A Blueprint for Cancer Screening and Early Detection: Advancing Screening’s Contribution to Cancer Control

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Abstract: From the mid-20th century, accumulating evidence has supported the introduction of screening for cancers of the cervix, breast, colon and rectum, prostate (via shared decisions), and lung. The opportunity to detect and treat precursor lesions and invasive disease at a more favorable stage has contributed substantially to reduced incidence, morbidity, and mortality. However, as new discoveries portend advancements in technology and risk-based screening, we fail to fulfill the greatest potential of the existing technology, in terms of both full access among the target population and the delivery of state-of-the-art care at each crucial step in the cascade of events that characterize successful cancer screening. There also is insufficient commitment to invest in the development of new technologies, incentivize the development of new ideas, and rapidly evaluate promising new technology. In this report, the authors summarize the status of cancer screening and propose a blueprint for the nation to further advance the contribution of screening to cancer control. CA Cancer J Clin 2019;69:50-79. © 2019 American Cancer Society.

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Introduction

In the 20th century, there was a growing appreciation that many cancers had a better prognosis if they were diagnosed early in their natural history, before they had spread regionally or to distant organs. This understanding led to efforts to detect symptomatic cancers earlier and, eventually, to detect occult cancers in asymptomatic persons through screening. The ultimate purpose of screening is to prevent death from cancer by reducing the incidence of advanced disease and implementing therapy when it is most effective. The opportunity to reduce cancer deaths is further enhanced for those cancers that have a natural history allowing for the detection and treatment of precursor lesions and rapidly evaluate promising new technology. The effectiveness of a population-level screening program is measured according to the degree to which a reduction in disease-specific mortality can be accomplished with an acceptable balance of benefit to harm. To ensure that screening would be efficacious and effective, in 1968, the World Health Organization published the landmark work by Wilson and Jungner, who defined the criteria that must be met to make a persuasive case to offer screening to the population.1

The American Cancer Society (ACS) has a long legacy of promoting the early detection of both symptomatic and occult cancers, and similar guidelines have been issued by the US Preventive Services Task Force (USPSTF) and specialty societies.2 In the United States, adults at average risk are recommended to undergo screening for breast, cervical, and colorectal cancer (CRC); adults at high risk for lung cancer are recommended to undergo lung cancer screening, and men are recommended to have an
opportunity to make an informed decision about undergoing prostate cancer screening. These cancers will account for an estimated 47% of the incidence and 46% of the mortality from cancer in 2015 and for 46% of the estimated 9.4 million person-years of life lost because of death from malignant neoplasms in 2015. In this article (the fourth in a series outlining an ACS vision for the future of cancer control), we provide an overview of cancer screening for these cancers and a blueprint for the future based on an assessment of what steps should be taken to maximize the fullest impact of the existing technology and to anticipate the next generation of cancer control strategies focused on early cancer detection.

The Evaluation of Cancer Screening

Among the most important and complex challenges in cancer control research is the evaluation of cancer screening, including determining the efficacy of a test for the early detection of an occult cancer, evaluating the real-world effectiveness of screening for that cancer in the population, and evaluating the effectiveness of evolving screening technology for that cancer. Although today’s evidence standards require at least one well designed and well executed randomized clinical trial (RCT) to establish the efficacy of a screening test, the necessary size, inherent costs, duration, and management of these studies is an immense challenge, which explains why there have been so few cancer screening RCTs and perhaps why the initiation of these trials often lags years after compelling evidence exists that the efficacy of a new cancer screening test should be evaluated.

Conducting an RCT requires defining a target population at sufficient risk, meticulous randomization to establish a group that will be invited to screening versus usual care, ensuring that baseline risks are the same in the intervention and control groups, the achievement of high rates of screening in the invited group while also measuring screening outside of the trial in the control group, sufficient follow-up periods, and the collection of relevant outcome data for all randomized subjects. With the exception of screening for cervical cancer and the rapid uptake of prostate cancer screening in the late 1980s, the efficacy of early cancer detection was evaluated first with RCTs before the widespread use of currently recommended screening tests. The classic treatise by Wilson and Jungner was influential in establishing the importance of RCTs for the evaluation of cancer screening, but at the time of its publication cervical cancer screening already was established in many countries based on inferential evidence. Eventually, stronger evidence of the effectiveness of cervical cytology in reducing cervical cancer mortality was demonstrated through the evaluation of trends in cumulative cervical cancer mortality rates in Nordic countries, which showed a strong association between the extent and intensity of organized programs and mortality reductions from 1965 to 1982, ranging from 80% fewer cervical cancer deaths where high rates of screening were occurring to only 10% in settings where screening rates were low.

Once RCT data have confirmed the efficacy of screening, additional RCTs usually are judged to be both unnecessary and impractical to answer enduring and new questions; instead, observational study designs, such as prospective cohort studies, trend studies, ecological designs, case-control studies, and microsimulation models, are used to address important screening questions. There are exceptions, such as when a national system seeks to directly measure the efficacy of a test that has not been evaluated with an RCT, such as the UK trial of once-only flexible sigmoidoscopy (FS), the Colonoscopy Versus Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer Trial (CONFIRM), or the Tomosynthesis Mammographic Imaging Screening Trial (TMIST), which is comparing digital breast tomosynthesis (DBT) with conventional digital mammography. However, since the efficacy of screening has been demonstrated, with few exceptions, these trials generally do not have a group invited to usual care, and primary endpoints tend to be screening outcomes rather than mortality, although some may build in the potential for long-term evaluation of mortality differences between the 2 study arms. In either case, once favorable evidence from RCTs has led to the initiation of screening, there is a need to evaluate the implementation of screening in the community to measure screening outcomes among those who participate in screening, monitor quality, and identify opportunities to improve effectiveness. These opportunities include improving sensitivity and specificity, improving detection characteristics overall and in specific subgroups, reducing the interval cancer rate, exploring the potential for risk-based screening, reducing harms, and identifying operational/protocol changes that can bring the fullest benefits of a screening program to the target population. Observational study designs bring their own methodological challenges, and they are not equally suited to measure the effectiveness of screening. In particular, ecological studies using registry data have major limitations because of the inability to distinguish screened and unscreened cohorts, the challenge of adjusting for relevant underlying differences and trends in risk, and the need to isolate cancer deaths in the screening era attributable to cases diagnosed before the introduction of screening. Finally, there will be questions for which sufficient empirical data simply do not exist, and predictive or microsimulation modeling, which assumes various screening protocol scenarios given

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a set of empirically based assumptions, also may be used to examine various measures of benefits and harms. Modeling studies have become a common source of evidence in guideline development. In sum, the synthesis of data from many sources is usually required to establish the absolute and relative effectiveness of cancer screening strategies. However, this complexity, and different views about the quality of evidence from RCTs versus observational and modeling studies, contribute to sustained differences in judgments regarding the relative benefits and harms of various screening strategies.\textsuperscript{11,12}

**Population-Based Screening**

Developing the capacity to screen for select cancers in the population constitutes one of the most important advances in cancer control. The success of a cancer screening program in reducing mortality depends on the sensitivity of the protocol (the test, screening interval, etc), the exposure rate in the population, and, of course, the timely evaluation of positive tests and triage to appropriate treatment for those diagnosed with cancer. Cancer screening can be delivered to the population opportunistically during encounters with health services or through an organized program. In some settings, both types of programs may exist, and there can be degrees of organization in a screening program that still is largely opportunistic. For the most part, organized cancer screening is distinguished from opportunistic screening based on how invitations to cancer screening are issued to the target population. In an organized program, invitations are issued systematically and tracked from centralized population registries, whereas opportunistic screening depends on encounters with health care providers or on individuals who initiate cancer screening on their own. Another key difference is that organized screening programs tend to assume centralized responsibility for the other programmatic elements of cancer screening, such as eligibility, quality assurance, follow-up, and evaluation. In a setting of opportunistic screening, which principally is the US model, these elements usually do not receive systematic attention, thus achieving the fullest potential of cancer screening is unlikely to be realized.\textsuperscript{13} Organized screening programs also may have greater potential to achieve higher population coverage, because equality of access usually will be a central goal of the program.

Age-adjusted mortality rates for solid cancers amenable to screening have declined substantially since the introduction of effective screening tests and the maturing of organized or opportunistic programs, in large part because of the greater effectiveness of state-of-the-art therapy when the disease is detected earlier in its natural history. Declines in cervical cancer deaths since the mid-20th century\textsuperscript{14} and in CRC deaths in the past 2 decades\textsuperscript{15} are principally related to the introduction of effective screening. Screening and improvements in treatment also have contributed substantially to declining mortality for breast and prostate cancer.\textsuperscript{16-18} Modern lung cancer screening with low-dose computed tomography (LDCT) was first recommended by the ACS and the USPSTF in 2013. It may be some years before the influence of lung cancer screening on lung cancer mortality rates will be evident because of the slow pace at which risk assessment and screening referral are integrated into primary care and the incorporation of the indicators of routine lung cancer screening into national population-based surveys of recent preventive care.\textsuperscript{19}

**The Benefits, Limitations, and Harms of Screening**

Although cancer screening has proven to be one of the most impactful cancer control strategies, screening is an inherently imperfect intervention. Screening tests are associated with benefits, limitations, and harms, and each of these must be considered when establishing guidelines and when communicating to patients about the value of screening. Benefits principally are the potential to reduce the risk of being diagnosed with an advanced cancer, the peace of mind of having a normal test result, and, for some cancers, the potential for prevention because of the detection and elimination of precursor lesions. Potential limitations and harms include false-positive and false-negative test results, overdiagnosis, and, in very rare instances, significant injury and death associated with the screening examination and diagnostic evaluations. False-positive results can lead to additional diagnostic evaluation and anxiety in some patients; overdiagnosis leads to both unnecessary diagnostic evaluation and cancer treatment. In addition to these harms, emotional and physical adverse effects as a result of screening and diagnostic tests will be experienced by a small proportion of individuals who undergo screening. Over time and multiple rounds of screening, a growing proportion of the target population will have experienced some of the downsides associated with screening.\textsuperscript{20} There is limited evidence on methods to reduce the stress associated with false-positive findings, but providing advance information about the possibility of false-positive findings and potential undesirable outcomes has been associated with lower stress levels associated with being recalled for further evaluation.\textsuperscript{21}

Robust quality-assurance programs can mitigate these limitations and harms, for example, initiatives to improve the accuracy of screening, which can reduce false-positive and false-negative rates. Timely follow-up and communication can reduce anxiety associated with a positive test
result. In contrast to this potential to reduce harms associated with being recalled for further evaluation, reducing the harms associated with overdiagnosis is a much greater challenge. Overdiagnosis is the detection by screening of a nonprogressive cancer that would have remained undetected for the remainder of the patient’s lifetime if they had not undergone screening. Alternatively, a patient may be diagnosed with a progressive cancer that has an average growth rate or with a very slow-growing cancer; either way, it is detected in a patient who was destined to die from another cause before the cancer would have become symptomatic and diagnosed. In each instance, treatment is unnecessary and thus represents a significant harm. For each type of overdiagnosis, in the absence of screening, these patients never would have known they had cancer and thus never would have undergone treatment.

The rate of overdiagnosis of cancer in patients with life-limiting comorbidity can be reduced by careful ascertainment of the patient’s overall health status and expected longevity, and thus the likelihood that the patient has the potential to benefit from screening.\textsuperscript{24,25} All cancer screening guidelines recommend careful assessment of a patient’s overall health status and longevity to determine when screening is no longer likely to be beneficial.\textsuperscript{26,27}

Because there are no absolutely reliable criteria on an individual basis by which to distinguish a truly nonprogressive cancer from one that is progressive (and thus avoid overtreatment), the rate of overdiagnosis can only be estimated by determining whether there is excess incidence after a long duration of follow-up in a group exposed to screening compared with an unexposed group.\textsuperscript{28} Overdiagnosis is most common in screen-detected prostate cancer\textsuperscript{29,30} and, to a much lesser extent, in breast cancer, of which a greater fraction of ductal carcinoma in situ may represent overdiagnosis compared with invasive disease.\textsuperscript{28,31} Overdiagnosis in lung cancer screening also is a concern because of both inappropriate screening and the detection of nonprogressive cancers, although there is comparatively much less evidence from which to derive estimates given the limited duration of follow-up in existing studies\textsuperscript{32} and the low population screening rates.\textsuperscript{19} Intuitively, it would seem that overdiagnosed cancers are those with the least aggressive features and, although generally this may be true, these features may simply distinguish a cancer that is slower growing and has less lethal potential compared with a faster growing, more aggressive cancer. Recent decisions to increase the threshold of a positive scan from 4 to 6 mm\textsuperscript{33,34} may contribute to reducing overdiagnosis by reducing the detection of a high volume of mostly benign nodules that may also include some nonprogressive malignancies. Greater attention to avoiding screening adults who have life-limiting comorbidity will reduce overdiagnosis that occurs when a patient would have died from another cause before their lung cancer was detected by screening, and it is possible that treatment may be postponed or avoided altogether for some patients who have adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma, which previously were classified as bronchioloalveolar carcinoma.\textsuperscript{35} Although the detection of invasive cervical cancer and CRC is not considered to be subject to overdiagnosis, the considerable rate of detection and treatment of precursor lesions, most of which will not become cancer, leads to interventions that ultimately may be judged to have been unnecessary, because the majority of these lesions are nonprogressive. However, the detection and treatment of precursor lesions to prevent progression of the small fraction of high-risk lesions is a goal of cervical and CRC screening. Although it may seem appropriate to broaden the concept of overdiagnosis to include these lesions, the definition of overdiagnosis should be confined to in situ and invasive tumors.

The increasing use of diagnostic imaging has led to the incidental overdiagnosis of several types of cancer, particularly thyroid\textsuperscript{36,37} and kidney cancer,\textsuperscript{38} but, in the United States, screening for these cancers is not recommended. Although the absolute risk of overdiagnosis in a population that attends screening is substantially lower than the risk of being diagnosed with a progressive cancer, determining how to avoid overdiagnosis and overtreatment of both nonprogressive and progressive cancers is an important research priority.

**Screening Guidelines**

Organizations that develop screening guidelines must carefully and systematically evaluate the evidence and then make a judgment about the relative balance of benefits and harms to arrive at recommendations for policy makers, clinicians, and the public. If benefits clearly outweigh harms, then there should be an effort to implement high-quality screening, and the target population should be informed about the screening test, including their role (ie, the importance of adherence to regular screening) and the benefits, limitations, and potential harms. If benefits are proven but the balance of benefits and harms is close, then a direct recommendation for screening should not be made; rather, a shared decision-making conversation between the patient and the provider should take place with eligible individuals, discussing potential benefits and harms, to help guide the individual to a value-based decision to undergo or forgo screening. For some emerging technologies, evidence is insufficient to recommend for or against screening, and individuals should be counseled that there may not be enough information to confidently describe benefits and harms.
Finally, when evidence shows that a screening test is ineffective or that harms clearly outweigh benefits, a guideline should recommend against its use. Guideline developers should rate the strength of the evidence supporting each recommendation, and these ratings should be applied when rating of the strength of the recommendation.

The remainder of this article reviews the current status of screening for breast, colorectal, cervical, prostate, and lung cancer screening, including the burden of disease, screening guidelines (summarized in Table 1), utilization of screening, and a blueprint for initiatives specific to each cancer, as well as initiatives that are cross-cutting and represent opportunities to achieve higher performance from screening than is being achieved today and to prepare for future opportunities for improved disease control.

Breast Cancer
Breast cancer is the most common cancer diagnosed in US women, and the second leading cause of cancer death, accounting for 30% of cancers diagnosed and 14% of cancer deaths in women. The ACS estimates that 266,120 invasive breast cancers and 63,960 ductal carcinoma in situ (DCIS) cancers will be diagnosed in US women in 2018 and that 40,920 women will die from breast cancer. Among US women, the lifetime risk of breast cancer is 12.4% (1 in 8 women), the median age at diagnosis is 61 years, and the median age of death is 68 years. The 5-year survival rate is 99% when breast cancer is diagnosed while still localized to the breast, 85% for regional disease, but only 27% when distant metastases are present; for the period from 2008 to 2014, the distribution of localized, regional, and distant metastases was 62%, 31%, and 6%, respectively. Breast cancer is much less common in men—approximately 2550 new cases and 480 deaths are estimated to occur in men in 2018.

Trends in Incidence and Mortality
For the period from 2006 to 2015, delay-adjusted breast cancer incidence rates increased at an average annual percentage change (AAPC) of 0.4% per year, mostly attributable to increases in incidence among Hispanic and black women and Asians/Pacific Islanders. From 1989 to 2015, the death rate from female breast cancer dropped 39%, generally attributable to earlier diagnosis through screening and improvements in therapy, and very likely the contribution over time of greater alertness to breast changes, leading to earlier diagnosis of symptomatic disease, which is an indirect benefit of the influence of screening programs on awareness of the importance of early detection. This higher level of awareness and readiness to report changes to a clinician has been shown in RCTs to result in the diagnosis of smaller palpable tumors among women diagnosed with interval cancers compared with women in a control group, resulting in a lower rate of breast cancer mortality.

Screening Guidelines
Breast cancer screening has been recommended since the late 1970s, when the ACS and the National Cancer Institute first issued joint recommendations to guide screening in the Breast Cancer Detection Demonstration Project. The ACS guideline for breast cancer screening was last updated in 2015 (Table 1). There are relatively minor differences in the breast cancer screening guidelines of major medical and public health organizations. The main difference concerns the age at which mammography screening should start without the need for shared decision making and the recommended age-specific screening intervals, which, in turn, are influenced by different approaches to assessing the burden of disease, evaluating the evidence for the benefit of screening, the age to stop screening, and different judgements about the balance of benefits and harms. All major guidelines recommend that women have the opportunity to choose to start screening at age 40 years; some recommend using a shared decision-making process for women in their early 40s, and some recommend using a shared decision-making process throughout the age range from 40 to 49 years. Some guidelines recommend stopping screening at age 75 years, whereas others emphasize overall health status and projected longevity as the basis for the decision to stop screening.

Trends in Breast Cancer Screening
The most recent data from the National Health Interview Study (NHIS) (2015) indicate that mammography screening rates have changed very little over the 10-year period from 2005 to 2015 (Table 2). Table 3 lists reported breast cancer screening rates in 2015 by race/ethnicity, health insurance status among adults aged <64 years, and education. A meta-analysis of the accuracy of self-reported screening, compared with medical records, found that the sensitivity of self-reported mammography was high (95%), but the specificity was lower (61%), and that Hispanic and black women had lower concordance, leading to an overestimate of screening prevalence in national surveys and the potential underestimation of differences between racial/ethnic groups.

Benefits, Limitations, and Harms
There have been 10 prospective RCTs of mammography screening, including 3 in North America and 7 in Europe. These studies were initiated over a period of 28 years (1963-1991), during which substantial evolution in both imaging technology and screening protocols occurred.
### TABLE 1. American Cancer Society Recommendations for the Early Detection of Cancer in Average-Risk, Asymptomatic Adults<sup>a</sup>

| CANCER SITE | POPULATION | TEST OR PROCEDURE | RECOMMENDATION |
|-------------|------------|-------------------|----------------|
| Breast      | Women aged 40-54 y | Mammography | Women should undergo regular screening mammography starting at age 45 y; women aged 45 to 54 y should be screened annually; women should have the opportunity to begin annual screening between ages 40 and 44 y |
|             | Women aged 55 y and older | Mammography | Women aged 55 y and older should transition to biennial screening or have the opportunity to continue screening annually; women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 y or longer |
| Cervix      | Women, aged 21-29 y | Pap test | Cervical cancer screening should begin at age 21 y; for women aged 21-29 y, screening should be done every 3 y with conventional or liquid-based Pap tests |
|             | Women, aged 30-65 y | Pap test and HPV DNA test | For women ages 30-65 y, screening should be done every 5 y with both the HPV test and the Pap test (preferred), or every 3 y with the Pap test alone (acceptable) |
|             | Women aged 66 y and older | Pap test and HPV DNA test | Women aged 66 y and older who have had 3 or more consecutive negative Pap tests or 2 or more consecutive negative HPV and Pap tests within the last 10 y, with the most recent test occurring in the last 5 y, should stop cervical cancer screening |
|             | Women who have had a total hysterectomy | — | Women who have had a total hysterectomy should stop cervical cancer screening |
| Colorectal  | Men and women aged 45-75 y, for all tests listed | Fecal immunochemical test (annual); or high-sensitivity, guaiac-based fecal occult blood test (annual); or multi-target stool DNA test (every 3 y, per manufacturer’s recommendation); or colonoscopy (every 10 y); or CT colonography (every 5 y); or flexible sigmoidoscopy (every 5 y) | Adults aged 45 y and older should undergo regular screening with either a high-sensitivity, stool-based test or a structural (visual) examination, depending on patient preference and test availability; as part of the screening process, all positive results on noncolonoscopy screening tests should be followed with timely colonoscopy; adults in good health with a life expectancy of greater than 10 y should continue screening through the age of 75 y |
|             | Men and women aged 76-85 y | — | Screening decisions should be individualized, based on patient preferences, life expectancy, health status, and prior screening history; if a decision is made to continue screening, the patient should be offered options as listed above |
|             | Men and women older than 85 y | — | Individuals should be discouraged from continuing screening |
| Endometrial | Women, at menopause | — | At the time of menopause, women should be informed about the risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physicians |
| Lung        | Current or former smokers aged 55-74 y in good health with at least a 30–pack-y history of smoking | Low-dose helical CT | Annual screening in adults who: currently smoke or have quit within the past 15 y; and have at least a 30–pack-y smoking history; and receive evidence-based smoking-cessation counseling, if they are current smokers; and have undergone a process of informed/shared decision making that included information about the potential benefits, limitations, and harms of screening with low-dose CT; and have access to a high-volume, high-quality lung cancer screening and treatment center |
| Prostate    | Men, aged 50 y and older | Prostate-specific antigen test with or without digital rectal examination | Men who have at least a 10-y life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer after receiving information about the potential benefits, risks, and uncertainties associated with prostate cancer screening; prostate cancer screening should not occur without an informed decision-making process |

Abbreviations: CT, computed tomography; HPV, human papillomavirus; Pap, Papanicolaou.

<sup>a</sup>All individuals should become familiar with the potential benefits, limitations, and harms associated with cancer screening.
Individual RCTs and meta-analyses of these trials demonstrated the efficacy of an invitation to breast cancer screening on reducing breast cancer mortality of approximately 20%, whereas age-specific meta-analyses of reported RCT results have tended to show more favorable mortality reductions among women invited to screening who were aged 50 to 69 years at the time of randomization compared with women who were randomized in their 40s (21% and

| CANCER SITE | 2005 | 2008 | 2010 | 2013 | 2015 | ABSOLUTE CHANGE: 2015 to 2005, % |
|-------------|------|------|------|------|------|----------------------------------|
| CRC: Adults aged 50 y and older | | | | | | |
| Up to date<sup>b</sup> | 46.8 | 53.2 | 59.1 | 58.6 | 62.6 | 15.8 |
| Up to date (including CT colonography)<sup>c</sup> | — | — | 59.2 | — | 62.6 | 20.6 |
| Colonoscopy in the past 10 y | 39.2 | 48.0 | 55.5 | 55.2 | 59.8 | 20.6 |
| Sigmoidoscopy in the past 5 y | 3.9 | 2.2 | 3.5 | 3.6 | 2.5 | —1.5 |
| Stool-based testing in the past y<sup>d</sup> | 12.1 | 10.0 | 8.8 | 7.8 | 7.2 | —4.9 |
| CT colonography in the past 5 y | — | — | <1.0<sup>e</sup> | — | <1.0<sup>e</sup> | |
| CRC: Adults aged 45 y and older | | | | | | |
| Up to date<sup>b</sup> | 40.7 | 44.7 | 51.9 | 51.9 | 55.4 | 14.7 |
| Up to date (including CT colonography)<sup>c</sup> | — | — | 52.0 | — | 55.5 | 18.8 |
| Colonoscopy in the past 10 y | 34.1 | 42.0 | 48.6 | 48.7 | 52.9 | 18.8 |
| Sigmoidoscopy in the past 5 y | 3.3 | 1.9 | 3.1 | 3.3 | 2.2 | —1.1 |
| Stool-based testing in the past y<sup>d</sup> | 10.5 | 8.7 | 7.6 | 6.8 | 6.3 | —4.2 |
| CT colonography in the past 5 y | — | — | <1.0<sup>e</sup> | — | <1.0<sup>e</sup> | |
| Breast cancer: Women aged 40 y and older | | | | | | |
| Mammogram in the past y | 51.2 | 53 | 50.8 | 51.3 | 50.2 | —1.0 |
| Breast cancer: Women aged 40-54 y | | | | | | |
| Mammogram in the past y | 49.3 | 49.4 | 48.8 | 50.0 | 48.4 | —0.9 |
| Breast cancer screening: Women aged 55 y and older | | | | | | |
| Mammogram in the past y | 54.1 | 57.9 | 54.2 | 53.9 | 53.1 | —1.0 |
| Mammogram in the past 2 y | 69.0 | 71.5 | 69.1 | 69.4 | 67.7 | —1.3 |
| Cervical cancer: Women aged 21-65 y | | | | | | |
| Pap test in the past 3 y<sup>f</sup> | 85.4 | 84.6 | 83.1 | 80.9 | 81.6 | —3.8 |
| Prostate cancer: Men aged 50 y and older | | | | | | |
| PSA test in the past y<sup>g</sup> | 40.7 | 44.1 | 41.3 | 34.5 | 34.4 | —6.3 |
| Lung cancer among high-risk smokers aged 55-80 y<sup>h</sup> | | | | | | |
| LDCT in the past y | — | — | 3.3 | — | 3.9 | — |

Abbreviations: CRC, colorectal cancer; CT, computed tomography; LDCT, low-dose computed tomography; Pap, Papanicolaou; PSA, prostate-specific antigen.

<sup>a</sup>Estimates for colorectal, breast, cervical, and prostate cancer screening are age-adjusted to the 2000 US standard population.

<sup>b</sup>Up-to-date CRC screening included stool-based tests within the preceding year, or sigmoidoscopy within the preceding 5 years, or colonoscopy within the preceding 10 years.

<sup>c</sup>Up-to-date CRC screening included stool-based tests within the preceding year, or sigmoidoscopy within the preceding 5 years, or colonoscopy within the preceding 10 years, or CT colonography in the past 5 years. Data on CT colonography were collected only in 2010 and 2015.

<sup>d</sup>Stool-based tests included fecal occult blood tests or fecal immunochemical tests using a home test kit.

<sup>e</sup>The relative standard error exceeds 30% (unstable estimate); the estimated prevalence was <1%.

<sup>f</sup>Pap testing was measured among women with intact uterus.

<sup>g</sup>PSA testing was measured among men without a history of prostate cancer.

<sup>h</sup>Lung cancer screening was among high-risk smokers, defined as individuals aged 55 to 80 years who have a smoking history of 30 or more pack-years and currently smoke or have quit within the past 15 years.
| SCREENING SITE | RACE AND ETHNICITY, % | HEALTH INSURANCE: AGE <64 YEARS, % | EDUCATIONAL LEVEL, % |
|---------------|-----------------------|-----------------------------------|----------------------|
|               | HISPANIC              | WHITE, NON-HISPANIC                | BLACK, NON-HISPANIC  | ASIAN    | YES | NO | SOME HIGH SCHOOL OR LESS | HIGH SCHOOL DIPLOMA OR GED | SOME COLLEGE | COLLEGE GRADUATE |
| CRC: Adults aged 50 y and older | | | | | | | | |
| Up to date<sup>b</sup> | 49.9 | 65.4 | 61.8 | 49.4 | 59.6 | 25.1 | 47.4 | 58.6 | 64.3 | 71.3 |
| Up to date (including CT colonography)<sup>c</sup> | 50.0 | 65.5 | 61.8 | 49.1 | 59.6 | 25.1 | 47.4 | 58.5 | 64.4 | 71.3 |
| Colonoscopy in the past 10 y | 46.8 | 63.0 | 58.3 | 44.3 | 56.4 | 23.5 | 44.7 | 56.1 | 61.3 | 68.4 |
| Sigmoidoscopy in the past 5 y | 3.3 | 2.4 | 2.5 | 2.0 | 1.9 | <1.0<sup>d</sup> | 2.8 | 1.8 | 2.4 | 3.0 |
| Stool-based testing in the past y<sup>e</sup> | 7.3 | 6.9 | 8.0 | 9.2 | 6.2 | 4.0 | 6.3 | 7.1 | 7.2 | 7.7 |
| CT colonography in the past 5 y<sup>f</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> |
| CRC: Adults aged 45 y and older | | | | | | | | |
| Up to date<sup>b</sup> | 41.4 | 58.7 | 55.1 | 43.1 | 47.6 | 20.8 | 41.4 | 51.9 | 57.3 | 62.8 |
| Up to date (including CT colonography)<sup>c</sup> | 41.4 | 58.8 | 55.2 | 42.9 | 47.7 | 20.8 | 41.4 | 51.8 | 57.4 | 62.9 |
| Colonoscopy in the past 10 y | 38.6 | 56.4 | 51.8 | 38.6 | 45.1 | 19.4 | 38.8 | 49.6 | 54.5 | 60.2 |
| Sigmoidoscopy in the past 5 y | 2.9 | 2.1 | 2.2 | 1.8 | 1.6 | <1.0<sup>d</sup> | 2.5 | 1.5 | 2.1 | 2.5 |
| Stool-based testing in the past y<sup>e</sup> | 6.1 | 6.1 | 7.1 | 7.7 | 4.8 | 3.2 | 5.5 | 6.2 | 6.3 | 6.8 |
| CT colonography in the past 5 y<sup>f</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> | <1.0<sup>d</sup> |
| Breast cancer: Women aged 40 y and older | | | | | | | | |
| Mammogram in the past y<sup>g</sup> | 45.7 | 50.3 | 55.4 | 47.1 | 52.5 | 20.9 | 38.9 | 45.0 | 51.2 | 57.9 |
| Breast cancer: Women aged 40-54 y | | | | | | | | |
| Mammogram in the past y<sup>g</sup> | 43.7 | 48.3 | 55.2 | 49.8 | 51.6 | 20.3 | 39.9 | 41.3 | 50.0 | 53.8 |
| Breast cancer screening: Women aged 55 y and older | | | | | | | | |
| Mammogram in the past y<sup>g</sup> | 49.0 | 53.5 | 56.5 | 47.0 | 57.4 | 20.3 | 39.5 | 50.4 | 53.7 | 62.0 |
| Mammogram in the past 2 y<sup>g</sup> | 65.4 | 68.0 | 70.9 | 60.1 | 74.1 | 31.4 | 51.9 | 64.7 | 67.8 | 78.1 |
| Cervical cancer: Women aged 21-65 y | | | | | | | | |
| Pap test in the past 3 y<sup>d</sup> | 77.4 | 83.1 | 84.7 | 73.3 | 84.4 | 60.8 | 69.9 | 75.1 | 83.9 | 88.6 |
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These age-specific differences are less evident in the evaluation of modern service-screening data in settings where women in their 40s are invited to screening. Although there have been long-standing debates related to the overall and age-specific findings among the individual trials, ranging from no mortality reduction to reductions exceeding 40% after 13 years of follow-up, the mortality outcomes of the RCTs are strongly associated with the effectiveness of the protocol and the influence of the attendance rate on reducing the overall relative risk of a diagnosis of advanced disease. Reducing the diagnosis of advanced cancer is the fundamental goal of screening, and this observation is an important lesson for modern screening programs.

The RCTs clearly demonstrated the efficacy of detecting occult breast cancer, but meta-analysis estimates from the RCTs of the efficacy of an invitation to screening (attenders and nonattenders) underestimated the benefit of modern mammography screening at the population level and among women who attend screening. More recently, the accumulation of well-designed observational studies of modern service screening has provided new evidence on the effectiveness of population-based mammography screening programs and estimates of the benefits of mammography screening among women who actually attend screening. Given the background of RCT evidence and the greater ability to adjust for known biases based on evidence from the experimental studies, there has been growing acceptance of moving beyond the RCTs as the “best” estimate of the benefit of modern mammography screening.

Mammography screening has inherent limitations in the detection of breast cancer. Sensitivity and specificity improve as women age, mostly because of the reduction in mammographic breast density. The accuracy of mammography decreases with increasing mammographic breast density because of masking (ie, the obscuring of a breast cancer by dense breast parenchyma). Inadequate positioning of the breast may lead to breast tissue not being included on the mammographic image, and inadequate compression can result in poor image quality. Interpreting physicians vary in their ability to accurately read a mammogram, resulting in a wider than optimal range of recall rates and sensitivity. The harms associated with mammography...
include being recalled for further evaluation and the associated short-term anxiety experienced by some women,\textsuperscript{64} false-positive mammography resulting in biopsy, and the theoretically rare possibility that repeated exposures to radiation during imaging examinations could cause breast cancer.\textsuperscript{65}

Assessments of the accuracy of mammography interpretation in the United States demonstrate considerable variation among interpreting physicians. Lehman et al established interpretation benchmarks for digital mammography, measuring the performance of 359 radiologists across 95 facilities in 6 Breast Cancer Surveillance Consortium registries.\textsuperscript{60} Mean screening performance measures were estimated for the recall rate (11.6%), the cancer detection rate per 1000 screening examinations (5.1), sensitivity (86.9%), and specificity (88.9%). Although 92% of radiologists were within the recommended ranges for sensitivity, only 63% achieved the recommended levels of specificity.\textsuperscript{60,66–70} The sensitivity and specificity of mammography are improved if prior studies are available to the interpreting physician.\textsuperscript{71,72} Hayward et al evaluated outcomes of over 46,000 consecutive mammograms and observed a recall rate 16.6% when prior examinations were not compared, but the rate was only 7.8% when 1 prior examination was available for comparison, and it was 6.3% when 2 or more prior examinations were available.\textsuperscript{71} A statistically significant improvement in the cancer detection rate of 2.3 cases per 1000 examinations also was observed for mammograms that were interpreted with multiple prior examinations versus a single prior examination.\textsuperscript{71} Ideally, not only the prior mammogram but also additional prior examinations should be available to radiologists to improve the accuracy of interpretation, improve sensitivity, and reduce the recall rate and associated anxiety.

Breast imaging technology has evolved since the introduction of mammography, from film to digital image receptors. Currently, full-field digital mammography (FFDM) is rapidly being replaced by DBT, also known as 3-dimensional (3D) mammography.\textsuperscript{73} Digital mammography has a performance similar to that of film-screen mammography in women aged 50 to 79 years; however, sensitivity is improved in women aged 40 to 49 years because of the higher prevalence of mammographic breast density, but at a cost of reduced specificity.\textsuperscript{74} The unique feature of DBT is the ability to take images of the breast from different angles to produce both 2D and pseudo-3D images of the breast. The 3D image allows radiologists to look through the breast, eliminating the influence of superposition (ie, overlapping layers of breast tissue that can obscure the ability to see cancer or give the appearance of an abnormality when none is present). Studies to date trend in the direction of showing that DBT has superior, or at least equivalent, performance compared with 2D mammography in terms of both sensitivity and specificity and appears to have some additional advantages compared with FFDM in screening performance among women with mammographically dense breasts, defined as a mammographic density >50%.\textsuperscript{75,76} A large prospective trial comparing FFDM versus DBT has been launched to determine whether DBT is superior to FFDM in reducing the detection rate of advanced breast cancer.\textsuperscript{8}

Breast density is an independent risk factor for breast cancer\textsuperscript{77} and is associated with reduced mammographic accuracy because of masking and superimposition of dense tissue.\textsuperscript{78,79} The accuracy of mammography decreases with increasing mammographic breast density, and women with significant mammographic breast density are at higher risk of false-negative findings, interval cancers, the diagnosis of a more advanced breast cancer, and breast cancer mortality.\textsuperscript{61,80} Although test sensitivity for women with dense breast tissue has improved with the evolution of mammography technology, sensitivity still is inversely associated with various measures of increased density and, among women with the highest breast density (Breast Imaging-Reporting and Data System type 4), mammography is largely ineffective for breast cancer screening. Greater awareness of the association between mammographic breast density and reduced sensitivity has led a growing number of states to pass legislation mandating that mammography reports communicate information about a woman’s breast density so that she will be informed that the interpretation of her mammogram may be limited by the presence of masking and that she may wish to seek supplemental screening with ultrasound, DBT, or magnetic resonance imaging (MRI).\textsuperscript{81} Each of these technologies consistently has demonstrated an increase in the detection rate of favorable stage cancers among women with mammographically occult breast cancer, in particular MRI.\textsuperscript{82,83} However, lack of infrastructure, workforce limitations, provider awareness and readiness to provide counseling, variation in coverage by health plans (uncertainty about which women with potential for masking will truly benefit from supplemental imaging), costs, and willingness to incur out-of-pocket costs have limited the uptake of supplemental screening.\textsuperscript{82,84–88}
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Colorectal Cancer

CRC is the third most common cancer diagnosed in women and men, the third most common cause of cancer-related death in women and men, and the second leading cause of cancer death in US adults when men and women are combined, accounting for 8% of cancers diagnosed and 8% of cancer deaths. The ACS estimates that 140,250 cases of invasive CRC will be diagnosed among US women and men in 2018 and that 50,630 women and men will die from the disease. For men, the lifetime risk of being diagnosed with CRC is 4.5% (1 in 22 men), whereas the lifetime risk for women is 4.2% (1 in 24 women); among men, the median age at diagnosis and death is 66 and 70 years, respectively, and, among women, the median age at diagnosis and death is 69 and 76 years, respectively. The 5-year survival rate is 90% when CRC is diagnosed while still localized, 71% for regional disease, but only 14% when distant metastases are present; for the period from 2008 to 2014, the distribution of localized disease, regional spread, and distant metastases was 39%, 35%, and 21%, respectively.

Trends in CRC Incidence and Mortality

For the period from 2006 to 2015, delay-adjusted CRC incidence rates decreased at an AAPC of −2.5% per year. Declines in incidence before 2000 have been attributed to the combination of screening and risk factor modification, whereas declines since 2000 are chiefly attributed to the high prevalence of screening with colonoscopy and the removal of precursor lesions. Between 1970 and 2015, mortality from CRC has declined 52%. In contrast to overall trends, among adults younger than 55 years, there was a 51% increase in the incidence of CRC from 1994 to 2014 and an 11% increase in mortality from 2005 to 2015. Increased incidence rates in younger adults have been particularly notable for rectal cancer, doubling between 1991 (2.6 per 100,000 population) and 2014 (5.2 per 100,000 population) in individuals aged 20 to 49 years. Siegel et al demonstrated that this rising incidence was the result of a strong birth cohort effect, which is expected to carry forward with age. A recent analysis indicated that adults born around 1990 have twice the risk of colon cancer and 4 times the risk of rectal cancer compared with adults born around 1950, who have the lowest risk. Deaths also have been increasing in adults younger than 55 years at an annual percentage rate of approximately 1% per year between 2005 and 2014.

Screening Guidelines for CRC

CRC screening has been recommended since the 1970s, but the first formal guideline was issued by the ACS in 1980. The most recent update of the ACS CRC screening guideline was in 2018 (Table 1).

The principle options for CRC screening are either a stool-based test (fecal immunochemical test [FIT] annually; high-sensitivity, guaiac-based fecal occult blood test [HS-gFOBT] annually; multitarget stool DNA test [mt-sDNA] every 3 years) or a structural examination (colonoscopy every 10 years, computed tomography colonography [CTC] every 5 years, and FS every 5 years). Apart from the ACS now recommending that CRC screening begin at age 45 years, there are relatively minor differences in the CRC screening guidelines of major medical and public health organizations. The USPSTF, which updated their CRC screening recommendation in 2016, recommends beginning screening at age 50 years and adds an additional FS option (FS every 10 years combined with annual FIT). In 2017, the US Multi-Society Task Force...
preferentially recommended screening with colonoscopy every 10 years or annual FIT for individuals declining colonoscopy while still endorsing the other screening methods described as second-tier tests.99

Trends in CRC Screening
The most recent data from the NHIS (2015) indicate that CRC screening rates increased from 46.8% in 2005 to 62.6% in 2015 (Table 2). Although screening rates are rising, screening in adults aged 50 to 54 years lags well behind screening in those older than 60 years. In the 2015 NHIS data, only 48% of adults aged 50 to 54 years report being up to date with screening.47 Table 3 shows reported CRC screening rates in 2015 by race/ethnicity, health insurance status among adults younger than 64 years, and education.47

Benefits, Limitations, and Harms
There is good evidence from RCTs that screening for CRC with a gFOBT or FS is associated with a reduction in CRC incidence and mortality.6,97,100–102 Screening is associated with a reduction in CRC incidence through the detection and removal of precursor lesions during colonoscopy after a positive noncolonoscopy screening test or the direct identification of such lesions during a screening colonoscopy. CRC mortality is reduced through reduced incidence or the detection of occult cancers during screening. On the basis of the RCT evidence supporting the efficacy of stool testing and structural examinations, the evidence of benefit for all other analogous screening tests has been accepted based on observational studies of test performance data demonstrating the ability to detect early-stage CRC and/or advanced adenomas.102,103

Evidence from the Cancer Intervention and Surveillance Modeling Network (CISNET) CRC Group microsimulation modeling analyses also has provided support for comparing long-term outcomes in the US population of various testing strategies and the projected burden and harms associated with different screening strategies based on projected lifetime colonoscopies and adverse events.104 These models104–106 have been used to provide supporting evidence for both USPSTF98 and ACS97 CRC screening recommendations. The long-term similarity of the benefit among recommended strategies is evident in the Microsimulation Screening Analysis (MISCAN) model estimates of CRC deaths avoided (19-22 deaths) and life-years gained (215-248 life-years gained) for 1000 adults aged 40 years who undergo screening between ages 50 and 75 years.104

Adverse experiences associated with colonoscopy mostly are associated with bowel preparation, abdominal pain, examination-related pain, and vasovagal syncope or presyncope. Significant harms associated with CRC screening are rare and principally are those associated with colonoscopy (bleeding, perforation, cardiorespiratory complications of sedation) as a primary screening test or as a follow-up of positive noncolonoscopy tests, and the risk of harms is greater in older adults compared with younger adults and those with significant comorbidity.102,107,108 Colonoscopy also is associated with a small increased risk of cardiovascular events within 30 days postprocedure, and the risk typically is higher in older adults. In one study of Medicare beneficiaries, the rate of cardiovascular events within 30 days that required hospitalization or emergency department visits was 0.45 per 1000 procedures.109 In a separate study of registry data, the 30-day event rate for angina, myocardial infarction, stroke, or transient ischemic attack was 1.4 per 1000 procedures, with the risk increasing with age, comorbid conditions, and procedures during the examination.110 The harm conventionally associated with a workup of false-positive test results from noncolonoscopy CRC screening tests is partly mitigated when a follow-up colonoscopy is interpreted as normal, which removes the patient from the screening pool for 10 years, per recommended screening intervals after a normal colonoscopy.

No direct harms are associated with undergoing HS-gFOBT, FIT, or mt-sDNA (apart from the stress associated with positive tests111), as noted above, and the harms associated with stool testing principally are those that may occur during follow-up colonoscopy. However, concerns have been raised about the situation in which an mt-sDNA test is positive and colonoscopy is negative, based on the assumption that a test that is sensitive for exfoliated DNA may have detected an indication of cancer in another organ. Whereas the few follow-up studies that have been undertaken have not identified any excess non-CRC cancer rate or excess mortality,112 more reassuring evidence about unresolved positive test results comes from a recent study by Cooper et al, who retested 12 patients with prior positive mt-sDNA and negative colonoscopy results 11 to 29 months after the initial test. During reexamination, 7 patients had negative stool tests and colonoscopy; among the remaining 5 patients, 3 had positive findings on their follow-up colonoscopy (2 advanced adenomas and 1 nonadvanced adenoma), suggesting that the initial follow-up colonoscopies were false-negative findings.113

Adverse events associated with CTC are similar to those of colonoscopy and include events associated with bowel preparation, abdominal pain, examination-related pain, and vasovagal syncope or presyncope. Potentially more serious harms, although very rare, include perforation (estimated to occur in only 0.02 procedures) and the possibility of an induced cancer associated with radiation exposure from single or multiple examinations.102 As with any x-ray imaging test,
radiation exposure is cited as a potential harm, although the average dose from CTC (from <1 to 2 milliSieverts [mSv]),\textsuperscript{114} is less than the 3-mSv-per-year estimate of the average background radiation exposure in the United States.\textsuperscript{115} This low level of exposure every 5 years has been judged to be a negligible possible harm when considered within the context of the potential life-years gained from avoiding a premature death from CRC.\textsuperscript{116} A more common occurrence, which may or may not be beneficial in any individual case, is the identification of extracolonic findings during the screening examination. In a review of 21 studies, Lin et al observed that potentially important findings that warranted follow-up (E4 findings) ranged from 1.7\% to 12\%.\textsuperscript{102} The USPSTF systematic evidence review concluded that, based on empiric evidence, it remains unclear whether the detection of extracolonic findings represents a net benefit or harm.\textsuperscript{102}

Challenges and Opportunities to Increase the Effectiveness of CRC Screening

Despite the effectiveness of screening at reducing CRC incidence and mortality, CRC screening rates remain well below the rates of breast and cervical cancer screening prevalence.\textsuperscript{117} There are several, nonmutually exclusive barriers to CRC screening, including lack of awareness, physician recommendation, and cultural beliefs/fear as well as indirect and direct financial barriers.\textsuperscript{118} Increasing the uptake of CRC screening also faces unique barriers. Regardless of the choice of screening test, completing the multistep screening process demands a highly activated patient. An individual undergoing screening must either gather and submit the specimen for testing or must undergo a full bowel preparation (perceived and judged by many as arduous and unpleasant), potentially miss a day of work, and undergo a structural procedure with rare but important risks. Multicomponent interventions, which include patient and provider reminders and the removal of cost and structural barriers, have been shown to be effective at increasing CRC screening rates.\textsuperscript{119} For example, in federally qualified health centers where such interventions have been implemented, rates have risen 12\% in 5 years.\textsuperscript{120} Clinical trials have demonstrated that outreach and patient navigation are effective at boosting screening rates in underserved populations.\textsuperscript{121}

Although screening rates vary between ethnic and racial groups, the availability of colonoscopy and the ability to afford it are persistent and overarching barriers; depending on a patient’s insurance status, a colonoscopy for screening or follow-up may result in significant costs. The Patient Protection and Affordable Care Act (ACA) requires commercial plans to provide colonoscopy screening without cost-sharing, but a patient who is screened with any noncolonoscopy test that is positive will face copays for their follow-up colonoscopy. Colonoscopy cost-sharing has not been eliminated for some patients covered by Medicare. Patients with Medicare insurance who undergo a screening colonoscopy and have a polyp detected or who have a screening examination in response to a positive initial noncolonoscopy screen are subject to being charged deductibles and copays, which can be quite substantial. A Texas study demonstrated an 18\% increase in colonoscopy utilization when all copays were eliminated.\textsuperscript{122} Policy groups have endorsed legislation to eliminate cost-sharing for patients with Medicare who have a polyp identified during a screening examination.

Although options among stool test and structural examinations are available, the completion of each of them poses some complexity for the individual patient. Studies have shown that some people with a positive stool or noncolonoscopy visual test will not receive adequate or timely follow-up, even in integrated health systems where overall screening rates are high.\textsuperscript{123} In addition to addressing issues of follow-up, future technologies based on the detection of circulating molecular markers through blood testing hold the potential to increase screening rates in the persistently nonadherent population but must perform as well or better than currently available screening tests.

Despite these obstacles, awareness of the recommendation that everyone should be screened at least by age 50 years is high, screening rates are rising, and the goal of increasing CRC screening rates has been adopted almost universally as a cost-effective, highly valued public health imperative. Although screening rates are rising, screening in adults aged 50 to 54 years lags well behind screening in those older than 60 years. As noted above, in the 2015 NHIS, only 48\% of adults aged 50 to 54 years reported being up to date with screening.\textsuperscript{47} In light of the increasing risk for colon and rectal cancers in individuals born more recently, focusing on beginning screening either between ages 45 to 49 years, as recommended by the ACS, or absolutely no later than age 50 years, defines an important public health opportunity.

CRC screening has contributed to declining incidence and mortality from CRC, and, given that screening rates are rising, continued decline is virtually assured. Within a decade, it is highly pro 2006 to 2015, delay-adjusted prostate cancer incidence rates bable that CRC will no longer be the second leading cause of cancer-related death. The ACS, Centers for Disease Control and Prevention, and National Colorectal Cancer Roundtable’s 80\% by 2018 CRC screening campaign has catalyzed unified national action, and screening rates will continue to rise.\textsuperscript{124} CRC screening is highly cost-effective, largely because polyp detection and removal is far more common than the detection of cancer,
thus contributing to the avoidance of all treatment costs when CRC is prevented.

The ACS is currently working with multiple partners of the National Colorectal Cancer Roundtable and others to rebrand the 80% by 2018 effort beyond 2018, focusing on achieving 80% screening rates in all communities as quickly as feasible. This will demand unified effort and will, addressing all known barriers to screening while ensuring access to high-quality care.

Cervical Cancer

The ACS estimates that 13,240 cases of invasive cervical cancer will be diagnosed among US women in 2018 and that 4170 women will die from the disease. For American women, the lifetime risk of cervical cancer is 0.6% (1 in 162 women), the median age at diagnosis is 50 years, and the median age of death is 58 years. The 5-year survival rate is 92% when cervical cancer is diagnosed while still localized, 56% for regional disease, but only 17% when distant metastases are present; for the period from 2008 to 2014, the distribution of localized disease, regional spread, and distant metastases was 45%, 36%, and 15%, respectively.

Trends in Cervical Cancer Incidence and Mortality

The declines in cervical cancer incidence and mortality since the midpoint in the past century are among the largest declines in the burden of a single cancer that have ever been observed. From the later 1940s until 1983 and 1984, cervical cancer incidence and mortality declined by 70% to 75%, a drop largely attributable to screening with cervical cytology. Average decreases in both incidence and mortality averaged approximately 4% per year during this period. More recently, for the period from 2006 to 2015, delay-adjusted cervical cancer incidence rates decreased at an AAPC of −0.2% per year. During this period, rates increased in white women at an AAPC of 0.5% per year but declined in black women at an AAPC of −3.6%. Among all US women, cervical cancer mortality declined from 2006 to 2015 at an AAPC of −0.7%; declines in white women occurred at an AAPC of −0.2%, whereas mortality rates declined in black women at an AAPC of −2.4%. Devesa et al noted in 1987 that rising rates of hysterectomy also were contributing to declines in mortality, because fewer women were at risk for cervical cancer. In 2017 Beavis et al reported that cervical cancer incidence and mortality rates actually were underestimated, because women who had undergone a hysterectomy were still included in the denominator from which these rates were estimated. The rates of cervical intraepithelial neoplasia grade III (CIN III) and AIS are significantly higher than the rates of invasive disease, and 4 population-based registries that collect data on CIN report an overall rate of CIN III/AIS of 47.0 per 100,000 population (range, 19.2–69.8 per 100,000 population).

Screening Guidelines for Cervical Cancer

The 2012 joint guideline of the ACS, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology recommends screening strategies and options based on a woman’s age, screening history, and choice of screening tests (Table 1). Additional details for managing cervical cancer screening in women who have abnormal findings or different levels of risk are detailed in the guideline.

The USPSTF recommendation statement for women at average risk of cervical cancer was updated in 2018 and is similar to the joint guidelines, with the exception that high-risk human papillomavirus (hrHPV) testing alone every 5 years is an additional option for women aged 30 to 65 years. It is expected that hrHPV testing alone eventually will replace cervical cytology screening in this age group and potentially for some women younger than 30 years. Guidance for hrHPV testing alone has been issued by a consortium of organizations, but it remains unclear at this time whether and how soon hrHPV testing alone will become broadly acceptable and accessible to women and clinicians.

Trends in Cervical Cancer Screening

The most recent data from the NHIS (2015) indicate that rates of cervical cancer screening with cytology every 3 years have declined from 85.4% in 2005 to 81.6% in 2015 (Table 2). Table 3 shows reported cervical cancer screening rates in 2015 by race/ethnicity, health insurance status among adults younger than 64 years, and education.

Benefits, Limitations, and Harms

The Papanicolaou (Pap) test is highly effective, although it is relatively “low tech” and has a significant error rate. Liquid-based cytology, in which a sample from the cervix is suspended in a fixative solution, dispersed, filtered, and distributed on a glass slide, has replaced the conventional Pap test as the most common form of cervical cytology. Although liquid-based cytology has equivalent sensitivity compared with the conventional Pap test, its technical quality is superior. The success of the Pap test in large part has been because of frequent, repeated testing, given the high false-negative rate observed with one-time testing (range, 28%–41%).

There is a strong association between persistent infection with certain hrHPV subtypes and cervical cancer. Testing for the presence of hrHPV DNA infection (hrHPV DNA) or hrHPV RNA is currently used for screening as a
cotest with the Pap test or to triage women who have abnormal cytologic test results, such as atypical squamous cells of undetermined significance and atypical glandular cells of undetermined significance and, in some countries, hrHPV testing alone is used for cervical cancer screening. There currently are 5 US Food and Drug Administration-approved HPV assays that use different technologies to identify the presence of high-risk genetic DNA from HPV or are specific for between 2 and 14 hrHPV types. HPV testing, whether as a stand-alone test or cotesting with the Pap test, measurably improves the sensitivity of cervical cancer screening compared with cytology alone, although at a cost of diminished specificity.

Harms linked to cervical cancer screening include short-term anxiety associated with positive test results and, for women who undergo colposcopy and biopsy, harms include pain, bleeding, and potential infection. Potential harms associated with the treatment of CIN include procedure-related harms, such as pain, bleeding, infection, etc, and longer term effects, such as weakening of the cervix, leading to an increased risk of preterm birth.

Challenges and Opportunities to Increase the Effectiveness of Cervical Cancer Screening
Screening for cervical cancer has profoundly altered cancer epidemiology for women in the United States, but the full potential of screening still is not being realized. Some women are not up to date with screening or have never been screened; in 2015, it was estimated that 14 million women had not had a recent cervical cancer screening. Clinical interventions, policy changes, and research directed at reaching these women is worthy of pursuit. In contrast, a recent survey revealed that 41% of physicians reported screening in excess of guidelines for at least 1 age group, including 10% who reported Pap testing in sexually active women younger than 21 years and 22% who reported annual Pap testing in women aged 21 to 29 years. Encouraging clinicians to adhere to recommended guidelines regarding screening interval is a worthwhile goal. The emergence of HPV immunization and testing undoubtedly will change our entire approach to the prevention of and screening for cervical cancer, and there is an expectation that hrHPV testing eventually will be the sole modality for cervical cancer screening.

Prostate Cancer
Among American males, prostate cancer is the most commonly diagnosed nonskin cancer and the second leading cause of cancer death. The ACS estimates that 164,690 cases of invasive prostate cancer will be diagnosed in US men in 2018, and 29,430 men will die from the disease. The lifetime risk of being diagnosed with prostate cancer is 11.6% (1 in 9 men), the median age at diagnosis is 66 years, and the median age at death is 80 years. The absolute risk is considerably higher in black men compared with white men; in black men, the 30-year risk from age 40 years is 15.9% (1 in 6.3 men), whereas for white men it is 10.9% (1 in 9.2 men). The 5-year survival rate is 100% when prostate cancer is diagnosed while still localized, 100% for regional disease, but only 30% when distant metastases are present; for the period from 2008 to 2014, the distribution of localized disease, regional spread, and distant metastases was 78%, 12%, and 5%, respectively.

Trends in Incidence and Mortality
The incidence of prostate cancer increased dramatically in the late 1980s and early 1990s after the commercial introduction of prostate-specific antigen (PSA) as a test for monitoring patients with prostate cancer quickly evolved into utilization for screening. This pattern of use resulted in a marked increase in prostate cancer incidence rates in the United States from 1988 to 1992, an AAPC of 16.5% among all men, and an AAPC of 23.4% among men younger than 65 years. From 1992 to 1996, incidence rates dropped 29%, exhibiting a classic pattern of a rise and fall in incidence consistent with the detection of a sizable prevalence of slow-growing, occult disease that potentially would have been detected subsequently if screening had not taken place; or never would have been detected because of the detection of a true, indolent prostate cancer; or death from another cause. Over the remainder of the 1990s decade, the incidence rate rose to “catch up” with the earlier, pretesting incidence trend and, since 2001, prostate cancer incidence rates have been declining. For the period from 2006 to 2015, delay-adjusted prostate cancer incidence rates have declined at an AAPC of −5.5% (−5.6% in white males and −5.0% in black males), and they have declined at an AAPC of −7.4% since 2011, the year that the USPSTF signaled that the prostate cancer screening recommendation would change from a recommendation for shared decision making to a recommendation against screening. From 1975 to 1987, prostate cancer mortality increased at an AAPC of approximately 1%, and it increased from 1987 to 1991 at an AAPC of 3%. Since 1991, prostate cancer mortality has declined in US men; in the most recent period (2006-2015), the AAPC in prostate cancer mortality has been −2.9% (−2.7% in white men and −4.2% in black men).
opportunity to make an informed/shared decision with their health care provider about whether to be screened for prostate cancer with serum PSA, with or without digital rectal examination, after receiving information regarding the benefits, risks, and uncertainties associated with prostate cancer screening (Table 1). The 2018 USPSTF guideline is similar to the ACS guideline, stating that decisions about prostate cancer screening should be individualized in men aged 55 to 69 years after a discussion of the potential benefits and harms of screening, incorporating values and preferences in their decision. The American Urology Association guideline also emphasizes shared decision making about the balance of benefits and harms associated with prostate cancer screening for men aged 55 to 69 years and recommends screening every 2 years for men who choose to be screened. The American Urology Association also recommend that screening decisions be individualized for higher risk men aged 40 to 54 years and for men older than 70 years in who are excellent health.

Trends in Prostate Cancer Screening and Shared Decision Making
In 2005, 41% of men aged 50 years and older reported having undergone a PSA test for prostate cancer screening in the previous year. Reported screening in the past year rose to 44% in 2008, but has declined since then to 35% in 2013, and has remained relatively stable between 2013 and 2015 (Table 2). Table 3 shows reported prostate cancer screening rates in 2015 by race/ethnicity, health insurance status among adults younger than 64 years, and education. The recent decline in PSA testing has been predominately attributed to the change in the USPSTF prostate cancer screening recommendation in 2012 from a recommendation for shared decision making to a recommendation against screening, which was then returned to shared decision making in the 2018 update. Data on shared decision making indicate that 63% of men aged 50 years and older reported receiving at least 1 element of shared decision making in 2015. During the same year, only 17% of men with a recent PSA test reported participating in full shared decision making, and receipt was even lower among men without a high school diploma compared with college graduates.

Benefits, Limitations, and Harms of Prostate Cancer Screening
Serum PSA is a glycoprotein secreted by epithelial cells of the prostate. As noted above, it was approved to monitor patients with prostate cancer for metastatic disease in 1989, but a significant proportion of US men already were undergoing testing before guidelines for screening were developed. Three large RCTs have evaluated the efficacy of screening for prostate cancer: 1) the US Prostate, Lung, Colorectal, and Ovarian Screening Trial (PLCO); 2) the European Randomized Study of Screening for Prostate Cancer (ERSPC); and 3) the recently published Cluster Randomized Trial of PSA Testing for Prostate Cancer. Only the ERSPC demonstrated a significant reduction in prostate cancer mortality associated with an invitation to screening (relative risk [RR], 0.79; 95% confidence interval [95% CI], 0.69-0.91). The PLCO, which concluded with an excess of prostate cancer deaths in the group invited to screening (RR, 1.04; 95% CI, 0.87-1.24), was significantly underpowered because of the prevalence of screening in the population before the start of the trial and in the control group during both the trial and the follow-up period. The Cluster Randomized Trial of PSA Testing for Prostate Cancer, which also did not demonstrate a statistically significant association between an invitation to a single round of PSA screening and prostate cancer mortality (RR, 0.96; 95% CI, 0.94-1.03), has been criticized for low uptake in the invited group (34%) and a nearly 40% prevalence of PSA testing in the general population during the study period. Tsodikov et al sought to reconcile the findings between the PLCO and the ERSPC by estimating the mean lead time (MLT) (ie, the average time that diagnosis is advanced by screening) gained in each arm of the 2 trials. To overcome the bias from control group contamination in the PLCO, the investigators treated the estimated MLT as a covariate to capture the level of screening in both arms of both studies. After adjustment for screening intensity and the influence of the MLT in reducing the risk of prostate cancer death, the investigators observed similar reductions in the expected risk of prostate cancer death over 11 years of follow-up, from 25% to 31% in the ERSPC and from 27% to 32% in the PLCO. These new findings reconcile the disparate results from the 2 RCTs and provide support for the conclusion that PSA screening is associated with a reduction in prostate cancer mortality. However, given the significant harms associated with prostate cancer treatment, the importance of informed/shared decision making before undergoing screening is not diminished.

There is considerable professional disagreement regarding the value of the PSA test for early prostate cancer detection, deriving largely from the finding that PSA does not distinguish less aggressive versus more aggressive prostate cancer and that there is no specific PSA threshold that can provide complete confidence that a man does not have prostate cancer. Vickers et al have argued that, in fact, PSA levels in previously unscreened men are strong predictors.
of prostate cancer death within 25 years and also that isoforms of PSA versus a single measure of PSA have the potential to be more informative about the underlying aggressiveness of the disease.

Harms associated with prostate cancer screening include false-positive findings, biopsy, and overdiagnosis. False-positive rates in the PLCO among men who had at least a single PSA test were 10.4%, and they were 12.6% among men in the screening arm who underwent 1 or more biopsies. False-positive rates in the ERSPC were higher (17.8%), which was attributable to a lower cutoff for a positive PSA. Complications associated with biopsy in the PLCO were low (2%) and consisted mostly of bleeding, urinary difficulties, and infection. Estimates of overdiagnosis in the PLCO, applying the method of excess incidence to screen-detected cancers only, were 20.7%. A modeling analysis by Gulati et al estimated that lower PSA thresholds for biopsy referral resulted in an increased risk of overdiagnosis. Although these protocols may be more appropriate for men at higher risk, they still may be associated with unacceptable tradeoffs. Because there is uncertainty about the balance of benefits and harms associated with prostate cancer screening, potential treatment-related harms are relevant to shared decision making. The most common treatment-related harms are urinary incontinence and erectile dysfunction, and the absolute risk of each varies according to type of treatment (radical prostatectomy, radiation therapy, or conservative management) and patient characteristics. In the Cancer Intervention Versus Observation Trial (PIVOT), among men who underwent radical prostatectomy, 17.1% experienced urinary incontinence, and 81.1% experienced erectile dysfunction, compared with 8.4% and 44.1%, respectively, in the group that received conservative management. When comparing radiation therapy with conservative management, a similar pattern of higher rates of harms is evident. However, across all treatment protocols, there is considerable variability in outcomes.

Challenges and Opportunities to Improve the Effectiveness of Prostate Cancer Screening

After years of responding to discordant screening guidelines, clinicians and the public can now move forward with a greater sense of certainty to implement prostate cancer screening using shared decision making for all eligible men. Not surprisingly, the percentage of men who report recent screening has declined since publication of the USPSTF 2012 recommendation to not screen for prostate cancer. Furthermore, many clinicians have not overcome barriers to routinely using shared decision making in presenting options for screening to men. As a result, it is likely that some clinicians simply recommend screening, recommend against screening, or do not discuss screening at all. One of the most important challenges to improving the quality of prostate cancer screening is helping primary care clinicians universally offer screening and to do so with a high-quality, shared decision-making process. The ACS has produced decision aids to help clinicians offer screening to men.

The optimal way to evaluate and manage men found to have an elevated PSA is evolving. The recognition that there is no level of PSA that can reliably rule out the presence of prostate cancer has led to considering PSA levels within the context of risk profiles. For example, the ACS guideline states that individual risk assessment should be considered for men with a PSA level between 2.5 and 4.0 ng/mL and that health care providers should consider an individualized risk assessment that incorporates other risk factors for prostate cancer, such as African American race, family history of prostate cancer, increasing age, an abnormal digital rectal examination, history of a prior negative biopsy, and age-specific PSA level. A widely used risk calculator, the Prostate Cancer Prevention Trial Prostate Cancer Risk Calculator, was first available in 2006 and was updated in 2012 to include the ability to predict the risk of low-grade (Gleason grade <7) versus high-grade prostate cancer, which can aid in making decisions about issues such as whether to undergo a biopsy. An alternative approach to risk stratification that integrates age, age-specific PSA levels, and risk factors into prostate cancer screening recommendations and the consideration of referral for biopsy has been proposed by investigators at the Memorial Sloan Kettering Cancer Center. These risk-stratification/decision-making algorithms are intended to increase the benefit of testing and reduce the harms associated with biopsy and treatment of low-risk prostate cancer.

Perhaps the greatest opportunity to improve the balance of benefits and harms is to continue to study how to predict the course of prostate cancer. The results of numerous treatment trials show that a subset of prostate cancers is aggressive, with significant risk of death, and a substantial subset is indolent. Efforts to distinguish clinically significant versus nonsignificant, localized prostate cancer include pathologic grading and genomic testing. The Gleason system, which sums the grades of biopsied tissue on a scale from 1 to 5 (from most to least differentiated cells) of the largest and next largest areas of the biopsied tissue, has substantially evolved during the 5 decades since its introduction. This means that a Gleason score 3 + 3 cancer (a score of 6) diagnosed today is much more likely to be indolent compared with a 3 + 3 cancer diagnosed 15 years ago. The current classification, which emphasizes grade groups rather than Gleason scores, was recently included in the
American Joint Committee on Cancer eighth edition staging manual. Instead of Gleason scores with a potential range of 2 through 10, the range for grade groups is 1 through 5. Gleason scores of 2 through 5, which are rarely used and should not even be considered as an interpretation based on core needle biopsies, have been condensed together with Gleason score 6 cancers (grade 3 + 3) into grade group 1. Classifying Gleason 3 + 3 cancers as 1 on a scale of 1 through 5 rather than 6 on a scale of 2 through 10 is intended to emphasize their indolent nature. Genomic profiles of less aggressive versus more aggressive tumors have been created. The tests used to assess the risk of progression are evolving, as is our understanding of the best way to use these tests in clinical decision making.

Recent evidence indicates that over 40% of men with lower Gleason score cancers detected on screening are now opting for active surveillance rather than immediate curative-intent treatment. Guidelines to help select men who should be offered active surveillance are now available. Increasing the percentage of men who choose active surveillance in the management of lower risk prostate cancer represents progress in reducing the rate of harms. The ability to make treatment decisions with greater certainty and confidence remains an important goal.

Lung Cancer
Lung cancer is the most common cancer diagnosed in the United States and is the leading cause of cancer death. The ACS estimates that 234,030 cases of invasive lung cancer will be diagnosed in US women and men in 2018, and 154,050 women and men will die from the disease. For men, the lifetime risk of being diagnosed with lung cancer is 6.9% (1 in 15 men), whereas for women, it is 5.9% (1 in 17 women); these are population estimates and do not reflect the much higher risk among current and former smokers nor the much lower risk among never-smokers. Among men, the median age at diagnosis and death is 70 and 72 years, respectively, and, among women, the median age at diagnosis and death is 71 and 76 years, respectively. The 5-year survival rate is 56% when lung cancer is diagnosed while still localized, 30% for regional disease, but only 5% when distant metastases are present; for the period from 2008 to 2014, the distribution of localized disease, regional spread, and distant metastases was 16%, 22%, and 57%, respectively.

Trends in Lung Cancer Incidence and Mortality
For the period from 2006 to 2015, delay-adjusted lung cancer incidence rates decreased at an AAPC of −2.0% per year and declined at a slightly higher AAPC (−2.2%) for the period from 2011 to 2015. Trends in lung cancer incidence and mortality vary by sex. Incidence rates in men have been declining since the 1980s, whereas the lung cancer incidence rate did not begin to decline in women until the mid-2000s, and the long-term rate (2003-2015) in men has been declining at approximately twice the rate compared with the decline observed in women. Among men, age-adjusted mortality rates have declined by 45% since 1990 and, among women, mortality rates have declined by 19% since 2002.

Screening Guidelines for Lung Cancer
The ACS lung cancer screening guideline was updated in 2013 and, in 2018, the wording of the guideline was modified to improve clarity (Table 1). Lung cancer screening guidelines for most organizations closely follow the age and risk study-eligibility criteria requirements for the National Lung Screening Trial (NLST), although there are some exceptions. The USPSTF updated their lung cancer screening recommendation in 2014, recommending lung cancer screening in adults aged 55 to 80 years who met the same smoking history and general health requirements listed above. The Centers for Medicare and Medicaid (CMS) covers lung cancer screening for Medicare beneficiaries according to the NLST criteria but will cover lung cancer screening until age 77 years. The National Comprehensive Cancer Network (NCCN) recommends annual lung cancer screening according to the NLST criteria for adults who do not have additional risk factors for lung cancer (group 1), although the NCCN does not have a stopping age, stating that an adult undergoing screening should continue screening until they are no longer candidates for definitive treatment. The NCCN recommends that adults who have additional risk factors for lung cancer (group 2), such as a personal history of other cancers or lung disease (chronic obstructive pulmonary disease and diffuse pulmonary fibrosis), a family history of lung cancer, radon exposure, and occupational exposure to carcinogens, that elevate their 5-year risk above 1.3% should begin screening at age 50 years if they have a history of at least 20 pack-years. Group 2 patients who are former smokers also should continue to undergo screening regardless of the time since they quit.

Trends in Lung Cancer Screening
The NHIS began collecting data on lung cancer screening in 2010. In 2010, 3.3% of adults who meet USPSTF criteria reported having had an LDCT for lung cancer screening in the past year and, in 2015, this proportion was similar at 3.9% (Table 2). Table 3 shows reported lung cancer screening rates in 2015 by race/ethnicity, health insurance status among adults younger than 64 years, and education.
Benefits, Limitations, and Harms

Spiral CT, also known as LDCT, uses an average 1.5 mSv of radiation to perform a lung scan in 15 seconds. On the basis of encouraging observational studies demonstrating the substantially superior performance of LDCT compared with chest x-ray in the detection of small, early-stage lung cancers, the NLST was launched in 2002. The NLST enrolled approximately 53,000 persons at high risk for lung cancer. With median follow-up of 6.5 years, there was a 20% relative reduction in lung cancer mortality compared with the chest x-ray arm and a 6.7% decrease in death from any cause in the LDCT group.

The principal benefit of lung cancer screening is the detection of small lung cancers that can be cured with modern treatment. All published studies indicate that lung cancer screening, even with the 4-mm threshold, is likely to be cost-effective, although the incremental cost-effectiveness ratio varies by risk. Thus, for the entire group of former and current smokers who meet the NLST screening eligibility criteria for screening, the actual risk for developing lung cancer varies considerably between individuals at lowest and highest risk, and recent studies suggest that the benefit of screening is higher in those at particularly high risk for lung cancer compared with those at the lower end of the risk spectrum. For example, a smoker aged 55 years who had a 30–pack-year history and a 60-year history of smoking has a substantially lower risk than a current smoker aged 60 with a 40–pack-year history. Others have suggested consideration of factors other than smoking history to more accurately predict the risk for developing lung cancer and that NLST eligibility criteria do not fully identify all individuals at high risk of lung cancer.

The limitations of lung cancer screening are not fully known. Although lung cancer-specific mortality was reduced by 20% in the NLST in the LDCT arm compared with the chest x-ray arm, and all-cause mortality was 7% lower, not all patients whose lung cancer was detected by screening avoided a lung cancer death. Thus, much remains to be learned about the factors associated with screening outcomes. Likewise, the fallest potential benefit of a program of lung cancer screening, including potential mortality reductions, are not known. The NLST protocol consisted of offering 3 annual examinations followed by 6 years of follow-up with no further screening. Continued annual screening likely would have contributed to additional benefit. Although a European trial has yet to publish final results, further refinement of lung cancer screening will depend mostly on observational studies to answer remaining and new questions.

Harms of lung cancer screening include radiation risks, false-positive results, harms associated with invasive diagnostic tests, and overdiagnosis. A radiation-induced lung cancer resulting from multiple screening and follow-up examinations is a theoretical possibility, although estimates suggest that the risk of a radiation-related lung cancer death resulting from LDCT screening is very small.

The NLST considered nodules of 4 mm or greater to be abnormal, warranting either short-term follow-up or other diagnostic evaluation. Most nodules detected at screen are initially evaluated with short-term LDCT follow-up, and stable nodules are followed without further intervention. This 4-mm threshold resulted in a very high number of subjects categorized as “positive.” In the LDCT arm of the NLST, 27.3% of adults undergoing screening had a positive test result on the first round of screening and, over 3 rounds of screening, 39.1% had at least 1 abnormal CT scan. New guidelines recommend that 6 mm is a more appropriate cutoff to define a positive screen for the large majority of nodules. This larger threshold reduces the recall rate by more than one-third, and thus reduces the rates of all potential harms with the possibility of a very small tradeoff in lower benefit. McKee et al reported outcomes of baseline LDCT screening from 2180 high-risk adults in a community screening program and observed that the higher size threshold for a positive result reduced the overall positive rate from 27.6% to 10.6% and increased the positive predictive value for a diagnosed malignancy from 6.9% to 17.3%. However, even using the 6-mm threshold to define a positive result, the most common adverse outcome associated with screening will be the detection of a nodule that requires further evaluation or short-term follow-up. Properly following and evaluating these patients requires a highly organized approach to patient recall and communication.

Depending on the size, radiologic characteristics, location of the nodule, and growth on follow-up, a small percentage of nodules require sampling, usually through CT-guided fine-needle or core needle biopsy or bronchoscopic biopsy. In the NLST, the rate of invasive procedures among adults with abnormal LDCT findings who did not have lung cancer was low (<3%), and the rate of serious complications in this group also was very low (0.06%). Although some deaths occurred in the NLST within 60 days of a procedure, the majority of these occurred in patients who were diagnosed with lung cancer, and none have been directly linked with the procedure. A meta-analysis of risks of CT needle-guided biopsy reports that deaths probably occur among some individuals but are rare, and the precise rate is unknown.

At this time, the rate of overdiagnosis of lung cancer attributable to screening is not known. As noted above, overdiagnosis may occur because of a screen-detected cancer.
that is indolent or the detection through screening of a progressive cancer in a patient who was destined to die of other causes before symptoms of lung cancer would ever have become apparent. The latter is important in the case of lung cancer, because current and former smokers have higher risks of premature mortality from other chronic conditions. Using NLST data, Patz et al estimated that the overdiagnosis rate associated with lung cancer screening was 18%. The estimate from Patz et al has been criticized as being excessive based on limited follow-up of the NLST cohort, failing to adjust for lead time, and failing to isolate bronchioloalveolar carcinomas (now classified as AIS or minimally invasive adenocarcinoma), which are increasingly understood to have a very high likelihood of being overdiagnosed and amenable to surveillance versus immediate treatment.

The latter critique is apt, because the impact of overdiagnosis is mitigated if an invasive cancer can be identified as an overdiagnosed cancer and no treatment takes place. Modeling studies of the effectiveness of lung cancer screening conducted for the USPSTF estimated that the rate of overdiagnosis was between 8.7% and 13.5%. Using the 6-mm nodule threshold will result in a lower overdiagnosis rate than estimated from the NLST, but the new expected rate is not known and is likely to be below 10% to 12%, which is the rate used by the USPSTF in formulating their screening guideline derived from the NLST.

Challenges and Opportunities to Improve the Effectiveness of Lung Cancer Screening

Implementing high-quality lung cancer screening faces the same challenges that have been faced with the implementation of other cancer screening tests, which means we can anticipate that lung cancer screening rates will rise slowly in the near future. Compared with other screening tests, the requirements for determining screening eligibility, shared decision-making requirements put in place by the CMS, and identifying a facility that provides LDCT lung cancer screening all place not only new but also greater demands on the primary care provider. Coverage for lung cancer screening under the ACA was not available until 2015 and, although CMS coverage also was established in 2015, procedural and reimbursement issues took longer to resolve. As is evident in Table 3, having health insurance is a major determinant of recent cancer screening, and Jemal and Fedewa noted that over 50% of current and former smokers who met USPSTF criteria were uninsured or Medicaid insured. Awareness among health care professionals and adults at risk will take time to establish, and it will take time to integrate referral routines into daily practice.

Lung cancer screening is unique, in that the target population is defined by both age and specific risk factors. Electronic health records should be up to the task of identifying adults who meet tobacco exposure and other eligibility requirements, but early experience has shown that they fall short. Identifying adults who are eligible for screening and conducting shared decision making add an additional burden on primary care, which must be given the tools and the incentives to fulfill their important role. An additional barrier to screening was recently revealed by Jemal and Fedewa, who noted that one-half of adults who were eligible for lung cancer screening according to USPSTF criteria either had no health insurance or were covered by Medicaid. One important step was a decision by the CMS to impose documentation of quality measures, including reporting data to a registry, as a basis for reimbursement, which will likely broadly enhance the uptake of quality-assurance practices.

Conclusions: Challenges and Opportunities

In the near term, the greatest potential for reducing death from cancer is through early detection and appropriate treatment. The fullest benefit of early detection remains unfulfilled because of limitations in access, insufficient resources, uneven quality, and lack of organized systems. All adults are vulnerable to uneven quality and nonadherence to guideline-recommended care, but some adults face more pronounced challenges.

The effectiveness of population-based cancer screening depends on the attendance rate, the sensitivity of the protocol, the management of positive findings, and timely access to treatment for those diagnosed with cancer. Failure to identify adults at higher risk for early-onset cancers because of family history and inherited genetic syndromes, failure to initiate cancer screening or attend screening regularly, and failure to provide consistently high-quality screening prevents achievement of the fullest potential of cancer screening to reduce avoidable morbidity and mortality. Our nation’s cancer incidence and mortality rates can be reduced substantially through the establishment of a system of cancer screening, the removal of barriers to equal access to care, and broad implementation of interventions that are proven to increase cancer screening rates and improve the quality of cancer screening. Beyond applying what we know, we must invest research dollars to address vital questions whose answers can further advance cancer screening science and practice. The sections below provide a review of interventions known to improve cancer screening rates and identify high-priority research opportunities.

Barriers to Cancer Screening

There are several barriers to increasing enduring adherence to cancer screening guidelines. Studies of obstacles to screening reveal consistent findings. Individuals with lower
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Income, with lower educational achievement, and without insurance are less likely to be up to date with screening. Barriers may not be mutually exclusive, may occur and interact at multiple levels (ie, patient, provider, health system, and policy levels), and may include lack of access to care, knowledge gaps, low awareness, and inconsistent physician recommendations for cancer screening. In addition, patient beliefs, such as the belief that testing should only occur if someone has symptoms or a family history of an illness, are commonly reported barriers to screening. Studies in specific ethnic and racial subgroups reveal additional, culturally specific barriers to screening uptake. There are direct and indirect costs associated with cancer screening. Direct costs may involve the inability to pay for out-of-pocket expenses, including copays, deductibles, and office visit charges, whereas indirect costs may stem from time spent off work. Some barriers may require intervention at the health system and patient levels, whereas others may be more adequately addressed with large-scale policy changes.

Policies Influencing Cancer Screening

There are several examples of how policies increased cancer screening utilization in the past. In mid-2001, Medicare began covering up to 80% of the cost of colonoscopy for average-risk beneficiaries, leading to steep increases in its use. More recently, the ACA has several provisions that appear to influence cancer screening rates. The ACA provided subsidies to low-income and middle-income individuals to purchase insurance and facilitated the expansion of Medicaid eligibility to more low-income adults, although some states have opted not to expand eligibility. The passage of the ACA was associated with a decline in the percentage of the population without health insurance, especially in states that expanded Medicaid. Gains in insurance coverage and Medicaid expansion have been associated with an increasing proportion of screen-detected cancers diagnosed at an earlier stage. For individuals covered by most commercial insurance plans, the ACA eliminated cost-sharing charges for cancer screening tests that receive A or B ratings from the USPSTF. The removal of cost may be associated with higher uptake of CRC screening in low-income adults and has substantially improved test affordability for millions of insured individuals. It is established that copays and deductibles negatively influence utilization of preventive services, whereas the elimination of these out-of-pocket costs increases utilization.

The recent ACA provision has been criticized for not fully addressing circumstances that allow the imposition of cost-sharing on screening and diagnostic procedures. One common circumstance that affects the costs of screening is that abnormal findings on initial screens almost always generate the need for additional evaluation, which may take place with immediate imaging studies of the suspicious area, follow-up colonoscopy in the case of an abnormal initial noncolonoscopic screen, short-term follow-up imaging, and biopsy, as in the case of a man with an elevated PSA. These supplemental tests are treated by both private and public insurers as diagnostic tests and thus are subject to deductibles and copays. In addition, a history of nonmalignant abnormalities on imaging or a clinician judgment that a patient is at higher than average risk may result in an asymptomatic patient receiving regular screening that is coded as diagnostic and thus is not eligible for full coverage free of cost-sharing under the ACA.

One potential problem that arises from linking coverage to USPSTF A and B ratings is that screening tests that receive a C recommendation, such as prostate cancer screening and breast cancer screening for women in their 40s, for which shared decision making is recommended, also are not covered under the no–cost-sharing provision of the ACA. Although some health plans will cover services with a C recommendation, they are not obligated to do so. The ACS advocates for the elimination of cost-sharing for all screening tests that are appropriate for an individual to undergo, which should be judged to include not only screening tests that are directly recommended but also screening tests for which the USPSTF has endorsed individualized decisions. When a screening test has a “C” rating, an individual who has reached a decision that potential benefits outweigh potential harms usually faces the barrier of higher out-of-pocket costs for cancer screening.

Health System Barriers and Interventions to Increase Screening

Some individuals with adequate insurance coverage still choose to obtain all their care from specialists and/or from acute care settings, such as urgent care or emergency departments. For these individuals, lack of a regular source of primary care, or for women, a regular source of care from a gynecologist, is associated with a reduced likelihood of receiving a screening recommendation or order. For all individuals, a physician recommendation to have a screening test, or lack thereof, is a consistently strong determinant of screening status. An effort to increase and maintain increased screening rates demands coordinated and sustained efforts on many fronts. Both private and governmental health care plans play an important role in promoting screening by designing and tracking screening-related quality metrics, promoting screening directly to members, and designing effective, value-based payment systems that shift incentives from volume of care to rewarding high-quality care, including the achievement of high rates of cancer
screening. Achieving high rates of cancer screening in the absence of an organized system of cancer screening means that providers and the public are dependent on an inefficient model in which most cancer screening referrals depend on encounters between the health care provider and the patient.

Finally, every integrated health care system and each individual practice must be responsible for measuring and improving screening rates. This requires establishing efficient ways to harness electronic health records to serve as registries and quality improvement tools, including facilitating the gathering and assessment of critical elements that establish risk, such as family and smoking history. Preventive health examinations (ie, checkups) are associated with higher rates of cancer screening, because they provide an opportunity to assess whether the patient is up to date with cancer screening, discuss cancer screening, and make appropriate referrals. These regular encounters also provide the important opportunity to address whether a patient should continue cancer screening when it may no longer be beneficial.

Several categories of interventions have been proven effective for increasing screening rates. Both provider and patient reminders in their many forms (paper, electronic, etc), population outreach guided by registries, and eliminating barriers to accessing tests all have been shown to increase screening rates. Screening navigation is consistently effective in increasing screening rates, particularly for individuals facing substantial economic, cultural, and structural barriers and in patients who are seen in settings that lack reminder systems and registries. Determining how to pay for screening navigation outside of the research setting is a persistent challenge. Evidence-based messaging and broad public health campaigns are variably effective at increasing screening. Finding the financial support to implement and sustain many of these interventions defines an ongoing challenge for our health care system, principally because the existing system in the United States has not systematized organized cancer screening in the same manner as many European nations.

Research Priorities for Cancer Screening

Given the proven effectiveness of evidence-based cancer screening to reduce cancer mortality and, in some instances, to reduce the incidence of cancer, a substantially greater investment in screening research is warranted, even if it requires shifting resources from therapeutic strategies to screening strategies. Although the benefits of all recommended screening tests outweigh the associated harms of screening, no screening test performs perfectly. Furthermore, effective screening strategies are only available to screen individuals at average risk for 6 cancers: breast, cervix, colon, rectum, lung, and prostate. Accordingly, the ACS advocates for research in the following domains.

1. **Research to improve the implementation of existing screening modalities**

Research directed at facilitating the uptake of organized screening, including for populations that are less likely to undergo screening, is a priority. Elements of this research should include the study of reminder systems, population management, public messaging, team-based care, and navigation. On a broader scale, studies of different approaches to organizing and paying for health care are needed, and cancer screening rates are an important outcome indicator for these experiments. The implementation research that encourages and tests the development of effective health information technology is an essential investment. Specific outcomes that should be evaluated are consistency and quality of documentation of family history, including strategies for regular updates; the generation of effective reminders derived directly from information available in the electronic health record; and the capacity to harness technology to outreach directly to patients and prompt them to be screened, and ensure follow-up for those who do not respond to screening invitations.

2. **Research to improve the quality and performance of currently available screening tests**

Two research and policy pathways are important. First, we need increased financial commitment to evaluate the performance of current screening technology in the community, to support research and development to improve and evolve existing technology, and to develop new technology that is promptly evaluated if it appears promising. As examples, mammography has evolved over time, from film to FFDM, which is now being replaced by DBT. A large study to evaluate DBT (the TMIST trial, as described above) to determine whether 3D mammography is superior at detecting aggressive breast cancers earlier than 2D digital mammography, has just been initiated. However, by the time the study is completed, DBT already will dominate the installed base of mammography equipment. New, novel technologies need to be evaluated long before they become widely implemented based on promising observational research. Abbreviated MRI may be the solution to screening women with significant mammographic breast density, who are at increased risk of breast cancer and late diagnosis; however, to our knowledge, only one prospective trial is underway to evaluate this new technology for screening this subgroup of women. An improvement in the way we use PSA testing, or an altogether different test for the early detection of prostate cancer, is needed to improve discrimination between prostate cancers that potentially are lethal versus those that do not pose a significant risk to the patient during his remaining years of life. The second pathway is no less important. Strong quality assurance programs that are targeted to both the test and screening can be improved by...
ensuring that performance is monitored and steps are taken to improve performance when it falls below minimally acceptable levels.

3. Research to develop entirely new screening strategies to screen for cancers currently amendable to screening

New directions in breast cancer screening that are functional versus anatomic, including contrast-enhanced MRI and molecular breast imaging, are being tested, with promising results in overcoming the limits of 2D and 3D mammography in women with significant mammographic breast density. Blood tests that detecting circulating DNA and potentially can detect many types of asymptomatic cancers are in development.

Developing new higher performing, more affordable, and/or more culturally acceptable screening tests warrants a substantial research investment.

4. Research to develop increasingly refined, risk-based screening strategies

All approaches to screening incorporate assessments of risk, taking into account sex, age, life expectancy, and personal and family history at a minimum. Organizations have issued guidelines to screen individuals who are at higher than average risk for some cancers, but the depth of data supporting these recommendations is highly variable. Lung cancer screening requires an assessment of smoking history to determine eligibility for screening. Research using limited genetic analysis is currently being conducted to determine whether more targeted screening for breast cancer is feasible. Refining eligibility for screening based on measures of risk holds the potential to identify individuals who are likely to benefit from more intense screening protocols. Someday, it also may be possible with genetic risk analysis to identify individuals who are well below average risk and might choose to forgo screening or to be screened differently. However, to date, reducing the intensity of screening to levels below those currently recommended for average-risk individuals has led to a loss of screening effectiveness overall in exchange for reducing the number of adults who undergo screening and reducing the overall rate of harms.

5. Research to develop effective ways to screen for cancers for which screening tests do not currently exist

By 2030, pancreatic cancer is likely to become the second leading cause of cancer-related death in the United States when deaths for men and women are combined, and, to date, treatment outcomes for patients with advanced pancreatic cancer remain poor. At this time, no screening strategy has been developed and tested. Liver cancer and bladder cancer are other diseases for which reliable and practical risk-based screening tests are needed. Screening for less common causes of cancer-related death may be possible but demands highly accurate screening tests and well-defined and acceptable diagnostic and treatment approaches. Resources should be invested in developing potential screening tests.

In summary, the capacity to screen for asymptomatic cancer and cancer precursors defines one of the great successes in the history of cancer control, but the full potential of cancer screening is not being achieved. Millions of individuals who should be screened are not being screened, and millions who are being screened are not receiving the highest quality testing available. The barriers that are impeding improvements in screening rates need to be systematically identified and rectified with no less than a mission-oriented commitment. Research dedicated to improving existing screening strategies and finding new ones is necessary, and the current level of investment in this type of research is insufficient.

The ACS has made major commitments to leading national efforts that promote screening for several cancers, particularly cervical cancer, breast cancer, colon cancer, and lung cancer. Considering the proven value of early cancer detection, improving rates of recommended, high-quality screening should be a collective, shared commitment that engages all sectors of the health care delivery system, including industry, government, health care payers and delivery systems, practitioners, and disease advocacy organizations. Parallel to applying the knowledge we have today, we must achieve consensus on near-term and long-term priorities for screening research. Finally, we must achieve consensus on what defines high-quality screening and then initiate the efforts to ensure that high-quality screening is universally available. The ACS is committed to working with all stakeholders to attain these goals.

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