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PII: S0012-3692(21)01307-6

DOI: https://doi.org/10.1016/j.chest.2021.06.063

Reference: CHEST 4412

To appear in: *CHEST*

Received Date: 11 February 2021

Revised Date: 11 May 2021

Accepted Date: 16 June 2021

Please cite this article as: Mazzone PJ, Silvestri GA, Souter LH, Caverly TJ, Kanne JP, Katki HA, Wiener RS, Detterbeck FC, Screening for Lung Cancer: CHEST Guideline and Expert Panel Report, *CHEST* (2021), doi: https://doi.org/10.1016/j.chest.2021.06.063.

Word Count: 25,015

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Conflicts of Interest: (Table 1)

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

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Abstract

Background: Low-dose chest CT screening for lung cancer has become a standard of care in the United States, in large part due to the results of the National Lung Screening Trial. Additional evidence supporting the net benefit of low-dose chest CT screening for lung cancer, as well as increased experience in minimizing the potential harms, has accumulated since the prior iteration of these guidelines. Here, we update the evidence base for the benefit, harms, and implementation of low-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 reviewed previously 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 using MEDLINE via PubMed, Embase, and the Cochrane Library on a quarterly basis since the time of the previous guideline publication. Reference lists from relevant retrievals were searched, and additional papers were added. Retrieved references were reviewed for relevance by two panel members. The quality of the evidence was assessed for each critical or important outcome of interest using the GRADE approach. Meta-analyses were performed when enough evidence was available. Important clinical questions were addressed based on the evidence developed from the systematic literature review. Graded recommendations and un-graded statements were drafted, voted on, and revised until consensus was reached.

Results: The systematic literature review identified 75 additional studies that informed the response to the 12 key questions that were developed. Additional clinical questions were addressed resulting in 7 graded recommendations and 9 ungraded consensus statements.

Conclusions: Evidence suggests that low-dose CT screening for lung cancer can result in a favorable balance of benefit and harms. The selection of screen-eligible individuals, the quality of imaging and image interpretation, the management of screen detected findings, and the effectiveness of smoking cessation interventions, can impact this balance.

Abbreviations

ACR = American College of Radiology
AHRQ = Agency for Healthcare Research and Quality
CCI = Charlson Comorbidity Index
CHEST = American College of Chest Physicians
CISNET = Cancer Intervention and Surveillance Modeling Network
CMS = Centers for Medicare and Medicaid Services
COI = Conflict of interest
COPD = Chronic obstructive pulmonary disease
CT = Computed Tomography
CXR = Chest radiograph (x-ray)
DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays Trial
DLCST = Danish Lung Cancer Screening Trial
FDG-PET = Fluorodeoxyglucose – Positron emission tomography
GDT = Guideline Development Tool
GOC = Guidelines Oversight Committee
GRADE = Grading of Recommendations, Assessment, Development, and Evaluation
HR = Hazard ratio
ITALUNG = Italian Lung Cancer Screening Trial
LDCT = Low-Dose Computed Tomography

LUSI = German Lung Cancer Screening Intervention Trial
LSS = Lung Screening Study
MD = Mean difference
MILD = Multi-centric Italian Lung Detection Trial
NELSON = Nederlands-Leuvens Longkanker Screenings Onderzoek Study
NLST = National Lung Screening Trial
NSCLC = Non-small Cell Lung Cancer
PICO = Population, Intervention, Comparator, Outcome
PSC = Professional Standards Committee
QALY = Quality-adjusted life year
RCT = Randomized controlled trial
RR = Risk ratio
SEER = Surveillance, Epidemiology, and End Results
STR = Society of Thoracic Radiology
UKLS = United Kingdom Lung Screening Study
USPSTF = United States Preventative Services Task Force
VA = Veterans Affairs

SUMMARY OF RECOMMENDATIONS

Selection of Individuals for Lung Cancer Screening

1. For asymptomatic individuals 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 recommend that annual screening with low-dose CT should be offered. (Strong recommendation, moderate-quality evidence)

Remark: These eligibility criteria align with the eligibility criteria for CMS coverage at the time of publication.

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

2. For asymptomatic individuals who do not meet the smoking and/or age criteria in Recommendation #1, are age 50 to 80, have smoked 20 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: These criteria align with the 2021 recommendations from the USPSTF[1].

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

Remark: Some individuals eligible by Recommendation #2 may have low net-benefit from screening and may choose not to undergo screening.

3. For asymptomatic individuals who do not meet the smoking and/or age criteria in Recommendations #1 and 2 but are projected to have a high net benefit from lung cancer screening based on the results of validated clinical risk prediction calculations and life expectancy estimates, or based on life-year gained calculations, we suggest that annual screening with low-dose CT should be offered. (Weak recommendation, moderate quality evidence)

Remark: Augmenting the criteria outlined in Recommendations #1 and 2 with risk prediction and life-year gained calculators leads to greater equity across race and gender in eligibility for lung cancer screening and the net benefits of screening.

Remark: Life-year gained calculators combine the results of risk prediction and life expectancy estimates into one measure.

Remark: Examples of calculated thresholds that identify individuals with a high net benefit from lung cancer screening include:

Life-gained: ≥16.2 days of life-gained by screening on the Life Years Gained From Screening-CT (LYFS-CT) calculator

Lung-cancer death risk: ≥1.33% 5-year risk on the Lung Cancer Death Risk Assessment Tool (LCDRAT) calculator and ≥10 years of life-expectancy

Lung-cancer incidence risk: ≥2.0% 5-year risk on the LCRAT calculator and ≥10 years of life-expectancy; ≥2.6% 6-year risk on the Prostate, Lung, Colorectal, and Ovarian ($PLCO_{M2012}$) calculator and ≥10 years of life-expectancy; ≥5.2% 10-year risk on the Bach calculator and ≥10 years of life-expectancy.

Remark: The application of risk calculators or life year gained calculators to identify screen eligible individuals is more burdensome than identification using the criteria in Recommendations #1 and 2 alone. Lung cancer screening programs that choose to identify eligible individuals based on this recommendation should develop tools to support ordering providers in identifying screen eligible individuals.

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 or 2.

Remark: Molecular biomarkers are being developed to assist with risk prediction and/or early lung cancer detection. They have not reached a phase of evaluation to be included in this recommendation at the time of publication.

4. For individuals who have accumulated fewer than 20 pack years of smoking or are younger than age 50 or older than 80, or have quit smoking more than 15 years ago, and are not projected to have a high net benefit from lung cancer screening based on clinical risk prediction or life-year gained calculators, we recommend that low dose CT screening should not be performed. (Strong recommendation, moderate-quality evidence)

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

Remark: When an individual has a very severe comorbid condition it is easier to determine that low-dose CT screening is not indicated (e.g. advanced liver disease, severe 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 of comorbid conditions, it can be difficult to determine if an individual's comorbidities are significant enough that they should not receive low-dose CT screening.

Remark: The use of a life-year gained calculator may assist clinicians with this decision by accounting for reduced life-expectancy in persons at advanced age or with comorbidities.

Implementation of High-Quality Lung Cancer Screening

6. 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 communicates 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 (e.g. reminders built into electronic medical records).

7. 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 (including the absence of symptoms and 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 or communicate 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: Life year gained calculators, or lung cancer risk calculators combine with tools to aid life-expectancy estimation, may be useful in identifying those with a high net benefit, those unlikely to have net benefit, and those between these extremes where there is a closer balance of benefits to harms associated with screening. This calculation may help to tailor the discussion during the shared decision-making visit.

8. 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: Screening programs should develop messages to share with providers and patients about the likelihood of having a positive test, and the meaning of the finding, particularly the low likelihood that a small solid nodule will be found to be a cancer.

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. Nodule diameter should be measured using lung windows.

Remark: An equivalent volumetric threshold can also be considered.

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

9. We suggest that low-dose CT screening programs develop strategies to maximize compliance with annual screening exams and evaluation of screen-detected findings. (Ungraded Consensus-Based Statement)

Remark: These strategies may include education during the shared decision-making visit, communication through EHR reminders, letters, phone calls, and tools to address screening participants' concerns about the LDCT results and follow-up plan, insurance coverage, and other questions or barriers to returning for follow-up.

10. We suggest that low-dose CT screening programs develop a comprehensive approach to lung nodule management that includes access to 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: Programs without lung nodule management expertise available on site could collaborate with centers capable of high-quality lung nodule management (e.g. referral, telehealth evaluation).

11. 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 on imaging that is most likely to represent an indolent cancer.

12. For individuals who currently smoke and are 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)

13. 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, tracking of the radiation dose being administered, and appropriate management of screen detected findings.

14. 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 lung nodules, guideline-based recommendations for surveillance of small lung nodules, and a description of other potentially actionable findings.

Remark: The ACR LungRADS structured report is the most prevalent system used today. The ACR National Registry requires data to be submitted using the LungRADS categories.

15. We suggest that low-dose CT screening programs develop strategies to guide the management of non-lung 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 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 non-lung nodule findings by the screening program. Clear communication between providers is important to prevent misunderstandings about who will assume responsibility for evaluation of these findings.

Remark: The description of non-lung nodule findings in the structured reports should be standardized to assist with interpretation of the findings.

16. 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.

BACKGROUND

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 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 impact this balance.

In this manuscript, we update the evidence base for the benefit, harms, and implementation of low radiation dose chest CT (LDCT) screening. We use this evidence base to update recommendations where the evidence allows, and update statements based on experience and expert consensus where it does not. We have updated the description of the evidence and discussion where it has changed and have maintained the text from the prior version where it did not. We have not provided updates for other forms of lung cancer screening (i.e. chest radiography (CXR), sputum analysis) as the evidence base and recommendations related to chest radiography and sputum analysis have not changed since the previous iterations of these guidelines (latest version, 2018).[2,3] The intended audience for this guideline is practicing clinicians, administrators, and policy makers.

METHODS

Expert Panel Composition

The chair of the panel (P.M.) was appointed by CHEST's Lung Cancer Guideline Executive Committee and subsequently reviewed and approved by CHEST's Professional Standards Committee (PSC). Panelists were nominated by the chair based on their expertise relative to potential guideline questions. The final panel consisted of the guideline chair, 6 panelists (T.C., F.D., J.K., H.K, G.S., and R.W.) including specialists in pulmonary medicine, thoracic surgery, and chest radiology, a primary care physician, an epidemiologist, and a methodologist (L.S.).

Conflicts of Interest

All panel nominees were reviewed for their potential conflicts of interest (COI) by CHEST's PSC. After review, nominees who were found to have no substantial COIs were approved, whereas nominees with potential intellectual and financial COIs that are manageable were "approved with management". Panelists approved with management are prohibited from participating in discussions or voting on recommendations in which they have substantial COIs. A grid was created listing panelists' COIs for each recommendation for use during voting. The COI grid can be found in Table 1. None of the panelists reported conflicts directly related to the recommendations.

Review of Key Questions

The expert panel reviewed the previously drafted 12 key clinical questions, phrased in a PICO (population, intervention, comparator, outcome) format (Table 2). The key questions were felt to be comprehensive. The panel organized the manuscript in sections to help frame the presentation of data. Where the evidence reviews from the key questions did not fully address the considerations of a particular section, the expert panel supplemented the evidence review with relevant literature.

Literature Search

The literature search was performed every 3-6 months since the prior guideline publication. Using the literature search strategy developed for the prior guideline (Figure 1), Doctor Evidence LLC (Doctor Evidence: Library Management

System. Santa Monica, CA: Doctor Evidence, LLC) systematically searched the MEDLINE and EMBASE databases from September 2017 through June 2019 and L.S. systematically searched the MEDLINE and EMBASE databases from July 2019 through January 2020. Searches were conducted 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 1/2020. Studies were limited to English language, but no other restrictions (i.e. publication date, study design) were put on the searches. Additional details on the literature searches and the selection of studies can be found in Figure 2 (PRISMA diagram).

Study Selection and Data Extraction

A review of the titles and abstracts that resulted from the updated searches was performed by two reviewers (P.M, G.S). Relevant studies were organized into specific content areas by P.M. Data was extracted from all studies that were flagged to include in updates of the meta-analyses or tables (Tables 3, 4, 5). Data from studies flagged for narrative synthesis by P.M. and G.S. were extracted based on inclusion of relevant outcomes as outlined during the development of the prior guideline, where 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 extracted from eligible studies. All data was extracted by one reviewer (L.S.) into a pre-approved data extraction form which was then reviewed by P.M. and revised where necessary. Data and meta-data (variables that characterize numerical data points) were obtained from text manually.

Quality Assessment

Individual Study Quality and Potential for Bias

Important quality features, such as study design, comparison type, power calculation reporting, sources of bias, and sources of funding were extracted for each study. To evaluate the risk of bias within the identified studies, the Cochrane Risk of Bias Tool[4] was used for randomized studies (RCT) and post-hoc analyses, and the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool[5] was used for cohort studies.

Quality of Evidence by GRADE

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[6] system was used to determine the aggregate evidence quality for each outcome. GRADE defines a body of evidence in relation to how confident guideline developers can be that the estimate of effects as reported by that body of evidence is correct. Evidence is categorized as high, moderate, low and very low quality, and assessment is based on the aggregate risk of bias for the evidence base, plus limitations introduced as a consequence of inconsistency, indirectness, imprecision and publication bias across the studies (Table 6). Quality of evidence assessment was completed for both conducted meta-analyses.

Synthesizing the Evidence

For both questions where a meta-analysis was appropriate, pooling of data was conducted using RevMan[7]. Relative risks for lung cancer mortality reduction and smoking cessation were calculated used a random-effects inverse variance method. A p-value less than 0.05 was considered statistically significant for all tests. Statistical heterogeneity was assessed using the Higgins I_2 test. An I_2 value of 50% was defined as one that may represent substantial heterogeneity[8].

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.[9,10] 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 Table 7.

In instances in which there was insufficient evidence, but a clinically relevant area was felt to require a guiding comment, a suggestion was developed and "Ungraded Consensus-Based Statement" replaced the grade.[11]

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.[12] According to CHEST policy, each recommendation and statement required a 75% voting participation rate (100% actually participated) and at least 80% consensus to "pass". Any recommendation or suggestion that did not meet these criteria was revised by the panel based on feedback received, and a new survey that incorporated those revisions was completed.

Peer Review Process

Reviewers from the GOC, 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

Seventy-five studies were identified that met the inclusion criteria. Of these 75 studies, nine were identified to either update a prior meta-analysis or perform a new meta-analysis, six were identified to update the cohort studies of the original guideline (Table 5), and 61 were flagged for potential narrative synthesis.

Selection of Individuals for Lung Cancer Screening

The selection of individuals for lung cancer screening requires an understanding of the evidence supporting benefit from screening and describing the potential harms from screening. The decision about who to screen requires an understanding of trade-offs in the balance of benefits and harms at a population and individual level. In the sections that follow key questions about the benefit and harms from LDCT screening, as well as the influence of the health and values of those who may be screened, frame descriptions of the evidence from which our recommendations were derived.

Benefit of Screening for Lung Cancer: Lung Cancer Mortality Reduction

Key Question 1. What is the rate of death from lung cancer (i.e. lung cancer mortality) among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared to either no screening or screening with another modality?

Four new publications from RCTs[13-16] were identified to update the lung cancer mortality meta-analysis. The studies provide longer follow-up results for the Dutch-Belgian randomized LDCT screening trial (NELSON)[14], the Multi-centric Italian Lung Detection (MILD) trial[16], the German Lung Cancer Screening Intervention (LUSI) trial[13], and the Lung Screening Study (LSS)[15] than were available for the prior guideline. The study design and outcomes of these studies have been added to prior summary tables (Tables 3 and 4).

Of the eight randomized controlled trials that report on lung cancer mortality[13-20] only the National Lung Screening Trial (NLST)[20,21] and the NELSON trial[14] were adequately powered to answer the question of whether a mortality benefit from screening can be achieved. The NLST included 53,452 individuals who currently or formerly smoked age 55-74 with at least a 30-pack year history of cigarette use. Individuals who previously smoked 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 7% reduction in overall mortality, favoring LDCT screening.[20] 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%.[21] In absolute terms, for every 1000 persons screened approximately 3 lung cancer deaths were prevented. The NELSON trial differed from the NLST by risk group assessed (age 50-75, 15 cigarettes per day for 20 years or 10 cigarettes per day for 30 years, smoked within the past 10 years), screening interval (baseline, year 1, year 3, and year 5.5), length of follow-up (10 years), and nodule identification strategy (volumetric).[22] The results showed a statistically significant 24% reduction in lung cancer specific mortality in men (who made up 86% of the study cohort), and a non-significant but larger 33% reduction in women. There was no

overall mortality reduction. None of the other trials were individually powered to adequately address a mortality benefit (smaller size, screened a lower risk group than the NLST). The updated MILD trial[16] report demonstrated a lung cancer mortality benefit (39% reduction) while none of the other trials was able to individually show a benefit to screening.

The meta-analysis of all included trials combined is interpreted with an understanding of the heterogeneity of the study designs and results. This revealed a statistically significant 19% relative reduction in lung cancer deaths (Figure 3). This equates to four fewer deaths per 1000 persons screened (Table 8a). When separately analyzed to include only trials with usual care as the control arm there was a statistically significant 21% reduction in lung cancer deaths. When analyzing LDCT versus chest x-ray separately there was a non-significant 4% reduction in lung cancer deaths when chest x-ray was the control arm. This subgroup includes only the NLST and the NLST feasibility trial (LSS study), with the much larger NLST study reporting a significant reduction in lung cancer mortality and the feasibility trial indicating no significant difference (Figure 3). Although the complete pooling of all eight RCTs uses a random-effects model and shows a non-significant reduction in the CXR subgroup, a fixed-effect pooling of the NLST and its feasibility trial, which showed limited clinical and methodological heterogeneity would have placed greater weight on the larger NLST and would have shown a significant 13% reduction in lung cancer deaths with LDCT when compared with chest x-ray (data not shown). Although the subgroup pooling of NLST and its feasibility study showed a non-significant reduction, the much larger NLST demonstrated a significant 20% reduction in lung cancer mortality [20] when considered alone. Both annual and other screening protocols led to significant reductions in lung cancer deaths (13% for annual, 26% for other) (Figures 4 and 5). The aggregate quality of the evidence of the eight RCTs[13-20] reporting on lung cancer mortality was moderate (Table 8a).

Key Question 2. What is the rate of death from lung cancer (i.e. 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 to either no screening or screening with another modality?

We evaluated lung cancer mortality reduction in men and women separately, combining studies where this was reported. Individual studies were not powered to detect differences between genders. Lung cancer mortality reduction appeared to be greater among women but was significant for both men and women. When trials with usual care or chest x-ray control arms were included there were significant mortality reductions in both men (12%) and women (31%). When only trials with usual care control arms were included, lung cancer mortality reduction was significant for men (18%) and non-significant but larger for women (46%). Similarly, we evaluated lung cancer mortality reduction based on the starting age (50, 55, or 60). There was a significant lung cancer mortality reduction in trials with a starting age of 50 (23%). At starting age 55 the lung cancer mortality reduction was not significant (13%) in part due to the nature of random effects modeling. There was only one study with a 60-year-old starting age. There were no significant differences in lung cancer mortality reduction between those age < 65 and those ≥ 65 (RR 0.82 vs. 0.87, p = 0.60) in the NLST.[21,23] The results of these analyses are summarized in Table 9, and in Figures 4-9. Finally, we also evaluated lung cancer mortality reduction based on age at screening cessation (69-71 or 74-75). There was a significant 18% reduction for screening trials that stopped at age 74 or 75, but an insignificant reduction for screening trails that stopped at age 69-71 (Table 9).

Limited data comparing lung cancer mortality outcomes by race, smoking status, malignancy risk, and the presence of COPD were available. The NLST was the only trial for which there is data reporting lung cancer mortality stratified by race. Black individuals had a non-statistically significant larger benefit than white individuals (HR 0.61 vs. 0.86, p = 0.29).[24] There were no significant differences between individuals who currently or previously smoked in the NLST (RR 0.81 vs. 0.91, p = 0.40).[21,23] Lung cancer deaths from squamous cell carcinoma were not reduced by screening whether male (RR 1.31) or female (RR 1.04). The reduction in relative risk of lung cancer mortality was similar among lung cancer risk quintiles in the NLST, though the number needed to screen to avert a lung cancer death was much higher in the lowest compared to the highest risk quintile (5,276 vs. 161).[25]In the DLCST the difference in lung cancer mortality in those with a < 35 pack year smoking history compared to a ≥ 35 pack year smoking history (RR 1.26 vs. 0.92, p = 0.52) or between those with or without COPD (RR 0.85 vs. 1.38, p = 0.30) did not reach statistical significance.[18] In the NLST-ACRIN subgroup, patients with COPD had an increase in lung cancer incidence (IRR 2.15), no excess lung cancers in the LDCT arm, and a more favorable stage shift.[26]

The aggregate quality of the evidence of the five RCTs[18,21,25-27] reporting on lung cancer mortality based on clinical phenotypes was low (Table 8a).

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. 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 over-treatment of lung cancer.

The cost-effectiveness of lung cancer screening is an important societal consideration that we have positioned in the harms section, though it could fit elsewhere. A final potential harm is the consequence of evaluating other imaging findings, unrelated to lung cancer (e.g. 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. While 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.

Death and Complications Resulting from Biopsies

Key Question 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 to either no screening or screening with another modality?

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 (e.g., 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.[21] A “real world” 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.[27] By contrast, using criteria that incorporate nodule volume and volume doubling-time, the NELSON trial labeled 2.3% of male participants as having a “positive” prevalence scan, and an additional 19.7% as having “indeterminate” results.

In the NLST a total of 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. Procedure rates across all reviewed studies varied dramatically, in part based on study length and design (0.7-7.6%), with a mean of 3.0% of individuals having an invasive procedure in LDCT arms from 19 studies (Figure 10). 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 are available that carefully assess this (Table 10). 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 (Figure 11, Table 8b).[18,21,24,28-30] 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. 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.[21] 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 that the deaths reported in the NLST were related to the procedure.

Rates of major complications were higher among participants 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%).[21] 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.[21] Overall, eleven studies contributed data on major complications, showing that among individuals who underwent an invasive procedure following LDCT, 4.2% experienced adverse events (not including death). This evidence is summarized in Table 10, Figure 12, and graded in Table 8b.

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

Key Question 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 to either no screening or screening with another modality?

A post-hoc analysis of NLST data examined overall rates of invasive procedures and complications compared to rates within high-risk subgroups.[31] Overall, among 26,999 individuals in the CXR arm, 1.5% underwent an invasive procedure, 0.3% experienced a complication, and 0.1% a serious complication. Among 26,453 individuals who underwent LDCT screening, 4.2% underwent an invasive procedure, 0.9% experienced a procedure-related complication and 0.3% a serious complication. In the LDCT arm, participants with COPD (n=4632, defined by self-report) were more likely than participants without COPD to undergo an invasive procedure (6.0% vs. 3.8%; adjusted OR, 1.41; P < .01) and more likely to experience any complication (1.5% vs. 0.7%; adjusted OR, 1.83; P < .01) or a serious complication (0.6% vs. 0.3%; adjusted OR, 1.78; P < .01).

Surgery and Non-Surgical Procedures for Benign Disease

Key Question 5. What is the rate of surgery for benign disease among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared to either no screening or screening with another modality?

The rate of surgical procedures for benign disease varied across studies. 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[17,20,28,32-45]). In the LDCT arms, 22.0% of surgeries were performed for benign disease (Figure 13, Table 10, and graded in Table 8b). In the LDCT arm 37.0% of nonsurgical procedures were performed for benign disease (Figure 14). Nonsurgical procedures were defined as needle biopsies and bronchoscopies.

Psychosocial Impact

Key Question 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 to either no screening or no nodule detected on LDCT screening?

Three randomized trials and two observational cohort studies examined the potential for an adverse psychological impact among those patients found to have a screen-detected nodule.[46-50] 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.[46] 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).[48] 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.[47,48] In the overall cohort of screened individuals in the Pan-Can study, women and those with higher levels of lung cancer worry were more likely to experience an increase in short-term

anxiety, but there was no significant association of the finding of an indeterminate nodule with short-term anxiety or HRQOL. Neither the NELSON trial, the NLST, nor a cohort study of LDCT screening among those meeting NCCN2 criteria found a difference in health-related quality of life among those with indeterminate vs. normal results.[46,47,50] In summary, these trials suggest that finding a screen-detected nodule may transiently increase distress but does not adversely affect anxiety levels or quality of life.

Overdiagnosis

Key Question 7. What is the rate of overdiagnosis among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared to 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 (i.e., 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.[51] 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 that 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.[52-56]

The challenge of estimating rates of overdiagnosis is illustrated in considering two analyses of clinical trial data.[52,57] Investigators from the NLST 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.[52] It was estimated that 1.38 lung cancers were overdiagnosed for every lung cancer death averted.[52] By contrast, a post-hoc analysis of overdiagnosis in the Danish Lung Cancer Screening Trial estimated the overdiagnosis rate to be 67.2% (95%CI, 37.1-95.4%)[57]; of note it is not clear how overdiagnosis was defined in this analysis.

Cost-effectiveness

Key Question 8. What is the cost-effectiveness of LDCT screening of individuals at elevated risk of lung cancer, compared to 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 (QALY) gained.[29] 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.[58] Several models were tested with the optimal scenario for screening identified as individuals who currently and previously smoked 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 QALY while highlighting that cost-effectiveness varies by sex, smoking status, and the risk of having lung cancer.[59] For example, the cost per QALY 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.

Five additional studies on cost-effectiveness of lung cancer screening programs were identified[60-64] The first study compared annual with biennial screening over 20 years.[60] While QALYs gained were similar between protocols, life years gained was higher with the annual screening arm (77,000 vs 61,000). However, the incremental cost of annual screening was estimated at 2.9 billion Canadian dollars versus 1.7 billion for biennial screening. The second study, conducted in Germany, reported the incremental cost-effectiveness ratio (ICER) as €19,302 per life year saved and €30,291 per QALY gained.[61] The study stated that the model included high-risk patients but did not define the LDCT screening protocol. A third study, conducted in Denmark and designed to evaluate the direct and indirect costs of LDCT screening, reported that the mean total annual healthcare cost for LDCT would be 60%.[62] A US based study that modeled an untargeted screening program that would increase screening from 3,900 per 100,000 eligible patients to 10,000 per 100,000, reported that the program would result in 12,300 life years saved and would be a net monetary benefit of $771 million.[63] The final study compared risk-targeted screening with the NLST screening criteria.[64] Five stepwise risk groups were created and the ICER were similar across the groups.

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 (i.e., not lung nodules) has not been completely factored into cost-effectiveness analyses.[65,66]

Radiation Exposure from the LDCT

Although a LDCT 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 FDG PET/CT scans for the evaluation of screen detected findings.

The risk of ionizing radiation to an individual undergoing LDCT screening depends on the age at which screening begins, gender, 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 relies 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 in the NLST was 1.5 mSv.[20] Lower average estimated effective doses can be achieved on currently available CT scanners.

In one analysis, authors estimated the lifetime attributable risk of radiation related lung cancer mortality, assuming annual LDCT examinations from age 55 to age 74, with technique like that of the NLST, to be approximately 0.07% for males and 0.14% for females.[67] 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[68]; cumulative radiation doses exceeding lifetime radiation exposures of nuclear power workers and atomic bomb survivors[69]; lower expected lung cancer mortality reduction when radiation risk is incorporated into models of the benefit of LDCT screening[27]; and the need for substantial mortality reduction from LDCT screening to overcome the radiation risk (e.g. 25% for female never smokers age 50-52, 2% for males who currently smoke age 50-52).[30] Another study based on a retrospective analysis of screening and additional imaging workup doses estimated a risk of 0.05% of developing a serious cancer after 10 years of screening with CT doses 40% lower than NLST. This translates theoretically to one radiation induced cancer for every 108 lung cancers detected over 10 years.[70]

Considerations when Assessing the Balance of Benefit and Harms

Clinical Lung Cancer Risk and Screening Benefit Assessment Tools

Key Question 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 to the use of the NLST or USPSTF criteria?

The ability to predict which individuals are at high risk for developing lung cancer, or could gain high life-years (benefit) from lung cancer screening, is limited when using dichotomized age and smoking history criteria. More precise accounting of age, smoking history, and additional lung cancer risk factors may improve risk or benefit prediction and screening efficiency, as well as reduce racial/ethnic/gender disparities in eligibility for screening.

There are 2 kinds of prediction models. Risk models predict lung cancer incidence (e.g. Bach, LCRAT, or $PLCO_{M2012}$) or lung cancer death (e.g. LCDRAT).[71-73] A benefit model, (e.g. LYFS-CT), calculates the life-years gained by undergoing lung-cancer screening.[74] These 5 models have been shown to have improved discriminatory ability compared to other models,[75] and are available through websites[76-79] or as downloadable excel files[80,81]. Risk models incorporate major lung cancer risk factors, including age, sex, race/ethnicity, the presence of COPD, smoking intensity, smoking duration, and smoking quit time. Benefit models also include factors that influence life expectancy.

Use of $PLCO_{M2012}$ at a low threshold (1.34% 6-year lung cancer risk) improved sensitivity for lung cancer detection versus 2013 USPSTF criteria (83.0% vs. 71.1%; p<0.001), without decreasing specificity (62.9% vs. 62.7%; p=0.54) in a cohort recruited in the 1990s.[73] Use of LCDRAT at a stringent threshold (1.40% 5-year risk of lung-cancer death) increased the fraction of screen-preventable deaths versus 2013 USPSTF criteria (61% vs. 46%) in the US in 2015, while screening the same number of people.[74] Use of LYFS-CT at a stringent threshold (16.2 days of life-gained by screening) increased the fraction of gainable life-years versus 2013 USPSTF criteria (48% vs. 41%) in the US in 2015, while screening the same number of people.[74] Studies investigating the use of these models in clinical practice are ongoing.

A fundamental question when applying these models is whether the identification of patients for screening based on a risk score rather than age, pack-year and quit-year cutoffs 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 impact nodule presence[82], the risk of nodule evaluation[83], the risk of lung cancer treatment[84], survival after lung cancer treatment[85], and overall survival.[86] In particular, risk models, when used in isolation, choose people at older ages with more comorbidities than USPSTF criteria.[74,87]

While use of risk-calculators might increase the number of preventable deaths, they may not appreciably increase the life-years gained in a population when used in the absence of an additional life-expectancy criterion.[64,87-89] In contrast, adding a life-expectancy criterion or defining eligibility based on benefit models of life-years gained from screening, could optimize the life-years gained by screening in a population.[74,90] Life-gained models choose somewhat older, but healthier, people than USPSTF criteria.[74]

The eligibility criteria, interval and duration of screening were explored in a sophisticated study conducted by the Cancer Intervention and Surveillance Modeling Network (CISNET) group to inform the USPSTF in an AHRQ summary report.[89] Four centers built independent models that were calibrated to the NLST and PLCO data; two models yielded generally similar predictions and two performed very differently. The models explored 1,093 screening strategies (289 risk factor-based and 804 risk model-based), varying the screening interval, age to begin screening, age to end screening, minimum smoking history, duration since quitting, and choice of risk-model and risk-threshold. The models developed did not account for race/ethnicity and they did not examine the use of both risk-thresholds and life-expectancy thresholds combined or models of benefit (i.e. LYFS-CT).

The CISNET models[89] provide insight into the inherent trade-offs of lung cancer screening. Most importantly, 2013 USPSTF criteria, previously found to being efficient for the 1950 US birth cohort using data through 2013[91], are no longer efficient for the 1960 US birth cohort for either deaths averted or life-years gained. Instead, annual screening strategies with a 20 pack-year minimum[71] and starting at age 50 were more efficient. The new 2020 USPSTF criteria could result in considerably more lifetime lung cancer deaths averted (381 to 503 per 100,000) and LYG (4,882 to 6,918 per 100,000) than 2013 USPSTF criteria. However 2020 versus 2013 USPSTF criteria also nearly double current screening eligibility

(increase from 8.1M to 15.1M eligible in 2015), could result in more lifetime false-positive tests (2.2 vs. 1.9 per person screened), overdiagnosed cases (84 vs. 69 per 100,000), and radiation-related lung cancer deaths (38.6 vs. 20.6 per 100,000).

Risk of harms generally increases with age and the number and severity of comorbidities. Thus, an individual's life-expectancy could serve as a proxy for the risk of harms from screening. Life-expectancy is primarily driven by age, comorbidities, and smoking history. Persons with limited life-expectancy may be less likely to benefit, and more likely to be harmed by lung cancer screening, even if deemed to have high lung cancer risk.[90]

The application of life-gained models requires a days-of-life-gained threshold, while the application of risk models should include both a risk threshold and a life-expectancy threshold. In the absence of clinical trials that evaluate outcomes upon enrollment based on model thresholds a conservative approach to their application would be to establish thresholds that would be considered "preference-insensitive". Individuals who exceed such a threshold would have such an estimated high lung cancer mortality benefit from screening that even high levels of concern about the harms of screening would not outweigh this benefit.[90]

To date, risk and benefit model studies have reported thresholds that identify the same number of screen eligible people as would application of the 2013 USPSTF criteria.[72,73,87,92,93] Such thresholds cannot guarantee that the benefits outweigh the harms for the individuals selected. In addition, the implications of such thresholds change over time.[93] For example, a 1.3% lung cancer risk by $PLCO_{M2012}$[94] has been suggested as a threshold. When this threshold was developed, its application was meant to identify the same number of eligible individuals from the PLCO cohort (established in the 1990s) as the 2013 USPSTF criteria would. When evaluated in 2015, this threshold actually identified 57% more (12.6M vs 8.0M) eligible individuals because of declines in smoking rates since the 1990s.[93]

Probabilities for benefit in the target population vary greatly across individuals with different combinations of risk factors. Those at very high lung cancer risk with good life-expectancy will have a much higher chance of benefitting than those at lower risk or with only fair life-expectancy.

Across this continuum, it may be more justifiable to set 2 thresholds (Figure 15), which allows room for scientific uncertainties (e.g., real-world rates of false positives across different health systems) and a range of patient preferences across the target population (the preference-sensitive zone). To the left of the preference-sensitive threshold #1 in Figure 15, patients are unlikely to experience more than negligible benefit or screening is potentially net harmful. In the gray area to the right of this threshold, screening would still only be considered appropriate if a patient prefers it after shared decision making and being informed of the uncertain or smaller chance of net benefit. For patients to the right of the preference-insensitive threshold #2, clinicians should have more confidence that, even given uncertainties about extrapolating trial evidence to individual patients and assuming higher rates of harm, screening offers a high chance of net benefit and should thus be routinely encouraged.

One study used NLST data to estimate the benefits and harms of screening USPSTF-eligible members of the 2015 US population.[90] This microsimulation study integrated evidence on individualized cancer risk, individualized life-expectancy, screening harms, key scientific uncertainties (e.g., uncertainty about rates of false-positives and overdiagnosis), and variation in patient preferences.[90] The analysis produced lifetime quality-adjusted life-year gains with 3 annual LDCT screens. To ensure a preference-insensitive high net benefit, the life-expectancy threshold had to be ≥10 years.[90] The lung cancer incidence thresholds identified as high benefit in this analysis exceeded most other thresholds evaluated.[72,73,87,92,93] The following "high benefit" risk thresholds for individuals with an estimated life-expectancy ≥10 years were identified: ≥2.0% 5-year lung-cancer incidence risk on the LCRAT; ≥5.2% 10-year lung-cancer incidence risk on the Bach risk calculator; and ≥2.6% 6-year lung-cancer incidence risk on the $PLCO_{m2012}$ calculator. The stringency of the risk and life-expectancy thresholds ensures that people chosen have a high chance of net benefit. Setting decision thresholds is inherently a value judgment. A systematic approach to setting thresholds, which allows for a range of patient preferences and acknowledges scientific uncertainties, should almost always include a preference-sensitive zone and at least 2 decision thresholds, as described above. The example high-benefit thresholds provided in this guideline offer important guidance on the upper bound (threshold #2) but should not be taken as proscriptive.

We do not try to identify threshold #1 that indicates when screening may start to be a preference-sensitive decision. More research is needed to identify prediction model estimates for threshold #1, as there have been no comprehensive analyses examining this threshold to date. In addition, updated guideline recommendations now include lower age and pack-year cutoffs; and this likely greatly expands screening to include many lower-risk persons for whom screening is highly preference-sensitive. This decreases the urgency of identifying prediction model estimates for threshold #1.

Minimizing Disparities

Among patients enrolled in the NLST, individuals who currently smoke 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 currently smoke) 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, those with a lower educational status, and individuals with low SES.[95-97] 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 to addressing cultural beliefs about lung cancer and its treatment is needed to reduce barriers to screening acceptance.[98,99] 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.

Current age and smoking history based eligibility criteria engender disparities with respect to race/ethnicity, sex, smoking intensity, years since quitting, and for special populations such as people living with HIV; see[100] for a comprehensive review. By reducing the age and the pack-years eligibility for screening from 55 to 50 and 30 to 20, respectively, as in the USPSTF draft recommendations, more African Americans will be eligible for screening which may partially eliminate this particular disparity.[101]

However, even after a screen detected lung cancer was diagnosed in the NLST, surgical resections were performed less in African American men than Caucasians (65% versus 93%, respectively).[102] Regarding follow-up of incidental findings from lung cancer screening those with a high school degree were nearly three times more likely to receive appropriate follow-up for screen detected abnormalities than those without a high school degree suggesting that screening programs should tailor their shared decision-making discussions to an appropriate education level that stresses the need for follow-up of incidental findings.[103]

[100]Reducing disparities by improving equity requires managing people with equal net-benefit from screening as equally as possible.[100] Because risk of lung cancer or lung cancer death (paired with life-expectancy), or life-years gained from screening, more directly attempt to estimate the net-benefit from screening, use of risk or benefit calculators could improve equity by applying the same threshold to everyone regardless of race/ethnicity, sex, or any other factor accounted for by the calculators. Use of risk calculators may increase eligibility for African-Americans relative to whites[72] and thus increase the number of lung-cancers detected relative to whites[72,104]. Use of benefit calculators may increase the life-years gained for African-Americans relative to whites.[74]

Impact of comorbidity and quality of life

Compared to NLST participants, a US-representative sample meeting NLST eligibility are older, more likely to currently smoke, and more likely to have comorbidities.[51] Also, compared with the NLST group undergoing surgery for stage I disease, those in a community sample with $\geq$2 comorbidities had significantly worse surgical outcomes and 5-year overall survival, suggesting that competing causes of death played a role.[105] Similarly, LDCT screening was less efficacious in NLST participants with two or more pulmonary conditions.[25]

Older people or people with more comorbidities may be more likely to have a serious harm from screening and may have a higher mortality risk from surgical resection.[106] Moreover, older persons and those with more comorbidities will

have fewer life-years gained from screening. Thus, 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 critical. As above, risk models can help estimate lung cancer risk for an individual but by their nature, for a population, will choose older people with multiple comorbidities. For example, the mean number of comorbidities in a US-representative group chosen by NLST eligibility criteria is 2.0 vs 2.3 for a group chosen by a lung cancer risk-model.[72] Some persons deemed high risk may have multiple comorbidities and may not live long even if a lung cancer related death is avoided by screening.[74] By selecting younger, healthier people at medium-high risk but with good life-expectancy, screening effectiveness is maximized and decades of life-year gains can be achieved for those averting a lung cancer death with screening.[74,90] Another approach is to choose people based on directly estimating their life-years gained if undergoing screening.[74] Selection based on estimated life-year gains with screening (benefit-based selection) can identify a healthier population with fewer comorbidities. The mean number of comorbidities in persons chosen by an estimated life-year gain criterion was only 1.8 (vs. 2.0 for USPSTF and 2.3 for risk-based).[74]

These considerations are especially important for persons with COPD. COPD confers a much higher risk of lung cancer but also confers a higher risk of competing mortality and a higher risk for treatment related harms (e.g., complications from biopsy or surgical resection).[106] Persons with mild-moderate COPD may experience large health gains with screening due to the increased lung cancer risk and still reasonable life-expectancy, whereas those with more advanced COPD, in particular those with severe COPD and poor functional status, may have limited net benefit from LDCT screening. Careful assessment of a person's ability to tolerate the diagnostics and treatment of early stage lung cancer is essential in persons with more advanced COPD.[106]

Molecular Biomarkers

Key Question 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 to 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. No applicable studies comparing molecular biomarkers to 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 specificity of 81%. This was not compared to the NLST or USPSTF criteria.[107] A pan-cancer biomarker based on DNA-methylation patterns has been validated in a large diverse population. At 99% specificity, the biomarker had an approximately 25% sensitivity for stage I and 80% sensitivity for stage III lung cancer.[108]

Frequency and Duration of LDCT Screening for Lung Cancer

The interval and duration of screening were explored in the CISNET modeling study that informed the USPSTF.[91,109-111] Regarding duration of LDCT screening, 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). 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 lung cancer mortality reduction as well as the number of scans increases slightly (~10% increase in both for a 5-year increase in the age at which screening is ended). The USPSTF considered the CISNET models and concluded that screening from age 50 to 80 was a reasonable balance of trade-offs.[1]

It is logical that screening should be ongoing provided the individual being screened does not have competing causes of death that make lung cancer less of a threat to their longevity. The MILD trial, which continued screening for 10 years, showed increased benefits for ongoing screening beyond 5 years.[16] This was also suggested by a follow-up study of patients 5-7 years after prior LDCT screening; 21% of patients had developed lung cancer (nearly 1/3 of those had died of lung cancer).[112]

The NELSON trial has brought the interval between scans into greater focus (NELSON used LDCT at baseline, 1 year, 3 years and 5.5 years).[14] The overall mortality reduction cannot be parsed to specific screening intervals. The stage shift for screen-detected cancers was less favorable for the 2.5 year interval compared to the 1 year interval (Stage I 61 vs 76%, Stage IV 13 vs 3%); for both screen-detected and interval cancers stage IIB/IV accounted for 15% in the 1 year interval and 35% in the 2.5 year interval.[113,114] The much smaller MILD trial that randomized annual vs. biennial LDCT did not find a clear difference in stage shift (but also had an unusually high number of interval and stage IV cancers in both arms).[115] The CISNET models found that scanning every 2-3 years vs. annually diminished lung cancer mortality reduction but also decreased costs; however in all of the CISNET model scenarios annual screening was near or at the efficiency frontier whereas biennial screening lagged behind. Another model suggested annual screening was more cost-effective than longer screening intervals.[58] A final modeling study considered several scenarios of reduced stage shift with biennial vs. annual screening and found that the proportional effect for biennial screening on decreasing cost was greater than on decreasing life years gained, and even less for QALYs.[60] This study suggested that biennial screening could be a favorable trade-off and warranted exploration.

With longer intervals, the importance of compliance with scheduled screening rounds increases, but it is likely that compliance will decrease. In a report of annual screening in an underserved population compliance at 1, 2 and 3 years was 46%, 38% and 28%,[116]. As the interval between screening examinations increases, fewer cancers will be screen-detected and more will be interval-detected, while the proportion of screen-detected tumors that have low aggressiveness increases ("overdiagnosed" cancers). These issues potentially decrease the effectiveness of screening at longer intervals beyond just the number of scans alone.

The panel considered the difficulty in assessing a balance between inherently dissimilar issues (cost vs. reducing lung cancer deaths), the incomplete ability to evaluate biennial vs. annual screening, the uncertainties associated with implementation that are likely magnified with biennial screening (compliance, overtreatment of indolent lung cancers) as well as the major modeling results.[60,91,109-111] The panel felt the evidence was strongest for annual screening. This is also the conclusion reached by the USPSTF: annual screening until age 80, assuming one remains healthy enough to benefit from treatment for a screen detected cancer. The GRADE profiles for Recommendation Statements 1 through 5 are included in Table 8. The profiles include studies identified to inform Key Questions 1 through 10 and details on outcome rankings for each statement are included in the footnotes.

1. For asymptomatic individuals 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 recommend that annual screening with low-dose CT should be offered. (Strong recommendation, moderate-quality evidence)

Remark: These eligibility criteria align with the eligibility criteria for CMS coverage at the time of publication.

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

2. For asymptomatic individuals do not meet the smoking and/or age criteria in Recommendation #1, are age 50 to 80, have smoked 20 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: These criteria align with the 2021 recommendations from the USPSTF[1].

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

Remark: Some individuals eligible by Recommendation #2 may have low net-benefit from screening and may choose not to undergo screening.

3. For asymptomatic individuals who do not meet the smoking and/or age criteria in Recommendations #1 and 2 but are projected to have a high net benefit from lung cancer screening based on the results of validated clinical risk prediction calculations and life expectancy estimates, or based on life-year gained calculations, we suggest that annual screening with low-dose CT should be offered. (Weak recommendation, moderate quality evidence)

Remark: Augmenting the criteria outlined in Recommendations #1 and 2 with risk prediction and life-year gained calculators leads to greater equity across race and gender in eligibility for lung cancer screening and the net benefits of screening.

Remark: Life-year gained calculators combine the results of risk prediction and life expectancy estimates into one measure.

Remark: Examples of calculated thresholds that identify individuals with a high net benefit from lung cancer screening include:

Life-gained: ≥16.2 days of life-gained by screening on the LYFS-CT calculator

Lung-cancer death risk: ≥1.33% 5-year risk on the LCDRAT calculator and ≥10 years of life-expectancy

Lung-cancer incidence risk: ≥2.0% 5-year risk on the LCRAT calculator and ≥10 years of life-expectancy; ≥2.6% 6-year risk on the $PLCO_{M2012}$ calculator and ≥10 years of life-expectancy; ≥5.2% 10-year risk on the Bach calculator and ≥10 years of life-expectancy.

Remark: The application of risk calculators or life year gained calculators to identify screen eligible individuals is more burdensome than identification using the criteria in Recommendations #1 and 2 alone. Lung cancer screening programs that choose to identify eligible individuals based on this recommendation should develop tools to support ordering providers in identifying screen eligible individuals.

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 or 2.

Remark: Molecular biomarkers are being developed to assist with risk prediction and/or early lung cancer detection. They have not reached a phase of evaluation to be included in this recommendation at the time of publication.

4. For individuals who have accumulated fewer than 20 pack years of smoking or are younger than age 50 or older than 80, or have quit smoking more than 15 years ago, and are not projected to have a high net benefit from lung cancer screening based on clinical risk prediction or life-year gained calculators, we recommend that low dose CT screening should not be performed. (Strong recommendation, moderate-quality evidence)

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

Remark: When an individual has a very severe comorbid condition it is easier to determine that low-dose CT screening is not indicated (e.g. advanced liver disease, severe 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 of comorbid conditions, it can be difficult to determine if an individual's comorbidities are significant enough that they should not receive low-dose CT screening.

Remark: The use of a life-year gained calculator may assist clinicians with this decision by accounting for reduced life-expectancy in persons at advanced age or with comorbidities.

Implementation of High-Quality Lung Cancer Screening

To optimize the net benefit from LDCT screening it is critical that high quality screening programs are developed. Several manuscripts have outlined phases of program development, implementation considerations, and key program components.[109,117-119] Each program needs to develop approaches to screening that fit their local environment. Programs require plans for 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 where the ordering provider may identify potentially eligible individuals, 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 tradeoffs 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.

Lung Cancer Symptoms

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.[120,121] Symptoms and signs related to paraneoplastic syndromes (confusion, nausea, constipation, weakness, 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.

6. 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 communicates 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 (e.g. reminders built into electronic medical records).

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."[122] 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 clinicians and patients is to inform patients about tradeoffs of screening vs. not screening and to help them make a choice that is 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 aid individual decision-making.

Though not including lung cancer screening specifically, a systematic review of the effects of SDM interventions on breast, colorectal, and prostate cancer screening found that SDM typically improves knowledge and decisional conflict, but has limited impact on intentions to screen or screening utilization.[123] In individuals who currently smoker and are eligible for LDCT screening, one RCT has examined the impact of providing a decision aid through tobacco quit lines vs. usual care.[124] Similar to the systematic review for SDM interventions for other cancer screenings, this RCT found that the decision aid improved knowledge and reduced decisional conflict but did not change screening intentions or behaviors. Two observational, single-center studies have reported outcomes from face-to-face and telephonic lung cancer screening counseling and shared decision-making visits, both as part of centralized screening programs.[125,126] These

limited studies suggest that this visit may improve screening knowledge and lead to high levels of patient satisfaction whether in-person or telephonic. Multiple smaller observational studies evaluating lung cancer screening decision aids have shown that diverse populations believe decision aids are useful and able to increase patient knowledge about LDCT screening and its tradeoffs.[127-130]

In an evaluation of the rollout of lung cancer screening in the Veterans Health Administration that included a structured patient decision aid, 58% of veterans who met screening criteria and were approached about lung cancer screening agreed to undergo screening.[131] A study among Medicare enrollees found that 60.8% underwent LDCT in the 3 months following the SDM visit, although uptake of the SDM visit was quite low (≤10%) during the 2015-2016 study timeframe. The reasons for patients' declining screening were not recorded in these studies. In a separate qualitative study during another health system's rollout of LDCT screening, which did not include formal decision aids, patients opting out of screening reported fear of the disease/treatment, a perceived low value of screening, and worry about false-positives or cost.[132] Despite recalling few specific harms or benefits of screening after a shared decision making visit, participants have reported satisfaction with the amount of information provided. Similarly, though reporting that clinicians did not explicitly ask about their values and preferences, participants were satisfied with their role in the decision-making process.[133]

Detailed initial presentations of information during SDM may not be feasible for lung cancer screening in routine primary care practice.[134,135] Lack of time is a consistent barrier to SDM in primary care [134] and has been reported as a potential barrier to SDM for LDCT screening.[136,137] In health systems with decentralized programs, or for patients not able to make a visit to a centralized program's screening coordinator, creative models of SDM and streamlined SDM tools may be necessary. One recently proposed model of brief SDM[134] emphasizes guidelines and decision tools that use risk/benefit calculators to identify ideal candidates for screening (high-benefit screening), and to distinguish high-benefit screening from preference-sensitive screening, where clinicians should merely offer screening in a more neutral fashion (Figure 15). By estimating each patient's lung cancer risk and considering life-expectancy, or estimating life-year gains, clinicians can more accurately inform their patients about the net benefit of CT screening for them personally.[134]

7. 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 (including the absence of symptoms and 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 or communicate 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: Life year gained calculators, or lung cancer risk calculators combine with tools to aid life-expectancy estimation, may be useful in identifying those with a high net benefit, those unlikely to have net benefit, and those between these extremes where there is a closer balance of benefits to harms associated with screening. This calculation may help to tailor the discussion during the shared decision-making visit.

Lung Nodule Size: Threshold for a "Positive" Result

Key Question 11. What is the stage distribution of lung cancer, the rate of death from lung cancer (i.e. 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 to 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. The trials varied in the size of nodules found on low dose CT scans that were defined as "positive", ranging from ≥4 mm in the NLST and LSS trials to ≥5 mm for solid nodules in the DANTE, LUSI, ITALUNG and UKLS trials, to size and growth based on volumetric measurements in the MILD, DLCST, and NELSON trials (Table 3).

It is crucial to note that "positive" in this context only means a finding that warrants further evaluation, not a nodule that is deemed likely to be a lung cancer. The major screening studies have shown that judicious evaluation (primarily an additional imaging test) reveals that the vast majority (>90%) of these "positive" findings are benign. The proportion of "positive" scans that resulted in an invasive test was low (3.04%) but with substantial variability (Figure 10).

The size threshold (solid portion, average of perpendicular diameters on thin section CT) for positivity on a screening CT affects several aspects of lung cancer screening. The most obvious is the number of nodules that are noted and flagged for further evaluation. A higher threshold could also cause a delay in diagnosis for those lesions that do turn out to be cancer. Applying the LungRADS criteria of 6 mm instead of 4 mm in the NLST has been estimated to reduce false positives at baseline and incidence scans by 52% and 76%, with a potential delay in diagnosis in 9% and 16% of those with lung cancer.[138] In an analysis of I-ELCAP data, 6 mm instead of 5 mm was estimated to reduce false positives by ~35% with no potential delay in lung cancer diagnosis of ≥9 months.[139] In the NLST 7 mm vs. 4 mm was estimated to cut false positive detection in half, with a delay in diagnosis in 7%.[140] Note that the NELSON study used a different definition of a positive scan (nodules that were deemed highly suspicious, usually due to growth during serial evaluation); using the definition of a nodule prompting further evaluation as applied in this GL the rate of positives at baseline was 22.0%.

Whether the stage shift attributed to screening is maintained (as a surrogate for mortality benefit) by a more restrictive threshold for further investigation is unclear. Comparing across studies the stage distribution ranged from 58-62% stage 1 and 12-13% stage IV in the 2 studies with the ≥4 mm nodule size definition to 30-69% stage 1 and 5-36% stage IV in the studies with a larger nodule size definition. Another potential issue with a more restrictive threshold for further investigation is increased importance of compliance with either ongoing screening or follow-up of a finding. Given the challenge with compliance in real world implementation and the available data, it is not clear that altering the size threshold will maintain the same lung cancer mortality benefit. This may be dependent on local characteristics of a program and the screened population. Therefore, the panel felt that endorsement of a specific threshold (e.g. 6mm) for all sites was not appropriate and that programs should evaluate this decision carefully. The aggregate quality of evidence of the six studies[138-143] informing this statement is low (Table 11).

8. 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: Screening programs should develop messages to share with providers and patients about the likelihood of having a positive test, and the meaning of the finding, particularly the low likelihood that a small solid nodule will be found to be a cancer.

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. Nodule diameter should be measured using lung windows.

Remark: An equivalent volumetric threshold can also be considered.

Remark: The LungRADS structured reporting system currently uses a 6 mm threshold for a positive test on the baseline scan and 4 mm if a new nodule is found on the annual scan for solid nodules; and 6 mm on 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.[20,144] 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.[145] Patients enrolled in the NLST were better educated, > 90% were white, had a higher socioeconomic status (SES), and were more likely to have previously smoked 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 (e.g. 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 currently smoking.[146-148]

Recently data from the VA lung cancer demonstration project revealed an adherence rate of 65% at 2 years, however the variation among the 8 sites in that cohort was between 52% and 82%.[149] One academic medical center documented an even lower 51% adherence rate.[150]

Poor adherence can substantially reduce the efficacy of screening. The Cancer Intervention and Surveillance Model Network (CISNET) modeled lung cancer mortality benefit when patient adherence varied and found that if adherence dropped to 46% the mortality benefit from screening was reduced by half.[151] Malignant micronodules (those < 4 mm in diameter in the NLST) represented 1.2% of cancers detected in the NLST, highlighting the importance of annual follow-up in this group.[152] 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%).[146] A study of colorectal cancer screening assessing > 35,000 patients found that < 50% were compliant with screening recommendations over the study period.[147]

Observational studies suggest that the addition of a nurse navigator to a screening program can improve compliance with annual screening[153], as does the provision of reminders to screening participants.[150] 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 in the development of tools to assist screening programs.

9. We suggest that low-dose CT screening programs develop strategies to maximize compliance with annual screening exams and evaluation of screen-detected findings. (Ungraded Consensus-Based Statement)

Remark: These strategies may include education during the shared decision-making visit, communication through EHR reminders, letters, phone calls, and tools to address screening participants' concerns about the LDCT results and follow-up plan, insurance coverage, and other questions or barriers to returning for follow-up.

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 because as noted in the section on harms, 22% of those undergoing surgery for screen detected nodules are diagnosed with benign disease.

Equally important is underreacting to malignant nodules which can lead to a missed opportunity for cure of an early stage lung cancer.

Conceptually, one can categorize pulmonary nodules into several types: clearly benign (e.g. calcified nodules, subpleural lymph nodes), solid nodules ≤ 8 mm in diameter, solid nodules > 8 mm in diameter, and sub-solid (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.[154-157] 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.[52] 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 nodule guidelines.[158] Other resources include the Fleischner Society recommendations, which focus on the surveillance frequency of smaller solid and subsolid nodules, and LungRADS, which focuses on small nodules identified in the screening setting.[159] One of the nodule risk prediction calculators, developed in the screening setting, has been shown to be more accurate at predicting malignancy[143] than LungRADS, and could be incorporated into screen-detected nodule management algorithms.[157]

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 systems in place. By contrast, surveys indicate that systems and processes of care to facilitate nodule evaluation have not been consistently adopted in US medical facilities.[160,161] Studies that include more diverse practice settings have reported higher and more variable rates of biopsy and complications during incidental nodule management.[83,162]

10. We suggest that low-dose CT screening programs develop a comprehensive approach to lung nodule management that includes access to 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: Programs without lung nodule management expertise available on site could collaborate with centers capable of high-quality lung nodule management (e.g. referral, telehealth evaluation).

11. 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 on imaging that is most likely to represent an indolent cancer.

Incorporating Smoking Cessation into Lung Cancer Screening

Key Question 12. What is the rate of smoking cessation among individuals who currently smoke, are at an elevated risk of lung cancer, and who receive smoking cessation counseling as part of a LDCT screening program, compared to those who do not receive smoking cessation counseling, and compared to those who do not participate in LDCT screening?

LDCT screening represents a potential teachable moment to counsel individuals who currently smoke about smoking cessation. The Centers for Medicare & Medicaid Services (CMS) policy requires smoking cessation counseling to be delivered at the time of LDCT screening. Based on meta-analysis of four trials[163-166], those undergoing LDCT screening appear to have higher smoking quit rates than those in usual care arms (RR 1.22, 95% CI 1.03-1.44; p=0.04) (Figure 16 and graded in Table 12). It is unclear what the driver of this finding is given that three of the trials varied in the smoking cessation intervention delivered to enrolled subjects and the fourth did not provide a smoking cessation intervention. Additionally, of the four studies, two reported smoking cessation in the intent-to-treat (ITT) population,[164,166] one reported cessation in patients who completed screening,[163] and the final reported cessation rates for both the ITT population and for only those patients who completed screening.[165] A prior systematic review suggested that patients with a screen-detected nodule are more likely to quit smoking than patients with negative screening results.[167]

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.[168,169] 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.[170,171]

12. For individuals who currently smoke and are 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)

Lung Cancer Screening Program Personnel

A high-quality lung cancer screening program requires a diverse group of health care personnel, components, and processes to maximize the net benefit of screening. Key professional groups, including the American College of Radiology, the American College of Chest Physicians, the American Lung Association, and American Thoracic Society, have identified several essential components of lung cancer screening programs.[117,172]

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 experts, schedulers and administrative staff (Table 13). 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 participation in all steps of the screening process run smoothly.

Only a few reports on real-world implementation of lung cancer screening programs have been published to date.[131,173,174] Implementation challenges identified in these reports have included difficulty identifying and enrolling eligible individuals due to incomplete smoking history information, concern about insurance coverage, 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.[175-177]

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 ($CTDI_{vol}$) ≤ 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.

While specific LDCT protocols will vary across manufacturers and even individual scanner models, certain general principles apply to all LDCT protocols (Table 14). 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.

13. 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, tracking of the radiation dose being administered, and appropriate management of screen detected findings.

Structured Radiology Reporting

The American College of Radiology and Society of Thoracic Radiology (STR) Practice Parameter for the Performance and Reporting of Lung Cancer Screening Thoracic Computed Tomography provides guidance about how to report the LDCT screening exam.[178] 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 STR.[178] In 2019, Lung-RADS was updated to version 1.1. Notable changes include increasing the actionable threshold for pure ground-glass attenuation nodules from 20 mm to 30 mm, removing tissue sampling recommendation for category 4A, allowing for follow-up LDCT in 1 month for category 4 nodules instead of diagnostic testing, optional use of volumetric measurements, and treating small perifissural nodules with features of normal pulmonary lymph nodes as category 2.[179] 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.

14. 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 lung nodules, guideline-based recommendations for surveillance of small lung nodules, and a description of other potentially actionable findings.

Remark: The ACR LungRADS structured report is the most prevalent system used today. The ACR National Registry requires data to be submitted using the LungRADS categories.

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 (e.g. HTN in ~60%, hyperlipidemia in ~50%, COPD in ~30%, coronary artery disease in 15%, DM in 15%).[180] As such, it is not surprising that many LDCT screening scans reveal potentially actionable findings (other than pulmonary nodules).[65,66,180-183] The value of what amounts to screening for other findings is undefined; the balance of benefits and harms of lung cancer screening is impacted by these other findings and the appropriateness of further investigation. Professional organizations have developed general guidelines for many of these other findings (Table 15). It is reasonable to apply these general recommendations to a screening context – if anything we should be more restrained to intervene. Evidence of overtreatment of non-lung nodule findings detected during the NLST has been noted.[184] Therefore, management of these findings is an important part of implementation of a screening program.

The prevalence of other findings has varied, with most studies reporting high rates on baseline scans (41% to 94%).[65,66,131,180,181,185] The definition of a finding affects the prevalence. Reported rates of further investigation prompted by other findings on a baseline CT range from 9% to 15%.[65,66,103,180,181,186] In the majority of these instances a consultation

and additional imaging or other non-invasive testing was involved.[65,103] Few patients (<5%) underwent invasive procedures either for diagnosis or as part of a therapeutic intervention.[65,103,180] The rate of eventually identifying conditions that lead to a therapeutic intervention is estimated to be <1%.[65,66,180,181] Finally, while non-lung nodule findings are very common on the baseline scan, new findings are uncommon on subsequent scans (~5% per year).[65,66]

It may be practical to organize non-lung nodule findings into 3 categories: not clinically relevant, possibly clinically relevant, and concerning (Table 15). 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 developed with an awareness of formal guidelines for investigation and treatment of relevant conditions (Table 16).

Several common findings deserve specific mention. Emphysema is a common co-morbidity in patients at significant risk for lung cancer. The USPSTF published a systematic review and guideline regarding screening for COPD.[187] The study concluded that there was no data on the effect of screening for COPD on survival and no direct studies examining the benefit of COPD screening on health outcomes. There was a modest benefit in terms of reduction of exacerbations and dyspnea scores with treatment in patients with (known) moderate or severe COPD. Screening for COPD has involved questionnaires (which exhibit moderate performance, NPV and PPV of 76-98% and 17-45%) and PFTs (with somewhat better performance, NPV and PPV of 83-98% and 63-75%). However, no studies have defined the correlation between a LDCT finding of emphysema or bronchial wall thickening and moderate or severe COPD. Therefore, these findings on screening LDCT cannot be recommended as an indication for further investigation at this time. Additional research will be helpful.

Cardiovascular disease is another frequent comorbidity in individuals at risk for lung cancer. In fact, in the NLST slightly more patients died of cardiovascular disease than of lung cancer.[20] CT screening for CAD has been studied extensively and several validated scoring systems exist that correlate with increasing risk of cardiovascular deaths and major events. The main difference between LDCT for lung cancer screening and for CAD is that the latter uses ECG synchronization to minimize motion artifact. Several studies have found that coronary artery calcification assessed on a non-gated or a lung cancer screening LDCT is predictive of an increased risk of cardiovascular deaths in asymptomatic individuals and those undergoing lung cancer screening.[188-193] The various scoring methods, applied to lung cancer screening, appear to function equally well. Two methods are particularly appealing because of their simplicity and being based on well done studies: a simple visual assessment (none, mild, moderate, severe)[188] and a prediction algorithm using known characteristics (age, smoking) and automated quantification of coronary and aortic calcification.[189] The Society of Thoracic Radiology recommends reporting a simple visual assessment of CAC on all non-gated CT.[194]

Primary prevention of cardiovascular disease is based primarily on age, blood pressure, cholesterol, and assessment of risk factors (e.g. family history, diabetes, smoking). The 2016 European multisociety prevention guideline[195] and the 2019 American multisociety prevention guideline[196] suggest that a formal coronary calcium score can be considered in borderline cases (as a “risk enhancing factor”). It has been suggested that the impact of coronary artery calcification may be greater to guide avoidance of medication in borderline patients without such calcification.[197] . It is unclear whether reporting would have an impact in a lung cancer screening context; one study found that reporting coronary artery calcification seen on a CT led to a change in aspirin or statin therapy in only 5% of patients.[198] It is reasonable that lung cancer screening CT reports include a simple assessment of coronary artery calcification in the body of the report. Given the minor role that coronary artery calcification plays in decision-making regarding primary prevention and that the assessment is not a formal coronary artery calcification assessment, at best this is possibly clinically relevant if the primary care physician deems that this finding (or lack of calcification) fits into the context of a risk enhancing factor in borderline cases. Therefore, it appears better to be noted so that it can be identified if needed, but not flagged as a concerning finding.

It should be noted that in the NLST there was no difference in non-lung cancer mortality (p=0.28).[20] It is unknown whether this reflects that identifying elevated CV risk during LDCT lung cancer screening is not useful or whether the

ability to determine CV risk and thus react to it was not yet developed at the time of the NLST. As a result, it seems reasonable to record the degree of CAC on a lung cancer screening LDCT scan. However, a formal recommendation to use this to select patients for (more intense) intervention in a lung cancer screening program should await evidence that it makes a difference.

It is important to note several aspects regarding aortic dimensions in an asymptomatic screening population, summarized in a systematic review and multi-society guideline.[199] First, the normal aortic diameter increases with age (at age 70 the normal ascending aorta is 3.5 cm and the descending 2.7 cm; upper limit of normal is 4.2 and 3.2 cm, respectively).[199] Second, aortic enlargement should not be called an aneurysm until the size is >50% larger than normal. Third, there is no evidence of benefit or recommendation for screening individuals for thoracic aortic aneurysm unless there is a clear family history or known genetic defect associated with aortic disease.[199] Fourth, it is important to measure the outside of the aorta in a plane strictly perpendicular to the blood flow. While management of blood pressure and lipids is recommended for individuals with an aneurysm to decrease the rate of further expansion, the data comes primarily from patients with familial risk.[199] There is no clear data in other individuals, and presumably this is already part of the primary care management. Therefore, there is little evidence to suggest that reporting mild/moderate aortic dilation affects health outcomes. There are recommendations to monitor aortic aneurysms either annually or biannually based on the size, type and location of the aneurysm that programs should review and consider in the context of annual Lung cancer screening. Finally, consideration of surgical repair is recommended for patients with an ascending or descending aortic size of ≥5.5 cm (unless there is a familial syndrome).[199]

Benign liver lesions are very common; fortunately, the vast majority are not concerning. In low-risk patients (i.e. without cirrhosis, liver disease or a history of cancers that metastasize to the liver) no further workup is needed for lesions <1.5 cm or with benign features (sharply marginated, homogeneous, < 20 HU).[200] In other scenarios further imaging with MR or contrast-enhanced CT should be considered.

A taskforce of the ACR on incidental renal lesions recommends no further investigation for renal lesions that are too small to characterize, and those that are homogeneous and either -10 to 20HU or >70 HU. Other lesions (i.e. heterogeneous, thick/irregular wall, mural nodule, septations, 21 to 69 HU) should undergo further imaging (preferably MR).[201] This pertains to lesions that do not contain fat and lesions that are either completely characterized or incompletely characterized but with sufficient benign features to forgo further evaluation. Lesions that contain fat (<-10 HU) require further investigation if they also contain calcification, are multiple, or >4 cm; others do not require investigation.[201]

Several comprehensive guidelines for management of thyroid disease have been published[202,203] but were not written from the perspective of screening for other purposes; a white paper from the incidental thyroid findings committee of the American College of Radiology is much more specific.[204] This group recommends no further investigation for nodules detected incidentally by CT that are <1.5 cm, in patients >35 years old, and that have no suspicious CT features (no invasion of local tissues by the thyroid nodule or abnormal lymph nodes – i.e. calcifications, cystic components, and/or increased enhancement).[204] Nodules >1.5 cm or with suspicious features should undergo ultrasound. Ultrasound is much better at identifying features suspicious for malignancy; suspicious nodules by US should undergo FNA, others can be followed be serial US.[202,203] This approach can markedly decrease the number of patients needing further investigation, with indirect evidence that there is no clinically relevant effect on long term outcomes.[204] Of note, the thyroid guidelines do not recommend screening for thyroid nodules, even in patients with familial high risk.[202]

An enlarged adrenal is a common incidental CT finding; a taskforce has developed management recommendations .[205] Lesions that are <1 cm or have fat density (<10 HU) need no further investigation. Lesions of 1-2 cm with >10 HU should be re-imaged in a year. Larger lesions should receive dedicated imaging and possible biopsy.[205] Most biliary system findings are of no significance in asymptomatic patients; polyps ≥7 mm warrant ultrasound, and biliary duct dilation warrants consideration of serum bilirubin and alkaline phosphatase levels.[206] The ACR incidental findings committee recommends further investigation of all pancreatic cysts with benign features (absence of mural nodule, thickening or

ductal dilation).[207] Most often this involves serial imaging, the frequency depending on the size, age and communication with the main pancreatic duct. Homogeneous, thin walled splenic lesions require no further investigation.[208]

The evaluation of incidental findings accounts for about 50% of the reimbursement from LDCT screening.[65,66,180] Studies have estimated that costs arising from additional investigations of incidental findings amount to about $10-20 US dollars per screened individual at baseline;[65,66,209] when the reimbursement for interventions is included, it is approximately $400 per screened individual.[180]

15. We suggest that low-dose CT screening programs develop strategies to guide the management of non-lung 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 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 non-lung nodule findings by the screening program. Clear communication between providers is important to prevent misunderstandings about who will assume responsibility for evaluation of these findings.

Remark: The description of non-lung nodule findings in the structured reports should be standardized to assist with interpretation of the findings.

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 helps 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. While there are various approaches to lung nodule management, important elements of data collection include the number of surveillance and diagnostic imaging studies, non-surgical 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 Table 17 and Table 18. Soon, process and outcome quality indicators will be available to further guide programs about the collection and use of their data.

16. 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 with selecting individuals to screen and implementing 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, with literature reviews every 3 months, and editing of the guideline when new evidence suggests recommendations and suggestions should change.

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Table 1: COI Grid

Recommendation or Suggestion	TC	FD	JK	HK	PM	GS	LS	RW
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 recommend that annual screening with low-dose CT should be offered. (Strong recommendation, moderate-quality evidence)	none	none	none	none	none	none	none	none
2. For asymptomatic smokers and former smokers who do not meet the smoking and/or age criteria in Recommendation #1, are age 50 to 80, have smoked 20 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)	none	none	none	none	none	none	none	none
3. For asymptomatic smokers and former smokers who do not meet the smoking and/or age criteria in Recommendations #1 and 2 but are projected to have a high net benefit from lung cancer screening based on the results of validated clinical risk prediction calculations and life expectancy estimates, or based on life-year gained calculations, we suggest that annual screening with low-dose CT should be offered. (Weak recommendation, moderate quality evidence)	Developed models included in the development of this recommendation.	none	none	Developed models included in the development of this recommendation.	none	none	none	none
4. For individuals who have accumulated fewer than 20 pack years of smoking or are younger than age 50 or older than 80, or have quit smoking more than 15 years ago, and are not projected to have a high net benefit from lung cancer screening based on clinical risk prediction or life-year gained calculators, we recommend that low dose CT screening should not be performed. (Strong recommendation, moderate-quality evidence)	none	none	none	none	none	none	none	none
5. For individuals with comorbidities that substantially limit their life expectancy and adversely influence their ability to tolerate the evaluation of screen detected findings, or tolerate treatment of an early stage screen detected lung cancer, we recommend that low-dose CT screening should not be performed. (Strong recommendation, low-quality evidence)	none	none	none	none	none	none	none	none

6. 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)	none	none	none	none	none	none	none	none
7. 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)	none	none	none	none	none	none	none	none
8. 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)	none	none	none	none	none	none	none	none
9. We suggest that low-dose CT screening programs develop strategies to maximize compliance with annual screening exams and evaluation of screen-detected findings. (Ungraded Consensus-Based Statement)	none	none	none	none	none	none	none	none
10. We suggest that low-dose CT screening programs develop a comprehensive approach to lung nodule management that includes access to 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)	none	none	none	none	none	none	none	none
11. We suggest that low-dose CT screening programs develop strategies to minimize overtreatment of potentially indolent lung cancers. (Ungraded Consensus-Based Statement)	none	none	none	none	none	none	none	none
12. 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)	none	none	none	none	none	none	none	none
13. 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)	none	none	none	none	none	none	none	none
14. We suggest that low-dose CT screening programs use a structured reporting system to report the exam results. (Ungraded Consensus-Based Statement)	none	none	none	none	none	none	none	none

15. We suggest that low-dose CT screening programs develop strategies to guide the management of non-lung nodule findings. (Ungraded Consensus-Based Statement)	None	None	None	None	none	none	none	none
16. 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)	none	none	none	none	none	none	none	none
All Disclosures	Research grant from Genentech Corporate Giving Scientific Program	Data Safety Monitoring Board – Olympus-Spiration; Medical consultancy for Medala	Medical consultancy for Parexel Informatics; Legal Testimony – Drug-related lung toxicity; Royalties - Humana Press, Elsevier – Book Author	none	Research Grants – Veracyte, Onocyte, Tencent, SEER, Exact Sciences, MagArray Editor in Chief - CHEST	Grants – Aries Pharma, Exact Sciences, Veran, Inc, Auris Inc, Olympus	none	Employment – American Thoracic Society Associate Documents Editor

Table 2: PICO Questions

Study Characteristic	Inclusion Criteria	Exclusion Criteria
1. What is the rate of death from lung cancer (i.e. lung cancer mortality) among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared to 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 Low-dose CT (LDCT)	
Comparators	Chest radiograph (CXR) Sputum analysis No Screening	None
Outcomes	Rate of death from lung cancer (i.e. lung cancer mortality)	None
Study Design	Systematic Reviews, RCT, Observational	Case series/reports
2. What is the rate of death from lung cancer (i.e. 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 to 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 Low-dose CT (LDCT)	
Comparators	Chest radiograph (CXR) Sputum analysis No Screening	None
Outcomes	Rate of death from lung cancer (i.e. 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 to 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 Low-dose CT (LDCT)	
Comparators	Chest radiograph (CXR) 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 to 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 Low-dose CT (LDCT)	
Comparators	Chest radiograph (CXR) 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	
5. What is the rate of surgery for benign disease among individuals at elevated risk of lung cancer who undergo screening with LDCT, compared to 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 Low-dose CT (LDCT)	

Comparators	Chest radiograph (CXR) 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 to 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 Low-dose CT (LDCT)	
Comparators	Chest radiograph (CXR) 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 to 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 Low-dose CT (LDCT)	
Comparators	Chest radiograph (CXR) 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 to 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 Low-dose CT (LDCT)	
Comparators	Chest radiograph (CXR) 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 to 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
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 to 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 (i.e. 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 to 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 4mm	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 a LDCT screening program, compared to those who do not receive smoking cessation counseling, and compared to 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 a 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

Table 3: Summary of Design of Included Randomized Controlled Trials

Study	Sample Size	Age (years)	Smoking History	Smoking Cessation (years since quit)	Screening Interval and Duration	Follow-up (years)	Definition of Positive Scan
LDCT vs CXR							
LSS (NLST feasibility)[15,38,210]	3,258	55 - 74	≥30 pack-years	<10	2 annual screens	5.2 (median)	≥4mm
NLST[20,21,211]	53,454	55-74	≥30 pack-years	≤15	3 annual screens	6.5 (median)	≥4mm
Dépiscan[36]	765	50-75	≥15 cigarettes/day for ≥20yrs	<15	3 annual screens	NR	>5mm
LDCT vs Usual Care (no screening)							
DANTE[17,212,213]	2472 men	60-74	≥20 pack-years	<10	5 annual screens; baseline CXR for both study arms	8	>5mm
DLCST[18,42,214,215]	4104	50-70	≥20 pack-years	<10	5 annual screens	10	>15mm or rapid growing 5-15mm nodules (>25% increase in volume on 3 month repeat CT)
DLCST post-hoc analysis[57]	4,104	50 - 70	≥20 pack-years	<10	4 annual scans	10.5 (mean)	NR
NELSON[14,22,113]	15,774	50 - 75	≥15 cigarettes/day for ≥25yrs or ≥10 cigarettes/day for ≥30yrs	<10	4 screening rounds; interval after baseline: 1 year, 2 years, 2.5 years	10	Volume >500mm^3 or volume 50-500mm^3 with VDT <400 days on 3 month repeat CT
ITALUNG[19,39,216]	3206	55-69	≥20 pack-years	≤10	4 annual screens	6	≥5mm solid nodule, a ground glass nodule ≥10mm, or any part-solid nodule
MILD[16,32,115]	4,099	≥49	≥20 pack-years	<10	5 annual screens and 3 biennial screens combined	10	Volume >250mm^3 or rapid growing 60-250mm^3 (>25% increase in volume on 3 month repeat CT)

Study	Sample Size	Age (years)	Smoking History	Smoking Cessation (years since quit)	Screening Interval and Duration	Follow-up (years)	Definition of Positive Scan
LUSI[13,217,218]	4,039	50 - 69	≥15 cigarette/day for ≥25yrs or ≥10 cigarette/day for ≥30yrs	<10	5 annual scans	8.8 (mean)	≥5mm
UKLS[44,219]	4055	50-75	LLPv2 risk ≥5%		One screen	10	Volume >500mm^3 or volume 50-500mm^3 with VDT <400 days on 3 month repeat CT

Abbreviations: CT, computed tomography; LLPv2, Liverpool Lung Project lung cancer risk prediction algorithm version 2; mm, millimeter; VDT, volume doubling time; yrs, years.

Table 4: Results from Included Randomized Trials

Study	No. Randomized	Age, median (years)	Male (%)	Pack-years, median	Active Smokers (%)	Positive Scans[A] at T_0	Positive Scans[A] by end of Screening Period	LC Mortality, RR/HR (95% CI)
LDCT vs CXR								
LSS (NLST feasibility)[15]	3,258	NR	NR	NR	NR	NR	NR	RR, 1.24; 0.74-2.08
NLST[20,21,211]	53,454	61	59	48	48.1	n=7,191, 27.3%	n=10,287, 39.1%	RR, 0.85; 0.75-0.96
Dépiscan[36]	765	56	71	30	64	24%	NR	NR
LDCT vs Usual Care (no screening)								
DANTE[17,212]	2,472	64.6	100	45	56	n=199, 15.6%	n=471, 37%	RR, 1.01; 0.70-1.44
DLCST[18,214]	4,104	58	55	36	75.3	n=155, 7.6%	n=241, 11.8%	RR, 1.03; 0.66-1.60
NELSON[14]	15,789	58	83.6	38	56.0	Men Positive: n=147, 2.3% Indeterminate: n=1241, 19.7%	Men Positive: n=467, 2.1% Indeterminate: n=2069, 9.2%	Men: RR, 0.76; 0.61-0.94; p=0.01 Women: RR, 0.67; 0.38-1.14
ITALUNG[19]	3,206	61	64	40	66	n=426, 30.3%	n=1,044, 46.1%[B]	RR, 0.70; 0.48-1.04
MILD[16]	4,099	58	68.4	39	68.6	n=335, 1.4%	NR	HR, 0.61; 0.39-0.95; p=0.02
LUSI[13]	4,052	55	64.7	36	61.9	n=451, 22.2%	n=816, 8.7%	HR, 0.74; 0.46-1.19; p=0.21
UKLS[44]	4,055	67	75	NR	39	n=536, 26.9%[C]	NA	NR

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable; NR, not reported; RR, relative risk.

Footnotes:

A. For all RCTs, except NELSON, this represents number of patients with positive scans. In NELSON, this represents number of positive scans. See prior table for definition of positive scan in each study.
B. 1,044 refers to total number of positive scans for T0-T4; unable to determine if this excludes positive results from the baseline (T0) screen.
C. single screen trial; if follow-up imagining at 1 year was included, value would be 1,015 (50.9%).

Table 5: Summary of Design of Included Cohort Studies

Study	Sample Size	Age (years)	Smoking History (pack-years)	Smoking Cessation (years since quit)	Number of Screens	Planned Follow-up (years)	Definition of Positive Scan
Bastarrika et al, 2005[35]	911	≥40	≥10	NR	2	NR	≥5mm
Callol et al, 2007[37]	482	>50	≥10	<0.5	2	NR	≥5mm

Study	Sample Size	Age (years)	Smoking History (pack-years)	Smoking Cessation (years since quit)	Number of Screens	Planned Follow-up (years)	Definition of Positive Scan
Diederich et al, 2004[33]	817	≥40	≥20	NR	6	6	All nodules
Henschke et al, 2000[45,220-222]	1,000	≥60	≥10	NR	3	10	≥6mm
Kang et al, 2019[221]	28,807	40 - 75	Ever smokers: NR Never smokers: none	NR	1	2.21 (median)	≥3mm
Leleu et al, 2020[223]	1,307	55 - 74	≥30	<15	Varied, annual to age 75 or <15y since quit	NR	Positive: ≥10mm or <400d doubling time at 3 month CT repeat
MacRedmond et al, 2006[40]	449	50-74	≥10	NR	2	2	All nodules
Menezes et al, 2010[224]	3,352	≥50	≥10	NR	6	NR	Solid nodule ≥5mm, or non-solid nodule ≥8mm
Nawa et al, 2019[225]	25,385	≥50	NR	NR	NR	5.7	NR
Novello et al, 2005[226]	520	≥55	≥20	<10	5	NR	≥5mm
Ostrowski et al, 2019[227]	14,183	50 - 79	≥20 or ≥30	NR	1	NR	≥10mm or >500mm^3 or <400d doubling time
Pastorino et al, 2003[41]	1,035	≥50	≥20	NR	5	NR	>5mm
Picozzi et al, 2005[228]	60	≥50	≥20	NR	3	3	≥10mm
Shields et al, 2020[229]	4,170	NR	NR	NR	1	NR	≥4mm
Sobue et al, 2002[28]	1,682	≥40	≥20	NR	10	NR	>4.9mm
Swensen et al, 2003[183]	1,520	≥50	≥20	<10	5	5	>8mm
Veronesi et al, 2008[34]	5,201	≥50	≥20	<10	5	NR	>5mm
White et al, 2020[230]	962	55 - 80	≥30	<15	1	NR	≥4mm
Wilson et al, 2008[43]	3,755	50-79	≥12.5	<10	2	3	≥10mm

Abbreviations: CT, computed tomography; d, day; mm, millimeter; NR, not reported.

Table 6: 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.

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
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.

Table 7: Implications of strong and weak recommendations for different users of guidelines

	Strong Recommendation	Conditional (weak) Recommendation
For patients	Most individuals in this situation would want the recommended	The majority of individuals in this situation would want the suggested

	Strong Recommendation	**Conditional (weak) Recommendation**
	course of action and only a small proportion would not.	course of action, but some would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Table 8: GRADE Profiles for Recommendation Statements 1 through 5

Table 8a. Lung Cancer Mortality

Quality Assessment							Summary of Findings				Quality	Importance
							Events / No. of patients screened		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	LDCT	CXR / usual care	Relative (95% CI)	Absolute (95% CI)		
Lung Cancer Mortality – LDCT vs CXR or usual care (Key Question 1)												
8[13-20]	RCT	Serious [A]	Not serious	Not serious [B]	Not serious	None	779/45,546 (1.7%)	944/44,838 (2.1%)	RR 0.81 (0.74 to 0.89)	4 fewer per 1,000 (from 5 fewer to 2 fewer)	MODERATE	CRITICAL[C]
Lung Cancer Mortality – LDCT vs CXR or usual care, based on clinical phenotypes (Key Question 2)												
5[18,21,23-25]	Mixed (2 RCT, 3 OS)	Serious [D]	Not serious	Not serious	Serious [E]	None	**Gender** Female, RR 0.73 vs Male, RR 0.92; p=0.08[21] **Race** Black, RR 0.61 vs White, RR 0.86; p=0.29[24] **Age** <65, RR 0.82 vs ≥ 65, RR 0.87; p=0.60[21,23] **Smoking History** <35 pack years, RR 1.26 vs ≥ 35 pack years, RR 0.92; p=0.52[18] **COPD** Positive, RR 0.85 vs negative, RR 1.38; p=0.30[18]				LOW	CRITICAL

Table 8b. LDCT Screening Harms

Quality Assessment							Summary of Findings		Quality	Importance
							Events / No. of procedures	Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Ratio (raw %)	Proportion per 1,000 procedures (95%CI)		
LDCT Screening Harms – Adverse events (not including death) from biopsy (Key Question 3)										
11[18-20,33,34,116,212,214,215,227,231]	Mixed (5 RCT, 6 OS)	Serious [F]	Not serious	Not serious	Not serious	None	Major complications from invasive procedure[19,33,215] 92/2,190 (4.2%)	41.6 (33.2 to 49.9)	MODERATE	CRITICAL
LDCT Screening Harms – Death following invasive procedure (Key Question 3)										
6[20,33,34,212,215,231]	Mixed (5 RCT, 1 OS)	Serious [F]	Not serious	Not serious	Not serious	None	19/2,405 (0.8%)	7.7 (4.2 to 11.2)	MODERATE	CRITICAL
LDCT Screening Harms – Surgery for benign disease (Key Question 5)										
17[17,20,28,32-45]	Mixed (8 RCT, 9 OS)	Serious [F]	Not serious	Not serious	Not serious	None	314/1,431 (22%)	219.5 (172.0 to 267.0)	MODERATE	CRITICAL
LDCT Screening Harms – Psychological impact and quality of life (Key Question 6)										

Quality Assessment							Summary of Findings		Quality	Importance
							Events / No. of procedures	Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Ratio (raw %)	Proportion per 1,000 procedures (95%CI)		
5[46-50]	Mixed (2 RCT, 3 OS)	Serious [G]	Serious [H]	Not serious	Not serious	None	Studies suggest that finding a screen-detected nodule may transiently increase distress, but does not adversely affect anxiety level or quality of life		LOW	IMPORTANT
LDCT Screening Harms – Overdiagnosis (Key Question 7)										
2[52,57]	RCT	Serious [I]	Not serious	Not serious	Not serious	None	All lung cancers Range, 18.5% to 67.2%	185 to 672	MODERATE	CRITICAL

Table 8c. CXR Screening Harms

Quality Assessment							Summary of Findings		Quality	Importance
							Events / No. of procedures	Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Ratio (raw %)	Proportion per 1,000 procedures (95%CI)		
CXR Screening Harms – Adverse events (not including death) from biopsy (Key Question 3)										
1[20]	RCT	Not serious	Not serious	Not serious	Serious [J]	None	24/758 (3.2%)	31.7 (19.2 to 44.1)	MODERATE	CRITICAL
CXR Screening Harms – Death following invasive procedure (Key Question 3)										
1[20]	RCT	Not serious	Not serious	Not serious	Not serious	None	10/758 (1.3%)	13.2 (5.1 to 21.3)	HIGH	CRITICAL
CXR Screening Harms – Surgery for benign disease (Key Question 5)										
3[17,20,38]	RCT	Serious [K]	Not serious	Not serious	Not serious	None	56/278 (20.1%)	218.9 (105.3 to 332.6)	MODERATE	CRITICAL

Table 8d. LDCT Screening Eligibility Based on Risk Assessment Tools [L]

Quality Assessment							Summary of Findings		Quality	Importance
							Events / No. of procedures	Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Ratio (raw %)	Proportion per 1,000 procedures (95%CI)		
LDCT Eligibility – Lung cancer detection using risk assessment tools (Key Question 9)										
8[72,73,91,92,110,111,232,233]	MS	Very serious [M]	Not serious	Not serious	Not serious	None	Studies suggest that risk prediction and life-year gained calculators may predict patient who would experience a high net benefit from lung cancer screening		LOW	CRITICAL

Abbreviations (Table 8a-8d): CI, confidence interval; CXR, chest x-ray; LDCT, low-dose CT; MS, modeling study; No., number; OS, observational study; RCT, randomized controlled trial; RR, risk ratio.

Footnotes:

A. NLST and NELSON trials carried an overall low risk of bias, while the other six screening trials were limited by an overall unclear risk of bias. Unclear randomization in three studies and unclear allocation concealment in five studies. Two of the studies were rated as high risk of bias for baseline differences across groups and two studies were rated at high risk of bias for incomplete outcome date. All six studies with unclear risk of bias were also underpowered to detect a difference in the outcome of interest.
B. Recommendation 5 is based on studies informing all PICOs included in the profiles. Since the target patient population for Recommendation 5 was excluded from the screening trials based on their comorbidities, evidence from the trials has been downgraded for indirectness for this recommendation. There is no evidence of screening benefit in these patients and the panel has concluded that harms of screening would outweigh any possible downstream benefit.
C. Although several outcomes representing the harms of LDCT screening are rated as 'Critical', the lung cancer mortality outcome carries the most weight in the aggregate quality assessment for recommendation statements 1 through 4.
D. NLST carried a low risk of bias and DLCST carried an unclear risk. Post-hoc analyses for NLST carried a moderate overall risk of bias. The post-hoc analyses include many of same patient but stratified based on different characteristics. The aggregate serious risk of bias is also based on this confounding factor.
E. Low number of events. The NLST and DLCST trials were underpowered to detect a difference in the outcome of interest in these subgroups.
F. Included RCTs carried an overall low and unclear risk of bias. Observational studies were limited by moderate risk of selection, detection and/or reporting bias.
G. Both RCTs carried an overall unclear risk of bias based on unclear allocation concealment and blinding of outcome assessors. Observational studies were limited by an overall moderate risk of bias in patient selection and reporting domains.
H. Psychological impact was variable across the identified studies. Although this may be due to differences in assessment tools, domains, and follow-up times, the correlation is unclear, and evidence has been downgraded for this domain.
I. Post-hoc analyses for NLST and DLCST carried an overall unclear risk of bias.
J. Downgraded for a wide 95% confidence interval.
K. NLST carried an overall low risk of bias, while DANTE and LSS were limited by an overall unclear risk of bias.
L. Recommendations 3-5 include these studies in their evidence bases. For Recommendations 3 and 4, lung cancer mortality as reported in the LDCT screening trials carries the most weight in the aggregate quality assessment.
M. Risk of bias in modeling studies was assessed using the ROBINS-I tool[4] with the model/calculator defined as the intervention being tested in LDCT screening cohort patients. Identified studies were limited by a risk of selection bias as the models were retrospectively applied to the LDCT cohorts. Additionally, these studies focus on mortality benefits alone and not the harms associated with screening.

Table 9: Summary of Meta-Analyses of Lung Cancer Mortality Reduction

Comparison	Pooled Risk Ratio (RR; 95% CI)	Overall Effect [A]
Lung cancer mortality for LDCT by comparator		
LDCT vs usual care or no screening or CXR	0.81; 0.74-0.89	**p<0.001**
LDCT vs CXR	0.95; 0.61-1.46	p=0.80
LDCT vs usual care or no screening	0.79; 0.69-0.90	**p<0.001**
Lung cancer mortality for LDCT (vs. usual care) by screening protocol		
Annual screening	0.86; 0.70-1.06	p=0.15
Other (non-annual) protocol	0.74; 0.62-0.88	**p<0.001**
Lung cancer mortality for LDCT (vs. usual care or CXR) by screening protocol		
Annual screening	0.85; 0.74-0.98	**p=0.03**
Other (non-annual) protocol	0.74; 0.62-0.88	**p<0.001**
Lung cancer mortality for LDCT (vs. usual care) by age of screening initiation		
Beginning at age 50y	0.77; 0.66-0.90	**p<0.01**
Beginning at age 55y	0.71; 0.48-1.04	p=0.08
Beginning at age 60y	1.01; 0.70-1.44	p=0.97
Lung cancer mortality for LDCT (vs usual care or CXR) by age of screening initiation		
Beginning at age 50y	0.77; 0.66-0.90	**p<0.01**
Beginning at age 55y	0.84; 0.66-1.07	p=0.16
Beginning at age 60y	1.01; 0.70-1.44	p=0.97
Lung cancer mortality for LDCT (vs usual care or CXR) by age of screening cessation		
Screening until age 69-71	0.80; 0.62-1.02	p=0.08
Screening until age 74/75	0.82; 0.72-0.94	**p=0.005**
Lung cancer mortality for LDCT (vs. usual care) by gender		
Male	0.82; 0.70-0.98	**p=0.03**
Female	0.54; 0.27-1.08	p=0.08
Lung cancer mortality for LDCT (vs. usual care or CXR) by gender		
Male	0.88; 0.78-0.98	**p=0.02**
Female	0.69; 0.54-0.89	**p<0.01**

A. A p-value less than 0.05 (bolded) is considered statistically significant and indicates a lung cancer mortality reduction with LDCT.

Table 10: Summary of biopsies in included randomized controlled trials

Study	Non-surgical biopsy/ procedure	Non-surgical biopsy/ procedure with benign result	Surgical procedure	Surgical procedure with benign result	Complications from invasive procedure	Death after invasive procedures [A]
LDCT vs CXR						
LSS (NLST feasibility)[38]	n=29	n=16, 55.1%	n=46	n=18, 39.1%	NR	NR
NLST[20,21,211]	n=993	n=293	n=673	n=164, 24.4%	n=84[B]	n=16
Dépiscan[36]	NR	NR	n=9	n=3, 33.3%	NR	NR
LDCT vs Usual Care (no screening)						
DANTE[17,212]	NR	NR	n=90	n=17, 18.9%	NR	NR
DLCST[18,214]	NR	NR	n=25	n=7, 28.0%	n=4[C], 0.2%	NR
NELSON[14]	NR	NR	NR	NR	NR	NR
ITALUNG[19]	n=38	n=1, 2.6%	n=38	n=4, 10.5%	NR	n=6, 3.7%
MILD[32 D]	NR	NR	n=45	n=4, 8.9%	NR	NR
LUSI[13]	n=90	NR	NR	NR	NR	NR
UKLS[44]	NR	NR	n=39	n=4, 10.3%	NR	NR

Abbreviations: NR, not reported.

Footnotes:

A. Death after invasive procedures refers to mortality following and 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 (CVA)/stroke, congestive heart failure (CHF), death, hemothorax requiring tube placement, myocardial infarction, respiratory arrest, bronchial stump leak requiring tube thoracostomy or other drainage for more than 4 days, wound dehiscence, empyema, injury to vital organ or vessel, prolonged mechanical ventilation over 48 hours post-operatively, thromboembolic complications requiring intervention, chylous fistula, brachial plexopathy, lung collapse, infarcted sigmoid colon.
C. Major complications include: empyema, myocardial infarction.
D. Data reported in the 5-year MILD follow-up publication[31] are included here. Although the 10-year follow-up publication[15] reports on the number of surgical procedures and number of these procedures with benign results, it is not possible to determine if the reported data is for the cumulative 10 years, or if data represents procedures for years 5 through 10.

Table 11: GRADE profiles for Recommendation 8

Quality Assessment							Summary of Findings	Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
Lung cancer detection based on nodule size threshold (Key Question 11)									
6[138-143]	Mixed (1 RCT, 5 OS)	Very serious [A]	Not serious	Not serious	Not serious	None	Studies suggest that a positive finding on LDCT, defined as a solid or part-solid lung nodule of 4-6mm, may provide the fewest false positives paired with the fewest false negatives	LOW	CRITICAL

Abbreviations: CI, confidence interval; OS, observational study; CXR, chest x-ray; LDCT, low-dose CT; No., number; RCT, randomized controlled trial; RR, risk ratio.

Footnotes:

A. The NLST carried an overall low risk of bias. Of the five observational studies, two were retrospective analyses using NLST data, one was a retrospective analysis using I-ELCAP data, and two were post-hoc analyses using NELSON data. The observational studies were limited by moderate or critical risk of selection bias, moderate risk of reporting bias, and/or moderate risk of detection bias. In addition, the NELSON post-hoc analyses included some of the same patients.

Table 12: GRADE profiles for Recommendation 12

Quality Assessment							Summary of Findings				Quality	Importance
							Cessation events / No. of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Tobacco cessation program	Usual care	Relative (95% CI)	Absolute (95% CI)		
Rate of smoking cessation (Key Question 12)												
4[163-166]	4 RCT	Serious [A]	Serious [B]	Not serious	Not serious	None	760/4,184 (18.2%)	649/4,389 (14.8%)	RR 1.22 (1.03 to 1.44)	33 more per 1,000 (from 4 more to 65 more)	LOW	CRITICAL

Abbreviations: CI, confidence interval; OS, observational study; CXR, chest x-ray; LDCT, low-dose CT; No., number; RCT, randomized controlled trial; RR, risk ratio.

Footnotes:

A. Post-hoc analyses of DLCST and ITALUNG carried an overall unclear risk of bias based on unclear randomization in ITALUNG and unclear allocation concealment in both. Post-hoc analyses of UKLS and NELSON only included samples of the entire cohort and were limited by selection bias and reporting bias.
B. Analyses of ITALUNG, UKLS, and NELSON data demonstrated a significant benefit with tobacco cessation programs in patients enrolled in the LDCT arm of screening trials, while the analysis from DLCST did not report a significant difference between patients in LDCT and usual care arms.

Table 13: Program personnel

Discipline	**Potential Roles**
Primary Care Providers	Identify eligible patients, order screening, SDM visit, manage results, smoking cessation
Radiologists	Imaging protocols, results reporting, data reporting, program management, education
Pulmonary/IP	Identify eligible patients, order screening, program management, SDM visit, nodule evaluation, manage results, smoking cessation, data reporting, education
Thoracic Surgery	Nodule evaluation, cancer care
Other subspecialists	Manage other findings, cancer care
Advanced practice provider	SDM visit, manage results, smoking cessation
Administrator	Infrastructure support
Marketing	Program awareness, education
Billing	Billing compliance, financial data
Scheduling	Schedule coordination
EHR/IT specialist	Order sets, structured reports, and registries; assist with test follow-up, quality management, and data reporting

Table 14: Scanner requirements

Multidetector helical CT scanner (≥ 16 detector rows preferred)
Gantry rotation ≤ 0.5 seconds
Slice thickness ≤ 2.5 mm (≤ 1.25 mm preferred)
Scanner or viewing platform able to generate multiplanar reformations (MPRs) and maximum intensity projections (MIPs)
Acquisition parameters:
Suspended full inspiration
Entirety of lungs covered (apices to costophrenic sulci)
100-140 kVp
Appropriate mA and use of automatic exposure control (AEC)
Thin collimation
Appropriate table increment and gantry rotation to minimize helical and motion artifacts
Image reconstruction parameters:
Slice thickness ≤ 2.5 mm (≤ 1.25 mm preferred)
Reconstruction interval ≤ slice thickness
High spatial frequency reconstruction kernel
FOV to include entirety of lungs
Sagittal and coronal reformations (recommended)
Axial 8-10 mm MIPs (recommended)

Table 15: Potential categorization of non-nodule findings

Category	Incidence[A]	Likely next step	Examples
Not clinically relevant	50%	No directed investigation necessary	Mild-moderate coronary artery calcification,[B] emphysema, bronchial wall thickening, skeletal degenerative changes, liver cyst(s), renal cyst(s), hiatal hernia, focal atelectasis, mild mod aortic dilation, pleural plaques, pulmonary fibrosis, adrenal lesions <10 HU, other diaphragmatic hernia, bronchiectasis, low risk thyroid nodule[C], renal stone, gallstone, pancreatic cyst, splenic cyst
Possibly clinically relevant	10%	Further investigation may be indicated	adrenal lesions >10 HU, mediastinal adenopathy (>1 cm), compression fracture, breast nodule, suspicious thyroid nodule[c], pancreatic cyst, moderate-severe coronary artery calcification,[B] aortic aneurysm 4-5.5 cm

Category	Incidence[A]	Likely next step	Examples
Clinically concerning	<1%	Therapeutic intervention may be indicated	pneumonia, aortic aneurysm ≥5.5 cm, mass or lesion suspicious for malignancy (e.g. bone destruction), segmental/lobar atelectasis, large pleural effusion, large pericardial effusion

Examples are ordered according to reported frequency[65,66,131,180,181,190] This should not be considered a comprehensive list.

Footnotes:

A. Estimated
B. Although significant Coronary artery calcification is associated with increased risk of cardiovascular events, there is insufficient evidence that investigation or intervention is of benefit in asymptomatic patients.
C. Low risk thyroid nodule (by CT) is defined as <1.5 cm without evidence of tissue invasion or node enlargement

Table 16: Overview of guidelines related to non-nodule findings

Site (reference)	Source	Level of Evidence	Population[A]	No Further Investigation Recommended for:	Consider Further Investigation Recommended for:
Coronary Artery calcification[193-197]	ACC, AHA, ESC, SCCT, STR	Guideline	general population	Most patients - unless deemed helpful by primary care physician for specific patients;	Formal Coronary Calcification can be a minor factor in borderline cases regarding primary prevention; this decision rests with the primary care physician - note that absence of calcification may be more impactful
Aortic enlarge-ment[199]	ACCF, AHA	Guideline	general referral population (no high familial risk)	diameter <3.5 cm	Consider annual surveillance imaging if 3.5-4.5 cm, biannual if 4.5-5.4 cm consider therapeutic intervention if ≥5.5 cm
Liver[200]	ACR	Consensus, indirect	general population >40 [B]	< 1.5 cm, or any size with benign features (sharply marginated, homogeneous, < 20 HU)	MR or CT with IV contract if ≥1.5 cm and suspicious features (ill-defined margin)
Renal[201]	ACR	Consensus, indirect	general population	Small (TSTC), homogeneous and either -10 to 20HU or >70 HU; <-10 HU but solitary, no calcification, <4 cm	MR if 21-69 HU or heterogeneous (thickening, nodularity, calcification, septations) or if <-10 HU with calcifications, multiplicity or >4 cm
Thyroid[204]	ACR	Consensus, indirect	general population of adults >35	< 1.5 cm and no lack suspicious features	US±FNA if >1.5 cm or suspicious (invasion of local tissues or abnormal lymph nodes – i.e. calcifications, cystic components, and/or increased enhancement)
Adrenal[205]	ACR	Consensus, indirect	general population	<1 cm, or 1-4 cm but <10 HU, known to be stable for ≥ 1 year,	CT in 1 year if 1-2 cm, >10 HU, dedicated cm CT, MR if 2-4 cm and >10 HU if >4 cm, consider biopsy, resection, PET
Pancreas cyst[207]	ACR	Consensus, indirect	general population	none	serial imaging if benign features: every 4-24 mo depending on size (<1.5, 1.5-2.5, >2.5 cm) and age (< or ≥65) EUS/FNA if mural nodule, thickening, duct dilation (for any size cyst) more active workup (image every 4 mo or EUS/FNA) if no communication with main pancreatic duct
Biliary system[206]	ACR	Consensus, indirect	asymptomatic general population	Gallstones, GB wall calcification, GB sludge, GB wall thickening, polyps ≤6 mm, GB distention	consider LFT if there is biliary duct dilation, yearly US surveillance of polyps 7-9 mm; consider cholecystectomy for polyps ≥10 mm

Site (reference)	Source	Level of Evidence	Population[A]	No Further Investigation Recommended for:	Consider Further Investigation Recommended for:
Spleen[208]	ACR	Consensus, indirect	asymptomatic general population	Homogeneous, thin wall, <20HU	f/u imaging in 6-12 mo if indeterminate (heterogeneous, >20HU, smooth margins, enhancement) PET or FNA if suspicious (heterogeneous, irregular margins, enhancement, necrosis, parenchymal invasion)

Abbreviations: ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACR, American College of Radiology; AHA, American Heart Association; CT, computed tomography; ESC, European Society of Cardiology; EUS, endoscopic ultrasound; FNA, fine needle aspiration; GB, gallbladder; HU, Hounsfield units; IV, intravenous; LFT, liver function tests; MR, Magnetic resonance imaging; mo, months; PET, positron emission tomography; SCCT, Society of Cardiovascular Computed Tomography; STR, Society of Thoracic Radiology; TSTC, too small to characterize; US, ultrasound

Footnotes:

A. By definition these are incidental findings unless otherwise noted, implying that the patients are asymptomatic relative to the lesions addressed in the table. Entries in this table also exclude recommendations for patients that would not be eligible for lung cancer screening.
B. Excludes patients at high risk of developing liver cancer or a history of cancers likely to metastasize to the liver

Table 17: CMS Data Requirements

Data Type	Minimum Required Data Elements
Facility	Identifier
Radiologist	National Provider Identifier
Patient	Identifier
Ordering Practitioner	National Provider Identifier
CT Scanner	Manufacturer, Model
Indication	Lung cancer LDCT screening – absence of signs or symptoms of lung cancer
System	Lung nodule identification, classification and reporting system
Smoking history	Current status; Years since quit; Pack-years; Cessation interventions
Effective radiation dose	CT Dose Index (CTDIvol)
Screening	Screen date, initial screen or subsequent screen

Table 18: ACR National Registry data elements

LCSR Data Element	Required to submit a transaction
Transaction Header (Required)	
Transaction ID	Y
Transaction date time	Y
Number of exam included	Y
Facility ID	Y
Partner ID	Y
Application ID	Y
Previous transaction ID	N
Exam Data (Required)	
Exam_Unique_ID	N
Patient's first name	N
Patient's middle name	N
Patient's last name	N
Patient ID	Conditional

Refuesed to provide patient's social security number	N
Patient Social Security Number	Conditional
Refuesed to provide patient's medicare beneficiary ID	N
Medicare Beneficiary ID	Conditional
Patient's date of birth	N
Patient's date of death	N
How cause of death was determined	N
Other method of determining cause of death, specify	N
Cause of death	N
Non lung-cancer cause, specify	N
Invasive procedure within in the 30 days preceding date of death	N
Patient sex	N
Patient race	N
Patient ethnicity (Hispanic origin)	N
Health insurance	N
Smoking status	N
Number of packs-year of smoking	N
Number of years since quit	N
Did physician provide smoking cessation guidance to patient?	N
Is there documentation of shared decision making?	N
Patient height (inches)	N
Patient weight (lbs)	N
Other commorbidities listed on patient record that limit life expectancy	N
Other commorbidities, other specify	N
Cancer related history	N
Cancer related history, other specify	N
Radiologist (reading) NPI	N
Ordering practitioner first name	N
Ordering practitioner first name	N
Ordering practitioner NPI	N
Exam date	Y
Signs or symptoms of lung cancer	N
Indication of exam	N
Modality	N
CT scanner manufacturer	N
CT scanner model	N
CTDIvol (mGy)	N
DLP (mGy*cm)	N
Tube current-time (mAs)	N
Tube voltage (kV)	N
Scanning time (s)	N
Scanning volume (cm)	N
Pitch	N
Reconstructed image width (nominal width of reconstructed image along z-axis) (mm)	N
CT exam result by Lung-RADS category	N
Reason for recall	N

Other clinically significant or potentially significant abnormalities - CT exam result modifier S	N
What were the other findings	N
Mass, specify	N
Other interstitial lung disease	N
Other interstitial lung disease, specify	N
Prior history of lung cancer - CT exam result modifier C	N
Year since prior diagnosis of lung cancer	N
Education level	N
Education level, other	N
Radon exposure - documented high exposure levels	N
Occupational exposures to carcinogens targeting the lungs	N
History of cancers associated with an increased risk of developing a new primary lung cancer	N
History of cancers associated with an increased risk of developing a new primary lung cancer - other smoking-related cancers, specify	N
Lung cancer in first-degree relative	N
Family history of lung cancer, other than first-degree relative	N
COPD	N
Pulmonary fibrosis	N
Second hand smoke exposure	N
Follow-up Data	
Date of follow-up	Y
Follow-up diagnostic	Y
Follow-up diagnostic other, specify	N
Tissue diagnosis	N
Tissue diagnosis method	N
Location from which sample was obtained	N
Location other, specify	N
Histology	N
Histology - Non-small cell lung cancer	N
Other non-small cell lung cancer histology, specify	N
Stage - Clinical or pathologic?	N
Overall stage	N
T status	N
N status	N
M status	N

Figure 1. Literature Search Strategies

Key Questions 1-7, 10, 11, and 14

Embase

1. exp lung tumor/
2. (nsclc or sclc).ti,ab,kw.
3. (lung or lungs or bronchi$ or alveol$ or respiratory tract$ or bronchoalveolar).ti,ab,kw.
4. exp *lung/
5. (neoplasm$ or cancer or tumor or tumors or tumour or tumours or malignan$ or carcinoma$ or adenocarcinoma$ or lesion$ or blastoma$ or pneumoblastoma or nodule$).ti,ab,kw.
6. exp *neoplasm/
7. 3 or 4
8. 5 or 6
9. 7 and 8
10. 1 or 2 or 9
11. exp mass screening/
12. exp early diagnosis/
13. (screen$ or early detect$ or early diagnos$ or early discover$).ti,ab,kw.
14. (detect$ or surveillance).ti.
15. or/11-14
16. exp computer assisted tomography/
17. (computed tomograph$ or CT or spiral or helical).ti,ab,kw.
18. 16 or 17
19. (low dose or low radiation or low-dose or ultra-low-dose).ti,ab,kw.
20. screen$.ti.
21. exp early diagnosis/
22. or/19-21
23. 18 and 22
24. (ldct or ld-ct).ti,ab,kw.
25. 23 or 24
26. 10 and 15 and 25
27. limit 26 to (book or book series or chapter or conference abstract or conference proceeding or "conference review")
28. 26 not 27
29. (exp animal/ or nonhuman/) not exp human/
30. 28 not 29
31. limit 30 to English

MEDLINE

1. lung neoplasms/ or adenocarcinoma, bronchiolo-alveolar/ or nsclc.ti,ab. or nsclc.ot. or sclc.ot.
2. lung/ or lung.ti,ab. or bronchi*.ti,ab. or lung.ot. or lungs.ot. or bronchi*.ot. or alveol*.ot. or respiratory tract*.ot. or respiratory tract*.ti,ab. or pulmon*.ti,ab. or pulmon*.ot. or bronchoalveolar.ti,ab. or bronchoalveolar.ot.

3. neoplasms/ or neoplasm*.ti,ab. or cancer.ti,ab. or tumor.ti,ab. or tumors.ti,ab. or tumour.ti,ab. or tumours.ti,ab. or malignan*.ti,ab. or carcinoma*.ti,ab. or adenocarcinoma*.ti,ab. or lesion*.ti,ab. or blastoma*.ti,ab. or pneumoblastoma.ti,ab. or nodule*.ti,ab. or neoplasm*.ot. or cancer.ot. or tumor.ot. or tumors.ot. or tumour.ot. or tumours.ot. or malignan*.ot. or carcinoma*.ot. or adenocarcinoma*.ot. or lesion*.ot. or blastoma*.ot. or pneumoblastoma.ot. or nodule*.ot.
4. 2 and 3
5. 1 or 4
6. mass screening/ or early diagnosis/
7. screen*.ti,ab. or detect*.ti. or surveillance.ti. or early detect*.ti,ab. or early diagnos*.ti,ab. or early discover*.ti,ab. or screen*.ot. or detect.ot. or surveillance.ot. or early detect*.ot. or early diagnos*.ot. or early discover*.ot.
8. 6 or 7
9. Early Detection of Cancer/ or screen*.ti. or low dose.ti,ab. or low radiation.ti,ab. or low-dose.ti,ab. or ultra-low-dose.ti,ab. or screen*.ot. or low dose.ot. or low radiation.ot. or low-dose.ot. or ultra-low-dose.ot.
10. Tomography, X-Ray Computed/ or computed tomograph*.ti,ab. or CT.ti,ab. or spiral.ti,ab. or helical.ti,ab. or computed tomograph*.ot. or CT.ot. or spiral.ot. or helical.ot.
11. 9 and 10
12. (ldct or ld-ct).ti,ab. or ldct.ot. or ld-ct.ot.
13. 11 or 12
14. 5 and 8 and 13
15. animals/ not humans/
16. 14 not 15
17. limit 16 to English

Key Questions 8 and 9

Embase

1. exp lung tumor/
2. (nsclc or sclc).ti,ab,kw.
3. (lung or lungs or bronchi$ or alveol$ or respiratory tract$ or bronchoalveolar).ti,ab,kw.
4. exp *lung/
5. (neoplasm$ or cancer or tumor or tumors or tumour or tumours or malignan$ or carcinoma$ or adenocarcinoma$ or lesion$ or blastoma$ or pneumoblastoma or nodule$).ti,ab,kw.
6. exp *neoplasm/
7. 3 or 4
8. 5 or 6
9. 7 and 8
10. 1 or 2 or 9
11. exp computer assisted tomography/
12. (computed tomograph$ or CT or spiral or helical).ti,ab,kw.
13. 11 or 12
14. (low dose or low radiation or low-dose or ultra-low-dose).ti,ab,kw.
15. screen$.ti.

16. exp early diagnosis/
17. or/14-16
18. 13 and 17
19. (ldct or ld-ct).ti,ab,kw.
20. 18 or 19
21. exp risk assessment/
22. (Bach or Liverpool Lung Project or MyLungRisk or Spitz or Nutrition Examination Survey or MIcrosimulation SCreening Analysis or miscan or risk prediction or prediction model$ or risk assessment or risk model$ or mathematical tool or decision tool or risk stratification or patient selection or eligibility criteria or smoking or pack years or history or spirometry or (PLCO and model)).ti,ab,kw.
23. exp biological marker/
24. (biomarker$ or Autoantibodies or earlyCDT-test or Serum or plasma or microRNA or MSC test or Breath or Volatile organic compounds or hypermethylation or Blood based or Tissue based or Biofluid$ or sputum or SULF2 protein or C4d protein or urine or urinary protein or Telomere or P16 or MGMT or HYAL2 or FHIT or SFTPC or miR-21 or miR-486 or miR-375).ti,ab,kw.
25. or/21-24
26. 10 and 20 and 25
27. (exp animal/ or nonhuman/) not exp human/
28. 26 not 27
29. limit 28 to (book or book series or chapter or conference abstract or conference paper or conference proceeding or "conference review")
30. 28 not 29
31. limit 30 to English

MEDLINE

1. lung neoplasms/ or adenocarcinoma, bronchiolo-alveolar/ or nsclc.ti,ab. or nsclc.ot. or sclc.ot.
2. lung/ or lung.ti,ab. or bronchi*.ti,ab. or lung.ot. or lungs.ot. or bronchi*.ot. or alveol*.ot. or respiratory tract*.ot. or respiratory tract*.ti,ab. or pulmon*.ti,ab. or pulmon*.ot. or bronchoalveolar.ti,ab. or bronchoalveolar.ot.
3. neoplasms/ or neoplasm*.ti,ab. or cancer.ti,ab. or tumor.ti,ab. or tumors.ti,ab. or tumour.ti,ab. or tumours.ti,ab. or malignan*.ti,ab. or carcinoma*.ti,ab. or adenocarcinoma*.ti,ab. or lesion*.ti,ab. or blastoma*.ti,ab. or pneumoblastoma.ti,ab. or nodule*.ti,ab. or neoplasm*.ot. or cancer.ot. or tumor.ot. or tumors.ot. or tumour.ot. or tumours.ot. or malignan*.ot. or carcinoma*.ot. or adenocarcinoma*.ot. or lesion*.ot. or blastoma*.ot. or pneumoblastoma.ot. or nodule*.ot.
4. 2 and 3
5. 1 or 4
6. Early Detection of Cancer/ or screen*.ti. or low dose.ti,ab. or low radiation.ti,ab. or low-dose.ti,ab. or ultra-low-dose.ti,ab. or screen*.ot. or low dose.ot. or low radiation.ot. or low-dose.ot. or ultra-low-dose.ot.
7. Tomography, X-Ray Computed/ or computed tomograph*.ti,ab. or CT.ti,ab. or spiral.ti,ab. or helical.ti,ab. or computed tomograph*.ot. or CT.ot. or spiral.ot. or helical.ot.
8. 6 and 7
9. (ldct or ld-ct).ti,ab. or ldct.ot. or ld-ct.ot.

10. 8 or 9
11. risk assessment/ or eligibility determination/
12. (Bach or Liverpool Lung Project or MyLungRisk or Spitz or Nutrition Examination Survey or MIcrosimulation SCreening Analysis or miscan or risk prediction or prediction model* or risk assessment or risk model* or mathematical tool or decision tool or risk stratification or patient selection or eligibility criteria or smoking or pack years or history or spirometry or (PLCO and model)).ti,ab. or Bach.ot. or Liverpool Lung Project.ot. or MyLungRisk.ot. or Spitz.ot. or Nutrition Examination Survey.ot. or MIcrosimulation SCreening Analysis.ot. or miscan.ot. or risk prediction.ot. or prediction model*.ot. or risk assessment.ot. or risk model*.ot. or mathematical tool.ot. or decision tool.ot. or risk stratification.ot. or patient selection.ot. or eligibility criteria.ot. or smoking.ot. or pack years.ot. or history.ot. or spirometry.ot. or (PLCO and model).ot.
13. biomarkers, tumor/
14. (biomarker* or Autoantibodies or earlyCDT-test or Serum or plasma or microRNA or MSC test or Breath or Volatile organic compounds or hypermethylation or Blood based or Tissue based or Biofluid* or sputum or SULF2 protein or C4d protein or urine or urinary protein or Telomere or P16 or MGMT or HYAL2 or FHIT or SFTPC or miR-21 or miR-486 or miR-375).ti,ab. or biomarker*.ot. or Autoantibodies.ot. or earlyCDT-test.ot. or Serum.ot. or plasma.ot. or microRNA.ot. or MSC test.ot. or Breath.ot. or Volatile organic compounds.ot. or hypermethylation.ot. or Blood based.ot. or Tissue based.ot. or Biofluid*.ot. or sputum.ot. or SULF2 protein.ot. or C4d protein.ot. or urine.ot. or urinary protein.ot. or Telomere.ot. or P16.ot. or MGMT.ot. or HYAL2.ot. or FHIT.ot. or SFTPC.ot. or miR-21.ot. or miR-486.ot. or miR-375.ot.
15. or/11-14
16. 5 and 10 and 15
17. animals/ not humans/
18. 16 not 17
19. limit 18 to English

Key Question 13

Embase
1. exp computer assisted tomography/
2. (computed tomograph$ or CT or spiral or helical).ti,ab,kw.
3. 1 or 2
4. (low dose or low radiation or low-dose or ultra-low-dose).ti,ab,kw.
5. screen$.ti.
6. exp early diagnosis/
7. or/4-6
8. 3 and 7
9. (ldct or ld-ct).ti,ab,kw.
10. 8 or 9
11. exp smoking cessation/ or exp smoking cessation program/
12. amfebutamone/ or clonidine/ or nicotine gum/ or nicotine lozenge/ or nicotine patch/ or nicotine vaccine/ or varenicline/ or nortriptyline/

13. (Cessation or Abstinence or withdrawal or quitting or Stopping or Nicotine replacement or Patch or Gum or Lozenge or Inhaler or Nasal spray or Email or e-mail or text message$ or Hypnosis or Tobacco control or Antidepressants or bupropion or Nortriptyline or Clonidine or Varenicline or chantix).ti,ab,kw.
14. (freedom from smoking or quitters circle or smokefree).ti,ab,kw.
15. or/11-14
16. health behavior/ or health promotion/ or health education/
17. (intervention or therapy or program$ of counselling or counsellor).ti,ab,kw.
18. 16 or 17
19. exp smoking/
20. (smoking or smoker or tobacco).ti,ab,kw.
21. 19 or 20
22. 18 and 21
23. 15 or 22
24. 10 and 23
25. (exp animal/ or nonhuman/) not exp human/
26. 24 not 25
27. limit 26 to English
28. limit 27 to (book or book series or chapter or conference abstract or conference paper or conference proceeding or "conference review")
29. 27 not 28

MEDLINE

1. Early Detection of Cancer/ or screen*.ti. or low dose.ti,ab. or low radiation.ti,ab. or low-dose.ti,ab. or ultra-low-dose.ti,ab. or screen*.ot. or low dose.ot. or low radiation.ot. or low-dose.ot. or ultra-low-dose.ot.
2. Tomography, X-Ray Computed/ or computed tomograph*.ti,ab. or CT.ti,ab. or spiral.ti,ab. or helical.ti,ab. or computed tomograph*.ot. or CT.ot. or spiral.ot. or helical.ot.
3. 1 and 2
4. (ldct or ld-ct).ti,ab. or ldct.ot. or ld-ct.ot.
5. 3 or 4
6. smoking cessation/ or "tobacco use cessation products"/
7. (cessation or Abstinence or withdrawal or quit* or Stopping or Nicotine replacement or Patch or Gum or Lozenge or Inhaler or Nasal spray or Nicotrol or Nicorette or Nicoderm or Email or e-mail).ti,ab.
8. (text message* or telephone or smartphone).ti,ab.
9. freedom from smoking.ti,ab.
10. (smokefree or quitline or Hypnosis or Tobacco control).ti,ab.
11. (Antidepressants or bupropion or Nortriptyline or Clonidine or Varenicline or Chantix or Cessation).ot.
12. (Abstinence or withdrawal or quit* or Stopping or Nicotine replacement or Patch or Gum or Lozenge or Inhaler or Nasal spray or Nicotrol or Nicorette or Nicoderm or Email).ot.
13. (text message* or telephone or smartphone or freedom from smoking or smokefree or quitline or Hypnosis or Tobacco control).ot.

14. or/6-13
15. Patient Education/ or Patient Education Handout.ti,ab. or Health Behavior/ or Health Education/ or Health Promotion/ or Primary Prevention/ or Intervention*.ti,ab. or Therapy.ti,ab. or therapies.ti,ab. or Program*.ti,ab. or counseling.ti,ab. or counselor.ti,ab. or Counselling.ti,ab. or Counsellor.ti,ab. or Intervention*.ot. or Therapy.ot. or therapies.ot. or Program*.ot. or counseling.ot. or counselor.ot. or Counselling.ot. or Counsellor.ot.
16. smoking/ or smoking.ti,ab. or smoker.ti,ab. or tobacco.ti,ab. or cigarette*.ti,ab. or smoking.ot. or smoker.ot. or tobacco.ot. or cigarette.ot.
17. 15 and 16
18. 14 or 17
19. 5 and 18
20. animal/ not human/
21. 19 not 20
22. limit 21 to English

Figure 2: PRISMA Diagram for updated guideline

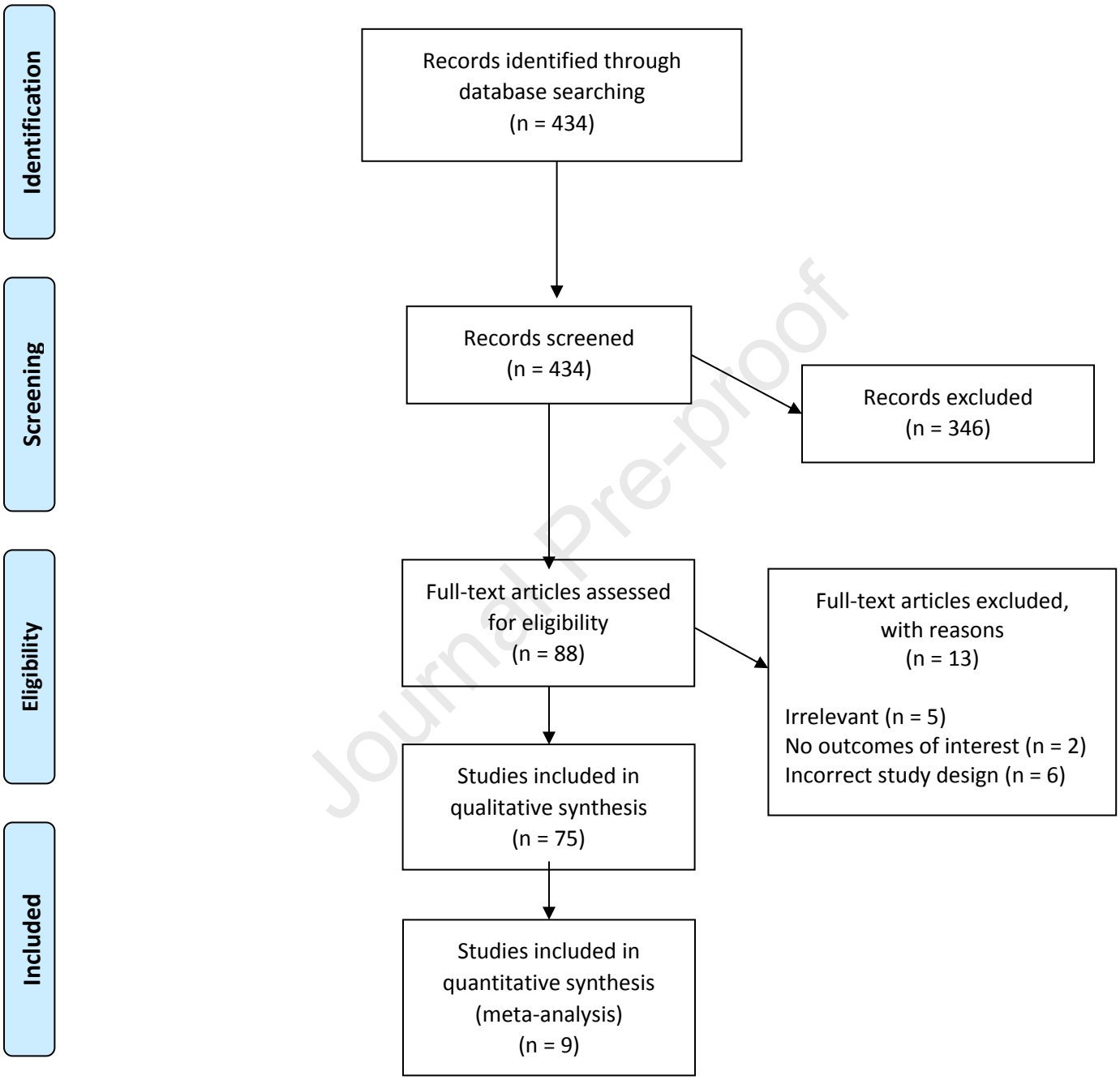

Figure 3: Lung Cancer Mortality in LDCT Screening Programs versus Usual Care or Chest X-Ray

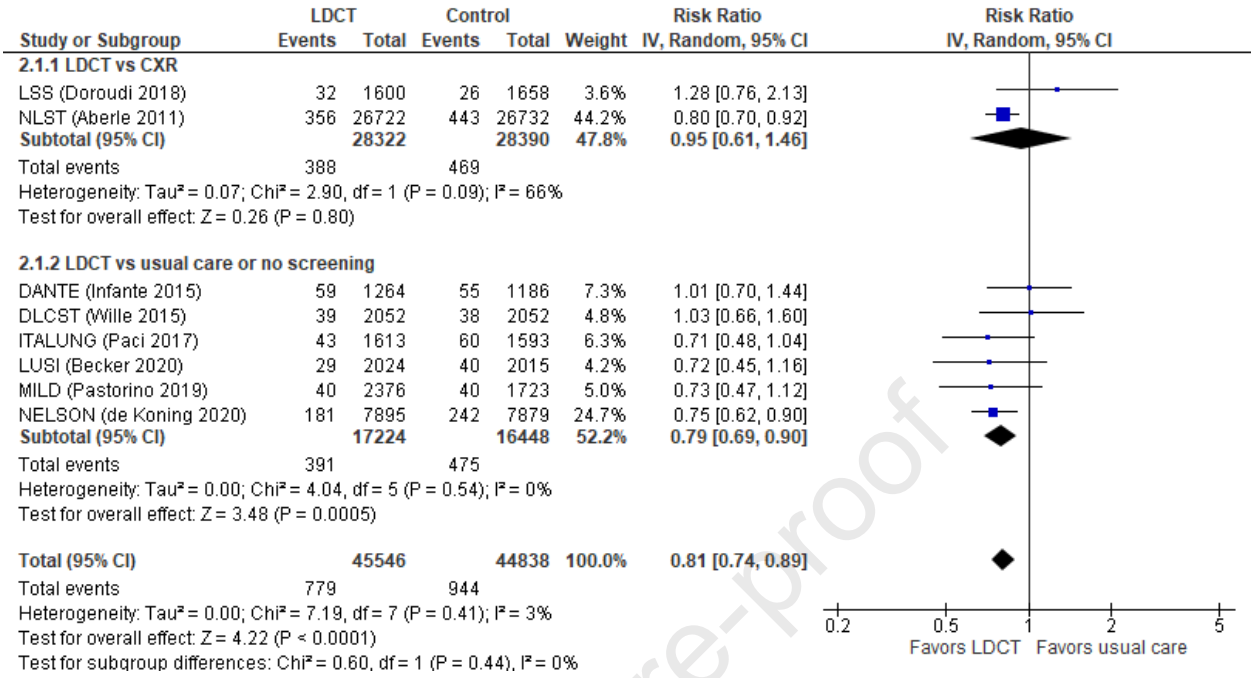

Figure 4: Lung Cancer Mortality by LDCT Screening Protocol in LDCT Screening Programs versus Usual Care

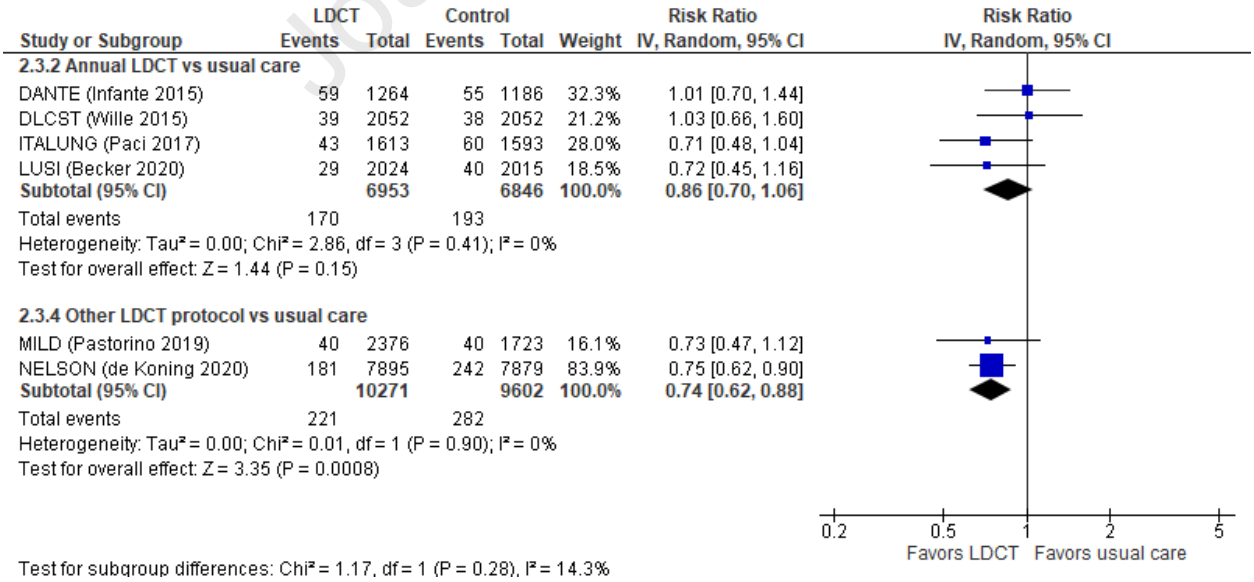

Figure 5: Lung Cancer Mortality by LDCT Screening Protocol in LDCT Screening Programs versus Usual Care or Chest X-Ray

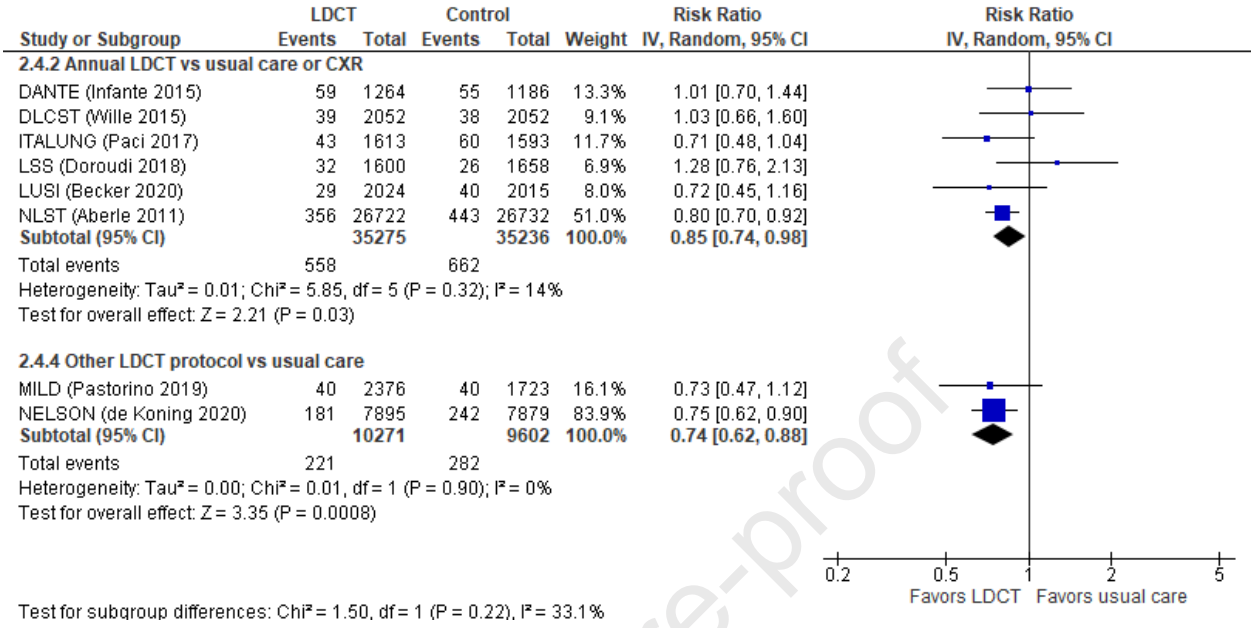

Figure 6: Lung cancer mortality by age of LDCT screening initiation in LDCT screening program versus usual care

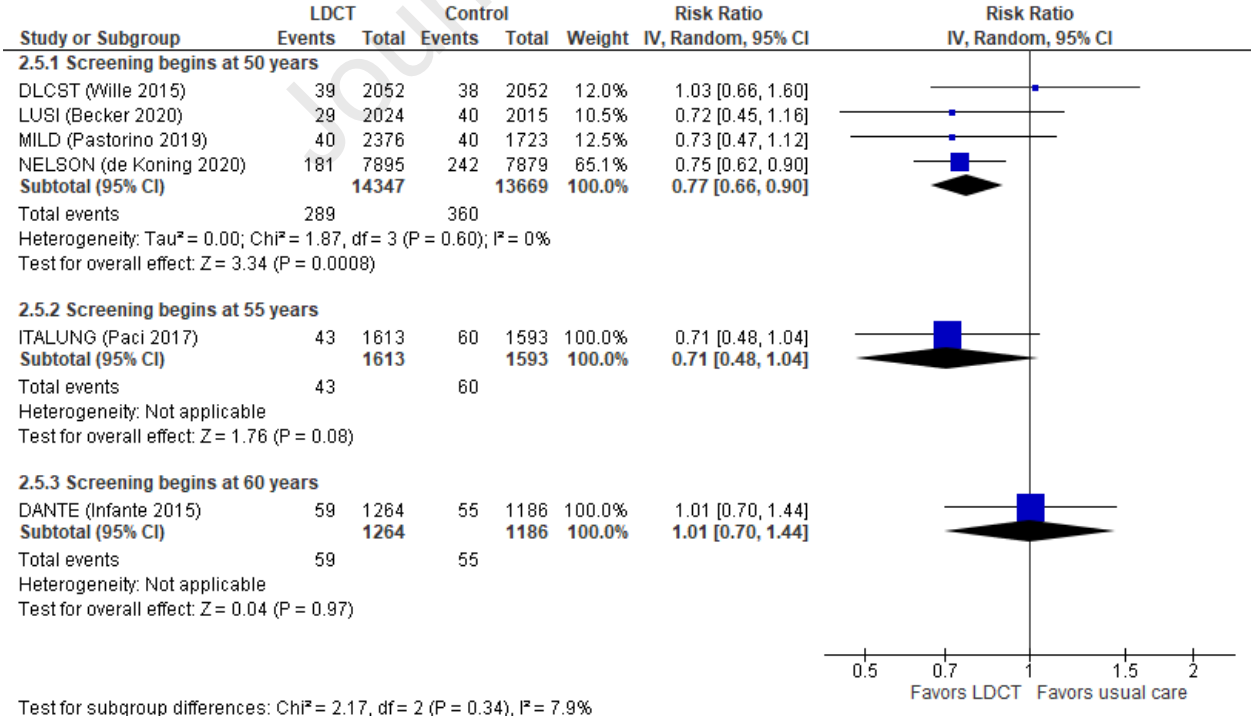

Figure 7: Lung cancer mortality by age of LDCT screening initiation in LDCT screening programs versus usual care or chest x-ray

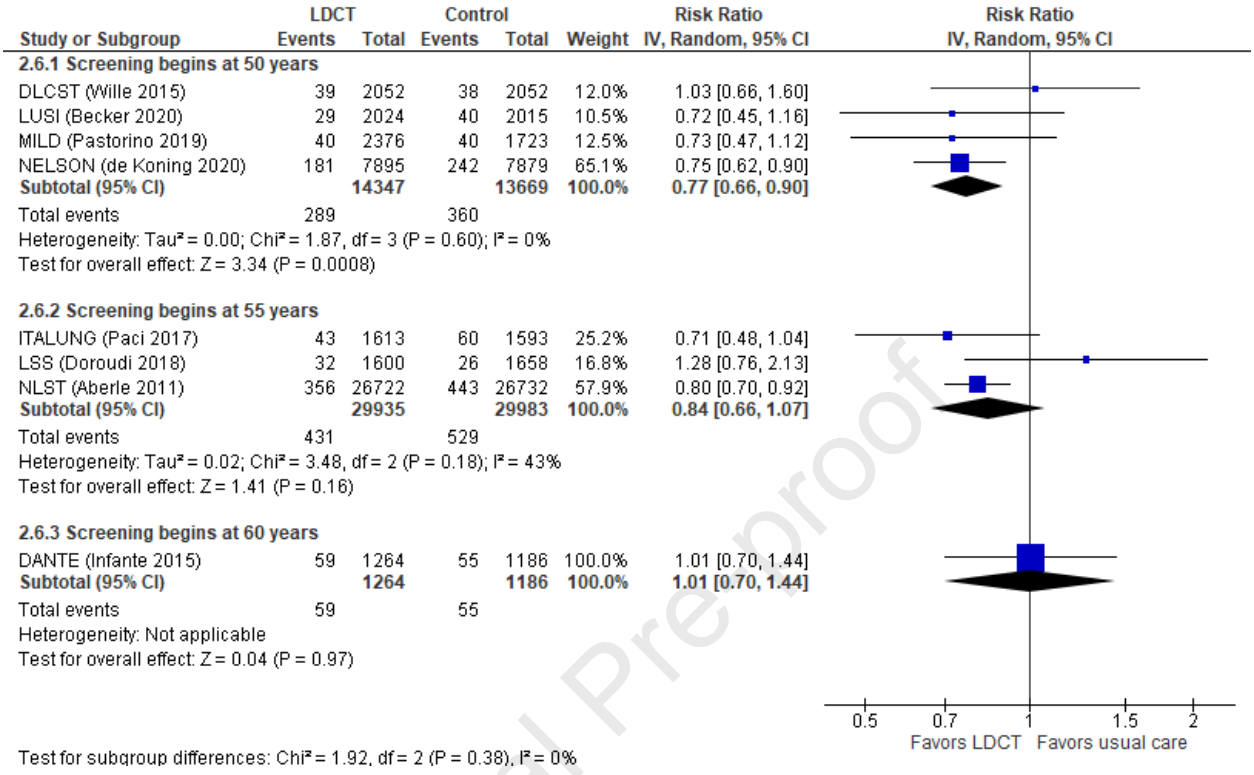

Figure 8: Lung cancer mortality by gender in LDCT screening programs versus usual care

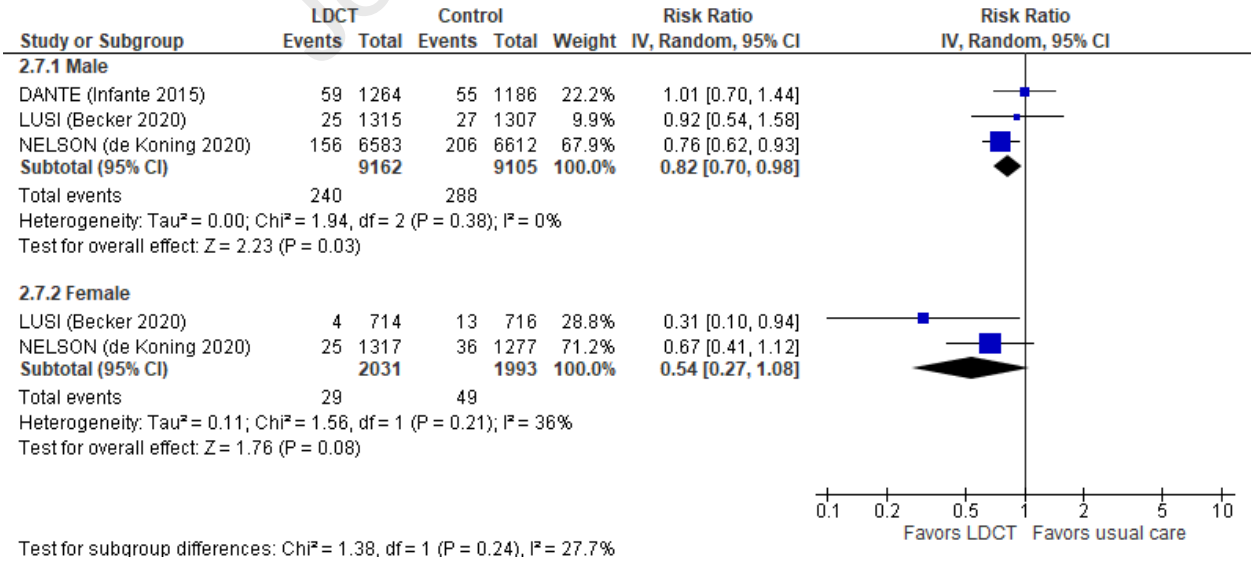

Figure 9: Lung cancer mortality by gender in LDCT screening programs versus usual care or chest x-ray

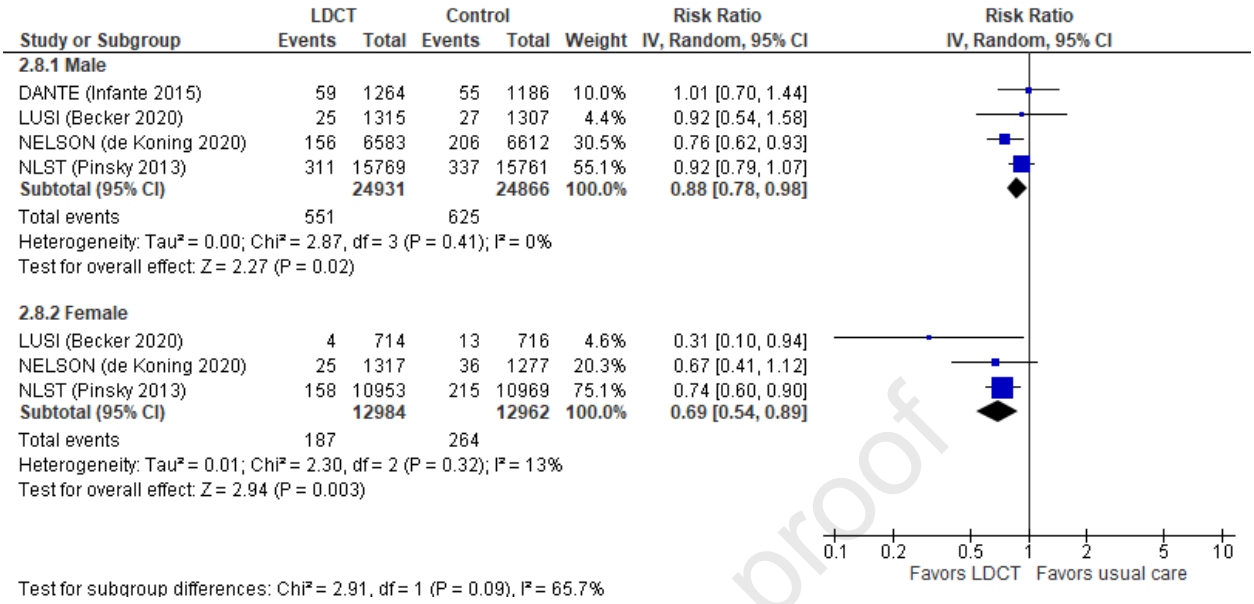

Figure 10: Number of invasive procedures per number of screened individuals over the period of screening (LDCT)

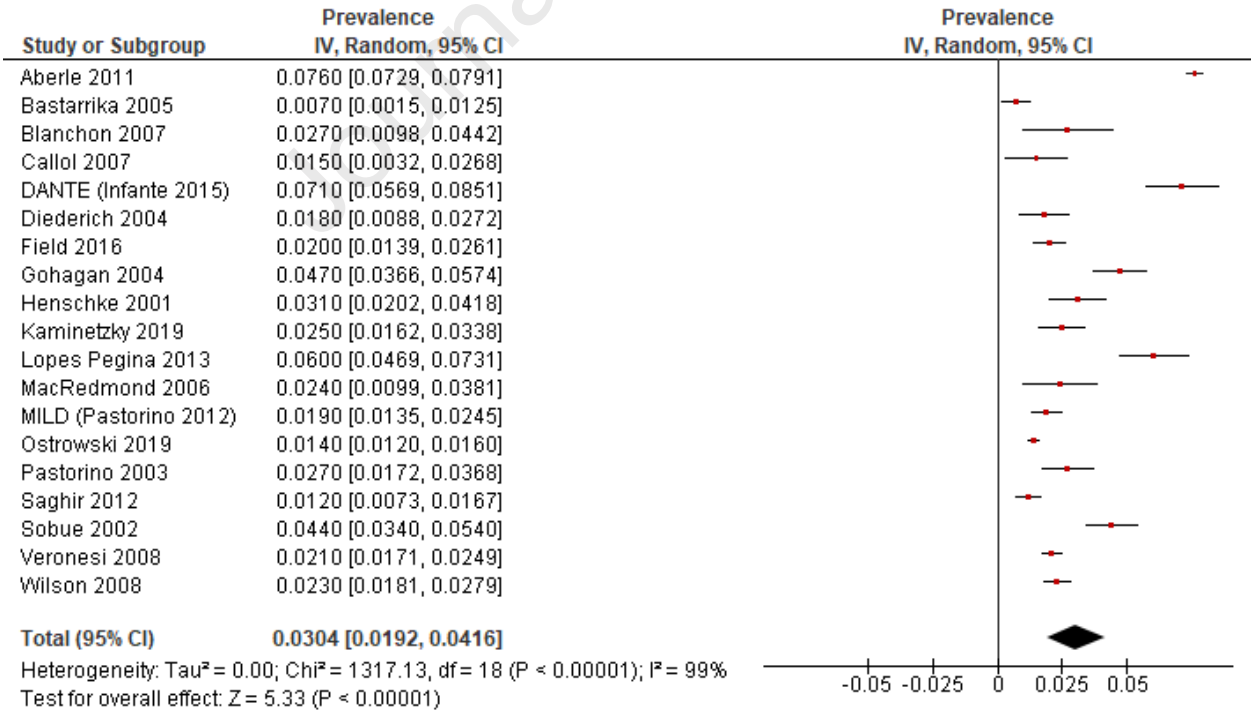

Figure 11: Number of deaths per invasive procedures – LDCT

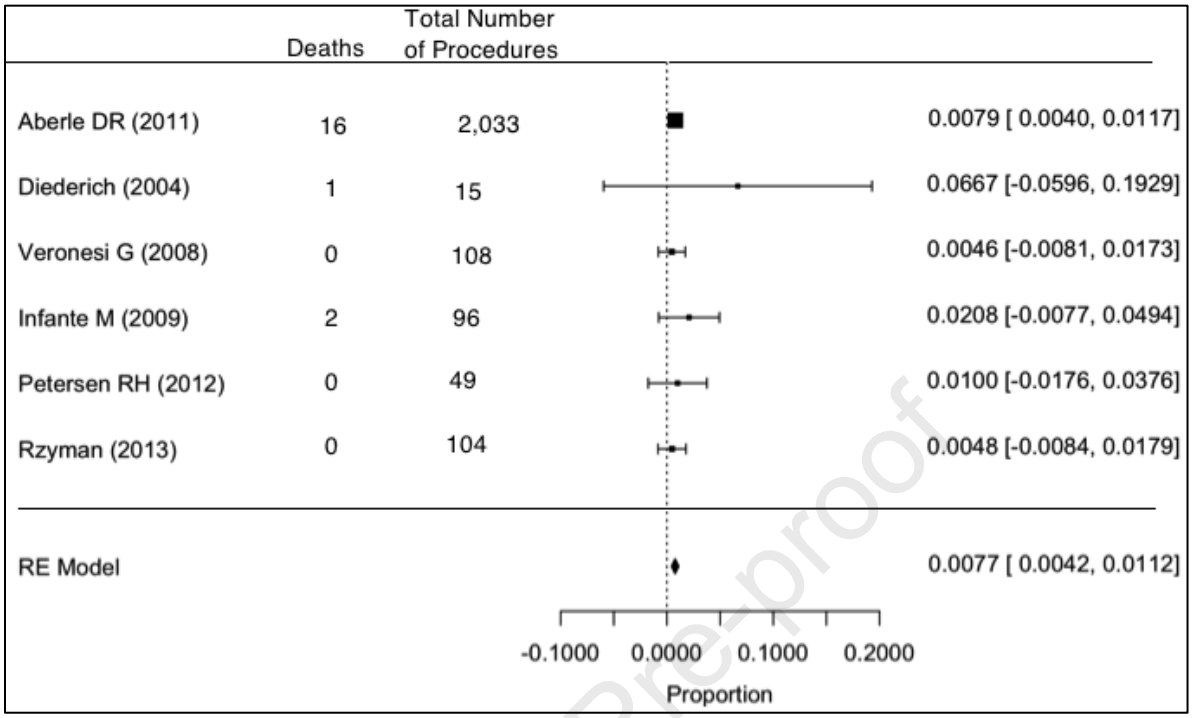

Figure 12: Number of major complications per invasive procedures – LDCT

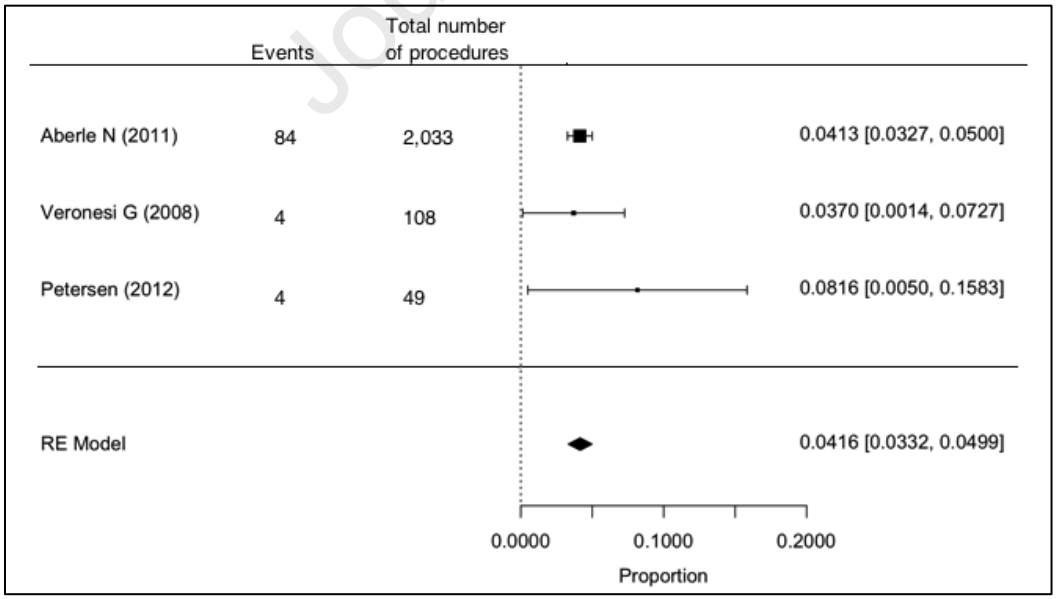

Figure 13: Number of surgical procedures for benign disease per total procedures – LDCT

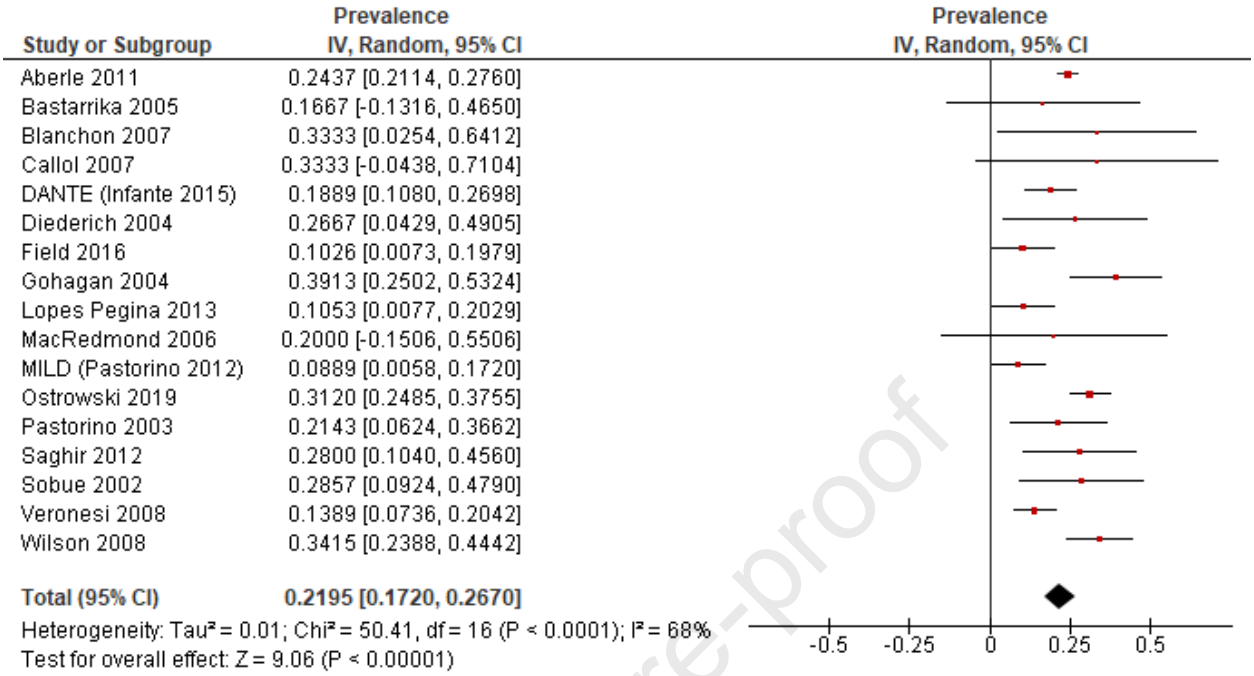

Figure 14: Number of non-surgical procedures for benign disease per total procedures – LDCT

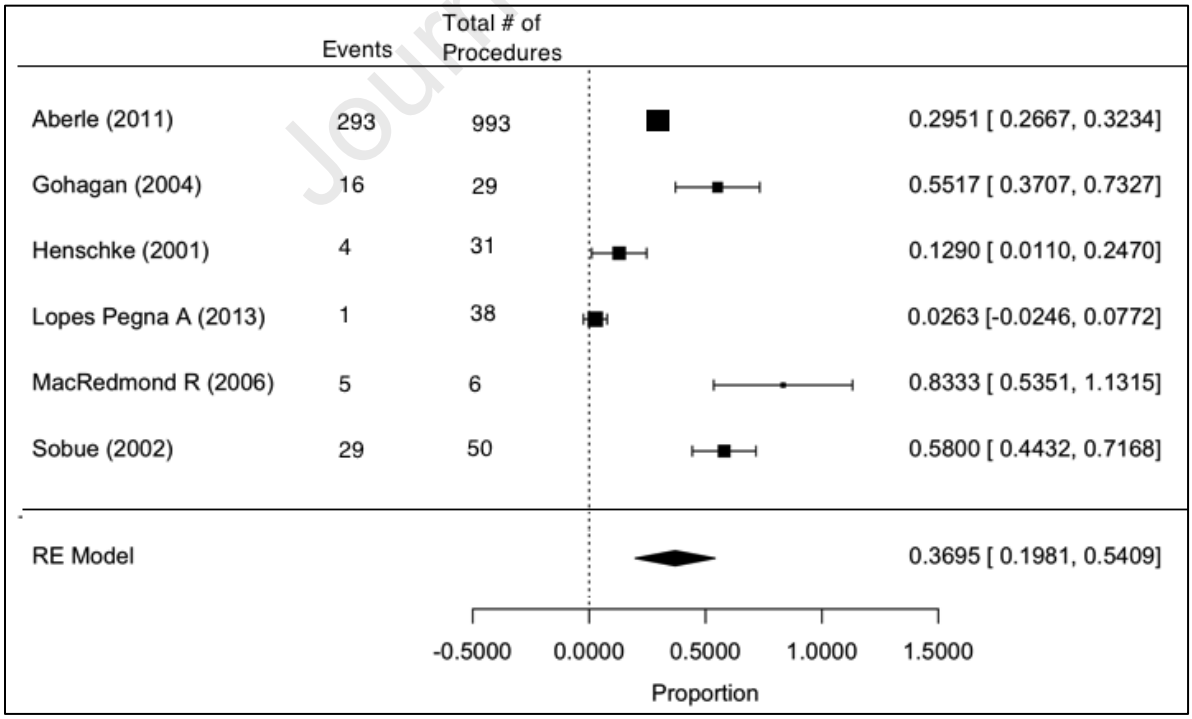

Figure 15: Continuum of net benefit of lung cancer screening for different patients

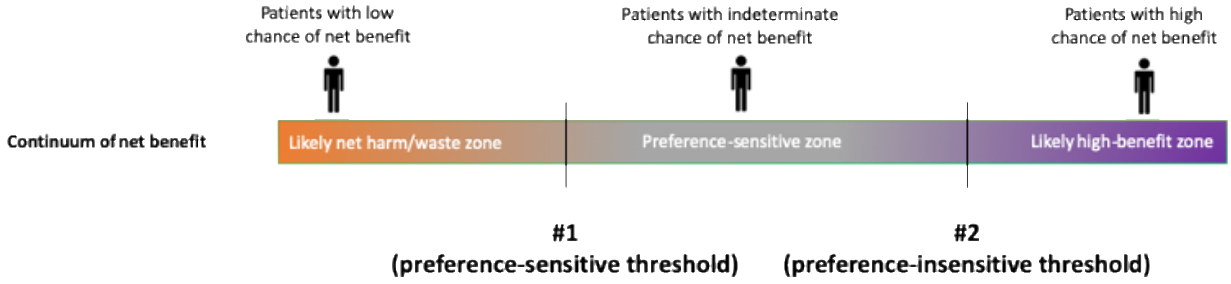

Figure 16: Risk of smoking cessation in patients enrolled in LDCT screening programs versus usual care