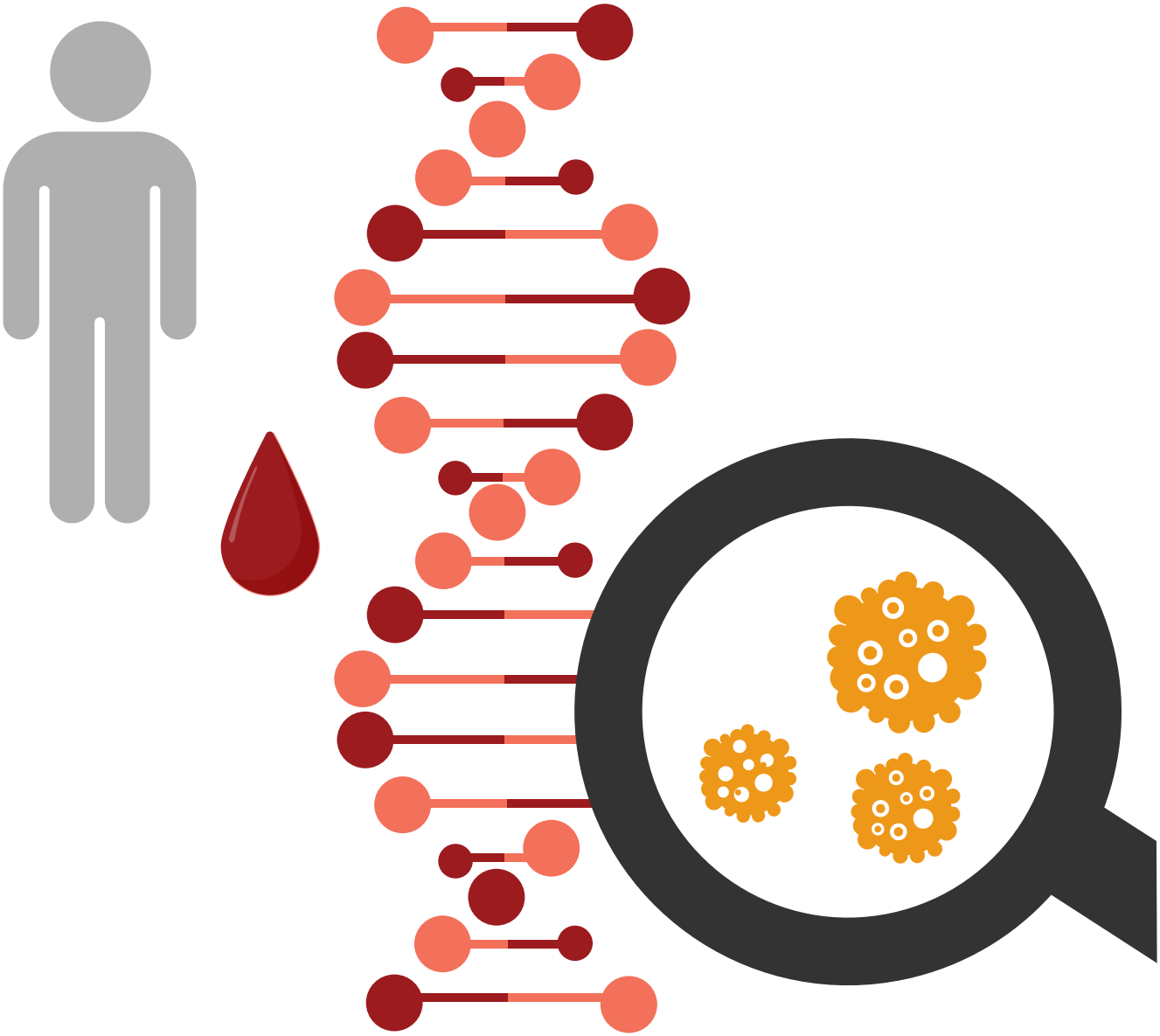
Cancer-Related Technologies Have Changed a Lot. So Should Cancer Screening.



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Cancer-Related Technologies Have Changed a Lot. So Should Cancer Screening.

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POLICY CONTEXT

Medicare and most insurers cover FDA-approved cancer screenings that the U.S. Preventive Services Task Force (USPSTF) recommends with a grade of A or B. Currently, there are only five types of cancer that have screening tests that meet those criteria—breast, cervical, colorectal, prostate, and lung cancers (only in high-risk people for lung).

New, multi-cancer early detection (MCED) tests can detect as many as 50 different types of cancers with a single blood draw.[1] They are designed to detect minute quantities of circulating tumor DNA and protein biomarkers shed into the blood of asymptomatic people. There is uncertain coverage for MCED tests, as these tests have not obtained a USPSTF recommendation, which can be an extremely lengthy process. Because USPSTF often requires large, randomized trials with mortality endpoints to address concerns related to false-positive results and diagnosis, coverage for cancer screening typically has taken considerable time. For example, Medicare did not cover Pap smears until 1990, 70 years after the screening was developed.[2]

Along with reducing the time it takes for screenings to receive USPSTF recommendation, policymakers and regulators may need to develop different coverage determinations because MCED technologies don't fit the current screening paradigm. MCED's greatest promise is in detecting many different types of cancers, which requires different data and determinations of efficacy. There remains the possibility that payers may review the clinical utility of MCED's on a cancer-by-cancer basis, as opposed to the test as a whole.

We argue that innovations in screening should be a priority in our efforts to reduce cancer mortality. Ensuring coverage of these types of screening technologies will require changes in policy. Determining who is eligible and how often to conduct MCED screenings should be a priority now, so that access can be ensured when the tests are available. A value-based approach to reimbursement could provide a pathway to faster coverage with evidence development.

Congress has introduced legislation that would provide for Medicare coverage of FDA-approved, multi-cancer early detection screening tests. While those who are wealthy enough to pay out-of-pocket can get MCED screening today, Medicare coverage is essential to making MCED testing available more equitably, ensuring its benefits reach across all socioeconomic groups.

KEY TAKEAWAYS

- **Cancer is the No. 2 cause of death in the U.S., killing roughly 600,000 people annually.**
- **We do not screen for many of the deadliest types of cancer, and most cancer deaths occur from cancers for which we do not screen.**
- **New cancer-screening technologies, known as blood-based, multi-cancer, early-detection testing, can detect multiple types of cancer with one blood draw and could lead to improved cancer outcomes.**
- **Cancer-screening guidelines can take decades to update. A value-based approach to reimbursement could provide a pathway to faster coverage with evidence development.**

ABSTRACT

Roughly 600,000 people die of cancer in the US annually—placing it alongside COVID-19 as one of our gravest health emergencies. President Biden has announced an ambitious goal of reducing cancer mortality by 50% in the next 25 years. We argue innovations in treatment are not enough to get us there, we also need to focus on cancer screening. New cancer-screening technologies, known as blood-based, multi-cancer, early-detection testing, can detect multiple types of cancer with one blood draw and could lead to improved cancer outcomes. Furthermore, recent advances in cancer treatment have extended cancer survival, particularly when the disease is treated early, raising the returns to early cancer detection through screening. Given these advances, our current cancer-screening and reimbursement paradigms should be revised to recognize the value of new technologies available.

INTRODUCTION

Roughly 600,000 people die of cancer in the U.S. annually.[3] To put this into context, the U.S. recorded 351, 386 COVID-19 deaths in 2020 and 470,902 in 2021.[4] As the No. 2 cause of death in the U.S., cancer ranks ahead of COVID-19 and behind heart disease. This is not for lack of investment: Cancer mortality remains high despite significant resources invested in finding ways to prevent, diagnose and treat the disease over the last 50 years. The National Cancer Institute (NCI) budget has increased steadily from $500 million in 1971 to $6.5 billion in 2021.[5]

Since 1971, when President Nixon first declared a war on cancer, we have screened for the disease one tumor site at a time. Pap smears, colonoscopies, mammograms and prostate screening dominate, each targeting a single type of cancer. That five-decade history has influenced all aspects of our current cancer-detection strategy: who has access to screening, how much it costs, what risks are tolerable and the public policy governing it all. But better screening increases the chances that cancers are detected early, which greatly reduces the probability of death.[6,7] If we are to meet President Biden's goal to reduce cancer mortality by 50% in the next 25 years, we will need to rethink our current screening paradigms.[8]

In addition, two scientific imperatives compel us to revisit our approach to cancer screening. First and foremost, cancer treatment is improving. Innovations in human genomics and machine learning have greatly expanded our therapeutic arsenal and extended cancer survival—especially when the disease is detected early. Improvements in cancer treatment yield greater benefits to early detection—now more than ever before. But we can only leverage these improvements if we detect the cancer soon enough.

Second, the scientific innovations driving new treatments are also making new screening technologies available. Instead of simply looking at cells, tissues and images, we can now observe a cancer's genomic and molecular features through blood-based tests. Multi-cancer early detection (MCED) tests detect molecular signals of cancer that are shared across many cancers, opening new doors to detecting aggressive tumors, including those in previously unscreened sites.

CURRENT CANCER SCREENING LEAVES A CRITICAL UNMET NEED

Today, we do not find the majority of cancers until it is too late to intervene effectively. Most cancer deaths occur in cancers for which we do not screen.[9] There is no routine screening for many of the deadliest cancers, including pancreatic (10% five-year relative survival), liver (20%), esophagus (20%), stomach (32%), and brain and nervous system (33%). Even among the cancers for which we do screen, only 16% of the cancers detected each year among adults ages 50 to 70 are attributed to current screening programs.[10]

In addition, many people skip screening with today's tests because they are inconvenient, time consuming and unpleasant. For example, in a study of 110 patients undergoing colonoscopy screening, the procedure involved, on average, more than three days (81.5 hours) of disruption, from dietary changes in preparation for the procedure through feeling completely back to normal afterward.[11] On average, patients were willing to pay $263 to avoid the time and discomfort associated with the process.

Discomfort and inconvenience—combined with other barriers such as poor insurance coverage, mistrust of the medical system, lack of a primary care provider, limited English proficiency and limited awareness about the importance of screening—keep many patients from adhering to recommended screening guidelines.[12-15] Data from the 2015 National Health Interview Survey (NHIS) reveal low adherence with recommendations for lung, breast, cervical and colorectal cancer screenings.[16,17] In one study, researchers found that only 4.4% of those who met U.S. Preventive Services Task Force (USPSTF) criteria for lung cancer screening were properly screened.[16] Another study demonstrated screening rates below the targets set forth in Healthy People 2020 for nearly every demographic category and screening subpopulation considered.[17,18] A third study estimated that only 27% of U.S. women had the age-appropriate level of mammography screening, while another estimated that half of all patients referred for screening colonoscopy failed to complete the procedure.[19,20]

Some of these estimates may be overstated, since studies have found that self-reported data such as that in the NHIS may not reflect actual, real-world screening prevalence. In one study, 39% to 52% of unscreened women over-reported having had a mammogram or Pap test.[21] In another study, self-reported estimates of mammography use from the Vermont Behavioral Risk Factor Surveillance System were 15 to 25 percentage points higher than actual screening rates across age groups.[22]

From tests that screen for more cancer types to less onerous tests with improved screening adherence, there is much room for improvement in the current screening paradigm. The addition of MCED tests would enable routine screening for many deadly cancers for which we do not now routinely screen.

CANCER-SCREENING GUIDELINES TAKE TOO LONG TO UPDATE

Screening guidelines established by the USPSTF are continually updated as new evidence comes to light. But these updates can take decades—much too long in the context of a public health emergency like cancer.

Prostate-specific antigen (PSA) screening for prostate cancer provides an instructive example. Prior to 2012, USPSTF guidelines held that there was insufficient evidence to make a recommendation for or against PSA-based prostate cancer screening in men younger than 75; in 2012, the USPSTF revised its recommendation downward, recommending against it in all age groups.

The 2012 downgrading was based on the massive, expensive and decade-long NCI Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, which found that PSA screening does not detectably improve prostate cancer mortality in the U.S., in contrast to multiple European randomized controlled trials (RCTs) that showed a mortality benefit from screening. But that was not the end of the story.

Subsequent evidence of increased death and diagnosis at an advanced stage after stopping PSA screening in the U.S. convinced the USPSTF to reconsider its position again. Six years later, in 2018, it endorsed individual decision-making for men ages 55 to 69. After this reversal, rates of PSA testing for men ages 40 to 89 showed a 12.5% relative increase from 2016 to 2019.[23] Significant increases were reported not only in patients ages 55 to 69, for whom screening is specified by the guideline, but also among patients ages 40 to 54 and over 70, for whom screening is not advised.

USPSTF guidelines for low-density CT (LDCT) scanning for lung cancer have also been revised multiple times in the face of changing evidence. In its 2004 recommendations, the USPSTF concluded that there was insufficient evidence to recommend LDCT screening for lung cancer. Ten years later, in 2014, those guidelines were updated, recommending annual LDCT screening for a subset of adults ages 55 to 80 years with a 30-pack-year smoking history (the equivalent of smoking one pack per day for 30 years). Seven years after that, in 2021, the guidelines were updated once again, this time recommending annual LDCT screening for adults ages 50 to 80 years with a 20-pack-year smoking history. With its 2004 and 2013 recommendations, the USPSTF properly concluded that there was uncertainty around the value of screening, but did not consider the risk of deaths while waiting until all uncertainty was resolved. If failure to adopt new technologies poses its own risks, waiting for certainty is not always the right thing to do.[24]

Patients and doctors find it challenging to keep up with changing recommendations. Two years after the USPSTF changed breast cancer-screening guidelines in 2009, a focus-group study of 77 women in Boston found that the majority were unaware of any change in mammography-screening guidelines.[25] Among a group of 250 primary care physicians in Los Angeles surveyed a year after the USPSTF updated its lung-cancer-screening guidance in 2014, less than half (46%) were aware that the USPSTF recommends LDCT for high-risk current and former smokers.[26]

Such lags in understanding likely contribute to low adherence to screening guidelines.

CONCERNS ABOUT OVERDIAGNOSIS ARE MISPLACED

Overdiagnosis, the diagnosis of a medical condition that would never have caused any symptoms or problems, is a particular concern with older, imaging-based screening technologies like those currently used to screen for thyroid, breast and lung cancers. The screens provide a static snapshot of a tumor, but are less effective in distinguishing between fast- and slow-moving cancers. Improvements in such technologies are particularly prone to "length bias," as they enable radiologists to see smaller lesions, which are statistically more likely to be slow-growing.[a]

When widespread prostate cancer screening via PSA testing was introduced in the early 1990s, a marked increase in prostate cancer incidence followed, with no corresponding increase in prostate cancer mortality, suggesting that prostate cancer was being overdiagnosed, and that cancers were being detected that would never result in symptoms or death.[27,28] Between 1989 and 2002, there was a "significant downward risk migration" in patients diagnosed with prostate

a. Such length bias can be mitigated by adapting guidelines as imaging technologies improve.

cancer.[29] The share of patients presenting with low-risk disease increased from 31.2% to 47.7%, while the share presenting with high-risk disease decreased from 40.9% to 14.8%. Some have estimated that up to 60% of prostate cancers are overdiagnosed, imposing unnecessary trauma and emotional suffering on patients and their families, and medical costs for unneeded treatment.[30]

Blood-based multi-cancer tests can address some of these drawbacks.[b] These tests are based on circulating or "cell-free" DNA (cfDNA) and help identify patients with cancers requiring treatment rather than indolent disease. As cells divide, they shed methylated DNA into the bloodstream; these new tests identify cfDNA in blood samples. Since shedding of methylated DNA is associated with cell division rate, faster-growing cancers likely shed more methylated DNA than slower-growing cancers. Indeed, a recent long-term follow-up study suggests that cancers detected by the methylation-based test required treatment, whereas cancers not detected were more likely to be indolent and have a better prognosis.[31] This is not to say that MCED tests do not pose any overdiagnosis risk, but the science underpinning these tests reduces those risks.

DECISIONS SHOULD BE MADE USING SURROGATE ENDPOINTS

Screening trials designed to ascertain improved survival can take decades. In an era of better treatment—and changing treatment guidelines—such delays could lead to a lot of needless suffering. The gold-standard measure of success for any cancer intervention should be either cancer-specific or overall survival. However, trials to ascertain these outcomes require a long time to complete, so regulatory agencies such as the Food and Drug Administration (FDA) frequently accept intermediate clinical endpoints such as progression-free survival, time to metastasis or measures of biomarkers such as PSA as surrogates for a given clinical outcome. Regulators are also now approving tissue-agnostic cancer treatments based on genomic and molecular cancer characteristics.[32]

The basic tradeoff in using these surrogate markers is between the speed and quality of the approval decisions that are based on them. While not every intervention demonstrates long-term survival outcomes, regulators should accept thoughtful approaches to evidence generation that balance the potential risks and benefits. Because of their speed and lower cost, trials with surrogate or intermediate markers facilitate a more innovative, balanced approach to development of new cancer treatments, enabling earlier patient access to beneficial new therapies. On the other hand, using surrogate endpoints may lead regulators to make the wrong decisions, either failing to approve a beneficial therapy or approving a therapy that is not beneficial. Regulators implicitly weigh this tradeoff every time they use a surrogate endpoint, hoping to reduce patient suffering by adopting treatments with positive expected value to patients instead of waiting for better evidence.

Determining whether to wait for definitive evidence for screening and early-detection tests involves a similar tradeoff, with the added complication that, by the time definitive evidence arrives, clinical innovation may have already made it obsolete.

The Cochrane review of mammography screening evidence provides an instructive example. Cochrane reviews are "recognized worldwide as the highest standard in evidence-based healthcare."[33] The most recent Cochrane review of mammography screening for breast cancer was published in 2013.[34] After reviewing the results of eight randomized clinical trials covering 600,000 women in Europe and North America ages 39 to 74, the authors concluded that "the time has come to re-assess whether universal mammography screening should be recommended for any age group. Declining rates of breast cancer mortality are mainly due to improved treatments and breast cancer awareness, and therefore we are uncertain as to the benefits of screening today." Articles in the media have used this evidence to conclude that "there is no reliable evidence that routine mammograms for healthy women save lives."[35] But after ten years, a closer look at the 2013 review is in order.

First, these reviews are (by design) backward looking. Although published in 2013, the Cochrane review only included trials that enrolled patients between 1963 and 1997; no patients enrolled in the present century were involved and only one trial enrolled patients after 1990.

Second, a lot has happened in the breast cancer world since 1990. Of particular importance, the first genetically targeted treatment for HER2+ breast cancer, trastuzumab (Herceptin) was developed and first approved for use in the U.S. in 1998. (The drug was subsequently approved for use in Canada (2000), the EU (2000) and the UK (2002)). Among more than 200 published studies included in the Cochrane review, 86% were published before trastuzumab was approved in 1998.

Therefore, although the 2013 Cochrane review concludes that breast cancer screening may not be useful for any age group, it is based almost entirely on data collected prior to the emergence of targeted therapies like trastuzumab, which represent one of the most important advances in breast cancer treatment in the last 50 years. The RCT data used—and the technologies evaluated—were outdated before they were even

b. PSA screening for prostate cancer is also a blood-based test, but rather than measuring cell-free DNA (cfDNA), it measures the amount of a protein (prostate-specific antigen) in the bloodstream. It was originally used to guide treatment of patients already diagnosed with prostate cancer. In contrast to blood-based MCED tests, PSA tests were not designed to selectively identify the most aggressive tumors, making them more prone to the kind of overdiagnosis risks noted above.

analyzed. Waiting for the kind of definitive data represented by the Cochrane review costs lives, particularly in the context of diagnosing cancer, a disease where treatment modalities are improving rapidly.[c]

New cancer treatments that could slow or stop disease progression are being discovered and brought to market every year, and the pace of this innovation has been increasing.[37] In this environment, the possibility that the next drug approved will be a lifesaving breakthrough is greater than ever, and diagnosing cancers earlier becomes even more important, since not knowing about an early-stage cancer could keep patients from accessing newly approved treatments for early stage disease. We can no longer assert that it is "better not to know" about asymptomatic disease just because it currently lacks good treatment options.

In addition, the fact that it is possible to identify patients at earlier stages will enable the development of earlier stage treatments and create incentives for drug companies to develop novel early-stage treatments. A quick search of clinicaltrials.gov finds more than 500 currently active or recruiting trials for adjuvant or neoadjuvant cancer treatments. Given that the next phase of reducing cancer mortality rests on earlier treatment, new treatments aimed specifically at early-stage disease will be especially important if we are to attain the goal of reducing cancer mortality over the next 25 years.

It will take decades to measure the definitive endpoint of survival, and if treatments continue to improve, and the tests themselves advance, those studies will be out of date and the treatment and testing technology obsolete by the time they are reported. We must consider explicitly the benefits of waiting for evidence to catch up to today's screening technology versus the costs of deferring adoption. Leveraging surrogate endpoints would enable a more timely evaluation of new screening technologies by regulators and payers, including Medicare, in coverage evaluations.

BETTER SCREENING—WITH COVERAGE—WOULD REDUCE DISPARITIES IN CANCER OUTCOMES

High-quality, affordable screening is already disproportionately accessible across racial and income groups. Although passage of the Affordable Care Act has helped decrease the number of uninsured Americans of all races, rates of insurance for Black and Hispanic Americans continue to lag behind those of white Americans.[38] Exacerbating these disparities are other social determinants of health that disproportionately affect those with lower incomes, such as difficulties getting transportation and time off from work to get a mammogram or colonoscopy. Black and Hispanic patients who are screened are more likely to be screened in lower-quality and understaffed facilities, and have their cancers detected at a later stage, compared to white patients.[39,40] There is an acute need for screening technologies that can close these disparities.

New blood-based screening modalities can make screening more widely available and disproportionately more effective in minority communities, in part because transportation and time-away-from-work requirements are more limited. Since the blood sample is sent to a central lab for analysis, the quality of the screen result does not depend on the local facility and is less subject to physician bias or discrimination, meaning that disparities in facility quality are less likely to translate into disparities in diagnosis.[41] However, racial and ethnic disparities in income and health insurance coverage would remain. While we do not yet know the negotiated prices for these tests, they should be value-based according to the most up-to-date value-assessment methods, and disparities in financial barriers to MCED must be addressed.

Blood-based screening that is thoughtfully implemented can help ameliorate the disparities that currently result from existing screening programs. But this will depend critically on the access policies for new technologies. Broad reimbursement policies like those proposed in the Medicare Multi-Cancer Early Detection Screening Coverage Act of 2021—which authorize the Centers for Medicare and Medicaid Services to evaluate and cover blood-based MCED tests and future test methods with FDA approval—can help improve existing disparities by making them equally available to patients from all backgrounds.[42]

WE CAN ADDRESS THE ISSUE OF FALSE POSITIVES

Existing screening technologies are not perfect. Their positive predictive value (PPV)—the likelihood that an individual with a positive test result actually has the disease—ranges from less than 1% for cervical cancer screening to 8.7% for colon cancer screening (via FIT test).[43,44] The new MCED technologies coming to market perform much better—one new test (Galleri) has a PPV of 45%.[45] Next-generation MCED tests generate many fewer false-positive results compared to existing screening modalities. One study estimated that current screening in the U.S. generates 43 false positives for every true positive result, while MCED tests generate fewer than two false positives per true positive.[46]

Cumulative, lifetime false-positive risks from our current cancer-screening paradigm are also much higher than many people realize, in large part because we use separate screens for individual cancers. In one study, in which men ages 55–74

c. Survival prognoses for late-stage cancers detected by MCED remain poor. [36]

received regular screens for lung, colon and prostate cancers, the risk of at least one false-positive result was greater than 60% after just three years of screenings (14 screens).[47]

Against this backdrop, the marginal, incremental false-positive risk of an MCED screen is very small and the rate of true negatives is correspondingly very high. While false positives will still generate costs associated with follow-up testing, the health impact of false positives on patients is small.[48] When patients receive a false-positive result, they often experience negative emotional effects such as feelings of worry and anxiety. But when follow-up testing reveals no cancer, those feelings are replaced by relief and assurance for most patients. In one small study of cancer-screening recipients who had received a false-positive result, feelings of relief and assurance appeared to eventually outweigh the negative emotions for most participants.[49]

CONCLUSION

Despite having declared "war" on cancer 50 years ago, we have a long way to go before we can declare victory. In 2019, cancer was the No. 1 or 2 leading cause of death in people under age 70 in 112 out of 183 countries, and is on track to become the leading cause of death over the next few decades.[50,51] Today, we routinely screen for only a handful of cancers. As a result, a large proportion of cancers are diagnosed in later stages, when treatments are less effective.[52] Furthermore, we still rely on decades-old screening technologies that look for one cancer at a time, rather than screening people for multiple cancers at once.

Improving our cancer-screening approach by adding many more single-cancer screens to those we already use will not work—the costs and the cumulative false-positive rates would be too great. Rather, a novel screening approach that looks for many cancers in a single test, such as blood-based MCED testing, is a better way forward. There is still uncertainty about how MCED will play out in the real world in terms of its effects on disparities and survival. A large, ongoing, UK National Health Service trial of this approach should resolve some uncertainty when results are reported in 2026.[53] We also do not yet know the cost of these tests, but they should be priced according to the value they deliver.[54]

President Biden's reignited Cancer Moonshot highlights the ambitious goal of reducing cancer mortality by at least 50% in the next 25 years. Public health solutions are unlikely to get us there. New cancer therapies show promise, but they require identification of cancer cases at a stage where their prognosis is mutable. Ultimately, progress will require better diagnostics and improved detection methods to identify the most aggressive cancers as soon as possible. Cancer-screening guidelines sometimes take decades to update. A value-based approach to reimbursement could provide a pathway to faster coverage with evidence development. This would help us optimize our current paradigms for cancer screening and reimbursement to take advantage of the new technologies available.

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