

Examining Developments in Multicancer Early Detection: Highlights of New Clinical Data from Recent Conferences

HIGHLIGHTS

- › Examining Developments in Multicancer Early Detection: Highlights of New Clinical Data from Recent Conferences
- › CE Posttest

Examining Developments in Multicancer Early Detection: Highlights of New Clinical Data from Recent Conferences

Release date: December 10, 2021

Expiration date: December 10, 2022

Estimated time to complete activity: 2.0 hours

Type of activity: Application

Medium: Print with internet-based posttest, evaluation, and request for credit.

Fee: Free

This activity is supported by an educational grant from GRAIL, Inc.

Intended Audience

Managed care payers, pharmacy directors, pharmacy benefit managers, specialty pharmacy directors, and any other pharmacist and/or healthcare professional interested in the treatment of cancer.

Activity Overview

The majority of deadly cancers do not have guideline-recommended screening tests available, many cancers are detected too late, after they have progressed to late stages when chances of survival are much lower, contributing to overall cancer deaths continuing to escalate worldwide. A broad set of these cancer types have been shown to be detectable simultaneously by new, noninvasive multicancer early detection (MCED) blood tests. These blood-based multicancer screening tools can potentially streamline the screening process to improve adherence and cost-effectiveness for patients. The development of new technologies for early detection of multiple types of cancer will have important clinical implications for managed care professionals involved in the identification, management, and treatment of patients with cancer. This article will review recent and ongoing advancements and present the newest clinical data surrounding multicancer detection for managed care professionals to become familiar with and potentially incorporate these preventive screening tools into treatment paradigms for patients.

Statement of Need

In the United States, cancer is the leading cause of death among those younger than 80 years of age. Due to improvements in cancer prevention, screening, treatment, and survivorship care, the mortality rates with cancer had decreased significantly in the United States between 1991

and 2015. Earlier cancer detection has been associated with improved prognosis, treatment success, and survival rates. However, just 4 routine cancer screening tests are available (breast, cervical, colorectal, and lung) and their screening rates are below national goals resulting in a large gap for cancer detection. There have been recently published data on blood-based multicancer early detection tests that can identify multiple cancers, many for which no screening currently exists, in a single blood test. Reliably detecting cancer at earlier stages has the potential to decrease mortality and reduce overall healthcare costs by initiating treatment early. It is essential that managed care professionals are informed on recent and ongoing advances and literature with multicancer detection tests in order to make recommendations for utilization.

Educational Objectives

At the completion of this activity, the participant will be able to:

- Examine the clinical and economic burden associated with cancer, as well as the need to engage in multicancer early detection to improve overall prognosis.
- Investigate recent clinical updates for emerging and novel multicancer early detection technologies from recent conferences and publications.
- Analyze the impact of new data on managed care considerations for enhancing cancer screening and care for patients with cancer.

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OVERVIEW

Through this article in *The American Journal of Managed Care*[®], managed care professionals will increase their knowledge regarding the development of multicancer early detection tests.

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GRANTS/RESEARCH SUPPORT

Paid to institution: Alliance Foundation Trials, Astellas Pharma, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Concept Therapeutics, Endocyte Inc./Advanced Accelerator Applications (AAA), Freenome, Grail Inc., Harpoon Therapeutics, Janssen Research & Development, Medivation Inc., Sotio, Theraclone Sciences/OncoResponse, Zenith Epigenetics.

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Examining Developments in Multicancer Early Detection: Highlights of New Clinical Data from Recent Conferences

Tomasz M. Beer, MD, FACP

Introduction

Nearly 2 million new cancers were expected to be diagnosed in the United States in 2021, with an estimated 608,570 cancer-related deaths. Despite significant advances in detection and treatment, cancer remains the second leading cause of death in the United States after cardiovascular disease (with the exception of temporal changes due to COVID-19).^{1,2} Delays in early diagnosis and treatment during the COVID-19 pandemic may further increase the burden of cancer in the coming years.¹ Direct US medical costs for cancer in 2020 were an estimated \$200.7 billion (in 2019 dollars), an increase of 10% since 2015.³ Given the aging population, costs are expected to reach \$246 billion by 2030.¹

Between 1991 and 2018, the age-adjusted cancer mortality rate in the United States declined 31%, due, in part, to declines in smoking, improvements in early detection, and advancements in treatment for some cancers. That translates to about 3.2 million fewer cancer deaths.¹ Those trends are largely driven by improvements in lung, colorectal, breast, and prostate cancer deaths. Many others (eg, pancreatic, ovarian, and liver) are primarily diagnosed in the later stages; thus, there are still disappointing 5-year survival rates. The 5-year relative survival rate (defined as the ratio of observed survival in a population to the expected or background survival rate) for pancreatic cancer, for instance, is just 10%.¹

Earlier diagnosis has the potential to reduce cancer-related deaths. One study estimated 15% fewer cancer-related deaths if those with stage IV cancers had been diagnosed at stage III.⁴ Other research predicts that early cancer detection could increase 5-year survival rates to 90%.⁵ In lung cancer, which was the leading cause of cancer death in the United States, patients diagnosed in the earliest stages have a 59% 5-year relative survival rate, while those diagnosed in stage IV have a 6% survival rate.¹ However, a study that implemented population-based ovarian cancer screening found earlier diagnosis did not reduce cancer-related deaths.⁶ This result is a reminder that shifts in stage at diagnosis may not always correlate with mortality reductions. Studies that measure both are important in establishing the efficacy of early detection efforts.

ABSTRACT

Cancer remains the second leading cause of death in the United States despite decades of treatment advances. While death rates have fallen for breast, cervical, and colorectal cancers, death rates remain high for the majority of malignancies, primarily given the late stage at which they are diagnosed. The US Preventive Services Task Force currently recommends routine screening for just 4 cancers: breast, cervical, colorectal, and lung (for high-risk individuals); for prostate cancer, recommendations support individual decision making. However, cancers without recommended screening tests account for 71% of cancer deaths in the United States. In addition, screening rates remain below national goals, with numerous barriers to population-based screening. Recently, initial results of studies on blood-based multicancer early detection tests, which rely on measurement of a range of analytes, demonstrate the potential to identify multiple cancers in a single blood test and detect many cancers for which no screening tests are currently recommended. Blood-based tests have the potential to be more accessible and easier to disseminate than organ-specific tests. However, it remains unclear if their use can reduce deaths from these cancers. Other issues include cost-effectiveness, the impact of false-positive and false-negative results on patients and costs, and uptake among individuals and clinicians. Research and development of blood-based multicancer early detection tests continue.

Am J Manag Care. 2021;27:S347-S355

For author information and disclosures, see end of text.

Cancer Detection: Current Screening

The US Preventive Services Task Force (USPSTF) recommends population-based screening for breast, colorectal, and cervical cancers.⁷ For prostate cancer, the Task Force recommends an individual decision based on a discussion of potential harms and benefits.^{8,9} The Task Force also recommends screening certain smokers for lung cancer.⁷ **Table 1**⁷⁻¹³ contains a summary of cancer screening tests and recommendations from the USPSTF. Early detection as well as advances in treatment are likely behind the declining mortality rates for these cancers. However, cancers without recommended screening tests account for 71% of cancer deaths in the United States.¹⁰

The Task Force's decisions on screening recommendations are based on 4 factors¹⁴:

1. Evidence related to benefits and harms from randomized clinical trials and observational studies.
2. Whether benefits outweigh harms and, if so, by how much and in which populations.

3. The degree of certainty the evidence provides for both benefits and harms.
4. Ages and other risk factors needed to specify when to begin and when to stop offering the service and in which populations.

As new data become available, the USPSTF continues to update its guidance. In 2021, it changed the 2013 screening recommendation for lung cancer by expanding the eligibility pool for low-dose computed tomography (LDCT) scans from adults aged 55 to 80 years with a 30 pack-year smoking history to those aged 50 to 80 years with a 20 pack-year history.¹² The same year, it also revised the 2016 colorectal screening recommendations from adults aged 50 years or older at average risk of colorectal cancer to those aged 45 years in light of increasing rates of the cancer being diagnosed in younger people.¹¹ Federal goals for 2030 are highlighted in **Table 2**.¹⁵

Despite well-publicized guidelines, screening uptake in the United States remains below goals (**Table 2**). Numerous barriers, including financial, a lack of awareness about screening as well as provider recommendations, psychosocial and logistical barriers, a lack of trust in the healthcare system, and access, contribute to this result.¹⁶⁻¹⁹ Screening for cervical and breast cancer declined between 2011 and 2019 in insured populations; additionally, for cervical and colorectal cancers, screening declined in uninsured populations.²⁰ A recent analysis of the Surveillance, Epidemiology, and End Results (SEER) Program database presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2021 virtual meeting found an increased incidence in cervical cancer among women younger than 50 years and a significant decrease in the 5-year survival rate, though the authors did not correlate it with the lower screening rate.²¹

Results of a study based on the 2018 Behavioral Risk Factor Surveillance System data found significant differences in meeting guidelines among women based on age, race, and ethnicity, as well as socioeconomic and insurance status. For example, women without health insurance had a 26% to 39% lower prevalence of breast cancer screening compared with those with insurance. Overall, women with annual household incomes less than \$50,000, education below the college level, those who live in rural counties, those without

TABLE 1. Cancer Screening Tests and Recommendations from the USPSTF⁷⁻¹³

Screening test	Indication	USPSTF recommendation
Sigmoidoscopy	Detect abnormal growth in the colon	Every 5 years from age 45-75 ^{7,11}
Colonoscopy	Detect abnormal growth in the colon	Every 10 years from age 45-75 ^{7,11}
Mammography	Breast cancer	Biennial screening for women aged 50-74 years and individual decision making for women aged 40-49 years ⁷
Human papillomavirus	Cervical cancer	Every 3 years with cervical cytology alone in women aged 21-29 years; every 3 years with cervical cytology alone, every 5 years with hrHPV testing alone, or every 5 years with hrHPV testing in combination with cytology (co-testing) in women aged 30-65 years ⁷
Papanicolaou test (Pap smear)	Cervical cancer	
Low-dose CT scan	Lung cancer	In adults aged 50-80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years ^{7,12}
PSA	Prostate cancer	For men aged 55-69 years, the decision to undergo periodic PSA-based screening for prostate cancer should be an individual one and should include discussion of the potential benefits and harms of screening with their clinician ^{8,9}
BRCA1/BRCA2 gene mutations	Breast, ovarian, pancreatic cancers	For women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer ⁷
CA-125 blood test	Ovarian cancer	Not recommended ¹³

CT, computed tomography; hrHPV, high-risk human papillomavirus; PSA, prostate-specific antigen; USPSTF, US Preventive Services Task Force.

insurance, or those who could not pay for healthcare were less likely to be screened.²⁰

A recent retrospective claims analysis of a large commercial and Medicare Advantage database from 2008 to February 2020 presented at Academy of Managed Care Pharmacists (AMCP) Nexus 2021 found cancer screening rates of 1.2%, 11.7%, 20.8%, 51.4%, and 64.4% for lung, prostate, colorectal, cervical, and breast cancers, respectively, based on guidelines during that period.²²

The COVID-19 pandemic exacerbated screening barriers. Early in the pandemic, medical centers closed to elective procedures, including screenings; individuals were loath to go to those still open (and even after they reopened) given fears of infection; nearly 2.7 million people lost employer-provided health insurance between April 23, 2020, and December 21, 2020, and thus coverage for screenings.^{1,23} In addition, several medical societies recommended postponing screening.²⁴ One large tertiary center saw 20.6% of its mammogram appointments cancelled in March 2020, before decreasing to 7% in August of that year.²⁴

A retrospective cohort screening of about 60 million Medicare Advantage and commercially insured individuals found a sharp decline in screening for breast, colorectal, and prostate cancers (90.8%, 79.3%, and 63.4%, respectively) between March 2020 and May 2020 compared with the same time in 2018 and 2019. Based on these declines, the authors estimated an absolute deficit in screening in the United States of 9.4 million people in 2020 (3.9 million, breast; 3.8 million, colorectal; and 1.6 million, prostate).²⁵ This, in turn, led to delayed cancer diagnoses, which may impact survival.^{26,27}

Another drawback to currently available screening tests is false-positive results, which can lead to anxiety as well as unnecessary medical tests. A study presented at the ISPOR 2021 virtual meeting found that cancer screening elicits significant anxiety in patients, particularly those with a high risk of cancer, with anxiety, worry, and distress highest while waiting for the results.²⁸ False-positive rate estimates can vary depending on what is defined as a positive result. There is evidence of false-positive rates for LDCT screening as high as 26.6%; overdiagnosis of indolent cancers is also cited as a concern.²⁹⁻³¹ In one study, the authors estimated that 49.1% of women undergoing annual mammography will have a false-positive result over 10 years, with 18.6% of those undergoing a biopsy.³² Other studies using extrapolated data estimated rates between 29% and 77% after 10 screening mammograms.³³ In addition, researchers have found that 23% of those undergoing annual fecal occult blood testing over 10 years will have a false-positive result.³⁴

Cancer screening tests also result in higher costs. One study of 1087 individuals enrolled in a large screening program with traditional screening methods for prostate, lung, colorectal, and ovarian cancer found that 43% had at least 1 false-positive result, 83% of which required follow-up care. This incurred significantly higher medical costs in the year after screening than those without

TABLE 2. Healthy People 2030 Cancer Screening Goals^{15,a}

Cancer	Most recent participation (%)	Target (%)
Breast cancer	72.8 (2018)	77.1
Colorectal cancer	65.2 (2018)	74.4
Cervical cancer	80.5 (2018)	84.3
Lung cancer	2.5 (2015)	7.5

^a Based on current guidelines.

false-positive results: \$1024 for women and \$1175 for men (in 2004 dollars).³⁵

New Paradigm of Multicancer Detection

In recent years, several companies have started developing screening blood tests to identify numerous cancers at an early stage. Called “pan-cancer tests” or multicancer early detection (MCED) tests, they represent a novel approach to screening with the potential to identify cancers at earlier stages.³⁶⁻³⁸ These tests typically combine artificial intelligence (AI) and machine learning with assays to detect a variety of circulating analytes, often including cell-free DNA (cfDNA) for early indications of cancer (Figure 1³⁹).^{37,39}

Blood-based MCED tests, which rely on measurement of a range of analytes, are being studied. These tests have several attributes that complement currently available screening tests, such as the potential to identify multiple cancers in a single blood test and detect many of the cancers for which no screening tests are currently recommended. They may also prove more accessible and easier to disseminate than more complicated, organ-specific tests. The next several paragraphs will examine the tests under investigation and available on the market.

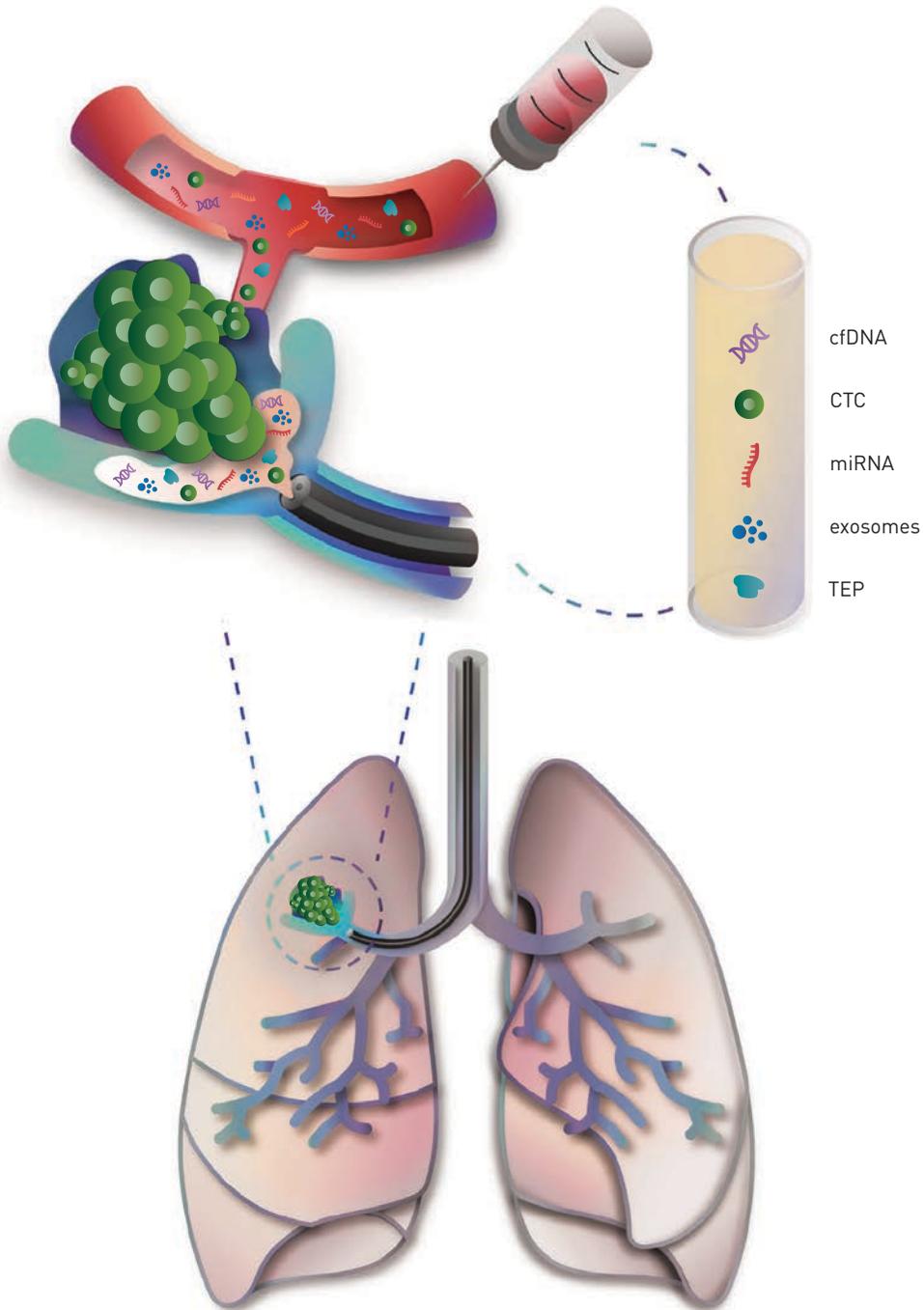
Galleri

Galleri examines cfDNA methylation patterns across a very large number of methylation sites and uses AI analysis to recognize patterns associated with the presence of cancer as well as the likely organ of origin of the suspected malignancy. It has been shown to detect more than 50 neoplasms.⁴⁰ It is currently marketed in the United States under a Clinical Laboratory Improvement Amendments (CLIA) waiver, and the manufacturer plans to submit data to the US Food & Drug Administration in 2023.¹⁰ It is intended for use in those older than 50 years with and without additional risk factors for cancer in conjunction with currently recommended screenings.^{10,41}

The Circulating Cell-free Genome Atlas (CCGA) Study

Galleri has been assessed in several studies. The Circulating Cell-free Genome Atlas (CCGA) is a prospective, multicenter, case-control, observational study conducted with specimens from 15,254 participants, 56% of whom had suspected cancer. It was divided

FIGURE 1. Components of Liquid Biopsy³⁹



CTC, circulating tumor cells; cfDNA, circulating cell-free DNA; TEP, tumor-educated platelets.

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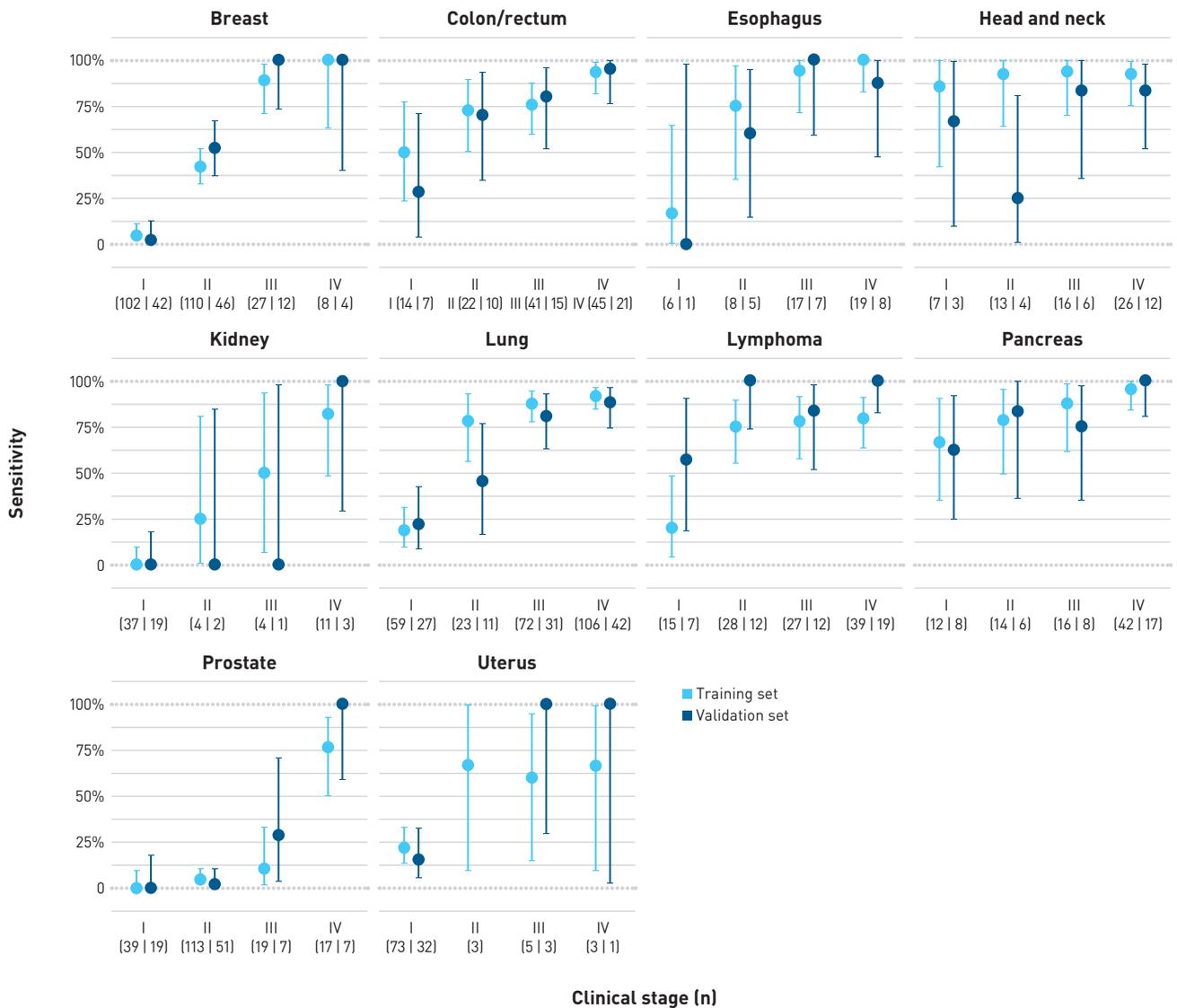
into 3 sub-studies: discovery, analysis (training/validation), and further validation.⁴⁰

In an early sub-study, 303 participants with suspected cancer were classified as either confirmed cancer (n = 239) or no cancer (n = 64) and evaluated for more than 20 cancer types in training and validation groups. The assay correctly predicted no cancer in the confirmed noncancer group (100% specificity). There was a 46.7% cancer detection accuracy in the confirmed cancer validation test (35/75; 95% CI, 35.1%-58.6%). The test detected 78.9% of cancers in

stage II during the validation stage, with tumor of origin predicted in all validation samples (35/35) with a 97.1% accuracy.⁴²

Results from a larger sub-study conducted in 6689 participants (2482 with cancer) found a 99.3% specificity overall in the validation cohort for more than 50 cancers. Sensitivity for stages I-III in a prespecified set of 12 cancers that account for 63% of all cancer deaths in the United States was 67.3% (CI, 60.7%-73.3%) and 43.9% (CI, 39.4%-48.5%) for all cancer types for early-stage detection. **Figure 2**⁴⁰ depicts the sensitivity in individual tumors by stage,

FIGURE 2. Sensitivity in Individual Tumors by Stage⁴⁰



Clinical stage is indicated below the plots as is the number of samples in training and validation (separated by a vertical line).
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with a sensitivity at 99.8% specificity (training) or 99.3% specificity (validation) with 95% CI for cancers with at least 50 samples.⁴⁰

A subanalysis of the potential prognostic significance of cancer detection in that study found that of those who died during a 3-year follow-up, 89% had cancer detected by the MCED test compared with 44% of those still alive at 3 years, with greater detection sensitivity among those who died. Cancers not detected by the MCED test showed better survival than expected from SEER data, while those detected by MCED test showed similar or slightly better survival. Investigators concluded that detection with the MCED test was prognostic beyond clinical stage alone ($P < .001$) and preferentially detected more aggressive cancers.³⁷ Participants in CCGA continue to be followed.

PATHFINDER Study

The PATHFINDER prospective study in 6629 adults 50 years and older evaluated the Galleri test's role in clinical practice. Participants and their physicians received the results of the MCED test and used those results to carry out a clinical evaluation for cancer. The clinical evaluation was not prespecified and was directed by a physician until the clinical assessment determined that diagnostic resolution had been reached. Participants and their healthcare providers received positive test results for further assessment. Interim results showed a cancer signal in 92 participants (1.4%) with a diagnostic resolution in 65 to date. Twenty-nine of those had a true-positive and 36 had a false-positive after imaging and procedures, resulting in a positive predictive value of 45%. The cancer signal origin prediction was 100% in those with first/second cancer signal origin in participants with elevated cancer risk (CI, 83.2-100) and 87.5% in those without additional cancer risk (CI, 52.9-99.4). It took about 50 days to diagnostic resolution from the time the test results were returned. The majority of cancers detected were diagnosed at stages I-III. The study is continuing.³⁶ Additional follow-up will enable more complete assessment of test performance.

TABLE 3. DETECT-A Test Performance⁴⁵

	Blood test without confirmation	Blood test with confirmation
Positive predictive value	5.9% [4.0-8.4]	19.4% [13.1-27.1]
Specificity	95.3% [94.9-95.7]	98.9% [98.7-99.1]
Negative predictive value	99.3% [99.1-99.4]	99.3% [99.1-99.4]
Number needed to screen to detect 1 cancer	342 [238-510]	381 [260-583]
Sensitivity		
All cancers	30.2% [21.3-40.3]	27.1% [18.5-37.1]
Cancers with SOC screening	27.5% [15.9-41.7]	23.5% [12.8-37.5]
Cancers with no SOC screening	33.3% [20.0-49.0]	31.1% [18.2-46.6]

SOC, standard of care.

STRIVE Study

The STRIVE study is an observational study to assess the ability of Galleri to detect invasive cancers in a breast cancer screening cohort of 99,308 women. Participants provide a blood sample and complete a health questionnaire at the time of screening mammogram and will be followed for up to 5 years to capture clinical information. It is currently closed to enrollment.⁴³

SUMMIT Study

SUMMIT is a United Kingdom-based study of about 25,000 participants at high risk of lung cancer and other smoking-related cancers. Participants provide a blood sample when they have an LDCT scan. The primary outcome is to evaluate the performance of the test and examine the feasibility of delivering an LDCT screening service.⁴⁴

CancerSeek

The CancerSeek test is designed to detect the presence of prespecified DNA mutation and protein markers associated with cancer. In its initial iteration, CancerSeek is designed as a 2-step test with an initial positive result triggering an additional analysis to exclude the possibility that findings reflect the presence of clonal hematopoiesis.

DETECT-A Study

The utility of this liquid biopsy test to identify cancer signals in a healthy population was evaluated in the prospective, interventional DETECT-A study. The clinical evaluation in DETECT-A was prespecified by the study design to be a positron emission tomography-computed tomography scan. Researchers screened 9911 women aged 65 to 75 years with no personal history of cancer and a high adherence to recommended screening guidelines. On the first stage of the test, 4.9% of participants scored positive, of which 1.35% (134) were confirmed in a second test component. Of those, 95% (127) received imaging. In half, the results were suspicious for cancer and, of those 64 patients, 41% (26) were subsequently diagnosed with cancer (**Table 3**).⁴⁵ In addition, standard screening identified 24 cancers not found with the blood test: 20 breast cancers, 3 lung cancers, and 1 colorectal cancer. Of the 24 cancers, 22 were early-stage cancers. Forty-six additional cancers were diagnosed clinically with neither the CancerSeek test nor standard screening tests during the course of the study.⁴⁵

DELFI

The DELFI test is based on fragmentomes, disordered DNA packaging in cancer cells, and uses machine learning algorithms to assess patterns. It was evaluated in the LUCAS trial,

which enrolled 365 individuals at high risk for lung cancer and with smoking-related symptoms. In this pilot study, the DELFI approach performed well. The receiver operator curve, which integrates sensitivity and specificity for cancer detection, showed an area under the curve of 0.9.³⁸

An earlier study analyzed fragmentation profiles of 236 patients with breast, colorectal, lung, ovarian, pancreatic, gastric, or bile duct cancer and 245 healthy individuals. It found a sensitivity ranging from 57% to 99% among the 7 cancers with a 98% specificity. The tissue of origin was identified in 75% of cases. Overall, it detected cancer in 91% of the patients with cancer.⁴⁶

Several trials are also underway to use AI and blood-based screening for colorectal cancer.⁴⁷⁻⁴⁹ Early results presented at the 2020 Digestive Disease Week suggest high specificity and sensitivity.⁵⁰

Managed Care Concerns

The economic burden associated with cancer is related to the stage at which the cancer is diagnosed. An analysis of a SEER-Medicare database found the highest costs in the most advanced stage of cancer, or the end-of-life stage, ranging from \$71,000 for prostate cancer to \$239,000 for acute myeloid leukemia. Costs were \$41.8 billion for all cancer sites treated in the early stage and \$105.5 billion for patients in the end-of-life stage.⁵¹

A more recent study presented at AMCP Nexus 2021 among 35,817 patients with cancer between 2016 and 2020 found absolute mean cost in stage I ovarian cancer of \$36,000 but that cost increased to \$169,999 by stage IV, a more than 4-fold difference. Costs for colorectal cancer were nearly doubled, from \$82,000 to \$157,999.⁵² Thus, earlier diagnosis could have economic as well as lifesaving benefits provided that it is not associated with a high burden of overdiagnosis and overtreatment.^{53,54}

However, the costs of testing would also have to be considered. MCED tests are largely still investigational with just one, Galleri, currently marketed in the United States at a cost of \$949 per test.⁵⁵ Up to 100 million Americans could be eligible for this test, which is being developed for use in individuals 50 years and older. The cost, if 50% of potentially eligible Americans were tested, would approach \$50 billion, with additional costs for the testing and treatment that would follow in those with identifiable cancers. The frequency with which such testing might be repeated has not been defined yet, so it is not possible to estimate annual costs. Economic analyses of these tests are just beginning to emerge.

A Markov model comparing annual MCED test plus standard of care (SOC) screening in US adults aged 50 to 79 years predicted that 10.7% of cancers would be detected at stage IV by adding an MCED test compared with 20.4% with SOC screening. That led to 0.17 more quality-adjusted life-years (QALYs) and reduced cancer-related treatment and diagnosis costs by \$5208. At a willingness-to-pay (WTP) threshold of \$50,000/QALY, the value-based price would be

\$923 per test; at a WTP threshold of \$100,000/QALY, the value-based price would be \$2069 per test.⁵⁶ These estimates represent a set of assumptions that will need to be confirmed as testing becomes more widely available.

One model compared colorectal screening methods (capsule endoscopy every 5 or 10 years; computed tomography colonography [CTC] every 5 years; multitarget stool DNA every 1 or 3 years; or the methylated *mSEPT9* DNA plasma assay every 1 or 2 years against annual fecal immunochemical testing [FIT] screening or colonoscopy every 10 years). At a WTP threshold of \$100,000 and the assumption of perfect adherence, the authors found that an annual *mSEPT9* test resulted in more QALYs gained and colorectal cases and deaths avoided than annual FIT screening, but high rates of colonoscopy referral (51% after 3 years; 69% after 5 years). In addition, a CTC every 5 years and annual screening with the *mSEPT9* every year were efficient strategies, with incremental cost-effectiveness ratios (ICERs) of \$1092 and \$63,253, respectively.⁵⁷

A recent health economic model comparing the clinical outcomes of adding an MCED test to current cancer screening versus current screening alone over a lifetime in people aged 50 to 79 years found those receiving an MCED test could have an incremental gain of 0.35 life-years and 0.34 QALYs per person, primarily due to earlier detection of cancers and improved mortality. At WTP thresholds of \$100,000 to \$150,000/QALY, that translated to a cost benefit of \$34,400 to \$51,600 per person.⁵⁸

A study estimating the impact of adding MCED screening for breast, cervical, colorectal, and lung cancers to current screening modalities estimated it would detect an additional 105,526 of these and other cancers with a 25% uptake and 422,105 with a 100% uptake. The estimated true-positive/false-positive (TP/FP) ratio, which demonstrates how many patients without cancer should undergo diagnostic evaluation to detect 1 person with cancer, was 1:43 (\$89,042 per cancer detected) with the 4 SOC tests and 1:1.8 with MCED (\$7060 per cancer detected). Combining the two yielded a TP/FP ratio of 1:14 in the United States, with diagnostic costs per cancer of \$32,461.⁵⁹

The authors noted that while reported sensitivities for MCED tests tended to be lower than currently used screening tests, they cover multiple cancers and have a relatively low false-positive rate, thus their impact in screening is expected to be greater. They also noted that a single test could overcome the high rates of nonadherence seen in the United States.⁵⁹ Naturally, all of these economic analyses are preliminary and built on a set of assumptions that will need to be further confirmed within clinical trials and real-world evidence-gathering efforts.

Given that just 1 MCED test has been marketed for 5 months at the time of this writing, uptake is unclear. However, an online discrete choice experiment answered by 303 individuals found that fewer false-negative and more true-positive rates were the most

important considerations for an MCEd screening test. In addition, 71.9% reported a preference for the MCEd test with currently recommended screenings.⁶⁰ Another consideration is that the lower false-positive rates of MCEd tests could reduce patient anxiety as well as costs.^{35,61}

Conclusions

Early diagnosis has the potential to improve cancer survival. Yet the majority of cancers are diagnosed in the late stages given a lack of effective population-based screening tests. Cancers without recommended screening tests account for 71% of cancer deaths in the United States.⁸ Current recommended screening tests reduce cancer mortality. However, they experience significant false-positive rates, invoke anxiety in patients, and have relatively less than optimal adherence rates. But, recently, several MCEd tests have demonstrated the ability to detect cancers in healthy people and those with the disease. Preliminary estimates suggest promising false-positive rates and economic analyses suggest that such tests may prove to be cost-effective.³⁶⁻³⁸ Further evidence that will inform understanding of test performance is expected. Currently, just 1 MCEd test is on the market under a CLIA exception, and none have been approved by the FDA for marketing. The USPSTF has not made any recommendation on their use for population screening. As with any screening tests, the MCEd tests must be carefully validated in prospective, population-based, long-term studies to determine not only their accuracy at detecting cancer but also their clinical utility to improve cancer outcomes. The economic costs of such tests, including direct testing costs as well as diagnostic evaluation for false-positive results, must be considered as should the emotional costs for patients who receive false-positive results. Widespread implementation will require additional evidence as well as extensive education of both providers and the public. Further economic analyses will inform payers' reimbursement decisions. □

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Funding source: This activity is supported by an educational grant from GRAIL, Inc.

Author disclosure: Dr Beer has the following relevant financial relationships with commercial interests to disclose:

CONSULTANT: Arvinas, Astellas Pharma, AstraZeneca, Bayer HealthCare Pharmaceuticals, Constellation, Grail Inc., Janssen, Myovant Sciences, Pfizer, Sanofi.

GRANTS/RESEARCH SUPPORT: Paid to institution; Alliance Foundation Trials, Astellas Pharma, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Corcept Therapeutics, Endocyte Inc./Advanced Accelerator Applications (AAA), Freenome, Grail Inc., Harpoon Therapeutics, Janssen Research & Development, Medivation Inc., Sotio, Theraclone Sciences/OncoResponse, Zenith Epigenetics.

STOCK/SHEARHOLDER: Arvinas, Salarius Pharmaceuticals.

Author information: Substantial contributions to analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and supervision.

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Medical writing and editorial support provided by: Debra Gordon, MS

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Release date: December 10, 2021

Expiration date: December 10, 2022

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Sample of Online Posttest

Choose the best answer for each of the following:

- By 2030, direct costs for cancer in the United States are expected to reach:**
 - \$186 billion
 - \$210 billion
 - \$246 billion
 - \$304 billion
- Diagnosing stage IV cancers just 1 stage earlier could lead to how many fewer cancer-related deaths in the United States?**
 - 5%
 - 15%
 - 20%
 - 23%
- JK is a 45-year-old man with a 20 pack-year smoking history. Which of the following screenings would be recommended for JK under current guidelines?**
 - He should undergo low-dose computed tomography screening.
 - He should have a chest x-ray.
 - He should have a liquid biopsy.
 - Current guidelines do not recommend any screening at his age.
- How many pan-cancer tests has the FDA approved?**
 - None
 - 1
 - 2
 - 3
- In the early Circulating Cell-free Genome Atlas (CCGA) sub-study with 303 participants, what was the specificity in the noncancer participants?**
 - 80%
 - 87%
 - 99.3%
 - 100%
- In the larger CCGA subanalysis of 6689 participants with or without cancer, what was the overall specificity rate for more than 50 cancers?**
 - 80%
 - 87%
 - 99.3%
 - 100%
- What was the goal of the PATHFINDER study?**
 - To evaluate the test's role in clinical practice.
 - To provide prognostic data on cancer deaths based on test results.
 - To validate the safety of the test.
 - To determine the false-positive rate.
- Which study is testing women when they go in for their screening mammogram?**
 - SUMMIT
 - STRIVE
 - DETECT-A
 - DELFI
- The highest costs for cancer occur in which stage?**
 - I
 - II
 - III
 - IV
- Which colorectal screening method was found to be the most cost-effective at a willingness-to-pay threshold of \$100,000 and assuming perfect adherence?**
 - Galleri
 - Colonoscopy
 - FIT
 - mSEPT9

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