How to Cite:
Alenezi, A. R., Alanazi, M. A., Aldhafeeri, F. S., Alotaibi, B. N., Alshamri, A. S., Alenezi, M. F., Al-Jasser, S. A., Alanazi, A. A., & Algfari, S. M. (2024). Cancer prevention and early detection: Emerging technologies and interventions. *International Journal of Health Sciences*, *8*(S1), 1347–1364. https://doi.org/10.53730/ijhs.v8nS1.15223

Cancer prevention and early detection: Emerging technologies and interventions

Abdulrahman Ramadhan Alenezi
KSA, National Guard Health Affairs

Mohammed Ayyat Alanazi
KSA, National Guard Health Affairs

Fares Saqir Aldhafeeri
KSA, National Guard Health Affairs

Bader Naif Alotaibi
KSA, National Guard Health Affairs

Ahmed Saer Alshamri
KSA, National Guard Health Affairs

Meshal Falah Alenezi
KSA, National Guard Health Affairs

Saleh AbdulLatif Al-Jasser
KSA, National Guard Health Affairs

Sultan Mohammed Algfari
KSA, National Guard Health Affairs

Ahmed Aidan Alanazi
KSA, National Guard Health Affairs

***Abstract*---Background:** Precision oncology is transforming early cancer detection among average-risk individuals. Advances in next-generation sequencing have led to significant insights into the cancer genome and the identification of biomarkers to improve early detection. **Aim:** This article examines emerging technologies and interventions in cancer prevention and early detection, focusing on the latest advancements in screening methodologies. **Methods:** The review analyzes various single- and multi-cancer early detection tests, discussing their methodologies, biomarker identification, clinical trial

International Journal of Health Sciences E-ISSN 2550-696X © 2024.
***Corresponding email**: akk29337@gmail.com*
Manuscript submitted: 01 Jan 2024, Manuscript revised: 09 Jan 2024, Accepted for publication: 15 Jan 2024

results, and the challenges associated with current screening approaches. **Results:** Innovative tests, such as multi-cancer early detection (MCED) assays, have shown superior sensitivity compared to traditional methods by identifying circulating tumor DNA (ctDNA) before symptoms arise. While promising, these technologies face challenges, including the potential for false positives and negatives, overdiagnosis, and disparities in access to testing. **Conclusion:** Emerging technologies in cancer detection hold great potential to revolutionize screening practices. However, careful consideration of their clinical utility and potential harms is necessary to ensure equitable access and effective implementation.

***Keywords*---**cancer prevention, early detection, precision oncology, biomarkers, multi-cancer early detection tests, liquid biopsies.

Introduction

Precision oncology is revolutionizing the paradigm of early cancer detection among individuals at average risk. Recent breakthroughs in next-generation sequencing have facilitated significant insights into various aspects of the cancer genome, epigenome, transcriptome, metabolome, and proteome, leading to the identification and development of biomarkers poised to enhance the early detection of cancer. The latest generation of cancer early detection assays, many of which are still in the research and development phase, focuses on an array of biomarkers, including DNA methylation patterns, DNA fragmentation, RNA sequences, proteins, and more. Concurrently, advancements in data science have enabled the formulation of intricate machine learning algorithms that enhance the sensitivity and specificity of these biomarkers. The era of precision cancer screening may finally be upon us.

Since the debut of the first cancer early detection test by George Papanicolaou—the Pap test—in 1928, efforts in cancer early detection have centered around the systematic testing of asymptomatic populations with no prior cancer history, aiming to identify individuals with disease at its most treatable stage. Nevertheless, cancer screening faces several challenges. Primarily, it has predominantly been confined to breast, colorectal, cervical, lung, and prostate cancers, which together constitute about half of the total cancer incidence and account for 43% of all cancer-related deaths [1]. Consequently, among the approximately 600,000 annual cancer fatalities in the United States, 57% are attributable to cancers that currently lack a screening test. Another obstacle is that among the cancers for which screening tests are available, only 14% are diagnosed through recommended screening procedures in the United States [2]; the majority of cancers are detected only after the onset of symptoms or during other medical interventions. The suboptimal effectiveness of cancer screening is primarily attributed to inadequate adherence to screening recommendations, along with the limitations of existing cancer screening technologies and the emergence of interval cancers [3]. As a result, a significant proportion of cancers in the United States are diagnosed at advanced stages, complicating treatment. For cancers that have screening options available, the percentage diagnosed at a

late stage varies, ranging from 21.9% for prostate cancer to 65.5% for lung cancer.

Further challenges associated with population-based cancer screening encompass false positive outcomes [4–6], which can lead to adverse psychosocial, medical, and financial repercussions [7, 8]; the overdiagnosis of very early-stage or precancerous lesions that may never progress, resulting in overtreatment [9, 10]; and rare yet severe adverse events stemming from the screening process or subsequent diagnostic evaluations [11]. The new frontier in early cancer detection has the capacity to address several shortcomings inherent in traditional cancer screening approaches. Firstly, emerging early detection tests may exhibit superior sensitivity compared to conventional cancer screening methodologies. For instance, these tests can identify small fragments of circulating tumor DNA (ctDNA) released into circulation by most cancer cells, often before standard imaging or blood tests indicate active disease [12, 13], thereby enhancing outcomes through earlier detection. Additionally, they facilitate the identification of a substantial proportion of the two-thirds of cancers for which no screening or early detection strategy currently exists. These advanced technologies can also simultaneously detect signals from multiple cancers through a single assay, collectively referred to as multi-cancer early detection (MCED) tests. Moreover, this innovative generation of early detection tests relies on the non-invasive or minimally invasive collection of biosamples, such as blood, urine, saliva, stool, or cerebrospinal fluid; these “liquid biopsies” provide enhanced accessibility for early cancer detection, reduced risks associated with the screening process, and potentially improved patient compliance. Furthermore, the false positive rate (FPR) associated with MCED tests appears to be significantly lower than that of current cancer screening methodologies. Additionally, diagnostic procedures such as imaging and biopsies tend to be costly [14, 15], and an MCED test with a very low FPR could theoretically represent a cost-effective strategy for determining which individuals require more invasive and expensive diagnostic evaluations, should clinical utility be demonstrated.

However, the implementation of MCEDs may entail potential harms:

- False negative results may postpone treatment or lead individuals to forgo evidence-based screening protocols.
- False positive results may compel individuals to undergo unnecessary diagnostic assessments that fail to confirm the presence of cancer, and the ensuing unwarranted procedures and surgeries may inflict harm.
- Positive findings may result in the overdiagnosis and overtreatment of indolent, non-lethal cancers.
- Early detection may elevate patient anxiety and distress.
- The testing may escalate the costs associated with cancer care and treatment.
- The testing could exacerbate disparities in cancer outcomes.

Single- And Multi-Cancer Early Detection Tests

Most studies currently published that establish the sensitivity and specificity of these early detection tests have utilized samples from individuals with preexisting

cancer. Below, we examine some of the tests that have participated in prospective clinical trials aimed at assessing their validity. It is crucial to acknowledge that tumor heterogeneity can significantly influence the evaluation of cancer early detection tests. Hence, comprehensive, population-based research is essential for accurate and dependable assessments. In 2016, Epi proColon became the first and is currently the only single-cancer blood test sanctioned by the FDA for the early identification of colorectal cancer. Epi proColon identifies the methylated septin 9 (mSEPT9) DNA. Initial findings indicated that Epi proColon outperformed fecal immunochemical testing (FIT), with sensitivities of 72.2% and 68%, respectively, and specificities of 80.8% and 97.4%, respectively (16). Nevertheless, in the PRESEPT prospective study involving 7,941 asymptomatic, average-risk adults aged 50 and older undergoing screening colonoscopy at 32 clinical sites in the United States and Germany, the mSEPT9 test exhibited a sensitivity of only 48% for colorectal cancer and 11% for advanced adenomas (17). Specificity was higher, with 92% of individuals without colorectal cancer receiving a negative test result. As a result, the FDA approved Epi proColon for colorectal cancer screening in average-risk individuals who have opted out of first-line screening tests. No studies have evaluated whether screening with mSEPT9 reduces colorectal cancer or overall mortality. Epi proColon has not been included in clinical practice guidelines established by the US Preventive Services Task Force (USPSTF) or the American Cancer Society (ACS). Following a coverage request from the product's manufacturer, Epigenomics, the Centers for Medicare and Medicaid Services (CMS) issued a decision memo in January 2021 outlining criteria for coverage of blood-based colorectal cancer screening tests. These tests must receive FDA approval and demonstrate a sensitivity of 74% or higher, with at least 90% specificity, as evidenced in pivotal studies supporting US registration (18). Epi proColon did not satisfy the sensitivity requirement, resulting in CMS denying coverage for this test. An updated version, Epi proColon 2.0, is currently under investigation (19).

Cologuard is the first FDA-approved stool DNA–based multitarget screening test for individuals at average risk. It assesses 11 biomarkers: two DNA methylation markers (NDRG4 and BMP3), seven K-Ras point mutations, β-actin, and fecal hemoglobin. In a prospective study involving 9,989 asymptomatic adults aged over 50, Cologuard demonstrated a sensitivity of 92.3% for detecting colorectal cancer, compared to 73.8% for FIT ($p = 0.002$) (20). The sensitivity for identifying advanced precancerous lesions was 42.4% for Cologuard and 23.8% for FIT. The specificities for Cologuard and FIT were 86.6% and 94.9%, respectively, among participants with nonadvanced or negative findings, and 89.8% and 96.4%, respectively, among those with entirely negative colonoscopy results. Although Cologuard is more sensitive than FIT, it presents a higher false positive rate (FPR), 13% versus 5%. The number of individuals required to be screened to identify one cancer was 154 with colonoscopy, 166 with Cologuard, and 208 with FIT. Cologuard’s enhanced sensitivity, despite a marginally lower specificity compared to FIT, led to its inclusion in the USPSTF and ACS guidelines as an option for colorectal cancer screening every three years (21, 22).

Guardant Health has developed a blood test for the early detection of colorectal cancer utilizing cell-free DNA (cfDNA) along with genomic and epigenomic analyses (23–25). The Evaluation of ctDNA LUNAR Assay In an Average Patient Screening Episode (ECLIPSE) trial (24, 26, 27, NCT04136002) enrolled 20,000

diverse individuals aged 45–84 at average risk for colorectal cancer across 200 clinical trial sites in urban and rural communities in 34 US states, retrospectively comparing the performance characteristics of the LUNAR-2 test with the outcomes of the index colonoscopy. Two configurations of a multimodal blood-based screening test were independently assessed: a cfDNA-only test and a cfDNA test combined with protein biomarkers. The cfDNA-only test demonstrated superior results, achieving 83% sensitivity for detecting colorectal cancer and 90% specificity for individuals without advanced neoplasia or those with a negative colonoscopy result. This test also exhibited 13% sensitivity for identifying advanced adenomas. These findings surpass the performance criteria established by CMS for reimbursement (28), and Guardant Health applied for premarketing approval to the FDA in 2023 (29).

EarlyTect™-Colon Cancer utilizes syndecan-2 (SDC2), a stool-based DNA methylation marker, for the early identification of colorectal cancer. The sensitivity and specificity of SDC2 methylation in stool DNA for detecting colorectal cancer exceed 90% (30). A trial comparing the EarlyTect™-Colon Cancer test to colonoscopy is currently ongoing (31, NCT04304131). Freenome is actively conducting PREEMPT CRC, a prospective multicenter observational study aimed at validating a blood-based test for colorectal cancer detection. PREEMPT CRC is assessing a multiomics platform that integrates both tumor and non-tumor signals using machine learning in 35,000 average-risk participants aged 45–85 who will undergo routine screening colonoscopy (NCT04369053). Beyond colorectal cancer, TriNetra, a circulating tumor cell detection test, has received FDA breakthrough device status for the early identification of breast cancer (32), glioblastoma (33), and prostate cancer detection (34). SelectMDx, a noninvasive urine test developed by MDx Health, evaluates two cancer-related mRNAs (HOXC6/DLX1) to assess prostate cancer risk. With the increasing array of tests available, we have only included those known at the time of this writing.

Multi-Cancer Early Detection Tests

Multi-cancer early detection tests (MCEDs) are blood tests designed to concurrently identify circulating tumor DNA (ctDNA) from various cancers through a single liquid biopsy. Each MCED is tailored to detect different cancer types, exhibiting varying levels of accuracy. The tests provide information on the presence or absence of cancer signals, and if a signal is detected, they may indicate potential primary and, in some cases, secondary cancer signal origins (CSOs). These CSOs necessitate further diagnostic confirmation. In patients who are asymptomatic and undergo routine cancer screenings, there may be instances where the diagnostic process fails to identify cancer in those with a true positive result, particularly if the top-predicted CSO or subsequent testing is incorrect. When the diagnostic evaluation does not confirm cancer, both the clinician and the patient face critical decisions: they may choose to extend the diagnostic investigation through additional testing (potentially guided by a second-predicted CSO or whole-body imaging), repeat the MCED, presume a false positive, or adopt a watchful waiting approach until symptoms manifest prior to the next recommended MCED or alternative screening (35). Several examples of MCEDs include Galleri (36), CancerSEEK (37), PanSeer (38), OneTest (39), and TruCheck (40, 41), which we will review in terms of their performance characteristics.

Galleri

The Galleri test, developed by GRAIL, Inc. (Menlo Park, CA), is the first publicly accessible blood-based MCED. It employs genome-wide methylation changes in cell-free DNA (cfDNA) alongside machine learning to detect and anticipate the CSO. The development and refinement of GRAIL's MCED were based on the Circulating Cell-free Genome Atlas (CCGA) study, which revealed that whole-genome methylation provided the most accurate prediction of CSO (36). The CCGA study was a prospective multicenter observational study enrolling around 15,000 participants, both with and without cancer, across 142 sites in the United States and Canada. The study aimed to evaluate whether genome-wide cfDNA sequencing, in conjunction with machine learning, could identify and localize a broad spectrum of cancer types with sufficient specificity to justify inclusion in a population-based cancer screening initiative. This study demonstrated that the test could detect over 50 cancer types with a specificity exceeding 99%. The sensitivity for 12 prespecified cancer types increased with the tumor stage, ranging from 39% sensitivity in stage I to 92% in stage IV disease. Importantly, the initial study noted frequent confusion in identifying tissue of origin, particularly among cancers driven by human papillomavirus (e.g., cervical, anal, and head and neck cancers), which limited the test's accuracy for these specific cancers.

The primary validation study for GRAIL's MCED involved a prospective multicenter case-control observational design with longitudinal follow-up (42). This study included 2,823 patients aged 20 and older diagnosed with cancer or highly suspected of malignancy, as well as 1,254 patients in a control arm. The primary objectives focused on the sensitivity and specificity for overall cancer signal detection, along with performance for predicting the site of origin, which were compared to standard clinical evaluations such as imaging, blood tests, and biopsies. Specificity was found to be 99.5% (95% confidence interval [CI] 99.0–99.8%), while sensitivity was 51.5% (95% CI 49.6–53.3%). The overall sensitivity for the 12 prespecified cancers, accounting for nearly two-thirds of annual cancer deaths in the United States, was 40.7% (95% CI 38.7–42.9%). Sensitivity varied significantly by stage: 16.8% (95% CI 14.5–19.5%) for stage I; 40.4% (95% CI 36.8–44.1%) for stage II; 77.0% (95% CI 73.4–80.3%) for stage III; and 90.1% (95% CI 87.5–92.2%) for stage IV. The accuracy of predicting the cancer site of origin across all cancers was 88.7% (95% CI 87.0–90.2%). Among the group of 12 prespecified cancers, sensitivity improved to 76.3% across all stages and 67.6% for stages I–III.

The study also revealed significant heterogeneity in sensitivity based on the cancer site. Notably low detection rates were observed for thyroid cancers (0/14 detected), prostate cancers (47/420 detected), breast cancers (160/524 detected), and uterine cancers (44/157 detected). Conversely, the test exhibited high sensitivity for liver/bile duct cancers (43/46 detected), head and neck cancers (90/105 detected), esophageal cancers (85/100 detected), pancreatic cancers (113/135 detected), and ovarian cancers (54/65 detected). As previously mentioned, sensitivity was comparatively poorer at earlier cancer stages. For example, sensitivities for anal cancer were 25.0%, 75.0%, 100.0%, and 100.0% for stages I–IV, respectively. Similarly, lung cancer sensitivity values were 21.9%,

79.5%, 90.7%, and 95.2% for stages I–IV. Interestingly, the test was more effective in detecting cancers in patients presenting with clinical symptoms (sensitivity 63.9%) compared to asymptomatic cancers identified through screening (sensitivity 18.0%; breast, colorectal, cervical, prostate). The CCGA study investigators extrapolated results to the Surveillance, Epidemiology, and End Results (SEER) prevalence data, estimating a positive predictive value (PPV) of 44.4% and a negative predictive value (NPV) of 94.4% for MCED positivity resulting in a cancer diagnosis.

Another CCGA substudy evaluating GRAIL's MCED tracked 2,129 patients with the prespecified 12 cancers over three years to investigate the association between MCED positivity and cancer detection through other means, as well as overall survival (43). The study concluded that cancers detected by MCED exhibited significantly poorer survival rates compared to cancers identified through conventional methods with a negative MCED, even after adjusting for covariates such as clinical stage and diagnostic method (i.e., standard-of-care screening or clinical presentation with signs/symptoms). MCED positivity was associated with a higher likelihood of detecting more aggressive cancers, such as triple-negative breast cancer and small cell lung cancer. These findings suggest that incorporating this MCED test into existing screening frameworks may not result in overdiagnosis and could, in fact, facilitate the detection of more clinically significant cancers. Additionally, the study found that only 6% of prostate cancers identified through prostate-specific antigen screening were detected by the MCED test, whereas 41% of clinically symptomatic prostate cancers were identified by the MCED test, highlighting the test's limited efficacy in prostate cancer detection.

The PATHFINDER study represents the first prospective evaluation of the early and refined iterations of GRAIL's MCED test (44). According to GRAIL (45), the early version of the MCED was adjusted to minimize the detection of less common premalignant hematologic conditions and enhance CSO prediction accuracy. The PATHFINDER study employed the early test version, which was subsequently retested in a predetermined retrospective analysis using the refined version. This investigation screened 6,662 individuals aged 50 and older, both with and without cancer risk factors, defined as having smoked more than 100 cigarettes, possessing a genetic predisposition to cancer, or having a history of untreated cancer for at least three years. In an analysis conducted one year post-PATHFINDER study, which focused on the diagnostic testing needed to resolve cancer signals detected by the MCED, signals were identified in 92 (1.4%) participants; cancer was confirmed in 35 (38%) and not confirmed in 57 (62%) (46). The specificity was 99.1% (6,235/6,290). For the refined test version, PPV was 43.1% (95% CI 31.2–55.9) and NPV was 98.5% (95% CI 98.2–98.8), with a CSO prediction accuracy of 88% (95% CI 70.0–95.8). Within three months, 73% of participants with a positive test received a positive cancer diagnosis. Furthermore, 71% of those with MCED-detected cancers had malignancies for which standard screening tests are not currently available, with half detected at stage I/II. Notably, the PATHFINDER results indicate a PPV exceeding 40%, significantly higher than that of single-cancer tests such as mammography (47), low-dose computed tomography for lung cancer (48), FIT (18), and Cologuard (49), all of which report PPVs below 10%. While the GRAIL Galleri panel has not yet obtained FDA approval, it has received lab-developed test status and is currently accessible

to patients in the U.S. through provider prescriptions at an out-of-pocket expense of $949.

CancerSEEK

CancerSEEK (Exact Sciences, Madison, WI) employs a blood sample to detect DNA mutations and protein biomarkers for 26 distinct cancer types, including colorectal, lung, and breast cancers. Cohen et al. assessed CancerSEEK in 1,005 patients with nonmetastatic, clinically identified cancers of the ovary, liver, stomach, pancreas, esophagus, colorectum, lung, or breast (50). The tests yielded positive results in a median of 70% across the eight cancer types evaluated. Sensitivities for detecting five cancer types (ovary, liver, stomach, pancreas, and esophagus) ranged from 69% to 98%, despite the absence of screening tests for average-risk individuals. Notably, only 7 out of 812 healthy controls tested positive, resulting in a specificity exceeding 99%. Moreover, CancerSEEK successfully localized cancer to a limited number of anatomical sites in a median of 83% of the patients.

The DETECT-A study (Detecting cancers Earlier Through Elective mutation-based blood Collection and Testing) (37) integrated the blood test with whole-body positron emission tomography (PET) imaging to evaluate an earlier iteration of CancerSEEK, which lacked the machine learning algorithms designed to enhance sensitivity and specificity (50). In this prospective interventional investigation, 10,006 female participants (aged 65–75 years) without a cancer history were screened through an initial blood draw that assessed both ctDNA (with a prespecified panel of 61 known oncogenic mutations) and cancer-associated proteins [e.g., cancer antigen 19-9 (CA19-9), carcinoembryonic antigen, alpha fetoprotein]. A positive result for ctDNA or elevated protein levels prompted a second blood draw for confirmation. If this result was also positive, a multidisciplinary review committee evaluated the necessity of a PET-computed tomography (CT) scan to accurately confirm and localize the disease's site and extent. Thus, the diagnostic PET-CT was incorporated into the screening protocol. Over the 12-month study duration, 96 (1%) cancer diagnoses were made, with 26 initially identified via blood testing. The specificity was determined to be 98.9%. The positive predictive value (PPV) and negative predictive value (NPV) for blood testing alone were 19.4% and 99.3%, respectively. When combined with PET-CT, specificity and PPV improved to 99.6% and 28.3%, respectively. Additionally, 65% of cancers were identified at an early stage, with sensitivity varying by tumor type. The blood test detected 14 of 45 cancers (31%) across seven organs for which no standard screening tests exist. The number needed to screen to identify one cancer was 661. CancerSEEK has been granted breakthrough device status by the FDA and is currently undergoing further clinical evaluations. It is not yet accessible to the general public.

PanSeer

PanSeer (Singlera Genomics, La Jolla, CA) represents a noninvasive blood test grounded in ctDNA methylation analysis. Preliminary validation has been conducted among a cohort of 123,115 healthy participants from the Taizhou Longitudinal Study, aged 25–90, who provided plasma samples for preservation

and were subsequently monitored for cancer incidence via local cancer registries and health insurance claims (38). Within 4 years of the initial blood draw, a total of 575 previously healthy subjects, who initially presented asymptomatically, were diagnosed with one of five prevalent cancer types in China (stomach, esophagus, colorectum, lung, or liver). Investigators retrospectively examined the initial blood samples to assess whether the PanSeer test could detect cancer prior to conventional diagnostic methods. The PanSeer test successfully identified cancer in 95% (95% CI 89–98%) of asymptomatic individuals who were later diagnosed with cancer, with some cases identified up to 4 years prior to standard screenings.

OneTest

OneTest (20/20 GeneSystems, Gaithersburg, MD) quantifies various tumor antigens, including alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), CA19-9, cytokeratin 19 fragment (CYFRA21-1), and prostate-specific antigen for males, alongside AFP, CEA, CA19-9, CYFRA21-1, cancer antigen 125 (CA125), and cancer antigen 15-3 (CA15-3) for females. OneTest targets multiple malignancies, including colon, ovarian, and lung cancers. When paired with artificial intelligence algorithms, the reported specificity is approximately 80%, with sensitivities of around 82% for males and 62% for females (39). Currently, OneTest is available as a complementary assessment to age-appropriate cancer screenings and necessitates an order from a healthcare professional. Priced at $189.00, it ranks among the more affordable multi-cancer early detection tests (MCEDs). The company has partnered with urgent care clinics to provide the blood draw for an additional fee of $39.00, along with telemedicine access for patients lacking a primary care physician. Following the OneTest, individuals receive a score ranging from 1 to 30, with elevated scores indicating a heightened cancer risk. However, there are no established protocols for subsequent actions should a patient receive a high score, nor are there recommendations for the frequency of repeating OneTest after a low score.

Trucheck

Trucheck's Intelli MCED (Datar Cancer Genetics, Raleigh, NC) identifies circulating tumor cells and clusters termed C-ETACs (circulating ensembles of tumor-associated cells), enabling the detection of 70 distinct types of solid tumors. Trucheck is also marketed for specific malignancies, including commercial versions such as Trucheck Breast and Trucheck Prostate. This test demonstrates a sensitivity of 92.1%, specificity of 99.9%, and accuracy of 93.1% when utilizing a blood sample (40, 41). It is exclusively available for purchase outside the United States, with a price of £1,035 in the United Kingdom. The emerging generation of cancer early detection assays exhibits exceptional potential to transform and redefine the framework of cancer screening. Numerous cancer early detection assays are currently under development on a global scale, with several already commercialized and available to complement existing recommended cancer screening protocols. At this time, none are designated as standalone cancer screening methods.

This review found that roughly 1% of individuals undergoing an MCED test will yield a cancer signal (37, 46). The characteristics of these early detection tests are quite promising, as most have reported sensitivity levels ranging from 70% to 100%. Nevertheless, sensitivity tends to be lower in the initial stages of cancer, increasing as the disease progresses. Furthermore, MCEDs exhibit elevated specificity, which, in conjunction with prevalence, significantly influences positive predictive value (PPV). In prospective studies, certain MCED tests have demonstrated PPVs of 40–50%, significantly surpassing those of current single-cancer tests recommended by the USPSTF, such as mammography for breast cancer (47), low-dose CT for lung cancer (48), and FIT (18) and Cologuard (49) for colorectal cancer screening, which exhibit PPVs below 10%. As anticipated, the high specificity of MCEDs leads to exceedingly low false positive rates (FPRs), approaching 1%. In contrast, traditional screening methods like mammography and prostate-specific antigen tests have FPRs ranging from 5% to 10% per screening session (4, 51, 52), with cumulative rates escalating with repeated screenings (53). There is variability in the detection capabilities for different cancer types; for instance, leukemias and tumors originating in the skin and central nervous system exhibit a markedly low probability of detection by certain blood-based ctDNA screening assays (54). Additionally, there is inconsistency in the accuracy of predicting tissue origin; some MCEDs demonstrate high accuracy (36, 46), while others do not.

Given that these tests necessitate merely a straightforward biosample collection without preparatory measures, they offer greater convenience than many conventional cancer screening procedures. Consequently, they may be favored by patients, potentially resulting in enhanced adherence. For instance, in a randomized trial involving 413 average-risk adults aged 50–75 who required colorectal cancer screening, 99.5% of participants in the mSEPT9 group completed the test within six weeks, compared to 88.1% in the FIT group (55). The capability to detect multiple cancers through a single assay and to identify malignancies before they metastasize could significantly influence public health, particularly since stage IV cancers account for 18% of all estimated diagnoses and constitute 48% of all projected cancer-related deaths within a five-year span (56). An analysis utilizing stage-specific incidence and survival statistics from SEER for 17 diagnosed cancer types among individuals aged 50 to 79 determined that if all stage IV cancers were identified at stage III via early detection tests, there would be an expected reduction of 51 cancer-related deaths per 100,000, translating to a 15% decrease in overall cancer-related mortality (56). The decline in all cancer-related fatalities would be even more pronounced if these tests were assumed to facilitate earlier stage diagnosis.

Concerning the potential adverse effects associated with single- and multi-cancer early detection tests, preliminary data is beginning to surface. Nonetheless, further research is necessary to enhance confidence in harm estimates. Possible adverse effects include false positive and negative results, risks of overdiagnosis and overtreatment, psychological and economic impacts, as well as the potential to exacerbate cancer inequities. False negative results may postpone treatment or lead individuals to forego evidence-based screening protocols. Additional research across the spectrum of commercialized cancer early detection tests is essential to ascertain their influence on adherence to standard-of-care screenings. However,

in the study conducted by Lennon et al. (37), blood testing did not dissuade participants from pursuing mammography after they were counseled on the necessity of maintaining standard cancer screening practices.

False positive outcomes may compel individuals to undergo unnecessary diagnostic evaluations that do not confirm cancer presence, leading to potential harm from diagnostic journeys resulting in superfluous procedures and surgeries. Although evidence is still being gathered, the PATHFINDER study (46) reported that of the 57 participants with false positive screening results, 89% required advanced imaging (e.g., CT, PET, MRI), 28% necessitated noninvasive procedures (e.g., endoscopies or biopsies), and 2% required surgical interventions to exclude disease (57). No serious adverse events related to the study were reported as a result of either MCED testing or diagnostic assessments triggered by a “signal detected” MCED result. MCEDs might identify some indolent cancers that are unlikely to progress to clinically significant conditions. This phenomenon, known as overdiagnosis, could potentially result in the overtreatment of a larger number of these non-threatening cancers. However, this risk is expected to be minimal, as MCED screening tests are tailored to detect more aggressive, rapidly proliferating cancers that release ctDNA into the bloodstream. In fact, the CCGA study (43) illustrated that cancers detected by MCEDs were associated with worse anticipated survival outcomes, indicating that GRAIL's MCED is more adept at identifying cancers with lethal potential, thus reducing the likelihood of overdetecting non-lethal cancers. Additional research is warranted to more accurately quantify this risk for other MCEDs.

Early detection tests may inadvertently heighten patient anxiety and distress levels. In the PATHFINDER study, participants completed the Patient Reported Outcomes Measurement Information System anxiety short form prior to their MCED test, and again after receiving results, upon diagnostic resolution, and at one-year intervals; they also filled out an adapted Multidimensional Impact of Cancer Risk Assessment at the time of results disclosure (58). Anxiety did increase following a positive MCED signal detection in comparison to no signal detection, as indicated by both assessment tools, with a more substantial increase observed in participants who had true positive results. However, anxiety scores returned to baseline levels by the conclusion of the study for participants with both true and false positive results. MCEDs may also potentially elevate the costs associated with cancer care and treatment. Currently, patient costs are considerable, as MCEDs lack health insurance coverage. This absence of coverage raises valid concerns about creating inequitable access to MCEDs, which could further exacerbate disparities related to race, ethnicity, and socioeconomic status in cancer care. Costs would be even more pronounced if a substantial number of patients required diagnostic testing due to false positive MCED results and/or treatment for non-lethal cancers. Nonetheless, as previously discussed, the FPR appears exceedingly low, nearing 1%. Moreover, several studies have modeled the cost-effectiveness of the GRAIL MCED. One analysis assessed the potential stage shift in cancers diagnosed by the GRAIL MCED, concluding that a 53% reduction in stage IV cancer diagnoses would result in a decrease of $5,421 in treatment costs per cancer and yield a gain of 0.13 and 0.38 quality-adjusted life-years across all individuals in the screening program and those diagnosed with cancer, respectively (59). A second study utilized previously published cancer-specific

sensitivities by stage and the true positive to false positive (TP) ratio for each cancer type to calculate the cost of diagnostic investigations among screen-positive individuals per detected cancer (Diagcost). For the United States, the estimated TP (Diagcost) was 1:43.0 ($89,042) under current screening methods, compared to 1:1.8 ($7,060) using an MCED test; for the United Kingdom, the corresponding figures were 1:18 (£10,452) for current screening and 1:1.6 (£2,175) utilizing an MCED test. The authors concluded that while randomized controlled trials are essential, incorporating an MCED blood test into recommended screenings could be a potentially efficient approach.

MCEDs may inadvertently contribute to further inequities in cancer care by widening disparities based on race, ethnicity, socioeconomic status, geographic location (rural vs. urban), and other factors. Given that most cancer early detection assays remain in the investigational phase, developers of these tests have a unique opportunity to mitigate inequities by designing and conducting studies that are inclusive and representative of all potential users of cancer early detection tests. Recruitment strategies aimed at ensuring diverse population representation can facilitate equitable access to these novel technologies through research participation, thereby enhancing the generalizability and efficiency of findings. For instance, the UK-Galleri trial established an equity recruitment framework that sampled participants from regions with high cancer mortality, socioeconomic deprivation, and ethnic diversity. This trial employed mobile phlebotomy clinics to enhance access in economically disadvantaged areas, monitored participant representativeness by postcode with adaptive enrollment strategies, provided language interpretation services, ensured wheelchair accessibility, and conducted targeted community outreach campaigns (60). Furthermore, initiatives established by the American Society of Clinical Oncology and the Association of Community Cancer Centers aim to increase racial and ethnic diversity in clinical trials and offer resources to cancer research teams at no cost to help diversify study populations (61).

Once MCED tests are commercially available, additional strategies to address inequities may include creating educational materials and test information in various languages and formats (e.g., print and video) to overcome literacy challenges, offering patient navigation services to ensure access to testing and diagnostic assessments, providing insurance coverage for all patients, including those enrolled in Medicaid, establishing financial assistance programs for uninsured patients, collaborating with community partners such as federally qualified health centers and community health workers, and deploying mobile phlebotomy clinics to address geographic barriers. Cologuard's patient navigation, which includes multilingual outreach, education, and reminders for patients receiving a Cologuard order (62), exemplifies a strategy aimed at enhancing adherence to cancer early detection tests, which is especially crucial for catering to diverse patient populations.

Conclusion

In summary, the landscape of cancer prevention and early detection is rapidly evolving due to technological advancements and a deeper understanding of cancer biology. Emerging methodologies, particularly multi-cancer early detection

(MCED) tests, offer a promising avenue to enhance the identification of various cancers, often before traditional screening methods can detect them. These innovations leverage genomic and epigenomic analyses to capture signals from circulating tumor DNA (ctDNA), which may be present long before clinical symptoms arise. This capability is especially critical given the statistics indicating that a significant portion of cancers are diagnosed at advanced stages, complicating treatment and negatively impacting patient outcomes. Moreover, the non-invasive nature of liquid biopsies used in MCED tests facilitates greater patient compliance and accessibility. With the potential to analyze multiple cancer types from a single sample, these tests could vastly improve early detection rates across cancers that currently lack effective screening options. However, the implementation of such advanced screening tools is not without challenges. The risks of false positives and negatives pose a significant concern, potentially leading to unnecessary stress for patients and additional medical procedures that may not yield beneficial outcomes. Furthermore, the economic implications of widespread MCED testing and the risk of exacerbating healthcare disparities warrant thorough examination and strategic planning. Ultimately, while the future of cancer screening appears promising with these emerging technologies, it necessitates ongoing research to refine their accuracy, evaluate long-term outcomes, and establish clear clinical guidelines to optimize their use in diverse populations. Continuous collaboration among researchers, clinicians, and policymakers will be essential to translate these technological advances into meaningful public health improvements, ensuring that the benefits of precision oncology are accessible to all.

References

1. American Cancer Society **2023**. *Cancer Facts & Figures 2023* Atlanta, GA: Am. Cancer Soc.
2. NORC **2023**. Percent of cancers detected by screening: all cancer, all ages. *Cancer Detection Tool* NORC Chicago, IL.: https://cancerdetection.norc.org/. Accessed Aug. 12, 2023
3. Sabatino SA, Thompson TD, White MC et al. **2021**. Cancer screening test receipt—United States, 2018. *Morb. Mortal. Wkly. Rep.* 70:29–35
4. Hubbard RA, Kerlikowske K, Flowers CI et al. **2011**. Cumulative probability of false-positive recall or biopsy recommendation after 10 years of screening mammography: a cohort study. *Ann. Intern. Med.* 155:481–92
5. Ibáñez-Sanz G, Garcia M, Milà N et al. **2019**. Adverse Effects on Colorectal Cancer Screening in Catalonia (EACC) Study Working Group. False-positive results in a population-based colorectal screening program: cumulative risk from 2000 to 2017 with biennial screening. *Cancer Epidemiol. Biomarkers Prev.* 28:1909–16
6. Petitti DB, Lin JS, Burda BU. **2018**. *Overdiagnosis in prostate cancer screening decision models: a contextual review for the US Preventive Services Task Force* AHRQ Publ. No. 17-05229-EF-3 Agency Healthc. Res. Qual. North Bethesda, MD:
7. Toft EL, Kaae SE, Malmqvist J, Brodersen J. **2019**. Psychosocial consequences of receiving false-positive colorectal cancer screening results: a qualitative study. *Scand. J. Prim. Health Care* 37:145–54

8. Lafata JE, Simpkins J, Lamerato L et al. **2004**. The economic impact of false-positive cancer screens. *Cancer Epidemiol. Biomarkers Prev.* 13:2126–32
9. Black WC. **2009**. Overdiagnosis: an underrecognized cause of confusion and harm in cancer screening. *J. Natl. Cancer Inst.* 92:1280–82
10. Srivastava S, Koay EJ, Borowsky AD et al. **2019**. Cancer overdiagnosis: a biological challenge and clinical dilemma. *Nat. Rev. Cancer* 19:349–58
11. Kim SY, Kim HS, Park HJ. **2019**. Adverse events related to colonoscopy: global trends and future challenges. *World J. Gastroenterol.* 25:190–204
12. Dasari A, Grothey A, Kopetz S. **2018**. Circulating tumor DNA-defined minimal residual disease in solid tumors: opportunities to accelerate the development of adjuvant therapies. *J. Clin. Oncol.* 36:3437–40
13. Pantel K, Alix-Panabieres C. **2019**. Liquid biopsy and minimal residual disease—latest advances and implications for cure. *Nat. Rev. Clin. Oncol.* 16:409–24
14. Dinan MA, Curtis LH, Hammill BG et al. **2010**. Changes in the use and costs of diagnostic imaging among Medicare beneficiaries with cancer 1999–2006. *JAMA* 303:1625–31
15. Vlahiotis A, Griffin B, Stavros AT, Margolis J. **2018**. Analysis of utilization patterns and associated costs of the breast imaging and diagnostic procedures after screening mammography. *Clinicoeconom. Outcomes Res.* 10:157–67
16. Johnson DA, Barclay RL, Mergener K et al. **2014**. Plasma Septin9 versus fecal immunochemical testing for colorectal cancer screening: a prospective multicenter study. *PLOS ONE* 9:e98238
17. Church TR, Wandell M, Lofton-Day C et al. **2014**. PRESEPT Clinical Study Steering Committee, investigators and study team. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. *Gut* 63:317–25
18. CMS **2021**. *Screening for colorectal cancer—blood-based biomarker tests* Decision memo CAG-00454N Cent. Medicare Medicaid Serv. Baltimore, MD:
19. Lamb YN, Dhillon S. **2017**. Epi proColon® 2.0 CE: a blood-based screening test for colorectal cancer. *Mol. Diagn. Ther.* 21:225–32
20. Imperiale TF, Ransohoff DF, Itzkowitz SH et al. **2014**. Multitarget stool DNA testing for colorectal-cancer screening. *N. Engl. J. Med.* 370:1287–97
21. US Prev. Serv. Task Force **2021**. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA* 325:1965–77
22. Wolf AMD, Fontham ETH, Church TR et al. **2018**. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J. Clin.* 68:250–81
23. Valouev A, Zotenko E, Snyder M et al. **2022**. Development of a highly sensitive multicancer, targeted, cell-free DNA epigenomic assay for integrated screening of lung and colorectal cancer. *J. Clin. Oncol.* 40:3542 Abstr.)
24. Jeeyun L, Kim HC, Kim ST et al. **2021**. Multimodal circulating tumor DNA (ctDNA) colorectal neoplasia detection assay for asymptomatic and early-stage colorectal cancer (CRC). *J. Clin. Oncol.* 39:3536 (Abstr.)
25. D'Auria K, Chang Y, Multhaup M et al. **2022**. Validation of a multi-modal blood-based test for the detection of colorectal cancer with sub single molecule sensitivity. *J. Clin. Oncol.* 40:3627 Abstr.)

26. Kim S-T, Raymond VM, Park JO et al. **2019**. Combined genomic and epigenomic assessment of cell-free circulating tumor DNA (ctDNA) improves assay sensitivity in early-stage colorectal cancer (CRC). *Cancer Res* 79:916 Abstr.)
27. Westesson O, Axelrod H, Dean J et al. **2020**. Integrated genomic and epigenomic cell-free DNA (cfDNA) analysis for the detection of early-stage colorectal cancer. *Cancer Res* 80:2316 Abstr.)
28. Guardant Health **2022**. *Guardant Health announces positive results from pivotal ECLIPSE study evaluating a blood test for the detection of colorectal cancer* Press Release, Dec. 15 Guardant Health Palo Alto, CA: https://investors.guardanthealth.com/press-releases/press-releases/2022/Guardant-Health-announces-positive-results-from-pivotal-ECLIPSE-study-evaluating-a-blood-test-for-the-detection-of-colorectal-cancer/default.aspx
29. Chung D, Gray DM, Greenson J et al. **2023**. Clinical validation of cell free DNA blood-based test for colorectal cancer screening in an average risk population. *Gastroenterology* 164:6 Suppl.S1573
30. Han YD, Oh TJ, Chung T-H et al. **2019**. Early detection of colorectal cancer based on presence of methylated syndecan-2 (SDC2) in stool DNA. *Clin. Epigenet.* 11:51
31. Kim CW, Kim H, Kim HR et al. **2021**. Colorectal cancer screening using a stool DNA-based SDC2 methylation test: a multicenter, prospective trial. *BMC Gastroenterol* 21:173
32. Crook T, Leonard R, Mokbel K et al. **2022**. Accurate screening for early-stage breast cancer by detection and profiling of circulating tumor cells. *Cancers* 14:3341
33. O'Neill K, Syed N, Crook T et al. **2023**. Profiling of circulating glial cells allows accurate blood-based diagnosis of glial malignancies. medRxiv 2022.07.06.22277300
34. Limaye S, Chowdhury S, Rohatgi N et al. **2023**. Accurate prostate cancer detection based on enrichment and characterization of prostate cancer specific circulating tumor cells. *Cancer Med* 12:9116–27
35. Hudnut AG, Hubbell E, Venn O, Church TR. **2023**. Modeled residual current cancer risk after clinical investigation of a positive multi-cancer early detection test result. *Cancer* 129:2056–63
36. Liu MC, Oxnard GR, Klein EA et al. **2020**. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann. Oncol.* 31:745–59
37. Lennon AM, Buchanan AH, Kinde I et al. **2020**. Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. *Science* 369:eabb9601
38. Chen X, Gole J, Gore A et al. **2020**. Non-invasive early detection of cancer four years before conventional diagnosis using a blood test. *Nat. Commun.* 11:3475
39. Wang HY, Chen CH, Shi S et al. **2020**. Improving multi-tumor biomarker health check-up tests with machine learning algorithms. *Cancers* 12:1442
40. Akolkar D, Patil D, Crook T et al. **2020**. Circulating ensembles of tumor-associated cells: a redoubtable new systemic hallmark of cancer. *Int. J. Cancer* 146:3485–94

41. Gaya A, Crook T, Plowman N et al. **2021**. Evaluation of circulating tumor cell clusters for pan-cancer noninvasive diagnostic triaging. *Cancer Cytopathol* 129:226–38
42. Klein EA, Richards D, Cohn A et al. **2021**. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann. Oncol.* 32:1167–77
43. Chen X, Dong Z, Hubbell E et al. **2021**. Prognostic significance of blood-based multi-cancer detection in plasma cell-free DNA. *Clin. Cancer Res.* 27:4221–29
44. Nadauld LD, McDonnell CH 3rd, Beer TM et al. **2021**. The PATHFINDER study: assessment of the implementation of an investigational multi-cancer early detection test into clinical practice. *Cancers* 13:3501
45. GRAIL **2022**. *GRAIL announces final results from the PATHFINDER multi-cancer early detection screening study at ESMO Congress 2022* News Release, Sept. 11 GRAIL Menlo Park, CA:
46. Schrag D, McDonnell CH III, Nadauld L et al. **2022**. A prospective study of a multi-cancer early detection blood test (Abstract 9030). *Ann. Oncol.* 33:S961
47. Lee JM, Ichikawa L, Valencia E et al. **2017**. Performance benchmarks for screening breast MR imaging in community practice. *Radiology* 285:44–52
48. Pinsky PF, Berg CD. **2012**. Applying the National Lung Screening Trial eligibility criteria to the US population: What percent of the population and of incident lung cancers would be covered?. *J. Med. Screen.* 19:154–56
49. FDA **2014**. *Premarket approval (PMA): Cologuard summary of safety and effectiveness data* Premarket Approval Applic. No. P130017, US Food Drug Adm. US Dep. Health Hum. Serv. Silver Spring, MD:
50. Cohen JD, Li L, Wang Y et al. **2018**. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science* 359:926–30
51. Grubb RL 3rd, Pinsky PF, Greenlee RT et al. **2008**. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian cancer screening trial: update on findings from the initial four rounds of screening in a randomized trial. *BJU Int.* 102:1524–30
52. Natl. Lung Screening Trial Res. Team, Aberle DR, Adams AM, Berg CD et al. **2011**. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N. Engl. J. Med.* 365:395–409
53. Croswell JM, Kramer BS, Kreimer AR et al. **2009**. Cumulative incidence of false-positive results in repeated, multimodal cancer screening. *Ann. Fam. Med.* 7:212–22
54. Bettegowda C, Sausen M, Leary RJ et al. **2014**. Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci. Transl. Med.* 224:224ra24
55. Liles EG, Coronado GD, Perrin N et al. **2017**. Uptake of a colorectal cancer screening blood test is higher than of a fecal test offered in clinic: a randomized trial. *Cancer Treat. Res. Commun.* 10:27–31
56. Clarke CA, Hubbell E, Kurian AW et al. **2020**. Projected reductions in absolute cancer-related deaths from diagnosing cancers before metastasis, 2006–2015. *Cancer Epidemiol. Biomarkers Prev.* 29:895–902
57. Schrag D, McDonnell CH III, Nadauld L et al. **2022**. *PATHFINDER: a prospective study of a multi-cancer early detection blood test* Paper presented at ESMO Congress, Sep. 11 Paris: https://grail.com/wp-content/uploads/2022/09/Schrag_903O_ESMO-2022_Pathfinder-Main_Proferred-Paper-Oral-Presentation.pdf

58. Schrag D, Beer TM, McDonnell CH III et al. **2022**. Evaluation of anxiety, distress and satisfaction with a multi-cancer early detection test. *Ann. Oncol.* 33:2417–26
59. Tafazzoli A, Ramsey SD, Shaul A et al. **2022**. The potential value-based price of a multi-cancer early detection genomic blood test to complement current single cancer screening in the USA. *PharmacoEconomics* 40:1107–17
60. Swanton C, Neal RD, Johnson PWM et al. **2022**. NHS-Galleri trial design: equitable study recruitment tactics for targeted population-level screening with a multi-cancer early detection (MCED) test. *J. Clin. Oncol.* 40:TPS6606-TPS
61. Am. Soc. Clin. Oncol. Assoc. Comm. Cancer Cent **2023**. ASCO-ACCC initiative to increase racial & ethnic diversity in clinical trials. *ASCO.* https://old-prod.asco.org/news-initiatives/current-initiatives/cancer-care-initiatives/diversity-cancer-clinical-trials
62. Exact Sciences **2023**. Cologuard offers comprehensive support designed with your practice and patients in mind. *Cologuard* https://www.cologuardhcp.com/coverage-and-support/specialized-support

الوقاية من السرطان والكشف المبكر: التقنيات والتدخلات الناشئة

الملخص:

الخلفية :تحول علم الأورام الدقيق (Precision oncology) عملية الكشف المبكر عن السرطان بين الأفراد ذوي المخاطر المتوسطة. أدت التقدمات في تسلسل الجيل التالي (Next-Generation Sequencing) إلى رؤى هامة حول جينوم السرطان وتحديد العلامات الحيوية لتحسين الكشف المبكر.

الهدف :تستعرض هذه المقالة التقنيات والتدخلات الناشئة في الوقاية من السرطان والكشف المبكر، مع التركيز على أحدث التطورات في أساليب الفحص.

الطرق :يقوم الاستعراض بتحليل مجموعة متنوعة من اختبارات الكشف المبكر عن السرطان الواحد والمتعدد، ويناقش منهجياتها، وتحديد العلامات الحيوية، ونتائج التجارب السريرية، والتحديات المرتبطة بأساليب الفحص الحالية.

النتائج :أظهرت الاختبارات المبتكرة، مثل اختبارات الكشف المبكر عن السرطان المتعدد(MCED) ، حساسية تفوق الطرق التقليدية من خلال تحديد الحمض النووي الورمي المتداول (ctDNA) قبل ظهور الأعراض. ورغم أن هذه التقنيات تبدو واعدة، إلا أنها تواجه تحديات، بما في ذلك إمكانية وجود نتائج إيجابية وسلبية زائفة، وتجاوز التشخيص، وعدم المساواة في الوصول إلى الفحص.

الخاتمة :تحمل التقنيات الناشئة في الكشف عن السرطان إمكانيات كبيرة لتغيير ممارسات الفحص. ومع ذلك، فإن النظر بعناية في فائدتها السريرية والأضرار المحتملة ضروري لضمان الوصول العادل والتنفيذ الفعال.

الكلمات المفتاحية :الوقاية من السرطان، الكشف المبكر، علم الأورام الدقيق، العلامات الحيوية، اختبارات الكشف المبكر عن السرطان المتعدد، الخزعات السائلة.