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Benefits and Harms of CT Screening for Lung Cancer

A Systematic Review

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Context Lung cancer is the leading cause of cancer death. Most patients are diagnosed with advanced disease, resulting in a very low 5-year survival. Screening may reduce the risk of death from lung cancer.

Objective To conduct a systematic review of the evidence regarding the benefits and harms of lung cancer screening using low-dose computed tomography (LDCT). A multisociety collaborative initiative (involving the American Cancer Society, American College of Chest Physicians, American Society of Clinical Oncology, and National Comprehensive Cancer Network) was undertaken to create the foundation for development of an evidence-based clinical guideline.

Data Sources MEDLINE (Ovid: January 1996 to April 2012), EMBASE (Ovid: January 1996 to April 2012), and the Cochrane Library (April 2012).

Study Selection Of 591 citations identified and reviewed, 8 randomized trials and 13 cohort studies of LDCT screening met criteria for inclusion. Primary outcomes were lung cancer mortality and all-cause mortality, and secondary outcomes included nodule detection, invasive procedures, follow-up tests, and smoking cessation.

Data Extraction Critical appraisal using predefined criteria was conducted on individual studies and the overall body of evidence. Differences in data extracted by reviewers were adjudicated by consensus.

Results Three randomized studies provided evidence on the effect of LDCT screening on lung cancer mortality, of which the National Lung Screening Trial was the most informative, demonstrating that among 53 454 participants enrolled, screening resulted in significantly fewer lung cancer deaths (356 vs 443 deaths; lung cancer–specific mortality, 274 vs 309 events per 100 000 person-years for LDCT and control groups, respectively; relative risk, 0.80; 95% CI, 0.73-0.93; absolute risk reduction, 0.33%; $P=.004$). The other 2 smaller studies showed no such benefit. In terms of potential harms of LDCT screening, across all trials and cohorts, approximately 20% of individuals in each round of screening had positive results requiring some degree of follow-up, while approximately 1% had lung cancer. There was marked heterogeneity in this finding and in the frequency of follow-up investigations, biopsies, and percentage of surgical procedures performed in patients with benign lesions. Major complications in those with benign conditions were rare.

Conclusion Low-dose computed tomography screening may benefit individuals at an increased risk for lung cancer, but uncertainty exists about the potential harms of screening and the generalizability of results.

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LUNG CANCER IS THE LEADING CAUSE of cancer death in the United States (and worldwide), causing as many deaths as the next 4 most deadly cancers combined (breast, prostate, colon, and pancreas).[1] Despite a slight decline in US lung cancer mortality rates since 1990, lung cancer will account for more than 160 000 deaths in the United States in 2012.[2] Most patients diagnosed with lung cancer today already have advanced disease (40% are stage IV, 30% are stage III), and the current 5-year survival rate is only 16%.[3]

Earlier randomized controlled trials (RCTs) involving chest radiographs and sputum cytology for lung cancer screening found that these strategies detected

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CME available online at www.jamaarchivescme.com and questions on p 2441.

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slightly more lung cancers, smaller tumors, and more stage I tumors, but the detection of a larger number of early-stage cancers was not accompanied by a reduction in the number of advanced lung cancers or a reduction in lung cancer deaths.[4-14] Renewed enthusiasm for lung screening arose with the advent of low-dose computed tomography (LDCT) imaging, which is able to identify smaller nodules than can chest radiographs.

This systematic review focuses on the evidence regarding the benefits and harms of LDCT screening for lung cancer. Other potential screening methods (eg, chest radiographs, sputum cytology or biomarkers, exhaled breath) are not addressed. This review is a collaborative initiative of the American Cancer Society (ACS), the American College of Chest Physicians (ACCP), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) and forms the basis for the clinical practice guideline of the ACCP and ASCO. This work will be reassessed when pertinent new data become available, consistent with the Institute of Medicine recommendations for guideline development.[15]

METHODS

The ACS, ACCP, ASCO, and NCCN assembled a panel of experts representing the relevant clinical disciplines and the consumer's perspective. All members cleared all organizations' conflict-of-interest policies for participation in guideline development; none received compensation for participation. The sponsoring organizations donated staff time supported by their general administrative funds. No industry funds were used.

The panel defined a process for selection, data extraction, and outcomes assessment to produce a thorough evaluation of LDCT screening relevant to patient-centered outcomes, including quantifying potential benefits and harms. The target patient population for this initiative is individuals at elevated risk of developing lung cancer because of age and smoking history; and the target audience includes physicians, allied professionals, and policy makers.

The panel was divided into evidence review and writing subcommittees, focusing on 4 key questions. (1) What are the potential benefits of screening individuals at elevated risk of developing lung cancer using LDCT? (2) What are the potential harms of screening individuals at elevated risk of developing lung cancer using LDCT? (3) Which groups are most likely to benefit or not benefit from screening? (4) In what setting is screening likely to be effective?

The literature search was developed and conducted by an experienced systematic reviewer using MEDLINE (Ovid: January 1996 to April 8, 2012), EMBASE (Ovid: January 1996 to April 8, 2012), and the Cochrane Library (April 20, 2012). Additional citations were gleaned from the reference lists of related papers and review articles. The literature search included Medical Subject Headings (MeSH) and Emtree headings and related text and keyword searches in a manner that combined terms related to lung cancer, population screening, and LDCT (eAppendix 1, available at http://www.jama.com). The search was limited to published data only.

Studies were eligible for inclusion if they involved either an RCT using LDCT screening for lung cancer in one intervention group or a noncomparative cohort study of LDCT screening, provided they reported at least 1 of the following outcomes: lung cancer–specific or all-cause mortality, nodule detection rate, frequency of additional imaging, frequency of invasive diagnostic procedures (eg, needle or bronchoscopic biopsy, surgical biopsy, surgical resection), complications from the evaluation of suspected lung cancer, or the rate of smoking cessation or reinitiation. For lung cancer–specific and all-cause mortality end points, only RCT data were considered eligible for inclusion; for other end points, data from the LDCT group of both RCTs and cohort studies were included.

Exclusion criteria covered studies that only assessed screening among participants with risk factors other than smoking (eg, asbestos), those not published in English, and meta-analysis or case-series reports of outcomes only among patients diagnosed with lung cancer.

The exclusion criteria were determined a priori and guided whether data identified by the systematic literature review were judged to have been reported in a manner appropriate for inclusion. Articles were selected and data were extracted independently by a minimum of 2 reviewers. At the point of abstract review, if 1 of 2 reviewers indicated that a citation may be relevant, the full-text article was retrieved. After full text review, if there was a discrepancy among the 2 reviewers, a third reviewer determined eligibility, and the reviewers came to consensus. In addition, the third reviewer also verified that articles deemed ineligible did not meet eligibility criteria.

Between the 3 reviewers, discrepancies occurred in approximately 12% of cases and were resolved through consensus. Most notably, the small RCT by Garg et al[16] and the smoking cessation study by Schnoll et al[17] were originally excluded, but the decision was reversed on further review. Common reasons for exclusion included the identification of narrative reviews, studies that did not involve high-risk smoking populations, and studies that only followed up patients diagnosed with lung cancer. A full list of the studies excluded from the systematic review and the reasons for exclusion is available from the authors. For included studies, the risk of bias was assessed by a minimum of 2 reviewers using prespecified criteria (eAppendix 2), and discrepancies were resolved through consensus.

The frequency of nodule detection across studies was analyzed both unadjusted and stratified by multiple study design characteristics (eg, CT collimation, minimum smoking exposure criteria for study enrollment, stated threshold for labeling a finding "positive" or "suspicious").

RESULTS

Eight RCTs (**TABLE 1**)[16,18-27] and 13 cohort studies of LDCT screening (**TABLE 2**)[28-47] were selected from 591 citations identified by the literature search (eAppendix 3). Two smaller RCTs are related to 2 larger RCTs: the

Lung Screening Study (LSS) was a pilot study of the National Lung Screening Trial (NLST) and there is a prespecified plan to combine data from the Danish Lung Cancer Screening Trial (DLCST) with the Dutch Belgian Randomised Lung Cancer Screening Trial (NELSON). Several trials were ongoing with only preliminary data available. Two RCTs were excluded because they lacked data on key end points; 1 RCT and several cohort studies were excluded because they involved populations at risk because of factors other than smoking or were for general population screening. For studies reported in multiple publications, all reports were reviewed, but earlier reports superseded by additional data in later reports are not referenced.

The NLST and DLCST had a low risk of bias (eTable 1). Other studies had variable risks of bias, in part because only preliminary reports of ongoing studies are available. The risk of bias in the cohort studies was variable and often high (usually because they lacked justification for the sample size, a definition of the primary end point, or description of funding sources).

Across the RCTs, the minimum smoking history required for enrollment ranged from 15 to 30 pack-years (ie, cigarette packs smoked per day multiplied by years of smoking), with a maximum time since quitting smoking ranging from 10 years to an unlimited number of years (Table 1). The lower age limit ranged from 47 to 60 years, and the upper limit from 69 to 80 years. There was greater variation in entry criteria in the cohort studies (Table 2).

The underlying risk for lung cancer varied substantially between the studies. The NLST,[23] LSS,[25] and study by Garg et al[16] generally focused on higher risk; DLCST,[19] ITALUNG,[21] and DANTE[22] on both higher and intermediate risk; and NELSON[18] and Dépiscan[27] on a broad range of risk among participants.

Although estimating the average risk of all participants in any of these studies is difficult because of a lack of granular data, the minimum risk level in each study was approximated using established formulas.[48,49] Over 10 years, the risks of being diagnosed with lung cancer for participants

Table 1. Randomized Controlled Trials Identified in the Search of the Literature

	No. Randomized (% Screened or Followed Up at Baseline)		Screening With LDCT[a]		Study Duration			Participant Characteristics			
										Smoking History Eligibility (Current or Former)	
Source	LDCT	Control	Collimation, mm	Nodule Size Warranting Workup, mm[b]	Years of Accrual	Planned Follow-up From Baseline, y	No. of Screens, Planned/ Completed (at Last Report)[c]	Male, %	Age Range, y	Pack-years[d]	Years Since Quit
LDCT vs Usual Care (No Screening)											
NELSON,[18] 2009	7907 (95)[e]	7915 (100)[e]	0.75	≥4.6, >9.8	2004-NR[e]	10	3/2	84	50-75	>15	≤10
DLCST,[19,20] 2012	2052 (100)	2052 (100)	0.75[f]	≥5, >15	2004-2006	10	5/5	55	50-70	≥20	<10[g]
ITALUNG,[21] 2009	1613 (87)	1593 (100)	1-1.25	≥5, ≥8[h]	NR	NR	4/1	65	55-69	≥20	<10
DANTE,[22] 2009	1276 (91)	1196 (85)	5	Any, ≥6	2001-2006	NR	5/5[i]	100	60-74	≥20	<10
Garg et al,[16] 2002	92 (100)[j]	98 (100)[j]	5	Any, >10	2001-NR[j]	NR	2/1	75	50-80	≥30	NR[k]
LDCT vs Chest Radiograph											
NLST,[23,24] 2011	26 722 (98)	26 732 (97)	≤2.5	≥4	2002-2004	>7	3/3	59	55-74	≥30	≤15
LSS,[25,26] 2005	1660 (96)	1658 (93)	5	Any[l]	2000	2	2/2[m]	59	55-74	≥30	<10
Dépiscan,[27] 2007	385 (86)[n]	380 (77)	1-1.5	>5, ≥10	2002-2004	NR	3/1	71	47-76	≥15	<15

Abbreviations: DLCST, Danish Lung Cancer Screening Trial; LDCT, low-dose computed tomography; LSS, Lung Screening Study; NELSON, Dutch Belgian Randomised Lung Cancer Screening Trial; NLST, National Lung Screening Trial; NR, not reported.

[a] All studies had a protocol in place except LSS. Studies by NELSON, DANTE, and Garg et al had a protocol reported; however, specific details on adherence or deviation from the protocol or actual procedures used were not reported. For NLST, " . . . trial radiologists developed guidelines for diagnostic follow-up, but no specific evaluation approach was mandated."[23]

[b] Indicates first the largest-size nodule warranting additional imaging and, second, the largest-size nodule warranting diagnostic testing.

[c] All studies had screening conducted annually except the study by NELSON, which had planned screening at years 1, 2, and 4.

[d] Defined as the number of cigarette packs (20 cigarettes per pack) smoked per day multiplied by the number of years smoked.

[e] Randomization is ongoing with a target accrual of 16 000 participants.

[f] Collimation = 16 × 0.75 mm.

[g] Former smokers had to have quit after the age of 50 years and less than 10 years ago.

[h] Diagnostic workup was a referral to a positron emission tomography scan.

[i] The median follow-up was 33.7 months and only 161 participants (6.5% of those screened or followed up at baseline) had 5 or more years of follow-up. Baseline data are mainly reported.

[j] Target accrual of 400 participants in total was planned.

[k] Study does not specify a maximum time since quitting.

[l] The size of the noncalcified nodule to warrant further imaging was increased to ≥4 mm at year 1 to reflect evolving practice.

[m] In the original design, 1 screen was planned; however, it was later amended to 2 screens (baseline and 1 repeat).

[n] Six patients randomized to chest radiography crossed over to receive LDCT at baseline.

meeting minimum entry criteria of each study, assuming they had quit smoking at time of study entry, were approximately 2% for NLST, 1% for DLSCT, and considerably less than 1% for NELSON. The nodule size deemed large enough to investigate further ranged from "any size" to greater than 5 mm; the size that triggered an invasive intervention (when specified) ranged from 6 to 15 mm.

Potential Benefits of LDCT Screening

Effect on Mortality. Three RCTs reported the effect of LDCT screening on lung cancer–specific mortality (TABLE 3). The NLST found that 3 annual rounds of screening (baseline and 1 and 2 years later) with LDCT resulted in a 20% relative decrease in deaths from lung cancer vs chest radiographs over a median of 6.5 years of follow-up (P=.004).[23] In absolute terms, the chance of dying from lung cancer was 0.33% less over the study period in the LDCT group (87 avoided deaths over 26 722 screened participants), meaning 310 individuals must participate in screening for typically 3 rounds to prevent 1 lung cancer death. Based on a slightly different denominator, the NLST authors reported the number needed to screen with LDCT was 320 to prevent 1 lung cancer death.

The considerably smaller ongoing DANTE and DLCST studies each compared 5 annual rounds of LDCT screening to usual care; after a median of 34 and 58 months of follow-up, respectively, no statistically significant difference in lung cancer mortality was observed in either study (DANTE: relative risk [RR], 0.97; 95% CI, 0.71-1.32; P=.84; DLCST: RR, 1.15; 95% CI, 0.83-1.61; P=.43).[19,22]

All 3 studies reported on the risk of death from any cause (TABLE 4) between study groups and directly or indirectly on the risk of death from any cause other than lung cancer. Only the NLST found a difference in this end point, with fewer deaths overall in the LDCT vs the chest radiograph group

Table 2. Cohort Studies of LDCT Identified in the Search of the Literature

		Screening With LDCT		Study Duration			Participant Characteristics			
									Smoking History Eligibility (Current or Former)	
Source	No. Enrolled (% Screened at Baseline)	Collimation, mm	Nodule Size Warranting Workup, mm[a]	Years of Accrual	Planned Follow-up From Baseline, y	No. of Screens, Planned/ Completed (at Last Report)[b]	Male, %	Age Range, y	Pack-years[c]	Years Since Quit
Veronesi et al,[28,29] 2008	5201 (NR)[d]	2.5	>5, >8[e]	2004-2005	NR	5/2	66	≥50	≥20	<10
Wilson et al,[30] 2008	3755 (97)	2.5	Any, ≥10[f]	2002-2006	3	2/2	51	50-79	≥12.5[g]	≤10
Menezes et al,[31] 2010	3352 (NR)[d]	1-1.25	≥5, ≥15	2003-2007	NR	6/6	46	50-80	≥10	NR
Sobue et al,[32] 2002	1682 (96)	10	Any	1993-1998	NR	~10/~10[h]	88	40-79	≥20	NR
Swensen et al,[33-35] 2005	1520 (100)	5	Any, >8[i]	1999	5	5/5	52	50-85	≥20	<10
Pastorino et al,[36] 2003	1035 (100)	10	>5	2000-2001	NR	5/2	71	50-84	≥20	NR
Henschke et al,[37,38] 2001	1000 (NR)	10	Any, ≥6[j]	1993-1998	10[k]	3/3	54	≥60	≥10	NR
Bastarrika et al,[39] 2005	911 (NR)[d]	8[l]	≥5, ≥10[e]	NR	NR	2/2	74	≥40	≥10	NR
Diederich et al,[40-42] 2004	817 (100)	5	Any, >10[m]	1995-1999	6[h]	6/6	72	40-78	≥20	NR
Novello et al,[43] 2005	520 (99)	8.8	≥5, >11	2001	NR	5/3	73	54-79	≥20	<10
Callol et al,[44] 2007	482 (97)	10	≥5, >10	2001-2004	NR	2/2	65	50-73	>10	<0.5
MacRedmond et al,[45,46] 2006	449 (100)	10	Any, ≥10	NR	2	2/2	50	50-74	≥10	NR
Picozzi et al,[47] 2005	60 (100)	10[m]	Any, ≥10[n]	2000-2001	3	3/3	78	57-78	≥20	NR

Abbreviations: LDCT, low-dose computed tomography; NR, not reported.
[a] Indicates first the largest-size nodule warranting additional imaging and, second, the largest-size nodule warranting diagnostic testing.
[b] Screening was conducted annually in all studies except that by Sobue et al, which was biannual, and Callol et al, which was semiannual. All studies had a diagnostic protocol in place except that by Wilson et al. For Henschke et al, the workup protocol was not rigid and could be adjusted.
[c] Defined as number of cigarette packs (20 cigarettes per pack) smoked per day multiplied by the number of years smoked.
[d] The total number of participants enrolled was not reported, only the total number scanned at baseline; thus, adherence with screening at baseline cannot be determined.
[e] Diagnostic workup was a referral to positron emission tomography scan.
[f] The following change to the protocol was reported: all patients with noncalcified nodules at baseline were referred to additional imaging; at repeat screening, only nodules ≥4 mm were referred.
[g] At least one-half pack per day for at least 25 years.
[h] Screening was discontinued after at least 1 normal annual repeat scan in participants <55 years old.
[i] The following change to the protocol was reported: nodules <4 mm were initially followed with repeat CT at 6 mo, but was then changed to 12 mo (repeat screening).
[j] Nodules ≤ 5 mm=follow-up with high-dose CT, nodules 6-10 mm=assessment of the possibility for biopsy, ≥ 11 mm=referred to pulmonary physician for biopsy.
[k] Planned follow-up of those with malignant disease.
[l] Two hundred ninety seven participants were studied with a single-slice helical scanner at a collimation of 8 mm and then, to precisely characterize any pulmonary nodule, same-day high-resolution CT. For the remaining 614 patients, a 4-row multislice helical CT scanner was used: collimation=1.25 mm.
[m] In the last round of screening, 14 participants were scanned according to a different protocol, including collimation=3 mm.
[n] Nodules <10 mm underwent repeat screening while nodules ≥10 mm were referred for biopsy.

(1303 vs 1395 deaths per 100 000 person-years, respectively). Analyses focusing exclusively on deaths not due to lung cancer found no significant differences in any of the 3 studies.[23]

Effect on Smoking Behavior. Speculation exists that undergoing LDCT screening may result in justification of continued smoking or, alternatively, may represent an opportunity for smoking cessation interventions. But studies examining the smoking behavior of LDCT-screened individuals have not found evidence that cessation or reinitiation rates are meaningfully altered by participation in screening (eTable 2).[50-52]

Potential Harms of LDCT Screening

Detection of Abnormalities. Low-dose computed tomography identifies both cancerous and benign noncalcified nodules; the latter are often called "false positives." Although most LDCT screening studies have reported on nodules detected, the categorization and manner of reporting are inconsistent (eg, it is sometimes unclear if newly identified nodules are assigned to that round or to an earlier round if they can be retrospectively seen on an earlier LDCT). Likewise, size thresholds that would trigger an invasive workup are variously and inconsistently reported, as are the potential denominators for estimating false-positive rates, such as per screening round or per person-year.

Based on the study's own size cutoffs, the average nodule detection rate per round of screening was 20% (**TABLE 5**, eFigure 1) but varied from 3% to 30% in RCTs and 5% to 51% in cohort studies. Most studies reported that more than 90% of nodules were be-

Table 3. Mortality Due to All Causes, Lung Cancer, and All Causes Other Than Lung Cancer in Randomized Trials: Trial Characteristics and Mortality Events

Source	Compared With	No. of Participants Screened or Followed Up		Median Follow-up, mo	*P* Value on End Point	Mortality Events, No. (%)	
		LDCT	Control			LDCT	Control
All-Cause Mortality							
DANTE,[22] 2009	Usual care	1276	1196	34	.84	46 (3.6)	45 (3.8)
NLST,[23] 2011	Chest radiographs	26 722	26 732	78	.02	1877 (7.0)	2000 (7.5)
DLCST,[19] 2012	Usual care	2052	2052	58	.43	61 (3.0)	42 (2.0)
Lung Cancer–Specific Mortality							
DANTE,[22] 2009	Usual care	1276	1196	34	.83	20 (1.6)	20 (1.7)
NLST,[23] 2011	Chest radiographs	26 722	26 732	78	.004	356 (1.3)	443 (1.7)
DLCST,[19] 2012	Usual care	2052	2052	58	.06	15 (0.7)	11 (0.5)
Mortality Not Due to Lung Cancer							
DANTE,[22] 2009	Usual care	1276	1196	34	.93	26 (2.0)	25 (2.1)
NLST,[23] 2011	Chest radiographs	26 722	26 732	78	.51	1521 (5.7)	1557 (5.8)
DLCST,[19] 2012	Usual care	2052	2052	58	.08	46 (2.2)	31 (1.5)

Abbreviations: DLCST, Danish Lung Cancer Screening Trial; NLST, National Lung Screening Trial; LDCT, low-dose computed tomography.

Table 4. Mortality Due to All Causes, Lung Cancer, and All Causes Other Than Lung Cancer in Randomized Trials: Rates and Relative Risk

Source	Events, No. (%)		Rate of Events per 100 000 Person-years		Relative Risk (95% CI)	Rate Ratio	Absolute Difference, %	No. Needed to Screen to Prevent 1 Event
	LDCT	Control	LDCT	Control				
All-Cause Mortality								
DANTE,[22] 2009	46 (3.6)	45 (3.8)	NR	NR	0.97 (0.80-1.20)[a,b]	NR	0.2	635
NLST,[23] 2011	1877 (7.0)	2000 (7.5)	1303[b]	1395[b]	0.93 (0.86-0.99)	0.93[b]	0.5	219
DLCST,[19] 2012	61 (3.0)	42 (2.0)	NR	NR	1.19 (1.01-1.40)	NR	–1.0	NR
Lung Cancer–Specific Mortality								
DANTE,[22] 2009	20 (1.6)	20 (1.7)	NR	NR	0.97 (0.71-1.32)[a,b]	NR	0.1	954
NLST,[23] 2011	356 (1.3)	443 (1.7)	247	309	0.80 (0.73-0.93)	0.80[b]	0.3	320
DLCST,[19] 2012	15 (0.7)	11 (0.5)	NR	NR	1.15 (0.83-1.61)	NR	–0.2	NR
Mortality Not Due to Lung Cancer								
DANTE,[22] 2009	26 (2.0)	25 (2.1)	NR	NR	0.99 (0.75-1.30)[b]	NR	0.1[b]	1898[b]
NLST,[23] 2011	1521 (5.7)	1557 (5.8)	1056[b]	1086[b]	0.99 (0.95-1.02)[b]	0.97[b]	0.1[b]	755[b]
DLCST,[19] 2012	46 (2.2)	31 (1.5)	NR	NR	1.20 (1.00-1.44)[b]	NR	–0.7[b]	NR

Abbreviations: DLCST, Danish Lung Cancer Screening Trial; NLST, National Lung Screening Trial; LDCT, low-dose computed tomography; NR, not reported.
[a] Based on count data.
[b] Calculated by authors.

nign. In general, there is a tendency toward lower nodule detection rates in repeat screening rounds, but the data and reporting are inconsistent (Table 5, eFigure 2). In the NLST, the rate of detection did not decrease until the third round. In that round, the study protocol allowed for ignoring nodules that had been present in the prior rounds. We were unable to find any statistically significant relation between study parameters, such as smoking history of study enrollees, CT scan settings, nodule size cutoffs, and reported nodule detection rates.

Most often, a detected nodule triggered further imaging, but the underlying management protocols were inconsistently reported in the studies. Whether all additional imaging tests were captured in the studies was also uncertain: reported follow-up imaging rates may be underestimated.

The frequency of further CT imaging among screened individuals ranged from 1% in the study by Veronesi et al[27] to 44.6% in the study by Sobue et al.[32] The frequency of further positron emission tomography (PET) imaging among screened individuals exhibited much less variation, ranging from 2.5% in the study by Bastarrika et al[39] to 5.5% in the NLST.[23] The frequency of invasive evaluation of detected nodules was generally low but varied considerably (**Table 6**, eFigure 3). No patterns were apparent that explained this heterogeneity. In the NLST, 1.2% of patients who were not found to have lung cancer underwent an invasive procedure such as needle biopsy or bronchoscopy, while 0.7% of patients who were not found to have lung cancer had a thoracoscopy, mediastinoscopy, or thoracotomy.[23] In the NELSON study, these numbers were 1.2% and 0.6%, respectively.[18] Invasive nonsurgical procedures in patients with benign lesions were common (eg, 73% in NLST).

Complications of Diagnostic Procedures. The only study reporting on complications resulting from LDCT screening is the NLST. Overall, the frequency of death occurring within 2 months of a diagnostic evaluation of a detected finding was 8 per 10 000 individuals screened by LDCT and 5 per 10 000 individuals screened by chest radiographs. Some of the deaths that occurred after a diagnostic evaluation were presumably unrelated to follow-up procedures, as 1.9 and 1.5 per 10 000 occurred within 2 months when the diagnostic evaluation involved only an imaging study.

Deaths most clearly related to follow-up procedures were those occurring within 2 months when the most recent procedure was a bronchoscopy or needle biopsy (3.4 per 10 000 screened by LDCT and 2.2 per 10 000 screened by chest radiographs). Approximately one-third of the deaths occurred within 2 months of a surgical procedure in both study groups, and the vast majority of these were in the patients with cancer, suggesting perhaps that the surgical procedures in those with cancer were more extensive (ie, resection rather than biopsy; such details were not reported). The 60-day perioperative mortality for patients with lung cancer who underwent a surgical procedure was 1% for the LDCT group and 0.2% for the chest radiographs group.

Overall, the frequency of major complications occurring during a diagnostic evaluation of a detected finding was 33 per 10 000 individuals screened by LDCT and 10 per 10 000 individuals screened by chest radiographs. The rate of (presumably unrelated) complications following imaging alone was similar and low (1.1 and 1.5 per 10 000 screened, respectively); the complication rate after a bronchoscopy or needle biopsy was also low (1.5 and 0.7 per 10 000 for LDCT and chest radio-

Table 5. Nodule Detection in CT Screening

Source	No. Screened	Adherence, %[a]	Round of Screening[b]	No. of Participants (%)				
				Noncalcified Lung Nodules Over Study Threshold[c]	Lung Cancer Nodules	Benign Nodules	Nodules Not Lung Cancer	Diagnosed With Lung Cancer Over Entire Study Period[d]
LDCT vs Usual Care (No Screening)								
NELSON,[18] 2009	7557	95	Baseline	1570 (21)	70 (0.9)	1500 (20)	1500 (96)	124 (1.6)
	7289	92	Year 1	570 (8)	54 (0.7)	516 (7)	516 (91)	
DLCST,[19,20] 2009	2047	100	Baseline	179 (9)	17 (0.8)	162 (8)	162 (91)	70 (3.4)
	1976	96	Year 1	NR	11 (0.6)	NR	NR	
	1944	95	Year 2	NR	13 (0.7)	NR	NR	
ITALUNG,[21] 2009	1406	87	Baseline	426 (30)	20 (1.5)	406 (29)	406 (95)	20 (1.5)
DANTE,[22] 2009	1276	91	Baseline	226 (18)	47 (3.7)	179 (14)	179 (79)	60 (4.7)
Garg et al,[16] 2002	92	100	Baseline	3 (3)	2 (2.2)	1 (1)	1 (33)	2 (2.2)
LDCT vs Chest Radiographs								
NLST,[23,24] 2011	26 309	98	Baseline	7191 (27)	270 (1.0)	6921 (26)	6921 (96)	1060 (4.0)
	24 715	92	Year 1	6901 (28)	168 (0.6)	6733 (27)	6733 (98)	
	24 102	90	Year 2	4054 (17)	211 (0.9)	3843 (16)	3843 (95)	
LSS,[25,26] 2005	1629	96	Baseline	316 (19)	30 (1.8)	286 (18)	286 (91)	40 (2.5)
	1398	86	Year 1	360 (26)	8 (0.6)	352 (25)	352 (98)	
Dépiscan,[27] 2007	336	87	Baseline	81 (24)	7 (2.4)	74 (22)	74 (91)	8 (2.4)

(continued)

graphs, respectively). The vast majority of major complications occurred after surgical procedures and in those patients with lung cancer. The rate of major complications in those patients with lung cancer who underwent surgery was 14%.

Focusing only on patients who had nodules detected by LDCT that were determined to be benign, death occurred within 60 days among 0.06% and major complications occurred among 0.36%. Approximately half of the deaths occurred after imaging alone, whereas the majority of major complications occurred after a surgical procedure (details unknown). Calculating these numbers for an entire screened population, the risks of death and major complications following diagnostic events (including imaging) for nodules that were determined to be benign is 4.1 and 4.5 per 10 000, respectively. These rates are higher than those in the chest radiographs group (1.1 and 1.5 per 10 000 for risks of death and major complications, respectively).

Table 5. Nodule Detection in CT Screening (continued)

				No. of Participants (%)				
Source	No. Screened	Adherence, %[a]	Round of Screening[b]	Noncalcified Lung Nodules Over Study Threshold[c]	Lung Cancer Nodules	Benign Nodules	Nodules Not Lung Cancer	Diagnosed With Lung Cancer Over Entire Study Period[d]
Cohort Studies of LDCT								
Veronesi et al,[28,29] 2008	5201[e]	100	Baseline	560 (11)	54 (1.1)	506 (10)	506 (90)	92 (1.8)
	4821	93	Year 1	500 (10)	19 (0.4)	481 (10)	481 (96)	
Wilson et al,[30] 2008	3642	97	Baseline	1477 (41)	53 (1.5)	1424 (39)	1424 (96)	80 (2.2)
	3423	89	Year 1	1450 (42)	24 (0.7)	1426 (42)	1426 (98)	
Menezes et al,[31] 2010	3352[e]	100	Baseline	600 (18)	44 (1.3)	556 (17)	556 (93)	65 (1.9)
	2686	80	Year 1	259 (10)	10 (0.4)	249 (9)	249 (96)	
	669	20	Year 2	70 (11)	6 (0.9)	64 (10)	64 (91)	
Sobue et al,[32] 2002	1611	96	Baseline	186 (12)	14 (0.9)	172 (11)	172 (93)	36 (2.2)
	1180	70	Year 0.5[f]	83 (7)	3 (0.3)	80 (7)[g]	80 (96)	
	891	53	Year 1[f]	60 (7)	5 (0.6)	55 (6)[g]	55 (92)	
Swensen et al,[34,35] 2005	1520	100	Baseline	780 (51)	31 (2)	749 (49)	749 (96)	68 (4.5)
	1464	97	Year 1	191 (13)	3 (0.2)	188 (13)	188 (98)	
	NR	NR	Year 2	NR	NR	NR	NR	
Pastorino et al,[36] 2003	1035	100	Baseline	199 (19)	11 (1.1)	188 (18)	188 (95)	22 (2.1)
	996	96	Year 1	99 (10)	11 (1.1)	88 (9)	88 (89)	
Henschke et al,[37,38] 2001	1000	100	Baseline	233 (23)	27 (2.7)	206 (21)	206 (88)	36 (3.6)[h]
	841	84	Year 1	30 (3)[h]	7 (0.6)[h]	23 (2)[h]	23 (77)	
	343	34	Year 2					
Bastarrika et al,[39] 2005	911[e]	100	Baseline	131 (14)	12 (1.3)	119 (13)	119 (91)	14 (1.5)
	424	47	Year 1	NR	2 (0.5)	NR	NR	
Diederich et al,[40-42] 2004	817	100	Baseline	378 (46)	11 (1.3)	367 (45)	367 (97)	15 (1.8)
	668	82	Year 1	73 (11)	NR	NR	NR	
	549	67	Year 2	25 (5)	NR	NR	NR	
Novello et al,[43] 2005	519	99	Baseline	114 (22)	5 (1)	109 (21)	109 (96)	12 (2.3)
	NR	NR	Year 1	26 (5)	3 (0.6)	23 (5)	23 (88)	
	NR	NR	Year 2	16 (5)	3 (0.6)	13 (3)	13 (81)	
Callol et al,[44] 2007	466	97	Baseline	98 (21)	1 (0.2)	97 (21)	97 (98)	5 (1.1)
	406	84	Year 2[i]	9 (2)	4 (1)	5 (1)	5 (56)	
MacRedmond et al,[45,46] 2006	449	100	Baseline	NR	2 (0.4)	NR	NR	6 (1.3)
	413	92	Year 1	NR	3 (0.7)	NR	NR	
Picozzi et al,[47] 2005	60	100	Baseline	20 (33)	1 (1.7)	19 (32)	19 (95)	2 (3.3)
	45	75	Year 1	8 (18)	1 (2.2)	7 (16)	7 (88)	
	42	70	Year 2	5 (12)	0	5 (12)	5 (100)	

Abbreviations: DLCST, Danish Lung Cancer Screening Trial; LDCT, low-dose computed tomography; NELSON, Dutch Belgian Randomised Lung Cancer Screening Trial; NLST, National Lung Screening Trial; NR, not reported.
[a] Adherence from time of randomization or enrollment.
[b] The majority of studies do not present results beyond the second repeat screening; see Tables 1 and 2 for information on the number of planned screens completed.
[c] Data are reported according to the nodule size warranting imaging workup in each study reported in Tables 1 and 2.
[d] Includes interval cancers and those detected by symptoms or other causes over multiple screens with the number screened at baseline as the denominator.
[e] The total number of participants enrolled was not reported, only the total number scanned at baseline.
[f] Scans were conducted twice per year.
[g] Reviewer calculation.
[h] The Early Lung Cancer Action Project reported cumulative nodule detection data for 2 follow-up rounds of screening. Total participants screened in both follow-up rounds of screening is used as the denominator.
[i] The first repeat scan was conducted 2 years after the initial baseline scan.

Overdiagnosis. Overdiagnosis refers to histologically confirmed lung cancers identified through screening that would not affect the patient's lifetime if left untreated. This includes patients who are destined to die of another cause (eg, a comorbidity or an unexpected event).[54] Earlier studies suggested that chest radiographs screening may have an overdiagnosis rate of roughly 25%.[55,56] The overdiagnosis rate for LDCT screening cannot yet be estimated; NLST data show a persistent gap of about 120 excess lung cancers in the LDCT group vs the chest radiographs group, but further follow-up is needed.

Radiation Exposure. The effective dose of radiation of LDCT is estimated to be 1.5 mSv per examination, but there is substantial variation in actual clinical practice. However, diagnostic chest CT (~8 mSv)[57] or PET CT (~14 mSv)[57-59] to further investigate detected lesions rapidly increases the exposure and accounts for most of the radiation exposure in screening studies. We estimate that NLST participants received approximately 8 mSv per participant over 3 years, including both screening and diagnostic examinations (averaged over the entire screened population). Estimates of harms from such radiation come from several official bodies and commissioned studies,[60,61] based on dose extrapolations from atomic bombings and also many studies of medical imaging.[62,63] Using the NLST data, these models predict that approximately 1 cancer death may be caused by radiation from imaging per 2500 persons screened.

Therefore, the benefit in preventing lung cancer deaths in NLST is greater than the radiation risk—which only becomes manifest 10 to 20 years later. However, for younger individuals or those with lower risk of developing lung cancer, the trade-off would be less favorable. Preliminary modeling studies suggest that potential risks may vastly outweigh benefits in nonsmokers or those aged 42 years or younger.[64] Further study is needed, including evaluation of the effects of ongoing annual LDCT beyond 3 successive years.

Quality of Life. The effect of LDCT screening on quality of life is uncertain. We found only 1 study, in which 88% to 99% of 351 participants re-

Table 6. Frequency of Follow-up Imaging and Surgical Biopsies and Procedures for Detected Nodules

Source	No. Randomized	No. of Screened Group Participants (%)						
		Had Nodules at Baseline	Additional Diagnostic CT	Additional PET	Nonsurgical Biopsy/Procedure		Surgical Biopsy/Procedure	
					Had Procedure	Benign Result	Had Procedure	Benign Result
LDCT vs Usual Care (No Screening)								
NELSON,[18] 2009	15 822[a]	1570 (21)	NR	0	257 (3.4)	138 (54)	153 (2.0)	45 (30)
DLCST,[20] 2009	4104	179 (9)	NR	NR	NR[b]	NR[b]	25 (1.2)[b]	8 (32)[b]
ITALUNG,[21] 2009	3206	426 (30)	NR	59 (4.2)	16 (1.1)	1 (6)	16 (1.1)	1 (6)
DANTE,[22,53] 2009	2811[c]	226 (18)	NR	57 (4.5)	NR	NR	72 (5.6)	17 (24)
Garg et al,[16] 2002	190	3 (3)	3 (3.3)	NR	NR	NR	NR	NR
LDCT vs Chest Radiographs								
NLST,[23] 2011	53 454	6561 (25)	8807 (33)	1471 (5.5)	402 (1.5)	293 (73)	673 (2.6)	164 (24)
LSS,[25,26] 2005	3318	316 (19)	NR	NR	NR[b]	NR[b]	53 (3.3)	23 (43)[b]
Dépiscan,[27] 2007	765	81 (24)	NR	NR	NR	NR	11 (3.3)[b]	3 (27)[b]
Cohort Studies								
Veronesi et al,[28,29] 2008	5201	560 (11)	54 (1)	157 (3)	101 (1.9)	15 (15)	106 (2.0)	15 (14)
Wilson et al,[30] 2008	3755	1477 (41)	NR	NR	NR	NR	82 (2.3)	28 (34)
Menezes et al,[31] 2010	3352	600 (18)	NR	NR	78 (2.3)	16 (21)	NR	NR
Sobue et al,[32] 2002	1682	186 (12)	719 (44.6)	NR	50 (3.0)	29 (58)	21 (1.2)	6 (29)
Swensen et al,[34,35] 2005	1520	780 (51)	NR	NR	NR	NR	39 (2.6)	8 (21)
Pastorino et al,[36] 2003	1035	199 (19)	95 (9.2)	42 (4.1)	NR[b]	NR[b]	28 (2.7)[b]	6 (21)[b]
Henschke et al,[37,38] 2001	1000	233 (23)	NR	NR	36 (3.6)	2 (6)	NR	NR
Bastarrika et al,[39] 2005	911	143 (16)	0	23 (2.5)	6 (0.7)	1 (17)	13 (1.4)	0
Diederich et al,[40-42] 2004	817	378 (46)	NR	NR	NR[b]	NR[b]	15 (1.8)[b]	4 (27)[b]
Novello et al,[43] 2005	520	114 (22)	NR	NR	NR	NR	NR	NR
Callol et al,[44] 2007	482	NR	NR	NR	NR	NR	7 (1.5)	2 (29)
MacRedmond et al,[45,46] 2006	449	NR	NR	NR	NR	NR	4 (0.9)	1 (25)
Picozzi et al,[47] 2005	60	20 (33)	NR	3 (5)	NR	NR	NR	NR

Abbreviations: DLCST, Danish Lung Cancer Screening Trial; LDCT, low-dose computed tomography; NELSON, Dutch Belgian Randomised Lung Cancer Screening Trial; NLST, National Lung Screening Trial; NR, not reported; PET, positron emission tomography.
[a] Randomization is ongoing with a target accrual of 16 000 participants.
[b] Values apply to any invasive procedure (surgical or nonsurgical).
[c] The median follow-up was 33.7 months, and only 161 participants (6.5% of those screened or followed up at baseline) had 5 or more years of follow-up. Baseline data are mainly reported.

ported no discomfort, but 46% reported psychological distress while awaiting results.[65] Although there may be quality-of-life benefits due to lower morbidity from advanced lung cancer, there are also potential detriments due to anxiety, costs, and harms from the evaluation of both false-positive scans and overdiagnosed cancers.

Patients Likely to Benefit

The NLST population is the only one for whom a lung cancer mortality benefit from LDCT has been demonstrated (those aged 55-74 years with ≥30 pack-years of smoking who quit ≤15 years prior to entry [if they have stopped smoking]). Other studies are too small, too preliminary, or too poorly designed to support meaningful conclusions. The value of LDCT screening is likely determined primarily by the risk of lung cancer vs competing causes of death. Little information exists regarding comorbidities, but presumably the NLST participants were deemed healthy. We estimate an average risk of developing lung cancer within 10 years of approximately 10% for the NLST population in the absence of screening (estimated median age 62 years and ~50 pack-years of smoking). However, the calculable risk for individual NLST participants most likely varied by more than 10-fold across the participants, from less than 2% to greater than 20%, and it is unclear which groups experienced benefit.[48,49] But there is no evidence base for determining how selection criteria for screening should be refined. Incorporating other well-known risk factors has not been studied.

Effective Screening Setting

A summary of the setting of the NLST (the only positive study) demonstrates that most (76%) of the NLST sites were National Cancer Institute–designated cancer centers, and 82% were large academic medical centers with more than 400 hospital beds, although screening may have taken place at satellite facilities in some cases (eTable 3). All of these centers are likely to have specialized thoracic radiologists and board-certified thoracic surgeons on staff. The CT scanners used in the NLST underwent ongoing extensive quality control, and the scans were interpreted by chest radiologists who underwent specific training and quality control in the interpretation of images and wording of screening LDCT findings.[58] A nodule management algorithm was included in the NLST, but adherence or the setting in which nodules were managed was not mandated or tracked by the study.[58]

Most other RCTs and cohort studies of LDCT screening were conducted in facilities similar to the NLST sites: academic medical centers, large hospitals, with the involvement of relevant subspecialist services and a defined nodule management algorithm. The association between the setting of LDCT screening and outcome has not been tested, but variability in rates of false-positive LDCT scans, further imaging, and procedures suggests these may be important.

COMMENT

This report summarizes the systematic review conducted by a multisociety collaborative effort examining the risks and benefits of LDCT screening for lung cancer and forms the basis of the American College of Chest Physicians and the American Society of Clinical Oncology clinical practice guideline (Box and eAppendix 4). The guideline is based on the finding that a reasonable amount of data has been reported regarding the outcomes for LDCT screening for lung cancer and that some conclusions can be drawn regarding its risks and benefits despite many areas of uncertainty.

A recent large, high-quality RCT (the NLST) found that annual LDCT screening reduced the relative risk of death from lung cancer by 20% and the absolute risk by 0.33% in a population with a substantially elevated risk for lung cancer. Two smaller RCTs (DANTE and DLCST) comparing LDCT with usual care found no benefit of LDCT screening but are best interpreted as neither confirming nor contradicting the NLST findings. Because a recent large RCT (N=154 901) demonstrated no lung cancer mortality difference between chest radiographs screening and usual care, the interventions in these 3 studies are reasonably comparable.[66]

The literature supports the conclusion that LDCT screening can lead to harm. It identifies a relatively high percentage of subjects with nodules (average ~20%), the vast majority of which are benign. The additional imaging that these nodules trigger increases radiation exposure. The rates of surgical biopsy are variable (<1%-4%) as are the percentages of surgical procedures performed for benign disease. The rate of major, and sometimes fatal, complications among persons with benign lesions is low.

The unexplained heterogeneous rates of nodule detection, additional imaging, and invasive procedures that occurred within the structured settings of the controlled trials of LDCT raise concerns about how easily LDCT can be more broadly implemented. There is already substantial variability in the United States in the rates and complications of pulmonary needle biopsy[67] and outcomes of lung cancer surgery, which are considerably better in dedicated centers (such as those conducting LDCT trials).[68,69] Furthermore, adherence with screening is consistently lower in cohort studies than in the NLST and could be worse with unstructured implementation, with resulting diminished benefits. Analogous concerns in breast cancer screening led to the Mammography Quality Standards Act.[70] The position statement by the International Association for the Study of Lung Cancer recommends demonstration projects to evaluate implementation of LDCT screening, establishment of quality metrics, and multiple task forces to address the many critical areas of uncertainty.[71] Given all of these issues, performing an LDCT scan outside of a structured organized process appears to be beyond the current evidence base for LDCT lung cancer screening.

Box. Role of Computed Tomography Screening for Lung Cancer: Recommendations From the American College of Chest Physicians and the American Society of Clinical Oncology

Recommendation 1

For smokers and former smokers aged 55 to 74 years who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years, we suggest that annual screening with low-dose computed tomography (LDCT) should be offered over both annual screening with chest radiograph or no screening, but only in settings that can deliver the comprehensive care provided to National Lung Screening Trial (NLST) participants. (Grade of recommendation: 2B.)

Remark 1

Counseling should include a complete description of potential benefits and harms (as outlined in the full guideline text) so the individual can decide whether to undergo LDCT screening.

Remark 2

Screening should be conducted in a center similar to those where the NLST was conducted, with multidisciplinary coordinated care and a comprehensive process for screening, image interpretation, management of findings, and evaluation and treatment of potential cancers.

Remark 3

A number of important questions about screening could be addressed if individuals who are screened for lung cancer are entered into a registry that captures data on follow-up testing, radiation exposure, patient experience, and smoking behavior.

Remark 4

Quality metrics should be developed such as those in use for mammography screening, which could help enhance the benefits and minimize the harms for individuals who undergo screening.

Remark 5

Screening for lung cancer is not a substitute for stopping smoking. The most important thing patients can do to prevent lung cancer is not smoke.

Remark 6

The most effective duration or frequency of screening is not known.

Recommendation 2

For individuals who have accumulated fewer than 30 pack-years of smoking or are either younger than 55 years or older than 74 years, or individuals who quit smoking more than 15 years ago, and for individuals with severe comorbidities that would preclude potentially curative treatment, limit life expectancy, or both, we suggest that CT screening should not be performed. (Grade of recommendation: 2C.)

Full text of the American College of Chest Physicians and the American Society of Clinical Oncology evidence-based practice guideline on the role of CT screening for lung cancer is available in eAppendix 4. This guideline has been endorsed by the American Thoracic Society.

The fear and anxiety that patients can experience once there is even a slight suspicion of lung cancer highlights the need for careful education of LDCT participants and the need for carefully worded scan interpretations. In addition, even a small negative effect of screening on smoking behavior (either lower quit rates or higher recidivism) could easily offset the potential gains in a population.[72] Smoking cessation should be considered a valuable component of any screening program.

In the setting of increasing health care costs, the relative cost-effectiveness of LDCT screening compared with other interventions will be a topic of discussion and concern in policy spheres. Medicare is allowed to contemplate a preventive service's cost-effectiveness before adding it to the package of preventive benefits (Medicare Improvements for Patients and Providers Act of 2008[73]). Now that an estimate is available of effectiveness, an estimate of cost-effectiveness could be generated.

Some critical elements of such an analysis will include determining what the price of the component services will be and how frequently follow-up procedures will be required.

The ACCP and ASCO recommendations for LDCT screening should be interpreted in light of several limitations. We did not conduct a formal cost-effectiveness evaluation. LDCT would be expected to be less cost-effective when applied to individuals at lower risk of lung cancer, because more individuals will need to be screened to prevent each death from the disease. Making screening available in settings without an organized approach to the evaluation and management of LDCT findings may also lower cost-effectiveness, if the frequency of unnecessary interventions and procedures is higher in these settings.[74-76]

Second, the data on which to base these recommendations are relatively limited. Although LDCT screening appears promising, it is also a clinical intervention in its infancy. Many questions that clinicians and patients might reasonably ask when considering whether or not to pursue screening remain unanswered. How large are the risks from radiation? How does an individual's smoking history interplay with the size of the expected benefit or the risk of harms? How serious a problem is overdiagnosis?

Third, it is not clear whether individuals across the range of risk in the NLST are all sufficiently likely to benefit that all such individuals should be considered for screening, or alternatively if a narrower or broader group should be targeted to achieve an appropriate balance between benefit, costs, and harms. How often to perform screening, or over what period of time it should continue, are also important questions that have not been answered by the available data. It is possible to speculate that benefits of screening could be enhanced if screening were continued for longer peri-

ods, but the risks could be amplified as well.

A substantial amount of data on LDCT screening should be reported in the near future, including numerous planned analyses of the NLST data both by its investigators and by the Cancer Intervention and Surveillance Modeling Network (CISNET) investigators. The ongoing RCTs in Europe will also be reporting estimates of both the magnitude of LDCT's mortality benefit and the extent of its harms soon. These data may help inform some of the important questions that still linger regarding LDCT screening.

CONCLUSION

Screening a population of individuals at a substantially elevated risk of lung cancer most likely could be performed in a manner such that the benefits that accrue to a few individuals outweigh the harms that many will experience. However, there are substantial uncertainties regarding how to translate that conclusion into clinical practice.

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Study concept and design: Bach, Mirkin, Azzoli, Berry, Brawley, Byers, Colditz, Gould, Smith-Bindman, Wood, Qaseem, Detterbeck.

Acquisition of data: Bach, Mirkin, Oliver, Detterbeck.

Analysis and interpretation of data: Bach, Mirkin, Oliver, Azzoli, Berry, Brawley, Byers, Colditz, Gould, Jett, Sabichi, Smith-Bindman, Wood, Qaseem, Detterbeck.

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Administrative, technical, or material support: Bach, Mirkin, Oliver, Brawley, Byers, Colditz.

Study supervision: Bach, Azzoli, Detterbeck.

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Online-Only Material: The eAppendixes, eTables, and eFigures are available at http://www.jama.com.

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