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Review Article

Multicancer Early Detection Tests for Cancer Diagnosis

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Abstract

Over time, the pursuit of unraveling the source and process of a regular cell's conversion into cancer has resulted in diverse theories. These can be as diverse as considering cancer to be a supernatural ailment or comprehending the complex dynamics found within specific cancer subtypes, where several biological challenges must be addressed. Several validated screening methods are scarce for many types of cancer, and the existing ones have their limitations. This often results in low patient adherence and unnecessary medical procedures, increasing the financial burden on healthcare systems. Consequently, there is a pressing demand for inventive, precise, and less intrusive instruments for detecting cancer at an early stage. In recent times, multicancer early detection (MCED) tests have emerged as a promising approach. These tests utilize molecular analysis of tumor-related markers found in bodily fluids and incorporate artificial intelligence to simultaneously identify various cancer types and distinguish between them. Despite ongoing evaluation in numerous significant clinical trials, MCED tests may become clinically available soon without a standardized framework for assessing their performance and safety. Currently, it is only a few of them are available to doctors with different mechanisms to detect cancer but have not been approved by the Food and Drug Administration for the market. In this article, we aim to highlight the currently developed various strategies for MCED and the major factors that are preventing their clinical implementation.

Introduction

Cancer is a significant public health issue, causing the highest number of deaths in most countries. In 2022, approximately there were 19.3 million instances of newly diagnosed cancer and 10 million fatalities related to the disease were reported worldwide. Figure 1 describes the path of cancer from the time it starts to its treatment. Late detection is the primary reason for the high mortality rate, as cancer is often found after it has progressed and spread, limiting effective treatment options.[1,2] According to estimates, the timely identification of cancer could potentially avert a minimum of 15% of cancer-associated fatalities over a span of 5 years.[3] Therefore, priority should be given to cancer screening and early detection measures, including the removal of precancerous lesions and the prompt treatment of localized disease, to prevent the progression of cancer as well as its development.[4]

Keywords: Cancer diagnosis; Early detection; Tumor screening; Circulating tumor cell; Multicancer early detection.

Abbreviations: cfDNA, cell-free deoxyribonucleic acid; CTC, circulating tumor cell; MCED, multicancer early detection; EGFR, epidermal growth factor receptor.

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Cancer is a state distinguished by the unrestrained proliferation and dissemination of specific cells within the body.[5] The human body, comprised of trillions of cells, can potentially develop cancer in various locations. Normally, cells undergo growth and division (known as cell division) to generate new cells as needed. Aging or damaged cells naturally die off, making way for the replacement of new cells.[6] As cells age or suffer damage, they undergo death, and fresh cells replace them. Occasionally, this systematic mechanism malfunctions, leading to the excessive growth and multiplication of abnormal or damaged cells. These cells can cluster together and form tissue masses known as tumors. Tumors can be categorized as either cancerous (malignant) or noncancerous (benign). While benign tumors typically do not invade or spread, malignant cells are more prone to metastasizing, meaning they can travel to different parts of the body. Malignant cells also exhibit a faster growth rate. Malignant tumors, known as cancerous tumors, can infiltrate adjacent tissues, and have the potential to disseminate to remote areas of the body, leading to the development of new tumors. This phenomenon is commonly referred to as metastasis and is shown in Figure 2.[7–11] Solid tumors are commonly associated with various types of cancer, while blood-related cancers like leukemia typically do not form solid tumors. On the other hand, benign tumors do not invade nearby tissues and lack the ability to spread. Once removed, benign tumors typically do not reoccur, unlike cancerous tumors, which may regrow over time. It is worth noting that although benign tumors may not possess invasive properties, they

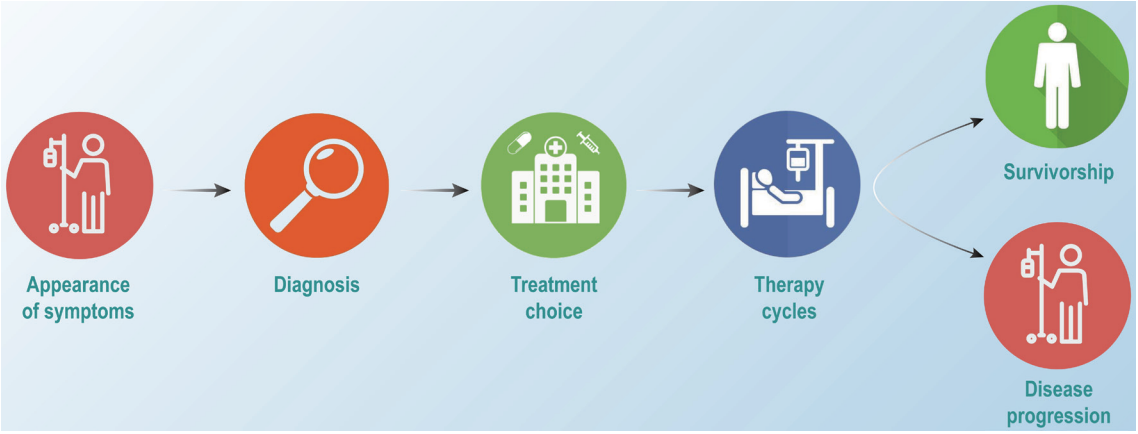

Fig. 1. Cancer diagnosis and treatment pathway in general. The figure shows how after the symptoms are recognized, the diagnosis and treatment for the specific cancer take place, leading to either disease progression or survivorship.

can still cause significant symptoms or pose life-threatening risks, particularly when located in critical areas such as the brain.[12]

Metastasis of cancer, which refers to the spreading of cancer cells from the initial tumor to other organs, is responsible for the majority of cancer-related deaths.[9,10] The dissemination of cells from the primary tumor involves various cellular processes. These processes involve infiltrating the nearby tissue, avoiding detection and suppression by manipulating the immune system, adapting to, and influencing the local tissue environment, and developing resistance to treatment approaches.[11] A comprehensive approach is required to understand the process of metastasis, which entails intricate molecular behaviors exhibited by cells having cancer and their interactions with the tumor microenvironment. This entails combining physiological metastasis models with thorough characterization of both phenotypic and molecular aspects.[13,14]

While these methods are extremely valuable, the early detection of cancer plays a critical role in preventing its progression. By identifying precancerous lesions and treating localized disease, early detection has the potential to avoid the need for more aggressive interventions. It is important to note, however, that currently recommended screening procedures are limited to certain types of cancer.[15] Unfortunately, more than 60% of cancer-related deaths are caused by malignancies that lack a screening test.[1] Early detection of cancer leads to more effective treatment and significantly

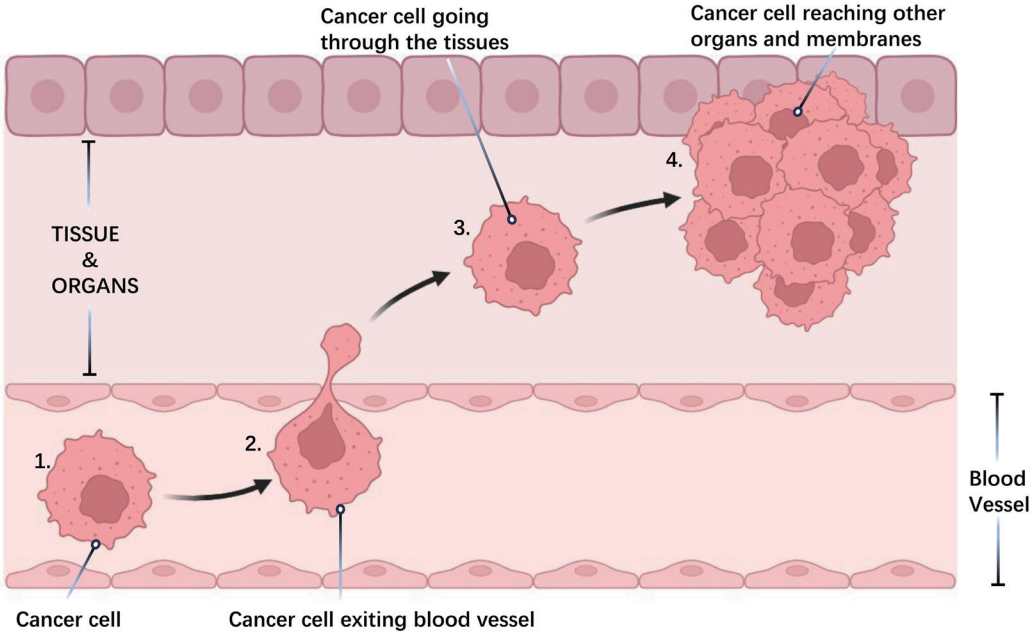

Fig. 2. Cancer cells enter the metastasis site from the blood vessel. (1) Cellular Breakaway: Cancer cells escape the primary tumor, invading nearby tissues. (2) Vessel Entry and Travel: Cells enter blood or lymph vessels, circulating to distant body parts; (3) Tissue Attachment: Cells adhere to new tissues; (4) Distant Tumor Formation: New tumors develop at remote sites. Metastasis of cancer, which refers to spreading cancer cells from the initial tumor to other organs, is majorly responsible for cancer-related deaths. The dissemination of cells from the primary tumor involves various cellular processes. These processes involve infiltrating the nearby tissue, avoiding detection and suppression by manipulating and adapting the immune system, influencing the local tissue environment, and developing resistance to treatment.[9–11]

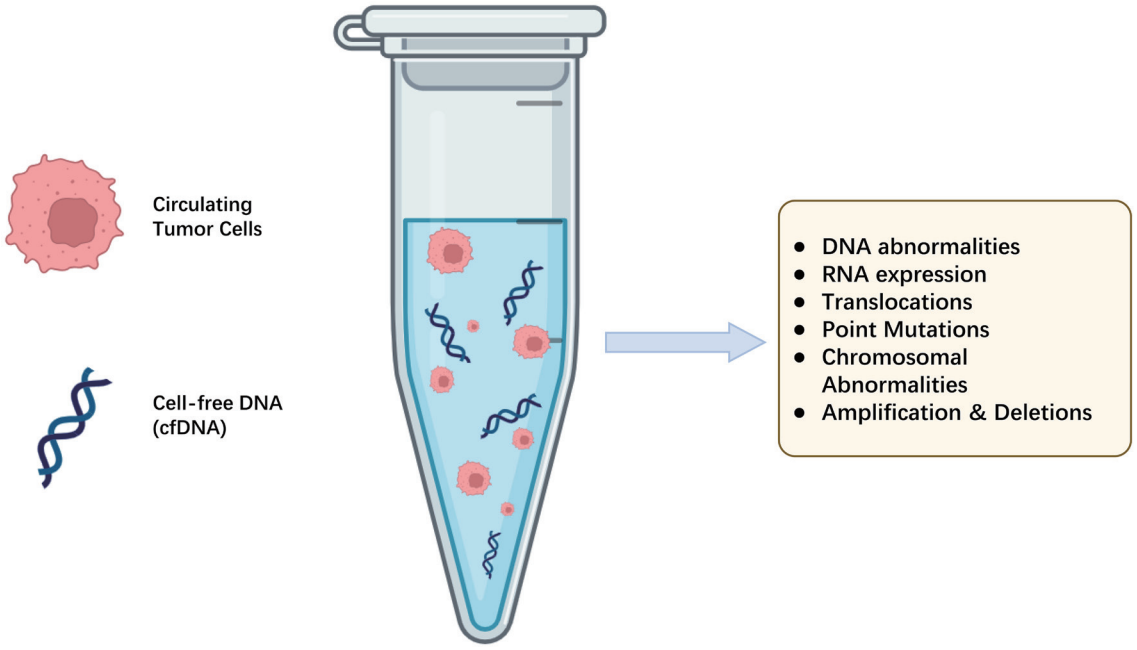

Fig. 3. Liquid Biopsy use for cancer therapy. Liquid biopsies operate under the principle that tumor material is released from a tumor into the patient's bloodstream in the form of circulating tumor cells or cell-free DNA. The figure shows different components that are shed from a growing tumor. cfDNA, cell-free DNA.

increases the chances of survival. However, nearly 50% of cancers are still diagnosed at an advanced stage, highlighting the need for better early detection methods. Enhancing early detection methods has the potential to significantly improve survival rates.[16–18] While recent advancements in early detection have already contributed to saving lives, it remains crucial to continue innovating and developing approaches for early cancer detection. The field of early cancer detection is evolving rapidly, driven by advances in biological understanding and the rapid pace of technological progress.[19] The delayed identification of cancer, often resulting from limited and ineffective treatment options, is a prominent contributor to global mortality rates. Consequently, there is an urgent requirement for innovative, precise, and minimally invasive tools to facilitate early cancer detection.[20,21] MCED tests have emerged as a promising screening tool in recent years. These tests employ molecular analysis of tumor-associated markers found in bodily fluids and leverage artificial intelligence to identify various types of cancer and differentiate between different cancer subtypes.[22]

One of the most captivating domains in cancer research involves the advancement of tests capable of detecting various types of cancer during the initial stages. These tests, commonly referred to as MCED tests, are designed to identify fragments of DNA or RNA that are released by tumor cells into the bloodstream as shown in Figure 3.[23,24] Artificial intelligence helps these tests to identify the most probable origin of the cancer. This development is exciting because a positive test result would allow physicians to detect early-stage cancers when they are most treatable.[25] MCED tests fall under the category of liquid biopsies, which employ a blood sample to identify specific biological signals present in DNA, RNA, or proteins released by cancer cells. Currently, liquid biopsies are used for individuals already diagnosed with cancer, assisting doctors in determining the most suitable treatment plan.[26–29] However, MCEDs differ from approved liquid biopsies in that they are used in individuals without any cancer-related symptoms or signs, aiming to assess multiple biomarkers to establish the likelihood of cancer presence and its potential location. This advance is indeed fascinating, but it is imperative to comprehensively evaluate the performance of these tests in large cohorts of individuals in order to validate their accuracy.[30,31] MCED tests involve collecting various samples such as blood, liquid biopsy, gene, LTD, and others to identify the presence of cancer cells in different parts of the body, including blood vessels, skin, colon, lungs, throat, and others. This diagnostic test is designed to detect tumors in the body.[32]

Several medical device manufacturing companies are developing different devices for detection of early-stage cancers.[33] The market growth is driven by government support and investment in this field. The MCED market is categorized into liquid biopsy, gene panel, LDT, and others based on the type of tests.[34] The current understanding of MCED tests primarily centers on their diagnostic performance. Previous investigations have primarily examined the sensitivity of the tests in confirmed cancer cases and the specificity in individuals without a cancer diagnosis. The outcomes have indicated that sensitivity varies based on factors such as the specific test used, the type of cancer, and the stage of cancer, and the reported specificity has consistently remained high (98–99%).[35–38]

Application of MCEDs

An early detection test potentially serves two purposes. First, in patients exhibiting symptoms, it can help minimize the time between their initial presentation and diagnosis. Second, it can be used as a screening test in seemingly healthy individuals, to identify those who may have asymptomatic cancer.[39,40] The discussion of early detection primarily revolves around its application in screening. When a cancer undergoes malignant transformation, it initially exists as a small, asymptomatic, and undetectable mass.

As a tumor progresses, there is a chance of detecting it using an early detection test prior to the manifestation of symptoms and clinical diagnosis.[41] Although cancer cells can metastasize at any stage, only a small fraction of them will ultimately develop into detectable metastases. Unfortunately, most cancer-related deaths occur following the spread of the disease throughout the body. It is important to note that as cancer predominantly affects older individuals, mortality from other causes can intervene at any time.[42–47]

Liquid biopsies potentially overcome numerous limitations associated with tissue biopsies. Nevertheless, it is anticipated that tissue biopsies will continue to be the preferred method until more advanced technologies are developed for liquid biopsy testing.[45] Tumor tissue analysis enables a more comprehensive assessment, including the detection of more mutations compared with blood samples. Nonetheless, the availability of a noninvasive blood draw to obtain genomic information about a particular cancer has significant value for several applications explored in this review.[48–50]

Liquid biopsy analysis presents several advantages and benefits:

1. It is noninvasive and is an alternative for patients who are unable to undergo tissue biopsy or as an additional evaluation for assessing drug response;
2. It is cost-effective. Liquid biopsies may be potentially less costly than tumor biopsy and analysis;
3. It is a comprehensive genomic snapshot. Liquid biopsies are an accurate representation of a tumor's genomic landscape, circumventing issues like intratumor heterogeneity;
4. Serial sampling enables the collection of multiple samples during treatment, allowing for the assessment of drug resistance and tumor progression;
5. Preservation of DNA quality in liquid biopsies avoids DNA cross-linking, which can occur with tissue biopsies preserved in formalin-fixed paraffin-embedded blocks. This preservation facilitates the sequencing of tumor DNA.

Early diagnosis refers to the identification of cancer at its earliest stage, which is typically achieved through a combination of patient awareness of early symptoms and healthcare professionals' training to recognize and refer individuals displaying potential early signs of cancer.[51,52] While not as comprehensive as screening programs, early diagnosis can be used for several common cancers like breast, skin, and stomach cancers, particularly in resource-limited settings where screening may not be feasible. It serves as a key component of any early detection initiative because not all adults have access to or participate in screening programs, which may also have limitations for detecting certain cancers.[52,53]

In the bloodstream, there are two distinct types of cancer-related substances that can be identified, intact circulating tumor cells (CTCs) and cell-free circulating tumor DNA (cfDNA), also referred to as circulating tumor DNA (ctDNA). As tumors grow, the ability of phagocytes to eliminate fragments resulting from apoptosis and necrosis may become overwhelmed, leading to the passive release of cfDNA into the bloodstream.[54] By analyzing the DNA released by tumors into the bloodstream, doctors can examine blood samples taken from a patient's arm. The amount of cfDNA present in the circulation can vary significantly, ranging from 0.01 to 90% of all DNA in the plasma, depending on the size and vascularity of the tumor. As a result, liquid biopsies provide a noninvasive approach to profiling tumor molecules without the need for acquiring tumor tissue.[55,56]

The progress made in highly sensitive detection technologies for CTCs and cfDNA has opened up avenues for the development of liquid biopsies with a wide range of clinical applications, which include:

1. Disease screening to determine the presence of the disease;
2. Patient stratification and selection of suitable therapies (companion diagnostics) ;
3. Monitoring treatment response and identifying the development of drug resistance;
4. Identifying minimal residual disease after surgery or detecting cancer recurrence.

Clinical trials

The US Surveillance, Epidemiology, and End Results program collected data on the occurrence and survival rates of invasive cancers in individuals 50–79 years of age between 2006 and 2015.[57] The data was then combined with published performance data of an MCED test using a state transition model, also known as an interception model.[58] That study aimed to forecast the diagnostic yield, stage shift, and potential reductions in mortality associated with the MCED test. Additionally, the model takes into account the long-term performance of the MCED test, considering limitations in detection due to repeated screening.

When considering a screening program, three primary types of harm should be taken into account, overdiagnosis, false positives, and direct harms from the test. Although the study did not explicitly incorporate overdiagnosis, there are competing mortality risks of approximately 2% per year within the age range of 50–79 years. If we assume that cancers detected by screening would have otherwise led to death from noncancer-related causes within the next five years, it is estimated that the diagnosis of these cancers would result in a 10% increase in cancer incidence.[59,60]

The test specificity, which was reported as 99.3%, determines the rate of false positives. This value represents the overall rate of false positives in individuals without cancer who undergo screening and remains consistent regardless of the number of cancer types screened for. To put it into perspective, out of every 100,000 individuals screened, approximately 692 would receive a false-positive result, potentially leading to further diagnostic investigations. In our analysis, we conservatively assume that this false-positive rate remains unchanged even with the use of an MCED test. Consequently, in the best-case scenario, the final positive predictive value would be 41%. However, considering the possibility of scheduling sensitivity, this positive predictive value could decrease to 31%.[61–65] In the absence of evidence from interventions, it is difficult to estimate additional harms. The MCED test involves a standard blood draw, which is generally regarded as safe and does not necessitate immediate invasive procedures. Previous studies examining other cancer screening tests with higher rates of false positives have demonstrated minimal indirect harms, such as heightened anxiety upon receiving test results.[66]

Early detection of cancer has a key role in achieving favorable clinical outcomes. While current clinics offer invasive diagnostic methods for specific types of cancer, there is a significant need for noninvasive diagnostic techniques that can detect any form of cancer. Liquid biopsy, which examines molecular components in peripheral blood, holds promise in this regard. However, existing methods based on liquid biopsy require improvement, particularly in their sensitivity to detect early-stage cancer. Enhancing sensitivity would likely involve the development of diagnostic assays that utilize a variety of biomarkers. Therefore, exploring novel cancer-related biomarkers that can be incorporated into liquid biopsies is essential. The noncoding component of the whole-blood transcriptome, despite being overlooked thus far, is a promising biomarker for comprehensive cancer detection.[67,68]

Cohen *et al*.[69] developed a method called CancerSEEK, which combines the detection of mutations in cfDNA with specific proteins in peripheral blood. This approach had a median sensitivity of 70% in detecting eight common types of cancer. Subsequently, Leon *et al*.[70] used this method in approximately 10,000 patients and successfully identified 26 cancers that had previously gone undetected by standard-of-care methods. In a study by Liu *et al*.[71] the analysis of methylation patterns in cfDNA from peripheral blood allowed the identification of 12 common cancers, for a sensitivity of 67.3%. Furthermore, this study tested 50 different cancers and achieved a sensitivity of 43.9% for detecting all cases.

Recent advancements have also shown that analyzing the transcriptome derived from tumor-educated platelets by RNA-seq analysis accurately distinguished cancer patients from noncancer patients, with an impressive accuracy rate of 96%.[72] In a comprehensive study conducted, liquid biopsies were utilized to investigate cancer mutations, revealing that these biopsies successfully detected mutations in 85% of advanced tumors. Remarkably, approximately 49% of these identified biomarkers were associated with targeted drugs that had received approval. The researchers employed a highly sensitive next-generation sequencing technique known as the Guardant360 assay (Guardant Health, Palo Alto, California, USA), which analyzed patterns of genetic alterations, including around 70 actionable tumor mutations, in a substantial number of blood specimens (17,628) obtained from 15,191 patients. The findings demonstrated a high degree of consistency between cfDNA mutation patterns and the distribution observed in tumor tissue, as reported by The Cancer Genome Atlas, with correlation values ranging from 0.92 to 0.99.[73–76]

Notably, the study revealed the presence of the Epidermal Growth Factor Receptor (EGFR) T790M-resistant mutation in the blood samples, despite its absence in the original tumor biopsies. This phenomenon occurred due to the emergence of the mutation following treatment with EGFR inhibitors, which were administered after the tumor biopsy. The cfDNA assay exhibited its potential by identifying potential treatment options for 63.6% of all patients, considering both FDA-approved agents and eligibility for clinical trials. When compared with matched tissue tests in a subset of 386 patients, the overall accuracy of cfDNA sequencing was 87%. Remarkably, when blood and tumor samples were collected within less than 6 months, the accuracy increased to an impressive 98%.[77,78]

MCED trials and results

The results of the trial mentioned above showed that per year, the MCED test had the potential to intercept 485 cancers for every 100,000 individuals, leading to a significant 78% reduction in the incidence of late-stage (III and IV) cancers among those treated. Considering the lead time provided by early detection, this interception could result in a 39% decrease in 5-year cancer mortality for the intercepted cases. This translates to a major decrease in death by 104 deaths per 100,000 individuals, which accounts for approximately 26% of all deaths from cancer. These findings hold strong across various scenarios related to tumor growth.[79–81]

Although the widespread use of liquid biopsies for cancer screening and diagnosis is still some years ahead, notable advancements have been achieved in the detection of actionable mutations. These mutations are relevant to therapy selection, patient stratification, tracking drug resistance, and monitoring disease progression.[82,83] The Galleri test uses advanced sequencing methods known as next-generation sequencing along with machine-learning algorithms to examine the methylation patterns of cfDNA present in the blood. The study evaluated the Galleri test and found that it had a remarkable 99.5% specificity. The high specificity indicated that the test was highly accurate in identifying individuals without cancer-related signals in their samples, greatly minimizing the occurrence of false-positive results. The Galleri test relies on detecting cancer by analyzing the DNA shed into the bloodstream. It may not detect cancers that do not shed DNA into the bloodstream, such as brain cancer.[84] Another test, the OneTest MCED was also evaluated, and the results showed that when used with biomarker measurements only, it had a sensitivity of 57% and a specificity of 89% for all cancers, including those like skin cancer where reliable biomarkers are currently lacking. It is among the pioneering multicancer screening panels that leverage artificial intelligence to increase the precision of tumor marker tests, aiding in the detection of over 20 different types of cancer.[85]

Additionally, a focused methylation cfDNA-based MCED test underwent five analytical validation studies using samples from 39 individuals with cancer, encompassing 12 distinct cancer types. These studies demonstrated that the MCED test had a remarkable specificity of 99.3% and accurately identified the source of cancer signals with exceptional reproducibility and consistency. The test workflow exhibited robust performance across various conditions, indicating its reliability.[86] Finally, a groundbreaking OncoVeryx-F test had an impressive 98% accuracy in identifying early-stage cancers, specifically in women. These findings highlight the potential of these tests in improving cancer detection and contribute to the advancement of early-stage diagnosis.[87–89]

Many companies are engaged in the development and investigation of MCED tests. It is important to note that these tests have not yet obtained clearance or approval from the USA Federal Food and Drug Administration. However, some of these tests fall within the scope of regulations outlined by the Clinical Laboratory Improvement Act as laboratory tests. This classification permits their use when ordered by a healthcare professional. Many of the companies involved in the development of MCED tests are actively collecting data and aspire to obtain Food and Drug Administration approval in the future.[90,91] Even though development is at an early stage, it raises several questions that are answered in Table 1.

To thoroughly evaluate the potential of peripheral blood transcriptome as a diagnostic marker for different types of cancer, it is essential to conduct further investigations involving large cohorts. Those studies should include diverse populations, including individuals of various sexes, races, and ethnicities, to ensure unbiased outcomes and the generalizability of the findings.[92] Validating transcriptome-based or transcriptome-inclusive methods for early cancer detection would require testing a significant number of individuals who are unaware of their cancer status. The testing would assess the effectiveness of the methods in detecting a relatively small number of early-stage cancers, similar to a study conducted by Leon *et al*.[70] However, current proof-of-principle studies pave the way for future endeavors by demonstrating the feasibility of precise transcriptome-based pan-cancer diagnostics. This approach underscores the significance of comprehensive profiling of all cellular RNAs, including protein-coding and noncoding transcripts as well as polyA+ and polyA− transcripts, instead of focusing on only a limited set of biomarker genes.[93–95]

Limitations and challenges

There is a requirement for fundamental research to understand the typical growth patterns of tumors and metastasis in different types

Table 1. Certain questions regarding MCED still need to be answered

Inquiry	Response
1. How good are MCED tests at detecting cancer?	There is still much to discover regarding the precision of these tests in detecting all types of cancers, as well as specific cancer subtypes. In the case of an MCED test that aims to identify multiple cancers, the accuracy will probably vary for each specific cancer type.
2. How much earlier can MCED tests detect a specific cancer than when it would be discovered after symptoms appear, assuming that they are effective at doing so?	To enhance the effectiveness of cancer treatment, a successful MCED test would be required to detect the presence of cancer at an early stage.
3. Do people who have MCED tests have better outcomes than those whose cancers were discovered after symptoms appeared? Does this test save lives, and if so, how many, specifically?	It is crucial to ensure that MCED tests can detect cancers at earlier stages, and that early treatment of cancer leads to improved outcomes, including reduced risk of cancer-related mortality.
4. What about false-positive results from MCED tests?	When a test indicates the presence of cancer, even though it is not actually present, it is referred to as a false positive. False-positive test results can cause stress, financial burden, and potential harm to individuals who may undergo additional tests to investigate the source of the positive result. Initial data suggests that false-positive results from MCED tests are infrequent.
5. What about false-negative results from MCED tests?	When a test fails to detect the presence of cancer in an individual who actually has it, it is referred to as a false negative. False-negative results can be problematic if a person assumes they are cancer-free based on the test result, when in reality they have cancer. Such false-negative results can potentially lead to harm if proper medical attention is not sought.
6. How often should the test be done?	In the scenario where an MCED test proves to be beneficial in early cancer detection, determining the optimal frequency of testing becomes crucial. Various types of cancers exhibit different growth rates. Waiting too long between tests increases the risk of missing certain cancers, while conducting tests too frequently (when unnecessary) could lead to the inefficient utilization of valuable medical resources. Thus, finding the right balance in the timing of tests is essential to maximize the effectiveness of early cancer detection while avoiding unnecessary resource allocation.

MCED, multicancer early detection.

of cancers. In the field of early detection research, there are several priorities. One is to develop methods that can identify small tumors with the potential for early metastasis. Another priority is the development of tests that can detect hidden metastases during the initial diagnosis. However, the ultimate challenge to early detection is to demonstrate a tangible improvement in patient outcomes.[96,97]

Relying solely on proxy outcomes, such as an increase in early-stage tumors or increased survival times for cases detected by screening, is insufficient to evaluate the impact of early detection on patient outcomes.[98] That is because a perceived survival benefit from early detection does not necessarily equate to a prolonged lifespan. Two biases, lead-time bias and length-time bias, contribute to this discrepancy. Lead-time bias occurs when a screening-detected tumor would have been clinically diagnosed later, after metastasis had occurred, or when the tumor was already incurable at the time of screening detection.[99] In both cases, there is no actual improvement in long-term outcomes. Length-time bias refers to the tendency of screening to preferentially detect slower-growing tumors, which may not significantly impact survival rates. Therefore, it is crucial to conduct randomized controlled trials to establish the effectiveness of different early detection methods in improving health outcomes. However, conducting clinical trials for all emerging early-detection tests is impractical because of cost and time requirements. Therefore, the research community must establish a strategy to rapidly assess and prioritize new tests based on their potential effectiveness, enabling focused efforts on the most promising approaches.[100–104]

Liquid biopsy has emerged as a promising approach to the detection of biomarkers in patients with non-small cell lung cancer. This minimally invasive method offers advantages by better capturing tumor heterogeneity and showing potential for lung cancer screening.[105] However, the lack of standardization has hindered the widespread implementation of liquid biopsy in clinical practice. To address this limitation, further studies are needed that focus on protocol standardization and encompass a larger number of cases. Such efforts are necessary to ensure more representative population samples, leading to accurate and applicable results. Another challenge in liquid biopsy is the fragility of certain biomarkers, which necessitates careful pre-analysis handling. The complex interplay between genetics and environmental factors further adds to the difficulty of controlling variables in this context. Moreover, specific and sensitive methodologies are required to isolate and analyze these biomarkers, especially considering their low concentration in bodily fluids.[106–109]

Overall, while liquid biopsy holds promise for NSCLC biomarker detection, addressing the limitations related to standardization, biomarker fragility, and methodological requirements is crucial to further enhance its clinical utility and reliability.[110,111] While liquid biopsies offer potential advantages in comparison to tissue

biopsies, it is expected that tissue biopsies will continue to be considered the standard approach for the foreseeable future.[112] Tumor tissue provides the opportunity for a more comprehensive analysis, allowing for the identification of a greater number of mutations compared to what can be detected in a blood sample. Unless advancements in technology significantly improve the capabilities of liquid biopsies, tissue biopsies will likely maintain their status as the preferred method for in-depth analysis.[113]

Future perspective

Early diagnosis and treatment significantly increase the chances of survival for cancer patients. This underscores the potential of early detection in improving cancer prognosis. However, it is important to consider that longer survival can be attributed to either delayed death or an earlier time of diagnosis, potentially leading to the identification of slow-growing tumors without impacting the timing of death. Despite decades of research, only a few early detection tests have been associated with a reduction in cancer-specific mortality. However, this benefit must be balanced with the risk of diagnosing and treating cancers that may not have posed a threat during the patient's lifetime. Further research is required to improve early detection methods for cancer. However, the complexities of tumor growth dynamics and the timing of metastasis present challenges in achieving early detection.

To overcome these challenges, the development and refinement of specific techniques for isolating and analyzing analytes from liquid biopsy samples are crucial. Enhancing the sensitivity and specificity of these tests is essential for their safe utilization in early detection, prognosis, and monitoring of diseases. Methods that enable the detection of rare variants or accommodate small initial sample inputs would be valuable in this area. Equally important is the training of professionals in the field to ensure reliable and accurate results. Furthermore, advancements in mathematical and computational methods, particularly those based on machine learning, hold potential for improving liquid biopsy approaches. These innovations have the potential to bring liquid biopsy closer to routine clinical settings and enhance its efficacy and reliability.

Conclusions

In summary, MCED tests hold significant promise in enhancing cancer survival rates by complementing existing screening and diagnostic methods. These tests aim to detect cancer at earlier stages, when curative treatments are more likely to be successful. Among the various approaches, DNA methylation-based tests are at the forefront of development. They are favored can because they identify abnormal tumor-specific patterns, their tissue-specific nature, and the ease with which they can be used to evaluate cfDNA. By integrating molecular analysis of liquid biopsies with artificial intelligence, MCED tests have the potential to greatly enhance their performance. This improvement not only increases the sensitivity of detecting multiple cancer types but also enhances the accuracy of distinguishing between different types of tumors.

To lessen the overall burden of cancer, it is essential to embrace the new technology that enables genomic MCED testing despite the difficulties and unknowns mentioned above. Within the next 5–10 years, it is anticipated that advances in cancer screening and detection, including the use of blood-based MCED tests, will be made possible by our growing understanding of the molecular biology of cancer. This can be achieved by making widely accessible blood-based MCED tests that are easy to use. By eliminating the need for complex equipment and repeated patient visits, blood-based tests have the potential to bridge the gap for underserved communities that typically receive lower-quality care. Additional research and study are required to find more accurate and easier-to-use MCED kits. Many other kits are undergoing clinical trials and very few have been approved by Food and Drug Administration recently. It is a very modern technology that will help in saving so many lives if accurately detected in the early stage. When it comes to our health, it is crucial to remember that we have the power and responsibility to take charge. If we notice any unusual signs or symptoms, it is important not to delay action. It is necessary to communicate with our doctor or contact cancer specialists for further investigation. In conclusion, addressing the challenges related to technique development, professional training, and computational methods, while also considering diverse population groups, will contribute to the broader adoption and improved effectiveness of liquid biopsy in clinical practice.

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Conflict of interest

The authors declare that they have no conflict of interests related to this publication.

Author contributions

Conducted the investigation, managed resources, and handled the methodology, validated the software, performed further investigation, prepared the original draft of the manuscript, and curated the data (KH); prepared and visualized data, and conceptualized the project (DT); and contributed to proofreading, reviewed the work, supervised the project, and managed project administration (DM).

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