EVALUATING MULTICANCER EARLY DETECTION (MCED) TECHNOLOGIES FOR CLINICAL USE

Initial Report by the Multicancer Early Detection Consortium

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Advances in Cancer Treatment, Prevention, & Early Detection

Cancer death rates 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. Additional advancements in understanding cancer biology are reshaping early detection and screening for cancers without current screening strategies. Despite these advancements, the cancer types without any mode of early detection available tend to be the deadliest and most understudied of all cancers.[1] In the United States., slightly over 1.9 million new cancer cases are expected to be diagnosed in 2022.[2] In the United Kingdom., cancer accounts for more premature deaths of people under 75 than cardiovascular, respiratory, and liver conditions.[3] 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 early detection and diagnosis for the more than 100 different types of cancer.[4]

A longstanding challenge in public health has been developing and expanding innovative solutions for earlier detection, screening, and diagnosis of cancers. The U.S. Centers for Disease Control and Prevention recommend screenings for breast, cervical, colorectal, and lung cancer, meaning the majority of cancer types do not have recommended screenings.5 With respect to early diagnosis in the clinical setting, recent research has demonstrated opportunities in primary care practices for earlier diagnosis.6 Further, current challenges abound with certain cancers that are difficult to diagnose in the early stage. For example, most ovarian cancers are detected in later stages when survival rates are lower, and the treatments are more toxic.

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[1] Byers T, Wender RC, Jemal A, Baskies AM, Ward Ee and Brawley OW. The American Cancer Society challenge goal to reduce US cancer mortality by 50% between 1990 and 2015: Results and reflections. CA: A Cancer Journal for Clinicians, 2016;66: 359-369. https://doi.org/10.3322/caac.21348

[2] Cancer Facts and Figures. American Cancer Society. 2022. Accessed August 2022. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf

[3] Mortality Profile. Office of Health Improvement and Disparities. 2020. Accessed July 2022. https://fingertips.phe.org.uk/profile/mortality-profile/data#page/1

[4] National Institute of Health. What is Cancer? National Cancer Institute. Updated May 5, 2021. Accessed June 2022. https://www.cancer.gov/about-cancer/understanding/what-is-cancer

[5] Cancer screening tests. Centers for Disease Control and Prevention. https://www.cdc.gov/cancer/dcpc/prevention/screening.htm. Published May 19, 2022. Accessed August 19, 2022.

[6] Walter FM, Thompson MJ, Wellwood I, Abel GA, Hamilton W, Johnson M, et al. Evaluating diagnostic strategies for early detection of cancer: the CanTest framework. *BMC Cancer* 2019;19:586. https://bmccancer.biomedcentral.com/articles/10.1186/s12885-019-5746-6

The development of new diagnostic technologies that have the potential to detect multiple cancers may present an opportunity in the clinical setting for earlier detection and diagnosis in the presence of symptoms among primary care patients that have proven challenging to accurately evaluate. 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.

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 in a range of areas. For example, the use of FIT and multi-target stool DNA screening tests has helped to advance early diagnosis for colorectal cancer.

Policymakers see the opportunity to advance efforts in this area. In 2018, the U.K. Prime Ministerial announcement to increase the proportion of cancer diagnoses at an early stage led to the NHS Long Term Plan commitment to 75 percent of all cancers being diagnosed at stage 1 or 2 by year 2028.[7] In the United States, President Biden's Cancer Moonshot initiative sets a goal for earlier cancer detection by greatly expanding the list of screening-targeted cancers. The initiative also urges the development of innovative screening tools, particularly those that expand the number of detectable cancers. In addition, last November, the United States and the United Kingdom jointly convened a scientific cancer summit to share ideas and identify opportunities for collaboration to accelerate advances in life saving approaches to cancer, including addressing and combatting racial and socio-economic disparities and outcomes.

One major approach in early cancer detection is screening of asymptomatic individuals, often at higher risk for cancer. Current recommended screening modalities are specific for a single cancer. Positive screens are the first step before a specific follow-up approach based on the cancer type for diagnostic resolution. To date, cancer screening standards rely on demonstration of the clinical benefit of an organ-specific cancer detection modality (e.g., mammography imaging, colonoscopy, cervical HPV testing).

Another approach has been building a body of research that can lead to earlier detection of cancers in the medical setting. For example, in ovarian cancer, once thought to be a "silent killer," several efforts to detect symptoms earlier have been developed and validated.[8] Similar efforts have resulted in the adoption of guidelines for pathways to accelerate evaluation of patients in the UK National Health Service.[9,10]

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[7] Areas of Work - Cancer. National Health System England. Accessed August 2022. https://www.longtermplan.nhs.uk/areas-of-work/cancer/

[8] Funston G, Hardy V, Abel G, et al. Identifying Ovarian Cancer in Symptomatic Women: A Systematic Review of Clinical Tools. *Cancers (Basel)*. 2020;12(12):3686. Published 2020 Dec 8. doi:10.3390/cancers12123686

[9] National Institute for Health Care and Excellence. NICE Guideline [NG12] Suspected cancer: recognition and referral. Department of Health and Social Care. June 23, 2015. Accessed July 2022. https://www.nice.org.uk/guidance/ng12

[10] British Association of Dermatologists. The two-week wait skin cancer pathway: innovative approaches to support early diagnosis of skin cancer as part of the NHS COVID-19 recovery plan. National Health Service. April 4, 2022.

Multicancer Early Detection (MCED) Technologies Promise a New Era in Cancer Detection

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. These new tests—referred to broadly as multicancer early detection (MCED) technologies—encompass a range of technologies that target multiple cancers using samples including blood, breath, urine, saliva, or stool.[11]

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. Clinicians also may be able to use emerging molecular targets and technologies across the cancer care continuum and more specifically in the monitoring of therapeutic efficacy, emergence of drug-resistant cells, and identification of tumor progression.

As with any new diagnostic technology, concerns exist about the impact of uncertainty in test results including potential for false positives, unnecessary and harmful care 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. Therefore, it will be important to ensure appropriate follow-up diagnostics.[12] Additional concerns relate to the amount of time for new technologies to reach those who would most benefit; a focus should be on reducing timelines. More broadly, MCED tests will require careful evaluation of benefits, harms, and impact to ensure consistency with the principles of equitable and informed participation.

A New Expert Initiative to Advance MCED – The MCED Consortium Background, Mission, Organization & Objectives

Background

Efforts to advance the development of MCED technologies in a manner that ensures their clinical utility and, if appropriate, to integrate them into the care delivery system and make them broadly accessible presents a range of challenges and questions as well as opportunities for the scientific and public health

Accessed July 2022. https://www.england.nhs.uk/wp-content/uploads/2022/04/B0829-suspected-skin-cancer-two-week-wait-pathway-optimisation-guidance.pdf

[11] National Institute of Health. Multi-Cancer Early Detection (MCED). National Cancer Institute Division of Cancer Prevention. Accessed June 2022. https://prevention.cancer.gov/major-programs/mced

[12] Marlow LAV, Schmeising-Barnes N, Brain K, Duncombe S, Robb KA, Round T, Sanderson SC, Waller J. Multi-cancer early detection tests for cancer screening: a behavioural science perspective. *PubMed.gov*. doi: 10.1016/S1470-2045(22)00161-9

communities. The emergence of scientific information related to early progress and prospects for MCEDs has underscored the need to initiate organized approaches to those challenges and questions. Given that context, a group of leading public and private health care stakeholders recommended forming a consortium dedicated to accelerating the evaluation, application, and, where appropriate, equitable adoption of MCED technologies in clinical settings.

Following this recommendation, a group of volunteers and advisors with perspectives spanning the health care sectors in the United States and the United Kingdom, designed a blueprint guiding action and the formation of the Consortium in 2021. The MCED Consortium subsequently formed comprises experts from a range of backgrounds including oncology, epidemiology, genomics, behavioral science, primary care, patient advocates, and others. Presently, the Consortium operates as an independent, not-for-profit entity with U.S.-U.K. public-private representation, administered by a third-party organization, Healthsperien, LLC.

The promise of MCED technologies has global reach as scientists across the world are focused on the range of issues in their development. While the initial scope of the Consortium limits contributors and participants to only those from U.S. and U.K.-based organizations, we hope and expect to grow and share findings and perspectives broadly and maintain an eye on global scientific developments.

Mission

The Consortium's mission is broad and ambitious, and includes a focus intended to support our health equity objectives:

> ***To reduce the burden of cancer by evaluating how MCED technologies may improve cancer detection, treatment, and care to benefit all people.***

Our Assessment of the Challenges and the Opportunity

The creation of the Consortium marks a major paradigm shift in thinking about multicancer early detection, and the widespread support it has received underscores the interest and commitment of researchers, scientists, innovators, and health experts in advancing the mission, addressing potential challenges, and identifying opportunities for future developments. This body has a unique and timely opportunity to offer perspectives on the challenges facing MCED technologies and on actionable steps for the broader health care community to consider in promoting widespread adoption and equitable participation.

A critical challenge to innovation in MCED technologies is the absence of standardization and universal acceptance; as such, the Consortium plans to evaluate the current landscape of cancer screening and diagnostics, develop recommendations for standardized procedures for use in a clinical setting and along the care delivery journey—while embedding the critically important health equity perspective—and communicate findings and recommendations clearly and concisely across populations. In doing so, the Consortium will recommend baseline criteria for implementation and will function as a comprehensive reference point for providers, patients, and the broader public. The output of our work,

including white papers, presentations, and other public-facing materials, will provide clarity and uniformity in a field that is rapidly developing and changing, and of which there is still limited awareness and understanding. Critical next steps include recognizing and forecasting the implications of 1) population-wide screening tools such as MCED tests and 2) diagnostic tools for use in clinical settings with symptomatic patients and disseminating the findings for broad adoption by health care providers.

The Consortium model enables the socialization of important ideas and information across a broad stakeholder base, while maintaining a foundational grounding in science, clinical adaptability, and patient impact. It also engenders thoughtful evaluation of benefits, risks, outcomes, costs, and value, coupled with guidance to effectively and pragmatically further public engagement with these technologies to improve health outcomes and address disparities in cancer outcomes.

As this opportunity continues to develop, the presence of a Consortium, comprised of experts in a range of fields, dedicated to the evaluation of MCED technologies and appropriate recommended use will serve as an ongoing resource for public health agencies, care providers, regulators, payers, and the scientific community. Having an organization with such a focus and capabilities that keep pace with scientific advances is a unique opportunity; it provides leadership and invites collaboration that otherwise would not occur in a rapidly evolving scientific and technical field.

The Structure and Focus of Our Work

The Consortium launched in 2022 with three overarching objectives:

- Evaluate and assess the benefits and risks, potential outcomes, costs, and value associated with introducing novel MCED technologies into society and clinical care
- Develop guidance for the potential introduction of these technologies into clinical care, including understanding public perceptions of MCED technologies and these technologies' potential to improve or exacerbate health disparities
- Accelerate additional lessons and evaluations on how MCED technologies could potentially improve outcomes for all people

Four distinct working groups support these objectives, and each has its own workplan, leadership, and set of deliverables. Workgroups will evaluate clinical utility, analyze needs to ensure effective care delivery, focus on ways to address concerns about access and health equity, and develop strategies for communicating with the public about MCED technologies. While each workgroup mostly operates independently, a Steering Committee comprised of leadership from each of the four workgroups ensures cross-cutting collaboration and important sharing of perspectives and resources. Other processes including quarterly convenings of the Steering and Executive committees, consultation with additional stakeholder experts, and regular and open communications between workgroups that allow for important collaboration on the various workstreams.

Issues related to reimbursement and regulation are important to stakeholders and present ongoing challenges in the evolution of MCED technologies. We recognize their importance and impact on technology adoption and access more generally and the specific considerations with our focus areas.

However, these issues are outside the scope of the MCED Consortium as the present time.[13] The foundational and challenging issues in our framework are a necessary beginning to guide the emergence and comprehensive evaluation of MCED technologies, and our work is thus limited to our four main areas, which we describe in greater detail below. They include:

- **Clinical Utility** – defining and reaching broad consensus on how to evaluate MCED tests in the clinical context and create processes for creating a clinical utility framework.
- **Care Delivery** - establishing a process to modify existing, and to create novel care pathways to accommodate MCED technologies, which includes recommending a process to test care pathways in the "real-world".
- **Health Equity** - identifying issues at the patient, provider, and health care system levels that amplify disparities in cancer outcomes and offering ideas for strategies that can ensure research and findings including insights and solutions for vulnerable populations and equal access to new therapies.
- **Communications** - developing strategies and materials to educate clinicians, primary caregivers, patients, public, and other relevant audiences on the findings of the Consortium and about MCED technologies more broadly.

It is important to note that for the lifetime of this Consortium, care delivery pathways, clinical utility frameworks, and other documents will be "living"; workgroups will make alterations and updates to incorporate new data and findings as needed.

Gathering Expert Perspectives – Consortium Areas of Focus

Engagement of experts allows inclusion of a broad range of perspectives to advance understanding of the future of MCED tests, including how to communicate the promise, including potential benefits and harms, of these technologies to patients and members of the public as well as care providers. Detail on workgroup approaches, goals, and perspectives shared to date follow in this section, with guiding questions for future work.

Clinical Utility

The Clinical Utility Working group aims to develop frameworks to evaluate and understand the impact MCED technologies will have on cancer screening by engaging and leveraging the knowledge of the broader health care community. This effort includes guideline developers, clinicians, academics, payers, regulatory experts, and patients as well as public health, health economics, and other subject matter experts including industry members. We will design interim clinical utility frameworks for the use of MCED technologies as a screening approach for asymptomatic individuals and a diagnostic approach for symptomatic patients.

[13] The potential clinical use of emerging molecular targets and technologies across the cancer care continuum and more specifically in the monitoring of therapeutic efficacy, emergence of drug-resistant cells, and identification of tumor progression, is also out of scope for the Consortium at the present time.

These frameworks will help clinicians identify the specific cancers and populations for which there is reasonable evidence that benefits of the new tests potentially outweigh the harms and propose pragmatic approaches for evidence generation. This approach will segment cancers included in MCED tests into manageable and rational groupings and consider currently established endpoints and measurements. As further evidence related to MCED technologies is generated and published, the approach will evolve to accommodate that new information. Importantly, developments in the Clinical Utility Workgroup's framework will incorporate emerging research from academia and industry.

Clinical Utility Landscape

A range of MCED tests are currently in development for cancer detection using different approaches involving the analysis of blood, breath, and other specimens. For example, liquid biopsies have recently been shown to permit the detection of multiple analytes (or substances) indicative of a growing cancer, such as circulating tumor cells, circulating tumor DNA (ctDNA), circulating exosomes, and other analytes in body fluids (e.g., blood plasma, urine, saliva, and sputum). That approach offers an opportunity to complete early detection of multiple cancers using a single blood draw or other methods.

However, 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, false negatives, and overtreatment. Experts assess clinical utility of interventions using a multi-dimensional approach, considering four factors including appropriateness, accessibility, practicability, and acceptability.[15]

Both the US and the UK governments have efforts in this area. The NHS is increasingly partnering with industry to accelerate adoption of new health technologies such as MCEDs. In partnership with the developers of one such blood test, which screens for over 50 types of cancer, the agency has recruited over 140,000 people across England to a randomized controlled trial.[16] In the United States, the National Cancer Institute (NCI) is soliciting feedback from developers of MCED liquid biopsy tests about their interest in participating in a randomized controlled screening trial.[17] The agency is testing different

[14] Liu, M.C. Transforming the landscape of early cancer detection using blood tests – Commentary on current methodologies and prospects. *Br. J. Cancer* 124, 1475-1477 (2021). ttps://doi.org/10.1038/s41416-020-01223-7

[15] Smart, A. A multi-dimensional model of clinical utility. *Int J Qual Health Care.* 2006 Oct;18(5):377-82. http://doi: 10.1093/intqhc/mzl034

[16] National Health Service. NHS to pilot potentially revolutionary blood test that detects more than 50 cancers. NHS News. November 27, 2020. Accessed June 2022. https://www.england.nhs.uk/2020/11/nhs-to-pilot-potentially-revolutionary-blood-test/

[17] National Cancer Institute. Request for Information (RFI): Seeking Input from Multi-Cancer Early Detection Test Developers on Readiness for Participation in an NCI-Sponsored Clinical Utility Randomized Controlled Screening Trial. National Institute of Health. Jan 2022. Accessed June 2022. https://grants.nih.gov/grants/guide/notice-files/NOT-CA-22-033.html

approaches and performance capacities being developed by different companies and academic institutions and their perceived challenges and barriers to participation. NCI has developed plans for a large national clinical trial of 250,000 participants to and will implement the trial in phases, beginning with a feasibility study.[18]

Challenges

Due to the novelty of MCED technology, challenges exist to determine the viability and clinical utility of such technologies. First, limited research and follow-up data available on endpoints and impact makes it difficult to develop needed frameworks for clinical utility. This is also an issue for well-established single-cancer screens; many stakeholders in the health care community remain divided over the ability of existing screens to identify clinically significant disease earlier in its natural history, particularly for asymptomatic populations.

Additional challenges to developing frameworks relate to study design, including variables to include, differences in participant eligibility, cancers targeted for detection, methodology, and the variability of performance metrics. Given that capturing mortality benefits of such a novel technology like MCED will take years, the Consortium must provide guidance regarding other endpoints or inputs for the framework.

MCED tests have the potential to be widely applicable in the general population. However, the ratio of benefits to harms may be more favorable in a higher risk population. One of several approaches is dividing tests into population-relevant categories which can help to evaluate populations with elevated risk of disease versus those with average risk, or symptomatic versus asymptomatic patients.

The balance of benefits versus risks may also vary across cancers. Approaches that may help address this issue include categorizing or segmenting the cancers that can be identified via MCED technologies to avoid the complexity of analyzing all cancers together. Potential categories can vary from cancers with existing screening tests to those cancers without existing tests, or common cancers versus rare cancers.

Questions That Still Need Answers

- What is a consensus definition of clinical utility, and more specifically in the context of MCED technologies?
- Should the tests aggregate endpoints across multiple cancer types as single MCED tests detect them?
- For sub-analysis of single cancers, what categories of cancer do we start with and how do we evaluate their complexities?
- What criteria should we use to bucket cancers into categories?
- How many different categories should we evaluate?
- Which populations do we begin with?
- When is the optimal time to administer an MCED test, and how often?
- What other endpoints or variables should the clinical utility frameworks include?

[18] National Cancer Institute. NCI Trials for July 2022. Cancer Letter Vol.48 No.27. July 8, 2022. Accessed July 2022. https://cancerletter.com/nci-trials/20220708_10/

In summary, the MCED Consortium and the Clinical Utility Workgroup are committed to highlighting the need for rigorous evidence for MCED technologies to demonstrate both effectiveness and cost-effectiveness prior to any recommendations for use of such technologies.

Care Delivery

As the care delivery context influences the clinical utility and cost-effectiveness of MCEDs, stakeholders must give careful consideration to care pathways and equitable access. They must assess a broad range of questions related to the integration of these tests in the delivery of care. How do clinicians and patients decide whether it is in the patient's best interest to take the test? How would a clinician care for a patient in response to an MCED test result? What would be the most appropriate care pathway for an individual with a positive screen from an MCED test?

The purpose of the Care Delivery workgroup is to develop guidance for the technologies' introduction into clinical care as both a screening and diagnostic test and suggest pathways for evaluation in clinical utility studies. Specifically, the workgroup will establish a process to assess and modify existing care pathways and to create new ones to accommodate MCED tests in support of recommendations for an approach to test care pathways in the "real-world". Generally, the standard of care in the United States involves screening asymptomatic individuals for a single cancer type through a particular modality (e.g., mammography, imaging, colonoscopy, cervical HPV testing, etc.) and following up with a targeted diagnostic evaluation.[19] These current screening modalities have been shown to decrease mortality from colon, breast, lung, and cervical cancers, but adherence to standard of care screening varies widely and often times screening is not recommended for average risk individuals for any other cancer types.[20] The approach in the diagnostic setting will be different than in the screening setting; for example, evaluating the potential to use MCED technologies in existing diagnostic pathways as a first step to rule out the need for further invasive testing.

This existing approach creates an opportunity for MCED tests to reduce morbidity and mortality, among other important outcomes, and positions the technology well to complement existing screening exams. An important role of this workgroup will be to collaborate with sites currently using MCED tests and those interested in offering feedback on proposed pathways. As thought leaders in this field, workgroup participants will publish a white paper on novel care pathways and will run workshops using them to disseminate lessons learned to a broader clinical audience.

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[19] National Cancer Institute. Request for Information (RFI): Seeking Input from Multi-Cancer Early Detection Test Developers on Readiness for Participation in an NCI-Sponsored Clinical Utility Randomized Controlled Screening Trial. National Institute of Health. Jan 2022. Accessed June 2022. https://grants.nih.gov/grants/guide/notice-files/NOT-CA-22-033.html.

[20] Hall IJ, Tangka FKL, Sabatino SA, Thompson TD, Graubard BI, Brenn N. Patterns and Trends in Cancer Screening in the United States. *Prev Chronic Dis.* 2018;15:E97. Published 2018 Jul 26. http://doi:10.5888/pcd15.170465

Challenges

The Care Delivery workgroup will consider multiple factors as they develop guidance on novel care pathways that providers and health systems can successfully implement. These factors include addressing the lack of access (physically and financially) for patients to receive screenings and subsequent diagnostics, poor care coordination, and infrastructure and operational barriers.[21] Factors such as site of care and local, regional, and/or geographical differences in delivery systems (e.g., small versus large practices or health systems, academic versus community health organizations, rural versus urban sites of care) influence the extent to which the health care system can adopt new care pathways.

Additionally, concerns about the supply and capacity of the oncology workforce need to inform discussion of new care pathways. Some stakeholders have noted that the current U.S. health care system faces pressures in the supply of oncologists, nurses, imaging and endoscopy technicians, and additional care team members to keep up with current oncology care demand, especially in rural communities. Importantly, additional concerns exist about developing a racially and ethnically diverse workforce representative of the patients most disproportionately impacted by cancer.

A 2020 snapshot on the state of the oncology workforce in the United States estimated that two-thirds of rural counties have no oncologist, and 32 million Americans live in counties without an oncologist.[16] Similarly in the United Kingdom, there is a major workforce gap among clinical oncologists that experts expect to worsen in the next five years. In areas that have acute staff shortages, access to services is likely to be in higher demand.[22] Assessing the potential shifts in workforce demands related to MCED technologies will remain a challenge for the workgroup. The Consortium acknowledges that there are both common and separate issues affecting the U.S. and UK health systems and the Care Delivery workgroup will take these into account.

Broader issues the workgroup may identify and consider include the downstream impact of MCED on the ability of the delivery system to care for patients who receive cancer diagnoses. As abnormal results from an initial screening typically lead to a recommended set of additional tests to determine whether there is a definitive cancer diagnosis, the system may need to evolve to help ensure that patients receive efficient, actionable results from MCED screening with well-designed diagnostic and treatment pathways.[23]

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[21] Wender RC, Brawley OW, Fedewa SA et al. A blueprint for cancer screening and early detection: Advancing screening's contribution to cancer control. *CA: A Cancer Journal for Clinicians*. 2018;69(1):50-79. http://doi:10.3322/caac.21550

[22] Clinical Oncology. UK Workforce census report 2020. The Royal College of Radiologists. July 2021. Accessed June 2022. https://www.rcr.ac.uk/system/files/publication/field_publication_files/clinical-oncology-uk-workforce-census-2020-report.pdf

[23] Fendrick, A Mark. Expanding Coverage for Early Detection: One Small Step for The Cancer Moonshot, One Giant Leap For Health Equity. *Health Affairs Forefront*, March 23, 2022. http://doi: 10.1377/forefront.20220322.171614

Health Equity

Longstanding disparities in cancer screening, treatment, and outcomes exist in both the United States and United Kingdom. Individuals with low incomes, poor education, or certain disabilities and those from ethnic minority groups often face challenges accessing health care services, leading to worse outcomes. In the United States, uninsured or underinsured individuals, recent immigrants, individuals living in rural or remote areas, and members of racial and ethnic minority groups are among those who experience disparities in cancer screening and follow-up care. For example, in the United States, racial and ethnic minorities have lower rates of insurance coverage and resulting challenges accessing screenings.[24] Black individuals have the highest mortality rate for most leading cancer types and research shows that the overall rate of cancer screening is lower in Black, Hispanic, Asian, and Native American populations compared to their white counterparts. In the United Kingdom, adults with severe mental illness were 2.1 times more likely to die from cancer under the age of 75 than people without the condition, and cancer was the leading cause of premature mortality among people with those individuals, above cardiovascular, respiratory, and liver diseases, based on recent research.

The Health Equity workgroup will develop guidance on designing studies and evaluating MCED technologies to reduce disparities in health care outcomes and advance health equity considerations and, if appropriate, guidance on improving access. This workgroup will include representatives from organizations focused on serving minority and vulnerable populations in their local communities. Members of the workgroup will engage with the Clinical Utility, Care Delivery, and Communications Workgroups to ensure collaboration on the issues. The workgroup will proactively elevate and address disparities in outcomes and health equity issues within other workgroups and advance its own stand-alone efforts.

The Health Equity Workgroup will consider how to respond to and create strategies to mitigate longstanding barriers to cancer screening and access to diagnostics among populations with high cancer rates. Important factors make this challenging. 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 and should be an important first area of focus.[25, 26] Second, many factors may deter people from seeking or receiving recommended screening, diagnosis and care, including geographic, financial (insurance), and logistical challenges. Cultural factors, lack of trust in health care

[24] Deverka PA, Douglas MP, Phillips KA. Multicancer Screening Tests: Anticipating and Addressing Considerations for Payer Coverage and Patient Access. *NIH National Library of Medicine.* 2022 Mar;41(3):383-389. doi: 10.1377/hlthaff.2021.01316. PMID: 35254936; PMCID: PMC8962120.

[25] Liu, D., Schuchard, H., Burston, B. *et al.* Interventions to Reduce Health care Disparities in Cancer Screening Among Minority Adults: A Systematic Review. *J. Racial and Ethnic Health Disparities* 8**,** 107–126 (2021). https://doi.org/10.1007/s40615-020-00763-1

[26] Young, B., Robb, K.A. Understanding patient factors to increase uptake of cancer screening: a review. *Future Oncol* 2021; 17(28): 3757-75 http://eprints.gla.ac.uk/241923/1/241923.pdf

systems, and discriminatory practices by health care providers are also important factors to consider.[27, 28, 29] Third, social determinants of health, such as transportation, greatly impact cancer screening behavior and prevalence; improvements or approaches that take social factors into account with MCED strategies will help to drive improvements in outcomes.[30] Additionally, the workgroup will also focus on how to improve the relevance of MCED tests, if proven to have clinical utility. Many tests are not validated in diverse populations and may have lower uptake or higher access barriers in racial and ethnic minorities, who have lower rates of insurance coverage.[31]

Given that greater screening and diagnosis of cancers cannot address broader issues of the availability and affordability of appropriate treatments, the workgroup will flag important issues in this area for broader consideration. In collaboration with the Communications Workgroup, this workgroup will ensure that recommended approaches and outreach are suited for specific groups or populations in the United States or the United Kingdom.

Areas that the Health Equity Workgroup plans to pursue to address health disparities and improve outcomes in the use of MCED technologies include:

- Reducing and avoiding health disparities by addressing barriers that prevent equitable access to MCED tests. Examples include identifying innovative methods to increase access to participation in research such as mobile tests or telehealth and collaborating with local community partners as part of care delivery.
- Urging and fostering the diversity of the patient population for current and future MCED randomized and other clinical trials to determine whether screening with MCED tests (in tandem with standard screening) reduces the occurrence of late-stage cancers, extends survival, and possibly reduces death, compared to usual care or standard screening alone.
- Inclusion of racial/ethnic groups in genetic studies. Evidence suggests that exclusion of relevant genes/mutations prevalent in racial/ethnic groups in the development of genetic tests can lead

[27] President's Cancer Panel. Goal 2: Facilitate Equitable Access to Cancer Screening. Closing Gaps in Cancer Screening: Connecting People, Communities, and Systems to Improve Equity and Access. February 2022. Accessed June 2022. https://prescancerpanel.cancer.gov/report/cancerscreening/Part2Goal2.html#ref1

[28] Wang GX, Baggett TP, Pandharipande PV, et al. Barriers to lung cancer screening engagement from the patient and provider perspective. *Radiology*. 2019;290(2):278-87. https://www.ncbi.nlm.nih.gov/pubmed/30620258

[29] Nagelhout E, Comarell K, Samadder NJ, Wu YP. Barriers to colorectal cancer screening in a racially diverse population served by a safety-net clinic. *J Community Health*. 2017;42(4):791-6. https://www.ncbi.nlm.nih.gov/pubmed/28168395

[30] Islami, F Guerra, CE Minihan, A et al. American Cancer Society's report on the status of cancer disparities in the United States, 2021. *CA Cancer J Clin*. 2022;72:112-143. https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.3322/caac.21703

[31] Deverka PA, Douglas MP, Phillips KA. Multicancer Screening Tests: Anticipating and Addressing Considerations for Payer Coverage and Patient Access. *NIH National Library of Medicine.* 2022 Mar;41(3):383-389. doi: 10.1377/hlthaff.2021.01316. PMID: 35254936; PMCID: PMC8962120.

to biases, and new diagnostic technologies and associated treatments may not benefit or apply to all populations equally.
- Ensuring the need for robust education efforts and specifically language and culturally appropriate communications towards relevant communities.

Communications

The Consortium strives to educate clinicians, patients and the public about benefits and risks of MCED technologies, whether they demonstrate clinical utility. A common understanding of MCED tests, their use and purpose, and the known associated risks and benefits will be important for successful integration into the delivery system.

A critical component of the Communications Workgroup's workplan will be to integrate with the findings and recommendations put forth by the Health Equity Workgroup. Understanding regarding MCED tests could vary based on many factors including geographic location and rurality, socio-economic status, disability, language, and cultural backgrounds. As such, it is critically important that health equity be a key element in the development of educational materials and strategy related to awareness.

The Communications Workgroup will design educational materials that promote lessons learned by the Consortium, prepare clinicians, primary care physicians, specialists, and the public on the science and the potential implementation of this testing in clinical care, in addition to educational messaging geared towards payers and regulators. Importantly, the Communications Workgroup will ensure consistent messaging on behalf of the Consortium about the landscape and field of MCED technologies. Creating and updating baseline communication relating to those new tests from an educational perspective will not only allow the other working groups to maintain consistency, but it will also allow for broader understanding of their potential use and benefits/risks across the health sector.

Key aims/activities of the Communications Workgroup fall into the following categories:

- **Health care professionals' education:** develop materials and strategies to communicate with and educate health care professionals about MCED tests so that they can engage in policy discussions and have resources available for delivery and discussion with patients.
- **Public engagement:** conduct activities to engage and involve the public in two-way communication about MCED tests, to increase public awareness and understanding.
- **Communications guidelines:** provide guidance for the Consortium to ensure the use of standardized language and concepts internally and externally.

Going Forward: Potential Barriers and Other Considerations

It's anticipated that the Consortium's efforts will be of interest to a range of stakeholders across the health care system and that its work will prompt important conversations and questions. The Consortium expects to discuss barriers and potential solutions as continued considerations of the many complex elements needed for potential integration of MCED tests into the care delivery system are addressed. The structure of the Consortium's process and workplan allows flexibility to adapt to any

challenges that might arise, and the Consortium has developed approaches that can help do so. For example, ongoing efforts will prioritize identifying gaps in expertise and perspectives, including public health considerations, and communicating information to the public about its work in an accessible way.

The Consortium also aims to ensure that the work remains transparent and relevant to stakeholder populations. Release of outcomes of the ongoing work should help to convey core information to all stakeholders and enable feedback where appropriate. Essential information might include what types of cancers an MCED test detects and at what stages; what patient populations will derive a net benefit from MCED screening; and whether clinicians should implement MCED tests in real-world practice.

Many issues will arise during this process beyond the overarching objectives of the Consortium, but nonetheless relevant in a broader sense. The Consortium aims to recognize those issues, but scientific considerations will remain a focus of this work. For example, MCED will not exist in a vacuum, and additional forms of diagnostic workups – including traditional single cancer tests - may be necessary following a positive test to confirm the presence of cancer.

Conclusions

The MCED Consortium will focus on the critical importance of rigorous proof of clinical utility of MCED tests, which necessarily requires concurrent consideration of care delivery, health equity, and communication with key stakeholders. As such, the Consortium sets out to explore foundational issues and problems necessary to advance the introduction of evidence based MCED technologies into clinical practice. The Consortium expects its work will serve as a robust, expert-informed resource for scientific, regulatory, advocacy and healthcare delivery stakeholders to advance the shared goal of reducing cancer incidence and mortality.