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TECHNICAL WHITE PAPER

Perspectives on the Future of Noninvasive Multi-Cancer Screening and Early Detection

Introduction

A revolutionary development in the oncology field is the emergence of technologies that enable clinicians to rapidly screen for multiple cancer types using a single blood sample. These tests, known as multi-cancer early dection (MCED) tests, are designed to detect circulating tumor biomarkers in the blood. In certain cases, they can also detect which organ the cancer originated from.

The aim of these technologies is to improve early detection, treatment, and outcomes for cancer patients. However, many questions remain unanswered relating to the benefits, risks, and value associated with introducing MCED technologies into clinical care. This paper summarizes discussions between Dr. Lori Minasian (Deputy Director, Division of Cancer Prevention, NCI), Dr. Girish Putcha (Principal, Precision Medicine & Diagnostics, LLC), Dr. Megan Hall (Vice President, Medical Affairs, Grail), and Dr. Ruth Etzioni (Professor, Public Health Sciences Division, Fred Hutch Cancer Center) about the challenges and opportunities of MCED tests.

Improving Early Cancer Detection

One of the benefits of early cancer detection is that intervention strategies can be implemented when the disease is potentially more amenable to treatment. Currently, single-cancer screening tests are available for a small number of cancers, including breast, cervical, colorectal, and lung. These tests screen asymptomatic individuals and involve either imaging procedures, direct observation tests, or analysis of laboratory samples. However, single-cancer screening tests have high cumulative false-positive rates and are unavailable for most cancer types. "Given that 70% of total cancer deaths occur from cancers lacking a screening test, there is a sense of urgency to have a method for early cancer detection," explained Dr. Hall. This raises the question of how to balance out clinical need with the requirement for long-term population-scale studies.

Due to the novelty of MCED technologies, there is limited research and follow-up data available on the population-based impact and clinical endpoints of multi-cancer screening. One of the first studies to publish MCED test data was the prospective PATHFINDER study (NCT04241796), which evaluated the implementation of MCED screening in over 6,600 individuals aged 50 years and over who were not known to have cancer. The study found that adding MCED testing to standard-of-care screening more than doubled the number of cancers detected compared to standard-of-care screening alone over a 12-month follow-up period.

While these results are certainly promising, Dr. Putcha believes there are still unknowns when it comes to the use of MCED screening in a clinical setting. "First, is the test going to include cancers for which standard-of-care screening already exists or only cancers for which screening is not currently recommended?" he questioned. "Second, if it does include cancers for which there is already a standard-of-care screen, where in the care pathway will it be used? And finally, in what patient population will the test be used?" Efforts are also needed to address barriers that prevent equitable access to MCED tests so that health disparities are reduced or avoided.

Assessing Test Performance

Another consideration for implementing population-scale MCED screening is that the tests must demonstrate adequate performance characteristics such as sensitivity, specificity, and positive predictive value (PPV). Several large, prospective studies have either been completed or are underway to clinically validate the utility of MCED screening. Notably, results from the PATHFINDER study showed that the specificity for the two MCED tests evaluated was above 99%, with a true false positive rate of less than 1%. "MCED technologies were designed to maximize the specificity or minimize the number of false positives," said Dr. Hall. "They detect a cancer signal at a fixed specificity level which is exhaustively high so that the number of false positives is minimized. This is one of the fundamental differences between single-cancer tests which were designed to optimize sensitivity and tolerate a much higher false positive rate."

The PATHFINDER study also reported a PPV of just over 40%. "To put that into context, the PPV for a mammography is about 4.5%, meaning that between four and five of every 100 positive mammograms are actually cancer," explained Dr. Hall. "If you look at MCEDs, the PPV is ten times as high, so there is a huge sense of urgency around that positive result as there is an approximately one in two chance that a positive result will go on to be cancer."

In addition to the performance indicators mentioned above, a gold standard endpoint for cancer screening trials is a reduction in cancer-specific mortality. However, the feasibility of conducting mortality studies within a reasonable timeframe for MCEDs is unclear. "We have a tremendous challenge ahead

of us because even with the few single cancer tests that we've had in the past, trials to evaluate them have taken a tremendous amount of time and effort, and the answer is not always clear," said Dr. Etzioni. "Also, we have never been in a situation where we have to evaluate so many technologies with such a sense of urgency."

Endpoints based on late-stage cancer incidence or stage shift have been proposed as surrogate endpoints in a number of MCED screening trials. However, Dr. Etzioni cautions that the available data does not confirm that these endpoints translate to a reduction in mortality. "All cancers are different, so while we could expect that advanced stage reduction will lead to a significant reduction in mortality in some cancers, for others, that same advanced stage reduction won't really change mortality," she said. "While it's certainly important to show a reduction in advanced stage, we can't have stars in our eyes as to what that will translate to in terms of mortality."

Real-world Benefits

Regardless of how these tests are implemented, Dr. Minasian emphasized the importance of communication between clinicians and patients if a positive signal is detected. "Unlike diagnostic tests such as pregnancy tests, where a positive result suggests an individual is highly likely to be pregnant, a positive MCED result does not necessarily mean they have a diagnosis of cancer; it indicates that further diagnostic workup is required," she said. But in the absence of any clear recommendations, there is currently no definitive continuum of care for patients who receive a positive test. Guidance is also lacking for patients that receive a positive test result but a negative workup. Are they screened again? At what frequency? And for how long? To address these shortcomings, consortia such as MCED and BLOODPAC are developing consensus care pathway guidelines for clinicians so that patients are provided with appropriate care, guidance, and downstream diagnostic workup in each of these scenarios. Finally, considerations need to be made about the real benefits of early detection for patients, especially if no early-stage treatment is available. "Detecting cancer early is what everybody wants, but everybody wants that cancer to be detected early, taken care of, and not to worry about it again," concluded Dr. Minasian.

Conclusion

The development of technologies that detect multiple cancers from a single blood test could transform the cancer detection landscape, presenting opportunities for cancer to be detected and treated earlier than ever before. However, before MCED tests are widely implemented in the clinical setting, there are many fundamental questions that remain unanswered.

- What additional testing is necessary after a positive test to confirm the presence of cancer?
- What types of cancers are detected by an MCED test and at what stages are these cancers?
- Which people will derive a net benefit from MCED screening?
- Can MCED tests be successfully implemented in real-world practice?

Guidance developed by consortia such as MCED and BLOODPAC will be critical to answering these questions, as will the results of ongoing and future clinical trials that evaluate the clinical utility and diagnostic performance of MCED tests in different populations.

For more information

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