CHEST

Screening for Lung Cancer
CHEST Guideline and Expert Panel Report

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PODCAST

BACKGROUND: Low-dose chest CT screening for lung cancer has become a standard of care in the United States in the past few years, in large part due to the results of the National Lung Screening Trial. The benefit and harms of low-dose chest CT screening differ in both frequency and magnitude. The translation of a favorable balance of benefit and harms into practice can be difficult. Here, we update the evidence base for the benefit, harms, and implementation of low radiation dose chest CT screening. We use the updated evidence base to provide recommendations where the evidence allows, and statements based on experience and expert consensus where it does not.

METHODS: Approved panelists developed key questions using the PICO (population, intervention, comparator, and outcome) format to address the benefit and harms of low-dose CT screening, as well as key areas of program implementation. A systematic literature review was conducted by using MEDLINE via PubMed, Embase, and the Cochrane Library. Reference lists from relevant retrievals were searched, and additional papers were added. The quality of the evidence was assessed for each critical or important outcome of interest using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. Important clinical questions were addressed based on the evidence developed from the systematic literature review. Graded recommendations and ungraded statements were drafted, voted on, and revised until consensus was reached.

RESULTS: The systematic literature review identified 59 studies that informed the response to the 12 PICO questions that were developed. Key clinical questions were addressed resulting in six graded recommendations and nine ungraded consensus based statements.

CONCLUSIONS: Evidence suggests that low-dose CT screening for lung cancer results in a favorable but tenuous balance of benefit and harms. The selection of screen-eligible patients, the quality of imaging and image interpretation, the management of screen-detected findings, and the effectiveness of smoking cessation interventions can affect this balance. Additional research is needed to optimize the approach to low-dose CT screening.

CHEST 2018; 153(4):954-985

KEY WORDS: evidence-based medicine; guidelines; lung cancer

ABBREVIATIONS: ACR = American College of Radiology; CHEST = American College of Chest Physicians; CISNET = Cancer Intervention and Surveillance Modeling Network; CMS = Centers for Medicare & Medicaid Services; COI = conflict of interest; CXR = chest radiograph; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; HR = hazard ratio; LDCT = low-dose CT; PICO = population, intervention, comparator, outcome; SES = socioeconomic status; RR = risk ratio; SEER = Surveillance, Epidemiology, and End Results; STR = Society of Thoracic Radiology; USPSTF = United States Preventative Services Task Force

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Summary of Recommendations

1. For asymptomatic smokers and former smokers age 55 to 77 who have smoked 30 pack years or more and either continue to smoke or have quit within the past 15 years, we suggest that annual screening with low-dose CT should be offered. (Weak recommendation, moderate-quality evidence)

Remark: Age 77 represents the oldest age of participants in the NLST at the end of the screening period. Age 77 also matches the oldest age of CMS coverage for low-dose CT screening. Age 80 has been recommended by the USPSTF based on modeling studies. Recommendation #2 can be applied to individuals age 78 to 80.

Remark: Asymptomatic refers to the absence of symptoms suggesting the presence of lung cancer.

2. For asymptomatic smokers and former smokers who do not meet the smoking and age criteria in Recommendation #1 but are deemed to be at high risk of having/developing lung cancer based on clinical risk prediction calculators, we suggest that low-dose CT screening should not be routinely performed. (Weak recommendation, low-quality evidence)

Remark: It is recognized that clinical risk prediction calculators may be slightly more efficient at identifying individuals who have or will develop lung cancer than the eligibility criteria listed in Recommendation #1. It is also recognized that the variables included in the clinical risk prediction calculators are risk factors for morbidity from the evaluation and treatment of screen detected findings, and death from any cause. Thus, a cohort at high risk for lung cancer based on a clinical risk prediction calculator may be less likely to benefit and more likely to be harmed by lung cancer screening than the cohort identified by the eligibility criteria listed in Recommendation #1. Thus, we do not believe the evidence supports a policy to screen this group.

Remark: It is also recognized that there will be individuals within the cohort deemed to be at high risk for lung cancer from a clinical risk prediction calculator who are healthy enough to benefit from lung cancer screening, and that low-dose CT screening could be considered in these individuals.

Remark: A risk threshold of 1.51% over 6 years on the PLCOm2012 calculator is an example of high risk.

Remark: In the United States, health insurance providers may not pay for low-dose CT screening for those who do not meet the eligibility criteria listed in Recommendation #1.

Remark: Additional lung cancer screening trials that include patients who do not meet the eligibility criteria listed in Recommendation #1 but have a high risk of having/developing lung cancer based on clinical risk prediction calculators are needed.

3. For individuals who have accumulated fewer than 30 pack years of smoking or are younger than age 55 or older than 77, or have quit smoking more than 15 years ago, and do not have a high risk of having/developing lung cancer based on clinical risk prediction calculators, we recommend that low-dose CT screening should not be performed. (Strong recommendation, moderate-quality evidence)

4. For individuals with comorbidities that adversely influence their ability to tolerate the evaluation of screen-detected findings, or tolerate treatment of an early-stage screen-detected lung cancer, or that substantially limit their life expectancy, we recommend that low-dose CT screening should not be performed. (Strong recommendation, low-quality evidence)

Remark: At very severe stages of a comorbid condition it can be clear that low-dose CT screening is not indicated (eg, advanced liver disease, COPD with hypoventilation and hypoxia, NYHA class IV heart failure) because competing mortality limits the potential benefit, and harms are magnified. At less severe stages it can be difficult to determine if an individual's comorbidities are significant enough that they should not receive low-dose CT screening. Further research is required to assist clinicians with this decision.

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FUNDING/SUPPORT: This study was funded in total by internal funds from the American College of Chest Physicians.

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DOI: https://doi.org/10.1016/j.chest.2018.01.016

5. We suggest that low-dose CT screening programs develop strategies to determine whether patients have symptoms that suggest the presence of lung cancer, so that symptomatic patients do not enter screening programs but instead receive appropriate diagnostic testing, regardless of whether the symptomatic patient meets screening eligibility criteria. (Ungraded Consensus-Based Statement)

Remark: In centralized low-dose CT screening programs, the provider that meets with the patient prior to the low-dose CT should ask about symptoms that would suggest diagnostic testing is indicated.

Remark: In de-centralized low-dose CT screening programs, the screening program should assist the ordering provider through educational outreach and/or the provision of clinical tools (eg, reminders built into electronic medical records).

6. We suggest that screening programs define what constitutes a positive test on the low-dose CT based on the size of a detected solid or part-solid lung nodule, with a threshold for a positive test that is either 4 mm, 5 mm, or 6 mm in diameter. (Weak recommendation, low-quality evidence)

Remark: A positive test is defined as a test that leads to a recommendation for any additional testing other than to return for the annual screening exam.

Remark: Nodule diameter is the average of long- and short-axis diameters obtained on the same sagittal, coronal, or transverse image. For part-solid nodules, nodule diameter should be based on the size of the solid component of the nodule.

Remark: An equivalent volumetric threshold can also be considered.

Remark: The LungRADS structured reporting system currently uses 6 mm at the baseline scan and 4 mm if a new nodule is found on the annual scan for solid nodules; and 6 mm at the baseline scan and any size if a new nodule is found on the annual scan for part-solid nodules.

7. We suggest that low-dose CT screening programs develop strategies to maximize compliance with annual screening exams. (Ungraded Consensus-Based Statement)

Remark: Additional research is needed to better understand the factors that influence compliance, and to develop tools to help screening programs maximize compliance with annual screening exams.

8. We suggest that low-dose CT screening programs develop a comprehensive approach to lung nodule management, including multi-disciplinary expertise (Pulmonary, Radiology, Thoracic Surgery, Medical and Radiation Oncology), and algorithms for the management of small solid nodules, larger solid nodules, and sub-solid nodules. (Ungraded Consensus-Based Statement)

Remark: For programs without lung nodule management expertise available on site, collaborations with centers capable of high quality lung nodule management can be formed (eg, referral, distance evaluation).

9. We suggest that low-dose CT screening programs develop strategies to minimize overtreatment of potentially indolent lung cancers. (Ungraded Consensus-Based Statement)

Remark: It is important to educate patients about the potential to detect an indolent lung cancer to help mitigate the psychological distress that could result from living with an indolent untreated lung cancer.

Remark: For malignant nodules, pure ground glass is the nodule morphology most likely to represent an indolent cancer.

10. For current smokers undergoing low-dose CT screening, we recommend that screening programs provide evidence-based tobacco cessation treatment as recommended by the US Public Health Service. (Strong recommendation, low-quality evidence)

Remark: Further research about the ideal approach to tobacco treatment specific to the lung cancer screening setting is needed.

11. We suggest that low-dose CT screening programs develop strategies to provide effective counseling and shared decision-making visits prior to the performance of the LDCT screening exam. (Ungraded Consensus-Based Statement)

Remark: Components of the counseling and shared decision making visit include a determination of screening eligibility (eg, age, smoking history, the absence of symptoms, confirmation of overall health), the use of decision aids with information about benefits and harms of screening, a discussion about the potential

CT findings and need for follow-up testing, the need for annual screening exams, confirmation of the willingness to accept treatment for a screen-detected cancer, and counseling about smoking cessation.

Remark: In centralized low-dose CT screening programs, a screening program provider may meet with the patient prior to the low-dose CT to perform the counseling and shared decision-making visit.

Remark: In de-centralized low-dose CT screening programs, the screening program should ensure that ordering providers are trained, and/or have the tools necessary, to deliver an effective counseling and shared decision-making visit. These tools may include decision aids, information brochures, videos, and links to electronic resources.

Remark: Additional research about the most effective way to conduct counseling and shared decision-making visits is needed.

12. We suggest that low-dose CT screening programs follow the ACR/STR protocols for performing low radiation dose chest CT scans. (Ungraded Consensus-Based Statement)

Remark: An awareness of the potential for radiation related harm can help programs thoughtfully plan ways to minimize this risk through proper patient selection, the performance of the CT scan, and appropriate management of screen-detected findings.

13. We suggest that low-dose CT screening programs use a structured reporting system to report the exam results. (Ungraded Consensus-Based Statement)

Remark: The structured reporting system should include a description of the number, location, size, and characteristics of all lung nodules, guideline based recommendations for surveillance of small lung nodules, and a description of other incidental findings.

Remark: The ACR LungRADS structured report is the most prevalent system used today. LungRADS categories translate directly into data requests from the ACR National Registry.

14. We suggest that low-dose CT screening programs develop strategies to guide the management of non-nodule findings. (Ungraded Consensus-Based Statement)

Remark: Examples include coronary artery calcification, thyroid nodules, adrenal nodules, kidney and liver lesions, thoracic aortic aneurysms, pleural effusions, and parenchymal lung disease.

Remark: A lung cancer screening program should anticipate such incidental findings and have a system in place to address them. Examples include evidence based guidance within the structured report to assist the ordering provider, or centralized management of all incidental findings by the screening program. Clear communication between providers is important to prevent misunderstandings about who will assume responsibility for deciding what needs attention and ensuring appropriate follow-up evaluation.

Remark: The wording of how incidental findings are reported should be systematically developed to minimize anxiety and misunderstanding.

15. We suggest that low-dose CT screening programs develop data collection and reporting tools capable of assisting with quality improvement initiatives and reporting to the current National Registry. (Ungraded Consensus-Based Statement)

Remark: Data categories include patient eligibility criteria, imaging findings and their evaluation, results of the evaluation of imaging findings including complications, smoking cessation interventions, and lung cancer diagnoses including histology, stage, treatment, and outcomes.

The benefit of cancer screening is a reduction in the number of cancer-related deaths in the group that is screened. Even within groups at high risk of developing a cancer, only a small fraction of those screened will benefit, while everyone screened is exposed to potential harms. The benefit and harms of screening differ in both frequency and magnitude. This makes it difficult to determine an acceptable balance of benefit and harms at the population level. For an individual patient, it highlights the importance of education to foster informed, value-based decisions about whether to be screened.

Even when large studies suggest that the value of the benefit of screening outweighs identified harms, the translation of this favorable balance into practice can be difficult. In lung cancer screening, the selection of screen-eligible patients, the quality of imaging and image interpretation, the management of screen-detected findings, and the effectiveness of smoking cessation interventions can affect this balance.

In the present article, we update the evidence base for the benefit, harms, and implementation of low radiation dose chest CT (LDCT) screening. We use the updated evidence base to provide recommendations where the evidence allows, and statements based on experience and expert consensus where it does not. We have not provided updates for other forms of lung cancer screening (ie, chest radiography [CXR], sputum analysis) as the evidence base and recommendations related to CXR and sputum analysis have not changed since the previous iteration of these guidelines.[1] The intended audience for this guideline is practicing clinicians, administrators, and policy makers.

Methods

Expert Panel Composition

The chair of the panel (P. J. M.) was appointed by CHEST's Lung Cancer Guideline Executive Committee and subsequently reviewed and approved by CHEST's Professional Standards Committee. Panelists were nominated by the chair based on their expertise relative to potential guideline questions. The final panel consisted of the guideline chair, five panelists (F. C. D., J. P. K., L. S. K., G. A. S., and R. S. W.), a methodologist (S. P.), and a member (G. S. H.) serving as a liaison to CHEST's Guidelines Oversight Committee.

Conflicts of Interest

All panel nominees were reviewed for their potential conflicts of interest (COI) by CHEST's Professional Standards Committee. After review, nominees who were found to have no substantial COIs were approved, whereas nominees with potential intellectual and financial COIs that were manageable were "approved with management." Panelists approved with management were prohibited from participating in discussions or voting on recommendations in which they had substantial COIs. A grid was created listing panelists' COIs for each recommendation for use during voting. The COI grid can be found in e-Table 1.

Formulation of Key Questions

The expert panel drafted a total of 19 key clinical questions in a PICO (population, intervention, comparator, outcome) format (six related to questions from the 3rd Edition of the Lung Cancer Screening Guidelines[1] and 13 new questions). The panel independently assessed, then discussed and reached consensus about which of the PICO questions to pursue. This resulted in 12 PICO questions (nine of which were new questions) (Table 1). The panel organized the manuscript in sections to help frame the presentation of data. Where the evidence review from the PICO questions did not fully address the considerations of a particular section, the expert panel supplemented the evidence review with relevant literature.

Literature Search

CHEST partnered with Doctor Evidence, LLC (Doctor Evidence: Library Management System. Santa Monica, CA: Doctor Evidence, LLC) to conduct components of the systematic review process, including literature searches, study selection, and data abstraction. Systematic searches were conducted in August 2016 using the following databases: MEDLINE via PubMed, Embase, and the Cochrane Library. Searches were conducted by using a combination of the National Library of Medicine's Medical Subject Headings and other key words specific to each topic. Reference lists from relevant retrievals were also searched, and additional papers were manually added if needed through August 2017. Studies were limited to English language, but no other restrictions (ie, publication date, study design) were put on the searches. Additional details on the literature searches and the selection of studies can be found in e-Figure 1 (Preferred Reporting Items for Systematic Reviews and Meta-analyses diagram).

Study Selection and Data Extraction

Studies retrieved from the completed literature searches were reviewed for relevance through two rounds of screening. During the first round, screening was performed against the predefined PICO selection criteria using the Doctor Evidence Library Management System (Doctor Evidence: Library Management System. Santa Monica, CA: Doctor Evidence, LLC). The Library Management System is a web-based software platform featuring key word emphasis (coloring or bolding of key words), search, and ranking functionalities, as well as the ability to assign and manage the reasons references were rejected at all stages of screening, resulting in generation of a Preferred Reporting Items for Systematic Reviews and Meta-analyses diagram. Title/abstract screening was initially performed by a single reviewer with subsequent quality control by an independent reviewer. Additional quality control was performed by an independent methodologist validating all included abstracts and a random sample of excluded abstracts. All quality control was performed by using the tools and functions available in the Library Management System. Systematic reviews or meta-analyses of studies meeting the selection criteria were hand-checked, and individual studies were included for extraction if they met the selection criteria. The reference lists of individual studies were also manually checked for relevant studies.

Studies that met the inclusion criteria based on the population, intervention, and study design reported in the title/abstract were retrieved for full-text review to determine their final inclusion. Members of the guideline panel were divided into pairs, with each pair assigned a portion of the included studies to review. Disagreements were resolved through discussion.

Data extraction was conducted using the DOC Data version 2.0 software platform (Doctor Evidence, LLC, Santa Monica, CA, USA) and its universal electronic extraction form. Before data extraction began, a standardized Data Configuration Protocol, completed by the panel, was used to define the study level variables, intervention variables, patient characteristics, and specific outcomes to be digitized from eligible studies. Data and meta-data (variables that characterize numerical data points) were obtained from text manually, and digitizer software was used to capture relevant data points from figures, charts, and tables. Data integrity was supported by automated DOC Data quality control features such as the prevention of incorrect data-type entry into incompatible fields. Each collected data point was extracted by two highly trained and proctored evidence analysts.

Risk of Bias Assessment

The methodologist assessed the risk of bias in all included studies. The Cochrane Risk of Bias tool was used to assess the risk of bias for randomized controlled trials[2] and the Risk of Bias in Non-randomized Studies of Interventions tool to evaluate risk of bias for observational studies.[3] In cases in which existing systematic reviews were available, we used the Documentation and Appraisal Review Tool to assess methodological quality.[4]

Meta-Analysis

When individual studies were available or a meta-analysis needed to be updated, we used the Cochrane Collaboration Review Manager,

TABLE 1] PICO Questions

Study Characteristic	Inclusion Criteria	Exclusion Criteria
1. What is the rate of death from lung cancer (ie, lung cancer mortality) among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared with either no screening or screening with another modality?		
Population	Asymptomatic adults with no history of lung cancer but at elevated risk of lung cancer (as defined by author)	Individuals not defined as elevated risk
Interventions	Screening with LDCT	
Comparators	Chest radiograph Sputum analysis No screening	None
Outcomes	Rate of death from lung cancer (ie, lung cancer mortality)	None
Study design	Systematic reviews, RCT, observational	Case series/reports
2. What is the rate of death from lung cancer (ie, lung cancer mortality) among individuals at elevated risk of lung cancer with different clinical phenotypes (sex, age, race, risk, COPD, comorbidities) who undergo screening with LDCT, compared with either no screening or screening with another modality?		
Population	Asymptomatic adults with no history of lung cancer but at elevated risk of lung cancer (as defined by author) with different clinical phenotypes (sex, age, race, risk, COPD, comorbidities)	Individuals not defined as elevated risk
Interventions	Screening with LDCT	
Comparators	Chest radiograph Sputum analysis No screening	None
Outcomes	Rate of death from lung cancer (ie, lung cancer mortality)	None
Study design	Systematic reviews, RCT, observational	Case series/reports
3. What is the rate of death or complications resulting from biopsies of detected lesions among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared with either no screening or screening with another modality?		
Population	Asymptomatic adults with no history of lung cancer but at elevated risk of lung cancer (as defined by author)	Individuals not defined as elevated risk
Interventions	Screening with LDCT	
Comparators	Chest radiograph Sputum analysis No screening	None
Outcomes	Rate of death resulting from biopsies of detected lesions Rate of complications resulting from biopsies of detected lesions	None
Study design	Systematic reviews, RCT, observational	Case series/reports
4. What is the rate of death or complications resulting from biopsies of screen-detected lesions among individuals at elevated risk of lung cancer with different clinical phenotypes (sex, age, race, risk, COPD, comorbidities) who undergo screening with LDCT, compared with either no screening or screening with another modality?		
Population	Asymptomatic adults with no history of lung cancer but at elevated risk of lung cancer (as defined by author) with different clinical phenotypes (sex, age, race, risk, COPD, comorbidities)	Individuals not defined as elevated risk
Intervention	Screening with LDCT	
Comparators	Chest radiograph Sputum analysis No screening	None
Outcomes	Rate of death resulting from biopsies of screen-detected lesions Rate of complications resulting from biopsies of screen-detected lesions	None
Study design	Systematic reviews, RCT, observational	

(Continued)

TABLE 1] *(Continued)*

Study Characteristic	Inclusion Criteria	Exclusion Criteria
5. What is the rate of surgery for benign disease among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared with either no screening or screening with another modality?		
Population	Asymptomatic adults with no history of lung cancer but at elevated risk of lung cancer (as defined by author)	Individuals not defined as elevated risk
Interventions	Screening with LDCT	
Comparators	Chest radiograph Sputum analysis No Screening	None
Outcomes	Rate of surgery for benign disease	None
Study design	Systematic reviews, RCT, Observational	Case series/reports
6. What is the psychosocial impact (including distress, anxiety, depression, and quality of life) on individuals at elevated risk of developing lung cancer who undergo screening with LDCT and are found to have a screen-detected lung nodule, compared with either no screening or no nodule detected on LDCT screening?		
Population	Asymptomatic adults with no history of lung cancer but at elevated risk of lung cancer (as defined by author)	Individuals not defined as elevated risk
Interventions	Screening with LDCT	
Comparators	Chest radiograph Sputum analysis No screening	None
Outcomes	Quality of life (including distress, anxiety, depression)	None
Study design	Systematic reviews, RCT, observational	Case series/reports
7. What is the rate of overdiagnosis among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared with either no screening or screening with another modality?		
Population	Asymptomatic adults with no history of lung cancer but at elevated risk of lung cancer (as defined by author)	Individuals not defined as elevated risk
Interventions	Screening with LDCT	
Comparators	Chest radiograph Sputum analysis No screening	None
Outcomes	Rate of overdiagnosis	None
Study design	Systematic reviews, RCT, observational	Case series/reports
8. What is the cost-effectiveness of LDCT screening of individuals at elevated risk of lung cancer, compared with either no screening or screening with another modality?		
Population	Asymptomatic adults with no history of lung cancer but at elevated risk of lung cancer (as defined by author)	Individuals not defined as elevated risk
Interventions	Screening with LDCT	
Comparators	Chest radiograph Sputum analysis No screening	None
Outcomes	Cost-effectiveness	None
Study Design	Systematic reviews, RCT, observational	Case series/reports
9. What is the rate of lung cancer detection when clinical risk assessment tools are applied for the selection of individuals at elevated risk of lung cancer for LDCT screening, compared with the use of the NLST or USPSTF criteria?		
Population	Asymptomatic adults with no history of lung cancer but at elevated risk of lung cancer (as defined by author)	Individuals not defined as elevated risk
Interventions	Clinical risk assessment tools applied for the selection of individuals at elevated risk of lung cancer for LDCT screening	
Comparators	NLST inclusion criteria or USPSTF criteria	None
Outcomes	Rate of lung cancer detection by LDCT	None
Study design	Systematic reviews, RCT, observational	Case series/reports

(Continued)

TABLE 1] *(Continued)*

Study Characteristic	Inclusion Criteria	Exclusion Criteria
10. What is the rate of lung cancer detection when molecular biomarker results are applied to the selection of individuals at elevated risk of lung cancer for LDCT screening, compared with the use of the NLST or USPSTF criteria?		
Population	Asymptomatic adults with no history of lung cancer but at elevated risk of lung cancer (as defined by the study authors)	Individuals not defined as elevated risk
Interventions	Molecular biomarker results applied to the selection of individuals at elevated risk of lung cancer for LDCT screening	None
Comparators	NLST criteria or USPSTF criteria	None
Outcomes	Rate of lung cancer detection by LDCT	None
Study design	Systematic review, RCT, observational	Case series/reports
11. What is the stage distribution of lung cancer, the rate of death from lung cancer (ie, lung cancer mortality), and the portion of positive scans among individuals at elevated risk of lung cancer who undergo annual screening with LDCT with a 4-mm nodule size threshold for defining a positive LDCT, compared with other definitions of a positive LDCT?		
Population	Asymptomatic adults with no history of lung cancer but at elevated risk of lung cancer (as defined by author)	
Interventions	Positive LDCT defined as 4 mm	None
Comparators	Other definitions of positive LDCT	None
Outcomes	Stage distribution of lung cancer, lung cancer mortality, portion of positive scans	None
Study design	Systematic review, RCT, observational	Case series/reports
12. What is the rate of smoking cessation among active smokers at elevated risk of lung cancer who receive smoking cessation counseling as part of an LDCT screening program, compared with those who do not receive smoking cessation counseling, and compared with those who do not participate in LDCT screening?		
Population	Active smokers at elevated risk of lung cancer	
Interventions	Any smoking cessation intervention as part of an LDCT screening program	None
Comparators	No smoking cessation intervention No participation in LDCT screening	None
Outcomes	Smoking cessation rate (as defined by author)	None
Study design	Systematic review, RCT, observational	Case series/reports

LDCT = low-dose CT; NLST = National Lung Screening Trial; PICO = population, intervention, comparator, and outcome; RCT = randomized controlled trial; USPSTF = United States Preventative Services Task Force.

version 5.2,[5] as well as the DOC Data platform using the open-source R Project for Statistical Computing through a proprietary user interface. We used a random effects model and the method of DerSimonian and Laird to pool the individual estimates.[6] Risk ratio (RR) was used to report results of dichotomous outcomes and mean difference for continuous outcomes. A P value $< .05$ was considered statistically significant for all tests. Statistical heterogeneity was assessed by using the Higgins I^2 test and a χ^2 $P < .05$ was considered to represent significant heterogeneity.

For analyses on harms due to screening with binary data (ie, complications due to invasive procedures, surgery for benign disease), the number, proportion, or percentage of events was used to generate an overall summary measure of effect by using the DerSimonian and Laird random effects model.

Assessing the Overall Quality of the Evidence

The overall certainty (quality) of the evidence was assessed for each critical or important outcome of interest by using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach.[7] Evidence profiles were created by using the Guideline Development Tool, which categorized the overall quality of the body of evidence into one of four levels: high, moderate, low, or very low. Each level represented the confidence in the estimated effects for a specific outcome (Table 2).

Recommendations

The panel drafted and graded recommendations based on the results of the meta-analyses and evidence profiles. Recommendations were graded according to CHEST's grading system, which uses the GRADE approach.[8,9] The recommendations were either "strong" or "weak" according to this approach. Strong recommendations use the wording "we recommend" and weak recommendations use the wording "we suggest." The implications of the strength of recommendation are summarized in e-Table 2.

In instances in which there was insufficient evidence, but a clinically relevant area was believed to require a guiding comment, a weak suggestion was developed and "Ungraded Consensus-Based Statement" replaced the grade.[10]

TABLE 2] Quality of Evidence Grades

Grade of Recommendation	Benefit Vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are very confident that the true effect lies close to that of the estimate of the effect	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Strong recommendation, very-low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak (conditional) recommendation, high-quality evidence	Benefits closely balanced with risks and burden	We are very confident that the true effect lies close to that of the estimate of the effect	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect
Weak (conditional) recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Best action may differ depending on circumstances or patients' or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak (conditional) recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak (conditional) recommendation, very-low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Ungraded consensus-based suggestions			
Ungraded Consensus-Based Statement	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens, or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on our confidence in the estimate of effect and may change the estimate

Consensus Development

All drafted recommendations and suggestions were presented to the panel in an anonymous online voting survey to reach consensus and gather feedback. Panelists were requested to indicate their level of agreement on each statement based on a five-point Likert scale derived from the GRADE grid.[11] Panelists with COIs related to the individual recommendations were not allowed to vote (per the terms of management). According to CHEST policy, each recommendation and statement required a 75% voting participation rate and at least 80% consensus to "pass." Any recommendation or suggestion that did not meet these criteria was revised by the panel based on the feedback, and a new survey that incorporated those revisions was completed.

Peer Review Process

Reviewers from CHEST's Guidelines Oversight Committee, the CHEST Board of Regents, and the *CHEST* journal reviewed the methods used and the content of the manuscript for consistency, accuracy, and completeness. The manuscript was revised according to feedback from the reviewers.

Results

The literature search identified a total of 3,081 eligible studies. After two rounds of study screening, 59 were selected for the final evidence review. Ten trials (with multiple publications) and 13 cohort studies of LDCT screening that address the benefits and harms of screening were included. Table 3[12-36] describes the study design of the 10 lung cancer screening trials, and Table 4[12-16,21-23,35,36] and Table 5 present the relevant results of these trials. Table 6[37-52] describes the study design of the 13 cohort studies.

Benefit of Screening for Lung Cancer

Lung Cancer Mortality Reduction: PICO 1: What is the rate of death from lung cancer (ie, lung cancer mortality) among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared with either no screening or screening with another modality?

Five randomized controlled trials address the benefit of screening, although only the National Lung Screening Trial (NLST) was adequately powered to answer the question of whether a mortality benefit from screening can be achieved.[15,18,24,27,53] The NLST included 53,452 current or former smokers aged 55 to 74 years with at least a 30 pack-year history of cigarette use. Former smokers had to have quit within the past 15 years. Participants were randomized to a baseline and two annual LDCT scans or CXRs. The results, as initially reported, showed a 20% reduction in lung cancer-specific mortality and a 7% reduction in overall mortality, favoring LDCT screening.[12] In a subsequent report that used a later follow-up date for lung cancer deaths, the reduction in lung cancer-specific mortality (per 100,000 person years) was 16%.[53] In absolute terms, for every 1,000 persons screened, approximately three lung cancer deaths were prevented.

The other four trials randomized 12,673 patients to either annual LDCT or usual care. None of these trials were individually powered to adequately address a mortality benefit (smaller size, screened a lower risk group than the NLST). Several explicitly stated that they expected to pool their data with other European trials.[15,18,24,27] None of these trials showed a benefit to screening (Fig 1, e-Table 3). An additional 1,186 patients were randomized to biennial LDCT (ie, every 2 years) vs usual care within the Multi-centric Italian Lung Detection Trial (MILD) trial.[27] Again, no benefit was seen with screening on an every-other-year basis. The Dutch-Belgian randomized LDCT screening trial (Nederlands-Leuvens Longkanker Screenings Onderzoek Study [NELSON] trial), which has yet to report final results, may have adequate power to assess the mortality benefit of screening. This study differs from the NLST by risk group assessed (age 50-75 years, 15 cigarettes per day for 20 years or 10 cigarettes per day for 30 years, and smoked within the past 10 years), screening interval (baseline, year 1, year 3, and year 5.5), and nodule identification strategy (volumetric).[54]

PICO 2: What is the rate of death from lung cancer (ie, lung cancer mortality) among individuals at elevated risk of lung cancer with different clinical phenotypes (sex, age, race, risk, COPD, comorbidities) who undergo screening with LDCT, compared with either no screening or screening with another modality?

The NLST was the only study from which reports of lung cancer mortality stratified by sex, age, race, and cancer risk were identified. A nonsignificant trend toward women benefiting more than men was seen (RR: 0.73 vs 0.92; $P = .08$).[53] Similarly, a nonsignificant trend toward black individuals benefiting more than white individuals was reported (hazard ratio [HR]: 0.61 vs 0.86; $P = .29$).[55] There were no significant differences between those aged < 65 years and those aged ≥ 65 years (RR: 0.82 vs 0.87; $P = .60$) or between current and former smokers (RR: 0.81 vs 0.91; $P = .40$).[53,56] Patients diagnosed with squamous cell carcinoma did not seem to benefit whether male (RR: 1.31) or female (RR: 1.04). The reduction in RR of lung cancer mortality was

TABLE 3] Summary of Design of Included Randomized Controlled Trials

Study	Sample Size	Age (y)	Smoking History	Smoking Cessation (Years Since Quit)	Screening Interval and Duration	Follow-up (y)	Definition of Positive Result[a]
LDCT vs CXR							
NLST[12,13]	53,454	55-74	≥ 30 pack-years	≤ 15	3 annual screens	6.5 (median)	≥ 4 mm
Depiscan[14]	765	50-75	≥ 15 cigarettes/d for ≥ 20 y	< 15	3 annual screens	NR	> 5 mm
LDCT vs usual care (no screening)							
DANTE[15-17]	2,472 males	60-74	≥ 20 pack-years	< 10	5 annual screens; baseline CXR for both study arms	8	> 5 mm
DLCST[18-21]	4,104	50-70	≥ 20 pack-years	< 10	5 annual screens	10	> 15 mm or rapid growing 5- to 15-mm nodules (> 25% increase in volume on 3-mo repeat CT)
NELSON[22,23]	15,822	50-75	≥ 15 cigarettes/d for ≥ 25 y or ≥ 10 cigarettes/d for ≥ 30 y	< 10	4 screening rounds; interval after baseline: 1 y, 2 y, and 2.5 y	7	Volume > 500 mm^3 or volume 50-500 mm^3 with VDT < 400 d on 3-mo repeat CT
ITALUNG[24-26]	3,206	55-69	≥ 20 pack-years	≤ 10	4 annual screens	6	≥ 5 mm solid nodule, a ground-glass nodule ≥ 10 mm, or any part-solid nodule
MILD[27-29]	4,099	≥ 49	≥ 20 pack-years	< 10	Two study arms: 5 annual screens; or 3 biennial screens	5	Volume > 250 mm^3 or rapid growing 60-250 mm^3 (> 25% increase in volume on 3-mo repeat CT)
LUSI[30,31]	4,052	50-69	≥ 15 cigarettes/d for ≥ 25 y or ≥ 10 cigarettes/d for ≥ 30 y	< 10	4 annual screens	3	≥ 5 mm
UKLS[32-34]	4,055	50-75	LLPv2 risk ≥ 5%		One screening	10	Volume > 500 mm^3 or volume 50-500 mm^3 with VDT < 400 d on 3-mo repeat CT
LSS[35,36]	3,318	55-74	≥ 30 pack-years	< 10	One screening	1	≥ 4 mm

CXR = chest radiograph; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays Trial; DLCST = Danish Lung Cancer Screening Trial; ITALUNG = Italian Lung Cancer Screening Trial; LLPv2 = Liverpool Lung Project version 2; LSS = Lung Screening Study; LUSI = German Lung Cancer Screening Intervention Trial; MILD = Multi-centric Italian Lung Detection Trial; NELSON = Nederlands-Leuvens Longkanker Screenings Onderzoek Study; NR = not reported; UKLS = United Kingdom Lung Screening Study; VDT = volume doubling time. See Table 1 legend for expansion of other abbreviations.

[a]If benign features were present the nodule was considered negative.

TABLE 4] Results From Included RCTs

Study	No. Randomized	Age (y): Mean ± SD or Median (IQR)	Male (%)	Pack-Years Median (IQR)	Active Smokers (%)	Positive Results[a] at T_0	Positive Results[a] by End of Screening Period	Lung Cancer Mortality RR (95% CI)
NLST[12,13]	53,454	61 ± 5	59	48 (27)	48.1	7,191 (27.3%)	10,287 (39.1%)	0.85 (0.75-0.96)
Depiscan[14]	765	56 (NR)	71	30 (NR)	64	24%	NR	NR
DANTE[15,16]	2,472	64.6 ± 3.5	100	45 (28.5)	56	199 (15.6%)	471 (37%)	1.01 (0.70-1.44)
DLCST[21]	4,104	58 ± 5	55	36 (13)	75.3	155 (7.6%)	241 (11.8%)	1.03 (CI 0.66-1.60)
NELSON[22,23]	15,822	59 (IQR: 6)	84	42 (19)	55	120 (1.6%)	2.0% (overall) 6.0% (at least 1 positive scan)	NR
ITALUNG[24-26]	3,206	61 ± 4	64	40 (NR)	66	426 (30.3%)	1,044 (46.1%)[b]	0.70 (0.48-1.04)
MILD[27-29]	4,099	Annual: 57 (NR) Biennial: 58 (NR)	Annual: 68 Biennial: 69	Annual: 39 (NR) Biennial: 39 (NR)	Annual: 69 Biennial: 68	Annual: 177 (14%) Biennial: 158 (15%)	NR	Annual: 2.48 (0.98-6.29) Biennial: 1.24 (0.42-3.70)
LUSI[30,31]	4,052	58 (IQR: 5)	66	36 (18)	61	451 (22.2%)	805 (39.7%)	NR
UKLS[32-34]	4,055	67 ± 4	75	NR	39	536 (26.9%)[c]	NR, single screen	NR
LSS[35,36]	3,318	NR	58	54 (NR)	57.9	340 (20.5%)	573 (34.5%)	NR

IQR = interquartile range; RR = risk ratio. See Table 1 and 3 legends for expansion of other abbreviations.
[a]Number of patients with positive results, not number of nodules; see previous table for definition of positive result in each study.
[b]The total number of positives from T_0 to T_4 is 1,044; unable to determine if this excludes positive results from the baseline (T0) screen.
[c]If include follow-up imaging at 1 year (since a single screen trial), the number would be 1,015 (50.9%).

TABLE 5] Summary of Biopsies in Included RCTs

Study	Nonsurgical Biopsy/Procedure	Nonsurgical Biopsy/Procedure With Benign Result	Surgical Procedure	Surgical Procedure With Benign Result	Complications From Invasive Procedures	Death After[a] Invasive Procedures
NLST	993	293	673	164 (24.4%)	84[b]	16
Depiscan	NR	NR	9	3 (33.3%)	NR	NR
DANTE	NR	NR	90	17 (18.9%)	NR	NR
DLCST	NR	NR	25	7 (28%)	4 (0.19%)[c]	NR
NELSON	NR	6	NR	61	NR	NR
ITALUNG	38	1 (2.6%)	38	4 (10.5%)	NR	6 (3.7%)
MILD	NR	NR	45	4 (8.9%)	NR	NR
LUSI	NR	NR	NR	NR	NR	NR
UKLS	NR	NR	39	4 (10.3%)	NR	NR
LSS	29	16 (55.1%)	46	18 (39.1%)	NR	NR

See Table 1 and 3 legends for expansion of other abbreviations.
[a]Death after invasive procedures refers to mortality following an invasive follow-up procedure that was initiated by screening. In the NLST and ITALUNG studies, it is reported as death within 60 days of invasive procedure.
[b]Major complications include: acute respiratory failure, anaphylaxis, bronchopulmonary fistula, cardiac arrest, cerebral vascular accident/stroke, congestive heart failure, death, hemothorax requiring tube placement, myocardial infarction, respiratory arrest, bronchial stump leak requiring tube thoracostomy or other drainage for > 4 days, wound dehiscence, empyema, injury to vital organ or vessel, prolonged mechanical ventilation over 48 h postoperatively, thromboembolic complications requiring intervention, chylous fistula, brachial plexopathy, lung collapse, and infarcted sigmoid colon.
[c]Major complications include empyema and myocardial infarction.

similar among lung cancer risk quintiles in the NLST, although the number needed to screen to avert a lung cancer death was much higher in the lowest compared with the highest risk quintile (5,276 vs 161).[57]

In the Danish Lung Cancer Screening Trial (DLCST), there was no difference in lung cancer mortality in those with a < 35 pack-year smoking history compared with a ≥ 35 pack-year smoking history (RR: 1.26 vs 0.92; $P = .52$) or between those with or without COPD (RR: 0.85 vs 1.38; $P = .30$).[18] In the NLST-ACRIN (American College of Radiology Imaging Network) subgroup, patients with COPD had an increase in lung cancer incidence (incident rate ratio: 2.15), no excess lung cancers in the LDCT arm, and a more favorable stage shift.[58]

Harms of Screening for Lung Cancer

Harms in lung cancer screening are related to the performance of the screening test and the consequences of evaluating abnormal test results. A taxonomy of screening harms categorizes harms as either physical, psychological, financial, or related to opportunity costs.[59] Commonly discussed harms from LDCT screening include the physical and psychological consequences of identifying and evaluating lung nodules, the impact of the cumulative radiation exposure on cancer risk, and the potential for overdiagnosis and overtreatment of lung cancer.

The cost-effectiveness of lung cancer screening is an important societal consideration that we have positioned in the harms section, although it could fit elsewhere. A final potential harm is the consequence of evaluating other imaging findings, unrelated to lung cancer (eg, coronary artery calcification). Little is known about whether this evaluation is more likely to be an added harm or benefit of LDCT screening.

Here, the evidence collected from LDCT screening studies on each of these potential harms is described in turn. Although these results provide the best available evidence, it is critical to acknowledge that the impact of these harms may be magnified or minimized based on the quality of LDCT screening implementation outside the auspices of well-supported trials. Careful attention to patient selection, effective communication about the results of screening, and the judicious use of invasive procedures to evaluate and treat screen-detected nodules and cancers is required to meet or improve on the results of reported studies.

Death and Complications Resulting From Biopsies:

PICO 3: What is the rate of death or complications resulting from biopsies of detected lesions among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared with either no screening or screening with another modality?

TABLE 6] Summary of Design of Included Cohort Studies

Study (Author, Year)	Sample Size	Age (y)	Smoking History (Pack-Years)	Smoking Cessation (Years Since Quit)	No. of Screens	Planned Follow-up (y)	Definition of Positive Result
Bastarrika et al,[37] 2005	911	≥ 40	≥ 10	NR	2	NR	≥ 5 mm
Callol et al,[38] 2007	482	> 50	≥ 10	< 0.5	2	NR	≥ 5 mm
Diederich et al,[39] 2004	817	≥ 40	≥ 20	NR	6	6	All nodules
Henschke et al,[40-43] 1999-2001	1,000	≥ 60	≥ 10	NR	3	10	≥ 6 mm
MacRedmond et al,[44] 2006	449	50-74	≥ 10	NR	2	2	All nodules
Menezes et al,[45] 2010	3,352	≥ 50	≥ 10	NR	6	NR	Solid nodule ≥ 5 mm, or nonsolid nodule ≥ 8 mm
Novello et al,[46] 2005	520	≥ 55	≥ 20	< 10	5	NR	≥ 5 mm
Pastorino et al,[47] 2003	1,035	≥ 50	≥ 20	NR	5	NR	> 5 mm
Picozzi et al,[48] 2005	60	≥ 50	≥ 20	NR	3	3	≥ 10 mm
Sobue et al,[49] 2002	1,682	≥ 40	≥ 20	NR	10	NR	> 4.9 mm
Swensen et al,[50] 2003	1,520	≥ 50	≥ 20	< 10	5	5	> 8 mm
Veronesi et al,[51] 2008	5,201	≥ 50	≥ 20	< 10	5	NR	> 5 mm
Wilson et al,[52] 2008	3,755	50-79	≥ 12.5	< 10	2	3	≥ 10 mm

See Table 3 legend for expansion of abbreviation.

Lung nodules are commonly found at the time of LDCT screening for lung cancer (Table 4). The frequency of nodule detection is affected by the criteria used to label the finding positive (eg, nodule size, or a nodule resulting in additional testing), the imaging slice thickness, the duration of screening, and the geographic location of the screening program. In the NLST, 39.1% of those in the LDCT arm had a nodule identified by the end of the screening period.[12] In total, 2,033 procedures were performed for a screen-detected finding in 26,722 patients in the LDCT arm compared with 758 procedures in 26,732 patients in the CXR arm. A Veterans Administration demonstration project found 59.7% of those screened had any size nodule on the prevalence screen, with 12.7% > 8 mm in diameter.[60] The number of patients screened who underwent further diagnostic evaluation for screen-detected benign nodules (42 [2% of all patients screened]) was higher than the number of patients with screen-detected lung cancer (31 [1.5% of all patients screened]). Procedure rates in other reviewed studies varied in part based on trial length and design (1.2%-6.8%).[16,19,39,51,61] In total, three studies described procedure rates in those screened with CXR, and 17 studies in those screened with LDCT; 2.7% of those screened with CXR and 5.1% with LDCT had an invasive procedure performed (e-Fig 2A, 2B). A balance must be considered when reviewing data about procedures for screen-detected nodules. Ideally, procedures should be minimized in those with benign nodules without avoiding procedures and thus delaying treatment in those with malignant nodules.

The most serious concern is the risk of death as a result of the evaluation of a screen-detected nodule. As reported in the studies reviewed, it is difficult to determine if death soon after a procedure was the result of the procedure or was an unrelated event that occurred shortly after the procedure was performed. Limited data

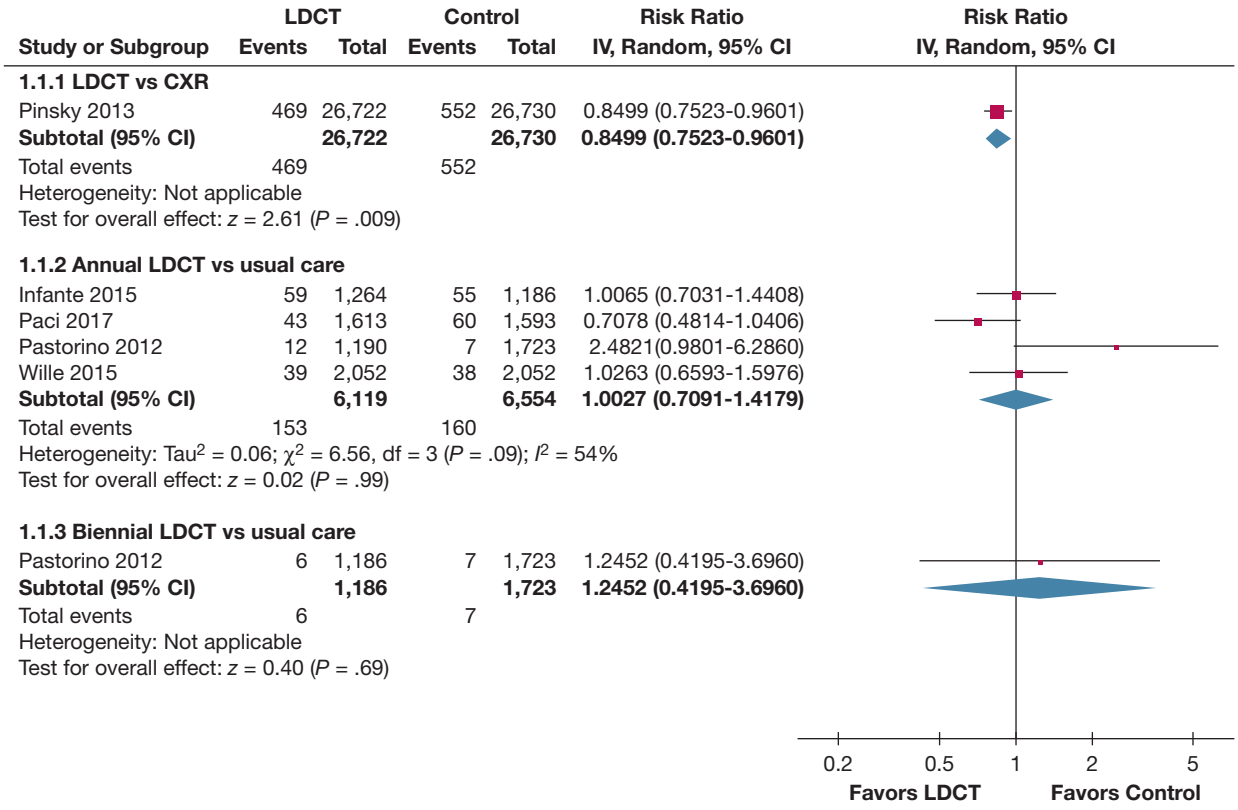

Figure 1 – *Forest plot for lung cancer mortality. CXR = chest radiography; LDCT = low-dose CT.*

are available that carefully assess this (Table 5). In the LDCT screening arms of six studies, 19 deaths were reported after invasive procedures performed for screen-detected findings, corresponding to an absolute number of 7.7 deaths per 1,000 patients undergoing invasive procedures (e-Fig 3A, 3B, e-Table 4).[12,16,19,39,51,61] The length of time after a procedure in which death was considered peri-procedural varied among the studies. The NLST provides the highest quality data at this time. In the NLST, the rate of death within 2 months of the most invasive procedure performed to evaluate a screen-detected finding during the entire screening period was six per 10,000 individuals screened by LDCT and four per 10,000 individuals screened by CXR.[12] This corresponds to 0.8% of procedures performed in individuals screened by LDCT and 1.3% of procedures performed in individuals screened by CXR. Focusing only on patients who had detected nodules eventually found to be benign, the risk of death following invasive procedures in the NLST was 2.2 per 10,000 screening participants in the LDCT arm. It is not clear if the deaths reported in the NLST were related to the procedure.

Rates of major complications were higher among patients who underwent LDCT compared with CXR screening in the NLST (3.1 vs 0.9 per 1,000 screened; 7.8% of procedures vs 6.3%).[12,19,51] Two additional studies of LDCT alone, with less inclusive definitions of major complications, were reviewed. Rates were 0.8 and 1.9 per 1,000 screened (3.7% and 8.2% of procedures).[19,51] Focusing only on those patients who had detected nodules eventually found to be benign, the risk of major complications following invasive procedures in the NLST was 4.1 per 10,000 screening participants in the LDCT arm and 0.37 per 10,000 screening participants in the CXR arm.[12] This evidence is summarized in e-Figure 4a and 4b and graded in e-Table 5.

In summary, LDCT screening led to an appreciable increase in the frequency of invasive procedures, the number of deaths soon after an invasive procedure, and the number of major complications resulting from invasive procedures compared with the control arms.

PICO 4: What is the rate of death or complications resulting from biopsies of screen-detected lesions among individuals at elevated risk of lung cancer with different clinical phenotypes (sex, age, race, risk, COPD, comorbidities) who undergo screening with LDCT,

compared with either no screening or screening with another modality?

There were no studies identified that described complications from biopsies of screen-detected lesions within different clinical phenotypes. Further research in this area is warranted.

Surgery and Nonsurgical Procedures for Benign Disease: **PICO 5:** What is the rate of surgery for benign disease among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared with either no screening or screening with another modality?

Some of the physical harms occur in patients who could not have benefited from the procedure, as their screen-detected nodules were ultimately found to be benign. The rate of surgical procedures for benign disease varied across studies but was consistently higher among patients who underwent LDCT vs CXR screening. The rate of surgery (any surgical resection by thoracotomy or video-assisted thoracoscopic surgery) for benign disease was 4.7 per 1,000 screened in those screened by LDCT (17 studies), compared with a rate of 2.6 per 1,000 screened by CXR (three studies).[12,14,15,20,22,25,27,32,35,37-39,44,47,49,51,52] This comparison is influenced by the length of the screening period of the studies included. A direct comparison in the three studies that included both LDCT and CXR showed rates of surgery for benign disease of 6.1 vs 1.7, 13.4 vs 4.2, and 11.3 vs 3.9 per 1,000 screened, respectively.[12,15,35] In the LDCT and CXR studies, 22.9% and 20.1% of surgeries were performed for benign disease (e-Fig 5A, 5B, e-Table 6). In the LDCT and CXR studies, 30.3% and 18.5% of nonsurgical procedures were performed for benign disease (e-Fig 6A, 6B and graded in e-Table 7).

Psychosocial Impact: **PICO 6:** What is the psychosocial impact (including distress, anxiety, depression, and quality of life) on individuals at elevated risk of developing lung cancer who undergo screening with LDCT and are found to have a screen-detected lung nodule, compared with either no screening or no nodule detected on LDCT screening?

Three randomized trials examined the potential for an adverse psychological impact among those patients found to have a screen-detected nodule.[62-64] Participants in the NELSON trial with an indeterminate result experienced an increase in lung cancer-specific distress, as measured by the impact of events scale, which persisted up to their follow-up examination.[62] Similarly, participants in the United Kingdom Lung Screening Study (UKLS) with an indeterminate nodule experienced an increase in lung cancer-specific distress, measured by using the Cancer Worry Scale, that had resolved at the time of a follow-up survey (mean: 16 months; range: 10-29 months).[64] In the NLST and UKLS trials, no clinically significant difference was found in either short-term or long-term anxiety among those with indeterminate vs negative results.[63,64] Neither the NELSON trial nor the NLST found a difference in health-related quality of life among those with indeterminate vs normal results.[62,63] In summary, clinical trials suggest that finding a screen-detected nodule may transiently increase distress but does not adversely affect anxiety levels or quality of life.

Overdiagnosis: **PICO 7:** What is the rate of overdiagnosis among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared with either no screening or screening with another modality?

The debate about the impact of overdiagnosis is in part related to how it is defined. Traditionally, overdiagnosis has been defined as the discovery of a cancer that is so indolent that it is clinically insignificant (ie, it would not have caused symptoms or presented clinically had screening not been undertaken). Alternatively, one may extend this definition to include any lung cancer diagnosed, whether indolent or aggressive, in a patient with a comorbid condition that leads to their death before the cancer would have affected their well-being. As the risk factors for lung cancer are shared with other potentially serious conditions, it is natural for a portion of screen-eligible patients to die of other causes while enrolled in a screening program. The overall 5-year survival of NLST-eligible, United States Preventative Services Task Force (USPSTF)-eligible, and Medicare-eligible patients in the general population has been estimated to be 89%, 87%, and 80%, respectively.[65] By extension, early-stage screen-detected lung cancers may not have affected the lives of those who died of other causes within the asymptomatic lung cancer phase. This definition of overdiagnosis highlights the importance of selecting patients for screening who are without comorbid conditions who carry a risk of death that overshadows the risk of death from lung cancer.

Overdiagnosis is associated with the harm of overtreatment, exposing patients to invasive procedures, including surgeries, that are essentially unnecessary and

the psychological impact of living following a cancer diagnosis. Overdiagnosis is difficult to quantify because a tumor cannot truly be called "clinically insignificant" unless it is observed indefinitely without treatment, causes no symptoms, and the patient ultimately dies of another cause. Pragmatically, and from multiple investigations, the slow growth rate of tumors that begin as pure ground-glass nodules (often lepidic predominant adenocarcinomas histologically) makes them more likely to represent overdiagnosed tumors.[66-70]

Investigators from the NLST attempted to quantify rates of overdiagnosis by calculating the excess lung cancers detected by LDCT (compared with CXR) screening divided by all lung cancers detected by screening in the LDCT arm.[66] They concluded that among all LDCT screen-detected tumors, 18.5% (95% CI: 5.4-30.6) were overdiagnosed and that 78.9% (95% CI: 62.2-93.5) of lepidic predominant adenocarcinomas detected by LDCT were overdiagnosed. It was estimated that 1.38 lung cancers were overdiagnosed for every lung cancer death averted. Grading of this evidence is provided in e-Table 8.

Cost-effectiveness: PICO 8: What is the cost-effectiveness of LDCT screening of individuals at elevated risk of lung cancer, compared with either no screening or screening with another modality?

By most currently used standards in the United States, LDCT screening is considered cost-effective. Results from a systematic review that included data from 13 studies found that cost-effectiveness estimates for LDCT screening range from $18,452 to $66,480 per life year gained and $27,756 to $243,077 per quality-adjusted life-year gained.[71] A study published after the systematic review used microsimulation modeling to estimate the cost-effectiveness of lung cancer screening in a population-based setting in Ontario, Canada.[72] Several models were tested with the optimal scenario for screening identified as current and former smokers aged 55 to 75 years with > 40 pack-years of smoking, who were active smokers or had quit smoking < 10 years ago, screened annually. In this group, the incremental cost-effectiveness ratio was $41,136 Canadian dollars ($33,825 US dollars) per life year gained. A cost-effectiveness analysis performed by using data from the NLST showed an overall cost-effectiveness of $81,000 per quality-adjusted life year while highlighting that cost-effectiveness varies by sex, smoking status, and the risk of having lung cancer.[73] For example, the cost per quality-adjusted life year was between $123,000 and $269,000 in the lowest three quintiles of lung cancer risk and between $32,000 and $52,000 in the highest two quintiles of lung cancer risk. Cost-effectiveness of LDCT screening could vary substantially as it is implemented in real-world settings depending on patient selection, false-positive rate, and rates of invasive procedures. The cost of evaluating and managing other findings on the LDCT (ie, not lung nodules) has not been completely factored into cost-effectiveness analyses.[74,75]

Radiation Exposure From the LDCT: Although an LDCT scan is a noninvasive procedure, patients are exposed to ionizing radiation during the scan. Patients enrolled in a lung cancer screening program may undergo many LDCT scans during long-term enrollment, as well as diagnostic CT and fluorodeoxyglucose-PET/CT scans for the evaluation of screen-detected findings.

The risk of ionizing radiation to an individual patient undergoing LDCT screening depends on the age at which screening begins, patient sex, number of CT scans received, and exposure to other sources of ionizing radiation, particularly other medical imaging tests. Assessing the risks to patients from ionizing radiation from lung cancer screening is challenging because of limited data that rely on modeling, and the unknown effects of estimated effective doses under 100 mSv (single exposure or cumulative). The average estimated effective dose of one LDCT scan in the NLST was 1.5 mSv.[76] Lower average estimated effective doses can be achieved on currently available CT scanners. In one analysis, the authors estimated the lifetime attributable risk of radiation-related lung cancer mortality, assuming annual LDCT examinations from age 55 to age 74 years, with a technique like that of the NLST, to be approximately 0.07% for males and 0.14% for females.[77] Other estimates of cumulative radiation exposure and health impact include: one cancer death caused by radiation per 2,500 persons screened with the NLST protocol[78]; cumulative radiation doses exceeding lifetime radiation exposures of nuclear power workers and atomic bomb survivors[79]; lower expected lung cancer mortality reduction when radiation risk is incorporated into models of the benefit of LDCT screening[80]; and the need for substantial mortality reduction from LDCT screening to overcome the radiation risk (eg, 25% for female never smokers aged 50-52 years, 2% for male active smokers aged 50-52 years).[81]

What to Consider When Implementing a High-Quality Lung Cancer Screening Program

It is critical that high-quality screening programs are developed that can optimize the tenuous balance of benefit and harms from LDCT screening described earlier. Several manuscripts have outlined phases of program development, implementation considerations, and key program components.[82,83] Each program will need to develop approaches to screening that fit their local environment. Questions will include who to screen; how to identify and schedule appropriate patients; how to conduct a shared decision-making visit; how to perform the LDCT; how to communicate the results of the LDCT; how to manage abnormal findings; how to assure compliance with annual screening; how to incorporate smoking cessation guidance; and how to collect, report, and use data for program improvement. We have attempted to develop recommendations that are applicable regardless of program design. In the remarks of some of the recommendations, we comment on implementation within a spectrum of program structures ranging from decentralized to centralized. In this context, decentralized is defined as allowing the ordering provider to perform the key program functions: final arbiter of patient eligibility, performance of the counseling and shared decision-making visit, provision of smoking cessation guidance, communication of the LDCT results, and management of the findings. In contrast, centralized is defined as a program structure in which the ordering provider may identify potentially eligible patients, but program personnel perform the key program functions. We do not recommend one program structure over the other, recognizing that local resources and health system designs will influence the structure, and trade-offs of quality and access must be considered. In this section, we describe some of the evidence available to help guide the implementation of high-quality programs, regardless of their structure.

Eligibility for LDCT Screening for Lung Cancer:

PICO 9: What is the rate of lung cancer detection when clinical risk assessment tools are applied for the selection of individuals at elevated risk of lung cancer for LDCT screening, compared with the use of the NLST or USPSTF criteria?

The ability to predict which individuals are at high risk for developing lung cancer using age and smoking history criteria alone is limited. Adding additional risk factors may improve risk prediction and thus screening efficiency. Three studies were identified that addressed the use of risk assessment tools for selecting individuals at elevated risk of lung cancer for LDCT screening.[84-86] Tammemagi et al[84] developed the $PLCO_{m2012}$ model, which includes age, race/ethnicity, education level, BMI, the presence of COPD, a personal history of cancer, a family history of lung cancer, smoking status (current vs former), smoking intensity, smoking duration, and smoking quit time. The accuracy of this model was compared with the NLST criteria (age and smoking history) by selecting the same number of individuals for lung cancer screening from the PLCO data set with the model as met the NLST criteria (required a model threshold of 1.35% probability of lung cancer over a 6-year period). The model showed improved sensitivity (83.0% vs 71.1%; $P < .001$) and positive predictive value (4.0% vs 3.4%; $P = .01$) compared with the NLST criteria, without decreasing specificity (62.9% vs 62.7%; $P = .54$). More recently, they found that the $PLCO_{m2012}$ model (at a threshold of 1.51% probability of lung cancer over a 6-year period) performed better than USPSTF criteria (sensitivity 80.1% vs 71.2%, specificity 66.2% vs 62.7%, and positive predictive value 4.2% vs 3.4%).[85] Application of the model to the intervention arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) trial, compared with use of the USPSTF criteria, would have resulted in 8.8% fewer patients being screened with the model and 12.4% more lung cancers being identified. A study by Katki et al[86] applied a risk-based model to NLST data and estimated that the use of model-based criteria to identify individuals with a predicted 5-year lung cancer risk of $\geq$ 1.9% would lead to a 17% reduction in the number needed to screen to prevent one lung cancer death. Studies investigating the use of these models in clinical practice are not yet available. The UKLS trial identified studied participants through use of the Liverpool Lung Project risk calculator version 2 ($\geq$ 5% 5-year lung cancer risk).[33] This was not compared with other eligibility criteria.

A fundamental question when applying these models is whether the identification of patients for screening based on risk factors other than age and smoking history would lead to changes in patient or cancer phenotype that would affect the balance of benefit and harms of screening. The risk models include variables that affect nodule presence,[87] the risk of nodule evaluation,[88] the risk of lung cancer treatment,[89] survival after lung cancer treatment,[90] and overall survival.[91] It is thus important to pursue clinical utility studies of the application of these models in clinical practice.

The inclusion criteria and the interval and duration of screening were also explored in a sophisticated study conducted by the Cancer Intervention and Surveillance Modeling Network (CISNET) group to inform the USPSTF.[92-95] Five centers built independent models that were calibrated to the NLST and PLCO data. The models yielded similar predictions, which were then averaged and coalesced in an Agency for Healthcare Research and Quality summary report.[93] The models explored 576 permutations of the screening interval (every year, every 2 years, every 3 years), age to begin screening (45, 50, 55, 60 years), age to end screening (75, 80, 85 years), minimum smoking history (10, 20, 30, 40 pack-years), and the duration since quitting (10, 15, 20, 25 years).

The CISNET models[92] provide some insights into the interrelationships and inherent trade-offs of lung cancer screening. Directly related to the inclusiveness of the eligibility criteria are the proportion of the population cohort ever screened (ranging from approximately 13% to approximately 30%), the number of scans done (ranging from about 170,000 to about 600,000 per 100,000 population cohort), and the rate of radiation-induced lung cancers (ranging from 17-37 per 100,000). The number of lung cancer deaths averted increases with more inclusive eligibility (range: approximately 11%-21%). This is also true for the number of life years gained (range: about 4,000-9,000 per 100,000). The trade-off between greater lung cancer mortality reduction and the harm of a greater number of screens is not linear. Decreasing the minimum smoking exposure from 30 to 20 pack-years increases the lung cancer mortality reduction (from about 14% to about 19%), at the cost of a larger increase in the number of screens (from approximately 300,000 to approximately 425,000 per 100,000). Increasing the minimum smoking exposure from 30 to 40 pack-years has less effect (approximately 1% less lung cancer mortality reduction with a slightly larger decrease in the number of screens). Increasing the time since smoking cessation from 15 to 25 years resulted in about 10% greater lung cancer mortality reduction and approximately 20% more scans. This modeling was used by the USPSTF to make a judgment about a set of criteria that reflects the best balance of mortality reduction for the number of scans performed. The criteria selected was annual screening, for ages 55 to 80 years, with a 30+ pack-year smoking history, who were either active smokers or former smokers who quit $\leq$ 15 years ago.[92,96]

Other estimates of the risk of lung cancer in individuals currently ineligible for screening based on smoking histories have been reported. Active smokers of 20 to 29 pack-years had a risk equal to former smokers in the NLST (HR: 1.07).[97] Never smokers were found to require a relative risk 15 to 35 times that of the average never smoker to have the potential to benefit from screening.[98]

Impact of Comorbidity and Quality of Life: For lung cancer screening to be effective, earlier stage lung cancer must be discovered than would have been without screening, the patient must be healthy enough to undergo treatment of early-stage disease, and the patient must not have competing causes of death that would substantially diminish the effect of screening. The population enrolled in the NLST met this basic tenant, so much so that of the 347 stage I lung cancers discovered during screening, only 7 (2%) were treated with radiation alone, suggesting the population was largely able to tolerate surgery. The surgical mortality for those undergoing resection for a screen-detected cancer in the NLST was extremely low (1%), whereas national data on surgical mortality for stage I disease report mortality rates between 2% and 5%.[12]

One study assessed the generalizability of the NLST surgical outcomes in a cohort of elderly patients by using Surveillance, Epidemiology, and End Results (SEER)-Medicare data to create NLST eligible (defined as a Charlson Comorbidity Index of 0 or 1) and ineligible (a Charlson Comorbidity Index of $\geq$ 2) cohorts.[99] Compared with the NLST group undergoing surgery for stage I disease, those in the SEER-Medicare NLST eligible group had no difference in 30-, 60-, and 90-day surgical mortality or 5-year cancer-specific survival. Patients in the SEER-Medicare NLST ineligible cohort had significantly worse surgical outcomes and 5-year overall survival, suggesting that competing causes of death played a role. Patients who did not receive surgery for early-stage disease (radiotherapy with curative intent) had vastly worse early and late outcomes. Similarly, using NLST data, it was found that LDCT screening was efficacious in those with zero or one coexisting pulmonary condition (6.2 and 9.6 prevented lung cancer deaths per 10,000 person-years respectively), whereas it was not efficacious in those with two or more pulmonary conditions (–0.5 prevented lung cancer deaths per 10,000 person-years).[57]

Those participating in the NLST were healthier than the general population of patients who meet NLST eligibility

criteria (refer to PICO 7). If comorbidities suggest a high risk from surgical resection, competing causes of death may diminish the benefit garnered from screening. When considering screening on an individual basis, balancing the risk of developing lung cancer vs the risk of dying of competing causes of death is an area that deserves further study.

Symptoms That Suggest the Presence of Lung Cancer: New symptoms that are poorly explained, such as coughing, hemoptysis, shortness of breath, chest pain, unintentional weight loss, hoarseness, bone pains, headaches, and vision changes, should make one consider lung cancer in the proper clinical setting.[100,101] Symptoms and signs related to paraneoplastic syndromes (confusion, nausea, constipation, weakness, and clubbing) may also be part of the initial presentation. Individuals who present with these symptoms should have diagnostic testing performed unrelated to their screening eligibility.

PICO 10: What is the rate of lung cancer detection when molecular biomarker results are applied to the selection of individuals at elevated risk of lung cancer for LDCT screening, compared with the use of the NLST or USPSTF criteria?

There is growing interest in investigating the use of molecular biomarkers to improve the sensitivity and specificity of lung cancer screening eligibility criteria. An accurate molecular biomarker could identify individuals who are more likely to benefit from lung cancer screening and/or reduce the harms of LDCT screening. Despite their potential promise, evidence that using such biomarkers would improve the efficiency of lung cancer screening is lacking. No applicable studies comparing molecular biomarkers vs NLST or USPSTF criteria were found that could be included in the systematic review for this guideline. One study assessed the accuracy of a microRNA signature classifier in 939 participants in the MILD screening trial (69 with cancer). The signature had a sensitivity of 87% and a specificity of 81%. This was not compared with the NLST or USPSTF criteria.[102] Further research in this field has the potential to optimize and expand the impact of lung cancer screening.

Frequency and Duration of LDCT Screening for Lung Cancer: As detailed earlier, the interval and duration of screening were explored in the CISNET modeling study that informed the USPSTF.[92-95] For the duration of LDCT screening, the models indicate that as the age to begin screening is increased, the lung cancer mortality reduction decreases (about one-quarter of the mortality reduction is lost by increasing the age from 50 to 60 years). Concomitantly, the number of scans (and the radiation-induced lung cancers) decreases by a similar amount. As the age to end screening is increased, the mortality reduction as well as the number of scans increases slightly (approximately 10% increase in both for a 5-year jump in the age at which screening is ended).

The models also show an effect on lung cancer mortality and the number of scans performed from altering the interval between LDCT examinations. Screening every 2 or 3 years appears to lower both the number of scans performed and the expected lung cancer mortality reduction to one-half or one-third that of annual screening. The number of radiation-induced deaths also decreases by one-half or one-third. As described earlier, the details of the modeling efforts and a judgment about the trade-off of mortality reduction and harm led the USPSTF to recommend an annual screening interval up until age 80 years, assuming one remains healthy enough to benefit from treatment for a screen-detected cancer.

Another important consideration, affected by the interval and duration of lung cancer screening, is cost and cost-effectiveness. A detailed model (described in the earlier cost-effectiveness section) suggested that annual screening was more cost-effective than longer screening intervals.[72]

A final consideration, described in detail earlier, is the rate of overdiagnosis. As the interval between screening examinations increases, the proportion of screen-detected tumors that have low aggressiveness increases. With a longer interval between screens, fewer cancers will be screen-detected and more will be interval-detected (symptomatic). A recent modeling study of the impact of overdiagnosis on screening effectiveness[103] found that the rate of overdiagnosis is higher in patients with higher smoking rates (pack-years) and in older patients (older starting age and older stopping age). This can be explained by a greater rate of competing causes of death in such individuals. In addition, the study found that overdiagnosis was lower with longer intervals between screening examinations. The models used did not account for a shift in tumor aggressiveness with screening, and assumed that the rate of non-lung cancer causes of death was like a general population with similar age and smoking histories. Hence the models minimized the type of overdiagnosis due to detection of

indolent tumors and accentuated the type of overdiagnosis related to competing causes of death.

1. For asymptomatic smokers and former smokers age 55 to 77 who have smoked 30 pack years or more and either continue to smoke or have quit within the past 15 years, we suggest that annual screening with low-dose CT should be offered. (Weak recommendation, moderate-quality evidence)

Remark: Age 77 represents the oldest age of participants in the NLST at the end of the screening period. Age 77 also matches the oldest age of CMS coverage for low-dose CT screening. Age 80 has been recommended by the USPSTF based on modeling studies. Recommendation #2 can be applied to individuals age 78 to 80.

Remark: Asymptomatic refers to the absence of symptoms suggesting the presence of lung cancer.

2. For asymptomatic smokers and former smokers who do not meet the smoking and age criteria in Recommendation #1 but are deemed to be at high risk of having/developing lung cancer based on clinical risk prediction calculators, we suggest that low-dose CT screening should not be routinely performed. (Weak recommendation, low-quality evidence)

Remark: It is recognized that clinical risk prediction calculators may be slightly more efficient at identifying individuals who have or will develop lung cancer than the eligibility criteria listed in Recommendation #1. It is also recognized that the variables included in the clinical risk prediction calculators are risk factors for morbidity from the evaluation and treatment of screen-detected findings, and death from any cause. Thus, a cohort at high risk for lung cancer based on a clinical risk prediction calculator may be less likely to benefit and more likely to be harmed by lung cancer screening than the cohort identified by the eligibility criteria listed in Recommendation #1. Thus, we do not believe the evidence supports a policy to screen this group.

Remark: It is also recognized that there will be individuals within the cohort deemed to be at high risk for lung cancer from a clinical risk prediction calculator who are healthy enough to benefit from lung cancer screening, and that low-dose CT screening could be considered in these individuals.

Remark: A risk threshold of 1.51% over 6 years on the PLCOm2012 calculator is an example of high risk.

Remark: In the United States, health insurance providers may not pay for low-dose CT screening for those who do not meet the eligibility criteria listed in Recommendation #1.

Remark: Additional lung cancer screening trials that include patients who do not meet the eligibility criteria listed in Recommendation #1 but have a high risk of having/developing lung cancer based on clinical risk prediction calculators are needed.

3. For individuals who have accumulated fewer than 30 pack years of smoking or are younger than age 55 or older than 77, or have quit smoking more than 15 years ago, and do not have a high risk of having/developing lung cancer based on clinical risk prediction calculators, we recommend that low-dose CT screening should not be performed. (Strong recommendation, moderate-quality evidence)

4. For individuals with comorbidities that adversely influence their ability to tolerate the evaluation of screen-detected findings, or tolerate treatment of an early-stage screen-detected lung cancer, or that substantially limit their life expectancy, we recommend that low-dose CT screening should not be performed. (Strong recommendation, low-quality evidence)

Remark: At very severe stages of a comorbid condition it can be clear that low-dose CT screening is not indicated (eg, advanced liver disease, COPD with hypoventilation and hypoxia, NYHA class IV heart failure) because competing mortality limits the potential benefit, and harms are magnified. At less severe stages it can be difficult to determine if an individual's comorbidities are significant enough that they should not receive low-dose CT screening. Further research is required to assist clinicians with this decision.

5. We suggest that low-dose CT screening programs develop strategies to determine whether patients have symptoms that suggest the presence of lung cancer, so that symptomatic patients do not enter screening programs but instead receive appropriate diagnostic testing, regardless of whether the symptomatic patient meets screening eligibility criteria. (Ungraded Consensus-Based Statement)

Remark: In centralized low-dose CT screening programs, the provider that meets with the patient prior to the low-dose CT should ask about symptoms that would suggest diagnostic testing is indicated.

Remark: In de-centralized low-dose CT screening programs, the screening program should assist the ordering provider through educational outreach and/or the provision of clinical tools (eg, reminders built into electronic medical records).

Lung Nodule Size Threshold (ie, Nodule Size That Triggers Additional Testing Prior to an Annual LDCT Screening Examination): PICO 11: What is the stage distribution of lung cancer, the rate of death from lung cancer (ie, lung cancer mortality), and the portion of positive scans among individuals at elevated risk of lung cancer who undergo annual screening with LDCT with a 4-mm nodule size threshold for defining a positive LDCT, compared with other definitions of a positive LDCT?

In lung cancer screening, the lung cancer mortality rate, stage distribution, and portion of positive scans may depend on the size of pulmonary nodules deemed appropriate for follow-up or further investigation. Nine LDCT screening trials have published results related to these outcomes.[12,15,18,20,22-24,26,29,30,32,36] Patient eligibility criteria (age, smoking history, and years since quitting) varied among the trials but generally focused on older individuals with substantial smoking exposure. The trials also varied in the size of nodules found on LDCT scans that were defined as "positive," ranging from ≥ 4 mm in the NLST and Lung Screening Study (LSS) trials, to ≥ 5 mm for solid nodules in the Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays Trial (DANTE), German Lung Cancer Screening Intervention Trial (LUSI), Italian Lung Cancer Screening Trial (ITALUNG), and UKLS trials, to size and growth based on volumetric measurements in the MILD, DLCST, and NELSON trials.

Only the NLST, which used a nodule size of ≥ 4 mm as a positive finding, has reported a statistically significant reduction in lung cancer mortality. Stage distribution ranged from 58% to 62% stage I and 12% to 13% stage IV in the two studies with the ≥ 4-mm nodule size definition to 30% to 69% stage I and 5% to 36% stage IV in the studies with a larger nodule size definition. Likewise, the portion of positive scans varied from 34.5% to 39.1% in the NLST and LSS studies to 2.0% to 39.7% in the other studies (Table 4). Owing to the number of differences in these studies, not only the varying definitions of a "positive" nodule size, drawing a conclusion about the optimal nodule size to label the screening test as "positive" is not possible.

The challenge with identifying an ideal cutoff for nodule size is the trade-off of fewer false-positives with the potential for delayed cancer diagnosis as the "positive" nodule size threshold increases. Using LungRADS criteria of a 6-mm nodule size threshold on the baseline scan, investigators assessed this trade-off against NLST criteria (4-mm nodule size threshold). At baseline and during the incidence screens, respectively, the 6-mm threshold would have led to a reduction in false-positives of 52.1% and 76.1%, with a potential delay in cancer diagnosis in 9.2% and 16.2% of those with lung cancer.[104] The impact of increasing the threshold for a positive nodule on the baseline CT scan was also evaluated in the International Early Lung Cancer Action Program (I-ELCAP) study. The percentage of positive scans for thresholds of 5, 6, 7, 8, and 9 mm were 16.1, 10.2, 7.1, 5.1, and 4.0, respectively. Potential delays in cancer diagnoses would not have occurred with an increase to the 6-mm threshold.[105] Similarly, the NLST reported nodule frequencies on the baseline scan at thresholds of 4, 7, and 11 mm of 26.7%, 12.6%, and 4.6%, respectively. Potential delays in cancer diagnosis with a threshold of 7 and 11 mm were 6.7% and 19.9% of all lung cancers, respectively.[106] The impact of potential delays in diagnosis would be magnified by poor compliance with annual follow-up.

6. We suggest that screening programs define what constitutes a positive test on the low-dose CT based on the size of a detected solid or part-solid lung nodule, with a threshold for a positive test that is either 4 mm, 5 mm, or 6 mm in diameter. (Weak recommendation, low-quality evidence)

Remark: A positive test is defined as a test that leads to a recommendation for any additional testing other than to return for the annual screening exam.

Remark: Nodule diameter is the average of long- and short-axis diameters obtained on the same sagittal, coronal, or transverse image. For part-solid nodules, nodule diameter should be based on the size of the solid component of the nodule.

Remark: An equivalent volumetric threshold can also be considered.

Remark: The LungRADS structured reporting system currently uses 6 mm at the baseline scan and 4 mm if a new nodule is found on the annual scan for solid nodules; and 6 mm at the baseline scan and any size if a new nodule is found on the annual scan for part-solid nodules.

Maximizing Compliance With Annual Screening: For a screening program to be effective, participants must return for yearly follow-up screening if they continue to meet eligibility criteria. Furthermore, when positive findings are discovered, compliance with follow-up testing is important. Many of the available clinical trials had high adherence rates for repeat screens. The NLST and the Mayo LDCT screening project reported 95% and 98% compliance over 3 years of annual screening, respectively.[12,107] Generalizing these high adherence rates is problematic for several reasons. First, patients in these studies received their scans at no cost. An analysis of two cohorts screened in the Early Lung Cancer Action Project (ELCAP) found that although adherence was 88% in those who did not pay for their LDCT, it dropped to 62% in those who had to pay for their scan.[108] Second, patients enrolled in the NLST were better educated, > 90% were white, had a higher socioeconomic status (SES), and were more likely to be former smokers compared with the population of Americans eligible for screening. Patients with these attributes are far more likely to adhere to their screening regimen. In studies of other commonly screened for cancers (eg, colorectal, breast, cervical) the factors associated with poor adherence include being unmarried, lower SES, black or Hispanic race, not having a primary care provider, and being a smoker.[109-111]

Although there are very few data on adherence for lung cancer screening in community settings, data from other established cancer screening programs highlight potential challenges. A meta-analysis of adherence in cervical cancer screening that included 24 studies and > 400,000 people showed mean adherence rate of 65% (24%-84%).[109] A study of colorectal cancer screening assessing > 35,000 patients found that < 50% were compliant with screening recommendations over the study period.[110] Given the potential for poor adherence with annual testing in the demographic eligible for LDCT screening, it is important that patients are informed about the value of annual testing, and that further research is performed to better understand the factors that influence compliance, which can then be used to inform the development of tools to assist screening programs.

7. We suggest that low-dose CT screening programs develop strategies to maximize compliance with annual screening exams. (Ungraded Consensus-Based Statement)

Remark: Additional research is needed to better understand the factors that influence compliance, and to develop tools to help screening programs maximize compliance with annual screening exams.

Managing Screen-Detected Lung Nodules: Given the frequency with which lung nodules are identified on LDCT screening examinations, the knowledge that the vast majority of screen-detected nodules are benign, and the implications of nodule management decisions on the benefit and harms of screening, nodule management strategies are a critical component of LDCT screening. It is essential that nodule management strategies are in place to avoid overreacting to inconsequential nodules and underreacting to malignant nodules.

Conceptually, one can categorize pulmonary nodules into several types: clearly benign (eg, calcified nodules, subpleural lymph nodes), solid nodules ≤ 8 mm in diameter, solid nodules > 8 mm in diameter, part-solid, and pure ground-glass nodules. Clearly benign nodules do not require additional surveillance. Solid nodules ≤ 8 mm in diameter may be followed with serial imaging at intervals based on the size of the nodule. Solid nodules > 8 mm in diameter are evaluated by first estimating the probability of malignancy. Several nodule risk prediction calculators are available that use clinical and imaging features to assist with nodule malignancy probability estimates.[112-115] Nodules with a very low probability of malignancy are monitored with serial imaging, those with a high probability of malignancy may proceed directly to resection (if the patient is otherwise fit), and those with a low to moderate probability of malignancy are assessed with fluorodeoxyglucose-PET imaging and/or nonsurgical biopsy if feasible. Part-solid nodules may be evaluated based on the size of the solid portion of the nodule. These nodules have a higher probability of malignancy than an equally sized solid nodule. Pure ground-glass nodules are evaluated based on their size and an understanding of the indolent nature of the malignancy they may represent. It is worth noting that lung cancers with a predominantly ground-glass appearance account for the majority of overdiagnosed lung cancers detected by screening.[116]

Specific recommendations for nodule management are beyond the scope of this guideline. An excellent resource for the management of all nodule types and sizes can be found in the CHEST lung cancer guidelines.[117] Other resources include the Fleischner Society recommendations, which focus on the surveillance frequency of smaller solid and subsolid nodules, and LungRADS, which focuses on the screening setting.[118] One of the nodule risk prediction calculators, developed

in the screening setting, can also be incorporated into screen-detected nodule management algorithms.[115]

As described in the harms section earlier, despite the high rate of identifying lung nodules, clinical trials have reported a low rate of procedures for lung nodules, major complications from procedures, and death potentially related to procedures. Most of the trials that informed this section were performed at large institutions with experience in lung nodule management, tools available to assess lung nodules, and a nodule evaluation policy and system in place. The majority of nodules found were managed without an invasive procedure. This reflects the experience of well-organized prospective screening studies, conducted mostly at major medical centers. By contrast, surveys indicate that systems and processes of care to facilitate nodule evaluation have not been consistently adopted in US medical facilities.[119,120] Studies that include more diverse practice settings have reported higher and more variable rates of biopsy and complications.[88]

8. We suggest that low-dose CT screening programs develop a comprehensive approach to lung nodule management, including multi-disciplinary expertise (Pulmonary, Radiology, Thoracic Surgery, Medical and Radiation Oncology), and algorithms for the management of small solid nodules, larger solid nodules, and sub-solid nodules. (Ungraded Consensus-Based Statement)

Remark: For programs without lung nodule management expertise available on site, collaborations with centers capable of high quality lung nodule management can be formed (eg, referral, distance evaluation).

9. We suggest that low-dose CT screening programs develop strategies to minimize overtreatment of potentially indolent lung cancers. (Ungraded Consensus-Based Statement)

Remark: It is important to educate patients about the potential to detect an indolent lung cancer to help mitigate the psychological distress that could result from living with an indolent untreated lung cancer.

Remark: For malignant nodules, pure ground glass is the nodule morphology most likely to represent an indolent cancer.

Incorporating Smoking Cessation Into Lung Cancer Screening: PICO 12: What is the rate of smoking cessation among active smokers at elevated risk of lung cancer who receive smoking cessation counseling as part of an LDCT screening program, compared with those who do not receive smoking cessation counseling, and compared with those who do not participate in LDCT screening?

LDCT screening represents a potential teachable moment to counsel current smokers about smoking cessation. The Centers for Medicare & Medicaid Services (CMS) policy requires smoking cessation counseling to be delivered at the time of LDCT screening. This is particularly important given that some smokers believe that LDCT screening will protect them from developing lung cancer, and they therefore feel little urgency to quit smoking.[121] Current evidence is conflicting regarding whether undergoing LDCT screening in and of itself motivates smokers to quit. Although the DLCST (11.9% vs 11.8%) and NELSON (13.7% vs 15.5%) trials found no difference in smoking cessation rates between LDCT screening and control groups, the UKLS trial found higher rates of smoking cessation at up to 2 years in the LDCT screening vs the control group (15% vs 10%; adjusted OR: 1.60 [95% CI: 1.17-2.18]; $P = .003$).[122-124] Trials do suggest that patients with a screen-detected nodule are more likely to quit smoking than patients with negative screening results.[125]

The most effective intervention to promote smoking cessation in the setting of lung cancer screening is currently unknown and is an area of active research. There are well-established smoking cessation interventions that have been studied in other settings that provide a basis for establishing a smoking cessation component to a lung cancer screening program.[126,127]

10. For current smokers undergoing low-dose CT screening, we recommend that screening programs provide evidence-based tobacco cessation treatment as recommended by the US Public Health Service. (Strong recommendation, low-quality evidence)

Remark: Further research about the ideal approach to tobacco treatment specific to the lung cancer screening setting is needed.

Counseling and Shared Decision-Making Visits: One of the requirements for Medicare coverage of lung cancer screening is that a beneficiary has a "lung cancer screening counseling and shared decision-making visit."[128] The visit is to include: determination of eligibility for lung cancer screening; shared decision-making, using decision aids with information about benefits and harms of screening, follow-up testing,

false-positive rate, and radiation exposure; counseling on the need for repeated annual screening and possible diagnostic testing and treatment; and counseling on smoking cessation or maintaining abstinence. The goal of shared decision-making between providers and patients is to increase the likelihood that patients understand the screening options, benefits, and harms, and can make decisions that are aligned with their preferences and values. Decision aids are usually print or video materials that provide information for patients, often in graphic and/or numeric formats, that may help them in reaching their decisions about screening. The optimal design of such aids is an area of active research.

The extent to which such visits improve patients' knowledge and satisfaction with screening decisions is not certain. A recent study reported on the experience of a lung cancer screening counseling and shared decision-making visit within a lung cancer screening program at one major medical center.[129] All but 5.4% (23) of 423 patients who had a shared decision-making visit went on to have an LDCT screening test (9 of the 23 did not meet eligibility criteria). Most patients did not have a good level of understanding of the screening criteria, benefits, or harms before the visit. Knowledge levels showed some improvement immediately following the visit but declined modestly at 1 month, suggesting that a counseling and shared decision-making visit may be useful prior to each annual round of screening to reassess eligibility, reinforce knowledge about screening, and provide further smoking cessation counseling. In a recent report from the Veterans Health Administration, the authors noted that only 58% of veterans who met screening criteria and were approached about lung cancer screening agreed to undergo screening.[60] The reasons for patients' declining screening were not recorded. One of the proposed components of the shared decision-making visit, the use of lung cancer screening decision aids, has been shown to increase patient knowledge about LDCT screening and its trade-offs.[130-133] Further study of patient experiences with making shared decisions about screening and about the most effective way to conduct these visits is needed.

11. **We suggest that low-dose CT screening programs develop strategies to provide effective counseling and shared decision-making visits prior to the performance of the LDCT screening exam.** (Ungraded Consensus-Based Statement)

Remark: Components of the counseling and shared decision-making visit include a determination of screening eligibility (age, smoking history, the absence of symptoms, confirmation of overall health), the use of decision aids with information about benefits and harms of screening, a discussion about the potential CT findings and need for follow-up testing, the need for annual screening exams, confirmation of the willingness to accept treatment for a screen-detected cancer, and counseling about smoking cessation.

Remark: In centralized low-dose CT screening programs, a screening program provider may meet with the patient prior to the low-dose CT to perform the counseling and shared decision-making visit.

Remark: In de-centralized low-dose CT screening programs, the screening program should ensure that ordering providers are trained, and/or have the tools necessary, to deliver an effective counseling and shared decision-making visit. These tools may include decision aids, information brochures, videos, and links to electronic resources.

Remark: Additional research about the most effective way to conduct counseling and shared decision-making visits is needed.

Lung Cancer Screening Program Personnel: A high-quality lung cancer screening program requires a complex set of health-care personnel, components, and processes to effectively maximize the benefits and minimize the harms for the population being screened. Key professional groups, including the American College of Radiology (ACR) and the American College of Chest Physicians/American Thoracic Society, have identified several essential components of lung cancer screening programs.[82,134]

Delivering a high-quality LDCT screening program requires close teamwork and effective communication among many stakeholders, including primary care physicians, pulmonologists, radiologists, thoracic surgeons, medical and radiation oncologists, nursing staff, information technology staff, and administrative staff (e-Table 9). Having dedicated clinicians, such as registered nurses or advanced practice providers, who interact with screening patients and assist with the management of screening findings, may be especially important for ensuring that patients' participation in all aspects of the screening program goes smoothly.

Only a few reports on real-world implementation of lung cancer screening programs have been published to date.[60,135,136] Implementation challenges identified in

these reports have included difficulty identifying eligible patients due to incomplete smoking history information, the time and effort required for shared decision-making, the inconsistent use of electronic tools and standardized templates in medical records, the capacity of clinical services to manage potentially large numbers of patients being screened, and the need for accurate data capture. Some primary care physicians and pulmonologists have questioned whether it is practical to implement lung cancer screening programs in their practice setting.[137-139]

LDCT Parameters: Appropriate technique is necessary to ensure that LDCT scans are obtained in a manner that produces high-quality images while minimizing patient exposure to ionizing radiation. Images should be optimized to avoid artifacts and provide high spatial resolution while maintaining a CT dose volume index $\leq$ 3.0 mGy for average size patients, adjusted accordingly for larger or smaller patients. To maintain a standardized approach to LDCT screening, a dedicated LDCT protocol should be developed and reviewed annually by the supervising radiologist, medical physicist, and radiology technologist.

Although specific LDCT protocols will vary across manufacturers and even individual scanner models, certain general principles apply to all LDCT protocols (e-Table 10). The American Association of Physicists in Medicine provides a free library of optimized protocols for LDCT screening scans for the most commonly installed CT scanners.

12. We suggest that low-dose CT screening programs follow the ACR/STR protocols for performing low radiation dose chest CT scans. (Ungraded Consensus-Based Statement)

Remark: An awareness of the potential for radiation related harm can help programs thoughtfully plan ways to minimize this risk through proper patient selection, the performance of the CT scan, and appropriate management of screen-detected findings.

Structured Radiology Reporting: The ACR and Society of Thoracic Radiology Practice Parameter for the Performance and Reporting of Lung Cancer Screening Thoracic Computed Tomography provides guidance about how to report the LDCT screening examination.[140] Current CMS requirements include the use of a standardized lung nodule identification, classification, and reporting system for all lung cancer screening LDCT scans as well as participation in a CMS-approved registry. The rationales for such practices are to reduce variability, minimize additional imaging, and limit potential overdiagnosis. Whether standardized classification and reporting systems improve outcomes has yet to be determined. The most prevalent structured reporting system, called LungRADS, was developed and described by the ACR and the Society of Thoracic Radiology. The ACR hosts the only national data registry, which accepts data on imaging findings based on the LungRADS system, making this a practical choice for most programs. The structured report categorizes lung nodules based on size/risk, provides recommendations for surveillance intervals for small nodules, and can be used to report other incidental findings.

13. We suggest that low-dose CT screening programs use a structured reporting system to report the exam results. (Ungraded Consensus-Based Statement)

Remark: The structured reporting system should include a description of the number, location, size, and characteristics of all lung nodules, guideline based recommendations for surveillance of small lung nodules, and a description of other incidental findings.

Remark: The ACR LungRADS structured report is the most prevalent system used today. LungRADS categories translate directly into data requests from the ACR National Registry.

Managing "Other Findings": A chest CT scan does not image only the lungs but everything from the lower neck to the upper abdomen. The cohort eligible for LDCT screening, based on smoking history and age, has been shown to frequently have comorbidities (eg, hypertension in about 60%, hyperlipidemia in approximately 50%, COPD in about 30%, coronary artery disease in 15%, diabetes mellitus in 15%).[141] As such, it is not surprising that many LDCT screening scans reveal incidental findings (other than pulmonary nodules).[50,74,75,141-143] The value of what amounts to screening for other findings is undefined; the balance of benefits and harms of lung cancer screening is affected if a significant portion of those screened undergo investigation of incidental findings. Therefore, management of incidental findings is an important part of implementation of a screening program.

The prevalence of incidental findings has varied, with most studies reporting high rates on baseline scans (41%-94%).[60,74,75,141,142,144] The definition of an incidental finding affects the prevalence. Reported rates of further investigation prompted by incidental findings

on a baseline CT range from 9% to 15%.[74,75,141,142] In the majority of these instances, a consultation and additional imaging or other noninvasive testing was involved.[74,141] Few patients (< 5%) underwent invasive procedures either for diagnosis or as part of a therapeutic intervention. The rate of eventually identifying conditions that lead to a therapeutic intervention is estimated to be < 1% (0.3%, 0.4%, 3%, and 0.2% in referenced work).[74,75,141,142] Finally, while incidental findings are very common on the baseline scan, new incidental findings are uncommon on subsequent scans (approximately 5% per year).[74,75]

It may be practical to organize incidental findings into three categories: not clinically relevant, possibly clinically relevant, and concerning (e-Table 11). These can be thought of in terms of next steps that might be considered: no investigation is necessary (in the context of annual screening), further investigation may be indicated (clinical judgment), and therapeutic intervention is likely to be indicated. These categories include an assumption of patient age and smoking status, the lack of significant acute symptoms, generally good health, and compliance with annual LDCT screening. These categories are also developed with an awareness of formal guidelines for investigation and treatment of relevant conditions, as is discussed in the e-Appendix 1 and e-Tables 11 and 12.

The evaluation of incidental findings accounts for about 50% of the reimbursement from LDCT screening.[74,75,141] Studies have estimated that costs arising from additional investigations of incidental findings amount to about $10 to $20 US dollars per screened individual at baseline[74,75,145]; when the reimbursement for interventions is included, it is approximately $800 per screened individual.[141]

14. We suggest that low-dose CT screening programs develop strategies to guide the management of non-nodule findings. (Ungraded Consensus-Based Statement)

Remark: Examples include coronary artery calcification, thyroid nodules, adrenal nodules, kidney and liver lesions, thoracic aortic aneurysms, pleural effusions, and parenchymal lung disease.

Remark: A lung cancer screening program should anticipate such incidental findings and have a system in place to address them. Examples include evidence based guidance within the structured report to assist the ordering provider, or centralized management of all incidental findings by the screening program. Clear communication between providers is important to prevent misunderstandings about who will assume responsibility for deciding what needs attention and ensuring appropriate follow-up evaluation.

Remark: The wording of how incidental findings are reported should be systematically developed to minimize anxiety and misunderstanding.

Minimizing Disparities: Among patients enrolled in the NLST, current smokers and black subjects experienced the highest lung cancer mortality and the greatest benefit from LDCT screening. However, minorities and those with low SES (who are more likely to be current smokers) often experience disparities in receiving appropriate preventive health care. LDCT screening has been slow to be implemented and is underused nationally despite coverage by private and public insurers. Lower rates of screening uptake have been found among minorities and individuals with low SES.[146,147] As screening is implemented more widely, outreach to underserved populations to ensure that eligible individuals receive LDCT screening will be of critical importance to prevent disparities. Little work has been done to establish the most effective strategies. Attention may need to be paid to addressing cultural beliefs about lung cancer and its treatment to reduce barriers to screening acceptance.[148,149] Smaller or geographically isolated locations may struggle to provide all the components of high-quality lung cancer screening. Linking with larger centers through emerging distance health tools may help to facilitate high-quality screening in underserviced communities.

Data Collection, Reporting, and Review: Data collection, reporting, and review helps screening programs reflect on their performance, and design and implement plans for improvement. Similarly, data reporting and review help inform the screening community and policy makers about the current state of lung cancer screening, aspects of screening that would benefit from additional research, and the policy level support required to expand access to high-quality screening. Data collection and reporting to a national registry is currently mandated by CMS. The only available national registry is run by the ACR.

There are requirements for the reporting of patient information related to eligibility criteria and other lung cancer risk factors. Patient compliance with the follow-up of screen-detected findings and with annual screening are important data elements that could help to uncover quality issues that a program may not be aware of.

Data on LDCT imaging technique and findings are part of mandatory data collection. Details about the presence, size/category, and features of lung nodules may help in planning for their evaluation. Reporting key findings in a way that conforms to a standardized system promotes uniformity in interpretation and comparison between programs.

Data on testing performed for the management of lung nodules and incidental findings may help programs make improvements to internal care pathways, and garner support for program infrastructure. Although there are various approaches to lung nodule management, important elements of data collection include the number of surveillance and diagnostic imaging studies, nonsurgical and surgical biopsies for screen-detected nodules, procedure-related adverse events (hospitalization, mortality), and cancer diagnoses. Data should also be collected on the impact of smoking cessation interventions managed by the screening program (types of program; utilization, success). Data collection requirements from CMS and the ACR national registry can be found in e-Tables 13 and 14.

15. We suggest that low-dose CT screening programs develop data collection and reporting tools capable of assisting with quality improvement initiatives and reporting to the current National Registry. (Ungraded Consensus-Based Statement)

Remark: Data categories include patient eligibility criteria, imaging findings and their evaluation, results of the evaluation of imaging findings including complications, smoking cessation interventions, and lung cancer diagnoses including histology, stage, treatment, and outcomes.

Summary

In this document, we have provided an update of the evidence related to the benefit and harms of lung cancer screening, as well as evidence that assists programs to implement high-quality LDCT screening. Based on this review, we have developed recommendations where evidence allowed and consensus-based statements in areas that we felt warranted comment despite a lack of high-quality evidence. Future updates to this guideline are planned as new evidence becomes available.

Acknowledgments

Author contributions: All authors contributed equally to this manuscript.

Financial/nonfinancial disclosures: The financial/nonfinancial disclosures reported by the authors to *CHEST* can be found in e-Table 1.

Role of sponsors: CHEST was the sole supporter of these guidelines, this article, and the innovations addressed within.

Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

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