Evaluating the Clinical Utility of Multi-Cancer Early Detection Tests: Key Takeaways

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

Evaluating the Clinical Utility of Multi-Cancer Early Detection (MCED) Tests: Envisioning A Path Forward

The Multicancer Early Detection Consortium Clinical Utility Workgroup paper, *Evaluating the Clinical Utility of Multi-Cancer Early Detection (MCED) Tests: Envisioning A Path Forward* is intended to inform providers, guideline developers, regulators payers and other decision-makers who will need to make judgments about the benefits and risks of MCED testing in the context of substantial uncertainty. While MCEDs also hold promise for diagnostic use in symptomatic patients, the focus here is screening. The paper provides an overview of the limitations of currently available cancer screening tests, the promise of MCEDs for cancers without established screening tests, the current state of MCED test development, the evolving evidence landscape for use of MCEDs in cancer screening, and the shape of clinical evidence needed for further development.

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

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

Therefore, rapid evaluation of clinical utility is needed. Yet randomized controlled trials (RCTs) with mortality endpoints, which are the gold standard for assessing new screening tests, can take decades and many thousands of patients to yield results. In the interim, MCED tests are likely to evolve rapidly, diminishing the relevance of trial results. There is also potentially significant opportunity cost in deferring adoption of screening tools that could reduce cancer mortality. One notable exception is a UK-based MCED screening trial that has been able to rapidly Service to assess an intermediate endpoint (stage shift) relatively quickly – within three to four years of randomization – followed by longer-term assessment of cancer-specific mortality.[5] Although it evaluates only one test among many, the trial demonstrates the possibility of rapid recruitment of large populations within large, integrated health systems and points the way towards one use of intermediate endpoints.

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

Developing a Clinical Utility Framework

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

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

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

Key Clinical Utility Framework Principles

- MCED tests are designed on the principle that all tumors have shared biological features, with a common set of cellular products accessible through the circulatory system. This biology allows for the detection of a cellular signature associated with many different types of cancer. As such, MCED tests are intended to be used and evaluated as a single, integrated test; not as a panel of individual cancer screening tests. Variations in natural histories of, and treatment options for, individual cancer types may create the need in some circumstances to evaluate MCEDs on a cancer-by-cancer basis (or even by subtypes of a given tissue of origin). The clinical utility

framework considers the circumstances where cancer-specific analysis and reporting may be needed while maintaining the fundamental principle that MCEDs function as a single test.

- Development and use of intermediate and surrogate endpoints likely to correlate with effectiveness of MCEDs in screening will be necessary to support nearer-term evaluation of MCEDs. Such endpoints should be judiciously chosen and standardized in their use so that comparisons can be made across studies, facilitating more rapid learning. At this time, a key candidate measure is an increase in detected incidence of early-stage cancers with a corresponding decrease in detected late-stage cancers (stage shift). Other useful tools might include assessment of the proliferative rate of detected tumors as determined by gene expression profiling and possibly the pathological grade of tumors. Proliferative rate is indicative of tumor aggressiveness, which is frequently correlated with tumor lethality. There may also be a similar relationship between pathological grade and lethality. These assessments may therefore provide insights about the impact of MCED screening tests on preferential detection of potentially lethal cancer types vs. possible overdiagnosis of indolent cancers. In addition, a more conventional endpoint in oncology trials, time-to-progression, might serve as a useful surrogate for mortality.
- If and when MCED tests are adopted for screening, it will be crucial to employ strategies for ongoing learning about test performance and associated outcomes that can complement data generated from screening RCTs and other studies. Plans for the development and use of real-world data (RWD) to generate real-world evidence (RWE) integrated meaningfully with other studies are therefore a central focus of the emerging framework. One key priority is to standardize data elements (e.g., data collected on patient characteristics, clinical confirmation procedures and pathology, MCED test screening characteristics, etc.) and definitions used to assure comparability between datasets. Furthermore, policy mechanisms to promote broad collection of these standardized data elements are essential.
- Evidence generation is viewed as a continuum over which study questions, study designs, and study outcomes will evolve. Although a continuum, the pathway for evidence generation will not be strictly linear. Improvements to testing technology are expected and will be accounted for. Results from completed studies will inform rethinking of other, ongoing work, and offer insights into the design of future products and future studies.
- Cooperation and collaboration of many stakeholders is needed for successful near- and intermediate-term evaluation of MCED screening. For example, this is necessary in the context of standards for clinical validation data and reporting needed to inform clinical utility study designs. The Consortium will seek alignment with others working in this area, notably the US FDA and BLOODPAC. Likewise, cooperation and alignment on collection of RWD must be sought from health systems, employers and other organizations that initiate MCED testing. In these and other ways, a community of stakeholders must be engaged and mobilized.

About the MCED Consortium

The MCED Consortium is an independent, nonprofit, US/UK public-private consortium. The MCED Consortium has brought together stakeholders from across the healthcare continuum to evaluate their benefits and risks, to develop guidance for their [potential] introduction into clinical care, including equitable access and use, and to accelerate education on how they may improve patient outcomes and survival. To learn more about the Consortium, please visit our website. The MCED Consortium's latest guidance on evaluating the clinical utility of MCED tests can be found here.

References

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