be released later this year.

Background

Cancer death rates overall have fallen by almost a third over the past three decades due in part to improvements in therapy, but also to prevention, screening, and early detection efforts. Important developments in cancer treatment are reshaping the delivery system landscape and enabling patients to live longer and better lives. It is important to note that while cancer mortality rates have declined across all racial and ethnic groups, with the largest decrease among Black people, Black populations continue to have the highest cancer mortality rate.[2] The higher mortality rate among Black people partly reflects a later stage of disease at diagnosis.[3] Demographic characteristics such as race/ethnicity, socioeconomic status, geography, disability and sexual orientation, and the intersections between these

characteristics, can also magnify barriers to participating in organized cancer screening and accessing medical care.

Advancements in understanding cancer biology are reshaping our approach to the early detection of cancer through asymptomatic screening. However, despite advancements, some of the cancer types without any mode of early detection available have high mortality rates and are relatively understudied compared to all cancers.[4] In the United States, slightly over 1.9 million new cancer cases are expected to be diagnosed in 2022.[5] In the United Kingdom, cancer accounts for more premature deaths of people under age 75 than cardiovascular, respiratory, and liver conditions.[6] Maintaining the current rate of progress in reducing cancer death rates will require escalation in the development of more effective treatments as well as broader capabilities in the detection of more than 100 different types of cancer.[7]

The development of new diagnostic technologies that have the potential to detect multiple cancers may present an opportunity for earlier detection. Life sciences researchers and scientists continue to produce new analytics and diagnostic methods and tools for identifying cancer early. Developments in biomarkers have spurred greater capacity for identifying single cancers across a range of anatomic sites. Growing interest across the scientific and medical community in new technologies that can enable early detection for multiple cancers in the same test (assay) offers hope for a new era in the cancer prevention and control landscape.

A range of MCED tests are currently in development, being tested, or commercially available (in the US) for cancer detection using different approaches involving the analysis of blood, breath, and other specimens. While all MCEDs are designed to indicate if a cancer signal is present, some provide additional molecular information about likely organ of origin. Depending on the MCED, the provider and patient may complete an MCED test in one or two steps. These tests generally first look for circulating tumour cells, tumour DNA, and other substances that might be present in several different types of cancer. When an initial signal is positive for cancer, further analysis can be conducted to determine the source of the cancer, which may provide clinicians with information for follow-up testing to achieve a confirmed cancer diagnosis. Current MCED tests are designed to complement certain single-cancer screening tests and intended for patients who otherwise present no signs of cancer (e.g., asymptomatic individuals).[8]

Three MCED tests have been designated as Breakthrough Devices by the Food and Drug Administration (FDA) in the US, which allows for expedited review of the devices. The three tests are the Galleri® from GRAIL Bio UK, Exact Sciences MCED Test, and the OverC Multi-Cancer Detection Blood Test (MCDBT). It is important to note that while all three tests have been granted FDA Breakthrough Designation, they have not been approved by the Agency nor received a UK Conformity Assessed marking. All tests have also not yet been recommended by any major screening guideline group (e.g., United States Preventive Services Task Force - USPSTF, United Kingdom National Screening Committee – UKNSC, etc.). The Galleri® test requires an order from a provider and is currently offered in a few U.S. hospital-owned health systems, private primary care practice settings, consumer initiated/telemedicine models, employer models, payor models, and life insurance models. It is not currently being offered for clinical use in the UK but is the subject of ongoing randomized trials.[9] The approximate cost of Galleri® is $949/test. The Exact Sciences MCED test and OverC MCDBT are not yet offered to the public. While our paper primarily highlights data points on MCED tests from Grail Bio and Exact Sciences, additional MCED tests are expected to be developed and released in the coming years.

Interpretation of Data

Tables 1 and 2 in the Appendix provide high-level overviews of two recently published data on Galleri® and two on the Exact Sciences MCED test. The GRAIL PATHFINDER Study, GRAIL Circulating Cell-free Genome Atlas (CCGA) Sub-study, and the Exact Sciences DETECT-A Study were all prospective studies meaning that they followed participants forward through time, collecting data in the process.[10] Prospective studies are generally beneficial for evaluating test performance (and utility) in the intended use population. The Exact Sciences Biomarker Study was a retrospective study, meaning it used data points that had already been gathered in the past. These types of studies are practical for rare diseases and can control for various confounders but do not allow for evaluation of test performance in the intended use population.

We outline in **Tables 1 and 2** summaries of the different study results and findings. Properly interpreting statistical data is an important guide for shared decision making.[11]

Specificity refers to a test's ability to designate an individual who does not have a disease as negative. A test with 100% specificity correctly identifies all patients without the disease with a negative result. A test with 90% specificity correctly reports 90% of patients without the disease as test negative (true negatives) but 10% of patients without the disease are incorrectly given a positive result (false positives).

Sensitivity refers to a test's ability to designate an individual who has a disease as positive. A test with 100% sensitivity correctly identifies all patients with the disease with a positive result. A test with 75% sensitivity correctly reports 75% of patients with the disease as test positive (true positive) but 25% of patients with the disease are incorrectly given a negative result (false negatives).

> *Sensitivity and specificity should always merit consideration together as they provide a holistic picture of a diagnostic test. It is important to note that specificity and sensitivity are almost always negatively correlated meaning that when specificity increases, sensitivity decreases and vice versa.*

The ***Positive Predictive Value*** (PPV) refers to the probability that a patient with a positive (abnormal) test result actually has the disease. In other words, it helps answer the question: How likely is it that this patient has the disease given that the test result is positive? A PPV of 80% would mean that 8 in 10 positive results would accurately represent the presence of the disease (true positives) with the remaining two representing "false positives." Providers need to take into account that PPV is linked to the prevalence of disease in the population tested. For example, there is a higher chance of a false positive test, and therefore a lower PPV, if the prevalence of disease is low as the vast majority of the population will not have the disease. An MCED test's PPV may provide a clinician with reassurance when deciding how best to manage a positive MCED result.

When considering the data points in the Appendix, it is critical to understand that while both false negatives and false positives should ideally be avoided, very few tests are perfect. Understanding the intrinsic qualities of a test (i.e., specificity, sensitivity, and PPV) is important for providers when considering the use of an MCED test. For example, specificity is particularly important for an MCED test

used for screening large numbers of asymptomatic individuals in a population, in order to optimize the necessity and efficiency of follow-up diagnostic testing. Additionally, MCED tests may have lower sensitivities since many cancers detected may not be caught until they are in their later stages.

It is important to note that MCED tests may require different statistical interpretation from single cancer tests and understanding those statistical differences can help inform a test decision or choice.

Additionally, while guideline-based single cancer tests can be extremely sensitive in detecting cancers (high true positive rates), the false positive rates can be very high, leading to a significant number of potentially invasive diagnostic procedures in patients who do not have cancer. Current performance characteristics and composition of MCEDs in development set limits on the benefits of aggregate prevalence and high specificity achieved at this time. It can be necessary to find a balance that matches the purpose of the testing to the individual being evaluated, particularly if the cancer being tested requires invasive follow-up.

Potential Benefits

A longstanding challenge in public health has been developing and expanding innovative solutions for earlier detection, screening, and diagnosis of cancers. While there are various recommended cancer screening guidelines from the USPSTF, American Cancer Society (ACS), and the National Comprehensive Cancer Network (NCCN), the majority of cancer types do not have available screening tests.[12] In addition, simultaneously screening for a broad range of cancers could create avenues for earlier and more effective delivery of life-saving interventions and treatments.[13]

MCED screening could increase the number and variety of cancers detected and could find those cancers earlier than they would otherwise be seen. This ability would potentially allow treatment interventions to take place sooner when cancers may be more amenable to intervention. In addition, 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). Many MCEDs can also provide insights on tumour biology (e.g., mutations) that may be informative for guiding treatment.

The benefits of MCED testing are not yet fully known. Continued research that includes randomized controlled trials and real-world evidence generation will continue to inform our efforts. Current studies do suggest that the potential benefits of MCED testing include:

- Screening for cancers where there is no screening test available.
- Screening of cancer in asymptomatic patients, which may improve the chances of successful treatments or allow for less invasive treatments and may increase testing adherence compared to current level of screening, which vary by cancer site.

Potential Risks

Standardized criteria do not yet exist for several important parameters, such as clinical validity, benefit-risk, and clinical utility.[14] Clinical utility is a scientific/medical concept that conveys the likelihood that a test will result in benefits to health from an intervention provided for positive test results. Individuals

evaluating test results must weigh the potential benefit of the test against the extent to which a test results in a negative outcome due to:

- ***False positives:*** While an MCED test may report a positive result, further diagnostic testing may not find a cancer. This may be because current diagnostic tests are not yet able to detect an existing cancer or because cancer is not present.
- ***False negatives:*** An MCED test may report a negative result when a person has cancer and provide a false sense of confidence that leads people to skip standard-of-care screening. Thus, it is crucial for providers and patients to understand the complementary nature of MCED tests and the need to adhere to existing standard of care, single cancer screening tests. A false negative may also lead persons to ignore symptoms that might be serious and lead to a delay in seeking diagnostic evaluation and workup.
- ***Overdiagnosis and overtreatment:*** MCED tests may not be able to distinguish the difference between cancers that grow slowly and may never become lethal from those that lead to illness and/or death. Although it is important to note that MCED biomarker identification activities are designed to select markers/panels that are associated with "clinically relevant" cancers. Appropriate safety-netting advice should be given.

It is important to note that there may also be harm from the evaluation and treatment of both true and false positive results. Since we do not yet have studies examining the impact of MCED testing, we do not yet know whether the benefits of early detection will outweigh the potential harms that can accompany follow-up testing to assess for the presence of cancer, and harms from treating cancers that are found.

To date, no medical society has made recommendations to use MCED tests for cancer screening and there remain unanswered questions about the use of MCED tests which include[15]:

- The entirety of benefits and harms of using MCED tests for cancer screening
- Whether detection of cancers by MCED tests results in improved survival for screened individuals
- Whether detection of cancers by MCED tests reduces deaths due to cancer

Health Equity Considerations

There are longstanding disparities in cancer screening, treatment, and outcomes in both the United States and United Kingdom. Individuals with low incomes, poor education, or certain disabilities and those from racial/ethnic minority groups often face challenges accessing health care services, leading to worse outcomes. Low patient awareness, knowledge, health literacy and negative attitudes including stigma, provider bias, and miscommunication between patients and providers are important factors that may contribute to low screening and diagnostic rates among adults in those populations.[16,17]

MCED tests hold the opportunity to reduce health inequities as well as the potential to exacerbate them. MCED tests may help reduce health disparities by increasing participation rates through improvement in access to screening, but if tests are not widely available, affordable, and acceptable to minority groups, inequities will increase. While the Galleri® test is available to acquire in the U.S. with a clinician's approval, most insurers do not currently cover MCED testing as many consider the tests experimental until FDA approval – broadly and differentially restricting the population that can access them. Additionally, the National Health Service (NHS) has yet to make MCED tests available until further evaluation is completed. For more information on building health equity through research study design, please see the Health Equity Work Group's white paper here.

Considerations When Offering MCED Testing

The Care Delivery Work Group has developed the following table for clinicians who are considering the use of an MCED test for a patient. We outline several process considerations:

1) Identifying potential risk factors,
2) Conducting a risk-benefit assessment,
3) Guiding an informed choice discussion with the patient,
4) Operationalizing MCED Testing and 5) Interpreting and managing results.

Process Considerations

Identify Potential Risk Factors 	Providers should take into consideration average risk patients and the following risk factors: • **Age:** Advancing age is the most important risk factor for cancer overall and for many individual cancer types. • **Alcohol:** The risk of cancer is much higher for those who drink alcohol and also use tobacco. • **Cancer-Causing Substances:** Environmental exposures (e.g., chemicals in tobacco smoke, or radiation, such as ultraviolet rays from the sun) can damage DNA and alter the way cells function which may cause cancer. • **Chronic Inflammation:** Over time, chronic inflammation can cause DNA damage and lead to cancer. • **Diet:** Many studies have looked at the possibility that specific dietary components or nutrients are associated with increases or decreases in cancer risk. • **Hormones:** Estrogens, a group of female sex hormones, are known human carcinogens. Although these hormones have essential physiological roles in both females and males, they have also been associated with an increased risk of certain cancers. • **Immunosuppression:** Many people who receive organ transplants take medications to suppress the immune system so the body won't reject the organ. These "immunosuppressive" drugs make the immune system less able to detect and destroy cancer cells or fight off infections that cause cancer. • **Infectious Agents:** Certain infectious agents, including viruses, bacteria, and parasites, can cause cancer or increase the risk that cancer will form. • **Overweight/Obesity:** People with obesity may have an increased risk of several types of cancer, including cancers of the breast (in women who have been through menopause), colon, rectum, endometrium (lining of the uterus), esophagus, kidney, pancreas, and gallbladder. • **Radiation:** Radiation of certain wavelengths, called ionizing radiation, has enough energy to damage DNA and cause cancer. • **Sunlight:** Exposure to UV radiation causes early aging of the skin and damage that can lead to skin cancer. • **Tobacco:** Tobacco use is a leading cause of cancer and of death from cancer. **Cancer affects all population groups in the United States, but** due to social, environmental, and economic disadvantages, **certain groups bear a disproportionate** burden of cancer compared with other groups.

	Additionally, health concerns, including the potential to diagnose cancer faster and earlier via MCED testing, **may not be a priority for individuals and communities with low resources**. For both the U.S. and the U.K., demographic characteristics such as race/ethnicity, socioeconomic status, geography, disability and sexual orientation, and the intersections between these characteristics, can also magnify barriers to cancer care. For more information on the health equity landscape of MCED tests, please see the Health Equity Work Group's white paper **here**.

Conduct Risk-Benefit Assessment 	• Understand the benefits of an MCED test
	  ○ Testing for cancers where there is **no screening test available**.
	  ○ Testing of cancer in **asymptomatic patients**, which may improve the chances of successful treatments or allow for less invasive treatments.
	  ○ Testing for multiple cancers using a blood test, which **may increase testing adherence** compared to current level of screening engagement, which vary by cancer site.
	• Understand the best option depending on a **patient's risk**
	  ○ Risk for morbidity and mortality based on concomitant conditions
	  ○ Risk of cancer based on risk factors (as outlined above)
	• Understand that MCED tests **do not replace standard of care screenings**
	• **Understand a patient's desires/resources/options: trials, studies, commercial**:
	  ○ What are their driving factors?
	  ○ Do they understand the MCED assay does not diagnose cancer and may result in needed follow-up scans?
	  ○ Are they agreeable to participate in a trial or is there an inherent misgiving about trials/research?
	  ▪ If they are, you can find ongoing trials for US patients to participate in **here** and UK patients **here**.
	  ▪ If they are not but would still like the MCED test, you may want to ask them if they would be willing to share their experience/data results. We encourage providers and patients utilizing currently available MCED tests to participate in programs or trials to capture outcomes data to help answer important questions.

Guide Informed Choice Discussion with Patient 	• Discuss the following: **risks/benefits; cost considerations; research data; post result expectations**.

Operationalize MCED Testing 	• The only test currently available in the US is Galleri®.
	  ○ Providers must submit a form to begin the ordering process (information requested includes first and last name, email address, phone number, NPI, practice name, practice zip code, and requested number of collection kits)
	  ○ A Galleri® representative will contact the provider to set up an account.

	○ After an account is set up, the Galleri® test kit will be delivered to the provider. ○ It is important to ensure that the process and data results are incorporated into the patient's electronic health record. • For providers participating in a health system that is utilizing Galleri®, it is important to leverage electronic health information and lab operation clinical decision support for: ○ Orders ○ Results ○ Patient engagement ○ Billing
Interpret and Manage Results 	• **Negative test follow up expectations** • **Positive test diagnostic workflows** • **Managing false negatives or positives**

Appendix 1

Table 1: Published Studies on Galleri®

PATHFINDER Study (September 2022)

- Type of Study: Prospective, interventional
- Type of Publication: Manuscript
- Number of Enrolled Participants: 6,662
- Number of Analyzable Participants: 6,578
- Target Population: Age 50+
- Positive Predictive Value: 43.1%
- Sensitivity: N/A[1]
- Specificity: 99.5%
- Identifies organ of origin: Yes
- Organizations Participating in Study: Dana Farber Cancer Institute, Sutter Health, OHSU Knight Cancer Institute, US Oncology, Intermountain Healthcare, Cleveland Clinic, Mayo Clinic

Circulating Cell-free Genome Atlas (CCGA) Sub-study (September 2021)

- Type of Study: Prospective, case-controlled, observational
- Type of Publication: Peer Reviewed Study
- Number of Enrolled Participants: 5,309
- Number of Analyzable Participants: 4,077
- Target Population: Adults (> 20 years old)
- Positive Predictive Value: 44.4%
- Sensitivity: 51.5%
- Specificity: 99.5%
- Identifies organ of origin: Yes
- Organizations Participating in Study: N/A

[1] Galleri®'s clinical studies did not measure sensitivity.

Table 2: Published Studies on Exact Sciences MCED Test

DETECT-A Study (April 2020)

- Type of Study: Prospective, interventional
- Type of Publication: Peer Reviewed Study
- Number of Enrolled Participants: 10,006 women
- Number of Analyzable Participants: 9,911
- Target Population: Age 65-75 with no prior history of cancer
- Positive Predictive value: 19.4%
- Sensitivity: 27.1%
- Specificity: 98.9%
- Identifies organ of origin: Yes
- Organizations Participating in Study: Geisinger

Biomarker Study (September 2022)

- Type of Study: Retrospective, case-control
- Type of Publication: Manuscript
- Number of Enrolled Participants: 4,196
- Number Of Analyzable Participants: 3,518
- Target Population: Age 50+
- Positive predictive value: N/A
- Sensitivity: 61%
- Specificity: 98.2%
- Identifies organ of origin: Yes
- Organizations Participating in Study: Johns Hopkins University School of Medicine

Appendix 2

Glossary

Term	Definition
Multi-Cancer Early Detection Test	MCED tests encompass a range of technologies that target multiple cancers using blood samples
Sensitivity	Proportion of people with disease who will have a positive result
Specificity	Proportion of people without the disease who will have a negative result
Positive Predictive Value	Proportion of people with a positive test result who actually have the disease
Negative Predictive Value	Proportion of people with a negative test result who do not have disease

Appendix 3

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