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Assessing Advancements in Early Cancer Detection: A Managed Care Review of New Diagnostics to Improve Outcomes

HIGHLIGHTS

Supplement to *The American Journal of Managed Care®*

Assessing Advancements in Early Cancer Detection: A Managed Care Review of New Diagnostics to Improve Outcomes

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Intended Audience

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

Activity Overview

Despite earlier detection and improved treatment, overall cancer deaths continue to escalate worldwide, and cancer remains the leading cause of death in the United States among those younger than 80 years. Considerable economic burden is associated with late-stage cancer as treatment costs can be up to twice those for early-stage disease. Only several cancers have guideline-recommended screening procedures; thus, many cancers are detected after symptoms appear and progress to late stages when treatment is more complex, and overall survival is reduced. Patient outcomes and overall economic and treatment burden may be significantly improved by earlier detection and diagnosis of cancer before it progresses. An array of technological advances in next-generation sequencing holds promise for future effective, early detection cancer screening tests for multiple cancer types. This activity will provide managed care professionals with an overview of trial data related to screening tests under development with a discussion of the potential impact if such technologies are incorporated into screening.

Statement of Educational Need

Cancer claims the lives of millions of individuals each year, with the number of cases continuing to rise, and imparts a significant personal and economic burden on patients, caregivers, and families. No accepted screening methods are currently available for most cancers, and some of the widely used screening methods that are available lack specificity and the ability to distinguish clinically insignificant cancers; this sometimes leads to false-positive results, overdiagnosis, and overtreatment. Better screening methods for early cancer detection have the potential to not only improve patient outcomes but lessen the economic burden on individuals and society. Several blood-based multicancer assays are in development and may address some of the limitations of current cancer screening methods. The accuracy, cost, and clinical implications of the tests in a real-world setting are crucial to assessing how valuable they will be in clinical practice. By using minimally invasive blood-based tests that identify multiple cancer types, healthcare providers have the opportunity to increase awareness and patient utilization of cancer screening. Earlier detection may ease the financial burden associated with a cancer diagnosis; it should also improve patient outcomes because cancer may be diagnosed earlier when there is a greater likelihood of achieving a cure or remission, particularly if new screening tests have high specificity for clinically significant cancers. Pharmacists often encourage the general population to receive recommended screenings and require continuing professional education to increase familiarity with the multicancer detection assays and consider clinical implications should these tests be adopted as a standard of practice. Managed care professionals need to understand the current gaps in cancer detection and the emerging early cancer detection technology in development with the potential to fill these gaps.

Educational Objectives

Upon completion of this activity, participants will be able to:

- Examine the health and economic burdens associated with early detection of cancer.
- Classify current recommendations for cancer screening and early detection.
- Analyze the recent and emerging published data associated with the novel multicancer detection blood tests.
- Explore the role of the managed care professional in integrating novel molecular diagnostic technologies for early cancer detection into treatment pathways and guidelines.

Accreditation Statement

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Obtaining Credit: Participants must read the article and complete the online posttest and an online evaluation and request for credit. Detailed instructions on obtaining CE credit are included at the end of this activity.

This CE activity is also offered free online at **www.ajmc.com/ce** and at **www.PharmacyTimes.org/go/early-cancer-detection**, where you will be directed to the activity in its entirety, including the online pretest and posttest, activity evaluation, and request for credit.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care®*, managed care professionals will increase their knowledge of early cancer detection technologies under development.

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Novel Blood-Based Early Cancer Detection: Diagnostics in Development

Tomasz M. Beer, MD, FACP

ABSTRACT

Cancer affects millions of Americans, and the number of cases is steadily rising. The increase in diagnosis of cancer cases comes with an associated increase in personal and economic burden. Earlier detection can improve treatment outcomes and may reduce the burden of cancer. Screening for cervical cancer is a good example of the potential of effective screening methods to dramatically reduce the morbidity and mortality associated with cancer. However, many current screening methods have high false-positive rates, increasing the concern for overdiagnosis and overtreatment. Blood-based tests capable of detecting multiple types of cancer represent an emerging approach to early cancer detection. Although there are several single-cancer detection tests in development, multicancer screening tests have greater potential to allow for widespread screening in the general population. Three multicancer screening tests are being validated in ongoing clinical trials, including the CancerSEEK assay, the Galleri test, and the PanSeer assay, all of which show high specificity in preliminary findings. Further validation is required before multicancer detection tests are incorporated into general population cancer screening.

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For author information and disclosures, see end of text.

Introduction

Cancer is the primary cause of death in those younger than 80 years and is the second leading cause of death in the United States.[1,2] Nearly 1700 people are expected to die from cancer each day in the United States in 2020.[3] The American Cancer Society (ACS) estimates the number of new cancer cases and cancer deaths in the United States each year, and the 2020 projections include just over 1.8 million new cancer cases and just over 600,000 cancer deaths.[1] The Centers for Disease Control and Prevention (CDC) provided similar estimations for new cancer cases and cancer deaths.[4] The efforts to increase awareness of cancer, including prevention and screening, contributed to the decrease in the cancer mortality rate in the United States over the past 20 years.[1,5] Notably, survival decreases significantly when cancer is detected at later stages. Even accounting for lead time bias (which occurs when patients live longer due to earlier detection) and length bias (which occurs when early detection tests preferentially detect slower growing cancers, creating a false impression of longer survival) inherent to earlier detection of disease, there remains a significant opportunity to reduce the burden of cancer with effective early detection. The true benefit of early detection is only realized if effective early treatment produces better results for patients and must not be confused with these biases. There are currently no general population screening recommendations for many types of cancer, which reinforces the need to develop reliable methods for early detection for all types of cancer.[5]

Cancer Burden

According to the National Cancer Institute, the most common cancer in the United States is cancer of the breast, followed by lung.[6] **Table 1** depicts a list of the top 10 cancers in the United States along with an estimate of new cases and deaths for these cancers in 2020.[6]

The number of cancer cases is expected to increase in 2020, with the distribution of increases across specific cancers varied between men and women. According to the CDC, melanoma is expected to increase in White men and women.[4] It is also estimated that males will experience an increase in prostate, kidney, liver, and bladder cancers, whereas an increase in lung, breast, uterine, and thyroid

cancers is expected in females.[4] Of the cancer cases expected to rise, only lung and breast have current screening recommendations for the general population.[7] Although some screening methods are available for several other types of cancers, including ovarian, prostate, testicular, pancreatic, and thyroid, screening is not recommended in the general population unless there is presence of specific risk factors.[7,8] The cancer mortality rate has steadily dropped since the 1990s, which is mostly attributed to a decline in death from lung, prostate, breast, and colorectal cancers; mortality rates per 100,000 people are expected to continue to decrease in these cancers in 2020, as well as with cancer of the oral cavity, pharynx, and cervix.[4] Prevention strategies, such as human papillomavirus (HPV) vaccination, earlier detection of some cancers, declining tobacco use, and improvements in treatment of both early-stage and advanced cancers, may be contributing factors to the decline in cancer-related mortality.

Cancer detection at later stages may be associated with a reduction in survival. For example, when renal carcinoma is detected while still localized in the kidney, the 5-year survival is 93%, but that survival estimate decreases to 12% when the cancer has metastasized.[9] Similarly, the 5-year survival of female breast cancer drops from 99% when detected locally, to 27% when the cancer has metastasized.[9] In fact, most types of cancer have a 5-year survival rate of less than 30% when detected after the cancer metastasized.[9] The potential for improvements in early detection of cancer to alter mortality was examined in a retrospective analysis using data from the Surveillance, Epidemiology, and End Results (SEER) program.[10] The population included men and women aged 50 to 79 years diagnosed with 17 different cancer types at various stages. Of the cancers diagnosed at the advanced or metastatic stage, lung, colorectal, non-Hodgkin lymphoma, pancreatic, and oral cavity cancers were most common. Lung and colorectal cancers specifically were the largest contributors to absolute cancer-related deaths when diagnosed at stage IV; however, overall cancer burden was increased by any cancer diagnosed at stage IV. Based on a hypothetical cohort, the researchers estimated that if all cancers diagnosed at stage IV were discovered at stage III over a 5-year time period, there would be 51 fewer cancer-related deaths per 100,000 people. When detecting cancer at any stage prior to stage IV, there would be an estimated 15% reduction in all cancer-related deaths within 5 years. Although this was a retrospective analysis, there appears to be a clear opportunity for reduction in the burden of cancer with earlier detection; with more research, earlier detection may also lead to reductions in cancer-related deaths.[10]

Economic Impact of Cancer

In addition to the mortality risk associated with a diagnosis of cancer, there are significant economic implications. Economic burden is evaluated by assessing both direct (eg, hospitalization, office visits, emergency department visits, treatment) and indirect costs (eg, time lost) associated with a diagnosis of cancer.[11] The total direct cost of cancer care in the United States in 2015 was estimated to be $80.2 billion.[3] Of that, over half (52%) of the costs were for outpatient or doctor office visits, while 38% were for inpatient hospital stays.[3] Direct costs vary widely depending on the type of cancer that is diagnosed. For example, breast cancer in the United States was associated with a total annual cost of $16.5 billion, and prostate cancer had a total annual cost of $11.9 billion in 2010; these annual costs for breast cancer and prostate cancer are projected to increase 32% (≈$22 billion) and 42% (≈$17 billion), respectively by 2020.[11] Treatment costs, especially newer, more expensive targeted therapies, may increase direct costs associated with cancer.[6,11]

In addition to a portion of the direct costs, patients and caregivers may be responsible for indirect costs, which may include the following:

- Time required for receiving medical care
- Morbidity (time lost from work or other activities)
- Lost productivity (missed days of work and/or early mortality)

Indirect costs are not always associated with direct payment (eg, fee-for-service); costs are estimated based on various models that assign a monetary value to time spent or time lost due to cancer.[11,12] A study analyzing cancer deaths, median incomes, and life expectancy in 2015 demonstrated the enormous impact cancer has on the US economy.[12] An estimated $94.4 billion (95% CI, $91.7 billion - $97.3 billion) was lost in overall earnings (productivity) due to cancer, with an average lost earnings per cancer death of $191,900.[12] Lung cancer accounted for the highest amount of lost earnings, totaling $21.3 billion. Colorectal cancer was second highest at $9.4 billion, with breast and pancreatic cancers following at approximately $6 billion each in lost earnings.[12] Considering the majority of the

TABLE 1. Most Common Types of Cancer in the United States[6]

Common types of cancer	Estimated new cases 2020	Estimated deaths 2020
1. Breast cancer (female)	276,480	42,170
2. Lung and bronchus cancer	228,820	135,720
3. Prostate cancer	191,930	33,330
4. Colorectal cancer	147,950	53,200
5. Melanoma of the skin	100,350	6850
6. Bladder cancer	81,400	17,980
7. Non-hodgkin lymphoma	77,240	19,940
8. Kidney and renal pelvis cancer	73,750	14,830
9. Uterine cancer	65,620	12,590
10. Leukemia	60,530	23,100
Cancer of any site	**1,806,590**	**606,520**

working-age population in the United States have employer-based health insurance, it is difficult to fully account for direct and indirect costs associated with cancer.[11] Patients and caregivers may lose health insurance coverage during the treatment of cancer due to limited opportunities for employment. Even with health insurance, high out-of-pocket costs may impact patient decisions to pursue further care and lead to delays in diagnosis and treatment.[11] Although these estimates provide some guidance, it is important to consider that the actual impact of cancer on individuals and society is likely even greater.

Current Cancer Screening Recommendations

In the United States, most cancers lack widely accepted or guideline-recommended screening methods. The National Cancer Comprehensive Network (NCCN) and the US Preventive Services Task Force (USPSTF) recommend routine screening for breast, cervical, colorectal, and lung cancers in specific subsets of the population.[7,13-17] **Table 2**[5,7,13-15,17,18] depicts the most commonly used screening methods for each of these cancers, including the advantages and disadvantages of the associated test.[5,7,13-17] Available cancer screening tests have multiple advantages, but some limitations, such as ability to screen for only 1 cancer organ of origin at a time, limited specificity and/or sensitivity, and, for some tests, complexity and burden of testing.[5] Sensitivity is defined as the test's ability to correctly classify the patient as diseased, or the probability of a patient testing positive when disease is present.[19] Specificity is defined as the test's ability to correctly classify the patient as disease free, or the probability of a patient testing negative when there is no disease present.[19] Screening tests that lack specificity can lead to false-positive results and unnecessary evaluations for confirmatory testing. A lack of sensitivity can lead to incomplete early detection of clinically significant cancers. Lack of ability to distinguish between clinically significant and clinically insignificant cancers can result in overdiagnosis and overtreatment. Breast, cervical, and colorectal cancers have established screening recommendations for the general population regardless of risk factors, whereas lung cancer screening is recommended in patients with specific risk factors, which include smoking.[7,13-17]

Breast Cancer

Mammography is the primary method of breast cancer screening and is recommended by the NCCN guidelines annually for average-risk women starting at age 40 years, or by the USPSTF biennially for average-risk women starting at age 50 years.[7,13] Additionally, the ACS recommendations endorse annual screening starting at age 45 years. Individuals at higher risk have more specific recommendations regarding the age at which screening should begin and how frequently the mammograms should be offered. Screening with mammography has been shown to decrease mortality; however, there is decreased sensitivity in women with dense breasts as well as limited specificity resulting in frequent false-positive results requiring further confirmatory testing.[13]

Cervical Cancer

Cervical cytology, or Papanicolaou (PAP) test, is recommended every 3 years in average-risk women aged 21 to 29 years by the USPSTF.[7] From age 30 to 65 years, average-risk women should either have a PAP test every 3 years or have a PAP test plus high-risk human papillomavirus (hrHPV) every 5 years. Although hrHPV or a PAP test may be used alone from ages 30 to 65 years, co-testing is preferred. Routine screening is not recommended after a hysterectomy or after the age of 65 years if the woman has had 10 years of regular screening with normal results.[7] The 2012 ACS guidelines were endorsed by the NCCN; however, the ACS recently published guideline updates in 2020 recommending screening begin at age 25 years rather than age 21.[17] Unlike the 2012 ACS guidelines where the PAP test was preferred, the 2020 ACS guidelines recommend primary HPV testing every 5 years through age 65.[16,17] If primary HPV testing is unavailable, then co-testing with HPV and cytology every 5 years or a PAP test every 3 years is acceptable. Additionally, HPV vaccination may decrease the efficiency of screening, specifically cytology-based screenings, yet there are currently no modifications of screening recommended if a patient has been vaccinated in the past.[16,17]

Colorectal Cancer

Many options for screening colorectal cancer exist, including colonoscopy, flexible sigmoidoscopy, computed tomography (CT) colonography, and stool-based testing.[14] Stool-based testing includes high-sensitivity guaiac- or immunochemical-based testing as well as multitarget stool DNA and occult blood testing (mt-sDNA).[14] Screening should start at 50 years of age for average-risk men and women, according to the NCCN and at age 45 years according to the ACS. In the fall of 2020, the USPSTF circulated a draft guideline that calls for screening to start at age 45 years rather than the previously recommended age 50 years.[7,14,18] The frequency of screening varies greatly depending on the type of test and patient-specific risk factors. There are many considerations when comparing the various colorectal cancer screening methods (see **Table 2**[5,7,13-15,17,18]). Colonoscopies are arguably the most invasive cancer screening method, yet they are the most common method of screening in the United States, in part because they allow for immediate removal of suspicious lesions. Conversely, stool-based testing is noninvasive and can conveniently be done at home; however, fecal occult blood tests have high false-positive rates and may lead to unnecessary follow-up procedures.[15]

Lung Cancer

Screening for lung cancer is done in patients who have a history of smoking with or without other risk factors for lung cancer, but

is not recommended for an asymptomatic person of average risk.[15] Low-dose CT (LDCT) scans utilized for qualifying patients based on risk factors are typically recommended annually, but may be done more frequently depending on the results of the first scan.[7,15] The USPSTF recommends screening in patients with a history of smoking of 30 pack-years; however, the NCCN screening guidelines include several additional risk factors, including, but not limited to second-hand smoke exposure, radon or occupational exposure, and cancer history.[7,15] LDCT scans are currently the only screening modality recommended and have an advantage of a reduced exposure to radiation compared with standard diagnostic CT. They are more efficacious in detecting adenocarcinoma and squamous cell carcinoma compared with chest x-rays.[15]

Prostate Cancer

The diagnosis of prostate cancer does not always require treatment; thus, early detection of prostate cancer may lead to overdiagnosis, unnecessary treatment, patient anxiety, and avoidable costs.[20] NCCN

TABLE 2. Select Cancer Screening Recommendations[5,7,13-15,17,18]

Cancer type	Method of screening	Age screening begins	Advantages	Disadvantages
Breast	Mammography	USPSTF: 50 years old NCCN: 40 years old	• Widely used • Detects early-stage cancer	• Cost • Radiation exposure • Dense breasts decrease sensitivity
Cervical	Cervical cytology (PAP test)	USPSTF: 21 years old ACS: 25 years old	• Widely used	• Cost • HPV vaccination decreases screening efficiency
	High-risk human papillomavirus (hrHPV)	USPSTF: 30 years old *(typically recommended in combination with PAP test)* ACS: 25 years old	• Detects HPV directly *(2020 ACS update prefers primary HPV testing over cytology testing)*	• Non-specific • HPV vaccination may decrease screening efficiency
Colorectal	Colonoscopy	USPSTF and NCCN: 50 years old; 2020 USPSTF draft guideline proposes change to 45 years old	• Entire colon screened • Combined treatment and screening • High sensitivity	• Cost • Bowel preparation • Invasive • Subjective results
	Fecal occult blood testing		• Reduces cancer mortality • Low cost	• High frequency of testing • Further tests required if positive • High false-positive rate
	Stool-based: high-sensitivity guaiac-based and immunochemical-based testing and multitarget stool DNA and occult blood testing (mt-sDNA)		• Non-invasive • At-home test • More accurate than blood test	• Ideal frequency unclear
	Flexible sigmoidoscopy		• Combined treatment and screening • High sensitivity • Reduces cancer mortality	• Only distal colon
	Computed tomography colonography		• Entire colon screened	• Low sensitivity • Radiation exposure • Further tests required if positive
Lung	Low-dose computed tomography	Dependent on risk factors	• High sensitivity	• Cost • Only test currently recommended • Radiation exposure

ACS, American Cancer Society; HPV, human papillomavirus; NCCN, National Comprehensive Cancer Network; PAP, Papanicolaou; USPSTF, US Preventive Services Task Force.

guidelines have a grade C recommendation for early detection of prostate cancer: with early detection offered only when patients fully understand benefits and the risks of participating, which is similar to the USPSTF recommendations.[20] Prostate-specific antigen (PSA) is one method of detection and is measured in a blood test, while a digital rectal exam (DRE) is a physical exam that may be used in conjunction with the PSA level.[20] Unfortunately, PSA is not a cancer-specific marker and instead is a prostate-specific marker. It may be elevated for a variety of reasons not linked to prostate cancer, such as infection, trauma, or ejaculation. Utilizing PSA testing has led to an increase in detection of early-stage disease and a decrease in detecting metastatic disease at diagnosis.[20] DRE tests are only considered in conjunction with PSA levels due to poor positive predictive value and to avoid unnecessary biopsies.[20] Neither ideal age nor frequency of screening for prostate cancer is established, nor are there clear universally agreed-upon recommendations for screening based on risk factors for prostate cancer.

Emerging Multicancer Detection Technology

Current screening methods assess for one cancer at a time, and many cancers currently do not have a viable option for early detection in the general population. The multicancer screening concept relies on a blood analysis designed to detect hallmarks of multiple cancers and may have the potential to be applied to cancer screening and early detection.[21,22] Compared with a tissue biopsy, blood-based tests, also referred to as liquid biopsies, can examine multiple analytes in the blood, including DNA mutations, DNA methylation (gene silencing markers), and proteins. Circulating cell-free DNA (cfDNA) is used in many blood-based assays because it is DNA released by a cell during apoptosis. The cfDNA can be analyzed for mutations and other alterations specific to cancer and methylation patterns specific to the tissue of origin.[21] Blood-based liquid biopsies can detect multiple cancers with one test, and are minimally invasive—two advantages over standard tissue biopsies.

Tests that address multiple cancers simultaneously have the potential to extend early detection to a broader spectrum of malignancies. The ideal cancer screening test would detect cancer before symptoms develop. The test would have a high sensitivity (low false-negative rate) and high specificity (low false-positive rate), the ability to detect clinically significant cancers and avoid the detection of insignificant cancers, the ability to pinpoint the specific cancer type, be noninvasive and introduce low harm, be easily accessible and cost-effective.[5]

CancerSEEK Test

CancerSEEK is a blood test that detects cfDNA and also identifies several protein biomarkers that are released by tumors.[21] The test aims to detect multiple types of cancer by combining the detection of cfDNA and protein biomarkers. The assay identifies 8 protein biomarkers, which were chosen by researchers based on their ability to distinguish between patients with and without cancer, as shown in previous literature. The assay also identifies cancer via mutations in 1933 genomic positions, and each genomic position has multiple mutation possibilities, such as substitutions, insertions, or deletions. Preliminary performance of the test was evaluated in a trial of approximately 1000 patients with a cancer diagnosis who were compared with approximately 800 patients without cancer (**Table 3**).[23,24] The specificity of the test was over 99% in 8 cancer types: ovarian, liver, stomach, pancreatic, esophageal, colorectal, breast, and lung.[21] Although the false-positive rate was low in the trial, it would be expected to be higher in the real-world setting when the test is applied to a healthy population without known cancer.[21] The performance of such tests with respect to false-positive and false-negative rates is dependent on the test's inherent characteristics as well as the prevalence of cancer in the population evaluated with the test. Findings show that sensitivity ranged from approximately 98% in ovarian and liver cancer and 33% in breast cancer, with a sensitivity of about 70% for the remaining cancers.[21] The tissue of origin was correctly identified in approximately 80% of patients.[21]

The Detecting cancers Earlier Through elective mutation-based blood Collection and Testing (DETECT-A) trial is a prospective, interventional trial that enrolled 10,006 women aged 65 to 75 years with no history of cancer.[23] Positron emission tomography-computed tomography (PET-CT) was used to evaluate a positive test result. Of the 9911 participants evaluated, cancer was detected in 26 participants by the blood test, including cancers without current screening recommendations.[23] Of the 26 women with cancer, 17 had early-stage cancer and 14 were in organs in which there are

TABLE 3. CancerSEEK Trials Summary[23,24]

Trial name	Status	Estimated completion	Trial design	Purpose	Participants
DETECT-A[a]	Complete	--	Prospective, interventional	Identify multiple cancer types using test	10,006 women 65-75 years old with no history of cancer
ASCEND	Recruiting	June 2020	Prospective, observational, cohort	Validate test	Estimated 3000 participants ≥50 years; 1000 with a cancer diagnosis and 2000 with no prior history of cancer in the United States

[a]Trial is not registered on clinicaltrials.gov; publication results used for summary.

currently no screening methods available, such as ovaries, kidney, and the lymphatic system.[23] The specificity during this trial was estimated to be 98.9%, which increased to 99.6% when done in combination with the PET-CT.[23] There were 24 false negatives, and the cancers that were missed by this blood test were breast, lung, and colorectal, of which 22 were early-stage cancers and have other screening methods.[23] This blood test is also being studied in the Detecting Cancers Earlier Through Elective Plasma-based CancerSEEK Testing - Ascertaining Serial Cancer Patients to Enable New Diagnostic (ASCEND) trial to compare patients with and without cancer. Accrual was completed in June 2020; results are awaited.[24]

Galleri Test

The Galleri multicancer early detection (MCED) test identifies cfDNA circulating in the blood through next-generation sequencing, which recognizes DNA methylation.[25] The test aims to identify distinct methylation patterns that are associated with specific cancers to detect a number of those cancers early and simultaneously provide information about the organ of origin.[25] Four trials are evaluating this technology, including the Circulating Cell-free Genome Atlas (CCGA), STRIVE, SUMMIT, and PATHFINDER studies (**Table 4**).[26-29] The CCGA study served in the initial development of the test by analyzing blood and tumor tissue samples from 15,254 individuals from 142 sites in North America, including patients with newly diagnosed cancer (56%, N = 8584) and blood samples from patients without a diagnosis of cancer (44%, N = 6670). More than 50 different cancer types were included in the samples analyzed. The trial includes 3 subsets to evaluate the different analytic methods of MCED, the test's ability to correctly identify the tissue of origin, and a confirmatory validation. Subsets 1 and 2 of the study have been completed with the third, a validation study, ongoing.[26] The preliminary trial results for the CCGA were presented at the 2019 American Society of Clinical Oncology (ASCO) meeting.[25] The trial included a sub-study of 6689 participants, of which 2482 had previously untreated cancer, and included 4207 without cancer.[25] The preliminary results showed that the MCED test could detect 12 types of cancer at early stages, including anorectal, colorectal, esophageal, gastric, head and neck, hormone receptor-positive breast, liver, lung, ovarian, and pancreatic cancers, in addition to multiple myeloma and lymphoid neoplasms. These 12 cancers are expected to account for over half of cancer deaths in the United States.[6] The specificity was set at 99.3%, and tissue of origin was correctly identified with 93% accuracy. The test had a 67.3% (95% CI, 60.7%-73.3%) detection rate for the 12 prespecified cancer types across stages I to III, including 39% for stage I, 69% for stage II, and 83% for stage III. The overall detection rate for all cancer types was 43.9% (95% CI, 39.4%-48.5%) across stages I to III.[25]

The STRIVE trial is ongoing and seeks to investigate and validate the ability of the MCED test to detect breast cancer (and other cancers) that might occur within 1 year by collecting blood samples from patients within 28 days of a screening mammogram.[27] The study aims to enroll about 100,000 women aged 18 years and older in the United States. The estimated primary completion date is June 2022. Another trial currently underway is the SUMMIT study, which is similar in design to the STRIVE trial, but investigating lung cancer detection in the United Kingdom.[28] The study aims to enroll 50,000 men and women aged 50 to 77 years who will be split into 2 groups based on the risk of lung cancer related to smoking history. Blood will be collected and an LDCT will be performed to validate the early lung cancer detection.[28] The primary completion date is estimated for August 2023. Finally, the PATHFINDER trial is the first to prospectively examine the application of the MCED test in

TABLE 4. Galleri Test Trials Summary[26-29]

Trial name	Status	Estimated completion	Trial design	Purpose	Participants
CCGA	Active, not recruiting	March 2024	Prospective, observational, longitudinal	Characterize the cfDNA in the blood of patients with cancer and without cancer	15,254 participants ≥20 years across 141 sites in the United States and Canada
STRIVE	Active, not recruiting	May 2025	Prospective, observational, longitudinal, cohort	Validate the test for early detection of cancer	99,481 women ≥18 years at time of mammogram screening across 35 sites in the United States
SUMMIT	Enrolling by invitation	August 2030	Prospective, observational, longitudinal, cohort	Validate the test by measuring cancer incidence	Estimated 50,000 participants 50-77 years without a cancer diagnosis, but with variable risks for cancer (specifically lung) at enrollment from London, United Kingdom
PATHFINDER	Recruiting	January 2022	Prospective clinical trial cohort	Evaluate implementation of test in clinical practice	Estimated 6200 participants ≥50 years, split into elevated risk group and nonelevated risk group

CCGA, Circulating Cell-free Genome Atlas; cfDNA, circulating cell-free DNA.

a real-world, early detection setting where test results are returned to participants and their physicians.[29] It is recruiting approximately 6200 participants 50 years or older with varying levels of cancer risk and without a focus on any single cancer. The 2 cohorts in the study include elevated risk (defined as 1 of the following: smoking history of ≥100 cigarettes, a genetic cancer disposition, or a history of invasive or hematologic malignancy with definitive treatment completed >3 years prior to enrollment) and non-elevated risk. The results of the test will be returned to healthcare providers as "signal not detected" or "signal detected" and trigger a diagnostic evaluation based on specific institutional practice rather than study protocol. The study seeks to determine the performance of the MCED test in a setting that resembles routine testing of healthy individuals. It also aims to define what evaluations are needed to arrive at a diagnostic resolution after a "signal detected" result (cancer that is either diagnosed or ruled out). The study will evaluate health resource utilization, the number and types of tests and time required to reach diagnostic resolution as well as test performance (specificity, positive predictive value, and tissue of origin accuracy). Several patient-specific factors will be assessed, including quality of life, anxiety, perception, and satisfaction with the test.[29,30] The PATHFINDER trial will evaluate experience in the context of a broad healthy population, including clinical evaluations and the patient experience. If successful, the experience of PATHFINDER will be helpful in defining the potential application of MCED for the general population and early detection of a variety of cancers. The trial has an estimated primary completion date of May 2021.[29]

PanSeer Test

The PanSeer test detects DNA methylation patterns linked to gene silencing that may contribute to cancer development. Of note, the test is designed to identify cancer in asymptomatic individuals and is unlikely to predict who will develop cancer if not present at the time of screening.[31] The longitudinal study evaluating this test used plasma samples from the Taizhou Longitudinal Study (TZL). In the TZL, 123,115 healthy subjects in China aged 25 to 90 years provided plasma samples. The subjects were monitored over 10 years for cancer, among other chronic conditions and specific diseases, at 3-year intervals via detailed questionnaires and additional plasma and tissue samples.[32] The preliminary results of the test included an evaluation of approximately 400 blood samples from cancer-free participants and 400 blood samples from participants who were diagnosed with cancer within 4 years of enrollment.[31] The cancers included were stomach, colorectal, liver, lung, and esophageal. The test showed a specificity of 96% in patients after being diagnosed with 1 of 5 types of cancer, and the test detected cancer in 95% of asymptomatic participants who were then diagnosed later.[31] One of the limitations of the test is it does not detect the tissue of origin; it detects abnormalities that need further workup to determine the exact location of the cancer. However, if validated, this test could be used as a first step in screening, meaning a positive result will prompt further diagnostic testing to localize the suspected cancer.[31]

Emerging Single-Cancer Detection Technologies

Several single-cancer detection methods are under investigation. One of the tests that has entered validation is a multiomics test for colorectal cancer.[33] The single-cancer detection (SCED) blood test is a multiomic blood test of cfDNA and protein biomarkers to detect early cancer.[33] The results from the AI-EMERGE trial were presented at the ASCO Gastrointestinal Cancers Symposium in January 2020.[33] By comparing blood and stool samples between healthy patients undergoing routine colonoscopies and patients diagnosed with colorectal cancer, the researchers concluded the test has a 94% sensitivity and specificity rate for stage I and II colorectal cancer and a sensitivity of 91% and specificity of 94% in stage III and IV colorectal cancer.[33]

Providing a stool sample was optional, and only about half of participants chose to do so, which underscores the known hesitation of patients to undergo colorectal cancer screening in this manner.[33] The specificity for the SCED blood test was similar to the fecal immunochemical (FIT) test, yet the sensitivity was much higher at 100% versus 67% for the FIT.[33]

A second trial, PREEMPT CRC, is expected to further validate the specificity and sensitivity of the assay by comparing the results from the SCED blood test to routine colonoscopy results in average-risk participants.[34] The prospective, observational trial will enroll around 14,000 participants and has an expected completion date of July 2021.[34]

Conclusions

With cancer cases on the rise, effective screening methods and novel modalities are needed. Cancer screening in the general population is recommended for a small number of cancers, including breast, cervical, and colorectal cancers. Multicancer detection blood tests in development are designed to address many of the limitations associated with current screening methods. Further validation through prospective clinical trials is underway, and if validated, blood-based assays may allow for minimally invasive early detection of multiple cancers, including neoplasms that currently are not detected early because of a lack of effective screening tests. It remains to be determined how MCED tests might be used in practice. One can envision periodic blood-based testing, for example, annually or every several years. Tests with robust organ of origin information may permit a specific diagnostic evaluation to confirm or rule out the suggested cancer in individual patients. ■

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30. doi: 10.3322/caac.21590
2. Centers for Disease Control and Prevention. An update on cancer deaths in the United States. Page reviewed May 29, 2020. Accessed July 16, 2020. cdc.gov/cancer/dcpc/research/update-on-cancer-deaths/index.htm
3. American Cancer Society. Economic impact of cancer. Page revised January 3, 2018. Accessed July 16, 2020. cancer.org/cancer/cancer-basics/economic-impact-of-cancer.html
4. CDC. Expected New Cancer Cases and Deaths in 2020. Page reviewed August 16, 2018. Accessed July 16, 2020. cdc.gov/cancer/dcpc/research/articles/cancer_2020.htm
5. Ahlquist DA. Universal cancer screening: revolutionary, rational, and realizable. *NPJ Precis Oncol.* 2018;2:23. doi: 10.1038/s41698-018-0066-x
6. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) program. Cancer stat facts: cancer of any site. Published 2020. Accessed July 16, 2020. seer.cancer.gov/statfacts/html/all.html
7. US Preventive Services Task Force (USPSTF). A and B recommendations. Published 2020. Accessed July 16, 2020. uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-and-b-recommendations
8. National Cancer Institute. Cancer screening. Updated January 16, 2019. Accessed July 29, 2020. cancer.gov/about-cancer/screening/screening-tests
9. American Cancer Society. Cancer facts & figures, 2020. Published 2020. Accessed July 16, 2020. cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf
10. Clarke CA, Hubbell E, Kurian AW, Colditz GA, Hartman AR, Gomez SL. Projected reductions in absolute cancer-related deaths from diagnosing cancers before metastasis, 2006-2015. *Cancer Epidemiol Biomarkers Prev.* 2020;29(5):895-902. doi: 10.1158/1055-9965.Epi-19-1366
11. Yabroff KR, Lund J, Kepka D, Mariotto A. Economic burden of cancer in the United States: estimates, projections, and future research. *Cancer Epidemiol Biomarkers Prev.* 2011;20(10):2006-2014. doi: 10.1158/1055-9965.epi-11-0650
12. Islami F, Miller KD, Siegel RL, et al. National and state estimates of lost earnings from cancer deaths in the United States. *JAMA Oncol.* 2019;5(9):e191460. doi: 10.1001/jamaoncol.2019.1460
13. National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis (Version 1.2019). Published 2019. Accessed July 29, 2020. nccn.org/professionals/physician_gls/pdf/breast-screening.pdf
14. National Comprehensive Cancer Network. Colorectal Cancer Screening (Version 2.2020). Published 2020. Accessed July 29, 2020. nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf
15. National Comprehensive Cancer Network. Lung Cancer Screening (Version 1.2020). Published 2020. Accessed July 29, 2020. nccn.org/professionals/physician_gls/pdf/lung_screening.pdf
16. Saslow D, Solomon D, Lawson HW, et al; American Cancer Society; American Society for Colposcopy and Cervical Pathology; American Society for Clinical Pathology. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol.* 2012;137(4):516-542. doi: 10.1309/ajcptgd94evrsjcg
17. Fontham ET, Wolf AM, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. Published online July 30, 2020. doi: 10.3322/caac.21628
18. Lin JS, Perdue LA, Henrikson LB, Bean SL, Blasi PR. Screening for colorectal cancer: an evidence update for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality. Published October 27, 2020. Accessed November 5, 2020. www.uspreventiveservicestaskforce.org/uspstf/document/draft-evidence-review/colorectal-cancer-screening3
19. Parikh R, Mathai A, Parikh S, Chandra Sekhar G, Thomas R. Understanding and using sensitivity, specificity and predictive values. *Indian J Ophthalmol.* 2008;56(1):45-50. doi: 10.4103/0301-4738.37595
20. National Comprehensive Cancer Network. Prostate Cancer Early Detection (Version 1.2020). Published 2020. Accessed July 29, 2020. nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf
21. Cohen JD, Li L, Wang Y, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science.* 2018;359(6378):926-930. doi: 10.1126/science.aar3247
22. Fidler B. Thrive, chasing Grail with a cancer blood test, finds tumors in seemingly healthy women. News release. April 28, 2020. Accessed August 3, 2020. biopharmadive.com/news/thrive-grail-liquid-biopsy-detect-cancer-aacr/576901/
23. Lennon AM, Buchanan AH, Kinde I, et al. Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. *Science.* 2020;369(6499):eabb9601. doi: 10.1126/science.abb9601
24. Detecting Cancers Earlier Through Elective Plasma-based CancerSEEK Testing (ASCEND). ClinicalTrials.gov. Updated January 14, 2020. Accessed October 19, 2020. clinicaltrials.gov/ct2/show/NCT04213326?term=NCT04213326&draw=2&rank=1
25. Liu MC, Oxnard GR, Klein EA, Swanton C, Seiden MV; CCGA Consortium. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol.* 2020;31(6):745-759. doi: 10.1016/j.annonc.2020.02.011
26. The Circulating Cell-free Genome Atlas Study (CCGA). ClinicalTrials.gov. Updated August 31, 2020. Accessed October 19, 2020. clinicaltrials.gov/ct2/show/NCT02889978?term=NCT02889978&draw=2&rank=1
27. The STRIVE Study: Development of a Blood Test for Early Detection of Multiple Cancer Types. ClinicalTrials.gov. Updated July 31, 2020. Accessed October 19, 2020. clinicaltrials.gov/ct2/show/NCT03085888?term=NCT03085888&draw=2&rank=1
28. The SUMMIT Study: A Cancer Screening Study. ClinicalTrials.gov. Updated May 2, 2019. Accessed October 19, 2020. clinicaltrials.gov/ct2/show/NCT03934866?term=NCT03934866&draw=2&rank=1clinicaltrials.gov/ct2/results?cond=&term=NCT03934866&cntry=&state=&city=&dist=
29. Assessment of the Implementation of an Investigational Multi-Cancer Early Detection Test Into Clinical Practice. ClinicalTrials.gov. Updated August 5, 2020. Accessed October 19, 2020. clinicaltrials.gov/ct2/show/NCT04241796?term=NCT04241796&draw=2&rank=1
30. Nadauld L, McDonnell CH III, Liu MC, et al. The PATHFINDER study: assessment of the implementation of an investigational multi-cancer early detection test into clinical practice. *Cancer Res.* 2020;80(suppl 16): Abstract CT291. Presented at American Association for Cancer Research Annual Meeting 2020; April 27-28, 2020 and June 22-24, 2020. Accessed November 5, 2020. cancerres.aacrjournals.org/content/80/16_Supplement/CT291
31. Chen X, Gole J, Gore A, et al. Non-invasive early detection of cancer four years before conventional diagnosis using a blood test. *Nat Commun.* 2020;11(1):3475. doi: 10.1038/s41467-020-17316-z
32. Wang X, Lu M, Qian J, et al. Rationales, design and recruitment of the Taizhou Longitudinal Study. *BMC Public Health.* 2009;9:223. doi: 10.1186/1471-2458-9-223
33. Putcha G, Liu T-Y, Ariazi E, et al. Blood-based detection of early-stage colorectal cancer using multiomics and machine learning. Poster presented at American Society of Clinical Oncology Gastrointestinal Cancers Symposium 2020. January 23-25, 2020. Accessed October 19, 2020. ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.66
34. Prevention of Colorectal Cancer Through Multiomics Blood Testing (PREEMPT CRC). ClinicalTrials.gov. Updated September 29, 2020. Accessed October 19, 2020. clinicaltrials.gov/ct2/show/NCT04369053?term=NCT04369053&draw=2&rank=1

REPORT

Screening for Cancer: The Economic, Medical, and Psychosocial Issues

Joel V. Brill, MD, FACP

ABSTRACT

Despite significant improvements in mortality over the past 20 years, cancer remains the second leading cause of death in the United States. One reason for the improvement in mortality is screening for several common cancers in people at average risk for breast, cervical, colorectal, and prostate cancers, and screening for lung cancer in those with a 20-plus pack-year history. Such screening may result in earlier diagnosis when the cancer is most likely to respond to treatment. However, there are no population-based screening recommendations for the majority of cancers in average-risk patients, most of which are not diagnosed until the later stages. One question is whether earlier diagnosis could not only reduce mortality rates but also reduce medical costs. Screening comes with several potential risks, including false positives and overdiagnosis, both of which can affect patients' mental health, increase morbidity and mortality, and lead to excess spending. Additionally, certain cancers can evade traditional screening tests and lead to false-negative results, which delays cancer detection, treatment, and may affect treatment efficacy. The advent of liquid biopsy tests that could screen for dozens of cancers holds promise for identifying more cancers early. However, the cost, the potential for overdiagnosis and false positives, and a lack of evidence demonstrating clinical utility or an improvement in health outcomes call into question their potential use for widespread screening. Government and managed care organizations will need to consider the risks and benefits of these assays in determining coverage.

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For author information and disclosures, see end of text.

Introduction

More than 1.8 million cases of cancer are projected to be diagnosed in 2020, and 606,520 individuals are projected to die from the disease, making it the second leading cause of death in the United States.[1] However, there has been a significant decline in the rate of cancer deaths in the United States since 1991, primarily due to smoking-cessation efforts, earlier detection, and improved treatments.[1] Between 1991 and 2017, the death rate from cancer fell 29%, resulting in 2.9 million fewer deaths. At the same time, the 5-year survival rate for all cancers combined has continued to increase, rising from 49% in 1975 to 69% in 2015 among all races and from 39% to 64% among African Americans.[2]

Cancer exerts a significant economic burden on the US healthcare system, with estimated medical costs in 2020 expected to reach $157.7 billion, a 27% increase from 2010 costs.[3] Annual mean costs (direct payments and patient out-of-pocket costs) for those aged 18 years and older with cancer in 2014 dollars were described as $16,346 compared with $4484 for those without cancer, with private insurance and Medicare being the 2 largest payers of cancer care. Hospital expenses accounted for 27%, ambulatory care visits for 41%, and prescription drug expenses for 21%.[4] The National Cancer Institute reports the national economic burden, defined as patient and payer medical costs for cancer (excluding oral drugs) in 2018 at $150.8 billion.[5]

Cancer has a significant impact on the financial health of patients and their families. Today, the estimated 16.1 million individuals living with cancer face annual out-of-pocket medical expenditures 61% higher than those without cancer ($1000 vs $622). About 1 in 4 report problems paying bills, and one-third worry about paying bills.[6] A 2017 systematic review of 45 studies found that 12% to 16% of those with cancer were in debt due to their treatment, about half reported some level of financial distress, and between 4% and 45% were nonadherent with medication because of cost.[7] Cancer also has significant indirect costs related to lost income. An analysis of 492,146 cancer deaths in persons aged 16 to 84 years in the United States in 2015 found $94.4 billion in lost earnings, with average loss of $191,900,[8] which likely underestimated productivity loss.

Preventive Care and Early Cancer Detection

Five-year survival rates for cancer are significantly higher for those diagnosed in earlier stages (**Table 1**[1]). The 5-year survival rate for patients diagnosed with metastatic lung cancer is 5% versus 57% for those diagnosed with localized disease, a mortality rate that can be significantly improved with low-dose computed tomography (LDCT) screening in current or former smokers.[1]

Clarke et al examined the potential reductions in cancer-related deaths if malignancies diagnosed after metastasis were, instead, diagnosed at earlier stages. Although stage IV cancers represented 18% of all diagnoses, they accounted for 48% of all cancer-related deaths within 5 years.[9] The researchers found that if these patients had been diagnosed at stage III, there would have been 51 fewer cancer-related deaths per 100,000 (or 15% of all cancer-related deaths). If one-third of metastatic cancers were diagnosed at stage III, one-third at stage II, and one-third at stage I, there would be 81 fewer cancer-related deaths per 100,000 (or 24% fewer cancer-related deaths).[9]

Early diagnosis can reduce the cost of treatment. One study estimated the national cost-savings in the United States from early diagnosis at $26 billion per year.[10] Studies in other industrialized countries find treatment costs for patients diagnosed early in the disease course to be 2 to 4 times less than those diagnosed at later stages.[11] Earlier diagnosis may also reduce the financial impact on the patient and their family given shorter treatment courses, which can allow patients to continue working and therefore incur fewer expenses related to therapies.[11]

Barriers to Early Detection of Cancer

There are numerous barriers to the early detection of cancer, both medical and socioeconomic, including:

- **Lack of symptoms.** Liver, pancreatic, and ovarian cancers are typically diagnosed late in the disease course because they rarely present with symptoms early within the disease course.[2]
- **Awareness.** Individuals may not be aware of the signs and symptoms of cancer or assume they are part of some other condition.[11]
- **Access.** Lack of access to screening and diagnostic testing can delay early diagnosis and treatment.[11]
- **Financial.** Those who are uninsured or underinsured, or who have low socioeconomic status, may be less likely to obtain screening or early diagnosis.[12]
- **Fear.** This includes fear of learning about the cancer as well as fear of its treatments.[12]
- **Human nature**. Many young people feel invincible and healthy and reject the need for screening. Yet, among adults younger than 50 years, rates of cancer linked to obesity are rising. Millennials born around 1985 are now twice as likely to develop 1 of 6 obesity-linked cancers as baby boomers born around 1950 were at the same age.[13]
- **Weak referral systems.** Many people present with early-stage symptoms to their primary care provider.[14,15] The clinician may not recognize the symptoms or may not have access to a robust referral network.[12,15]

TABLE 1. Five-Year Relative Survival Rates for Selected Cancers by Stage at Diagnosis, United States, 2009-2015[1]

	Localized	Regional	Distant	All stages
Colorectum	90%	71%	14%	**64%**
Esophagus	47%	25%	5%	**20%**
Female breast	99%	86%	27%	**90%**
Kidney & renal pelvis	93%	70%	12%	**75%**
Liver & intrahepatic bile duct	33%	11%	2%	**18%**
Lung & bronchus	57%	31%	5%	**19%**
Melanoma of the skin	99%	65%	25%	**92%**
Non-Hodgkin lymphoma	84%	75%	65%	**72%**
Oral cavity & pharynx	84%	66%	39%	**65%**
Ovary	92%	75%	29%	**48%**
Pancreas	37%	12%	3%	**9%**
Prostate	>99%	>99%	31%	**98%**
Uterine bladder	70%	36%	5%	**77%**
Uterine cervix	92%	56%	17%	**66%**
Uterine corpus	95%	69%	16%	**81%**

Adapted from Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.10.3322/caac.21590

- **Lack of confidence in healthcare providers.** This is particularly evident in Black women given the history of the medical establishment and the African American community (eg, Tuskegee syphilis study) and discrimination and racism in the healthcare system.[12]

Overcoming barriers to early cancer detection requires additional training of healthcare professionals, greater public awareness of the availability of screening and the signs and symptoms of cancer, and access to affordable specialty care.[11] It also requires realignment of the payment structure to provide financial incentives that prioritize screening. For instance, short-term plans without preventive service benefits or coverage that requires patients to pay out of pocket if a screening becomes diagnostic provides negative financial incentives for screening.[16,17] Patients may incur high out-of-pocket costs, which can be become a deterrent to screening.

Screening for Cancer

One of the most effective ways to identify early-stage cancers is by screening asymptomatic individuals.[18] Current guidelines from the American Cancer Society and the US Preventive Services Task Force (USPSTF) recommend age- and population-based screening for 4 cancers: cervical, colorectal, breast, and prostate[19,20] as well as screening current and former heavy smokers for lung cancer. In addition, those with hepatitis B or C infection and cirrhosis should be screened for hepatocellular cancer.[21]

Several considerations go into any recommendation for wide-scale screening, with one of the most important being the ability of screening to impact the disease itself. Cochrane and Holland, who wrote a seminal paper on screening in 1971, identified 3 categories for screening: (1) those who are considered scientifically and financially acceptable, (2) those for whom there is insufficient evidence to justify their routine use at present, and (3) those for whom there is possibly some benefit, at considerable cost, for relatively few people.[22]

The USPSTF considers several areas before recommending disease screening in a given population[23]:

- Evidence related to benefits and harms from randomized clinical trials and observational studies
- Whether benefits outweigh harms and, if so, by how much and in which populations
- The degree of certainty the evidence provides for both benefits and harms
- Ages and other risk factors needed to specify when to begin and when to stop offering the service and in which populations

Trends in Cancer Screening in the United States

The Healthy People 2020 goals for cancer screening for eligible individuals in the United States based on guideline recommendations are 93% for cervical screening, 81.1% for mammograms, and 70.5% for colorectal cancer.[24,25] However, despite national recommendations for such screenings, as well as the elimination of out-of-pocket costs for Medicare beneficiaries and most patients with other health insurance, screening rates in the United States remain below that goal.[24,26-28] In 2015, just 50.5% of women aged 50 to 64 years reported having a recent mammogram, and 63.4% of those aged 50 to 75 years reported having a recent colorectal screening test.[24] In addition, the rate of mammograms between 2000 and 2015 declined by 3%. Among men aged 50 to 75 years, 61.9% reported having a recent colorectal cancer screening test.[24] In 2018, 68.8% of US adults aged 50 to 75 years were up-to-date with colorectal screening, although the rate was far lower among those with no health insurance (40.1%) or without a regular healthcare provider (36.1%).[28]

At the same time, however, screening may be overdone. Results of 2 recent studies found a significant number of patients who did not meet the USPSTF criteria for LDCT lung cancer screening still received the test.[29,30] Results of studies also find unnecessary cervical cancer screening, including too-frequent screening, screening outside the age range, and screening after hysterectomy.[31] A review of 8 studies on colorectal cancer screening also found overuse. There were numerous factors impacting inappropriate testing, which included physicians who were unaware of, had low confidence in, or perceived conflict in the guidelines.[32,33] Results of other studies found overuse rates for repeat screening colonoscopy in primary care of 60.8% and between 16.1% and 36.1% for prostate cancer screening with prostate-specific antigen (PSA).[34-37]

Screening Risks

Although screening can certainly identify cancers at an earlier stage when the malignancy is potentially more treatable, it does not come without risks, including perforation or bleeding complications from invasive procedures (ie, colonoscopy),[38] false-negative and false-positive results,[39] and overdiagnosis of very early cancers or precancerous lesions that might never advance, leading to overtreatment.[40]

False positives are some of the greatest risks from psychosocial, medical, and economic perspectives.[41-43] Whereas about 12% of women undergoing screening mammograms have an abnormal result, just 5% of those have cancer.[2] Results of an observational study estimated a 61.3% probability of receiving at least 1 false-positive mammogram after 10 years if annual screening began at age 40 years (95% CI, 59.4%-63.1%) and 41.6% (CI, 40.6%-43.7%) with screening biennially, with similar findings even when screening began at age 50 years. Seven percent of women who started screening at age 40 years would receive a biopsy recommendation after 10 years of annual screening and 4.8% after 10 years of biennial screening.[41]

Meanwhile, an analysis of 48,499 individuals in Catalonia, Spain, who received 130,134 fecal occult blood tests (FOBT) between 2000

and 2017 estimated a 16.2% false-positive result over 7 rounds of biennial screening. Those who completed 10 rounds of screening between ages 50 and 69 years had a more than 20% risk of a false positive, resulting in an unnecessary colonoscopy for follow-up.[44] A similar study conducted between 1997 and 2009 in US patients aged 50 to 79 years found a 20.5% risk of at least 1 false-positive in those undergoing at least 10 years of annual FOBT and 8.8% in those undergoing 10 years of biennial FOBT.[45] The FDA identified a false-positive rate with Cologuard of 13.4% compared with 5.1% with fecal immunochemical test (FIT).[46]

False positives may result in significant stress, anxiety, and distress.[47] One study investigated the psychosocial consequences of false-positive colorectal screening and found that participants were more ambivalent about future screenings in addition to the discomfort and anxiety associated with a positive test result.[42] Another study found that women with false-positive mammography results were less likely to return for future screenings.[48] Study results further find higher rates of depression, mood-affecting worries, and lower mental functioning in patients who receive false positives.[47] False positives also increase healthcare-associated costs, with one study analyzing the associated costs in 1087 managed care members who participated in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, a 23-year multisite randomized trial in which participants were randomized to receive either recommended cancer screenings for 6 years or usual care.[43,49] The investigators found that 43% of the study sample had at least 1 false-positive test at baseline, with men more likely to receive a false positive. The majority of patients (83%) received follow-up tests, including laparoscopy, colonoscopy, flexible sigmoidoscopy, and transvaginal ultrasound. Medical costs for those with false positives were $1024 higher for women and $1171 for men (in 2000 dollars) than for those without false positives in the year following the initial screen ($P < .0001$).[43] Ong et al estimated national expenditures for breast cancer false positives in women aged 40 to 59 years at $2.8 billion per year.[50]

Screening and Overdiagnosis

Overdiagnosis is defined as cancers detected on screening that would not have otherwise been detected during the patient's lifetime and represents another potential risk of cancer screening.[51] One model of 1 million men undergoing PSA screening estimated that 23% of White men and 34% of Black men would be diagnosed with such very early cancers.[51] Another analysis based on national PSA screenings conducted between 1985 and 2000 predicted overdiagnosis rates between 22.9% and 42%, depending on the model used.[52]

Screening mammography for breast cancer also results in high rates of cancer diagnoses that would not otherwise have been found during a woman's lifetime. Bleyer et al estimated that 22% to 31% of all invasive screen-detected breast cancers were overdiagnosed.[53] A systematic review published in 2014 determined that over 10 years between 3 and 14 women, out of a 1000, would be overdiagnosed and needlessly treated.[54] Such instances may also lead to excessive costs. One study estimated national expenditures for these breast cancer diagnoses in women aged 40 to 59 years at $1 billion a year.[50] Screening can also increase the risk of morbidity and mortality, with models estimating 2 to 11 screening-related deaths due to radiation per 100,000 women using digital mammography.[47] Studies have shown that screening for colorectal cancer via colonoscopy is occurring more frequently than guidelines recommend and, because this is a more invasive procedure, there is an increased risk of complications. Major bleeding and perforations are potential harms in individuals undergoing screening colonoscopy, with complications occurring in up to 15 of 1000 patients screened.[55-57]

Cost-Effectiveness of Screening

Numerous studies find that population-based screening for breast, colon, and cervical cancers are cost-effective if not cost-saving.[58-61] A systematic review of 33 studies evaluating the cost-effectiveness of several types of colorectal cancer screenings between 2010 and 2016 found 10-year screening with colonoscopy had the greatest cost-effectiveness in the United States, although all methods were cost-effective compared with no screening.[59] Pataky et al concluded that biennial mammography screening from ages 50 to 69 years was most cost-effective, with an incremental cost-effectiveness ratio (ICER) of $28,921 per quality-adjusted life-year (QALY), while biennial screening from age 40 to 69 years demonstrated an ICER of $86,029/QALY. Researchers also found that screening women aged 70 to 74 years was less cost-effective than screening women aged 40 to 49 years, given the lower life expectancy and potential harms.[62,63] There is less evidence for the cost-effectiveness of prostate cancer screening.[64] Results of one study found it would be cost-effective if offered every 4 years and only if those with low-grade cancers identified on screening were followed with active surveillance.[65]

Liquid Biopsy for Cancer Screening

Liquid biopsies that analyze circulating tumor DNA and tumor cells in plasma are already used to identify genetic variants of tumors and guide real-time systemic therapy. They are less invasive than tissue biopsies and can provide greater information about the genetic variation of the tumor compared with a tissue biopsy.[66] They may also be cost-effective, particularly if used to inform decisions regarding treatment.[67] However, screening tests should not only be accurate and reliable, with high levels of sensitivity (ie, low rate of false negatives), specificity (ie, low rate of false positives), and robustness, but also should demonstrate clinical utility (ie, that screening improves outcomes compared with no screening).[66] This, in turn, requires large-scale clinical trials with longitudinal follow-up, even in participants with no signs of cancer. It should

also provide clear evidence of the origin of the tumor in order to minimize further testing, identify clinically insignificant early-stage tumors to reduce overdiagnosis and overtreatment, and distinguish between indolent versus lethal disease. Aravanis et al suggested that appropriately powering such a trial would require hundreds of thousands of participants.[68]

Results of a 2018 review of liquid biopsies found no evidence of clinical validity to suggest clinical use for screening outside of a clinical trial. The authors also noted that it is possible that the assays may detect very early circulating genomic variants that were never destined to become cancers (ie, "biologic false positives"), with the same overdiagnosis discussed above with traditional cancer screening approaches.[66] Regardless, once these tests are approved and on the market, payers, regulatory agencies, and medical societies will have to develop guidelines regarding the frequency and coverage of such screening.[18]

Estimates are that the broad, multigene panels under investigation would cost between $5000 and $10,000 each. There are currently no published cost-effectiveness studies, and there are differences in insurance coverage.[69] Currently, Medicare does not cover screenings in the absence of signs or symptoms of disease, with the exception of screenings for colorectal, breast, cervical, prostate, and lung cancers.[27] Individuals undergoing a screening test for 50 cancers will not have signs and symptoms for all. Medicare also does not cover the cost of further testing and treatment if the initial test was performed in the absence of signs and symptoms.[70]

Coverage of genomic tests may provide a clue as to coverage decisions of liquid biopsies for cancer detection. Douglas et al analyzed Medicare and commercial payer coverage of circulating tumor DNA (ctDNA)-testing panels in patients already diagnosed with cancer between 2015 and 2019. By mid-2019, 65 private payers and 4 Medicare advisory committees had published policies about liquid biopsy coverage. Although no private payers covered the tests in 2016, by mid-2019, 38% covered them. On the Medicare side, there were 8 final local coverage determinations (LCDs), 2 draft LCDs, and 2 LCDs expected to become final in early 2020. **Table 2** breaks down the coverage.[71] Two LCDs by CMS evaluated the use of liquid biopsies to guide treatment in solid tumors and prevent organ rejection in kidney transplants.[72,73] Wide divergence has been found in the coverage policies themselves. Private payers often based coverage on the cancer stage, limited coverage to certain tests, and varied on whether they covered monitoring for cancer progression. Medicare policies covered the use of liquid biopsies only for stage IIIB or IV non–small cell lung cancer (NSCLC), although private insurers covered its use for all stages. They also covered monitoring only if patients had not been previously tested or were not responding to epidermal growth factor receptor tyrosine kinase inhibitors (for NSCLC) or if there was a new primary cancer or different primacy.[71] In a national coverage analysis example, CMS defined specific criteria needed to achieve to obtain coverage for blood-based biomarker tests for colorectal cancer screening to be administered once every 3 years or at the time interval designated by the FDA label for average risk, asymptomatic people aged 50 to 85 years. CMS indicated that blood-based screening tests must meet the following criteria for coverage: FDA market authorization with an indication for colorectal cancer screening, proven test performance characteristics for a blood-based screening test with both sensitivity greater than or equal to 74% and specificity greater than or equal to 90% in the detection of colorectal cancer compared with the recognized standard (colonoscopy at this time), based on pivotal

TABLE 2. Coverage Policies for ctDNA[71]

Payer	2015	2016	2017	Type of cancers covered 2017 (n)	2018	Type of cancers covered 2018 (n)[b]	2019	Type of cancers covered 2019 (n)[b]
Private	0/6 positive (0%)	0/28 positive (0%)	1/42 positive (3%)	1 lung cancer only	13/66 positive (20%)	11 lung cancer only; 2 solid and hematologic malignancies	28/73 positive (38%)	24 lung cancer only; 4 solid and hematologic malignancies
Medicare[a]	0 positive	0 positive	0 positive	N/A	4 positive	4 lung cancer (Guardant360 only)	12 positive	8 lung cancer: 4 Guardant360 4 InVisionFirst-Lung 4 solid tumors[c] Guardant360 only

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ctDNA, circulating tumor DNA; LCD, local coverage determination; MAC, Medicare Administrative Contractor.
[a]Medicare coverage is provided by LCDs issued from 4 of 7 MACs. Medicare does not issue negative coverage policies, so percentage of policies with positive coverage were not calculated.
[b]Blue Cross Blue Shield Association-affiliated policies typically have 2 separate policy documents: 1 for lung cancer and 1 for all other cancers. These policies are counted individually.
[c]Solid tumors (12 types): non-small cell lung cancer, colorectal, breast, endometrial, gastric and gastroesophageal, gastrointestinal stromal tumor, melanoma, ovarian, pancreatic, prostate, thyroid, and chordoma.

studies included in the FDA labeling, and inclusion as recommended routine colorectal screening in at least one professional society guideline or consensus statement or USPSTF recommendation.[74]

Conclusions

Despite significant improvements in detection and treatment over the past 2 decades that have dramatically improved the 5-year mortality of many cancers, it remains the second most common cause of death in the United States. Cancer diagnosis also exerts a significant economic burden on the US healthcare system, with estimated medical costs in excess of $157 billion. Population-based screening may be responsible for mortality reductions in several cancers, particularly breast, cervical, and colorectal cancers. However, population-based screening comes with several risks, including the risk for false-positive and false-negative results as well as under- and overdiagnosis.

The advent of liquid-based biopsies that can screen for multiple cancers could revolutionize cancer screening and lead to early detection of numerous tumors, such as pancreatic and ovarian, which are typically diagnosed late in the disease course. However, their use in clinical practice does raise several questions for government, managed care organizations, payers, and medical organizations that develop screening recommendations. A useful test provides information necessary to make a clinical treatment decision that improves the net health outcome, that is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Consideration must be given to whether earlier detection can lead to a change in management and an improvement in health outcomes. Cost-effectiveness, sensitivity and specificity, and clinical utility are key issues that must be considered when determining coverage and screening recommendations, as well as the impact on the healthcare system if thousands more cancers are diagnosed. ■

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30. doi: 10.3322/caac.21590
2. American Cancer Society. *Cancer Facts & Figures,* 2020. Accessed October 21, 2020. cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf
3. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst.* 2011;103(2):117-128. doi: 10.1093/jnci/djq495
4. Park J, Look KA. Health care expenditure burden of cancer care in the United States. *Inquiry.* 2019;56:46958019880696. doi: 10.1177/0046958019880696
5. National Cancer Institute. Financial burden of cancer care. March 2020. Accessed October 14, 2020. progressreport.cancer.gov/after/economic_burden
6. Ekwueme DU, Zhao J, Rim SH, et al. Annual out-of-pocket expenditures and financial hardship among cancer survivors aged 18-64 years – United States, 2011-2016. *MMWR Morb Mortal Wkly Rep.* 2019;68(22):494-499. doi: 10.15585/mmwr.mm6822a2
7. Altice CK, Banegas MP, Tucker-Seeley RD, Yabroff KR. Financial hardships experienced by cancer survivors: a systematic review. *J Natl Cancer Inst.* 2016;109(2):djw205. doi: 10.1093/jnci/djw205.
8. Islami F, Miller KD, Siegel RL, et al. National and state estimates of lost earnings from cancer deaths in the United States. *JAMA Oncol.* 2019;5(9):e191460-e191460. doi: 10.1001/jamaoncol.2019.1460
9. Clarke CA, Hubbell E, Kurian AW, Colditz GA, Hartman AR, Gomez SL. Projected reductions in absolute cancer–related deaths from diagnosing cancers before metastasis, 2006–2015. *Cancer Epidemiol Biomarkers Prev.* 2020;29(5):895-902. doi: 10.1158/1055-9965.EPI-19-1366
10. Kakushadze Z, Raghubanshi R, Yu W. Estimating cost savings from early cancer diagnosis. *Data.* 2017;2(30):2-16.
11. World Health Organization. Guide to cancer early diagnosis. 2017. Accessed August 8, 2020. who.int/entity/cancer/publications/cancer_early_diagnosis/en/index.html
12. Jones CE, Maben J, Jack RH, et al. A systematic review of barriers to early presentation and diagnosis with breast cancer among black women. *BMJ Open.* 2014;4(2):e004076. doi: 10.1136/bmjopen-2013-004076
13. Sung H, Siegel RL, Rosenberg PS, Jemal A. Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry. *Lancet Public Health.* 2019;4(3):e137-e147. doi: 10.1016/S2468-2667(18)30267-6
14. Yabroff KR, Gansler T, Wender RC, Cullen KJ, Brawley OW. Minimizing the burden of cancer in the United States: goals for a high-performing health care system. *CA Cancer J Clin.* 2019;69(3):166-183. doi: 10.3322/caac.21556
15. Neal RD, Din NU, Hamilton W, et al. Comparison of cancer diagnostic intervals before and after implementation of NICE guidelines: analysis of data from the UK General Practice Research Database. *Br J Cancer.* 2014;110(3):584-592. doi: 10.1038/bjc.2013.791
16. Norris L. 'So long' to limits on short-term plans. Healthinsurance.org. July 16, 2020. Accessed October 14, 2020. www.healthinsurance.org/so-long-to-limits-on-short-term-plans/
17. AGA: It's time to close the Medicare colonoscopy loophole, reform Stark law. Healio Gastroenterology. April 4, 2018. Accessed October 14, 2020. healio.com/news/gastroenterology/20180404/aga-its-time-to-close-the-medicare-colonoscopy-loophole-reform-stark-law
18. Ahlquist DA. Universal cancer screening: revolutionary, rational, and realizable. *NPJ Precis Oncol.* 2018;2:23. doi: 10.1038/s41698-018-0066-x
19. American Cancer Society. American Cancer Society Guidelines for the Early Detection of Cancer. Revised July 30, 2020. Accessed August 10, 2020. cancer.org/healthy/find-cancer-early/cancer-screening-guidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer.html
20. US Preventive Services Task Force. A and B recommendations. 2020. Accessed August 10, 2020. uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-and-b-recommendations
21. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Clin Liver Dis (Hoboken).* 2019;13(1):1-1. doi: 10.1002/cld.802
22. Cochrane AL, Holland WW. Validation of screening procedures. *Br Med Bull.* 1971;27(1):3-8. doi: 10.1093/oxfordjournals.bmb.a070810
23. US Preventive Services Task Force. Use of decision models in the development of evidence-based clinical preventive services recommendations. May 2019. Accessed August 9, 2020. uspreventiveservicestaskforce.org/uspstf/use-decision-models-development-evidence-based-clinical-preventive-services-recommendations
24. Hall IJ, Tangka FKL, Sabatino SA, Thompson TD, Graubard BI, Breen N. Patterns and trends in cancer screening in the United States. *Prev Chronic Dis.* 2018;15:E97. doi: 10.5888/pcd15.170465
25. Healthy People 2020. Clinical Preventive Services. Updated October 8, 2020. Accessed October 21, 2020. healthypeople.gov/2020/leading-health-indicators/2020-lhi-topics/Clinical-Preventive-Services/data
26. Zhao J, Mao Z, Fedewa SA, et al. The Affordable Care Act and access to care across the cancer control continuum: a review at 10 years. *CA Cancer J Clin.* 2020;70(3):165-181. doi: 10.3322/caac.21604
27. Centers for Medicare & Medicaid Services. Preventive and screening services. 2019. Accessed July 27, 2020. medicare.gov/coverage/preventive-screening-services
28. Joseph DA, King JB, Dowling NF, Thomas CC, Richardson LC. Vital signs: colorectal cancer screening test use – United States, 2018. *MMWR Morb Mortal Wkly Rep.* 2020;69(10):253-259. doi: 10.15585/mmwr.mm6910a1
29. Richards TB, Doria-Rose VP, Soman A, et al. Lung cancer screening inconsistent with US Preventive Services Task Force recommendations. *Am J Prev Med.* 2019;56(1):66-73. doi: 10.1016/j.amepre.2018.07.030
30. Huo J, Shen C, Volk RJ, Shih YT. Use of CT and chest radiography for lung cancer screening before and after publication of screening guidelines: intended and unintended uptake. *JAMA Intern Med.* 2017;177(3):439-441. doi: 10.1001/jamainternmed.2016.9016

31. Alber JM, Brewer NT, Melvin C, et al. Reducing overuse of cervical cancer screening: a systematic review. *Prev Med.* 2018;116:51-59. doi: 10.1016/j.ypmed.2018.08.027
32. Predmore Z, Pannikottu J, Sharma R, Tung M, Nothelle S, Segal J. Factors associated with the overuse of colorectal cancer screening: a systematic review. *Am J Med Qual.* 2018;33(5):472-480. doi: 10.1177/1062860618764302
33. Goodwin JS, Singh A, Reddy N, Riall TS, Kuo YF. Overuse of screening colonoscopy in the Medicare population. *Arch Intern Med.* 2011;171(15):1335-1343. doi: 10.1001/archinternmed.2011.212
34. Krist AH, Jones RM, Woolf SH, et al. Timing of repeat colonoscopy: disparity between guidelines and endoscopists' recommendation. *Am J Prev Med.* 2007;33(6):471-478. doi: 10.1016/j.amepre.2007.07.039
35. Korenstein D, Falk R, Howell EA, Bishop T, Keyhani S. Overuse of health care services in the United States: an understudied problem. *Arch Intern Med.* 2012;172(2):171-178. doi: 10.1001/archinternmed.2011.772
36. Welch HG, Albertsen PC. Reconsidering prostate cancer mortality – the future of PSA screening. *N Engl J Med.* 2020;382(16):1557-1563. doi: 10.1056/NEJMms1914228
37. Shoag JE, Nyame YA, Gulati R, Etzioni R, Hu JC. Reconsidering the trade-offs of prostate cancer screening. *N Engl J Med.* 2020;382(25):2465-2468. doi: 10.1056/NEJMsb2000250
38. Kim SY, Kim HS, Park HJ. Adverse events related to colonoscopy: global trends and future challenges. *World J Gastroenterol.* 2019;25(2):190-204. doi: 10.3748/wjg.v25.i2.190
39. American Cancer Society. Mammograms. Revised October 3, 2019. Accessed September 8, 2020. cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/mammograms/limitations-of-mammograms.html
40. National Cancer Institute. Cancer screening. Updated April 9, 2018. Accessed August 8, 2020. cancer.gov/about-cancer/screening
41. Hubbard RA, Kerlikowske K, Flowers CI, Yankaskas BC, Zhu W, Miglioretti DL. Cumulative probability of false-positive recall or biopsy recommendation after 10 years of screening mammography: a cohort study. *Ann Intern Med.* 2011;155(8):481-492. doi: 10.7326/0003-4819-155-8-201110180-00004
42. Toft EL, Kaae SE, Malmqvist J, Brodersen J. Psychosocial consequences of receiving false-positive colorectal cancer screening results: a qualitative study. *Scand J Prim Health Care.* 2019;37(2):145-154. doi: 10.1080/02813432.2019.1608040
43. Lafata JE, Simpkins J, Lamerato L, Poisson L, Divine G, Johnson CC. The economic impact of false-positive cancer screens. *Cancer Epidemiol Biomarkers Prev.* 2004;13(12):2126-2132.
44. Ibáñez-Sanz G, Garcia M, Milà N, et al; Adverse Effects on Colorectal Cancer Screening in Catalonia (EACC) Study Working Group. False-positive results in a population-based colorectal screening program: cumulative risk from 2000 to 2017 with biennial screening. *Cancer Epidemiol Biomarkers Prev.* 2019;28(11):1909-1916.
45. Hubbard RA, Ripping TM, Chubak J, Broeders MJ, Miglioretti DL. Statistical methods for estimating the cumulative risk of screening mammography outcomes. *Cancer Epidemiol Biomarkers Prev.* 2016;25(3):513-520. doi: 10.1158/1055-9965.EPI-15-0824
46. US Food and Drug Administration. Summary of safety and effectiveness data: Cologuard. August 11, 2014. Accessed October 21, 2020. www.accessdata.fda.gov/cdrh_docs/pdf13/P130017B.pdf
47. Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L. Harms of breast cancer screening: systematic review to update the 2009 US Preventive Services Task Force recommendation. *Ann Intern Med.* 2016;164(4):256-267. doi: 10.7326/M15-0970
48. Brett J, Austoker J. Women who are recalled for further investigation for breast screening: psychological consequences 3 years after recall and factors affecting re-attendance. *J Public Health Med.* 2001;23(4):292-300. doi: 10.1093/pubmed/23.4.292
49. National Cancer Institute. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). Accessed August 10, 2020. prevention.cancer.gov/major-programs/prostate-lung-colorectal-and-ovarian-cancer-screening-trial
50. Ong M-S, Mandl KD. National expenditure for false-positive mammograms and breast cancer overdiagnoses estimated at $4 billion a year. *Health Affairs.* 2015;34(4):576-583. doi: 10.1377/hlthaff.2014.1087
51. Petitti DB, Lin JS, Burda BU. Agency for Healthcare Research and Quality. Overdiagnosis in Prostate Cancer Screening Decision Models: A Contextual Review for the US Preventive Services Task Force. AHRQ Publication No. 17-05229-EF-3. May 2018.
52. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst.* 2009;101(6):374-383. doi: 10.1093/jnci/djp001
53. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med.* 2012;367(21):1998-2005. doi: 10.1056/NEJMoa1206809.
54. Welch HG, Passow HJ. Quantifying the benefits and harms of screening mammography. *JAMA Intern Med.* 2014;174(3):448-454. doi: 10.1001/jamainternmed.2013.13635
55. Vermeer NC, Snijders HS, Holman FA, et al. Colorectal cancer screening: systematic review of screen-related morbidity and mortality. *Cancer Treat Rev.* 2017;54:87-98. doi: 10.1016/j.ctrv.2017.02.002
56. Lieberman D, Ladabaum U, Cruz-Correa M, et al. Screening for colorectal cancer and evolving issues for physicians and patients: a review. *JAMA.* 2016;316(20):2135-2145. doi: 10.1001/jama.2016.17418
57. Ransohoff DF. How much does colonoscopy reduce colon cancer mortality? *Ann Intern Med.* 2009;150(1):50-52. doi: 10.7326/0003-4819-150-1-200901060-00308
58. Ahern CH, Shen Y. Cost-effectiveness analysis of mammography and clinical breast examination strategies: a comparison with current guidelines. *Cancer Epidemiol Biomarkers Prev.* 2009;18(3):718-725. doi: 10.1158/1055-9965.EPI-08-0918
59. Ran T, Cheng C-Y, Misselwitz B, Brenner H, Ubels J, Schlander M. Cost-effectiveness of colorectal cancer screening strategies—a systematic review. *Clin Gastroenterol Hepatol.* 2019;17(10):1969-1981.e15. doi: 10.1016/j.cgh.2019.01.014
60. Esselen KM, Feldman S. Cost-effectiveness of cervical cancer prevention. *Clin Obstet Gynecol.* 2013;56(1):55-64. doi: 10.1097/GRF.0b013e3182823797
61. Ratushnyak S, Hoogendoorn M, van Baal PH. Cost-effectiveness of cancer screening: health and costs in life years gained. *Am J Prev Med.* 2019;57(6):792-799. doi: 10.1016/j.amepre.2019.07.027
62. Walter LC, Schonberg MA. Screening mammography in older women: a review. *JAMA.* 2014;311(13):1336-1347. doi: 10.1001/jama.2014.2834
63. Pataky R, Ismail Z, Coldman AJ, et al. Cost-effectiveness of annual versus biennial screening mammography for women with high mammographic breast density. *J Med Screen.* 2014;21(4):180-188. doi: 10.1177/0969141314549758
64. Booth N, Rissanen P, Tammela TL, et al. Cost-effectiveness analysis of PSA-based mass screening: evidence from a randomised controlled trial combined with register data. *PLoS One.* 2019;14(11):e0224479. doi: 10.1371/journal.pone.0224479
65. de Carvalho TM, Heijnsdijk EA, de Koning HJ. Comparative effectiveness of prostate cancer screening between the ages of 55 and 69 years followed by active surveillance. *Cancer.* 2018;124(3):507-513. doi: 10.1002/cncr.31141
66. Merker JD, Oxnard GR, Compton C, et al. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J Clin Oncol.* 2018;36(16):1631-1641. doi: 10.1200/JCO.2017.76.8671
67. Uzerman MJ, Berghuis AM, de Bono JS, Terstappen LW. Health economic impact of liquid biopsies in cancer management. *Expert Rev Pharmacoecon Outcomes Res.* 2018;18(6):593-599. doi: 10.1080/14737167.2018.1505505
68. Aravanis AM, Lee M, Klausner RD. Next-generation sequencing of circulating tumor DNA for early cancer detection. *Cell.* 2017;168(4):571-574. doi: 10.1016/j.cell.2017.01.030
69. Terry M. As liquid biopsies grow, who's going to pay? Biospace. September 20, 2018. Accessed October 21, 2020. biospace.com/article/fd1a-as-liquid-biopsies-grow-who-s-going-to-pay-/
70. Social Security Administration. Exclusions from coverage and Medicare as secondary payer. 2019. Accessed October 21, 2020. ssa.gov/OP_Home/ssact/title18/1862.htm
71. Douglas MP, Gray SW, Phillips KA. Private payer and Medicare coverage for circulating tumor DNA testing: a historical analysis of coverage policies from 2015 to 2019. *J Natl Compr Canc Netw.* 2020;18(7):866-872. doi: 10.6004/jnccn.2020.7542
72. Centers for Medicare & Medicaid Services. Medicare Coverage Database. Proposed Local Coverage Determination (LCD): MolDX: Liquid Biopsies for Solid Organ Transplantation (DL38582). Published 2020. Accessed October 27, 2020. cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=38581&ver=3&name=238*2&bc=AQAAAIAAAAAA&
73. Centers for Medicare & Medicaid Services. Medicare Coverage Database. Proposed Decision Memo for Screening for Colorectal Cancer - Blood-Based Biomarker Tests (CAG-00454N). October 16, 2020. Accessed October 27, 2020. cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=299
74. Centers for Medicare & Medicaid Services. Medicare Coverage Database. Local Coverage Determination (LCD): MolDX: Plasma-Based Genomic Profiling in Solid Tumors (L38168). Published 2020. Accessed October 27, 2020. cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=38168&ver=5&Cntrctr=All&UpdatePeriod=870&bc=AAAACAAAIAAA&

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Pharmacy Credit

Instructions for Receiving Continuing Pharmacy Education (CPE) Credit: Testing Information

This lesson is free online; request your CE credit at **www.PharmacyTimes.org/go/early-cancer-detection.**

Testing Directions

1. Each participant evaluating the activity is eligible to receive CE credit.
2. To receive your credit online, go to **www.PharmacyTimes.org/go/early-cancer-detection** and complete the online posttest and the online activity evaluation form before the expiration date. Your CE credit will be automatically uploaded to CPE Monitor. Please ensure that your *Pharmacy Times*® account is updated with your NABP e-profile ID number and your date of birth (MMDD format). Participation data will *not* be uploaded into CPE Monitor if you do not have your NABP e-profile ID number and date of birth entered into your profile on **www.PharmacyTimes.org**.

Sample of Online Posttest

Choose the best answer for each of the following:

1. Which type of cancer does not have screening recommendations for the general population?

A. Breast cancer
B. Cervical cancer
C. Hepatocellular cancer
D. Colorectal cancer

2. When cancer is detected at later stages, which of the following is true?

A. 5-year survival increases.
B. 5-year survival decreases.
C. Treatment is more effective.
D. More treatment options are available.

3. AM is a 56-year-old postmenopausal woman with a past medical history significant for gestational diabetes, hypertension, and anxiety disorder. She is married with 3 children and works as an elementary school teacher. She has no family history of cancer, has never smoked, and does not drink alcohol. She has not been to see a doctor in approximately 7 years, but she decided to make an appointment with her gynecologist for a check-up after receiving a notification that she is due for cancer screening. She has no specific complaints or concerns at this time. Which screening test is NOT appropriate for AM?

A. Mammogram
B. Colonoscopy
C. Cervical cytology
D. Low-dose computed tomography (LDCT)

4. AM completes the recommended screening and is diagnosed with left-side breast infiltrating ductal carcinoma. She starts chemotherapy and takes a leave of absence from work. Her mother also comes to live with her for the duration of treatment. Which is a direct cost for AM?

A. Time spent receiving infusions
B. AM's mother's time spent as a caregiver
C. Co-payment for the oncologist office visit
D. Morbidity, or time lost from work during the leave of absence

5. What advantage does new cancer detection technology have compared with traditional screening methods?

A. Minimally invasive
B. Low specificity
C. Single-organ detection
D. Radiation exposure

6. Which statement is false regarding the multicancer blood screening tests?

A. They can predict a person's chance of getting cancer.
B. Some tests detect the tissue of origin.
C. They detect multiple types of cancer.
D. Some tests detect circulating cell-free DNA in the blood.

7. Medicare and most other health insurance plans cover screening with no out-of-pocket payment for all of the following cancers, EXCEPT:

A. Prostate
B. Pancreatic
C. Cervical
D. Breast

8. Cancer costs the US healthcare system approximately how much each year?

A. $70 million
B. $180 million
C. $50 billion
D. $160 billion

9. One way to increase survival rates in patients with cancer is to:

A. Screen everyone at risk for cancer.
B. Diagnose cancer in the early stages.
C. Begin aggressive treatment upon diagnosis.
D. Intervene surgically as much as possible.

10. A 67-year-old patient just had her mammogram. The radiologist wants her to come back for additional screening. She is certain she has cancer. Which of the following is an appropriate response?

A. "Mammograms are very accurate."
B. "A significant number of women will have a false-positive mammogram."
C. "Instead of a mammogram, you should schedule an MRI to confirm."
D. "Even if you do have cancer, it is probably so early in its development you will not need to do anything."

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