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EXECUTIVE SUMMARY

Seizing the Transformative Opportunity of Multi-cancer Early Detection

STEPHEN EZELL | APRIL 2021

Cancer remains one of humanity's most implacable enemies, with over 25 million cases expected globally in 2025. In the United States, cancer claims 600,000 lives annually, making it the second-most common cause of death, and which is expected to become the leading cause by 2030, with one in two American women, and one in three men, likely to be diagnosed with the disease in their lifetimes. And progress, while real, has been slow. While the age-adjusted death rate per 100,000 U.S. population from heart disease fell by roughly two-thirds from 1950 to 2010, the similar rate for cancer just barely slightly decreased. Meanwhile, cancer remains one of the most difficult diseases to detect. Only about 20 percent of patients with cancer are detected through screening today, and 70 percent of U.S. cancer deaths occur from cancers for which there are no guideline-recommended screening alternatives.

Transformative New Approaches and Technologies for Cancer Screening Are Emerging

Cancer will not be solved without hard-fought, biomedical innovation. Fortunately, a revolutionary new approach, multi-cancer early detection (MCED)—powered by a suite of advanced technologies including artificial intelligence and gene sequencing—is emerging, heralding the opportunity to transform cancer screening, potentially detecting many more cancers much earlier, saving lives and potentially generating economic benefits. However, if America is going to lead in this field amidst growing global competition, enabling both its innovative companies to thrive and its citizens to receive the benefits of these technologies, policymakers will need to craft a supportive regulatory and coverage environment.

Blood-based multi-cancer early detection technologies hold the potential to detect, from a single blood draw, signals for as many as 50 different types of cancers with a very high rate of accuracy, a low false positive rate, and the ability to trace the detected cancer to its likely tissue of origin with a high degree of confidence. As all human cells shed nucleic acid fragments into the bloodstream, the technology works by detecting circulating tumor DNA (ctDNA) in the bloodstream as a biomarker for cancer detection. Further, the technology seeks to link detected cancers to their tissue of origin by analyzing methylation patterns. Methylation refers to an essential step in the process of cellular differentiation—what directs a cell to evolve into kidney, liver, or heart tissue, for instance. With each cell type in the body having a unique methylation pattern, or "fingerprint," MCED uses a combination of novel biochemistry and AI techniques to learn to connect detected cancers to their likely tissue of origin.

The Benefits of Screening for More Cancers and Detecting Them Earlier

Unfortunately, only five types of cancer—breast, cervical, colorectal, prostate, and "high-risk" lung—have guideline-recommended screening options available today, whereas the vast majority of cancers, including blood, head and neck, pancreatic, ovarian, and liver cancers, have none. As such, the vast majority of cancers are found when patients arrive at doctors' offices manifesting physical symptoms. MCED technologies hold the potential, perhaps within a decade, to reverse that, with three-quarters of cancers being screen-detected and just one-quarter symptom-detected, and where roughly half the screen-detected diagnoses are provided by MCED and half by single-cancer screening methods. However, to be clear, MCED should be viewed as a complement, not a substitute, to currently recommended cancer screening guidelines for the aforementioned five cancers.

MCED technologies are poised to expand the pool of cancers for which there exist effective treatment options and catch cancers earlier when treatment options are more effective and prognoses likely to be more positive. Overall, patients' survival rates are 5 to 10 times greater when cancer is detected at an early stage rather than at a late stage. In fact, when cancer is diagnosed after it has spread, the five-year cancer-specific survival rate is 21 percent, compared with 89 percent when the cancer is diagnosed early and still localized. If the United States could combine its strengths in developing effective cancer therapeutics with an ability to detect many more cancers much earlier, it could truly transform America's continuing war on cancer.

Doing so could also generate considerable economic benefits. Cancer is the second-most-costly disease in the United States; in 2017, cancer care cost an estimated $177 billion (39 percent higher than in 2010), equivalent to 1 percent of GDP. Cancer accounts for 11 percent of the annual U.S. health care budget. Detecting cancers earlier may indeed save on treatments costs, because treatment of metastatic cancer is as much as two times more costly than treatment of cancer before it metastasizes.

Thus, making significant progress on cancer could not only save lives, but money. For instance, one study finds that a 1 percent reduction in mortality from cancer could deliver roughly $500 billion in net present benefits, while a cure could deliver $50 trillion in benefits.

Specific Benefits of MCED Screening Approaches

In terms of cancer screening and detection, MCED approaches are poised to yield several additional benefits. First, the screening process (beyond the blood draw) is much less invasive and, with many cancers presenting as unspecified pains in certain parts of the body, which can even be difficult to physically biopsy, MCED can expand the range of cancers for which earlier detection is physiologically possible. Second, the logistical ease of such testing could benefit those living in rural communities who may experience more difficulty in seeing doctors for physical screening exams or more difficulty in accessing specialized screening services, such as for mammography or low-dose computerized tomography (LDCT). This could have a particularly important impact in ameliorating racial and socioeconomic disparities in cancer screening availability. Third, America is experiencing a significant COVID-19-induced cancer screening gap. To wit, a June 2020 report from the National Cancer Institute estimates that missed screenings and other pandemic-related impacts on cancer care could result in approximately 10,000 additional deaths from breast and colon cancer alone over the next 10 years. If there

were more-accessible cancer screening options, especially ones that could be carried out in a time of social distancing, many fewer people would have not waited to be screened.

Addressing Potential Misgivings About MCED Approaches

While there are potentially significant benefits from MCED screening, some concerns have been raised, including that they might lead to overdiagnosis or return very high false positive rates.

The first concern pertains to MCED's potential to detect indolent cancers, which are those that progress slowly and do not pose an imminent threat to a patient's health. Some have called these the types or stages of cancers that people will increasingly die "with," rather than "from." As such it's important that MCED technologies be attuned (or optimized) to identifying particularly the invasive, fastest-growing, most-lethal cancers. In this regard, it's fortuitous that scientific research appears to indicate that indolent, less-aggressive cancers are less likely to shed ctDNA into the bloodstream and that it tends to be the more-aggressive, faster-growing cancers that are shedding the most ctDNA, conferring better ability for MCED tests to discriminate between indolent and aggressive cancers.

Closely related to the challenge of minimizing overdiagnosis is minimizing the return of false positives. While this will certainly be a challenge to be addressed in MCED screening, the reality is that it's a challenge with the current single cancer-screening paradigm already. The $27 billion America spends on cancer screening yields about 9 million positive results annually; of these, only 204,000 turn out to be actual cancers, while 8.8 million being false positives. Likewise, the cumulative screening tests recommended for a 60-year-old U.S. female with a history of smoking (thus suggesting screening for breast, colon, cervical, and lung cancers) yield a 37 percent likelihood of at least one false positive result. Critical here are cancer screening tests' positive predictive value (PPV), which represents the probability that a patient with a positive (abnormal) test result actually has the disease. Here, MCED tests appear to at least be comparable to other cancer screening procedures in terms of their PPV.

To be sure, optimizing MCED systems to avoid overdiagnosis, increase their PPVs, and lower false positives will be crucially important to the overall success of MCED screening tests. However, it is important to note that the bigger problem today is underdiagnosis, and the potential to make quite significant progress in that area should not be sacrificed out of fears of overdiagnosis, which the scientific evidence to date suggests can be limited by MCED technologies, especially as they continually learn over time, which is likely to further improve their accuracy.

An Emerging and Intensely Competitive Global Industry

The global competition for leadership in the field of blood-based cancer detection has become increasingly fierce. Competitors such as China's Singlera Genomics and South Korea's Genecast are developing ctDNA-based cancer-detection systems. China in particular has identified the biopharmaceutical industry as one in which it seeks global leadership, showering the industry with support through funds and programs articulated in both its Made in Chins 2025 strategy and new 14th Five Year Plan. The country seeks to leverage its strength in gene sequencing, for which it holds the world's largest capacity, and AI to make itself a global leader in this field.

Other countries are also looking to ensure their citizens receive the benefits of these technologies first. For instance, in November 2020, the United Kingdom's National Health Service partnered

with GRAIL to test its MECD technology, Galleri, in a program involving 165,000 British citizens, which may be expanded to one million British citizens in 2024–2025, and a larger population thereafter, should the pilot go well.

Getting the Regulatory and Coverage Environment Right for MCED in the United States

If the promise of MCED is to be realized in the United States, policymakers will need to get the regulatory and coverage environment right. As medical science's understanding of cancer has evolved over the past half century, so too has the evolution of recommended cancer screening guidelines. Moreover, with persons over 65 accounting for 60 percent of newly diagnosed malignancies and 70 percent of all cancer deaths, this issue becomes even more important for Americans on Medicare—and that's why it's important that Medicare carefully review offering MCED screening as a covered benefit.

When Medicare was launched in 1966, it initially covered only acute health care situations (e.g., sicknesses or hospitalizations). However, over time, Congress directed Medicare to add a range of covered benefits for preventive services, such as for cardiovascular disease, diabetes, hepatitis C, and HIV. Today, in terms of cancer, Medicare provides covered screening benefits for cervical and vaginal cancer, colorectal cancer, lung cancer (LDCT, once each year), mammograms, and prostate cancer.

However, Medicare does not cover cancer screening as a preventive benefit except where Congress has explicitly amended Medicare laws to provide such coverage. Cancer screening was added for the first time as a statutorily covered Medicare benefit when the Omnibus Budget Reconciliation Act (OBRA) of 1989 added coverage for pap smear tests (and pelvic exams) to examine for cervical and vaginal cancers. A year later, the 1990 OBRA added a benefit for mammography to examine for breast cancer. In 1997, the Balanced Budget Act added prostate and colorectal cancer screening benefits.

Policy Recommendations

Today, as a new-generation of multi-cancer early detection technologies are coming to the fore, it's time for Congress to act again, by creating a pathway for Medicare coverage of MCED screening tests. And that's exactly what bipartisan, bicameral legislation in the Medicare Multi-Cancer Early Detection Screening Coverage Act seeks to do. The Act addresses the misalignment between advances in science and Medicare coverage by permitting Medicare coverage of multi-cancer screening. The legislation creates the authority for the Centers for Medicare & Medicaid Services (CMS) to use an evidence-based process to cover blood-based MCED tests and future test methods once approved by the U.S. Food and Drug Administration, while maintaining CMS's authority to use an evidence-based process to determine coverage parameters for these new types of tests.

Cancer has proven to be a relentless and wily enemy. To defeat it, we're going to need to embrace equally creative solutions and radically new approaches, such as how checkpoint blockading and immunotherapy transformed cancer therapy. MCED heralds the potential for another significant breakthrough to dramatically enhance patients' lives by detecting cancers earlier, and to put the nation's cancer response on a more-sustainable economic footing. It's time for policymakers to embrace this opportunity.

About the Author

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