JAMA | US Preventive Services Task Force | EVIDENCE REPORT

# Screening for Lung Cancer With Low-Dose Computed Tomography
## Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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**IMPORTANCE** Lung cancer is the leading cause of cancer-related death in the US.

**OBJECTIVE** To review the evidence on screening for lung cancer with low-dose computed tomography (LDCT) to inform the US Preventive Services Task Force (USPSTF).

**DATA SOURCES** MEDLINE, Cochrane Library, and trial registries through May 2019; references; experts; and literature surveillance through November 20, 2020.

**STUDY SELECTION** English-language studies of screening with LDCT, accuracy of LDCT, risk prediction models, or treatment for early-stage lung cancer.

**DATA EXTRACTION AND SYNTHESIS** Dual review of abstracts, full-text articles, and study quality; qualitative synthesis of findings. Data were not pooled because of heterogeneity of populations and screening protocols.

**MAIN OUTCOMES AND MEASURES** Lung cancer incidence, lung cancer mortality, all-cause mortality, test accuracy, and harms.

**RESULTS** This review included 223 publications. Seven randomized clinical trials (RCTs) (N = 86 486) evaluated lung cancer screening with LDCT; the National Lung Screening Trial (NLST, N = 53 454) and Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON, N = 15 792) were the largest RCTs. Participants were more likely to benefit than the US screening-eligible population (eg, based on life expectancy). The NLST found a reduction in lung cancer mortality (incidence rate ratio [IRR], 0.85 [95% CI, 0.75-0.96]; number needed to screen [NNS] to prevent 1 lung cancer death, 323 over 6.5 years of follow-up) with 3 rounds of annual LDCT screening compared with chest radiograph for high-risk current and former smokers aged 55 to 74 years. NELSON found a reduction in lung cancer mortality (IRR, 0.75 [95% CI, 0.61-0.90]; NNS to prevent 1 lung cancer death of 130 over 10 years of follow-up) with 4 rounds of LDCT screening with increasing intervals compared with no screening for high-risk current and former smokers aged 50 to 74 years. Harms of screening included radiation-induced cancer, false-positive results leading to unnecessary tests and invasive procedures, overdiagnosis, incidental findings, and increases in distress. For every 1000 persons screened in the NLST, false-positive results led to 17 invasive procedures (number needed to harm, 59) and fewer than 1 person having a major complication. Overdiagnosis estimates varied greatly (0%-67% chance that a lung cancer was overdiagnosed). Incidental findings were common, and estimates varied widely (4.4%-40.7% of persons screened).

**CONCLUSIONS AND RELEVANCE** Screening high-risk persons with LDCT can reduce lung cancer mortality but also causes false-positive results leading to unnecessary tests and invasive procedures, overdiagnosis, incidental findings, increases in distress, and, rarely, radiation-induced cancers. Most studies reviewed did not use current nodule evaluation protocols, which might reduce false-positive results and invasive procedures for false-positive results.

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In 2020, lung cancer was the second most common cancer and the leading cause of cancer-related death in both men and women in the US.[1] Most patients diagnosed with lung cancer presented with distant or metastatic disease; less than 20% were diagnosed with localized (ie, stage 1) disease.[1] Lung cancer has traditionally been classified into 2 major categories: (1) non–small cell lung cancer (NSCLC) (eTable 1 in the Supplement), which collectively comprises adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, and (2) small cell lung cancer, which is more aggressive and has worse survival rates.[2] Approximately 85% of lung cancers are NSCLC.[3] The risk of developing lung cancer is largely driven by age and smoking status, with smoking estimated to account for nearly 90% of all lung cancers.[4-6] Other risk factors for lung cancer include environmental exposures, radiation therapy, other (noncancer) lung diseases, race/ethnicity, and family history.[7]

In 2013, the US Preventive Services Task Force (USPSTF) recommended annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30-pack-year smoking history and currently smoke or have quit within the past 15 years (B recommendation).[8] The USPSTF recommended that screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.[8] This updated review evaluates the current evidence on screening for lung cancer with LDCT for populations and settings relevant to primary care in the US to inform an updated recommendation by the USPSTF.

## Methods

### Scope of Review

**Figure 1** shows the analytic framework and key questions (KQs) that guided the review. Detailed methods are available in the full evidence report.[7]

### Data Sources and Searches

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published through May 2019. Search strategies are listed in the eMethods in the Supplement. Clinical trial registries were searched for unpublished studies. To supplement electronic searches, investigators reviewed reference lists of pertinent articles, studies suggested by reviewers, and comments received during public commenting periods. Since May 2019, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on November 20, 2020.

### Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles to determine eligibility using prespecified criteria (eTable 2 in the Supplement). Disagreements were resolved by discussion and consensus. English-language studies of adults aged 18 years or older conducted in countries categorized as "very high" on the Human Development Index,[9] rated as fair or good quality, and published in or after 2001 were included. For all KQs, randomized clinical trials (RCTs) and nonrandomized controlled intervention studies were eligible. Cohort studies based on prospectively collected data that were intended to be used for evaluations relevant to this review were also eligible for KQs on harms of screening or workup (KQs 4 and 5) and treatment (KQs 6 and 7).

For KQ2 (on risk prediction), externally validated models aimed at identifying persons at increased risk of lung cancer using multiple variables, including at least age and smoking history, were included. Eligible risk prediction models had to be compared with either the 2013 USPSTF recommendations or criteria used by trials showing benefit. Eligible outcomes included estimated screen-preventable lung cancer deaths or all-cause mortality, estimated screening effectiveness (eg, number needed to screen [NNS]), and estimated screening harms.

### Data Extraction and Quality Assessment

For each included study, 1 investigator extracted pertinent information about the populations, tests or treatments, comparators, outcomes, settings, and designs, and a second investigator reviewed this information for completeness and accuracy. Two independent investigators assessed the quality of studies as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this topic.[10] Disagreements were resolved by discussion.

### Data Synthesis and Analysis

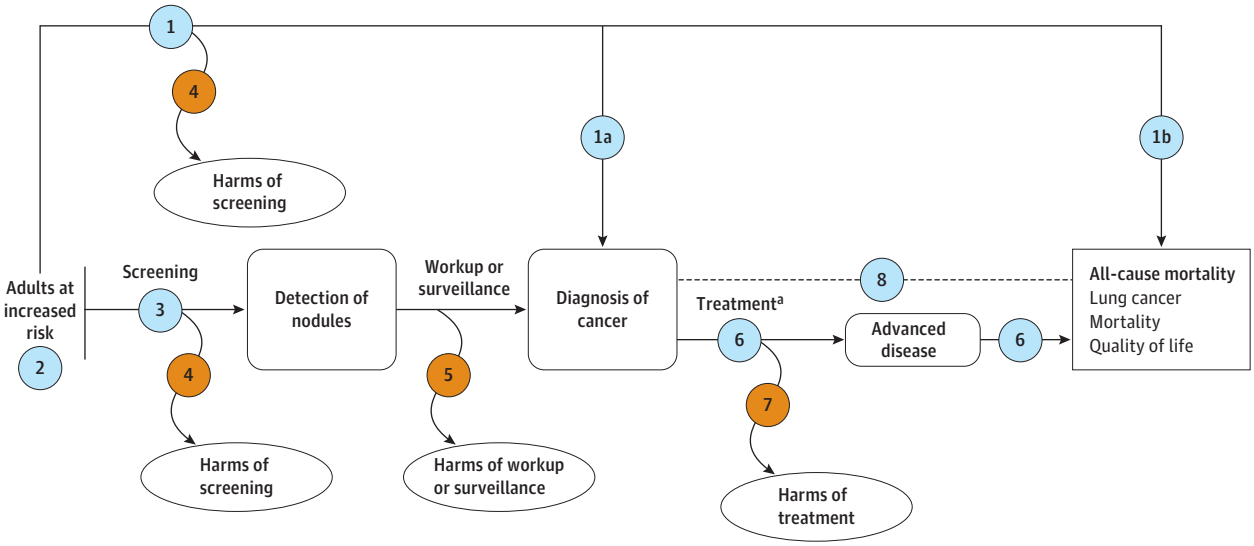
Findings for each KQ were summarized in tabular and narrative format. The overall strength of the evidence for each KQ was assessed as high, moderate, low, or insufficient based on the overall quality of the studies, consistency of results between studies, precision of findings, risk of reporting bias, and limitations of the body of evidence, using methods developed for the USPSTF (and the Evidence-based Practice Center program).[10] Additionally, the applicability of the findings to US primary care populations and settings was assessed. Discrepancies were resolved through discussion.

To determine whether meta-analyses were appropriate, the clinical and methodological heterogeneity of the studies was assessed according to established guidance.[11] Meta-analyses were not conducted because of substantial clinical and methodological heterogeneity. For example, the trials of lung cancer screening differed in eligibility criteria (eg, age, pack-years of smoking, years since quitting), number of screening rounds (from 2 to 5), screening intervals (eg, annual, biennial, or escalating), thresholds for a positive screen (eg, 4 mm, 5 mm, or based on volume), and comparators (chest radiograph or no screening). For KQ1, forest plots were created to display the findings of each study by calculating incidence rate ratios (IRRs), using number of events and person-years of follow-up, for lung cancer incidence, lung cancer mortality, and all-cause mortality. Quantitative analyses were conducted using Stata version 14 (StataCorp).

## Results

A total of 223 publications were included (**Figure 2**). Twenty-six articles addressed whether screening improves health outcomes. Most articles assessed accuracy, harms, or effectiveness of surgery or stereotactic body radiotherapy for early NSCLC. Results for KQs 6, 7,

Figure 1. Analytic Framework: Screening for Lung Cancer With Low-Dose Computed Tomography (LDCT)




Key questions

1 a. Does screening for lung cancer with LDCT change the incidence of lung cancer and the distribution of lung cancer types and stages (ie, stage shift)?

b. Does screening for lung cancer with LDCT change all-cause mortality, lung cancer mortality, or quality of life?

c. Does the effectiveness of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

d. Does the effectiveness of screening for lung cancer with LDCT differ by the number or frequency of LDCT scans (eg, annual screening for 3 years, the protocol used in the NLST vs other approaches)?

2 Does the use of risk prediction models for identifying adults at higher risk of lung cancer mortality improve the balance of benefits and harms of screening compared with the use of trial eligibility criteria (eg, NLST criteria) or the 2013 USPSTF recommendations?

3 a. What is the accuracy of screening for lung cancer with LDCT?

b. Does the accuracy of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

c. Does the accuracy of screening for lung cancer with LDCT differ for various approaches to nodule classification (ie, those based on nodule size and characteristics)?

4 a. What are the harms associated with screening for lung cancer with LDCT?

b. Do the harms of screening for lung cancer with LDCT differ with the use of Lung-RADS, IELCAP, or similar approaches (eg, to reduce false-positive results)?

c. Do the harms of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

5 a. What are the harms associated with workup or surveillance of nodules?

b. Do the harms of workup or surveillance of nodules differ with the use of Lung-RADS, IELCAP, or similar approaches (eg, to reduce false-positive results)?

c. Do the harms of workup or surveillance of nodules differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

6 a. What is the effectiveness of surgical resection or SBRT for the treatment of early (stage I) non-small cell lung cancer?

b. Does the effectiveness of surgical resection or SBRT differ for subgroups defined by age, sex, race/ethnicity, or presence of comorbid conditions?

7 a. What are the harms associated with surgical resection or SBRT for the treatment of early (stage I) non-small cell lung cancer?

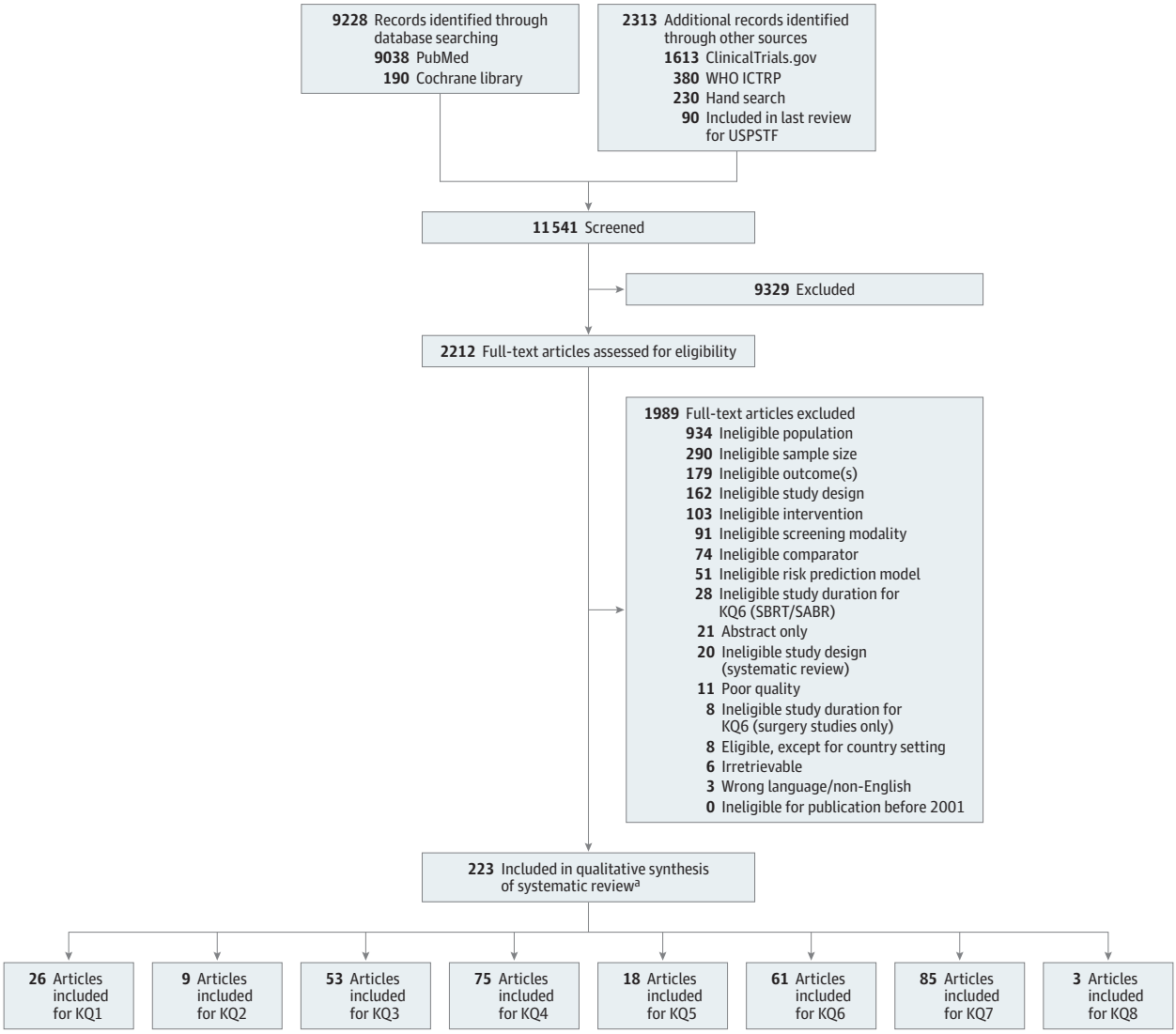
b. Do the harms of surgical resection or SBRT differ for subgroups defined by age, sex, race/ethnicity, or presence of comorbid conditions?

8 What is the magnitude of change in all-cause and lung cancer mortality that results from a specified change in lung cancer incidence (and change in distribution of lung cancer stages [ie, stage shift]) after screening?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Additional details are provided in the USPSTF Procedure manual.[10] I-ELCAP indicates International Early Lung Cancer Action Program; NLST, National Lung Screening Trial; and SBRT, stereotactic body radiotherapy.

[a] The evaluation of evidence on treatment was limited to studies of surgical resection or SBRT for stage I non-small cell lung cancer.

Figure 2. Summary of Evidence Search and Selection: Screening for Lung Cancer With Low-Dose Computed Tomography




ICTRP indicates International Clinical Trials Registry Platform; KQ, key question; SABR, stereotactic ablative radiation; SBRT, stereotactic body radiotherapy; USPSTF, US Preventive Services Task Force; WHO, World Health Organization.

[a] Because many articles contribute to 1 or more KQs, the number of articles listed per KQ in this section does not add up to 223.

and 8 are in the eResults in the Supplement. Individual study quality ratings are reported in eTables 3 to 13 in the Supplement.

## Benefits of Screening

**Key Question 1a.** Does screening for lung cancer with LDCT change the incidence of lung cancer and the distribution of lung cancer types and stages (ie, stage shift)?

**Key Question 1b.** Does screening for lung cancer with LDCT change all-cause mortality, lung cancer mortality, or quality of life?

**Key Question 1c.** Does the effectiveness of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

**Key Question 1d.** Does the effectiveness of screening for lung cancer with LDCT differ by the number or frequency of LDCT scans (eg, annual screening for 3 years, the protocol used in the National Lung Screening Trial [NLST] vs other approaches)?

Seven RCTs (described in 26 articles) were included (**Table 1**): NLST, Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE), Danish Lung Cancer Screening Trial (DLCST), Italian Lung Cancer Screening Trial (ITALUNG), Lung Screening Study (LSS), the German Lung Cancer Screening Intervention Trial (LUSI), and the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) study.[12-37] Two trials in the US compared LDCT with chest radiography (LSS and NLST), and 5 trials in Europe compared LDCT with no screening (DANTE, DLCST, ITALUNG, LUSI, and NELSON). Only the NLST (53 454 participants) and NELSON (15 792 participants) were adequately powered to assess for lung cancer mortality benefit.[24,31] The majority of participants were White in all trials; in

Table 1. Characteristics of Included RCTs Evaluating Screening With LDCT Compared With Chest Radiography or With No Screening

| Source | Recruitment years | Sample size; country | Mean age (ages eligible), y | % Male | Baseline smoking status, % | Eligibility criteria for pack-years; years since quitting | Screening rounds, No. | Screening intervals, y | Total median follow-up, y | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| DANTE[12-14] | 2001-2006 | 2472; Italy | 65 (60-74) | 100 | Current: 57<br>Former: 43<br>Mean No. of pack-years: 47 | ≥20; <10 y | 5 | 0, 1, 2, 3, 4 | 8.4 | Fair |
| DLCST[15,16] | 2004-2006 | 4104; Denmark | 58 (50-70) | 56 | Current: 76<br>Former: 24<br>Mean No. of pack-years: 36 | ≥20; quit after age 50 and <10 y ago | 5 | 0, 1, 2, 3, 4 | 9.8 | Fair |
| ITALUNG[17] | 2004-2006 | 3206; Italy | 61 (55-69) | 65 | Current: 65<br>Former: 35<br>Median No. of pack-years: 39 | ≥20 in the last 10 y or quit within the last 10 y | 4 | 0, 1, 2, 3 | 9.3[a] | Fair |
| LSS[18-20b] | 2000-2001 | 3318; US | NR (55-74) | 59 | Current: 58<br>Former: 42<br>Median No. of pack-years: 54 | ≥30; <10 y | 2 | 0, 1 | 5.2 | Fair |
| LUSI[21-23] | 2007-2011 | 4052; Germany | NR (50-69) | 65 | Current: 62<br>Former: 35<br>Mean No. of pack-years: NR | ≥25 y of 15 cigarettes or ≥30 y of 10 cigarettes; ≤10 y | 5 | 0, 1, 2, 3, 4 | 8.8 | Fair |
| NELSON[24-28] | 2003-2006 | 15 792; the Netherlands and Belgium | Median, 58 (50-74) | 84 | Current: 55<br>Former: 45<br>Median No. of pack-years: 38 | >15 cigarettes/d for >25 y or >10 cigarettes/d for >30 y; ≤10 y | 4 | 0, 1, 3, 5.5 | 10 | Fair |
| NLST[29-37b] | 2002-2004 | 53 542; US | 61 (55-74) | 59 | Current: 48<br>Former: 52<br>Mean No. of pack-years: 56 | ≥30; ≤15 y | 3 | 0, 1, 2 | 7 (and posttrial follow-up to 12.3 y) | Good[c] |

Abbreviations: DANTE, Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST, Danish Lung Cancer Screening Trial; ITALUNG, Italian Lung Cancer Screening Trial; LDCT, low-dose computed tomography; LSS, Lung Screening Study; LUSI, The German Lung Cancer Screening Intervention Trial; NELSON, Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST, National Lung Screening Trial; NR, not reported; RCT, randomized clinical trial.

[a] The ITALUNG study reported 9.3 years for lung cancer–specific mortality and 8.5 years for lung cancer incidence.

[b] NLST and LSS compared screening with LDCT vs screening with chest radiography. All other trials compared screening with LDCT with no screening. The LSS was a feasibility pilot study.

[c] NLST was rated as good quality for the main trial outcomes. The extended posttrial follow-up of the NLST was rated as fair quality.

the NLST, 91% were White, less than 5% were Black, and less than 2% were Hispanic or Latino.

Trials varied in their definition of a positive screen and in the follow-up evaluation process. NELSON was unique in using volumetric measurements of nodules and calculating volume doubling. Compared with the prior systematic review conducted for the USPSTF,[38,39] longer follow-up or more complete end point verification was available from DANTE,[12] DLCST,[16] LSS,[20] and the NLST,[33,37] and 3 additional trials—NELSON,[24] ITALUNG,[17] and LUSI[21,23]—reported data relevant to this KQ.

The cumulative incidence of lung cancer was higher in LDCT groups than in control groups for all studies except ITALUNG (eFigure in the Supplement). **Figure 3** shows the increases in early-stage (I-II) and decreases in late-stage (III-IV) lung cancer incidence.

**Figure 4** shows the calculated IRRs for the trials that reported lung cancer mortality. Over almost 7 years of follow-up and more than 140 000 person-years of follow-up in each group, the NLST found a significant reduction in lung cancer mortality with 3 rounds of annual LDCT screening compared with chest radiography (calculated IRR, 0.85 [95% CI, 0.75-0.96]). These findings indicate an NNS to prevent 1 lung cancer death of 323 over 6.5 years of follow-up. Analysis of extended follow-up data of NLST participants at 12.3 years after randomization found a similar absolute difference between groups (1147 vs 1236 lung cancer deaths; risk ratio [RR], 0.92 [95% CI, 0.85-1.00]; absolute difference between groups of 3.3 [95% CI, −0.2 to 6.8] lung cancer deaths per 1000 participants). The NELSON trial reported a reduction in lung cancer mortality for 4 rounds of screening with increasing intervals between LDCTs (combining data for males and females, calculated IRR, 0.75 [95% CI, 0.61-0.90]; NNS to prevent 1 lung cancer death of 130 over 10 years of follow-up). Results of the other trials were very imprecise and did not show statistically significant differences between groups (Figure 4).

The NLST found a reduction in all-cause mortality with LDCT screening compared with chest radiography (1912 vs 2039 deaths; 1141 per 100 000 person-years vs 1225 per 100 000 person-years; calculated IRR, 0.93 [95% CI, 0.88-0.99]). The other trials found no statistically significant differences between groups, but results were imprecise (**Figure 5**).

Figure 3. Trial Results of Incidence of Early- (I-II) and Late- (III-IV) Stage Lung Cancer (Key Question 1)

| Study, y | Male, % | Follow-up, y | Mean age, y | Mean pack-years | Screening times, y | Patients, No. | | Early-stage lung cancer, No. | | IRR (95% CI) | Favors LDCT | Favors control | Patients, No. | | Late-stage lung cancer, No. | | IRR (95% CI) | Favors LDCT | Favors control |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | LDCT | Control | LDCT | Control | | | | LDCT | Control | LDCT | Control | | | |
| NLST,[29-37] 2011-2019 | 59 | 11.3 | 61 | 56 | 0, 1, 2 | 26 722 | 26 732 | 818 | 615 | 1.33 (1.20-1.48) | | | 26 722 | 26 732 | 766 | 918 | 0.84 (0.76-0.92) | | |
| DANTE,[12-14] 2008-2015 | 100 | 8.4 | 65 | 47 | 0, 1, 2, 3, 4 | 1276 | 1196 | 54 | 21 | 2.38 (1.44-3.94) | | | 1276 | 1196 | 43 | 45 | 0.89 (0.59-1.35) | | |
| DLCST,[15,16] 2012-2016 | 56 | 9.8 | 58 | 36 | 0, 1, 2, 3, 4 | 2052 | 2052 | 54 | 10 | 5.42 (2.76-10.63) | | | 2052 | 2052 | 46 | 41 | 1.13 (0.74-1.72) | | |
| ITALUNG,[17] 2017 | 65 | 9.3 | 61 | 39 | 0, 1, 2, 3 | 1613 | 1593 | 29 | 13 | 2.17 (1.13-4.16) | | | 1613 | 1593 | 33 | 43 | 0.75 (0.47-1.17) | | |
| NELSON,[24-28] 2006-2020 | 100 | 10 | 58 | 38 | 0, 1, 3, 5.5 | 6583 | 6612 | 168 | 71 | 2.39 (1.81-3.16) | | | 6583 | 6612 | 153 | 216 | 0.72 (0.58-0.88) | | |




DANTE indicates Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST, Danish Lung Cancer Screening Trial; IRR, incidence rate ratio; ITALUNG, Italian Lung Cancer Screening Trial; NELSON, Nederlands-Leuvens Longkanker Screenings Onderzoek; and NLST, National Lung Screening Trial.

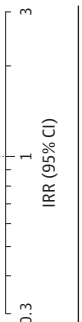
All included trials enrolled participants at high risk for lung cancer (based on age and smoking history). Seven publications using DLCST, LUSI, NELSON, or NLST data described subgroup analyses for age, sex, race/ethnicity, smoking status and pack-years, history of chronic obstructive pulmonary disease (COPD), or other pulmonary conditions.[16,23,24,33-35,37] A post hoc analysis of NLST data reported that 88% of the benefit (lung cancer deaths averted) was achieved by screening the 60% of participants at highest risk for lung cancer death.[29] Other post hoc analyses of NLST data reported lung cancer mortality by sex (RR, 0.73 for women vs 0.92 for men; $P = .08$), age (RR, 0.82 for <65 years vs 0.87 for ≥65 years; $P = .60$), race/ethnicity (hazard ratio [HR], 0.61 for Black individuals vs 0.86 for White individuals; $P = .29$), and smoking status (RR, 0.81 for current smokers vs 0.91 for former smokers; $P = .40$), and did not identify statistically significant differences between groups.[33-35] A long-term follow-up of NLST participants at 12.3 years reported similar results for subgroups and did not identify statistically significant interactions by sex, age, or smoking status (sex: RR, 0.86 for women vs 0.97 for men, $P = .17$; age: RR, 0.86 for <65 years vs 1.01 for ≥65 years, $P = .051$; smoking status: RR, 0.88 for current smokers vs 1.01 for former smokers, $P = .12$).[37] Both LUSI and NELSON reported a similar pattern for subgroups by sex as found in the NLST that was not statistically significantly different between groups (LUSI: women, HR, 0.31 [95% CI, 0.10-0.96] vs men, HR, 0.94 [95% CI, 0.54-1.61], $P = .09$) or without reporting an interaction test (NELSON: women, RR, 0.67 [95% CI, 0.38-1.14] vs men, RR, 0.76 [95% CI, 0.61-0.94] at 10 years of follow-up).[23,24] NELSON reported analyses by age group among the men in the trial (not including the women in those analyses) but did not report interaction tests for subgroups defined by age (RRs ranged from 0.59 [95% CI, 0.35-0.98] for persons aged 65 to 69 years at randomization to 0.85 [95% CI, 0.48-1.50] for persons aged 50 to 54 years at randomization).[24]

**Key Question 2.** Does the use of risk prediction models for identifying adults at higher risk of lung cancer mortality improve the balance of benefits and harms of screening compared with the use of trial eligibility criteria (eg, NLST criteria) or the 2013 USPSTF recommendations?

Detailed results for this KQ are in eResults and eTables 14-16 in the Supplement. In summary, 4 studies of 3 different risk prediction models (a modified version of a model developed from participants of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial [PLCOm2012], the Lung Cancer Death Risk Assessment Tool [LCDRAT], and Kovalchik model) estimating outcomes in 4 different cohorts reported increased screen-preventable deaths compared with the risk factor–based criteria used by the NLST or USPSTF (in the 2013 recommendations). Three studies demonstrated improved screening efficiency (determined by the NNS) of risk prediction models compared with risk factor–based screening, while 1 study showed mixed results. For harms, 8 studies of 13 different risk prediction models (PLCOm2012, simplified PLCOm2012, Bach, Liverpool Lung Project [LLP], simplified LLP, Knoke, Two-Stage Clonal Expansion [TSCE] incidence, TSCE Cancer Prevention Study death, TSCE Nurses' Health Study/Health Professionals Follow-up Study, the HUNT Lung Cancer model, LCDRAT, COPD-LUCSS [Lung Cancer Screening Score], Kovalchik) estimating outcomes in 4 different cohorts reported similar numbers of false-positive selections from risk prediction (ie, the risk

Figure 4. Trial Results for Lung Cancer Mortality (Key Question 1)

| Study, y | Male, % | Follow-up, y | Mean age, y | Mean pack-years | Screening times, y | Patients, No. | | Events, No. | | LDCT, deaths per 100 000 person-years | Control, deaths per 100 000 person-years | IRR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | LDCT | Control | LDCT | Control | | | |
| NLST,[29-37] 2011-2019 | 59 | 6.5 | 61 | 56 | 0, 1, 2 | 26722 | 26732 | 469 | 552 | 280 | 332 | 0.85 (0.75-0.96) |
| DANTE,[12-14] 2008-2015 | 100 | 8.4 | 65 | 47 | 0, 1, 2, 3, 4 | 1276 | 1196 | 59 | 55 | 543 | 544 | 1.00 (0.69-1.44) |
| DLCST,[15,16] 2012-2016 | 56 | 9.8 | 58 | 36 | 0, 1, 2, 3, 4 | 2052 | 2052 | 39 | 38 | 201 | 194 | 1.03 (0.66-1.61) |
| ITALUNG,[17] 2017 | 65 | 9.3 | 61 | 39 | 0,1,2,3 | 1613 | 1593 | 43 | 60 | 293 | 421 | 0.70 (0.47-1.03) |
| LSS,[18-20] 2004-2018 | 59 | 5.2 | NR | 54 | NR | 1660 | 1658 | 32 | 26 | 383 | 310 | 1.24 (0.74-2.07) |
| NELSON,[24-28] 2006-2020 | 84 | 10 | 58 | 38 | 0, 1, 3, 5.5 | 7900 | 7892 | 181 | 242 | 241 | 324 | 0.75 (0.61-0.90) |




DANTE indicates Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST, Danish Lung Cancer Screening Trial; IRR, incidence rate ratio; ITALUNG, Italian Lung Cancer Screening Trial; LDCT, low-dose computed tomography; LSS, Lung Screening Study; NELSON, Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST, National Lung Screening Trial; NR, not reported.

prediction model selected persons to be screened who did not have or develop lung cancer) and mixed findings for rates of false-positive selections when comparing risk prediction models with the risk factor–based criteria used by the NLST or USPSTF. In general, estimates were consistent but imprecise, primarily because of a lack of an established risk threshold to apply the model.

## Accuracy of Screening

**Key Question 3a.** What is the accuracy of screening for lung cancer with LDCT?

**Key Question 3b.** Does the accuracy of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

**Key Question 3c.** Does the accuracy of screening for lung cancer with LDCT differ for various approaches to nodule classification (ie, those based on nodule size and characteristics)?

Detailed results for this KQ are in eResults and eTables 17 and 18 in the Supplement. Fifty-three articles were eligible for this KQ.[12,13,19,21,22,24-28,30-32,34,40-77] Of those, 24 publications with the most complete data are described.[12,21,24,34,41,43-45,47-49,52,53,56,58,60,64,66-68,71,72,75,76] Sensitivity of LDCT from 13 studies (76 856 total participants) ranged from 59% to 100%; all but 3 studies reported sensitivity greater than 80%. Specificity of LDCT from 13 studies (75 819 total participants) ranged from 26.4% to 99.7%; all but 3 reported specificity greater than 75%. Positive predictive value (14 studies, 77 840 participants) ranged from 3.3% to 43.5%. Negative predictive value (9 studies, 47 496 participants) ranged from 97.7% to 100%. Variability in accuracy was mainly attributed to heterogeneity of eligibility criteria, screening protocols (eg, number of screening rounds, screening intervals), follow-up length (eg, to identify false-negative screens), and definitions (eg, of positive tests, indeterminate tests). Three studies (73 404 participants) compared various approaches to nodule classification (Lung-RADS or International Early Lung Cancer Action Program [I-ELCAP]) and found that using Lung-RADS in the NLST would have increased specificity while decreasing sensitivity and that increases in positive predictive value are seen with increasing nodule size thresholds.[44,49,52]

## Harms of Screening, Workup, or Surveillance

**Key Question 4a.** What are the harms associated with screening for lung cancer with LDCT?

**Key Question 4b.** Do the harms of screening for lung cancer with LDCT differ with the use of Lung-RADS, I-ELCAP, or similar approaches (eg, to reduce false-positive results)?

**Key Question 4c.** Do the harms of screening for lung cancer with LDCT differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

**Key Question 5a.** What are the harms associated with workup or surveillance of nodules?

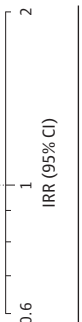
**Key Question 5b.** Do the harms of workup or surveillance of nodules differ with the use of Lung-RADS, I-ELCAP, or similar approaches (eg, to reduce false-positive results)?

**Key Question 5c.** Do the harms of workup or surveillance of nodules differ for subgroups defined by age, sex, race/ethnicity, presence of comorbid conditions, or other lung cancer risk factors?

Detailed results are in eResults in the Supplement.

Figure 5. Trial Results for All-Cause Mortality (Key Question 1)

| Study, y | Male, % | Follow-up, y | Mean age, y | Mean pack-years | Screening times, y | Patients, No. | | Events, No. | | LDCT, deaths per 100 000 person-years | Control, deaths per 100 000 person-years | IRR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | LDCT | Control | LDCT | Control | | | |
| NLST,[29-37] 2011-2019 | 59 | 6.5 | 61 | 56 | 0, 1, 2 | 26722 | 26732 | 1912 | 2039 | 1141 | 1225 | 0.93 (0.88-0.99) |
| DANTE,[12-14] 2008-2015 | 100 | 8.4 | 65 | 47 | 0, 1, 2, 3, 4 | 1276 | 1196 | 180 | 176 | 1655 | 1742 | 0.95 (0.77-1.17) |
| DLCST,[15,16] 2012-2016 | 56 | 9.8 | 58 | 36 | 0, 1, 2, 3, 4 | 2052 | 2052 | 165 | 163 | 849 | 834 | 1.02 (0.82-1.26) |
| ITALUNG,[17] 2017 | 65 | 9.3 | 61 | 39 | 0,1,2,3 | 1613 | 1593 | 154 | 181 | 1051 | 1270 | 0.83 (0.67-1.03) |
| LSS,[18-20] 2004-2018 | 59 | 5.2 | NR | 54 | NR | 1660 | 1658 | 139 | 116 | 1667 | 1384 | 1.20 (0.94-1.53) |
| NELSON,[24-28] 2006-2020 | 100 | 10 | 58 | 38 | 0, 1, 3, 5.5 | 6583 | 6612 | 868 | 860 | 1393 | 1376 | 1.01 (0.92-1.11) |




DANTE indicates Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST, Danish Lung Cancer Screening Trial; IRR, incidence rate ratio; ITALUNG, Italian Lung Cancer Screening Trial; LDCT, low-dose computed tomography; LSS, Lung Screening Study; NELSON, Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST, National Lung Screening Trial; NR, not reported.

### Radiation Exposure

Nine publications reported on radiation associated with LDCT.[16,31,56,69,75,78-81] Most of those reported the radiation associated with 1 LDCT, with ranges from 0.65 mSv to 2.36 mSv (eTable 19 in the Supplement). Two of the studies evaluated the cumulative radiation exposure for participants undergoing screening with LDCT[78,80]; using those studies to estimate cumulative exposure for an individual from 25 years of annual screening (ie, from age 55 to 80 years as recommended by the USPSTF in 2013) yields 20.8 mSv to 32.5 mSv. One study estimated the lifetime risk of cancer from radiation of 10 annual LDCTs was 0.26 to 0.81 major cancers for every 1000 people screened.[80]

### False-Positive Results and Follow-up Evaluations

Twenty-seven publications reported enough information to determine the rate of false-positives, defined as any result leading to additional evaluation (eg, repeat LDCT scan before the next annual screening, biopsy) that did not result in a diagnosis of cancer.[15,18,19,21,24,30-32,34,40,46,47,49,52,56,62,65-68,73,75-77,82-84] False-positive rates varied widely across studies, most likely because of differences in definitions of positive results, such as cutoffs for nodule size (eg, 4 mm vs 5 mm vs 6 mm), use of volume-doubling time, and nodule characteristics considered. The range of false-positive rates overall was 7.9% to 49.3% for baseline screening and 0.6% to 28.6% for individual incidence screening rounds, although rates for some subgroups were higher (eg, age ≥65 years) (eTable 20 in the Supplement). False-positive rates generally declined with each screening round.[34,47,65,66,73,76]

Among the trials that found lung cancer screening mortality benefit and cohort studies based in the US, false-positive rates were 9.6% to 28.9% for baseline and 5.0% to 28.6% for incidence rounds. The NLST reported false-positive rates for baseline, year 1, and year 2 of 26.3%, 27.2%, and 15.9%, respectively.[31] The NELSON trial noted false-positive rates of 19.8% at baseline, 7.1% at year 1, 9.0% for males at year 3, and 3.9% for males at year 5.5 of screening.[24,65] One study of 112 radiologists from 32 screening centers who each interpreted 100 or more NLST scans reported a mean (SD) false-positive rate of 28.7% (13.7) (range, 3.8%-69.0%).[46] Mean rates were similar for academic (n = 25) and nonacademic (n = 7) centers (27.9% vs 26.7%, respectively).[46] An implementation study through the Veterans Health Administration revealed a false-positive rate of 28.9% of veterans eligible for screening (58% of those who were actually screened) at baseline screening.[40] False-positive rates varied across 8 study sites, ranging from 12.6% to 45.8% of veterans eligible for screening.[40]

Fourteen studies reported on the evaluation of false-positive results.[22,30,31,34,43,62-64,66,72,75,79,81,85] Among all patients screened, the percentage who had a needle biopsy for a false-positive result ranged from 0.09% to 0.56% (eTable 21 in the Supplement). Surgical procedures for false-positive results were reported in 0.5% to 1.3% and surgical resections for false-positive results were reported in 0.1% to 0.5% of all screened participants.

In the NLST, false-positive results led to invasive procedures (needle biopsy, thoracotomy, thoracoscopy, mediastinoscopy, and bronchoscopy) in 1.7% of those screened (number needed to harm, 59). Complications occurred in 0.1% of those screened (number needed to harm, 1000), with major, intermediate, and minor

complications occurring in 0.03%, 0.05%, and 0.01%, respectively, of those screened. Death in the 60 days following the most invasive procedure performed occurred in 0.007% of those screened.[31] One study using NLST data estimated that 117 invasive procedures for false-positive results (23.4% of all invasive procedures for false-positive results from the NLST) would be prevented by using Lung-RADS criteria.[44]

### Overdiagnosis

Five studies specifically examined overdiagnosis,[81,86-89] and 7 additional trials were examined for differences in cancer incidence between LDCT and comparison groups.[14,17,19,24,31,90,91] Estimates of overdiagnosis ranged from 0% to 67.2% that a screen-detected lung cancer is overdiagnosed.

### Smoking Behavior

One RCT (DLCST; 4075 participants), studies of participants from RCTs (NELSON, NLST, LSS; 19 426 total participants), and 3 cohort studies (ELCAP, Mayo Lung Project, and Pittsburgh Lung Screening Study [PLuSS]; 5537 total participants) included evaluations of the effect of LDCT screening or screening results on smoking cessation and relapse.[91-100] Studies comparing LDCT vs controls (no screening or chest radiography) for smoking cessation or abstinence outcomes do not indicate that screening leads to false reassurance. Abnormal or indeterminate screening test results may increase cessation and continued abstinence, but normal screening test results had no influence. Regarding smoking intensity, evidence was minimal, and no study showed influence of screening or test result on smoking intensity.

### Psychosocial Harms

Four RCTs (DLCST, NELSON, NLST, and UK Lung Cancer Screening [UKLS] trial; 12 096 total participants) reported in 6 publications,[62,101-105] 1 uncontrolled cohort study (PLuSS, 400 participants),[106] and 2 studies of participants from the screening arm of an RCT (NELSON, 630 participants[107]; UKLS, 1589 participants[108]) included an evaluation of potential psychosocial consequences of LDCT screening. These studies evaluated general health-related quality of life (HRQoL; 3 studies),[101,104,107] anxiety (8 studies),[62,101-107] depression (2 studies),[62,102] distress (3 studies),[62,104,107] and other psychosocial consequences of LDCT screening (5 studies).[62,103,105,106,108] Taken together, there is moderate evidence to suggest that, compared with no screening, persons who receive LDCT screening do not have worse general HRQoL, anxiety, or distress over 2 years of follow-up. Some evidence suggests differential consequences by screening result such that general HRQoL and anxiety were worse, at least in the short-term, for individuals who received true-positive results compared with other screening results; distress was worse for participants who received an indeterminate screening result compared with other results. The strength of evidence is low for other psychosocial consequences, largely because of unknown consistency, imprecision, and only 1 or 2 studies assessed outcomes.

### Incidental Findings Leading to Additional Tests and Subsequent Harms

Studies reported a wide range of screening-related incidental findings (4.4% to 40.7%) that were deemed significant or requiring further evaluation (eResults and eTable 22 in the Supplement).[34,40,62,82,109-112] Rates varied considerably in part because there was no consistent definition of what constitutes an incidental finding nor which findings were "actionable" or "clinically significant." Older age was associated with a greater likelihood of incidental findings. Common incidental findings included coronary artery calcification, aortic aneurysms, emphysema, infectious and inflammatory processes, masses, nodules, or cysts of the kidney, breast, adrenal, liver, thyroid, pancreas, spine, and lymph nodes. Incidental findings led to downstream evaluation, including consultations, additional imaging, and invasive procedures with associated costs and burdens.

## Discussion

This evidence review evaluated screening for lung cancer with LDCT in populations and settings relevant to US primary care; a summary of the evidence is provided in **Table 2**. Screening high-risk persons with LDCT can reduce lung cancer mortality but also causes a range of harms. For benefits of screening, the NLST demonstrated a reduction in lung cancer mortality and all-cause mortality with 3 rounds of annual LDCT screening compared with chest radiography, and the NELSON trial demonstrated a reduction in lung cancer mortality with 4 rounds of LDCT screening with increasing intervals. Harms of screening include false-positive results leading to unnecessary tests and invasive procedures, overdiagnosis, incidental findings, short-term increases in distress because of indeterminate results, and, rarely, radiation-induced cancer.

NLST and NELSON results are generally applicable to high-risk current and former smokers aged 50 to 74 years, but participants were younger, more highly educated, less likely to be current smokers than the US screening-eligible population, and had limited racial and ethnic diversity. The general US population eligible for lung cancer screening may be less likely to benefit from early detection compared with NLST and NELSON participants because they face a high risk of death from competing causes, such as heart disease and stroke.[113] Data from the 2012 Health and Retirement Study showed a lower 5-year survival rate and life expectancy in screening-eligible persons compared with NLST participants.[113] NELSON did not allow enrollment of persons with moderate or severe health problems and an inability to climb 2 flights of stairs; weight over 140 kg; or current or past kidney cancer, melanoma, or breast cancer.

The trials were mainly conducted at large academic centers, potentially limiting applicability to community-based practice (eg, because of challenges with implementation [eContextual Questions in the Supplement], level of multidisciplinary expertise). Many of the trial centers are well recognized for expertise in thoracic radiology as well as cancer diagnosis and treatment.[31] The NLST noted that mortality associated with surgical resection was much lower in the trial than that reported for the US population (1% vs 4%).[31,114]

Guidelines recommend that clinicians conduct a rigorous process of informed and shared decision-making about the benefits and harms of lung cancer screening before initiating screening. However, given the complex nature of benefits and harms associated with screening, there is some concern that robust shared

Table 2. Summary of Evidence on Screening for Lung Cancer With LDCT

| No. of studies (k), No. of observations (n) | Summary of findings | Consistency and precision | Study quality | Limitations (including reporting bias) | Overall strength of evidence | Applicability |
|---|---|---|---|---|---|---|
| **KQ1: benefits of screening** | | | | | | |
| k = 7 RCTs (26 publications); 86 486 participants | The good-quality NLST (n = 53 542) reported a reduction in lung cancer mortality (IRR, 0.85 [95% CI, 0.75-0.96]) and all-cause mortality (IRR, 0.93 [95% CI, 0.88-0.99]) with 3 rounds of annual LDCT compared with chest radiography (NNS = 323 to prevent 1 lung cancer death over 6.5 y). NELSON (n = 15 792) found a reduction in lung cancer mortality (IRR, 0.75 [95% CI, 0.61-0.90]) but not all-cause mortality (IRR, 1.01 [95% CI, 0.92-1.11]) with 4 rounds of LDCT screening using volumetric measurements with increasing intervals (baseline, 1 y, 3 y, and 5.5 y) compared with no screening (NNS = 130 to prevent 1 lung cancer death over 10 y) | Consistent among trials adequately powered; precise | Good: 1<br>Fair: 6 | All but 2 of the 7 trials were underpowered to assess for a lung cancer mortality benefit | High for benefit[a] | High-risk current and former smokers (with ≥30 pack-years [NLST] or >15 cigarettes/d for >25 y or >10 cigarettes/d for >30 y [NELSON]); aged 50-74 y; NLST and NELSON participants were younger, more highly educated, and less likely to be current smokers than the US screening-eligible population; limited racial and ethnic diversity; US population eligible for screening faces higher risk of death from competing causes than trial participants; mainly conducted at large academic centers; NLST did not use current US screening protocols such as Lung-RADS; NELSON used volumetric measurements for screening |
| **KQ2. Risk prediction models** | | | | | | |
| k = 9; 13 Risk prediction models evaluated in 9 cohorts comprising 21 922 733 participants | Benefits: studies of 3 models (PCLOm2012, LCDRAT, and Kovalchik model) reported increased screen-preventable deaths compared with risk factor–based criteria (k = 4; 21 682 066 participants from 4 cohorts). Most findings from these studies also showed improved NNS<br>Harms: studies of all models reported similar numbers of false-positive selections for screening (ie, the model selected people to be screened who did not have or develop lung cancer or death from lung cancer) and mixed findings for rates of false-positive selections or false-positive selections per prevented death when comparing risk prediction models with risk factor–based criteria[b] | Consistent; imprecise (results highly dependent on risk threshold selected) | Good: 6<br>Fair: 3 | No trials have compared use of a risk prediction model with risk factor-based criteria; evidence base is limited by lack of an established risk threshold; most models were evaluated by a single study in 1 to 2 cohorts | Low for greater benefits and similar or reduced harms | High-risk current and former smokers; mainly applicable to NLST or USPSTF screen-eligible persons (aged 55-74 y or 55-80 y) |
| **KQ3. Accuracy of screening with LDCT** | | | | | | |
| k = 24<br>n = 107 200 | Sensitivity ranged from 59% to 100% (k = 13, n = 76 856) and was >80% in most studies. Specificity ranged from 26.4% to 99.7% (k = 13, n = 75 819) and was >75% in most. PPV ranged from 3.3% to 43.5%. NPV ranged from 97.7% to 100%. Reliability among radiologists was fair to moderate (k = 3) | Reasonably consistent; imprecise (except precise for NPV) | Good: 3<br>Fair: 21 | Incomplete or unreported follow-up length may have led to differential measurement<br>Heterogeneity in screening protocols and definitions (eg, positive tests, indeterminate tests) | Moderate | US and highly developed countries; most conducted in past 10 y. Similar LDCT technologies used across studies; varying nodule classification protocols that could likely be replicated in the US; few studies used nodule classification approach recommended by ACR (Lung-RADS) |
| **KQs 4 and 5. Harms of screening, workup, or surveillance** | | | | | | |
| Radiation<br>k = 9<br>n = 74 963 participants | Radiation from 1 LDCT: range, 0.65 mSv to 2.36 mSv<br>Cumulative radiation exposure: 20.8 mSv to 32.5 mSv for annual screening for 25 y<br>Radiation-induced cancer: 0.26 to 0.81 major cancers for every 1000 people screened with 10 annual LDCTs[c] | Consistent; imprecise | Good: 3<br>Fair: 6 | Estimates of radiation-induced cancers are based on modeling | Moderate for radiation-induced harms | Estimates were not provided for lifetime risk of radiation-induced cancers or fatal cancers from annual screening from age 55-80 y (ie, USPSTF 2013 recommendation) |

(continued)

Table 2. Summary of Evidence on Screening for Lung Cancer With LDCT (continued)

| No. of studies (k), No. of observations (n) | Summary of findings | Consistency and precision | Study quality | Limitations (including reporting bias) | Overall strength of evidence | Applicability |
|---|---|---|---|---|---|---|
| False-positives<br>k = 27<br>n = 115 654 participants<br>False-positive follow-up evaluations<br>k = 14<br>n = 56 223 participants | False-positive rates: range, 7.9% to 49.3% for baseline screening and 0.6% to 28.6% for incidence screening rounds; rates generally declined with each round. NLST reported 26.3%, 27.2%, and 15.9% for baseline, year 1, and year 2, respectively; rates were lower in NELSON; the VA implementation study reported 58% of those screened (28.9% of screen-eligibles) at baseline and >30% variation across 8 sites<br>Invasive procedures for false-positive results, range of rates for every 1000 people screened (NLST rate): 0.9 to 5.6 needle biopsies (2.5) resulting in 0.3 to 0.7 complications; 5 to 13 surgical procedures (17 total invasive procedures, resulting in <1 major complication)[d] | Consistent; imprecise | Good: 8<br>Fair: 19<br>Good: 4<br>Fair: 10 | Heterogeneity in screening protocols, definitions of positive and false-positive results, and reporting of procedures and complication rates | Moderate for harms due to false-positive results | Most studies did not use current nodule evaluation protocols such as Lung-RADS; an evaluation using NLST data estimated that 23.4% of all invasive procedures for false-positive results from the NLST would have been prevented by using Lung-RADS |
| Overdiagnosis<br>k = 12<br>n = 95 290 participants | Overdiagnosis: estimates ranged from 0% to 67.2% that a screen-detected lung cancer is overdiagnosed; NLST data indicate approximately 4 cases of overdiagnosis over 6.5 y (and 3 lung cancer deaths prevented) per 1000 people screened[e] | Inconsistent; imprecise | Good: 2<br>Fair: 10 | Inadequate duration of follow-up and heterogeneity limit the evaluation | Low for harms | NLST estimate is based on 3 annual screens and 6.5 y of follow-up; uncertain whether it would increase or decrease with ongoing screening and longer follow-up |
| Smoking behavior<br>k = 7<br>n = 29 038 participants | LDCT vs no screening (k = 2): evidence on cessation and intensity does not indicate harm of false reassurance<br>Positive or indeterminate results vs normal results: abnormal or indeterminate results may increase cessation and continued abstinence, but normal screening test results had no influence | Inconsistent; Imprecise | Good: 0<br>Fair: 7 | Most RCTs of LDCT did not report on outcomes to assess for false reassurance | Low for no harms | The 2 RCTs providing data for LDCT vs no screening were conducted in Denmark (DLCST) and the Netherlands and Belgium (NELSON) |
| Psychosocial harms<br>k = 9<br>n = 14 715 Participants | General HRQoL: no significant differences over 6 mo to 2 y of follow-up between LDCT and controls (k = 2 RCTs, n = 3937); worse HRQoL for persons receiving true-positive results vs other results<br>Anxiety and depression: no significant increase over 2 wk to 2 y of follow-up for LDCT vs controls (k = 6 RCTs, n = 12 096); increased anxiety for individuals receiving true-positive results vs other results<br>Distress: no significant increase over approximately 2 y of follow-up for LDCT vs controls (k = 2 RCTs, n = 5180); temporary increase for those receiving indeterminate results vs other results<br>Other potential psychosocial consequences of screening: each generally assessed by a single study, often without a non-LDCT comparison group, and not indicative of harm | Reasonably consistent and precise for HRQoL, anxiety and depression, and distress<br>Consistency unknown and imprecise for other outcomes | Good: 1<br>Fair: 8 | Relatively short follow-up (≤2 y); RCTs did not assess these outcomes over the duration of the trials | Moderate for no harm over 2 y (HRQoL, anxiety, and distress) for LDCT vs controls<br>Moderate for worse short-term HRQoL, anxiety, and distress for those who received true-positive or indeterminate results vs other results | High-risk current and former smokers; studies lacked racial and ethnic diversity; most studies conducted in Europe; trials did not use current protocols such as Lung-RADS |

(continued)

Table 2. Summary of Evidence on Screening for Lung Cancer With LDCT (continued)

| No. of studies (k), No. of observations (n) | Summary of findings | Consistency and precision | Study quality | Limitations (including reporting bias) | Overall strength of evidence | Applicability |
|---|---|---|---|---|---|---|
| Incidental findings (IFs)<br>k = 7<br>n = 80 485 | Rates of reported significant IFs ranged from 4.4% to 40.7%. Common IFs were coronary artery calcification; aortic aneurysms; emphysema; infectious and inflammatory processes; and masses, nodules, or cysts of the kidney, breast, adrenal, liver, thyroid, pancreas, spine, and lymph nodes. IFs led to consultations, additional imaging, and invasive procedures<br>Incidental detection of thyroid cancer: in NLST, thyroid cancer incidence was roughly double during 3 y of active LDCT screening compared with chest radiographic screening (HR, 2.19 [95% CI, 1.07-4.47]), but not during subsequent years (HR, 1.08 [95% CI, 0.49-2.37])[f] | Consistent; imprecise | Fair: 7 | No standard definition for which IFs were significant or actionable. Few studies on follow-up evaluations and distal outcomes | Moderate for harms | Screen-eligible adults undergoing LDCT in academic or tertiary lung cancer screening centers |
| **KQ6. Efficacy of surgical resection for stage I NSCLC** | | | | | | |
| k = 36 Uncontrolled cohort studies<br>n = 212 274 | 5-y OS for surgical resection (including lobectomy and SLR approaches); range, 33% to 86% for stage I, 58% to 83% for stage IA, and 42% to 79% for stage IB<br>In pathologic stage I patients in the NCDB from 2003 to 2006, the 5-y OS was 61% for surgical resection (n = 54 350). Survival rates in the NCDB, SEER, and VA VINCI databases for stage I, covering the years 2003-2015 ranged from 53% to 75% for lobectomy (n = 23 707)<br>Survival rates were generally higher for lobectomy than SLR, for smaller than larger tumors, and for patients who are female, younger, nonsmokers, or had fewer comorbidities than patients who are male, older, smokers, or sicker | Reasonably consistent; imprecise | Good: 5<br>Fair: 31 | Information related to deviations from intervention, missing data, and sources of survival outcomes often lacking; heterogeneity related to staging of NSCLC (clinical or pathologic) and surgical approaches (among studies and over time) | Moderate for benefit | Persons with stage I NSCLC; some studies were more than 10 y old and may be less applicable to current approaches and outcomes (studies were from 1983 to 2018) |
| **KQ6. Efficacy of SBRT for stage I NSCLC** | | | | | | |
| k = 27 Uncontrolled cohort studies<br>n = 38 915 | 5-y OS (and other measures of long-term survival) varied substantially across studies (range, 20%-80%) and by subgroups defined by clinical characteristics (eg, operability of tumor) and patient age; survival may be higher among younger than older patients | Inconsistent; imprecise | Good: 2<br>Fair: 25 | Information related to deviations from intervention, missing data, and sources of survival outcomes often lacking; substantial heterogeneity related to staging and operability of tumors | Low for benefit | Persons with operable or inoperable stage I NSCLC |
| **KQ7. Harms of surgical resection** | | | | | | |
| k = 29 Uncontrolled cohort studies<br>n = 755 427 | 30-d Mortality rates ranged from 0% to 4% in most studies; rates of 90-d mortality were slightly higher (range, 2%-5% in most studies). Less than one-third of patients in most studies experienced treatment-related adverse events. Adverse events reported in ≥10% of patients included pulmonary events (eg, air leak, pleural effusion) and cardiac arrhythmias | Reasonably consistent; reasonably precise | Good: 3<br>Fair: 26 | Information related to deviations from intervention, missing data, and sources of survival outcomes often lacking; potential selective reporting of adverse events | Moderate for harms | Persons having lobectomy or SLR for the treatment of stage I NSCLC |
| **KQ7. Harms of SBRT** | | | | | | |
| k = 1 RCT (comparing dosing regimens), 1 uncontrolled clinical trial, and 58 uncontrolled cohort studies<br>n = 49 654 | 30- and 90-d Mortality rates ranged from 0% to 3%. Adverse events were experienced by most patients, but most were of mild or moderate severity. Adverse events reported in ≥10% of patients included were pulmonary events (eg, cough, dyspnea, pneumonitis, fibrosis) or respiratory disorders (including dyspnea), chest wall pain, fatigue, and dermatologic reactions. Incidence of rib fracture ranged from 0% (n = 80 patients) to 42% (n = 169 patients) | Reasonably consistent; imprecise | Good: 1<br>Fair: 59 | Information related to deviations from intervention, missing data, and sources of survival outcomes often lacking; potential selective reporting of adverse events | Low for harms | Persons having SBRT/SABR for the treatment of operable or inoperable stage I NSCLC |

(continued)

Table 2. Summary of Evidence on Screening for Lung Cancer With LDCT (continued)

| No. of studies (k), No. of observations (n) | Summary of findings | Consistency and precision | Study quality | Limitations (including reporting bias) | Overall strength of evidence | Applicability |
|---|---|---|---|---|---|---|
| KQ8. Change in mortality from a specified change in lung cancer incidence (and stage shift) | | | | | | |
| k = 2 RCTs (NLST and NELSON)<br>n = 69 334 | An absolute increase in lung cancer incidence of 0.5% to 0.6%, increase in stage I lung cancers of 19% to 27%, decrease in stage IV lung cancers of 14% to 19% were associated with 52 to 83 fewer lung cancer deaths and 0 (NELSON) to 84 (NLST) fewer all-cause deaths per 100 000 person-years | Consistent; precise for lung cancer mortality but imprecise for all-cause mortality | Good: 1<br>Fair: 1 | Reporting bias not detected | High | 3 Annual rounds of screening with LDCT (compared with chest radiography) in NLST or 4 rounds of screening with increasing intervals as conducted in NELSON (volumetric approach); applicable to workup of lung cancers and subsequent treatments used in the NLST and NELSON; same applicability issues as listed for KQ1 |

Abbreviations: ACR, American College of Radiology; DLCST, Danish Lung Cancer Screening Trial; HR, hazard ratio; HRQoL, health-related quality of life; IF, incidental finding; IRR, incidence rate ratio; KQ, key question; LCDRAT, Lung Cancer Death Risk Assessment Tool; LDCT, low-dose computed tomography; NCDB, National Cancer Database; NELSON, Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST, National Lung Screening Trial; NNS, number needed to screen; NPV, negative predictive value; NSCLC, non–small cell lung cancer; OS, overall survival; PPV, positive predictive value; RCT, randomized clinical trial; SABR, stereotactic ablative radiation; SBRT, stereotactic body radiotherapy; SEER, Surveillance, Epidemiology, and End Results; SLR, sublobar resection; USPSTF, US Preventive Services Task Force; VA, Veteran's Administration; VA VINCI, VA Informatics and Computing Infrastructure.

[a] Strength of evidence was graded as moderate prior to final publication of NELSON because of unknown consistency (with a single good-quality study that was adequately powered) but was changed to high after including NELSON in the evidence report.

[b] The language "false-positive" refers to model performance metrics with respect to lung cancer events (diagnosis or deaths), not with respect to LDCT results.

[c] One study estimated a lifetime risk of fatal cancer of 0.11 per 1000 patients after the 4 screening rounds.[78]

[d] NLST reported 11 major complications and 6 deaths within 60 days of invasive procedures among those with false-positive results (2 deaths after surgical resections and 4 after bronchoscopy).

[e] Based on converting data to per 1000 screened from study that reported 1.38 cases of overdiagnosis in every 320 patients needed to screen to prevent 1 death from lung cancer.[87]

[f] This study specifically addressed the potential for overdiagnosis of thyroid cancer through incidental detection.

decision-making is impractical to implement in actual practice.[115-117] eContextual question 1 in the Supplement describes the barriers to implementing lung cancer screening and surveillance in clinical practice in the US.

Most studies reviewed in this article (including the NLST) did not use current nodule evaluation protocols such as Lung-RADS (endorsed by the American College of Radiology).[118] A study included in this review estimated that Lung-RADS would reduce false-positive results compared with NLST criteria and that about 23% of all invasive procedures for false-positive results from the NLST would have been prevented by using Lung-RADS criteria.[44]

Application of lung cancer screening with (1) current nodule management protocols and (2) the use of risk prediction models might improve the balance of benefits and harms, although the strength of evidence supporting this possibility was low. There remains considerable uncertainty about how such approaches would perform in actual practice because the evidence was largely derived from post hoc application of criteria to trial data (for Lung-RADS) and from modeling studies (for risk prediction) and does not include prospective clinical utility studies. Additional discussion of the evidence on risk prediction models is provided in the eDiscussion in the Supplement. When applied to current clinical practice, lung cancer screening programs have demonstrated significant variation, even within a single institution type.[40]

### Limitations

This review has several limitations. First, non–English-language articles were excluded, as were studies with sample size less than 500 or 1000 for some KQs to focus on the best evidence. Doing so omitted some smaller studies that reported on harms of screening. For example, a study of 351 participants in the NELSON trial examined discomfort of LDCT scanning and waiting for the LDCT results.[119] Most participants (88%-99%) reported experiencing no discomfort related to the LDCT scan, but about half reported at least some discomfort from waiting for the result (46%) and dreading the result (51%). Second, the KQ on risk prediction models (KQ2) was limited to how well risk prediction models perform vs current recommended risk factor–based criteria for lung cancer screening. KQ2 complements the decision analysis report[120] by evaluating previously published studies that apply risk prediction models to cohorts or representative samples of the US population rather than simulated populations. Third, for accuracy, some included studies did not report accuracy metrics; rather, when sufficient data were reported, values were calculated from the study data. This approach introduces uncertainty and may account for variability.

## Conclusions

Screening high-risk persons with LDCT can reduce lung cancer mortality but also causes false-positive results leading to unnecessary tests and invasive procedures, overdiagnosis, incidental findings, increases in distress, and, rarely, radiation-induced cancers. Most studies reviewed did not use current nodule evaluation protocols, which might reduce false-positive results and invasive procedures for false-positive results.

## ARTICLE INFORMATION

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**Author Contributions:** Dr Jonas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Jonas, Reuland, Nagle, Clark, Weber, Enyioha, Armstrong, Voisin.
*Acquisition, analysis, or interpretation of data:* Jonas, Reuland, Reddy, Nagle, Clark, Weber, Enyioha, Malo, Brenner, Armstrong, Coker-Schwimmer, Middleton, Harris.
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