

## ARTICLE

# Screening for lung cancer: 2023 guideline update from the American Cancer Society

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## Funding information

American Cancer Society Guideline  
 Development Group; National Comprehensive  
 Cancer Network

## Abstract

Lung cancer is the leading cause of mortality and person-years of life lost from cancer among US men and women. Early detection has been shown to be associated with reduced lung cancer mortality. Our objective was to update the American Cancer Society (ACS) 2013 lung cancer screening (LCS) guideline for adults at high risk for lung cancer. The guideline is intended to provide guidance for screening to health care providers and their patients who are at high risk for lung cancer due to a history of smoking. The ACS Guideline Development Group (GDG) utilized a systematic review of the LCS literature commissioned for the US Preventive Services Task Force 2021 LCS recommendation update; a second systematic review of lung cancer risk associated with years since quitting smoking (YSQ); literature published

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since 2021; two Cancer Intervention and Surveillance Modeling Network-validated lung cancer models to assess the benefits and harms of screening; an epidemiologic and modeling analysis examining the effect of YSQ and aging on lung cancer risk; and an updated analysis of benefit-to-radiation-risk ratios from LCS and follow-up examinations. The GDG also examined disease burden data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program. Formulation of recommendations was based on the quality of the evidence and judgment (incorporating values and preferences) about the balance of benefits and harms. The GDG judged that the overall evidence was moderate and sufficient to support a strong recommendation for screening individuals who meet the eligibility criteria. LCS in men and women aged 50–80 years is associated with a reduction in lung cancer deaths across a range of study designs, and inferential evidence supports LCS for men and women older than 80 years who are in good health. The ACS recommends annual LCS with low-dose computed tomography for asymptomatic individuals aged 50–80 years who currently smoke or formerly smoked and have a  $\geq 20$  pack-year smoking history (*strong recommendation, moderate quality of evidence*). Before the decision is made to initiate LCS, individuals should engage in a shared decision-making discussion with a qualified health professional. For individuals who formerly smoked, the number of YSQ is not an eligibility criterion to begin or to stop screening. Individuals who currently smoke should receive counseling to quit and be connected to cessation resources. Individuals with comorbid conditions that substantially limit life expectancy should not be screened. These recommendations should be considered by health care providers and adults at high risk for lung cancer in discussions about LCS. If fully implemented, these recommendations have a high likelihood of significantly reducing death and suffering from lung cancer in the United States.

#### KEYWORDS

American Cancer Society, humans, low-dose computed tomography, lung neoplasms/incidence, lung neoplasms/mortality/radiography, mass screening, neoplasms/diagnosis, prevent and control, United States

## INTRODUCTION

In 1980, the American Cancer Society (ACS) withdrew a prior recommendation for regular lung cancer screening (LCS) with chest radiography (CXR) in persons who currently or formerly smoked because a series of randomized controlled trials (RCTs) conducted in the 1970s had not demonstrated convincing evidence that LCS saved lives.<sup>1</sup> Thirty-three years later, after publication of the National Lung Screening Trial (NLST) (ClinicalTrials.gov identifier NCT00047385) demonstrating that three rounds of annual LCS with low-dose computed tomography (LDCT) were associated with a 20% relative mortality reduction compared with annual LCS with CXR,<sup>2</sup> the ACS issued a recommendation for annual screening with LDCT in adults who met the eligibility requirement for the NLST (i.e., individuals aged 55–74 years with a 30 or greater pack-year history of smoking who currently smoke, or formerly smoked and had not exceeded

15 years since smoking cessation, and did not have life-limiting comorbidity).<sup>3</sup> In this update of the 2013 LCS guideline, the ACS Guideline Development Group (GDG) addresses a broad spectrum of issues related to LCS, including the most recent evidence on the efficacy and effectiveness of LCS, the lung cancer risk in persons who formerly smoked and have exceeded 15 years since cessation, estimates of the benefits and harms of screening past age 80 years and screening in eligible adults with greater than 5 years of longevity, and updated benefit-to-radiation-risk ratios based on modern doses from ionizing radiation from screening and follow-up examinations. We also discuss the challenges of implementing LCS, enduring disparities in disease burden and screening rates, and the urgent need to significantly improve utilization and adherence to screening and follow-up testing among qualifying individuals.

In this update of LCS, the ACS recommends that individuals aged 50–80 years who currently smoke or who formerly smoked and are

at high risk for lung cancer because of a 20 or greater pack-year history of cigarette smoking undergo annual LCS with LDCT (Tables 1 and 2). We also recommend against using any duration of years since quitting smoking (YSQ) as a criterion to begin or end LCS in individuals who formerly smoked and who meet age and pack-year eligibility criteria. Individuals who smoke should be advised to quit and offered evidence-based smoking-cessation interventions. Existing comorbid conditions that may limit life expectancy or the inability or unwillingness to undergo evaluation of positive screening findings or to undergo treatment are factors that should preclude referrals for screening. Because of these considerations, the risks associated with LCS, and the relative newness of LCS to the target population, potentially eligible individuals should undergo a process of shared decision-making (SDM) that includes a discussion about the purpose of LCS, the consensus among leading organizations on recommendations endorsing LCS; the screening process and the importance of regular screening; the benefits, limitations, and potential harms of screening; and consideration of patient values and preferences. We also discuss the challenges of implementing LCS, enduring disparities in disease burden and screening rates, and the urgent need to significantly improve utilization and adherence to screening and follow-up testing among qualifying individuals. This guideline for LCS is based on the underlying burden of disease, an assessment of the strength of evidence, the balance of benefits and harms, and consideration of patient values and preferences.

**TABLE 1** American Cancer Society guideline for lung cancer screening, 2023.

These recommendations represent updated guidance from the American Cancer Society for asymptomatic persons who are at high risk of lung cancer based on cumulative exposure to tobacco by smoking.

#### Recommendation

The American Cancer Society recommends annual screening for lung cancer with low-dose computed tomography in asymptomatic individuals aged 50 to 80 years who currently smoke or formerly smoked and have a  $\geq 20$  pack-year<sup>a</sup> smoking history (*strong recommendation*<sup>b</sup>; moderate quality evidence).

- For individuals who formerly smoked, the number of years since quitting smoking is not included as an eligibility criterion to begin or to stop lung cancer screening.
- Individuals with comorbid conditions that substantially limit life expectancy should not be screened.
- Before undergoing lung cancer screening, individuals should:
  - Receive evidence-based smoking-cessation counseling and offered interventions if they currently smoke; *and*
  - Engage in a shared decision-making discussion with a health professional about the benefits, limitations, and harms of lung cancer screening (see Table 5 for core elements for shared decision-making).

<sup>a</sup>One pack-year is the equivalent of smoking an average of 20 cigarettes—one pack—per day for a year.

<sup>b</sup>A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening.

## BACKGROUND

Lung cancer is the second most common cancer diagnosed in both men and women in the United States and the leading cause of cancer death. In 2023, the ACS estimates that there will be 238,340 new cases of lung cancer, and 127,070 people will die from lung cancer, accounting for approximately 20% of all cancer deaths.<sup>4</sup> The principal cause of lung cancer is cigarette smoking, which accounts for approximately 80% of cases.<sup>5</sup>

Lung cancer incidence overall has been declining since 1992<sup>6</sup> and since 2006–2007 for both men (–2.7% annually) and women (–1.1% annually).<sup>4</sup> Substantially larger annual reductions in lung cancer mortality have been observed in more recent years, which, from 2014 to 2020, had accelerated to –5.3% annually in men and –4.3% annually in women.<sup>4</sup> Overall, the lung cancer death rate declined by 58% in men from 1990 to 2020 and by 36% in women from 2002 to 2020.<sup>4</sup> These trends have been influenced by tobacco-control efforts, historical trends in smoking uptake and cessation that differed between men and women, and, more recently, contributions to survival from improvements in therapy and early detection.<sup>7,8</sup>

The small differences between the distribution of age-specific incidence and mortality rates in the United States (Figure 1) and the distribution of lung cancer cases and deaths by age at diagnosis (Figure 2A,B) are indicative of the historically poor lung cancer survival, largely because the majority of incident cases are diagnosed at regional (22%) and distant (44%) stages.<sup>4</sup> The 5-year relative survival rate for lung cancer diagnosed from 2012 to 2018 was poor (23% overall; 18% in men and 28% in women)<sup>9</sup> but was a considerable improvement compared with the 12% 5-year survival rate in the mid-1970s.<sup>10</sup> For the estimated 26% of persons diagnosed with localized disease, 5-year survival is considerably more favorable (61%) compared with regional (33%) and distant (7%) stages.<sup>4</sup> Despite declining mortality and improvements in survival, death from lung cancer accounts for more person-years of life lost (PYLL) than all deaths from colorectal, breast, prostate, and cervical cancers combined.<sup>11</sup> In 2018, death from lung cancer was estimated to account for 2,114,000 PYLL and an average of 14.9 years of life lost per person dying of lung cancer.<sup>11</sup> The distribution of age-specific PYLL during 2016–2020 because of death from lung cancer is shown in Figure 2C. Lung cancer incidence and mortality rates are higher in men compared with women and are higher in some racial/ethnic minorities, primarily Black individuals and American Indian/Alaska Native peoples.<sup>4,7</sup> Individuals of lower socioeconomic status in the United States are disproportionately affected by lung cancer.<sup>12</sup>

Attempts to develop an LCS strategy for high-risk individuals, commonly with the combination of sputum cytology and CXR, date back to the late 1950s and early 1960s.<sup>13–16</sup> In the late 1960s, the National Cancer Institute (NCI) joined additional study groups (Mayo Clinic, Memorial Sloan-Kettering Cancer Center, University of Cincinnati) with the Johns Hopkins Lung Project to establish the Early Lung Cancer Cooperative Group, which led to a series of RCTs of LCS that were initiated in the 1970s.<sup>15</sup> Although early results were judged

**TABLE 2** Comparison of 2023 and 2013 American Cancer Society guidelines for lung cancer screening.

Eligibility	2023	2013 (2018) <sup>a</sup>
Age	50–80 years	55–74 years
Smoking status	Persons who currently smoke or who previously smoked.	Persons who currently smoke or who previously smoked and quit within the past 15 years.
Smoking history <sup>b</sup>	≥20 pack-year history <sup>b</sup>	≥30 pack-year history
Recommendation	Annual screening with LDCT	Annual screening with LDCT
Health status exclusions	Health conditions that may increase harm or hinder further evaluation, surgery, or treatment for lung cancer. Comorbid conditions that limit life expectancy <5 years; not willing to accept treatment for screen-detected cancer.	Life-limiting comorbid conditions. Metallic implants or devices in the chest or back. Requirement for home oxygen supplementation.
Decision making about screening	Undergo a process of SDM with a qualified health professional that includes information about the benefits, limitations, and harms of screening with LDCT; <i>and</i> A person who currently smokes should be advised to quit and offered counseling and pharmacotherapy to assist in quitting.	Undergo a process of SDM that includes information about the potential benefits, limitations, and harms of screening with LDCT; <i>and</i> Have access to a high-volume, high-quality lung cancer screening and treatment center <sup>c</sup> ; <i>and</i> A person who currently smokes should receive evidence-based smoking-cessation counseling.

Abbreviations: LDCT, low-dose computed tomography; SDM, shared decision-making.

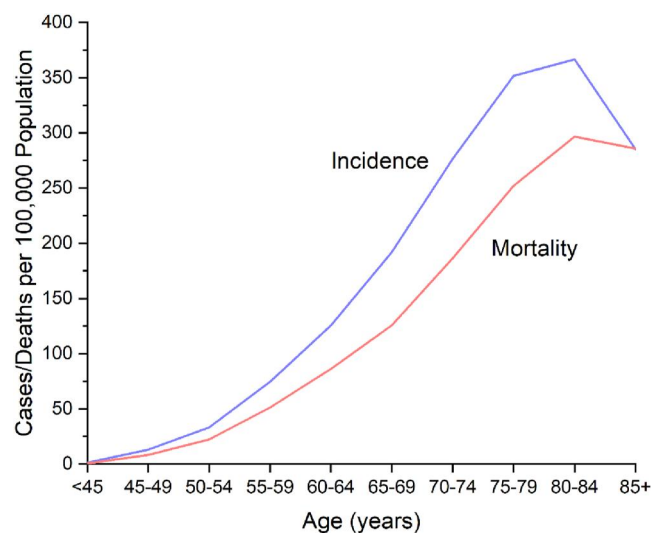
<sup>a</sup>In response to feedback from stakeholders requesting greater clarity about whether the American Cancer Society (ACS) recommended lung cancer screening (LCS) or decision making about LCS, the ACS issued a revised statement in 2018 to make it clear that the ACS recommended annual LCS with LDCT for eligible individuals. The statement also reiterated that clinicians should provide information for decision-making purposes on the benefits, limitations, and potential harms of screening.

<sup>b</sup>A pack-year is the equivalent of smoking an average of one pack of cigarettes per day for a year; one pack per day for 20 years or two packs per day for 10 years are each equivalent to a 20 pack-year smoking history.

<sup>c</sup>The recommendation to have access to high-quality services was made shortly after the completion of the National Lung Screening Trial and before LCS was implemented in most settings, hence a recommendation to seek information about imaging centers with experience. Ten years later, the ACS Guideline Development Group determined that this recommendation is no longer needed.

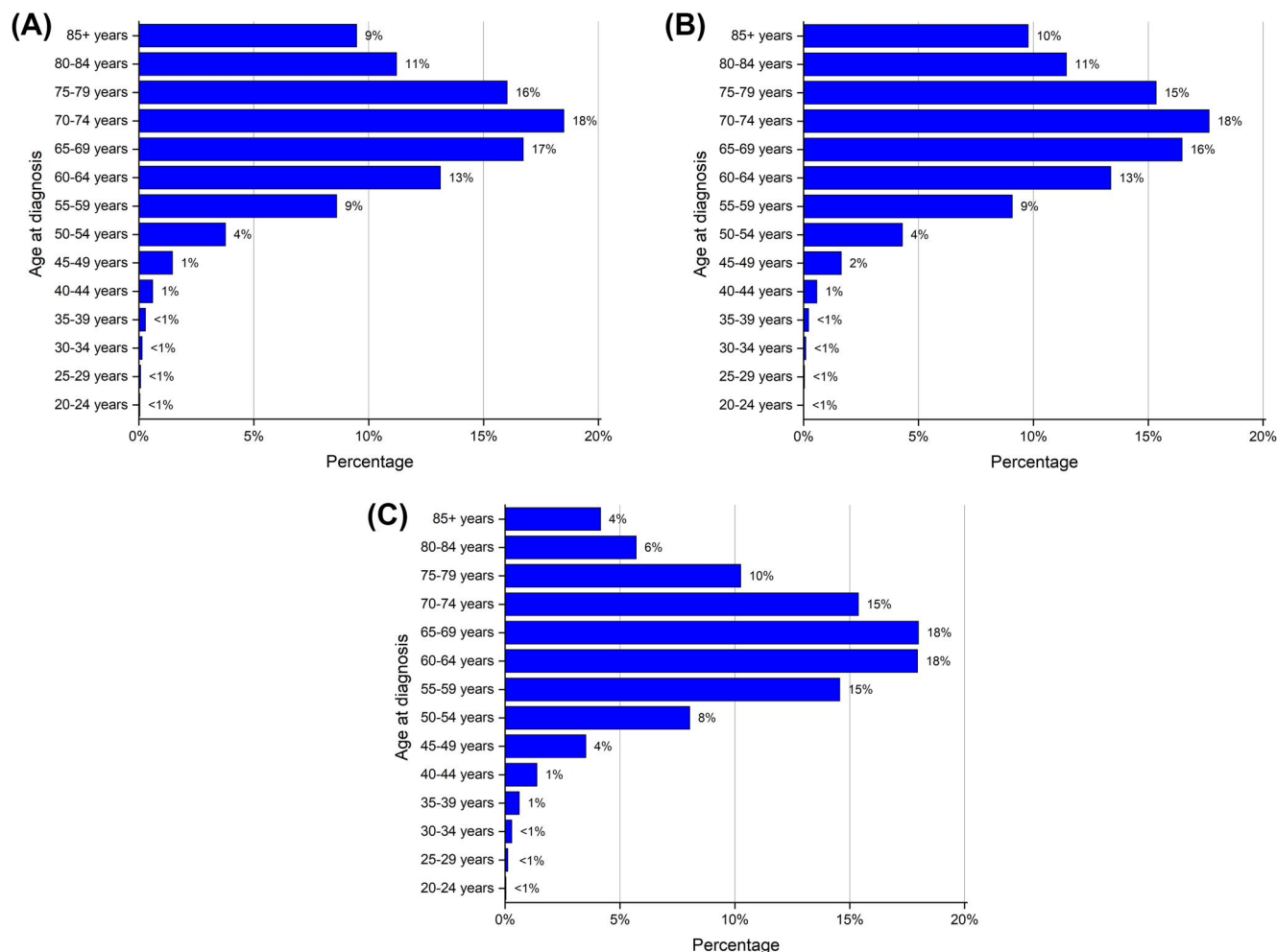
to be promising, the final results did not demonstrate that the combination of sputum cytology and CXR reduced lung cancer mortality compared with CXR alone; however, as Berlin observed in 2000, neither did the trials provide convincing evidence that annual CXR did not reduce lung cancer mortality.<sup>15</sup> The NCI continued to evaluate LCS by including an annual CXR arm in the Prostate, Lung, Colorectal, and Ovarian trial (PLCO) (ClinicalTrials.gov identifier NCT00339495), which launched in 1992.<sup>15,17</sup> Toward the end of the 20th century, with the PLCO ongoing, there was still equipoise about the potential for LCS.<sup>18,19</sup> The potential for application of LDCT for early lung cancer detection greatly renewed interest in LCS research when the Early Lung Cancer Action Project (ELCAP) published results in *The Lancet* in 1999 demonstrating that LDCT substantially outperformed CXR in the detection of small, resectable lung cancers.<sup>20–23</sup> Soon after publication of the ELCAP results, numerous RCTs were launched in the United States and Europe to evaluate the effectiveness of LDCT screening in reducing mortality from lung cancer<sup>24</sup>; simultaneously, international efforts were dedicated to promoting consensus in the design, methodology, and reporting of studies of LCS with LDCT.<sup>25</sup>

The two largest RCTs were the NCI-sponsored NLST,<sup>2</sup> and the Nederlands-Leuven Longkanker Screenings Onderzoek (NELSON) trial (Trial Registration No.: ISRCTN63545820).<sup>26</sup> The NLST compared the efficacy of three rounds of LDCT with three rounds of CXR in persons aged 55–74 with at least a 30 pack-year smoking history who currently smoked or had quit within 15 years. In 2011,



**FIGURE 1** Lung cancer incidence and mortality by age, United States, 2016–2020. Data sources: Incidence: Surveillance, Epidemiology, and End Results (SEER) 17 registries, with delay adjustment, 2023; Mortality: National Center for Health Statistics, 2022.

the first results of the NLST were published, showing a 20% relative reduction in mortality from lung cancer with LDCT screening compared with CXR in persons at high risk for the disease.<sup>2</sup>



**FIGURE 2** (A) Age distribution of lung cancer cases by age at diagnosis ( $n = 242,888$ ), United States, 2016–2020. (B) Distribution of lung cancer deaths by age at diagnosis ( $n = 138,248$ ), with patients followed for 20 years after diagnosis, United States, 2016–2020. (C) Distribution of person-years of life lost (PYLL) because of lung cancer by age at diagnosis (total = 1,982,262), United States, 2016–2020. Data source: Surveillance, Epidemiology, and End Results (SEER) 17 registries, 2023 (PYLL is based on 2020 life tables; Arias and Xu 2022<sup>71</sup>).

Recommendations for LCS in the United States with LDCT followed the publication of favorable results from the NLST,<sup>2</sup> and screening eligibility mostly followed the NLST eligibility criteria.<sup>3,27</sup> In 2013, the ACS issued guideline recommendations for LCS based mainly on evidence from the NLST, which recommended that clinicians initiate LCS discussions with patients in good health aged 55–74 years who had at least a 30 pack-year smoking history and who currently smoked or had quit smoking within the past 15 years.<sup>3</sup> In response to feedback from stakeholders requesting greater clarity about whether the ACS guideline was a recommendation for SDM or a recommendation for LCS with SDM, the ACS issued a revised statement in 2018 to make it clear that the ACS recommended annual LCS with LDCT for those who qualify based on the aforementioned criteria. The statement reiterated that clinicians provide information for decision-making purposes on the benefits, limitations, and harms of screening.<sup>28</sup>

Since the release of the 2013 ACS guideline for LCS, supporting evidence for LCS from multiple RCTs conducted in different countries has accumulated.<sup>26,29–33</sup> The second largest RCT, the NELSON

trial, provided evidence that supported significant changes in the eligibility criteria in guidelines and recommendations for LCS.<sup>26</sup> In 2021–2022, the US Preventive Services Task Force (USPSTF), the American College of Chest Physicians, the American Academy of Family Physicians, the National Comprehensive Cancer Network, and the Center for Medicare and Medicaid Services each lowered the age to begin screening from 55 to 50 years and lowered the number of pack-years of smoking from 30 to 20.<sup>34–38</sup> This 2023 ACS guideline integrates new evidence to update the 2013 guideline.

## METHODS

The ACS process for developing and updating cancer screening guidelines is described in detail elsewhere.<sup>39,40</sup> The LCS guideline is intended to provide guidance for screening to health care providers and their patients who are at high risk for lung cancer because of a history of smoking.



## Guideline Development Group process

The ACS GDG is a volunteer committee responsible for developing cancer screening guidelines. The GDG consists of generalist and specialist clinicians, biostatisticians, epidemiologists, economists, and a patient representative (see Supporting Materials and Table S1). The GDG adheres to a protocol designed to maintain rigor, transparency, independence, and consistency. This includes developing and agreeing on the key research questions for the systematic review when needed, interpreting the findings of systematic reviews on the benefits and harms of cancer screening, considering supplemental evidence and the findings from modeling analyses where evidence gaps exist, and formulating and assigning a grade to recommendations based on the totality of the evidence.<sup>41</sup> Similar to previous ACS guidelines, a workgroup consisting of six GDG members was primarily charged with these tasks in updating the LCS guideline. All members of the GDG are required to review the evidence and participate in deliberations before voting on drafted recommendations and the assigned grade proposed by the workgroup. The framing of recommendations and voting is an iterative process that attempts to achieve 100% consensus, but a three-quarter majority vote is accepted to finalize a recommendation and the assigned grade (see Supporting Materials).

The GDG is supported by ACS Early Cancer Detection Science staff, which includes epidemiologists, specialists in literature searches and systematic evidence reviews, and administrative staff. The staff provided guidance for adherence to the methodology for guideline development, provided expertise in cancer epidemiology and screening as requested by the GDG chair, assisted in drafting the rationale to support recommendations and in writing the guideline report, and other administrative support for the GDG. The ACS staff did not vote on or assign grades for the recommendations.

To provide a more comprehensive understanding of the complex factors related to LCS, the GDG was supported by an expert advisory group (EAG; see Supporting Materials and Table S2) with research and/or clinical expertise in lung cancer risk, screening, diagnosis, treatment, and decision-making. The members of the EAG did not participate in the framing or grading of recommendations. Instead, they addressed questions on the evidence and clinical practice posed by the GDG throughout the guideline development process, provided feedback on the draft recommendations and supporting rationale, and served as external reviewers for the guideline manuscript before submission for publication. The comments from the advisors were documented for review by the GDG. Any changes made to the recommendation wording, grade, or to the narrative of the guideline required GDG review, deliberation, and, as necessary, voting. As part of the external review process, representatives from 30 stakeholder organizations were invited to review the draft guideline recommendations and rationale statements and to provide feedback before finalizing the guideline (see Supporting Materials).

Throughout the guideline development, all persons participating in the process (ie, GDG members, EAG members, ACS staff) were required to disclose financial and nonfinancial (i.e., personal,

intellectual, practice-related) interests, relationships, and activities related to LCS and treatment that might be perceived as posing a conflict of interest. At the start of the guideline update, these disclosures of interests were shared with the GDG and reviewed by the chair and vice-chair of the GDG, ACS supporting staff, and a representative of the ACS Office of Corporate Counsel. The conflict of interest disclosures were made available at each meeting, and GDG members were asked to give relevant updates at the beginning of a meeting. The GDG chairs were responsible for calling attention to perspectives that could be perceived as being influenced by interests and for ensuring a balanced perspective in deliberation and decision-making. In addition to the disclosures listed in the article, the GDG members' nonfinancial disclosures are reported in the Supporting Materials (see Table S3).

## Evidence used in formulating the guideline

The primary evidence source used by the GDG for the guideline update was a systematic review of LCS with LDCT conducted for the USPSTF by the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center, which was published in 2021.<sup>24,42</sup> Although the RTI systematic review was the primary evidence source for the guideline update, it used a different rating system for appraising strength of evidence.<sup>42</sup> The GDG reviewed and concurred with the key questions that guided the evidence review. Although the key questions satisfied the evidence needs for the guideline update, it was determined that the YSQ eligibility criteria for LCS should be further evaluated. The GDG commissioned an additional systematic review of evidence on continuing lung cancer risk in individuals who quit smoking conducted by the ACS Cancer-related Evidence Synthesis Team (CrEST)<sup>43</sup> (see Supporting Materials and Table S4). Also, the GDG requested a study reviewing and updating calculations of the benefit-to-radiation-risk ratios associated with LCS and follow-up imaging using modern ionizing radiation dose levels.<sup>44</sup> The initial consideration in the decision to offer cancer screening to the population was predicated on the disease burden overall and in specific subgroups. The GDG examined the disease burden of lung cancer, including age-specific incidence, mortality, and incidence-based mortality data provided by the ACS Surveillance and Health Equity Science Department.

The GDG also used decision analyses based on mathematical disease-simulation models conducted by four Cancer Intervention and Surveillance Modeling Network (CISNET) Lung Cancer Working Groups (the Microsimulation Screening Analysis–Lung Model from Erasmus University Medical Center [Erasmus], the Massachusetts General Hospital–Harvard Medical School model [MGH–HMS], the Lung Cancer Outcomes Simulation model from Stanford University, and the University of Michigan model [Michigan])<sup>45,46</sup> commissioned by the USPSTF to inform its 2021 update of LCS recommendations.<sup>34</sup> In addition, a supplemental analysis was commissioned by the GDG using two of the CISNET Lung Cancer Working Group models (Erasmus and Michigan; the two other CISNET modeling groups, Stanford University and Massachusetts General Hospital–Harvard Medical

School, were invited but were not able to participate) to incorporate various YSQ scenarios, extended screening past age 80 years, and updated radiation risk data.<sup>47</sup> The GDG also benefited from the input of an epidemiologic and modeling analysis conducted by Landy et al. from the Division of Cancer Epidemiology and Genetics at the NCI. Their analysis demonstrated the counteracting effects of quit-years and concomitant aging on lung cancer risk in the PLCO and NLST trials, and modeled the impact of various screening guidelines in the United States 2015–2018 population on persons who ever smoked, including the use of prediction models, with an emphasis on risk after 15 YSQ.<sup>48</sup> Any references cited in the guideline outside of those included in systematic evidence reviews were obtained through discussions with the EAG or through ad hoc topical searches.

## Factors in developing recommendations

For this ACS guideline update, the GDG applied the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) principles and Evidence-to-Decision framework in formulating and assigning strength of recommendations.<sup>49–51</sup> In applying the GRADE principles, the GDG prioritized the following criteria: (1) *the quality of evidence*; (2) *the balance between desirable and undesirable effects*; and (3) *values and preferences*. The GDG also considered additional elements included in the GRADE Evidence-to-Decision framework: *equity, feasibility, acceptability, and cost/resource allocation*. Although the ACS does not formally apply cost and resource use as criteria for formulating recommendations, it may evaluate potential patient burdens and individual decision-making considerations relevant to guideline recommendations, in recognition that actual costs of screening and workup of findings vary widely in the United States, and individuals may consider insurance coverage and cost sharing (i.e., out-of-pocket costs) when making decisions about cancer screening options.

## Outcomes of screening

The GDG regarded reducing lung cancer mortality as a critical outcome; it was designated as the principal benefit of screening. Life years gained (LYG) and lung cancer deaths averted were identified as important beneficial outcomes of screening. The principal harm of screening, designated as a critical outcome, was follow-up evaluations involving invasive procedures undertaken because of positive findings on LDCT. The risks of overdiagnosis and of long-term effects of radiation exposure from successive LDCT and follow-up examinations were also considered as important outcomes that are potential harms of screening. Incidental findings during LCS were recognized as a potential harm but were ascribed as a harm of lower importance. The burden and psychosocial harms associated with being recalled for further evaluation were reviewed by the GDG, although lower importance was ascribed to these potential harms.

## Patient values, preferences, and adherence to screening

Although it was an important consideration in developing recommendations, the systematic review revealed that there is limited evidence on patient preferences and values.<sup>24</sup> Given the paucity of evidence, the GDG accepted that most individuals would value avoiding premature death from lung cancer but, for some high-risk individuals, screening preferences may be influenced by prior interactions with health services and stigma associated with smoking history and lung cancer; prediscussion perceptions of individual risk, benefits, and potential harms associated with screening and treatment; information received during discussions about LCS and during SDM; and clinician recommendations. In addition, the GDG looked at the available literature in consultation with the EAG to assist in the recommendation formulation process.

## RECOMMENDATION

The ACS recommends that individuals aged 50–80 years who currently smoke, or formerly smoked, and are at high risk for lung cancer because of a  $\geq 20$  pack-year history of cigarette smoking undergo annual LCS with LDCT (Table 1). We also recommend the elimination of the YSQ criterion for beginning or ending LCS among individuals who formerly smoked. Existing comorbid conditions that substantially limit life expectancy or the inability or unwillingness to undergo evaluation or treatment after positive screening findings are factors that should preclude referrals for screening. Individuals who smoke should be advised to quit and offered evidence-based smoking-cessation counseling and pharmacotherapy to assist in quitting. Eligible individuals should undergo SDM with a qualified health professional that includes a discussion about the purpose of LCS, the consensus among leading organizations who endorse LCS, the screening process and the importance of adherence to regular screening, and the benefits, limitations, and potential harms associated with LCS.

## RATIONALE FOR LUNG CANCER SCREENING

### Benefits of low-dose computed tomography lung cancer screening

The principal benefit of LCS is a reduction in lung cancer-specific deaths. The RCTs have provided a foundation of evidence that LCS with LDCT is efficacious, and the diagnostic accuracy studies support that it has high sensitivity and acceptable specificity for the early detection of lung cancer in persons judged to be at high risk due to smoking history.<sup>24,42</sup> Of the seven RCTs included in the systematic review, six reported lung cancer mortality results, although the systematic review noted that only the NLST and the NELSON trial were adequately powered to assess reduced lung cancer mortality associated with an invitation to screening.<sup>24,42</sup>

## Randomized controlled trials

The NLST randomized a high-risk group aged 55–74 with  $\geq 30$  pack-years of smoking to undergo three rounds of annual LCS with either LDCT or CXR.<sup>2</sup> In the NLST, individuals who formerly smoked were ineligible to participate in the trial if  $>15$  YSQ had elapsed. The mean pack-year smoking history in the NLST was 56 pack-years.<sup>2</sup> The earliest report from the NLST at a median of 6.5 years of follow-up showed a 20% relative reduction in lung cancer-specific mortality in the study arm compared with the control arm, a 6.7% relative reduction in death from any cause, and a number needed to screen (NNS) to prevent one lung cancer death of 320.<sup>2</sup> An analysis that extended follow-up approximately 1 year until the end of 2009 reported a lower relative benefit (16%) but a similar NNS (322).<sup>52</sup> The attenuated mortality reduction is likely explained by dilution of the relative risk in the follow-up period when no LCS was taking place, meaning that similar numbers of additional lung cancers were diagnosed in each study arm. This was described in an analysis of extended follow-up of NLST participants<sup>53</sup> and has been demonstrated theoretically in an analysis of RCT screening and follow-up strategies by Duffy and Smith.<sup>54</sup>

The NELSON trial randomized a high-risk group of men and women aged 50–74 years who currently smoked or formerly smoked and had a minimum of 15.00–18.75 pack-years based on two patterns of smoking history (individuals who smoked  $>15$  cigarettes a day for  $>25$  years or  $>10$  cigarettes a day for  $>30$  years). In the NELSON trial, individuals who formerly smoked were ineligible to participate in the trial if  $>10$  YSQ had elapsed. The median pack-year history of smoking in the NELSON trial was 38 pack-years. Study participants were invited to four rounds of LDCT screening versus usual care. A difference between the NLST and the NELSON trial was the screening interval. The four screening rounds in the NELSON trial consisted of two rounds of annual screening, a third round at 2 years, and the fourth round at 2.5 years, providing an opportunity to compare LCS outcomes associated with different screening intervals. In 2017, Yousaf-Khan et al. reported that a 2.5-year LCS interval resulted in a higher interval cancer rate and a higher proportion of advanced disease than the previous annual and biennial screening rounds.<sup>55</sup> In 2020, the NELSON investigators reported an overall 25% relative reduction in deaths from lung cancer in the study arm at 10 years of follow-up, including a 24% relative reduction in lung cancer deaths among men and a 33% (relative risk, 0.67; 95% confidence interval [CI], 0.38–1.14) relative reduction in lung cancer deaths among women, resulting in an NNS of 130 to prevent one lung cancer death over 10 years of follow-up.<sup>26</sup> The importance of the NELSON trial was the additional evidence supporting the efficacy of LCS with LDCT and the demonstration of a significant reduction in lung cancer mortality in a younger cohort that included individuals with a lighter smoking history.

## Modeling studies

In the analysis conducted for the 2021 USPSTF recommendation update, Meza et al. used four CISNET lung cancer natural history models to examine optimal screening age ranges, screening intervals, pack-year histories, and YSQ among people who formerly smoked.<sup>45,46</sup> The models simulated smoking histories (using the CISNET smoking history generator to simulate individual smoking histories) and life histories (including the risk of lung cancer) for 1 million individuals from the 1950 and 1960 birth cohorts, ages 45–90 years, from each sex and with no prior lung cancer diagnosis over a simulated study period. In the final report, results from the 1960 cohort were prioritized because they better reflected recent smoking patterns and future lung cancer risk of the US target population, which had a mean age of 60 years in 2020. Efficient strategies were LCS scenarios estimated to provide the greatest number of lung cancer deaths averted and LYG for a given level of screening (number of screening rounds per 100,000 population).<sup>46</sup> The most efficient LCS strategies had starting ages of 50 or 55 years, required a  $\geq 20$  pack-year history, and had a stop-screening age of 80 years. Compared with the 2013 USPSTF recommendation statement (which was based on 1950 birth cohort data), these strategies were efficient and resulted in increased screening eligibility, more lung cancer deaths averted, and additional LYG. Annual LCS for persons aged 50–80 years who had a  $\geq 20$  pack-year smoking history and who currently smoked or had quit within  $\leq 15$  years (the 2021 USPSTF recommendation; abbreviated as 50-80-20-15), compared with the 2013 USPSTF recommendation (abbreviated as 55-80-30-15), yielded a 13% reduction in lung cancer mortality (vs. 9.8%) compared with no screening based on expected lung cancer deaths in the population overall (not just the population eligible for screening), with 503 lung cancer deaths averted per 100,000 persons (vs. 381), 6918 LYG (vs. 4882), and an NNS of 45 (vs. 37) to prevent one lung cancer death from screening over the age-eligibility period (assuming 100% adherence to screening among eligible individuals).<sup>45,46</sup> The considerably lower estimates of the NNS from the modeling compared with the NLST findings is mainly attributable to the difference between three rounds of annual LCS compared with annual screening from age 50 to 80 years.

In the analysis performed for the ACS guideline update by two CISNET groups (Erasmus and Michigan), investigators used the natural history models (described above) to evaluate similar scenarios of age to start and stop screening, pack-year history, three scenarios of YSQ for individuals who formerly smoked, and ages older than 80 years to stop screening to measure outcomes (Tables 3 and 4). In all scenarios, individuals with a  $\geq 20$  pack-year history started LCS at age 50 years. Resource utilization measures included the percentage of adults eligible for LCS, the projected number of LDCT examinations, and the mean number of LDCT screens per person screened. Screening outcomes included the number of screen-detected lung cancers, the NNS to prevent one lung cancer death, lung cancer



**TABLE 3** Benefits of lung cancer screening scenarios of starting screening at age 50 years with a  $\geq 20$  pack-year smoking history, and various YSQ criteria and ages to stop screening, from the Michigan Cancer Intervention and Surveillance Modeling Network lung cancer natural history model applied to the US 1960 birth cohort. The 2023 ACS lung cancer screening guideline is shaded.

Screening scenario <sup>a</sup>	Eligible, %	LDCT screens, No.	Screen-detected LC, No.	LC mortality reduction, %	Deaths averted, No.	LYG, No.	NNS to save one life
With YSQ 50-80-20-15 <sup>b</sup>	22.6	419,030	1401	13.0	503	6918	45
With YSQ 50-80-20-15 <sup>c</sup>	23	425,373	1727	10.8	506	8471	45
NoYSQExit 50-80-20-15 <sup>d</sup>	23.0	556,275	2070	12.8	599	9920	38
NoYSQExit 50-80-20-30	24.0	584,013	2099	13.0	609	10,084	39
NoYSQ 50-80-20 <sup>e</sup>	24.0	584,062	2097	13.0	611	10,090	39
NoYSQ 50-80-20 with LE >5 years	23.4	544,580	1934	12.3	577	10,019	40
NoYSQ 50-85-20 with LE >5 years	23.4	584,815	2261	14.0	656	10,658	36

Note: Results are presented per 100,000 individuals in the general population who remained alive at age 45 years.

Abbreviations: LC, lung cancer; LDCT, low-dose computed tomography; LE, life expectancy; LYG, life-years gained; NNS, number needed to screen; YSQ, years since quitting.

<sup>a</sup>Screening scenarios in this table correspond to select YSQ scenarios that assume a screening starting age of 50 years, a minimum smoking history of 20 pack-years, and stopping screening at age 80 years unless otherwise specified. WithYSQ indicates a YSQ scenario in which *n* YSQ is enforced to begin screening and is a basis for exiting screening before age 80 years; NoYSQExit, a YSQ scenario in which *n* YSQ is enforced only when beginning screening, i.e., an individual who qualifies to begin screening and reaches *n* YSQ will not lose eligibility to continue screening, according to the National Lung Screening Trial screening protocol; NoYSQ, a screening scenario that is based only on age and pack-year history.

<sup>b</sup>Benefits based on the current US Preventive Services Task Force recommendation estimated from four Cancer Intervention and Surveillance Modeling Network models in 2021.

<sup>c</sup>Benefits based on the current US Preventive Services Task Force recommendation estimated from the Michigan model.

<sup>d</sup>Benefits based on the National Lung Screening Trial protocol in which  $\leq 15$  YSQ was enforced only as a criterion to begin screening and was not consider as a criterion to exit screening.

<sup>e</sup>Michigan model: benefits based on the 2023 updated American Cancer Society lung cancer screening guideline.

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deaths averted, lung cancer mortality, LYG, false positives, over-diagnosis, and more recent estimates of radiation-induced lung cancer deaths based on updated estimates of the average doses received during screening and follow-up examinations. The results from the Michigan and Erasmus models differ in the absolute magnitude of the estimated outcomes, but the outcome patterns and relative performance of alternative strategies were consistent across the two models.<sup>47</sup> We emphasize results from the Michigan model since screening outcomes (sensitivity and specificity) were based on the American College of Radiology (ACR) Lung Reporting and Data System (Lung-RADS) protocol, and it modeled radiation-induced lung cancer deaths, which we discuss in the section below on Harms associated with LCS.<sup>47</sup> Results from the Erasmus model, which produces outcomes that are more consistent with the NLST, are provided in the supplemental material from the CISNET analysis published online.<sup>47</sup>

Modeling results for the USPSTF 2021 recommended strategy (50-80-20-15) and the 2023 ACS guideline update with identical parameters were similar (Table 3, rows 1 and 2) but not directly comparable because results from the 2021 CISNET modeling were presented as mean estimates across the four models,<sup>46</sup> whereas only two of the four lung cancer CISNET models contributed to the ACS update, and results from each model were presented

separately. Maintaining the USPSTF-2021 criteria with YSQ15 (Table 3, row 2; WithYSQ 50-80-20-15) yielded a 10.8% lung cancer mortality reduction in the Michigan model, with 506 lung cancer deaths averted, 8471 LYG, and an NNS of 45 to save one life per 100,000 population (Table 3, row 2).<sup>47</sup> Removing the YSQ criterion (NoYSQ 50-80-20) resulted in a 13% lung cancer mortality reduction, 611 deaths averted, 10,090 LYG, and an NNS of 39 to save one life (Table 3, row 5). Compared with scenarios that include the  $\leq$ YSQ15 criterion for individuals who formerly smoked (Table 3, row 5 vs. row 2), removing YSQ resulted in a 37.3% increase in screening examinations, a 20.8% increase in lung cancer deaths averted, and a 19.1% increase in LYG per 100,000 population.<sup>47</sup>

Although there were too few scenarios to compare in an efficiency analysis (lung cancer deaths averted or LYG for a given level of screening), in the analysis conducted by Meza et al. in 2021 to compare efficiency by distance relative to a model-specific efficient frontier,<sup>46</sup> and in an analysis by Toumazis et al. in 2022 of the cost effectiveness of the 2021 USPSTF recommendation for LCS,<sup>56</sup> each study concluded that strategies with higher maximum YSQ criterion (ie, 20 and 25 YSQ) were more efficient and cost effective than strategies with more restrictive YSQ criterion, including the YSQ15 in the USPSTF 2021 recommendation.

**TABLE 4** Harms of lung cancer screening scenarios of starting screening at age 50 years with  $\geq 20$  pack-year smoking history, various years-since-quitting criteria, and age to stop screening from the Michigan Cancer Intervention and Surveillance Modeling Network lung cancer natural history model applied to the US 1960 birth cohort. The 2023 ACS lung cancer screening guideline is shaded.

Screening scenario <sup>a</sup>	LDCT screens, No.	Mean LDCTs per person screened, No.	Mean false positives per person screened, No.	Biopsies, No.	Overdiagnosis versus overdiagnosis if $\geq 5$ years' life expectancy, No.	Overdiagnosis as a % of all cases/as a % of all screen-detected cases	Radiation-induced lung cancer deaths, No.
With YSQ 50-80-20-15 <sup>b</sup>	419,030	18.5	2.2	518	84	1.7/6.0	38.6
With YSQ 50-80-20-15 <sup>c</sup>	425,373	18.5	1.06	754	72/37	1.2/4.1	12.8
NoYSQExit 50-80-20-15 <sup>d</sup>	556,275	24.2	1.35	945	98/45	1.7/4.7	16.0
NoYSQExit 50-80-20-30	584,013	24.3	1.36	966	100/45	1.7/4.7	16.7
NoYSQ 50-80-20 <sup>e</sup>	584,062	24.3	1.35	966	100/45	1.7/4.8	16.7
NoYSQ 50-80-20 with LE $> 5$ years	544,580	23.3	1.3	902	45	0.8/2.3	16.7
NoYSQ 50-85-20 with LE $> 5$ years	584,815	25.0	1.4	1029	63	1.1/2.8	18.2

Abbreviations: LDCT, low-dose computed tomography; LE, life expectancy; NNS, number needed to screen; YSQ, years since quitting.

<sup>a</sup>Screening scenarios in this table correspond to select YSQ scenarios that assume a screening starting age of 50 years, a minimum smoking history of  $\geq 20$  pack-years, and stopping screening at age 80 years unless otherwise specified. WithYSQ indicates a YSQ scenario in which  $n$  YSQ is enforced to begin screening and is a basis for exiting screening before age 80 years; NoYSQExit, a YSQ scenario in which  $n$  YSQ is enforced only when beginning screening, i.e., an individual who qualifies to begin screening and reaches  $n$  YSQ will not lose eligibility to continue screening, per the National Lung Screening Trial screening protocol; NoYSQ, a screening scenario that is based only on age and pack-year history.

<sup>b</sup>Benefits based on the current US Preventive Services Task Force recommendation estimated from four Cancer Intervention and Surveillance Modeling Network models in 2021, excluding estimates of radiation-induced lung cancer deaths, which were only estimated from the Harvard and Michigan Cancer Intervention and Surveillance Modeling Network models.

<sup>c</sup>Benefits based on the current US Preventive Services Task Force recommendation estimated from the Michigan model. The sharp reduction in the estimated numbers of radiation related lung cancer deaths from 2021 to 2023 is because radiation dose estimates were reduced from those involved in the National Lung Screening Trial to more current doses, such as those used in the COSMOS trial.

<sup>d</sup>Benefits based on the National Lung Screening Trial protocol in which  $\leq$ YSQ15 was enforced only as a criterion to begin screening and was not consider as a criterion to exit screening.

<sup>e</sup>Benefits based on the 2023 updated American Cancer Society lung cancer screening guideline.

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## Harms associated with lung cancer screening

The harms of LCS with LDCT include anxiety associated with recall and further evaluation, invasive procedures after abnormal findings, downstream harms associated with an evaluation of incidental findings, exposure to ionizing radiation, and the potential for overdiagnosis and overtreatment.<sup>24</sup>

### Recall for further evaluation and false-positive findings

In the RCTs, the frequency of LDCT results leading to recall for further evaluation varied widely, ranging from 7.9% to 49.3% at initial screening, and declined to 0.6%–28.6% during subsequent rounds of screening.<sup>24</sup> Baseline recall rates tend to be higher than recall rates in subsequent rounds because of the greater prevalence of larger nodules that need immediate evaluation and smaller nodules that are recommended for short-term follow-up, most of which showed no evidence of growth over time. In the NLST, recall rates declined from 26.3% at baseline to 15.9% by year 3.

The systematic review noted that variability in recall rates was caused in part by differences across the RCTs in the nodule size that defined a positive finding and prompted further evaluation. In the NLST, 4 mm was used as the nodule diameter threshold to prompt further evaluation. Pinsky et al. estimated that application of the currently used Lung-RADS threshold of 6 mm would have reduced the baseline recall rate by greater than one half to 12.8%, with a concomitant single-screen reduction in test sensitivity to detect lung cancer from 93.5% to 84.9%.<sup>57</sup> In another re-analysis of the NLST data using international ELCAP size criteria (mean of the short-axis and long-axis of the nodule), which is identical to the Lung-RADS criteria currently used in the United States, a noncalcified nodule size threshold of  $\geq 6$  mm (the current standard in the United States) would have reduced the recall rate in the NLST to 10.5%.<sup>58</sup> In the NELSON trial, which used volumetric-based rather than diameter-based criteria, 19.7% of participants in the screening arm had indeterminate results requiring short-interval follow-up scans in the initial screening round, which dropped to 1.9% in the fourth round (year 5.5).<sup>26</sup>

In the 2022 data from the ACR Lung Cancer Screening Registry, 3462 facilities reported 948,661 LCS examinations, of which 48%

were baseline examinations and 52% were annual repeat examinations. The overall recall rate for all LCS examinations was 13.2%; among individuals undergoing a baseline LCS examination, the recall rate was 15.7%, and, among individuals undergoing an annual repeat examination, the recall rate was 10.9% (Ella Kazerooni, personal communication, 2023), a recall rate similar to what is experienced by women undergoing routine mammography screening.<sup>59</sup>

The greater harm associated with recall for further evaluation pertains to patients who are referred for biopsy, in which there is a risk of complications. In the NLST, one in 59 patients (1.7%) who were recalled for further evaluation ultimately underwent invasive procedures, such as needle biopsy; complications were reported in 0.1% of those screened (one in 1000), and major complications occurred in 0.03%, (one in 3333), of which the majority were among patients with lung cancer.<sup>42</sup> In the NELSON trial, 1.2% of participants required further evaluation beyond surveillance computed tomography (CT) scanning.<sup>26</sup> Of these, there were no reported adverse events.<sup>26</sup>

Outside trial settings, researchers using real-world data reported that, among 18,887 individuals who were screened for lung cancer with LDCT between 2015 and 2017, 3.5% underwent invasive procedures (cytology or needle biopsy, bronchoscopy, thoracic surgery, and other surgical procedures) within 6 months of screening, in which the overall incremental complication rate from all procedures was 16.6%, including 1.7% with major complications, 9.3% with intermediate complications, and 11.2% with minor complications.<sup>60</sup> Based on this estimate, approximately one in 1700 experienced a major complication from an invasive procedure (i.e., 1.7% major complications among the 3.5% who underwent an invasive procedure).

In the CISNET modeling done for this update, the Michigan model estimates higher rates of harm per 100,000 individuals (recall for further evaluation with subsequent false-positive findings and biopsies) with NoYSQ versus  $\leq$ YSQ15 (Table 4), largely attributed to the greater number of adults undergoing screening at an older age.<sup>47</sup> The mean number of false positives per person screened with NoYSQ and  $\leq$ YSQ15 was 1.35 and 1.06, respectively (27.4% higher), and the number of biopsies was 966 and 754, respectively, per 100,000 individuals (28.1% higher).

## Overdiagnosis

Overdiagnosis can occur when a nonprogressive cancer is detected by screening or when a cancer detected by screening would not have been detected in the absence of screening because of death from another cause. We are not aware of estimates of how much lung cancer overdiagnosis falls into each type; however, in either case, the patient would not benefit from screening. The systematic review noted seven RCTs that addressed overdiagnosis by assessing differences in cancer incidence between invited and control groups. There is wide variation in estimates of overdiagnosed screen-detected lung cancer, ranging from 0% to 67.2%, suggesting limitations in both data and methodology.<sup>42</sup> The NLST cumulative incidence data indicated four cases of overdiagnosis and three lung cancer deaths prevented

per 1000 people screened with a median of 6.5 years of follow-up (4.5 years after the last scheduled screening examination).<sup>2</sup> In 2014, Patz et al. estimated that 18.5% of all lung cancers in the NLST LDCT arm were overdiagnosed based on the excess number of lung cancers in the LDCT arm compared with the CXR arm after a mean follow-up of 6.41 years.<sup>61</sup> However, a common confounding variable that inflates overdiagnosis estimates is lead time.<sup>62</sup> After a longer follow-up time of 11.3 years, the NLST research team reported that there was no overall increase in lung cancer incidence in the LDCT arm versus the CXR arm.<sup>53</sup> In contrast, the NELSON trial estimated 9% overdiagnosis at 11 years of follow-up.<sup>8</sup> Although RCTs presumably provide an ideal study design for measuring excess incidence in a group invited to screening compared with a noninvited group, inadequate follow-up, lack of complete post-trial incidence ascertainment, and the possibility of differential poststudy exposure to screening limit the ability to accurately estimate rates of overdiagnosis in a given study, and overall, with measurable confidence.<sup>62</sup>

In the CISNET modeling done for the USPSTF 2021 update (50-80-20-15), overdiagnosis among screen-detected cases over a lifetime of screening was estimated to be 6% versus 4.1% in the Michigan model alone in the analysis done for this ACS update (Table 4).<sup>46</sup> In the CISNET modeling done for this guideline update, which eliminates YSQ15 as an exclusion criterion, the estimated overdiagnosis rate was similar to that in the Michigan model alone (4.8% over a lifetime of screening).<sup>47</sup> However, when individuals undergoing screening had at least 5 years' life expectancy (Table 4), the estimated overdiagnosis rate was 52% lower (2.3% vs. 4.8%), emphasizing the importance of prioritizing an assessment of life-limiting comorbidity and longevity before offering screening.

## Risk from exposure to ionizing radiation

A single LDCT scan delivers approximately 1.5 millisieverts (mSv) of radiation, substantially less than a standard chest CT scan (6.1 mSv).<sup>63</sup> Although it is not possible to directly observe or measure harms that may occur from repeated radiation exposures from LDCT screening for lung cancer, assessing risk from radiation exposure commonly is conservative and conventionally based on the assumption that single and cumulative exposures of radiation may carry some potential for harm. These harms are estimated using a linear, no-threshold dose model to extrapolate from the observed risk in atomic bomb survivors to individuals undergoing low-dose exposures received during medical imaging.<sup>64</sup> The systematic review noted the results of two studies that provided estimates of cumulative radiation exposure from LDCT and, through extrapolation of those results, estimated that the cumulative radiation exposure from LDCT screening examinations would range from 20.8 to 32.5 mSv over a period of 25 years of annual screening from ages 55 to 80 years.<sup>24</sup> Although the evidence report did not include exposures from diagnostic examinations in their estimate of cumulative exposures or the lifetime risk of fatal cancers associated with annual screening, the report did cite estimates from the Continuing Observation of

Smoking Subjects (COSMOS) trial (ClinicalTrials.gov identifier NCT1248806),<sup>65</sup> which had 10 rounds of screening from 2004 to 2015, during which cumulative dose data from screening LDCT and follow-up LDCT and positron emission tomography (PET) CT studies were collected. Based on the National Academy of Sciences BEIR (Biologic Effects of Ionizing Radiation) VII estimates of organ-specific lifetime attributable risk from exposure to ionizing radiation, the COSMOS investigators estimated that 10 annual LDCT examinations would result in 0.46 radiation-induced major (organ) cancers per 1000 persons screened.<sup>65</sup>

In considering the benefit of LCS (lung cancer deaths averted) and the possible harms associated with exposure to radiation during LCS and follow-up examinations over a lifetime of screening, the ACS GDG sought to estimate the benefit-to-radiation risk based on modern LDCT doses and current follow-up rates over a lifetime of screening compared with the higher doses and follow-up rates in the NLST or estimates of risk over shorter durations. By using organ doses from Larke et al.<sup>66</sup> NLST median age and sex distribution, and age-specific/sex-specific lifetime mortality risks per unit dose of ionizing radiation from BEIR VII,<sup>64</sup> Hendrick and Smith estimated that the number of radiation-induced cancer deaths in the NLST from three rounds of LDCT screening is 5.53 (2.46 in males and 3.07 in females), yielding an estimated benefit-to-radiation-risk ratio for both sexes combined of approximately 16:1 when considering screening doses alone and 12:1 overall when screening doses and estimated follow-up examination doses are included.<sup>44</sup> To estimate the benefit-to-radiation risk ratios for a lifetime of recommended LCS, the authors used data from the COSMOS trial.<sup>65</sup> During the 2004–2015 study period, CT technology advanced from 8-slice to 16-slice scanners and from 16-slice to 64-slice scanners, approximating current CT technology.<sup>65</sup> Assuming sex-specific mortality benefits like those of the NELSON trial,<sup>26</sup> the benefit-to-radiation-risk ratio of the COSMOS trial was estimated to be 23:1. Based on COSMOS trial dose data and assuming a 20% lung cancer mortality benefit (which is conservative), annual screening in individuals aged 50–79 years with a  $\geq 20$  pack-year smoking history has estimated benefit-to-radiation-risk ratios from 23:1 (with follow-up examination doses adding a 40% additional dose to the screening doses) to 29:1 (with follow-up examination doses adding a 10% additional dose to the screening doses).<sup>44</sup>

From the modeling conducted for this guideline update (with YSQ15 removed as a screening exclusion and updated radiation dose estimates), Meza et al. estimated that, over a lifetime of screening from ages 50 to 80 years (24 LDCTs), there would be 16.7 radiation-induced lung cancer deaths (in contrast to 611 lung cancer deaths averted) per 100,000 population (Tables 3 and 4). This compares with 12.8 radiation-induced deaths (in contrast to 506 lung cancer deaths averted) with the  $\leq$ YSQ15 screening exclusion maintained (i.e., the current recommendation from the USPSTF<sup>47</sup>), which, with updated estimates of dose based on current technology, is approximately one third of the radiation-induced lung cancer deaths (38.6) estimated in the CISNET 2021 analysis for the USPSTF.<sup>45</sup> Based on the estimated deaths averted from LCS in the NoYSQ scenario, the model estimates

a benefit-to-radiation-risk ratio of 26:5, which is in good agreement with the estimates from Hendrick and Smith for long-term screening based on radiation doses from the COSMOS trial.<sup>44</sup> Although these estimates are theoretical, they demonstrate a very favorable benefit-to-risk ratio associated with LCS but are a cautionary reminder that avoiding unnecessary or excessive screening and diagnostic follow-up radiation doses over a lifetime of LCS should be strongly emphasized.

## Incidental findings

Incidental findings detected during LCS can lead to downstream evaluation, including consultations, additional imaging, and invasive procedures, each with associated costs and burdens. Incidental findings can represent either a benefit, a harm, or neither, depending on the findings. Reports of incidental findings interpreted as significant or leading to further evaluation varied widely among studies (from 4.4% to 40.7%) and were more likely to occur among older individuals.<sup>42</sup> The variability among studies was attributed to inconsistent definitions of an incidental finding and variability in which findings warranted further evaluation. Common incidental findings include coronary artery calcifications, aortic aneurysms, emphysema, infectious and inflammatory processes, and space-occupying lesions (masses, nodules, or cysts) of the kidney, breast, adrenal glands, liver, thyroid, pancreas, spine, and lymph nodes.<sup>42</sup> During the three rounds of LDCT screening, cancers involving the thyroid, kidney, or liver were diagnosed in 0.39% of NLST participants, with the highest malignancy-to-incidental LDCT finding ratio associated with thyroid cancer (1:14).<sup>67</sup> Overall, the systematic review concluded that the benefit of detecting nonlung cancer conditions during LDCT screening is uncertain.<sup>24</sup> Approximately 18.8% of adults undergoing LCS will receive an S examination modifier added to Lung-RADS categories 0 through 4 for having one or more clinically significant or potentially clinically significant findings unrelated to lung cancer.<sup>68,69</sup>

Out of the 1,165,746 screening exams entered into ACR lung cancer screening registry from 2015 to 2019, 18.8% of exams had one or more S modifier finding, with 15.6% having one finding, 2.2% having two findings and 0.4% having three or more findings. The most common S modifier findings reported were moderate or severe coronary arterial calcification on 11.6% of screens, a mass requiring further evaluation in 2.8%, interstitial lung disease on 2.7%, significant emphysema in 1.2% and an aortic aneurysm in 0.9%, and a reference guide has been published by the ACR to aid in management of these and other S modifier findings.<sup>69</sup>

## Eligibility criteria for lung cancer screening

### Age to begin lung cancer screening

The 2013 ACS guideline and others recommended starting LCS at age 55 years based on the NLST eligibility criteria and favorable

results from the trial.<sup>3</sup> Since then, other RCTs have reported results from studies that included participants as young as age 50 years, of which the largest is the NELSON trial, which enrolled persons aged 50–74 years.<sup>26</sup> Although not powered to detect differences among age-specific subgroups, a 15% reduction in lung cancer mortality was observed among men aged 50–54 years invited to screening (RR 0.85, 95% CI 0.48–1.50).<sup>26</sup>

The 2021 CISNET modeling studies estimated greater reductions in lung cancer deaths and increases in LYG with an annual screening strategy of 50-80-20-15 (USPSTF 2021) compared with the 2013 USPSTF recommendation of an annual screening strategy of 55-80-30-15 (see *Modeling Studies* in the benefits section above). Also, the models estimated an increase to almost 24% (from 14%) in the number of persons eligible for lung screening when the age to begin screening was decreased from 55 to 50 years and pack-years eligibility was decreased from 30 to 20. These changes were shown to be an efficient strategy in terms of benefit-harm trade-off, with the potential to avert premature mortality from lung cancer and increase LYG.

## Age to stop lung cancer screening

The GDG examined RCT and observational study evidence and the results of modeling studies in their consideration of when to stop LCS. The systematic review included seven RCTs, none of which enrolled participants older than 75 years.<sup>42</sup> However, based on the age range of the NELSON trial participants, the benefits of LDCT for LCS can be generalized to persons up to age 79.5 years who are in good health and meet the smoking criteria for LDCT screening.<sup>42</sup> Although it was not powered to detect a lung cancer mortality benefit associated with an invitation to screening by age subgroup, the NELSON trial demonstrated a similar, but not statistically significant, 23% risk reduction in the subgroup who were aged 70–74 years at the study entry, comparable to the risk reduction in all other age groups.<sup>26</sup>

The GDG also examined disease burden data, including lung cancer incidence and mortality, in older age groups. The distribution of lung and bronchus cancer incidence (2016–2020) and mortality (2016–2020) per 100,000 by 5-year age groups from the NCI's Surveillance, Epidemiology, and End Results (SEER) data show both incidence (366.5 per 100,000) and mortality (296.7 per 100,000) peaking in the group aged 80–84 years (Figure 1).<sup>70</sup> Figure 2A illustrates the proportional distribution of age-specific lung cancer incidence rates in men and women, showing that 20% of lung cancer cases are diagnosed after age 80 years. Figure 2B illustrates the proportional distribution of lung cancer deaths by age at diagnosis, showing a proportional distribution similar to that of deaths attributable to a diagnosis after age 80 years, and greater than 50% of lung cancer deaths are attributable to a diagnosis after age 70 years. Figure 2C illustrates age-specific PYLL attributable to the age at diagnosis, highlighting that greater than 80% of PYLL is attributable to a diagnosis within the age range (50–80 years) of the target population recommended to undergo LCS. Although these numbers

are derived from the entire population, the distribution is likely to approximate the burden of disease in the target population with a history of tobacco use that qualifies for LCS.

The CISNET modeling analyses conducted for the 2021 USPSTF update provided additional supporting evidence for extending screening to age 80 years for individuals who meet eligibility criteria. Several efficient strategies were reported for screening starting at ages 50 and 55 years and for all consensus scenarios and continuing to age 80 years, with pack-year smoking thresholds of 15, 20, and 25 years.<sup>45,46</sup> Given the high incidence of lung cancer in the group aged 80–84 years, the GDG asked the CISNET investigators to include scenarios that extended the age to exit screening beyond age 80 years in 5-year increments. The supplemental modeling demonstrated that extending screening (NoYSQ-50-85-20) from age 80 to age 85 years when all individuals have a life expectancy of at least 5 years yielded a 16.9% increase in lung cancer cases detected and 13%–14% more lung cancer deaths averted (Table 3), with only a 0.5% increase in the rate of overdiagnosis (a proportional increase of 21.7%, from 2.3% to 2.8%). Although it is unrealistic to successfully predict that all individuals referred to LCS will have >5 years' longevity, the model predicts that, if it were possible, the rate of overdiagnosis as a percentage of all screen-detected cases would be greater than 50% lower when screening to age 80 years (Table 4, rows 5 and 6).<sup>47</sup>

In their deliberation relating to the age to stop screening, the GDG concluded that the cumulative evidence supported a strong recommendation to screen for lung cancer up to age 80 years. This evidence included RCT data supporting a benefit to screening up to age 79.5 years, epidemiological data showing substantial disease burden at ages up to and older than 80 years, and modeling data demonstrating strong benefit over harm with strategies that involve screening to age 80 years and older, especially if all adults undergoing screening have at least 5 years' expected longevity. In addition, the GDG considered data on longevity from 2020 US life tables, noting that 74% of women aged 80 years and 66% of men aged 80 years will live at least 5 years,<sup>71</sup> but the group also noted that these data do not account for current or prior smoking status and the higher all-cause mortality risk of persons with a history of smoking.<sup>72</sup>

The GDG considered whether to extend the recommendation for LCS to individuals aged 81–85 years in good health based on the high incidence and mortality burden from lung cancer in this age group and the supportive modeling evidence described above. However, the paucity of trial evidence and observational studies of screening, and concern that the harms of diagnostic and therapeutic interventions in this age group have not been adequately studied, led the GDG to conclude there is insufficient evidence to issue a formal recommendation for a higher age cutoff. In addition, challenges to estimating life expectancy in this age group further complicate the screening decision, especially because common prognostic calculators may not be calibrated for smoking history (vs. ever smoked). Recognizing the potential value of screening in smoking history-eligible persons aged 81–85 years in otherwise excellent health, the GDG felt that individualized decision-making for this population can be appropriate



(see Decision making and clinical considerations, below) and considers this area a high priority for further research.

## Pack-year history

The seven RCTs in the systematic review included persons who formerly or currently smoked and were at higher risk for disease based on a combination of age and smoking history. The RCTs commonly used a smoking history of  $\geq 20$  or  $\geq 30$  pack-years.<sup>24,42</sup>

The eligibility criteria for LCS in the 2013 ACS recommendations, like most early guidelines and recommendations, were primarily based on inclusion criteria in the NLST for the population defined as being at high risk for lung cancer ( $\geq 30$  pack-years of smoking).<sup>2</sup> Since then, evidence has accumulated to show the benefit of LCS in persons with fewer pack-years of smoking. The NELSON trial demonstrated evidence of screening benefits in persons with as few as  $\geq 15$  pack-years of smoking because this was their minimum eligibility criterion (although most had significantly heavier smoking histories, in that the median pack-year history was 38.0 [interquartile range, 29.7–49.5 pack-years]).<sup>26</sup>

The 2021 CISNET modeling studies also provided data that helped support lowering the pack-year eligibility criterion for LCS. Meza et al. identified six consensus-efficient strategies for annual screening of persons up to age 80 years with a smoking history of  $\geq 20$  pack-years and at least 15 YSQ (but also including 20 and 25 YSQ), with lung cancer mortality reductions ranging from 12% to 14.4%.<sup>46</sup> The modeling studies consistently demonstrated that strategies including  $\geq 20$  pack-year thresholds were efficient, suggesting that the increased risk of harms, including false-positive scans, radiation exposure, and overdiagnosis, was offset by the increase in LYG and a reduction in deaths from lung cancer. Also, there is evidence from observational studies that lowering the pack-year history criterion for LCS will likely increase access to LCS by increasing the number of women and Black, Hispanic, and Asian individuals who will qualify for screening (see Disparities in lung cancer screening, below).

## Years since quitting smoking

The earliest LCS guidelines and recommendations restricted the eligibility of individuals who formerly smoked to  $\leq 15$  YSQ. Since then, guidelines and recommendations have evolved to reduce the number of pack-years of smoking and the age to begin screening; however, for individuals who formerly smoked, YSQ15 has been retained.

In the NLST, eligibility for people who formerly smoked and had a  $\geq 30$  pack-year history was limited to those who were within 15 years of quitting<sup>2</sup>; and in the NELSON trial, individuals who formerly smoked and who met age and pack-year history criteria must have been within 10 years of quitting.<sup>26</sup> None of the publications associated with either trial describe the evidence or rationale for these YSQ thresholds. Pinsky et al. speculated that the perception that lung

cancer risk declined significantly with further YSQ, combined with the desire to populate a trial with a group at higher risk to maximize the potential to measure a benefit from LDCT screening, may have led to choosing the  $\leq$  YSQ15 threshold in the NLST.<sup>73</sup> However, the GDG's conversations held with NLST and NELSON investigators and others to better understand the process that led to  $\leq$  YSQ15 did not reveal how or why these thresholds were chosen beyond similar trial design explanations offered above, but did report that they were only qualifying thresholds (i.e., no one could recall that study participants who reached 10 or 15 YSQ during the study period lost eligibility to continue screening). This means that evidence from the NLST cannot be assumed to reflect lung cancer risk in persons who formerly smoked and were not beyond 15 years since cessation, because, at the conclusion of the trial some individuals would have undergone screening with up to 18 years since smoking cessation. This feature of the NLST is at odds with current recommendations, guidelines, and insurance coverage criteria that specify screening should not begin or should cease once YSQ15 is reached.

The current recommendations for LCS were shaped by the RCT eligibility criteria, study outcomes from NLST and NELSON, and the contribution of simulation modeling that has provided additional supporting evidence for these ages, pack-year, and YSQ criteria, as well as justification to extend screening to age 80 years. However,  $\leq$  YSQ15 has been retained as a core criterion for LCS eligibility and health plan coverage of LCS without being addressed in either of the systematic reviews conducted to support the USPSTF in the 2013 or 2021 recommendations.<sup>24,42,74</sup> Although the 2021 modeling report for the 2021 USPSTF recommendation update did not include scenarios that excluded YSQ as a criterion, they did find that screening scenarios of 50-80-20 that extended YSQ to 20 and 25 years were both efficient strategies.<sup>46</sup> In a subsequent analysis, Toumazis et al. showed that screening scenarios of 50-80-20 that extended YSQ to 20 and 25 years were also more cost effective.<sup>56</sup>

Historical and emerging data indicate that two core assumptions about YSQ with respect to continuing lung cancer risk are incorrect: first, that persons who formerly smoked are on a continuous trajectory of declining absolute risk,<sup>75</sup> and second, that individuals who are past YSQ15 are no longer at sufficiently elevated risk to justify screening.<sup>73</sup>

## The ACS CrEST systematic review

The GDG requested that the ACS CrEST conduct a systematic review of lung cancer incidence, risk, and mortality beyond YSQ15 in persons with  $\geq 20$  pack-years of smoking for this guideline update.<sup>43</sup> The search identified articles through February 14, 2023, and yielded 22 studies from 26 publications. The reviewers concluded that, although the risk of lung cancer declined gradually after cessation compared with continuing smoking, there were no clinically significant differences when comparing individuals in the quit-year categories just before and beyond YSQ15 (six studies, moderate certainty of evidence [COE]).<sup>43</sup> Similarly, compared with individuals

who never smoked, lung cancer incidence for those beyond YSQ15 can remain up to 10 times greater through 30 YSQ (three studies, low COE). The review included two studies examining lung cancer mortality or recurrence-free survival.<sup>76,77</sup> Although both studies reported better outcomes with increasing YSQ, one of the studies found that the risk of lung cancer mortality remained three to four times higher for up to 30 years in individuals who formerly smoked compared with individuals who never smoked,<sup>77</sup> and neither study found a significant difference when comparing groups with 10–20 YSQ. Because of heterogeneity in these two studies, the COE is insufficient to form conclusions about YSQ and mortality or recurrence-free survival.

The research examining lung cancer incidence, risk, and mortality among individuals with a  $\geq 20$  pack-year history who are beyond YSQ15 is largely composed of observational studies of fair methodological quality that were designed to investigate other primary and secondary aims. Studies vary in the categorization of YSQ and outcome reporting, and many of the studies may not be as applicable to current US populations because of factors such as publication date, country, or sociodemographic population. However, despite these limitations, these studies consistently found no statistically and/or clinically significant differences in lung cancer incidence and risk until and beyond 15 YSQ.<sup>43</sup>

Most of the literature examined in the CrEST systematic review compared relative risk and outcomes in individuals who formerly smoked versus individuals who currently smoke. Given the importance and emphasis on smoking cessation, this comparison is more common and has provided a strong incentive for individuals to stop smoking—when a person quits smoking, not only does their risk of lung cancer drop within a few years, it also continues to decrease over time *relative* to a person who continues to smoke, whose risk continues to increase. The CrEST systematic review concluded that there is moderate COE that lung cancer risk does not drop dramatically or significantly at 15 YSQ. However, fewer studies address an equally important question that is central to addressing risk in the context of YSQ: once a person quits smoking, how long does their lung cancer risk remain higher than that of a person who never smoked? This smaller body of literature found that medium-to-large contemporary studies conducted in the United States, such as Tindle et al.'s analysis of Framingham Heart Study data,<sup>78</sup> Pinsky et al.'s cross-sectional follow-up to the NCI's PLCO study,<sup>73</sup> and the analysis of the ACS' Cancer Prevention Study II–Nutrition Cohort published in the 2020 Surgeon General's Report, all observed that, even at 25–30 YSQ or longer, lung cancer risk remained more than three times greater than the risk for individuals who never smoked.

## Modeling studies

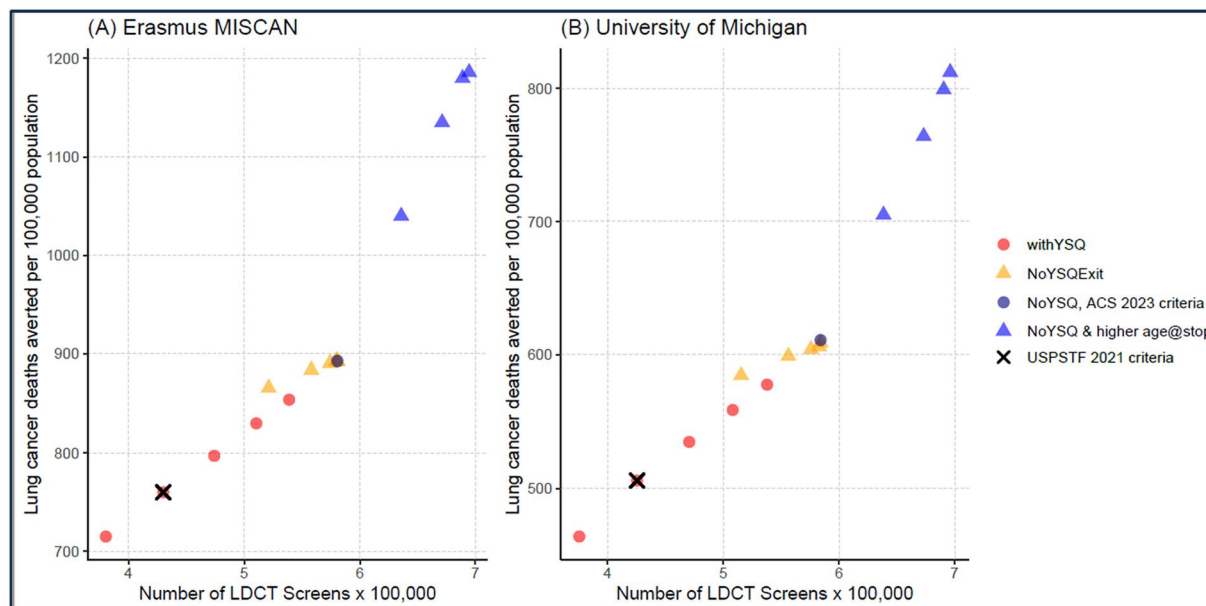
In the modeling analysis performed by the Michigan and Erasmus CISNET groups for the ACS guideline update, Meza et al. examined three different YSQ scenarios. The first two YSQ scenarios (*WithYSQ*

and *NoYSQExit*) compare outcomes based on YSQ durations of 10, 15, 20, 25, and 30 years and differ based on whether the YSQ strategy influences both starting and stopping screening (*WithYSQ*), which includes the 2021 USPSTF recommendation<sup>34</sup> and Medicare coverage,<sup>38</sup> or just influences eligibility to start screening but would not disqualify continuing screening if the YSQ threshold is met (*NoYSQExit*). The third YSQ scenario (*NoYSQ*) is a scenario in which YSQ is eliminated as a criterion for starting or stopping screening, and the age to stop screening varies from 80 to 100 years to explore the incremental effectiveness of screening past the age of 80.<sup>47</sup> Outcomes associated with the different scenarios are compared with a no-screening scenario.

Maintaining the same age range and pack-year criteria (50–80–20) but easing or removing the YSQ criterion resulted in an increase in the number of individuals eligible for LCS and the number of screening examinations and an increase in lung cancer deaths averted and LYG in both the Erasmus and Michigan models (see Tables 3 and 4, Figures 3–5). Each scenario of easing and eliminating YSQ resulted in increased eligibility for LCS, increased numbers of deaths averted and LYG, and increased harms (false positives, biopsies, and estimates of overdiagnosis and radiation-induced lung cancer deaths), although, as demonstrated elsewhere, easing the YSQ criterion up to 25 years was more efficient and cost effective compared with enforcing YSQ15 to start and continue screening.<sup>46,56</sup> Furthermore, with respect to harms, Meza et al. noted that harms would be reduced by ensuring that LCS was restricted to individuals with reasonable life expectancy ( $>5$  years).<sup>47</sup>

Figure 5 illustrates the relative influence of enforcing different numbers of YSQ on the percentage of the 1960 US birth cohort eligible to start and continue LCS. It appears that very few individuals accumulate a  $\geq 20$  pack-year history and quit smoking  $\geq 15$  years before age 50 years. As shown in Figure 5, the greater impact of the  $\leq$ YSQ15 criterion on limiting the potential of LCS to avert deaths is not because of ineligibility to begin screening at age 50 years, but rather because of the steady loss of eligibility from reaching YSQ15, which accelerates after age 60 years.<sup>47</sup> Compared with the current recommendations and coverage with YSQ15, eliminating YSQ criterion to continue screening for adults who were eligible to begin screening with  $<15$  YSQ results in 18% more deaths averted versus 21% more deaths averted by eliminating the YSQ criterion (to start or stop screening) altogether. In other words, not exiting screening accounts for 86% of the additional deaths averted from eliminating YSQ as a criterion. Under the current USPSTF recommendations, an individual aged 50 years who ceased smoking in the year they initiated screening would be disqualified from continuing screening at age 65 years, the midpoint of their age-based screening eligibility when their risk of lung cancer is rising with increasing age.

Further evidence supporting eliminating YSQ15 from LCS eligibility criteria came from Landy et al., who used PLCO (adults with  $\geq 20$  pack-years), NLST (adults with  $\geq 30$  pack-years), and National Health Interview Survey (NHIS) 2015–2018 data in an analysis for the 2023 ACS guideline update of persons who ever smoked to

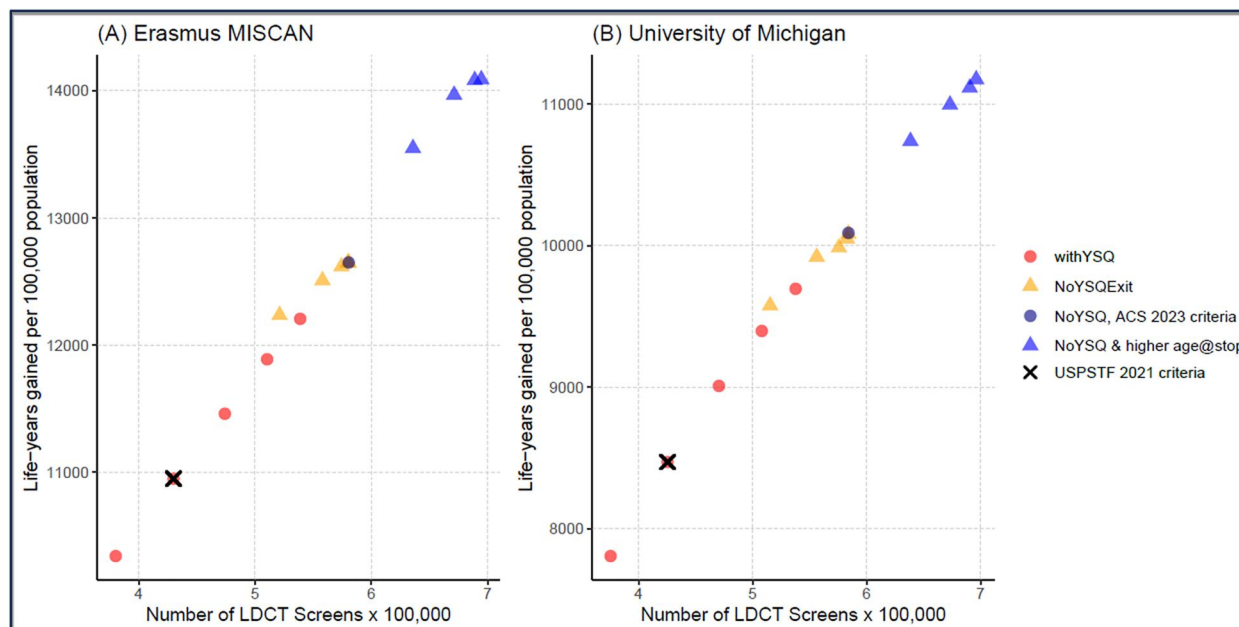


**FIGURE 3** The number of LDCT screens versus the number of lung cancer deaths averted according to the (A) Erasmus MISCAN and (B) University of Michigan models. Three different years-since-quitting (YSQ) scenarios were considered: (1) varying the maximum YSQ criterion in the current 2021 USPSTF guidelines (withYSQ: YSQ threshold of 10, 15, 20, 25 and 30 years), (2) enforce the maximum YSQ criteria only at entry to the screening program (NoYSQExit: YSQ threshold of 10, 15, 20, 25, and 30 years), and (3) screening eligibility criteria based on only age and pack-years of smoking (NoYSQ). NoYSQ strategies also varied the age at which screening stops (ages 80, 85, 90, and 95 years). The USPSTF 2021 criteria (50-80-20-15) are highlighted with an X, and the ACS 2023 scenario criteria (50-80-20, noYSQ) are highlighted with a solid dark circle. ACS indicates American Cancer Society; CISNET, Cancer Intervention and Surveillance Modeling Network; LDCT, low-dose computed tomography; MISCAN, Microsimulation Screening Analysis-Lung Model from Erasmus University Medical Center; USPSTF, US Preventive Services Task Force; YSQ, years since quitting. Reproduced with permission from Ref. 47.

estimate absolute lung cancer risk over time in adults who quit smoking.<sup>48</sup> Their analysis also examined the impact of relaxing USPSTF recommendations to 20, 25, and 30 YSQ, and eliminating YSQ entirely. Furthermore, the authors evaluated augmenting USPSTF 2021 criteria with high-potential-benefit individuals according to the life-years from screening-CT (LYFS-CT) prediction model.<sup>48</sup> Consistent with observations described by Halpern et al. in 1993,<sup>75</sup> Landy et al. examined PLCO data and observed decreasing risk in all ages after smoking cessation in the first 5 YSQ, with a relative annual percentage change (RAPC) of  $-4.4\%$ . However, at 5 YSQ the decline in the RAPC slows, and beyond 10 YSQ the effect of aging overcomes the effect of quit-years, with an observed RAPC in absolute risk of  $+3.8\%$ .<sup>48</sup> The same pattern of declining and then increasing risk was also observed in the NLST CXR arm (see Supporting Materials and Figure 1 in Landy et al.<sup>48</sup>). Furthermore, risk increases even more substantially beyond YSQ15 among persons who entered the PLCO with  $\geq 20$  pack-years, with an RAPC of  $+8.7\%$  (95% CI 7.7–9.7%,  $P < 0.001$ ).<sup>48</sup> At each age (55, 60, etc) that a person with  $\geq 20$  pack-years who formerly smoked reaches YSQ15, their risk is rising and continues rising over time to age 74, which was the age cutoff in Landy et al.'s analysis of PLCO data. Ironically, the data show that lung cancer risk is rising, not declining, as an individual approaches YSQ15, and continues rising after exceeding

YSQ15. Figure 6 shows estimates of 5-year lung cancer risk as quit-years and age increase among individuals with  $\geq 20$  pack-years from the NHIS 2015–2018 data. Except for individuals who quit smoking at age 65 or older and would not be disqualified from screening before age 80 due to YSQ15, all other individuals who meet eligibility to begin screening and who quit smoking at younger ages experience rising lung cancer risk over time, but are ineligible to continue LCS under current recommendations.

Landy and colleagues concluded that increasing or removing YSQ criteria would have a significant influence on the number of people who ever smoked who would be eligible for LCS, and this increased eligibility would have a significant influence on averting preventable lung cancer deaths. Among individuals with  $> 20$  pack-years smoking history, increasing YSQ eligibility to 20, 25, and 30 years, or eliminating the YSQ criterion, would result in 1.6, 2.5, 3.7, and 4.9 million additional individuals becoming eligible for LCS, respectively. Eliminating YSQ15 would result in an 11% absolute increase or 34% relative increase in eligibility for LCS among individuals who formerly smoked and meet current age and pack-year criteria.<sup>48</sup> Although this number seems quite large, NHIS data reveals that among individuals with a significant history of smoking ( $\geq 20$  pack-years), half (50.5%) have  $\geq 15$  YSQ, and over half of these individuals have pack-year histories  $\geq 30$  years.<sup>48</sup> Landy et al. estimated that removing the



**FIGURE 4** (A, B) The number of LDCT screens versus the life-years gained according to each of the CISNET models. Three different years-since-quitting (YSQ) scenarios were considered: (1) varying the maximum YSQ criterion in the current 2021 USPSTF guidelines (withYSQ: YSQ threshold of 10, 15, 20, 25, and 30 years), (2) enforce the maximum YSQ criteria only at entry to the screening program (NoYSQExit: YSQ threshold of 10, 15, 20, 25, and 30 years), and (3) screening eligibility criteria based on only age and pack-years of smoking (NoYSQ). NoYSQ strategies also varied the age at which screening stops (ages 80, 85, 90, and 95 years). The USPSTF 2021 criteria (50-80-20-15) are highlighted with an X, and the ACS 2023 scenario criteria (50-80-20, NoYSQ) are highlighted with a solid dark circle. ACS indicates American Cancer Society; CISNET, Cancer Intervention and Surveillance Modeling Network; LDCT, low-dose computed tomography; MISCAN, Microsimulation Screening Analysis-Lung Model from Erasmus University Medical Center; USPSTF, US Preventive Services Task Force. Reproduced with permission from Ref. 47.

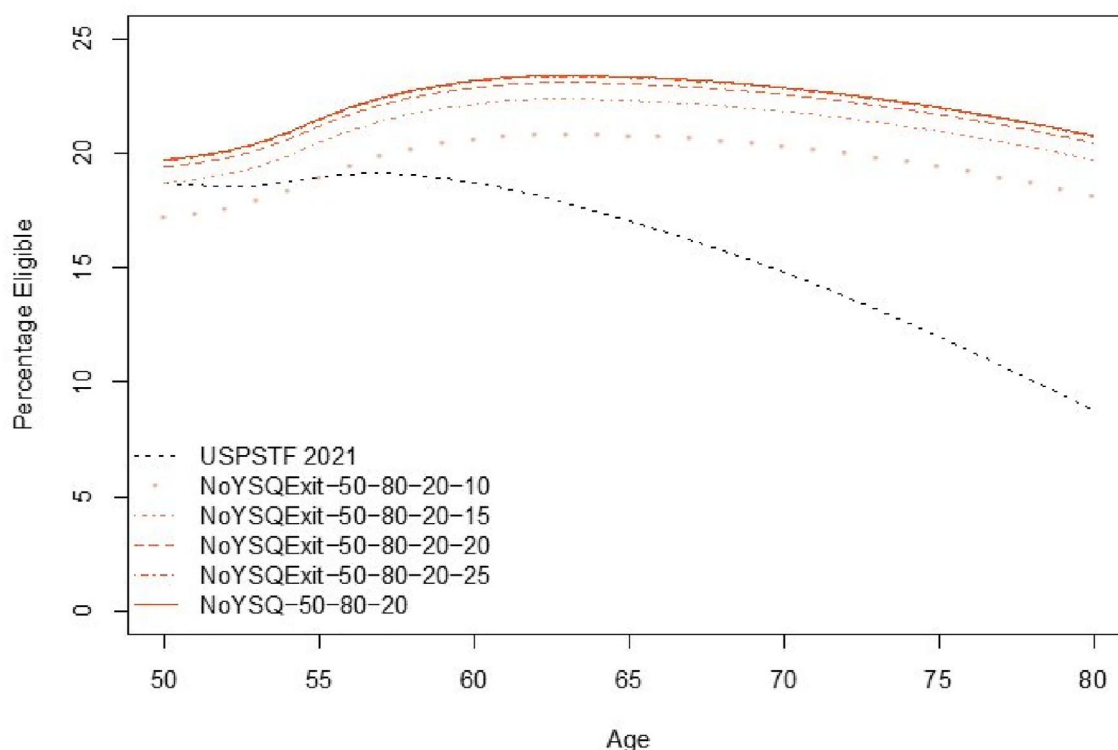
YSQ criterion could result in an additional 8,275 lung cancer deaths averted, and 115,107 LYG over five years (ie, each person whose life is saved by screening gains an average of 14 years of life).<sup>48</sup>

### Patient preferences and values related to lung cancer screening

The systematic review revealed limited evidence related to patient preferences regarding LCS with LDCT, either before or after SDM.<sup>24,42</sup> Clark and colleagues assessed the impact of a decision aid used in a primary care setting on 219 qualified patients' LDCT screening preferences.<sup>79</sup> Those authors observed that reducing the chance of death from lung cancer rated considerably higher than any of the listed harms by the majority of study participants, including postscreening out-of-pocket costs, being recalled for further evaluation, and complications of diagnostic procedures. Two smaller studies that focused on LCS uptake after an online educational intervention observed lower interest in LCS. Reuland et al. focused on an educational video, and preintervention and postintervention surveys indicated that the educational intervention improved knowledge, but only 50% of individuals preferred LCS after viewing the video decision aid.<sup>80</sup> Dharod et al. recruited screening-eligible adults through a patient portal to view an online LCS decision aid

and reported that 30% desired LCS, 44% were unsure, and 26% declined.<sup>81</sup> In contrast, in a larger study of patient decisions after referral from primary care or specialty practices, Mazzone et al. examined the impact of a visit that incorporated the use of individualized risk assessment, centralized counseling, and SDM and observed that only 5.4% of 423 patients did not proceed to screening.<sup>82</sup> The systematic review noted that studies in the primary care setting revealed heterogeneous decisions, which the authors concluded was an indication that decisions about LCS were preference sensitive; and, in contrast, when SDM takes place in the specialty clinic, the high rate of acceptance of screening suggests that patient preferences can be influenced by the context, timing, and content of SDM.<sup>24</sup> However, an alternative interpretation, without knowing the nature of the conversations that took place in the referral practices, is that the high rate of acceptance in the study by Mazzone et al.<sup>82</sup> reflects the value of a more lengthy discussion with patients with the support of a qualified health professional and thus is more consistent with most high-risk individual's preferences. Although we do not know the rate at which eligible individuals rejected the opportunity to participate in the NLST, the rapid rate of enrollment and the high rate of adherence to the three rounds of screening suggest the latter may be the case.<sup>83</sup>

Patients' decisions about LCS may be affected by risk and individual life expectancy (i.e., individuals who are at higher risk or with



**FIGURE 5** Percentage of the US 1960 birth cohort eligible for low-dose computed tomography screening at each age for the scenarios with the maximum years-since-quit (YSQ) criterion enforced only at entry into the program (YSQ = 10, 15, 20, 25, 30) to illustrate the small effect of the YSQ criterion on eligibility to initiate screening and the larger effect of  $\leq 15$  YSQ on eligibility to continue screening. The USPSTF 2021 scenario with the 15 YSQ criterion for screening entry and exit and the ACS 2023 scenario with no YSQ criterion (NoYSQ-50-80-20) are shown for comparison. ACS indicates American Cancer Society; USPSTF, US Preventive Services Task Force. Reproduced with permission from Ref. 47.

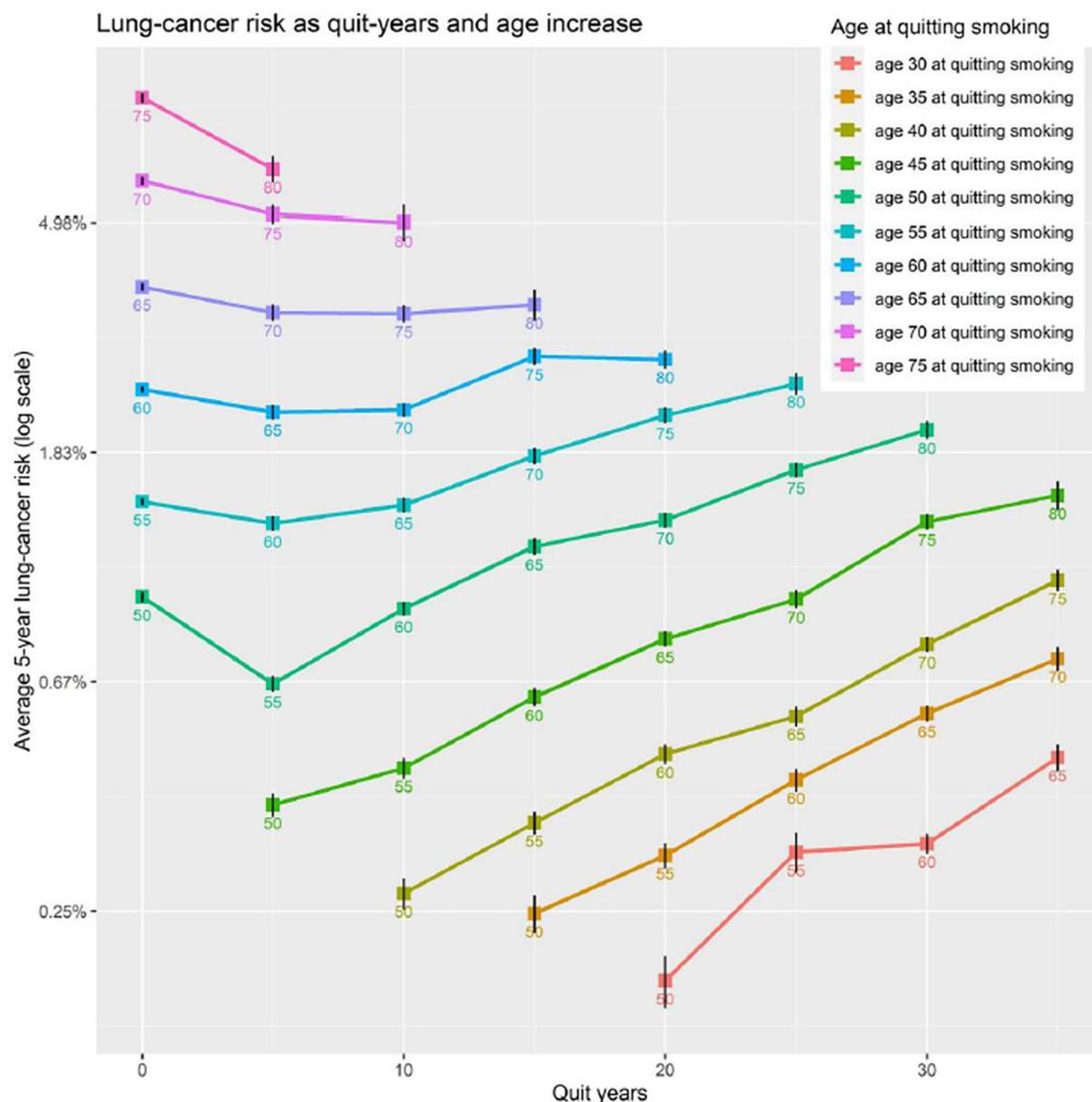
longer life expectancy may be more likely to prefer screening and are not as dissuaded by descriptions of the potential downsides). A report from a microsimulation modeling analysis showed that for individuals at higher risk ( $>0.4\%$  annual risk of lung cancer) or with longer life expectancy ( $\geq 10$  years), the decision to undergo screening is not preference-sensitive because they would strongly favor screening over a wide range of harm estimates.<sup>84</sup> For those at lower risk or with shorter life expectancies, however, the screening decision was identified as preference-sensitive, indicating it would depend on how the individual patient rated the importance of avoiding a death from lung cancer or diagnosis and treatment of late-stage cancer when considered against the potential harms of screening. Carter-Harris et al. similarly observed that both patient factors and clinician recommendation were associated with participation in screening. Among 515 screening-eligible participants recruited through a social media portal, those investigators observed that clinician recommendation, higher self-efficacy scores, and lower mistrust scores were positively associated with screening participation, whereas fatalism, lung cancer fear, and greater medical mistrust were significantly associated with less likelihood to go forward with LCS.<sup>85</sup>

Currently, the evidence on patient preferences and values regarding LCS is limited by the small number of studies, small

sample sizes, low survey response rates, the complexity of assessing risk and eligibility, and the slow integration of LCS into health systems, especially primary care practices. Moreover, because high proportions of eligible adults with lower socioeconomic status are underinsured and uninsured, are less likely to have a relationship with a trusted provider, and are more likely to view LCS through a lens of fatalism and stigma, it is difficult to draw conclusions regarding preferences and acceptance about LCS. Low rates of uptake after educational interventions that were solitary and independent of an opportunity to be counseled or respond to questions, versus the high rates of uptake in patients referred to a specialty clinic with more robust SDM, suggests that the challenge of increasing uptake of LCS rests, in part, on improving the SDM process in all settings, a challenge health systems and clinicians must be prepared to meet.

The GDG determined that, although the level of evidence related to preference for LCS is weak, most individuals who are eligible for LCS value reducing their odds of lung cancer death over the potential harms associated with screening, especially when they have had direct contact with a health professional. The heterogeneity of individuals' concerns about screening-related harms highlights the importance of providing thorough and up-to-date information for decision making.





**FIGURE 6** Five-year lung cancer risk and 95% CIs, shown on a log scale, by quit-age and quit-years among individuals with  $\geq 20$  pack-year histories in the 2015–2018 NHIS. Five-year lung cancer risks were calculated using the LCRAT model (relative annual percent change, 3.3%; 95% CI, 2.4%–4.2%;  $p < .001$ ). We note that individuals on the same quit-age line are different individuals at each point. CIs indicates confidence intervals; LCRAT, Lung Cancer Risk Assessment Tool; NHIS, National Health Interview Survey. Reproduced with permission from Ref. 48.

## Disparities in lung cancer screening

In framing the recommendations, the GDG considered the impact of guideline changes on health equity, specifically the potential to reduce disparities in LCS eligibility, uptake, and subsequent mortality reduction. In a literature review on disparities in LCS, Sosa et al. highlighted three major areas of concern: screening eligibility based on current screening recommendations, screening utilization, and postscreening behavior and follow-up care.<sup>12</sup> With respect to eligibility, screening for breast, cervical, and colorectal cancers depends

on age, whereas screening eligibility for lung cancer also depends on smoking history. Therefore, discussions of disparities in LCS eligibility must consider the risk of lung cancer by age and sex or gender and by smoking behavior across racial/ethnic and socioeconomic groups.

Understanding disparities in LCS begins with examining the racial and ethnic composition of the participants in the NLST. In the NLST, less than 5% of participants were Black, slightly over 2% were Asian, and less than 2% identified as Hispanic. The NELSON trial did not report on the race and ethnicity of participants but was conducted in populations more homogeneous than the United States.<sup>24</sup> Although

findings from the RCTs on the efficacy of LCS and screening recommendations were presumed to be applicable to all racial/ethnic groups, in the period after the USPSTF released the LCS recommendation in 2013, a growing number of publications expressed concerns that LCS recommendation criteria (age, pack-years, YSQ) for beginning and continuing screening were too conservative to maximize the number of qualifying Black persons who currently or formerly smoked.<sup>86,87</sup> Han et al. estimated the proportion of the population who would be eligible for screening per comparable absolute risk-based criteria (6-year risk from 1.3% to 2.5%) for individuals aged 50–90 years using the PLCom2012 model<sup>88</sup> (risk-based criteria) and age-specific screening eligibility determined by USPSTF guidelines (age and tobacco use history).<sup>87</sup> They concluded that, by not including the age range of 50–54 years, the 2013 USPSTF recommendation would have missed 15.6% of Black individuals and 4.8% of White individuals who were screening-eligible based on absolute risk over 6 years. Also, among risk-eligible individuals in the group aged 71–80 years, some would lose eligibility under the USPSTF screening eligibility criteria because of the YSQ15 criterion—specifically, 14.2% of Black individuals and 10.8% of White individuals. As mentioned in the pack-year history section above, additional evidence suggested that lowering the pack-year history and age to qualify for LCS would increase the number of women and persons of racial minority groups who would be eligible for screening. Aldrich and colleagues observed that a larger proportion of Black persons reported currently smoking but smoked fewer cigarettes per day and hence had a lower pack-year history compared with White individuals—a median of 25.8 pack-years among Black individuals compared with 48.0 pack-years among White individuals.<sup>86</sup> In their subanalyses of lung cancer cases in people who smoke, a significantly greater percentage of Black persons compared with White persons did not meet the  $\geq 30$  pack-years requirement (45.3% vs. 16.1%;  $p < .001$ ) and were more likely to be diagnosed with lung cancer at age younger than 55 years (24.3% vs. 19%;  $p = .03$ ). Similarly, among persons who currently smoke and formerly smoked, women had lower pack-year histories compared with men.<sup>89</sup>

When the USPSTF lowered the LCS starting age from 55 to 50 years and reduced the pack-year smoking history from 30 to 20 pack-years,<sup>34</sup> there was speculation that the updated recommendation would reduce disparities.<sup>24,90</sup> However, Landy et al. showed that, although the change in recommendations increased eligibility for LCS in all racial/ethnic groups and increased estimated LYG and deaths prevented, disparities in eligibility between White, and Black, Hispanic, and Asian individuals worsened for all comparisons except for the comparison of deaths prevented in White and Black individuals, for which disparities remained but with a small reduction from 15% to 13%.<sup>91</sup> Landy and colleagues demonstrated that supplementing the proposed 2021 USPSTF LCS recommendation (their analysis was based on the draft recommendation statement issued in July 2020) with the LYFS-CT model,<sup>89</sup> which combines individual risk of lung cancer death with life expectancy to predict LYG from annual screening, the augmented risk model increased LYG and deaths prevented and reduced or did not worsen disparities. Although

disparities in LYG and deaths prevented were nearly eliminated between Black and White individuals, some disparities remained between non-Hispanic White, Hispanic, and Asian individuals.<sup>91</sup> In the analysis on relaxing or eliminating the YSQ criterion in LCS eligibility, as noted above, the number of adults eligible for screening increased in all racial/ethnic groups. Eliminating YSQ increased LCS eligibility overall in White (+35%), Hispanic (+34%), Asian (+34%), and Black (+27%) individuals and increased lung cancer deaths prevented and LYG in all groups. However, eliminating YSQ slightly worsened disparities in *proportionate* eligibility between White (+2%) and Black (−2%) individuals, whereas the proportion of eligible Asian and Hispanic individuals among all individuals eligible for LCS remained the same.<sup>48</sup>

Because recent evidence has indicated that individuals in different racial/ethnic groups can have the same age and smoking history but different lung cancer risk, Landy et al. concluded that guidelines based only on age, pack-years, and quit-years cannot eliminate disparities in desirable outcomes from LCS.<sup>48</sup> As observed by Robbins et al., the disparity in identifying qualifying risk for LCS is most evident among persons with lower smoking intensity.<sup>92</sup> Furthermore, although the implementation of risk-prediction models to be used along with current age-based and tobacco history-based criteria has the potential to reduce disparities further, in Landy et al.'s 2021 and 2023 analyses<sup>48,91</sup> supplementing USPSTF 2021 with LYFS-CT did not perform equally well across all racial/ethnic groups because they observed that a higher proportion of lung cancers in Asian and Hispanic individuals occur in lower risk individuals, resulting in a higher NNS to save one life and thus a worse imbalance in the benefit-to-risk ratio. This higher NNS resulting from current indicators of risk indicates that additional research is needed to identify as yet unknown factors that could further tailor recommendation criteria, reduce disparities in adverse lung cancer outcomes, and promote equity.<sup>91</sup> The GDG concluded that lowering the starting age and pack-year threshold and eliminating the YSQ criterion will expand eligibility for both sexes and all racial and ethnic groups but that some disparities will persist. The differential effect on specific racial and ethnic groups warrants further research, and efforts to reduce disparities in access to LCS should be a high priority for health care systems.

## Evidence-to-recommendation GDG decision making

In considering the evidence related to the benefits, harms, and eligibility criteria for LCS, there was a consensus among GDG members that the benefits of mortality reduction and LYG substantially outweigh the harms, warranting a strong recommendation to screen for lung cancer with LDCT. This decision was based on the RCT evidence, the observational studies in the CrEST evidence review, and epidemiological and simulation modeling results against a backdrop of the heavy lung cancer disease burden. In deliberations, the GDG carefully considered the risk of complications from invasive procedures as the most significant harm, but the evidence showed

that this is infrequent. The high recall rate associated with LCS was also considered a harm because it can result in invasive procedures and thus complications. However, the GDG determined that the recall rate is similar to other cancer screening interventions (such as mammography for breast cancer screening) and is not associated with diminished quality of life; thus the GDG did not consider the recall rate, in and of itself, to pose a serious burden or harm to patients. The systematic review conducted by Jones et al. concluded that there was moderate quality evidence to suggest that individuals who undergo LCS have worse short-term, but do not have worse long-term general health-related quality of life, anxiety, or distress over two years of follow-up compared with individuals who were not screened for lung cancer.<sup>24</sup> Although radiation risk was acknowledged as a potential harm, updated benefit-to-radiation-risk ratios showed that the estimated harms are lower than previous estimates; therefore, the balance of benefit-to-radiation risk is even more favorable than previous estimates. The GDG judged that the RCT evidence, data from observational studies, lung cancer disease burden, and modeling results were sufficient to support a strong recommendation for LCS with LDCT for persons aged 50–80 years with a  $\geq 20$  pack-years smoking history.

Regarding the decision to eliminate YSQ as an entry or exit criterion, the GDG recognized that RCTs included 10-YSQ or 15-YSQ thresholds among their inclusion criteria, but it appears they did not exclude individuals who exceeded the YSQ thresholds once enrolled in the trials, thus lending support to the recommendation to eliminate YSQ as an exit criterion. Moreover, the GDG did not find a rationale for a YSQ threshold entry criterion in the RCTs. The GDG ascribed high importance to the evidence from observational studies demonstrating that absolute lung cancer risk in the population with  $>15$  YSQ remains high, largely because of the influence of increasing age. Also, a high value was placed on the modeling results showing that current guidelines that include YSQ disqualify a substantial number of individuals who have equally high or higher lung cancer risk compared with individuals who qualify for screening, contradicting the principle of equal treatment for equal risk. In discussions, it was also noted that all four models used by the USPSTF, the two models commissioned by the ACS for this guideline, and the epidemiological and modeling analyses by Landy et al.<sup>52</sup> corroborated the net benefit of eliminating the 15 YSQ threshold for screening eligibility. Although eliminating the YSQ criterion will lead to a greater number of older individuals being screened, who may be at higher risk for complications from lung cancer evaluation and treatment, the GDG also considered that the risk of developing and dying from lung cancer peaks at older ages and that modeling consistently demonstrated a positive benefit-harm trade-off by eliminating the YSQ criterion.

In the external review process, concerns were raised regarding a strong recommendation despite the overall quality of evidence regarding YSQ being rated by GRADE criteria as low to moderate. The GDG acknowledged this argument and the challenge of separating the evidence for each LCS eligibility criterion. However, based on the moderate COE in the CrEST report that there is no clinical

difference in the relative risk of lung cancer just before and beyond YSQ15, the consistency of the modeling studies, and the high potential for greater lung cancer mortality reduction, the GDG judged that the benefit-to-harm balance warranted a strong overall recommendation.

## Decision making and clinical considerations

This update of the ACS LCS guideline underscores the importance of SDM and patient health status to improve the uptake, adherence, and outcomes from LCS (see Table 5).<sup>71</sup> The initial responsibility of clinicians in the LCS process is to identify appropriate candidates. Many electronic health record (EHR) systems can facilitate this process by flagging eligible persons, but further vetting by the clinician or office staff is necessary to determine pack-year eligibility and the presence of comorbid conditions and/or frailty that may adversely affect life expectancy. The ability to use electronic records to identify eligible individuals will likely increase as the National Committee for Quality Assurance gets closer to completing its development of a Healthcare Effectiveness Data and Information Set measure for LCS.<sup>93</sup>

Prognostic indices, such as ePrognosis (<https://eprognosis.ucsf.edu/calculators/>),<sup>94</sup> that integrate age, comorbidities, and functional status to predict long-term mortality, can be useful for corroborating clinical judgment about life expectancy and the likelihood of an individual to benefit from early detection and endure postscreening evaluation and treatment.<sup>95</sup> However, ePrognosis has known limitations for use under these circumstances, and other longevity estimators, such as the Lung Cancer Screening Risk Calculator ScreenLC (<https://screenlc.com/dpp-vue/index.html>), which is tailored for LCS decisions, will likely return more reliable results.<sup>96</sup> Self-reported health status also has been repeatedly shown to be a strong predictor of mortality.<sup>97</sup> Although there is no clear life expectancy cutoff for when LCS likely would not benefit a patient in good health, the relatively short time to benefit seen in the NLST and NELSON trials suggests that patients with a life expectancy of at least 5 years who meet other eligibility criteria would potentially benefit from screening. As noted above, modeling showed that the successful identification of patients with  $\geq 5$  years' longevity had a substantial effect on reducing rates of overdiagnosis.

Examples of conditions that would be considered to preclude a benefit from LCS are listed in Table 5. Many individuals who qualify for screening based on age and pack-year history may not have a single, dominant, comorbid condition but, instead, may present with multiple, less severe conditions, which together may sufficiently limit life expectancy and impair health so that screening would not be beneficial. For example, it is reasonable to consider the health status exclusion criteria used by the NLST and NELSON trials.<sup>2,26</sup> The NLST excluded individuals who required home oxygen, had active cancer in the last 5 years (other than in-situ carcinoma and nonmelanoma skin cancers), had unexplained weight loss of  $\geq 15$  pounds in the past year, and had recent hemoptysis, although the latter two criteria would warrant diagnostic evaluation for lung cancer rather than

**TABLE 5** Core elements for shared decision making for lung cancer screening with low-dose computed tomography.

Screening test	<ul style="list-style-type: none"> <li>• Lung cancer screening is done with LDCT.</li> <li>• An LDCT machine takes an x-ray image of the lung using a low amount of radiation while a person is lying on a table.</li> <li>• Annual LDCT screening is recommended by leading organizations for individuals at high risk for lung cancer.</li> </ul>
Eligibility criteria	<ul style="list-style-type: none"> <li>• Persons aged 50 to 80 years who currently smoke or formerly smoked.</li> <li>• Accumulated a 20 pack-year or greater history of smoking.<sup>a</sup></li> <li>• Years since quitting smoking among individuals who formerly smoked is not an inclusion or exclusion criteria for lung cancer screening.</li> </ul>
Benefits of screening	<ul style="list-style-type: none"> <li>• The main benefit of screening is a reduction in lung cancer mortality.</li> <li>• When lung cancer is detected at an earlier stage, it is easier to treat, and prognosis is improved.</li> </ul>
Health status that may preclude screening benefits	<ul style="list-style-type: none"> <li>• Persons with health conditions that may hinder further evaluation or surgery for lung cancer. These include but are not limited to:               <ul style="list-style-type: none"> <li>NYHA class 4 congestive heart failure.</li> <li>GOLD stage 3 or 4 COPD.</li> <li>Cirrhosis with a history of decompensation (ascites, variceal bleed, hepatic encephalopathy, jaundice).</li> <li>End-stage renal disease.</li> <li>Moderate or severe dementia.</li> <li>Current or recent (within 5 years) treatment of advanced-stage nonlung cancer.</li> <li>Dependence on home oxygen.</li> <li>Symptoms of lung cancer (e.g., hemoptysis, unexplained weight loss of &gt;15 pounds in the past year; such symptoms warrant the diagnostic evaluation, not screening).</li> <li>Clinical <a href="#">Frailty Index Score</a> of 5 or greater.</li> <li>Persons with limited life expectancy (&lt;5 years); if uncertain, tools such as <a href="#">ScreenLC</a> may be used to estimate life expectancy.</li> <li>Not willing to accept treatment for screen-detected cancer.</li> </ul> </li> </ul>
Harms and limitations of screening	<ul style="list-style-type: none"> <li>• There may be abnormal results from screening, but most abnormal LDCT scans do not lead to a diagnosis of lung cancer.</li> <li>• Abnormal results on LDCT, including incidental findings, may require follow-up with more scans and invasive procedures, such as lung biopsy.</li> <li>• There may be complications from invasive procedures for follow-up of abnormal results on LDCT, although they are rare.</li> <li>• There is exposure to radiation from repeated LDCT scans; and, although the magnitude of possible harms can only be estimated, it is small compared with the benefit from screening.</li> <li>• LDCT may not find all lung cancers.</li> <li>• Incidental findings on LDCT are common and may require further evaluation.</li> </ul>
How often to get screened	<ul style="list-style-type: none"> <li>• Screening should be done every year with LDCT.</li> <li>• It is important to adhere to regular screening.</li> <li>• Stop screening if a person has a change in health status that limits life expectancy or the ability to undergo diagnostic evaluation or treatment for lung cancer.</li> </ul>
Importance of smoking cessation	<ul style="list-style-type: none"> <li>• Screening is not a substitute for smoking cessation.</li> <li>• Persons who currently smoke should be advised to quit and offered counseling and pharmacotherapy to assist with quitting.</li> <li>• Not smoking is the best way to lower lung cancer risk.</li> <li>• Resources to help patients quit:               <ul style="list-style-type: none"> <li>The American Cancer Society (<a href="https://www.cancer.org/cancer/latest-news/how-to-quit-smoking.html">https://www.cancer.org/cancer/latest-news/how-to-quit-smoking.html</a>).</li> <li>The Centers for Disease Control and Prevention Practical Guide to Help Your Patients Quit Using Tobacco (<a href="https://www.cdc.gov/tobacco/patient-care/pdfs/hcp-conversation-guide.pdf">https://www.cdc.gov/tobacco/patient-care/pdfs/hcp-conversation-guide.pdf</a>).</li> <li>The National Cancer Institute created a quit-smoking app (<a href="https://smokefree.gov/tools-tips/text-programs">https://smokefree.gov/tools-tips/text-programs</a>).</li> </ul> </li> </ul>

**Note:** The American Cancer Society suggests these as key points to include in the discussion process of decision making for lung cancer screening with LDCT. These factors should not be substituted for clinical judgment. Individuals should be given information on the benefits, limitations, and harms related to screening for lung cancer to make an informed decision, integrating their preferences with the guidance of their health care provider on whether to undergo screening. See Table S5 in the supplementary materials for examples of SDM tools. For individuals who currently smoke, the options for and benefits of smoking cessation should be emphasized as a part of the decision-making process.

Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LDCT, low-dose computed tomography; NYHA, New York Heart Association.

<sup>a</sup>One pack-year equals smoking an average of 20 cigarettes (one pack) per day for a year.

screening.<sup>34</sup> Relevant additional exclusion criteria for the NELSON trial included fair or poor self-reported health status and inability to climb two flights of stairs.<sup>97,98</sup> Current guidelines and recommendations include an age range for starting and ending screening based on factors that apply generally to a target population. However, across the 30-year period covered by current recommendations (ages 50–80 years), clinicians must be alert to individuals' overall health status and be prepared to use their clinical judgment to assess the likelihood that the benefits of starting or continuing LCS will outweigh the potential harms.

## Shared decision making and lung cancer screening

SDM is defined as a collaborative process that allows a patient and clinician to make health care decisions together, taking into account the best scientific evidence available and the patient's values and preferences.<sup>99</sup> Informed decision making (IDM) is defined as occurring when an individual understands the disease or condition being addressed; comprehends what the clinical service involves, including its benefits, risks, limitations, alternatives, and uncertainties; and has considered his or her preferences, makes a decision consistent with them, and believes he or she has participated in decision-making at the level desired.<sup>100</sup> To participate in SDM, patients must be provided with sufficient information to meet the criteria for IDM. In general, the fulfillment of either SDM or IDM should satisfy the objective of an informed individual who is confident in their decision to undergo, or not undergo, LCS. However, the unique feature of SDM is the collaborative process, in which most individuals eligible for LCS likely will benefit from a discussion about lung cancer risk, the process of LCS, and the benefits, limitations, and potential harms associated with a screening test that is widely recommended by guideline-issuing organizations but may still be unfamiliar to most eligible individuals.

The Centers for Medicare and Medicaid Services (CMS) requires SDM as part of LCS counseling for Medicare beneficiaries before screening referral.<sup>38</sup> According to the CMS mandate, SDM should include the use of one or more decision aids. Because a large proportion of LCS-eligible persons are Medicare beneficiaries, SDM may affect the implementation and acceptability of recommendations for screening in the clinical setting. A health care provider's recommendation for cancer screening plays an important role in screening uptake and has been shown to have a positive association with adherence.<sup>101</sup> Peterson et al. noted in their review of the literature on provider-patient communication and cancer screening that screening behavior is more nuanced than a provider making a simple recommendation. Rather, the quality and content of the communication around the recommendation are significant and have an important influence on a patient's decision to get screened.

There is evidence related to breast, colon, and prostate cancer screening that the process of SDM is effective for improving knowledge about screening and the trade-offs and may reduce decisional conflict, but it may have limited impact on the decision to undergo

screening.<sup>102</sup> The use of decision tools is recommended by the CMS for LCS and has been shown to be effective in the SDM communication process.<sup>103</sup> In a review of studies examining the impact of 15 print or video decision tools to support SDM for LCS, Fukunaga et al. concluded that the existing tools to promote SDM for LCS may help patients by improving knowledge about LDCT screening and reducing decisional conflict, but the impact on screening utilization is inconsistent. Among the included studies that reported on the completion of LDCT, results were variable, ranging from 45% to 95% using tools with SDM counseling, and much lower when tools were used without counseling (range, 2%–20%).<sup>103</sup> An RCT of the impact of a patient decision aid video versus standard educational material on LCS among persons who currently smoke reported higher screening knowledge and better preparedness for decision making among the patient decision aid group but found no difference in screening behaviors.<sup>104</sup> More recently, a study using insurance claims for SDM found that individuals with a documented SDM consultation were 25% more likely to adhere to annual LCS than those without SDM documentation.<sup>105</sup>

The GDG acknowledges the time constraints of health care professionals in the clinical setting that may hinder the SDM process and LCS implementation. However, according to new CMS requirements, SDM can be conducted by anyone on the clinical team, does not need to be in person, and the discussion only needs to occur at the initiation of LCS and does not need to be repeated annually.<sup>38</sup> Given the importance of and requirement for SDM, office practices and health care systems should identify strategies that efficiently and effectively support decision-making. Although the guideline does not endorse a particular tool for SDM, given the aforementioned indication that decision tools may be helpful in the SDM process, they should be considered and used in the clinical setting to improve communication and subsequently screening utilization. Also, health care providers should be mindful in using SDM tools to select those that best fit their population. A list of tools is provided in the Supporting Materials for consideration (see Table S5).

## Smoking cessation

This guideline emphasizes smoking-cessation counseling and offering interventions to quit for persons who currently smoke as part of the discussion about LCS. Among persons who currently smoke, it should be emphasized that quitting smoking is the most effective way to lower their risk of developing lung cancer and that combining smoking cessation with LCS is the optimal strategy to reduce their risk of dying from lung cancer.

There have been concerns that normal findings on LCS will incentivize persons who smoke to continue smoking or persons who formerly smoked to begin smoking again. The systematic review summarized the evidence examining the impact of LCS on smoking behavior. Overall, normal LCS findings do not appear to provide reassurance that individuals who smoke, or formerly smoked, are immune to the harmful effects of smoking.<sup>42</sup> The RCTs have demonstrated mixed results regarding smoking cessation among



screened versus unscreened participants. The Danish Lung Cancer Screening Trial data showed that subsequent smoking cessation among those currently smoking at baseline was comparable in both screening and no-screening groups at year 1, and the annual proportion of those who quit continued to increase over 5 years in both study arms.<sup>106,107</sup> The NELSON trial reported no difference in smoking intensity between the screening and control arms; and, although abstinence among persons who formerly smoked was high in both arms, it was slightly higher in the control arm (15.1% vs. 19.8%;  $p = .04$  for no smoking in the past 7 days).<sup>24</sup> Analyses from the Georgetown University site of the NLST pilot study (the Lung Screening Study) and the NLST found that the majority of individuals who smoked were interested in receiving cessation counseling and were ready to make a quit attempt in the next 6 months.<sup>108</sup> In the NLST, Clark et al. observed that screening-arm participants who received positive or indeterminate screening results were more likely to quit smoking and/or remain abstinent than those who received normal results.<sup>109</sup> Taylor et al. concluded that these findings suggest that LCS is a “teachable moment” for smoking cessation.<sup>110</sup>

## Management of abnormal LDCT results

Adherence to an established protocol for coding and management of positive LDCT screening results is critical to achieving optimal outcomes from screening. The ACR Committee on Lung-RADS<sup>48</sup> recommends that LCS examinations should be coded 0–4 (including 4A, 4B, and 4X). A Lung-RADS code 0 is an examination that is incomplete; Lung-RADS 1–2 findings are negative screens, and patients should return for regular screening in 12 months. More specifically, Lung-RADS 1 includes no nodules and definitely benign nodules, and Lung-RADS 2 includes small nodules that are benign in appearance or behavior with a very low likelihood of becoming a clinically active cancer due to size or lack of growth. Under Lung-RADS, the solid nodule size threshold for a probably benign lesion (Lung-RADS 3) is  $\geq 6$  mm to  $< 8$  mm on baseline screening and 4 mm to  $< 6$  mm on repeat screening, which warrants an interval LDCT in 6 months. For partially solid nodules, these thresholds are  $\geq 6$  mm and  $< 6$  mm on baseline and annual repeat screening, respectively, and for non-solid nodules (i.e., pure ground glass nodules) the size threshold is 30 mm for both baseline and annual repeat screening. Suspicious lesions (Lung-RADS 4A) apply to larger or growing nodules, and should be followed with an interval LDCT in 3 months, whereas Lung-RADS 4B and 4X findings are very suspicious for lung cancer and usually warrant immediate further diagnostic evaluation and/or tissue sampling. Lung-RADS also includes an “S” modifier to be added to codes 0–4 to indicate a significant or potentially significant finding unrelated to lung cancer.<sup>68</sup> The ACR estimates that approximately 15% of individuals undergoing screening will have a Lung-RADS code of 3 or 4, and 18.8% of exams will have one or more S modifier findings. ACR Lung-RADS guidance for the management of LDCT screening results should be regarded as integral to the success of LCS screening. The failure to follow-up a positive screening test in a manner that is

concordant with Lung-RADS guidance undermines the screening process, can delay diagnosis, or can result in unnecessary imaging examinations and radiation exposure. In addition, if a positive screening test is not followed according to recommendations, the screening process is incomplete. It is the position of the ACS that follow-up tests are integral to the screening process, and patients should not face cost sharing for any follow-up procedure associated with a positive LCS test.<sup>110</sup>

## LIMITATIONS

The ACS guideline for LCS with LDCT is primarily based on data from RCTs with participant pools that are not representative of populations in the United States who are eligible for LCS based on smoking history. The RCTs generally were conducted in larger, specialty settings with experience in running RCTs and enrolled participants who were healthier, reported higher education levels, were less likely to currently smoke, and mostly identified as White ( $> 90\%$ ). In the NLST  $< 5\%$  of participants identified as Black and  $< 2\%$  identified as Hispanic, and approximately 70% reported education beyond the high school level.<sup>111</sup> It is not expected that LDCT will perform differently in non-White persons; however, as described above, the available evidence has shown that risk-based criteria used to inform screening eligibility do not identify at-risk population groups equally.

To supplement the empirical evidence, or fill gaps where the evidence is limited, the GDG relied on the results of modeling studies. There are limitations of modeling inherent in the underlying assumptions of the models, these are described in their methodology. One such assumption in the CISNET models is 100% adherence to all screening strategies. Actual screening adherence rates in real-world settings vary by clinical setting and population group, meaning that actual outcomes will diverge from predicted outcomes based on differential uptake of LDCT screening. However, the assumption of full adherence is intended to allow for comparisons of the screening strategies under uniform scenarios, and when understood in that context is not really an inherent limitation. The fact that the simulations model 100% adherence is acknowledged by the CISNET investigators and was considered by the GDG in the deliberations of the modeling results.

The guideline does not address screening for lung cancer among persons who never smoked. The GDG acknowledges that up to 20% of cancer cases occur in persons who never smoked and that deaths from lung cancer in persons who never smoked would rank eighth among the leading causes of cancer deaths (approximately 20,500) if they were tabulated separately.<sup>4</sup> However, a history of tobacco use is still the major risk factor for lung cancer, and we lack a similar indicator of risk specifying the potential for high benefit in persons who never smoked. Although it is beyond the scope of this guideline to address early detection of lung cancer in persons not at risk because of a heavy tobacco smoking history, the GDG considers the challenge of identifying this at-risk group a matter of urgency. Furthermore, to avoid delays in diagnosis, it is important to consider an evaluation for

lung cancer in individuals without a smoking history who present with a persistent cough, hemoptysis, involuntary weight loss, recent-onset night sweats, or other unexplained, persistent respiratory symptoms.

It is reasonable to ask what impact the updated guideline will have on the existing imaging infrastructure. The modeling studies have estimated that nearly 5 million additional individuals will qualify for regular lung cancer screening by removing YSQ, either as newly eligible individuals, or as individuals who retain eligibility between the ages of 50 and 80 as long as they are in good health and do not lose eligibility due to exceeding 15 YSQ. The US ranks sixth globally in CT scanners with an estimated 43 per 1,000,000 population.<sup>112</sup> In an analysis of access to lung cancer imaging facilities participating in the ACR Lung Cancer Screening Registry, Sahar, et al. estimated that only 5% of the U.S. population eligible for LCS did not live within 40 miles of a imaging facility, although approximately 25% of eligible adults living in rural counties would have to travel more than 40 miles for LCS.<sup>113</sup> Although we do not have the data to predict the impact of removing YSQ on the average imaging facility, in general overall uptake of LCS presently is low, and screening guideline changes do not generally result in a sudden increase in new demand. It is also the case that increases in capacity commonly are not anticipatory, that is, capacity growth follows increase in demand. Further, the guideline change targets a group with qualifying absolute risk who should not be prevented from starting screening or continuing screening. However, the existing data on the disparity in access to imaging services in rural areas already is a concern, and warrants greater attention now.

## DISCUSSION

The major changes from the 2013/2018 ACS LCS guideline are a reduction in the age to begin screening from age 55 to 50 years, a reduction in the pack-year history from  $\geq 30$  to  $\geq 20$  pack-years, and the elimination of the YSQ criterion for starting and stopping screening for persons who formerly smoked. The GDG relied on more recent RCT data demonstrating reduced lung cancer mortality in persons with  $<30$  pack-years of smoking and screening age beginning at 50 years; CISNET modeling studies; application of risk models to lung cancer RCTs; and national survey data, burden of disease data, and updated risk estimates of radiation-induced cancers from screening and follow-up examinations. Although there is variation among the RCTs in eligibility criteria, screening intervals, number of screening rounds, and years of follow-up, together with modeling studies and observational data, the totality of the evidence supports annual LCS with LDCT starting at age 50 years and stopping at age 80 years for persons who currently smoke, or formerly smoked, and have accumulated at least 20 pack-years of tobacco smoking, with no consideration of YSQ as an eligibility factor to start or end LCS.

Modeling and observational data persuasively demonstrate that people who formerly smoked and meet the current age, smoking

pack-years, and general health criteria for LCS maintain a lifetime risk of lung cancer sufficiently elevated to warrant continuous LCS until they reach age 80 years or a point when life-limiting comorbidity should curtail continuing screening to avoid harms. It appears that the YSQ15 criterion in current recommendations, including the previous ACS guideline, has been carried over from the RCT designs without questioning the long-held assumption that lung cancer risk declines continuously after smoking cessation. It is critically important that this previously unverified and erroneous assumption is corrected immediately given the evidence presented herein and in accompanying articles<sup>43,47,48</sup> demonstrating that a significant fraction of high-risk adults is excluded from screening eligibility because of exceeded YSQ criteria.

The two modeling analyses that informed the 2023 ACS guideline update each showed that the elimination of YSQ criteria increases the number of lung cancer deaths averted and LYG, with similar screening efficiency among newly eligible individuals compared with those who were previously eligible. The elimination of YSQ also shifts the current eligibility for LCS to older adults because an estimated 52% of the individuals who gain eligibility are aged 70–80 years.<sup>48</sup> Although this group is healthier and has a longer average life expectancy than individuals who currently smoke,<sup>114–116</sup> the larger numbers of eligible individuals older than 70 years emphasize the importance of assessing overall health status and longevity before referral to screening. In the initial guidelines for LCS, annual LDCT was recommended up to the mid-70s by some organizations, was covered by the CMS up to age 77 years, and was recommended up to age 80 years by the USPSTF, so the challenge of being attentive to overall health status and longevity in referrals to LCS has been an important consideration from the beginning. However, inappropriate cancer screening in older adults who are unlikely to benefit because of life-limiting comorbidity or other factors is common for other cancers with screening recommendations, and early evidence suggests that ill-advised screening in adults with limited longevity exists in LCS as well.<sup>117</sup> As demonstrated by Meza et al. in the modeling for this guideline update, ensuring that individuals referred to LCS at any age, but especially older ages, have at least 5 years of expected longevity retains most of the benefits of screening while minimizing most of the harms associated with overdiagnosis and overtreatment.<sup>47</sup>

The modeling evidence also suggests that screening past age 80 years can be beneficial when an individual meets eligibility criteria, most importantly  $\geq 5$  years' expected longevity. Continuation past age 80 years may be considered on a year-by-year basis in an individual who has never been screened or only recently initiated screening, who is in good health, and who wishes to continue screening. For example, the Lung Cancer Screening Risk Calculator predicts that a non-Hispanic, White male aged 80 years with a 50-year pack-year history of smoking who quit when they were aged 70 years and is without chronic obstructive pulmonary disease can expect to live 8.75 years without screening, and LCS is judged to be a high benefit for this individual.<sup>96</sup> These decisions in older adults should be revisited regularly to assess patient preferences and the

potential for benefit and harm. Some relevant comorbid conditions are described in Table 5.

### Risk factor-based guidelines versus the use of risk-prediction models

In this era of growing emphasis on precision medicine, there is increasing attention to the limits of risk factor-based guidelines for identifying risk groups and tailoring screening. Guidelines based on age and sex may fail to identify a group with lower or higher risk determined by factors not specified in the guideline, leading to overscreening or underscreening. Numerous individual risk models have shown superior sensitivity at identifying individuals in groups that have a higher risk at younger ages and lighter smoking histories, higher risk with nonqualifying YSQ, or greater potential LYG, risk of death, or short-term risk of a lung cancer diagnosis, and also have shown greater cost effectiveness.<sup>48,91,118–124</sup> Although some risk models have prioritized improved efficiency, in which the same or greater mortality reductions or LYG are achieved by screening fewer or the same number of individuals, it is also possible to establish risk thresholds that include a wider range of risk, a wider range of contributing risk factors, the potential to recommend screening protocols that are tailored to these levels of risk, and include all individuals who meet a baseline level of risk.

What is the potential for individualized risk programs to replace a categorical guideline as the basis for screening recommendations? In an organized health care system, the potential appears to be high. In a commentary accompanying the modeling study by Meza et al.<sup>47</sup> Tammemagi noted that a growing number of jurisdictions (i.e., some Canadian provinces and the UK National Health Services) already are using risk-prediction models to determine LCS eligibility or are preparing to use them.<sup>125</sup> In the United States, which does not have a system of organized screening, the answer is less clear. Landy et al. have demonstrated a hybrid approach that could accommodate the lack of readiness to fully pivot from conventional risk factor-based LCS guidelines to individual risk estimation. This approach augments the USPSTF 2021 recommendation with risk-prediction models that identify guideline-ineligible individuals who likely would have a high net benefit from screening, such as those who are at equivalent or greater benefit measured by a gain of  $\geq 16.2$  days of life estimated by the LYFS-CT model<sup>118</sup> or 5-year risk of lung cancer death  $\geq 1.33\%$  estimated by the Lung Cancer Death Risk Assessment Tool model.<sup>119</sup> This approach has been included as an option in the American College of Chest Physicians guidelines, which also include a group of incidence calculators as a third option.<sup>35</sup> The GDG considered the modeling evidence for a risk-based screening strategy but, without clinical trial or observational evidence, or known readiness by referring clinicians to incorporate an alternative strategy for assessing screening eligibility, considered it premature to incorporate it into a screening recommendation. However, given the limitations of risk-factor based guidelines, transitioning to individualizing risk assessment should be a high priority for the future.

### Meeting the challenge to increase lung cancer screening rates

For decades the only opportunities to reduce tobacco-related deaths were to reduce access to tobacco products, reduce opportunities for smoking, and aggressively promote smoking cessation. The demonstration of the efficacy of LCS with LDCT and, nearly in parallel, the emergence of targeted and immunotherapies for advanced-stage disease, together have vastly increased the potential to reduce the burden of suffering and mortality from lung cancer. Although growth in access and uptake of new therapies has been substantial, growth in the uptake of screening has been disappointingly low. The ACR Lung Cancer Screening Registry estimated that the national rate of LCS was only 5% in 2018, although it varied significantly by state.<sup>39</sup> The most recent LCS rates come from four US states that included LCS questions in the Behavioral Risk Factor Surveillance System in 2021.<sup>126</sup> Individuals eligible for LCS reported recent screening ranging from 17.5% in New Jersey to 30.3% in Rhode Island.<sup>126</sup>

Low screening uptake a decade after LCS was first recommended is a cause for considerable concern. Although all currently recommended cancer screening tests experienced slow uptake initially, LCS faces greater challenges. Individuals who meet LCS eligibility criteria are more likely to have lower socioeconomic status, are less likely to have health insurance, are more likely to have experienced stigma about smoking, have low awareness about screening, and hold fatalistic attitudes toward screening for lung cancer compared with other screening tests.<sup>127,128</sup> Inadequate health care provider knowledge and awareness of LCS and readiness to identify individuals at high risk and engage in discussions about LCS have been identified as significant barriers. Unique challenges of reaching the target population in rural areas have also been identified, including greater average distance to an imaging facility.<sup>129</sup> In a nationwide geospatial analysis assessment of access to LCS, Sahar et al. observed that 25% of rural adults meeting USPSTF 2021 eligibility criteria lived  $\geq 40$  miles from an imaging center reporting data to the ACR Lung Cancer Screening Registry.<sup>113</sup>

However, it is important to consider the primary reason given by individuals for why they did or did not have a recent screening test: advice, or lack thereof, from their health care provider.<sup>130</sup> In this context, it is important to recognize that the impact of provider advice may be diminished by the persistent stigma related to all aspects of lung cancer, and this has been recognized as a significant barrier to receiving quality care, negatively influencing psychosocial, communication, and behavioral outcomes.<sup>131</sup> Thus, recognizing the importance of empathic communication during discussions about LCS and during SDM can improve clinical outcomes.<sup>132</sup>

Among important provider-related and practice-related barriers to screening, most EHRs are little help in identifying eligible patients based on smoking history and pack-year history, and people who formerly smoked are less visible as potential candidates for screening than people who currently smoke. EHRs are adapting to the need to be an effective tool for identifying individuals eligible for screening, and greater motivation to improve the functionality

of EHRs likely will follow the completion of a new LCS Healthcare Effectiveness Data and Information Set measure by the National Center for Quality Assurance. In the meantime, strategies are being developed to overcome the lack of supporting infrastructure, such as a quick, two-question method to determine pack-year history.<sup>133</sup> LCS also carries obligations for an SDM conversation, which it appears the average clinician is not prepared to deliver because of low awareness of the key information points and perceived or real lack of time. The absence of an office policy, a team-based approach to risk assessment and referral to screening, misconceptions about the benefits of screening, and concerns about incidental findings all likely contribute to low LCS rates. In addition, it appears that some of the highest LCS rates have been achieved in settings where the clinician can refer the patient to an LCS clinic, where risk assessment, SDM, smoking-cessation support, screening referral, and follow-up tracking are managed. However, one interesting observation is that LCS-eligible individuals who have not been screened do undergo other cancer screening tests. Smith et al. examined rates of screening for breast, colorectal, and prostate cancer in individuals who meet eligibility criteria for LCS. Although only 3.9% of high-risk individuals reported LCS in 2015, 23.8% of men reported having been screened for colorectal cancer, and 37.5% reported having had either colorectal cancer screening or prostate cancer screening. Among women eligible for LCS, 70.2% had either breast or colorectal cancer screening or both. These data show that men and particularly women who had not undergone LCS were not averse to cancer screening in general, suggesting that missed opportunities to assess risk, and to discuss and refer eligible individuals to LCS, are common.<sup>134</sup> Efforts are underway to determine the feasibility of increasing LCS by using mammography appointments as opportunities for offering LCS.<sup>135</sup>

## Comparison with other guidelines and recommendations

The 2021 USPSTF LCS recommendation calls for annual screening with LDCT for persons aged 50–80 years who have a  $\geq 20$  pack-year smoking history and currently smoke or have quit within the past 15 years, with an assigned B recommendation grade.<sup>34</sup> The 2021 American College of Chest Physicians guideline is broken into recommendations that align with different subpopulations.<sup>35</sup> Recommendation 1 aligns with CMS coverage (aged 55–77 years,  $\geq 30$  pack-year history, YSQ15) before the 2022 CMS update (aged 50–77 years,  $\geq 20$  pack-year history, YSQ15),<sup>38</sup> recommendation 2 aligns with the 2021 USPSTF recommendation,<sup>34</sup> and recommendation 3 augments recommendation 1 or 2 with risk-prediction and YG calculators for individuals who are believed to be at high risk for lung cancer but do not meet eligibility criteria under recommendation 1 or 2. The National Comprehensive Cancer Network recommends annual screening for lung cancer with LDCT in individuals aged 50 years or older with a  $\geq 20$  pack-year history of cigarette smoking. The National Comprehensive Cancer Network guideline does not include an

assessment of YSQ, nor does it include an upper age limit for screening eligibility, stating that LCS in older adults should be contingent on an assessment of eligibility for curative-intent treatment rather than an arbitrary chronological age cutoff.<sup>136</sup> The American Academy of Family Physicians updated its lung cancer recommendation in 2021, citing support for the USPSTF recommendation for annual LCS in individuals aged 50–80 years who have a  $\geq 20$  pack-year smoking history and currently smoke or have quit within the past 15 years.<sup>36</sup>

## CONCLUSION

Lung cancer is the leading cause of death from cancer and accounts for the most PYLL compared with other cancers.<sup>4,70</sup> Despite declining lung cancer incidence and mortality caused by decades of successful efforts to curb the uptake of smoking and to support people who smoke to quit smoking, the burden of the disease will remain very high for years to come, as tens of millions of individuals with a history of smoking reach the ages when lung cancer risk rises. Jeon et al. projected that age-adjusted mortality will decrease by 79% from 2015 to 2065 because of tobacco-control efforts. In contrast, during this period, 4.4 million lung cancer deaths are projected to occur.<sup>137</sup> A large fraction of these deaths can be prevented if we embrace the urgent challenge to improve our ability to identify the population at risk and apply our knowledge to achieve high rates of participation in regular LCS.

## ACKNOWLEDGMENTS

Members of the American Cancer Society Guideline Development Group serve as volunteers and received no compensation from the American Cancer Society. The current members who participated in the update of this guideline are: Timothy R. Church, PhD; Elena B. Elkin, PhD; Ruth D. Etzioni, PhD; Elizabeth T. H. Fontham, DrPH; Carmen E. Guerra, MD; Kevin C. Oeffinger, MD; Rebecca B. Perkins, MD, MSc; Tina Ya-Chen Shih, PhD; Louise C. Walter, MD; and Andrew M. D. Wolf, MD (Chair). We thank the group of expert advisors (*listed in the Supporting Materials*) for their time and expertise throughout the guideline update and the representatives of stakeholder organizations (*listed in the Supporting Materials*) who reviewed the draft recommendations and rationale. We thank our colleagues from the Division of Cancer Epidemiology and Genetics, National Cancer Institute (Rebecca Landy, PhD; Li Cheung, PhD; Anil Chaturvedi, PhD; Corey Young, PhD; and Hormuzd Katki, PhD), for their epidemiologic and modeling analyses and use of the lung cancer risk-assessment tool to examine the continuing risk of lung cancer with increasing age after smoking cessation. We also thank colleagues from two Cancer Intervention and Surveillance Modeling Network (CISNET) teams for their adaptation of two validated lung cancer models (University of Michigan [M] and Erasmus University [E]) to assess the benefits and harms of lung cancer screening with various years-since-quit smoking thresholds (10, 15, 20, 25, 30, and 0 years since quitting) and screening-stopping ages (University of Michigan:



Rafael Meza, PhD [now at the British Columbia Cancer Research Institute]; Pianpian Cao, PhD; and Jihyoun Jeon, PhD; Erasmus University: Koen de Nijs, MSc; Kevin ten Haaf, PhD; and Harry de Koning, MD). Thanks to R. Edward Hendrick, PhD (University of Colorado School of Medicine), for calculating updated benefit-to-risk ratios for lung cancer screening and follow-up imaging studies based on modern radiation exposures over a lifetime of screening. Finally, thanks to Ella Kazerooni, MD and the American College of Radiology for current screening and follow-up imaging dose data from the American College of Radiology Lung Cancer Screening Registry for inclusion in the Michigan model for estimating radiation-induced deaths. The development of the ACS 2023 lung cancer screening guideline was supported by the American Cancer Society, Inc.

## CONFLICT OF INTEREST STATEMENT

American Cancer Society (ACS) cancer prevention and screening guideline development is supported by ACS operational funds. BrightEdge, LLC ("BrightEdge"), the Society's philanthropic, donor-funded, charitable impact fund, has made an investment in Freenome, a San Francisco-based corporation applying a multiomics platform to develop blood tests for early cancer detection. BrightEdge is a wholly owned subsidiary of the ACS. It operates under a charitable fund model that invests in companies developing novel, cancer-focused therapies and technologies to advance the mission goal of accelerating market delivery of promising cancer-related solutions. BrightEdge's investment decisions are led by BrightEdge's Investment Fiduciary Committee. Investment or another financial vehicle of BrightEdge in a company does not constitute an express or suggest endorsement of any products or services of the company by the ACS or BrightEdge. BrightEdge's committee members do not have any approval rights over the content of the ACS's screening guidelines. Deana Manassaram-Baptiste, Karli K. Kondo, Tyler B. Kratzer, William L. Dahut, and Robert A. Smith are employed by the ACS, which receives grants from private and corporate foundations, including foundations associated with companies in the health sector, for research and initiatives outside of the submitted work. These authors are not funded by any of these grants, and their salary is solely funded through ACS funds. Tina Ya-Chen Shih is a recipient of research grants from the National Cancer Institute and reports personal fees and travel expenses from Sanofi, all outside the submitted work. Ruth D. Etzioni reports holding stock in Seno Medical Instruments of San Antonio, Texas, an imaging device company, and is a recipient of National Cancer Institute grants for research on cancer diagnostic tests. Carmen E. Guerra reports receiving research grants from the Genentech Foundation; owns stock in Crispr Therapeutics, BEAM Therapeutics, Intellia Therapeutics, and Editas Medicine; and also reports serving on the advisory boards for Freenome and Guardant Health outside the submitted work. The remaining authors disclosed no potential conflicts of interest. The sources of funding described in this disclosure have not made any financial contribution and have not had any role or involvement in ACS prevention and screening guideline development or approval.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Wolf AMD, Oeffinger KC, Shih TY-C, et al. Screening for lung cancer: 2023 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2024;74(1):50-81. doi:10.3322/caac.21811