



EDITORIAL

Multi-cancer early detection: from promise to practice and the next frontier

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The paradigm of cancer screening is poised for a transformation from single-cancer, modality-specific tests toward a unified approach enabled by liquid biopsy. Multi-cancer early detection (MCED) tests, which analyze circulating biomarkers such as cell-free DNA (cfDNA) from a single blood draw, offer revolutionary potential to detect a broad spectrum of cancers simultaneously, many of which lack standard screening methods. Although technological advancements in methylation and fragmentomics have shown promising performance in case-control studies, major challenges remain regarding real-world sensitivity and the critical need to detect precancerous lesions. This article explores the evolving landscape of MCED technologies; highlights the imperative of targeting precancerous conditions as the next frontier; and outlines the foundational pillars, encompassing natural history studies, risk stratification, pragmatic endpoint evaluation, and health economic modeling, which will be essential for its responsible integration into public health strategies to ultimately decrease the global cancer burden.

The critical role and current limits of cancer screening

The continuing global burden of cancer underscores the critical importance of early detection. Numerous landmark

randomized controlled trials (RCTs) have unequivocally demonstrated that screening for specific cancers, such as low-dose computed tomography for lung cancer¹, mammography for breast cancer², and upper gastrointestinal endoscopy for esophageal and gastric cancer³, significantly decreases disease-specific mortality. Screening asymptomatic individuals enables intervention at curative stages and therefore can fundamentally improve patient outcomes.

However, the current model of single-cancer screening is inherently inefficient. Recommended screenings cover only a limited number of cancer types, addressing less than 30% of the annual cancer incidence in countries such as the US and UK⁴. This approach requires a complex, fragmented schedule of tests for different organs, thus leading to suboptimal patient adherence because of inconvenience and invasiveness. Combining multiple tests also increases the cumulative false-positive rate, thus causing patient anxiety and potential harm from unnecessary diagnostic workups. Furthermore, the positive predictive value (PPV) for any single-cancer screening is often low, because of the relatively low incidence of that specific cancer in the general population⁵. Consequently, developing a unified, “one size fits all” screening method has been a longstanding scientific quest.

From proteins to liquid biopsy: the evolution of MCED

Early enthusiasm focused on protein biomarkers, such as carcinoembryonic antigen (CEA) and CA15-3. However, these markers were found to be inadequate for population-level screening, because they exhibit poor sensitivity for early-stage diseases and cannot identify the tissue of origin (TOO), whose identification is crucial for guiding subsequent clinical

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workup⁶. Therefore, they are not recommended for multi-cancer screening in asymptomatic populations.

The advent of next-generation sequencing and the rise of liquid biopsy have revolutionized this field and made the vision of MCEd a reality. By analyzing circulating biomarkers in the blood, such as cfDNA, MCEd tests can detect a broad spectrum of cancers simultaneously from a single minimally invasive blood draw⁴.

Two technological pathways have emerged as frontrunners. The first is the cfDNA methylation approach, epitomized by GRAIL's Galleri test. DNA methylation patterns are stable, cancer-specific, and highly informative regarding tissue origin. In the large-scale, case-control Circulating Cell-free Genome Atlas (CCGA) study, the Galleri assay demonstrated impressive performance, with an overall sensitivity of 51.5% for more than 50 cancer types, a specificity of 99.5%, and a TOO accuracy of 88.7%⁷. These results generated considerable excitement within the scientific community and suggested that a paradigm shift was within reach. However, the subsequent prospective, interventional PATHFINDER study, which screened a real-world asymptomatic population, presented a more sobering picture. Although the specificity remained high, at 99.1%, and the TOO accuracy was robust, at 85%, the overall sensitivity was only 28.9%⁸. This discrepancy between case-control efficacy and real-world effectiveness highlights the substantial challenge of detecting early-stage cancers with low levels of circulating analytes. The ongoing NHS-Galleri RCT in the UK, with cancer-specific mortality as its ultimate endpoint, is expected to provide the critical evidence needed to determine whether this technology can fulfill its promise on a population level⁹.

Currently, research on cfDNA methylation-based MCEd is advancing rapidly in China. Preliminary data on detection performance have demonstrated the potential utility of MCEd in population-based screening^{10,11}. Given the geographic heterogeneity in cancer incidence, cancer subtypes, and molecular profiles, the demographic characteristics of cohorts used during both biomarker selection and clinical validation phases must be carefully evaluated in selecting among different MCEd products.

The second prominent pathway leverages cfDNA fragmentomics, a technique identifying intricate patterns of cfDNA fragmentation, such as fragment size distribution, end motifs, and nucleosomal positioning, which are markedly altered in cancer. Companies including Geneseeq have developed models such as MERCURY, which integrates multiple fragmentation features with machine learning. In case-control

studies, this approach has achieved remarkable performance, for instance, 87.4% sensitivity and 97.8% specificity for 13 cancer types, with a TOO accuracy of 83.5%¹². Recent interim results from the prospective JINLING study continue to show promising performance in 3,724 asymptomatic participants, with a sensitivity of 53.5% (predominantly early-stage cancers) and specificity of 98.1%¹³.

Beyond methylation and fragmentomics, the MCEd landscape is rich with innovation⁴. Other modalities being explored include 1) cfDNA mutations, integrated with protein biomarkers in tests such as CancerSEEK¹⁴; 2) cfRNA, as used in the ThromboSeq assay, which analyzes tumor-educated platelets¹⁵; 3) metabolomics, with techniques such as multiplexed nanomaterial-assisted laser desorption/ionization mass spectrometry imaging (MNALCI) to detect cancer-specific metabolic shifts¹⁶; and 4) proteomics, with panels such as OncoSeek that combine multiple circulating proteins to achieve multi-cancer detection¹⁷. Each of these biomarker classes has distinct advantages and inherent limitations (summarized in **Table 1**).

The challenge of MCEd: targeting precancerous lesions

We are confident that continuous advancements in technology and algorithmic intelligence will yield more MCEd products with progressively enhanced performance in detecting early-stage cancers. However, in this pursuit of higher sensitivity for frank cancers, the field is confronting a critical and largely unaddressed challenge: the need to optimize and enhance the detection of precancerous lesions.

Precancerous lesions, such as advanced colorectal adenomas, cervical intraepithelial neoplasias, and high-grade gastric intraepithelial neoplasias, represent a critical window of opportunity. Their timely detection and intervention can prevent malignant transformation, thereby decreasing cancer incidence and ultimately mortality, and providing a "holy grail" for cancer prevention. However, the current discourse and development in the MCEd arena have focused almost exclusively on established cancers, whereas their ability to identify precancerous conditions has rarely been described or has been demonstrated to be poor.

The reasons for this poor performance are primarily biological and technical. Precancerous lesions may shed minuscule amounts of aberrant DNA or other biomarkers into the

Table 1 Summary of liquid biopsy markers for multi-cancer screening

Biomarkers	Advantages	Limitations	Representative research/products	Evaluation
cfDNA methylation	<ul style="list-style-type: none"> – High TOO – High cancer specificity – High early signal sensitivity 	<ul style="list-style-type: none"> – Weak signal in some cancer types (such as sarcoma) – Requirement for large panels to cover multiple cancers 	Galleri ⁷ , OverC ¹⁰	This is the core marker of MCED, which has been extensively studied and clinically translated. Methylation-based NGS is the preferred technology for MCED.
ctDNA mutation	<ul style="list-style-type: none"> – Driver gene mutations – High value in targeted therapy 	<ul style="list-style-type: none"> – Low mutation abundance in early stages – CHIP interference – No TOO 	CancerSEEK ¹⁴	This biomarker must be combined with other markers to improve sensitivity. Tissue tracing cannot be performed.
cfDNA fragmentation	<ul style="list-style-type: none"> – No need to explore tumor-specific markers – Low cost 	<ul style="list-style-type: none"> – Requirement for large-scale training sets for verification – Relatively low TOO accuracy 	DELFI ¹⁸ , MERCURY ¹²	Combining this emerging supplementary technology with methylation can optimize MCED's performance.
cfRNA	<ul style="list-style-type: none"> – Dynamic monitoring of TME – High stability of exosomal RNA 	<ul style="list-style-type: none"> – Potential sample degradation – No standardized processes 	ThromboSeq ¹⁵	This direction is promising, but bottlenecks of stability and standardization must be addressed. This marker is currently in the stage of case-control development.
Proteins	<ul style="list-style-type: none"> – Clinical validation, e.g., PSA – Rapid detection 	<ul style="list-style-type: none"> – Low specificity (single marker) – Weak early signals 	OncoSeek ¹⁷	The value of traditional markers is limited, and proteomics based on new technology combined with other markers is a growing trend.
Metabolomics	<ul style="list-style-type: none"> – Indicative of tumor metabolic reprogramming – Low cost 	<ul style="list-style-type: none"> – Significant individual variation – Lack of cancer type-specific markers 	MNALCI ¹⁶	This biomarker is in early research stages and requires larger-scale studies for verification.
Multi-omics	<ul style="list-style-type: none"> – Improved performance – Feature complementarity 	<ul style="list-style-type: none"> – High cost – Complex data 	AlphaLiquid ¹⁹	The features are complex and difficult to explain biologically, but they can be used as a supplementary application. Cost-effectiveness must be balanced.

TOO, tissue of origin; MCED, multi-cancer early detection; NGS, next-generation sequencing; CHIP, clonal hematopoiesis of indeterminate potential; TME, tumor microenvironment.

bloodstream, far below the levels released by even early-stage tumors²⁰. Their molecular signatures might be more subtle and heterogeneous, thus making them exceedingly difficult to distinguish from the background noise of normal cellular turnover.

Therefore, the next major frontier in MCED research must be the deliberate and focused inclusion of precancerous lesions in model development and validation. Concerted efforts will be necessary to achieve the following:

- 1) Discover precancer-specific biomarkers: actively seek out methylation patterns, fragmentomic features, or other features that are characteristic of the transition from normal tissue to precancer, rather than to only cancer.
- 2) Optimize algorithms for precancer detection: intentionally train machine learning models to recognize these faint precancerous signals and treat them as a distinct class, rather than categorizing them as negative.
- 3) Pursue ultra-sensitive assays: develop next-generation platforms with limits of detection sufficiently low to capture the scant biological evidence released by these precursor lesions.

Overcoming this hurdle would transform MCED from a tool that intercepts late-stage and early-stage cancers into a powerful system for primary cancer prevention. The public health effects of such a capability would be profound, by moving the line of defense earlier in the disease continuum and saving countless lives.

Foundational pillars for responsible MCED implementation

However, the journey from a technologically impressive assay to an impactful public health screening program is complex and will require several foundational pillars to be addressed. The following elements are critical for the responsible development and deployment of MCED tests.

Cancer natural history studies: the indispensable foundation

The valid development of any cancer screening test, particularly one designed to detect multiple cancers, fundamentally relies on a robust understanding of cancer natural history, that is, the unperturbed progression of cancer from its inception to clinical manifestation. This knowledge is not merely a preliminary step but a continuous prerequisite that informs every stage of MCED development.

First, the design of definitive RCTs is contingent on natural history data. Understanding the detectable preclinical phase for various cancers, i.e., the window during which a cancer can be detected by a biomarker before symptoms become apparent, is crucial for determining optimal screening intervals. For rapidly progressive cancers, annual screening might be ineffective, whereas for indolent cancers, longer intervals might be sufficient and more cost-effective. Furthermore, the validity of surrogate endpoints, such as a decrease in late-stage incidence, depends on established links to mortality reduction, but these associations can be validated only through a deep understanding of disease progression.

Second, natural history data are essential for informing biomarker and test development²¹. Regulatory agencies, including the U.S. FDA, explicitly state that a target condition for a screening test must possess a recognizable early stage and a detectable marker²². Natural history studies help answer critical questions: Which cancers are suitable for inclusion in an MCED panel? What are the kinetics and timing of biomarker release into the bloodstream? Without this foundational

knowledge, developing an effective MCED test is analogous to building a house on sand.

Therefore, intensified research on the natural history of cancers, particularly in their earliest stages, is not an optional academic endeavor but a non-negotiable cornerstone for transforming MCED from a promising technological innovation into a validated public health tool.

Artificial-intelligence (AI)-based risk stratification: enhancing MCED efficiency through precision

Deploying MCED as a uniform screening tool across the general population, although broad in scope, might be inefficient. Precision screening, which focuses resources on individuals who stand to benefit the most, is critical to maximizing the clinical utility and cost-effectiveness of MCED.

Targeting high-risk populations for MCED screening offers several advantages. First, targeting increases diagnostic yield: because cancer prevalence is higher in risk-enriched groups, more cancers can be detected per test performed. Second, targeting increases the PPV: in a higher-prevalence population, the same test will yield a higher PPV, thus decreasing the false-positive rate, and minimizing the physical, psychological, and financial harms associated with unnecessary diagnostic workups. Finally, targeting optimizes cost-effectiveness: directing a relatively expensive MCED test toward the patients most likely to have a certain cancer significantly improves the incremental cost-effectiveness ratio, thus enhancing the overall value proposition and facilitating reimbursement²³.

However, an important critical distinction is that, unlike traditional single-cancer screening, which often focuses on specific risk factors (e.g., smoking for lung cancer), MCED requires a shift toward assessing an individual's comprehensive, multi-cancer risk profile. Achieving this goal is inherently complex, because it involves integrating diverse risk factors that collectively contribute to the likelihood of developing multiple cancer types. This complexity underscores the importance of leveraging AI in risk factor analysis. Future research should focus on using AI methods to identify and synthesize common risk factors across multiple cancers, thereby enabling more accurate identification of high-risk populations for targeted MCED screening²⁴. Beyond risk analysis, AI's applications extend to other critical facets of MCED, including the enhancement of the core detection algorithms themselves and the post-diagnostic monitoring of patients (**Figure 1**).

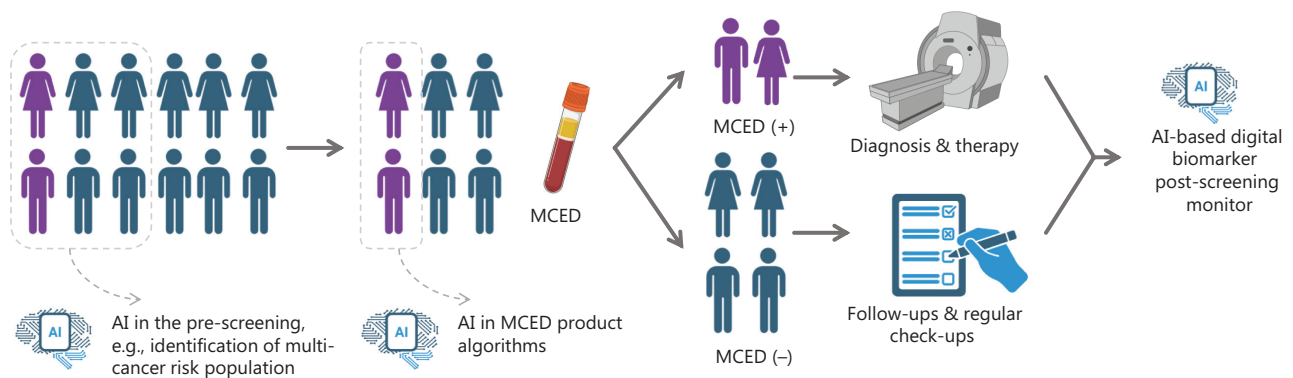


Figure 1 Workflow for artificial intelligence (AI)-integrated multi-cancer early detection (MCED) screening. This diagram illustrates a practical workflow for population-level MCED screening enhanced by AI. The process begins with AI-driven risk stratification to identify high-risk individuals, thereby improving the economic utility of screening. This targeted high-risk cohort then undergoes AI-augmented MCED testing. Positive test results are integrated into standardized diagnostic and therapeutic pathways, whereas negative results trigger routine follow-up with periodic re-screening. After the initial testing phase, all participants are enrolled in a program of AI-powered digital biomarker monitoring for longitudinal surveillance.

Endpoints for evaluation: the gold standard and pragmatic surrogates

A rigorous evaluation framework is essential to substantiate the clinical value of MCED tests. The gold standard for such evaluation remains cancer-specific mortality reduction. Demonstrating that screening saves lives through a statistically significant decrease in mortality is the most definitive evidence of population-level benefit. Large-scale RCTs, such as the NHS-Galleri trial, were designed with this outcome as their primary endpoint⁹. However, such studies require extended follow-up periods, often spanning 6–8 years, to observe a meaningful separation between the screened and control groups, thus making them time-consuming and costly endeavors.

Given the practical constraints of mortality-based trials, a pressing need exists to identify and validate reliable surrogate endpoints that can predict long-term survival benefits within shorter timeframes. Among the candidate surrogates, a decrease in late-stage (stage III/IV) incidence is currently the most endorsed²⁵. The rationale is meaningful, because an effective screening test would shift the distribution of cancer stages at diagnosis from late to early. Because early-stage cancers are strongly associated with better survival outcomes, an observed decline in the incidence of advanced-stage disease serves as a validated proxy for mortality decreases in several cancer types. Other potential surrogate measures include the magnitude of stage shift and a decrease in cancer-related morbidity²⁵. The

use of such endpoints, which can generate compelling evidence of clinical utility within 2–4 years, is critical for accelerating the translation of MCED tests from research into clinical practice and facilitating regulatory approval.

Modeling and health economics: informing decision-making with foresight

Before a commitment to the substantial investment required for widespread MCED implementation, quantitative modeling provides an indispensable preview of its potential effects and can guide strategic decision-making²¹. Microsimulation modeling allows researchers to project long-term outcomes by creating virtual populations and simulating the effects of MCED screening, according to observed test characteristics such as sensitivity, specificity, and the ability to induce a stage shift. These models can quantify the “stage-shift” effect, by estimating how many cancer cases might be intercepted in earlier, more treatable stages, and subsequently project how this shift might translate into gains in overall survival or decreases in cancer-specific mortality²⁶. This approach directly addresses critical questions for policymakers regarding the expected potential public health benefits of implementing MCED screening.

Health economic modeling provides a critical bridge between technical efficacy and actionable health policy. Through comprehensive cost-effectiveness analyses, often using structures such as Markov models, stakeholders can

evaluate the economic implications of MCED deployment²⁷. These analyses are instrumental in identifying optimal screening strategies by comparing the cost-effectiveness ratios of various protocols, which may differ in test pricing, screening intervals, starting ages, and risk-stratified approaches. Furthermore, modeling helps inform value-based pricing and reimbursement strategies by establishing a price range for the MCED test that aligns with a healthcare system's willingness-to-pay threshold, a benchmark often referenced to per-capita GDP. Beyond direct medical costs, these models can assess broader economic impacts, including indirect societal benefits such as averted productivity losses due to disability and premature death, thereby providing a holistic view of the test's value.

Conclusions

The emergence of MCED technologies has heralded a paradigm shift in cancer screening, by offering a unified strategy to overcome the inherent limitations of single-organ, modality-specific tests. Although remarkable progress has been made across various technological platforms, translating this promise into public health effects will require critical challenges to be overcome. These challenges include increasing real-world sensitivity for early-stage cancers and, crucially, advancing the detection of precancerous lesions to enable true cancer prevention. The responsible integration of MCED into clinical practice will rely on a foundational framework encompassing robust natural history studies, risk stratification, pragmatic endpoint evaluation, and comprehensive health economic modeling. As definitive evidence from large-scale RCTs accumulates, collaborative efforts of researchers, clinicians, and policymakers will be essential to harness the full potential of MCED, and ultimately decrease the global cancer burden through precision screening and prevention.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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