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Multi-Cancer Early Detection Testing: Closing the Gap in Cancer Prevention

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Abstract

Early detection and screening of cancer can lead to far more favorable outcomes through early treatment and preventative measures. The field of Multi-Cancer Early Detection (MCED) is predicated on the capability to detect a signal of cancer from one blood-draw. This is clearly a transformational breakthrough but it is still early days and more work is needed. Certainly, there seem to be very positive early signs on the sensitivity, specificity and concordance of the testing. Moving forward, there would appear to be a clear economic case to be made for paying for one single test as opposed to multiple tests and who should be testing, when to test and how often. For cancers where there are currently no screening strategies in place—MCED testing is primed to be fine-tuned and developed further to offer preventive medicine for those high-risk populations.

Keywords: Multi-cancer • Early detection • Liquid biopsy • Methylation • Biomarker

Introduction

Cancer screening works by reducing the risk of death and morbidity through the detection at the earliest possible stage of well-defined and clinically important precancerous or early invasive lesions, which are more amenable to curative treatments than when detected from clinical presentation. Overall, survival rates improve dramatically for cancers detected before metastasis. Despite today's detection technology advancement, however, many cancers still go undetected until after the disease has spread (Figure 1). Instead of detecting cancers one by one, various technologies promise multi-cancer early detection (MCED) and some of these approaches are already being used. Routine population-based screening is currently recommended only for breast, cervical, colorectal and lung cancers, which are relatively common and have evidence of benefits related to reductions in the risk of death that outweigh the harms for the respective screening tests.

Literature Review

Patients could gain huge benefits from MCED. Experts have estimated 85% of cancers as somewhat likely to extremely likely to be cured in stage I, 60% in stage II, 5% in stage III, 0% in stage IV [1,2]. These opinions revealed the stark outcomes of cancer that is discovered late, often too late. In addition to saving more lives, MCED could save money spent on healthcare. It has been estimated that current methods of screening a patient for breast, cervical, colorectal and lung cancer could cost nearly $90,000, but MCED could do all of that screening in one run for about $7,000 making it nearly 13 times less expensive [3]. Such healthcare savings quickly grow into gigantic financial returns. To reach those clinical and economic benefits, oncologists need cutting-edge MCED technology that is accessible, affordable and accurate. A collection of advanced breakthroughs might eventually make late-stage cancer diagnosis a thing of the past for humans (Figure 1).

Current status of MCED

Rather than analyzing a tissue or scanning a patient, modern MCED tests encompass a range of technologies that target multiple cancers using samples such as blood, breath, urine, saliva, or stool. When combined with the existing standard-of-care for single-cancer screening, these emerging technologies could provide clinicians with the opportunity to identify a broad range of cancers earlier and more accurate in the course of the disease, raising the potential to treat patients more effectively. Crucially, companies are developing MCED tests for high-risk and asymptomatic populations. To accomplish this goal, an MCED test looks for cancer-specific biomarkers or signatures, such as DNA mutations, gene expression or methylation patterns, signals that are representative of tumor and/or from its microenvironment. While all MCED tests indicate if a cancer signal is present, some provide molecular information about the likely tissue of origin. When an initial signal is positive for cancer, further analysis can be conducted to determine the primary site of the cancer, which can provide clinicians with insights for follow-up testing for a confirmed diagnosis.

Although many MCED tests are going through various stages of research and development, none have been approved by the U.S. Food and Drug Administration (FDA). Nonetheless, the FDA has granted Breakthrough Device designation to a few. Most of MCED tests rely on methylation sequencing (or bisulfite conversion sequencing) using plasma cell-free DNA (cfDNA), followed by analysis based on algorithms derived from machine training and learning—all of which takes about 2-3 weeks to complete. Although MCED can significantly reduce the cost of long-term cancer management, the commercialization process suggested that reaching such economic goals could be long and expensive [4].

A cancer-free person's blood always contains trace amounts of cfDNA, but it's usually just from blood cells. In cancer patients, though, the blood can be enriched with circulating tumor DNA (ctDNA) due to high turnover rate of tumor cells. Multiple studies have demonstrated the value of ctDNA analyses at various stages throughout the clinical course of cancer [5]. However, ctDNA is a challenging biomarker. First, there's not much of it, compounding with a huge dilution effect which makes detection difficult. Plus, the heterogeneity of ctDNA creates another layer of complexity. Different types of cancer and even different tumors within the same type of cancer can have different genomic alterations. Therefore, it can be challenging to develop a single blood test that can catch all types of cancer. Accuracy can also be problematic. Healthy individuals can have altered cfDNA, e.g., background somatic mutations which might be misidentified

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as ctDNA and there can be no detectable ctDNA in patients with certain types of cancer. Digital analytics can help scientists analyze cfDNA patterns and trending. Machine training and learning can be used to develop algorithms that can analyze large amounts of genomic data and identify patterns that are associated with specific types of cancer, enabling the improvement of the accuracy and reliability of cfDNA-based MCED tests. Consequently, machine-built algorithms can help to distinguish between healthy individuals and patients with cancer [6].

Beyond just identifying mutations in cfDNA, scientists also explore other molecular characteristics. For example, cfDNA methylation can provide information on the tissue of origin of the cancer, which can be useful for early cancer detection and diagnosis. In addition, the potential of using cell-free messenger RNA (cfmRNA) [7] and open chromatin regions, such as starting sites for transcription, as signatures of cancer have been explored [8]. The finding that LINE-1 (long interspersed nuclear element 1) transposon insertions are ubiquitous, overexpressed and appear early in cancer, suggesting instead of being a byproduct of cancer, these LINE-1 insertions may play a role in the development of disease. Plasma LINE-1 has shown promise for early detection of ovarian cancer, improved diagnostic performance in a multi-analyte panel [9]. The MCED test innovation is growing increasingly complex and multiomic, especially as these new technologies inform precision-oncology applications. It is thus essential to bridge the gap between technologies and clinical outcomes.

The U.S. National Cancer Institute (NCI) will be running its Vanguard Study, which is part of President Joe Biden's Cancer Moonshot initiative. This clinical trial will start enrolling participants in 2024. A White House fact sheet describes Vanguard as "a large national trial that, if successful will identify effective blood tests for the detection of one or more cancers, providing the opportunity for additional, less-invasive tools for early detection [10].

Real-world questions

Despite the appeal of MCED and the large investments in the technology, many questions remain. The top of the list is positive predictive values (PPV), the percentage of patients with a positive MCED screening test actually have cancer. That is a key question. Although the answer varies between MCED tests. In terms of identifying a cancer and its source, some MCED tests produce impressive results (Table 1). For example, addition of MCED test to standard-of-care screening has more than doubled the number of cancers detected and the MCED-predicted cancer signal origin had 97.1% accuracy [11]. Other key questions regarding clinically available MCED tests are concentrated on clinical outcome, cost and accessibility. Even though some studies suggest that MCED testing might be less expensive than conventional methods, the big spending going on in this section of oncology research and development raises questions about the overall economy that will surround the MCED sector. One additional fundamental question that must be answered is: When would MCED tests be used? In fact, this general question spawns a collection of related concerns, such as: Should patients be retested? If so, how often and based on what criteria? Like many new technologies in healthcare, the questions can outstrip the answers and MCED testing is not immune to that challenge. Providing answers to these crucial questions about MCED testing will take more time, research and investment (Table 1).

MCED clinical implementation

Much like MCED combines multiple cancer tests in one, teams of medical and scientific communities need to work together to advance this technology. The mission at this critical phase is to evaluate emerging data from MCED studies and establish standards in MCED technology by defining the clinical and public-health value of the technology, providing guidance for its use in clinical practice and developing a public-outreach approach that identifies and mitigates potential health inequities that could arise from the use of MCED technology.

Although this industry approaches MCED testing from a broad perspective, one urgent objective is to define and reach broad consensus on how to evaluate MCED tests in the clinical context and create processes for creating a clinical utility framework. Scientists push on to find new early-stage biomarkers for cancer and better technologies to detect them, companies invest large amounts of resources in developing MCED tests, governments set up clinical trials, still, the oncology community must wait for the ultimate answers to the clinical utility and validity of MCED tests. Manufacturers of currently available MCED tests are now conducting trials to develop the evidence needed to fully assess the benefits and harms and therefore, to support applications for regulators and payer. Recognizing that, until that threshold is met, many commercial insurers and the medicare program may not cover these tests, though some may engage in pilot programs. And without payer coverage, the use of currently available MCED screening tests – and their potential health benefits - will likely be limited to more affluent individuals who can afford to pay out of pocket.

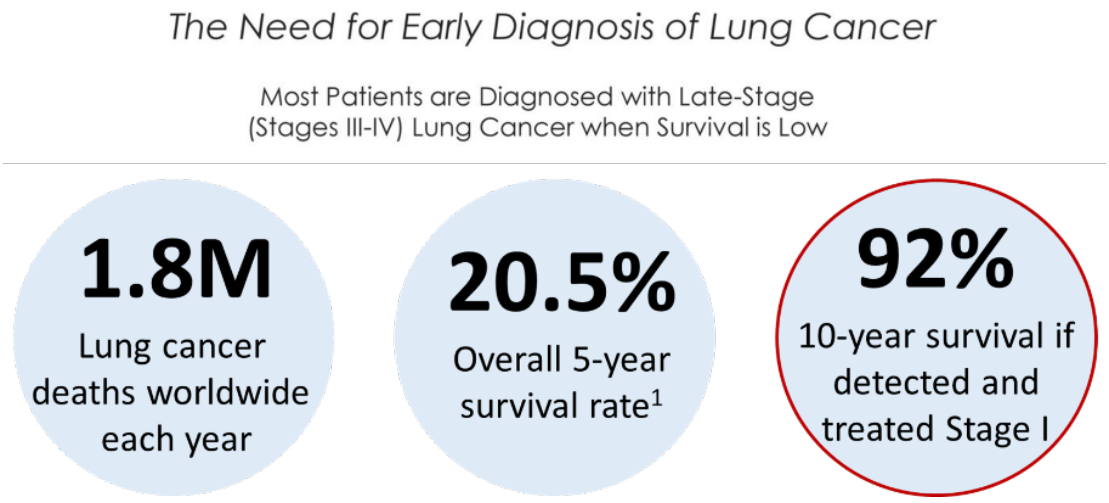

Figure 1. Early detection of lung cancer increases long-term survival.

Table 1. Performance of representative MCED tests on market.

Test/Company	Galleri (Grail)	Over C (Burning rock)	Delfi (Delfi Dx)	Lunar (Guardant health)	CancerSEEK (Exact sciences)	MCED (OncoDxRx)
Platform	Bisulfite NGS	Bisulfite NGS	Whole genome sequencing	Bisulfite NGS	NGS	Proprietary (non-NGS)
Biomarker	Methylation	Methylation	Fragmentation profile	Mutation; Methylation	Multiomics	CpG Methylation
Indication	>50 Cancer types	6 Cancer types	7 Cancer types	4 Cancer types	8 Cancer types	14 Cancer types
Sensitivity	51.5%	80.6%	73%	90%	62%	ND
Specificity	99.5%	98.3%	98%	90%	99%	ND
AUC	ND	ND	0.94	ND	0.91	0.895

Discussion

An early cancer diagnosis, one far earlier than is currently possible, will definitely benefit a patient. The greatest challenge is that it may take more than 10 years to assess the effect of MCED test on mortality and it will be critical to consider evaluating intermediate endpoints, such as an increase in cases diagnosed at an earlier stage with a concomitant decrease in the number of advanced stage cases. The industry must balance the many years it will take for trials enrolling tens of thousands of randomly assigned patients to demonstrate a net survival benefit of adding MCED tests to standard screening against the potential harms of delaying their use.

Conclusion

There is a tremendous public health urgency to screen and identify potentially lethal cancers at the earliest possible stage, when there is a greater chance for improved survival. Currently, there are five different screening recommendations and tests for breast, colorectal, cervical, lung and prostate cancers in the US, by contrast, transformative liquid biopsy-based MCED tests can screen for multiple cancers simultaneously based on a simple blood-draw. However, MCED tests will also present challenges to healthcare system because of intrinsic features of the tests and the complexity of payer coverage assessments for screening tests.

DNA methylation-based tests are in forefront of development, being the most frequently chosen source of biomarkers, due to its features of aberrant tumor-specific patterns, tissue-specificity and easiness to assess in cfDNA. By combining molecular analysis with artificial intelligence and machine learning, the performance of MCED tests could be greatly improved. Nevertheless, MCED tests still lack validation in large-scale prospective trials to enable their implementation into population-based screening programs and make their way into routine clinical practice.

The successful creation of a national regulation that removes financial barriers for the entire cancer screening process warrants that similar policies be quickly put into place for individuals who need follow up care after an abnormal initial screening test. Access to MCED tests provides additional opportunities to enhance equity. The convenience associated with a single blood test to screen for multiple cancers may lead to a reduction in disparities because of the proposed ability to detect more aggressive tumors that disproportionately affect minority patients. Moreover, although the impact of the availability of MCED tests on recommended cancer screening rates is unknown, there is potential that the increased convenience of a MCED blood test can lead to a "educational moment" in which eligible individuals, not yet up to date on recommended screenings, increase their use. Finally, there is a strong emphasis that MCED tests are to be used in conjunction with and not as a substitute for, recommended screenings. Clinicians and policy makers must closely follow this interaction between MCED availability and recommended screening rates as the use of MCED tests evolves in various patient groups.

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Conflict of Interest

The authors declare no conflict of interests.

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