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Multicancer Screening Tests: Anticipating And Addressing Considerations For Payer Coverage And Patient Access

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Abstract

There is a tremendous public health need to identify potentially lethal cancers at earlier stages, when there is a greater chance for improved survival. Although in the US there are currently screening recommendations for only five cancers (breast, colorectal, cervical, lung, and prostate), new tests can screen for up to fifty cancers simultaneously based on a simple blood draw. However, these multicancer screening tests (also called “liquid biopsy” tests) will also present challenges to payers because of intrinsic features of the tests and the complexity of payer coverage assessments for screening tests. We describe these considerations while also offering potential solutions that can inform payers’ decision making if these tests prove to be beneficial.

Approaches to cancer diagnosis, treatment, and monitoring have been revolutionized by advances in precision medicine. Tests that analyze genetic changes in tumor tissue are routinely used to guide cancer management, and germline genetic testing is used to assess a person’s inherited risk of developing cancer—for example, tests for alterations in genes that predispose a person to breast and ovarian cancer. Now the armamentarium of cancer precision medicine tests is being expanded to include novel approaches to screening for multiple cancers simultaneously in older adults without additional known cancer risk factors.[1]

These tests are an important advance, as more than 50 percent of cancer diagnoses and deaths occur in cancers that currently do not have a screening test.[2] The U.S. Preventive Services Task Force has an A or B rating for screening recommendations for four cancers in the US: breast, colorectal, cervical, and lung. Individualized decision making regarding prostate cancer screening is recommended for men ages 55–69.[3] Although the underlying rationale for using a blood test to detect cancer has been known to the scientific community for many decades, the first contemporary example was discovered serendipitously by scientists when maternal tumor DNA was found in the blood of asymptomatic pregnant women undergoing noninvasive prenatal testing for fetal chromosomal abnormalities.[4]

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These insights became the basis for developing a clinical application for cancer screening in adults at average risk for cancer.

Multicancer Early Detection Tests

Multicancer early detection (MCED) screening tests, also called “liquid biopsy” tests, are designed to detect minute quantities of circulating tumor DNA and protein biomarkers shed into the blood of asymptomatic people by up to fifty different tumor types.[5] The justification for screening for evidence of diverse common and rare cancers in one blood test is that this will improve screening efficiencies over individual, organ-specific tests.[6] The first MCED screening test was recently launched in the US as a laboratory-developed test,[7] but there are numerous other tests in the development pipeline.[8] For example, GRAIL’s Galleri test[7] claims to detect up to fifty different cancers and is marketed without payer coverage, and companies such as Exact Sciences and Freenome also have MCED screening tests in development.[9] All of these tests use next-generation sequencing technology—a test category that has encountered challenges from payers because of the complexity of the test results. The goal is to detect cancers at earlier stages (downstaging) when the chances of increased survival or even cures may be much higher compared with the shortened survival and high costs associated with advanced disease.

Rationale For MCED Screening Tests

Because cancer remains one of the leading causes of death in the US, the ability to add a simple blood draw to detect multiple cancers noninvasively would represent a major public health advance if the evidence reveals that early detection leads to reductions in cancer-specific mortality and morbidity and improved quality of life. Because multicancer early detection screening tests can identify signals from a variety of potentially lethal cancers that currently have no recommended screening tests, the cancer detection rate could increase significantly for cancers such as pancreatic, liver, and ovarian cancers that currently have five-year survival rates of less than 50 percent.[10(p18)]

Despite the optimism based on published results of clinical validation studies,[11,12] there are unanswered questions regarding clinical utility, and MCED screening tests are likely to present many challenges for public and private payers’ coverage decision making. This is because the tests represent an entirely different approach to cancer screening and will require modified methods of evaluation to ensure appropriate patient access. Without payer coverage, MCED screening tests and their potential health benefits will be limited to more affluent patients who can afford to pay out of pocket, assuming that there is evidence of net benefits of multicancer screening. Prior reviews of liquid biopsies have examined the potential clinical benefits of MCED screening tests,[1,13] but none has identified the coverage challenges or outlined a path forward to developing the necessary evidence of clinical utility.

Screening Test Paradigm Shift

This commentary aims to prepare payers and other policy makers for a foreseeable paradigm shift in cancer screening methods while also describing evidence-generation strategies that

could be pursued now to inform payers' decision making. Our perspective is informed by our research evaluating coverage policies for a wide range of genomic tests.[14] We have found that although payers' coverage decisions for tests based on next-generation sequencing are highly variable, payers generally state that they require evidence of analytic validity (test is accurate and reliable), clinical validity (test is medically meaningful), and clinical utility (test results affect clinical decisions and improve health outcomes) to be considered "medically necessary and not investigational" (private payers) or "reasonable and necessary" (Medicare), and therefore covered. Although the lack of clinical utility data is a frequently cited reason for noncoverage when tests are first introduced, over time we and others have documented increasing payer coverage for tests based on next-generation sequencing. This shift to positive coverage decisions is often associated with the publication of additional clinical and economic studies and changes in professional practice guidelines.[14]

Considerations For Payer Coverage

The features that make MCED screening tests a potentially breakthrough innovation may also complicate payers' decision making (see online appendix exhibit 1).[15] There is no established evidentiary framework for payers to apply to a multicancer test assessment where the sensitivity of the test varies by cancer and by stage so the benefits and harms of screening vary by tumor type. It is unclear whether payers will continue to review the clinical utility of the new test for each cancer type individually rather than for the test as a whole. Payers may also question the utility of classification of results leading to a diagnosis of metastatic disease as early (or "earlier") detection, as this is unlikely to support improved health outcomes for patients. In this section we outline some of the major considerations, including the need for robust evidence, Medicare requirements, challenges of clinical integration, and avoiding disparities in cancer coverage.

ROBUST EVIDENCE REQUIRED

There is a high evidence bar for new cancer screening tests in presumably cancer-free patients.[16] The vast majority of people screened will not have asymptomatic cancer, so the harms of testing center primarily, but not exclusively, on false positives. Another harm is the potential for overdiagnosis (detecting indolent cancers that would not have caused the individual to die of cancer). However, this possibility is hypothesized to be small, given that MCED screening tests are designed to detect more aggressive, rapidly growing cancers that shed circulating tumor DNA into the blood-stream.[17] Even for patients with undiagnosed cancer, early detection might not represent a true benefit because of the erroneous conclusion that the additional time between a positive test result and symptoms from cancer has extended survival, whereas the time of death from cancer remains unchanged.

Decision makers often require large, randomized trials with mortality endpoints to address these concerns and to quantify harms associated with false-positive results and overdiagnosis —for example, the multiple large studies conducted over twenty or more years before the U.S. Preventive Services Task Force recommendation and Medicare coverage of low-dose computed tomography (CT) scanning as a screening test for lung cancer in patients with a

history of smoking.[18] In the case of studying the effectiveness of MCED screening tests in average-risk patients (typically ages 50–79 without known clinical or lifestyle risk factors for cancer), these studies will require tens of thousands of patients randomly assigned to the new MCED screening test versus standard-of-care screening, with many years of follow-up to demonstrate a net survival benefit due to cancer detection and downstaging. An example of such a study is the GRAIL Bio UK–sponsored pragmatic trial under way with the National Health Service (NHS) England to assess the Galleri test in 140,000 people ages 50–77.[19] In the meantime, as Galleri is currently on the market in the US, policy makers will need to rely on sophisticated models that predict how detection of cancers at earlier stages of growth could lead to a reduction in cancer-related morbidity and mortality compared with current standard-of-care practices.[20] There will also need to be longitudinal studies of real-world data to document outcomes of MCED screening tests in a variety of clinical practice settings. These strategies are intended to bridge the current evidence gaps, recognizing the potential harms (lives lost because of cancer) of delaying clinical use of effective MCED screening tests. A balance will need to be struck between conducting clinical trials and developing robust models and real-world data studies of the benefits and harms of implementing MCED screening tests alongside standard screening.

MEDICARE REQUIREMENTS

The traditional Medicare fee-for-service program was designed to cover services that are medically necessary for the diagnosis and treatment of an illness, injury, or malformation of a body part. Screening tests are preventive services that are not part of this defined benefit unless there are specific legislative exception categories (for example, breast and colorectal cancers) or the tests are endorsed by the U.S. Preventive Services Task Force (for example, lung cancer). After passage of the Affordable Care Act, a U.S. Preventive Services Task Force grade of A or B makes screening tests a contractual benefit that private payers must cover without patient out-of-pocket payment.[21]

Obtaining coverage for the U.S. Preventive Services Task Force–graded services in Medicare is a more complicated journey. The Medicare Improvement for Patients and Providers Act of 2008 authorized the secretary of health and human services to add additional preventive services through a national coverage determination process if they are determined to be reasonable and necessary for the prevention or early detection of an illness or disability. These preventive services must also have a U.S. Preventive Services Task Force recommendation grade A or B and must be considered appropriate for people entitled to benefits under Part A or Part B of Medicare.[22] The process for obtaining a task force assessment of a screening test includes review of topic nominations for relevance to prevention, primary care, and public health; development of a research plan that is subject to revision based on public comments; a rigorous evaluation of peer-reviewed evidence leading to draft recommendations; and then final recommendations accounting for public comments.[23]

Against this complicated backdrop of evidence requirements for Medicare coverage of preventive services, there are two possible paths that MCED screening test developers could pursue: facilitate the passage of new legislation that creates a specific screening exception

for MCED screening tests or develop the requisite evidence to achieve a U.S. Preventive Services Task Force A or B grade. Both strategies would still require a national coverage determination before Medicare beneficiaries would obtain access to a new MCED screening test.

With respect to the first path, Rep. Terri Sewell (D-AL) recently reintroduced the Medicare Multi-Cancer Early Detection Screening Coverage Act to provide Medicare coverage for MCED screening tests approved or cleared by the Food and Drug Administration (FDA).[24] As of January 2022, this legislation had not been advanced, and it is difficult to predict whether and when the legislation might pass. Nevertheless, the legislative route still requires that new MCED screening tests be FDA approved or cleared, which requires convincing evidence of clinical validity. With respect to the second path, the evidence bar to obtain an U.S. Preventive Services Task Force recommendation grade A or B is high, and even after a topic has navigated the nomination process and been selected for task force review, the process for development of a recommendation statement takes approximately two to three years.[25] Parallel review of medical devices, an approach in which the FDA and the Centers for Medicare and Medicaid Services (CMS) agree to review information about a medical device concurrently, is also not an option, given that MCED screening is not now a covered benefit for Medicare beneficiaries.

Notably, even with endorsement by the FDA or the U.S. Preventive Services Task Force, CMS maintains authority to use an evidence-based process to determine coverage parameters for approved or recommended tests. An example of the difficulty of overcoming these additional evidence hurdles is illustrated by Epi proColon, a blood test for colorectal cancer screening in people who are unable to be screened by the recommended methods. Although the test received FDA approval, CMS denied coverage[26] of this specific test because it failed to meet CMS's test performance requirements based on comparison to colonoscopy.

CLINICAL INTEGRATION CHALLENGES

There are several factors related to the proposed clinical implementation of MCED screening tests that will also strain the standard evidentiary framework used by payers. Because MCED screening tests are intended to be added to standard-of-care cancer screening modalities and not substituted for them, payers' interpretation of the net benefits of screening by tumor site will be complicated. For example, the effects of MCED screening tests on adherence to standard-of-care screening tests such as mammography or colonoscopy are uncertain, and there may be positive or negative downstream effects regarding how people continue to follow current screening recommendations. Also, all MCED screening tests require diagnostic confirmation of the tissue of origin in patients who screen positive for cancer. Some MCED screening tests may predict tumor type relatively accurately based on specific changes to tumor DNA, but others could require whole-body radiologic imaging for tumor localization.[12] Patients, clinicians, and payers may be faced with scenarios with undefined diagnostic follow-up procedures for patients who initially test positive for cancer, which adds to concerns regarding the clinical and psychological harms as well as unnecessary costs of false-positives, overdiagnosis, and overtreatment. Although the cost

of the MCED screening test may be fully covered, patients may face high out-of-pocket expenses for follow-up diagnostic procedures.[27]

AVOIDING CANCER DISPARITIES

There are disparities in cancer screening, detection rates, and health outcomes by geographic location, income, education, national origin, and race and ethnicity.[28] Because the people at greatest risk for missed cancers may be the least likely to be able to pay out of pocket for MCED screening tests, payer coverage is required to avoid exacerbating disparities in cancer screening and early cancer diagnoses. Conversely, the ease of use of a single blood test for multiple cancers added to current screening recommendations may lead to a reduction in disparities because of the ability to detect more aggressive tumors that disproportionately affect minority patients.[29] Removing low rates of insurance coverage as a barrier to access will be critical if the benefits of MCED screening tests outweigh the harms.

ECONOMIC CONSIDERATIONS

Economic considerations will be a critical part of payers' evaluations of MCED screening tests. *Economic* refers both to an evaluation of affordability measured in terms of the short-term financial impact of adding MCED screening tests to the current screening paradigm and to cost-effectiveness analysis that assesses the tests' direct medical costs in relation to lifetime impacts on both cancer-specific mortality and quality of life. Evidence from early modeling studies indicates that the main clinical benefits of MCED screening tests are driven by the effects of downstaging (detecting cancers at earlier stages compared with the standard of care) and the retesting interval (more frequent testing detects more cancers).[20] Although in the long term MCED screening tests may be cost-effective because of their net positive effects on downstaging and survival, the costs of testing average-risk people (the Galleri test was introduced at $949 for self-pay)[30] and the predicted increase in the number of new cancers diagnosed in the initial few years after MCED screening test adoption will raise concerns about the budget impact and affordability of these tests. Test developers are apt to model MCED screening tests by showing the impact on lifetime costs and outcomes, but private payers may be less influenced by cost-effectiveness data, given member turnover and the need to account for not only the substantial increase in per member per month costs of covering MCED screening tests but also the downstream costs associated with confirmatory diagnostic testing and false positives.

Also, although Medicare does not rely on cost-effectiveness data in treatment coverage determinations, in the case of preventive services such as screening tests, there is a clear track record of considering the cost-effectiveness of the intervention.[31] In addition, the Congressional Budget Office will evaluate the budget impact if MCED screening tests become a covered benefit for the Medicare population. Collectively, these issues are likely to lead to a crossroads where test developers cannot predict with certainty the evidence level they need to meet for MCED screening tests to be covered, whereas payers lack a multicancer framework to know what data they need for coverage decisions.

A Path Forward

The following steps may help provide the necessary evidence for payers and ensure equitable patient access to MCED screening tests as clinically appropriate. Although the initiatives are presented sequentially, the goal would be to pursue many of them in parallel. What is unique about these considerations is that there is no precedent for multicancer screening, so these recommendations are intended to address uncertainty regarding how these tests and their follow-up interventions should be integrated into primary care and cancer screening guidelines.

EVALUATION OF CLINICAL VALIDITY AND UTILITY

Now is the time to develop more clarity regarding how payers are likely to evaluate the clinical validity and utility of MCED screening tests. For clinical validity, will payers accept the definition of an overall cancer detection rate based on aggregate prevalence, or will they insist on evaluating the positive and negative predictive values of the test for cancers individually or stratified by cancers with and without current standard-of-care tests for screening? For clinical utility, there needs to be transparency regarding the criteria that payers may use, the evidence that may be required, and whether evidence will be interpreted within the context of the payer's current coverage framework for cancer screening tests or a modified framework. For example, prioritizing evidence development efforts targeting the most prevalent and lethal unscreened cancer types may help overcome the enormous challenge of prospectively developing clinical utility evidence for fifty individual cancers.

Payer engagement is the typical approach to developing these insights; however, payer engagement needs to be ongoing to adapt to emerging scientific, clinical, and policy information. The consequences of adapting the evidentiary framework for coverage determinations has profound implications for test developers, patients, and clinicians, as all groups share a vested interest in understanding the benefit and risk profile of a single test that can be used to screen for multiple cancer types.

VALUE AND PAYER EVIDENTIARY FRAMEWORKS

There should be an adaptation of value frameworks for economic value assessment and payer coverage evidence evaluation for MCED screening tests. As one example, a multistakeholder international precision medicine group[32] recently described the decision-making perspectives and framework for determining the value of precision medicine tests broadly. These considerations could be adapted for MCED screening tests to appropriately capture the full economic value of both ruling in and ruling out cancer while also accounting for the quality-of-life impact on patients. Although today there is no publicly funded technology assessment group in the US that examines both the clinical effectiveness and costs of cancer screening, the Institute for Clinical and Economic Review is a privately funded organization that conducts value assessments primarily for drugs. However, it is possible that in the future, the institute will address innovative tests such as MCED screening tests, given their projected broad use and profound cost and patient implications—a position that is consistent with the institute's reports on supplemental imaging practices for women with dense breasts.[33] As previously described, Medicare is also likely to consider

cost-effectiveness analysis for MCED screening test coverage decision making, which relies on both the clinical evidence required to demonstrate clinical utility and evidence of the impact on resource use.

There is a critical window of opportunity to ensure that all MCED screening test stakeholders, including patients and providers, are consulted regarding how value (cost relative to outcome) is defined and measured in this clinical scenario. Economic evaluations such as cost-effectiveness models should be conducted and the findings published in peer-reviewed journals to promote transparency. In parallel, assessments of the budget impact of MCED screening tests should be conducted to elucidate the impact on payer expenditures and the Medicare program.[34]

NEED FOR REAL-WORLD EVIDENCE

There should be a systematic effort to collect real-world data as part of test development and early adoption of laboratory-developed tests. Both insurer claims and electronic health record data could be analyzed to develop real-world evidence demonstrating cancer detection rates by cancer type and stage, the diagnostic paths for true positives and false-positive cases, adherence to standard-of-care screening, cancer treatment outcomes, and cancer-specific mortality. Integrated delivery networks that offer both coordinated provider services and health insurance plans with the goal of improving population health would be logical sites for real-world evidence studies to complement results from registrational studies designed to support premarket approval by the FDA. These studies could include pragmatic trials, observational studies, or MCED screening test registries. A national registry of MCED screening tests using a common data model and linkage to existing cancer registries such as the Surveillance, Epidemiology, and End Results (SEER) Program and claims data would provide both larger sample sizes and information about survival and costs for patients who are screened positive and then confirmed to have cancer. The goal of these studies is to characterize not only the benefits of adding MCED screening tests to clinical practice but also the economic, humanistic, and clinical harms of testing, particularly for the most prevalent and lethal cancer types.

Performance-based risk-sharing arrangements such as outcomes-based contracts between laboratories or test developers and private payers could be another source of real-world evidence, assuming that the results of such undertakings would be made public. A specific example is the arrangement between Illumina and Harvard Pilgrim focused on the use of noninvasive prenatal testing in average-risk women.[35] Study results formed the basis of expanded coverage by private payers for this expanded indication. Coverage with evidence development is another commonly suggested—but rarely implemented—approach for gathering real-world evidence for tests with uncertain clinical utility. *Coverage with evidence development* refers to provisional coverage by a payer (typically Medicare) contingent on further collection of population-level evidence from a prespecified study. Assuming that the policy hurdles could be overcome (Medicare is able to cover MCED screening tests as a new screening benefit), coverage with evidence development could be another mechanism for payers such as Medicare to manage the uncertainties of covering the tests. It is important to note that prior Medicare coverage with evidence development

studies has led to both more generous coverage (for example, implantable cardioverter-defibrillators)[36] and less generous coverage (for example, lung volume reduction surgery),[37] so the outcome remains uncertain regarding how this approach would ultimately affect MCED screening test coverage.

ENGAGING PATIENTS IN RESEARCH

Additional information should be collected from patients regarding the behavioral and quality-of-life effects of MCED screening. Before initiating any real-world evidence study, adults at average and high risk for cancer and patients with screen-detected cancers should be engaged to define patient-relevant outcomes and participate in the design of studies that will generate results that will be meaningful for patients and families. Incorporating the patient perspective in studies of multicancer screening will be necessary to fully understand the implementation barriers and enablers.

Conclusion

Multicancer early detection screening tests may prove to be a notable scientific advance toward the societal goal of detecting cancers at earlier stages to improve patient outcomes. By anticipating coverage considerations and identifying potential solutions now, we increase the likelihood that test developers will be prepared to address payers' evidence expectations regarding MCED screening tests and support patient access to tests that deliver the promised health benefits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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