Lung Cancer Screening: Review and 2021 Update

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Abstract

Purpose of Review Lung cancer screening with low-dose CT (LDCT) scans has been widely accepted within the last decade. Our knowledge and ability to implement screening has greatly increased because of significant research efforts and guidelines from multiple professional societies. The purpose of this review is to summarize some of the significant findings pertaining to lung cancer screening.

Recent Findings Screening with LDCT decreases lung cancer mortality in multiple studies. Use of validated risk prediction calculators can improve patient selection and screening efficiency. Shared decision making and smoking cessation counseling are essential screening components. Multidisciplinary involvement is required for the success of a screening program.

Summary Lung cancer screening is complex, and implementation of a successful program requires multidisciplinary expertise. Further prospective studies are required to determine optimal patient selection, screening intervals, and strategies to maximize benefit while further decreasing harms.'

Keywords Lung cancer · Cancer screening · Early detection of cancer · Low-dose computed tomography

Introduction

Lung cancer (LC) is the number one cause of cancer-related deaths in the United States and the world in both men and women [1, 2]. Worldwide, there are approximately 1.8 million new cases and 1.6 million deaths every year [3], and in the US alone, LC accounts for approximately 23% of cancer related mortality [1]. The overall 5-year survival rate for LC remains poor at approximately 19% [1]. The mortality rate for LCs is predictably much lower in early compared to late stages [4], when it is potentially curable by surgical resection. There has been a longstanding intense focus on the development of effective LC screening strategies, designed for early identification and intervention in patients who are well enough to benefit. However, unlike in breast, prostate, and colon cancers, there was no widely recommended and effective screening method for LC until this past decade.

The goal of this paper is to briefly review the background of LC screening, recent updates in guidelines and clinical practice, discuss recent challenges, and consider future directions.

Background and History

LC is strongly linked to tobacco smoking [4]. In fact, the rise in LC parallels the increase in tobacco smoking during the late 1800s and 1900s [5]. However, this association was only proved epidemiologically in 1950, and smoking cessation and abstinence was promoted as a public health effort by the US Surgeon General in 1964 [5]. Through widespread efforts, the rates of smoking cigarettes have been steadily decreasing [4].

Earlier studies in the 1980s [6–9] evaluating the role of chest X-rays (CXRs) and sputum cytology as screening tools suggested an overall survival advantage attributed to length or lead time bias and overdiagnosis [10], but failed to show a LC-specific mortality difference. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was a randomized-controlled trial (RCT) evaluating 154,901 participants aged 55 to 74 years from 1993 to 2001 [11]. Annual screening with CXR for 4 years in the intervention group...
was compared to usual care without intervention in the control group, and follow-up was continued for up to 13 years. There was no significant LC mortality benefit detected with CXR screening (mortality RR, 0.99; 95% CI, 0.87–1.22).

Studies in the 2000s [12–15] evaluated low-dose computed tomography (LDCT) scans for LC screening, and while CT scans were able to detect more early stage cancers, there was no conclusive proof of a mortality benefit. Some of these studies had design flaws and either lacked controls, adequate power, or sufficient enrollment. The National Lung Screening Trial (NLST) was a landmark study published in 2011, showing for the first time that dedicated annual screening for LC in a high-risk population was effective in decreasing mortality by as much as 20%, when using LDCT compared to CXRs [16••]. The study showed that for every 320 patients screened with CT, one death was prevented. This finally provided the evidence required for wider acceptance of LC screening with LDCT, and set into motion the gradual implementation process of dedicated screening programs.

In 2013, various organizations started recommending LC screening in selected high-risk populations. The US Preventive Services Task Force (USPSTF) recommended it for high-risk smokers age 55–80 [17]. Compared to the NLST criteria, the age limit had been increased to 80 based on modeling results from the National Cancer Institute’s Cancer Intervention and Surveillance Modeling Network (CISNET) for the Agency for Healthcare Research and Quality [18].

In 2015, the Centers for Medicare and Medicaid Services (CMS) announced their decision to approve LDCT for screening in high-risk individuals. However, CMS mandated that counseling with a shared decision-making (SDM) visit also be performed, in addition to ensuring eligibility criteria for the interpreting radiologist and imaging facility were met [19].

Both the LUSI and the NELSON trials [25, 27••, 28] showed a significant decrease in LC deaths among women more than men, with 69% decrease in women (HR = 0.31, 95% CI = 0.10–0.96, p = 0.04) compared to 6% in men (HR = 0.94, 95% CI = 0.54–1.61, p = 0.81) in the LUSI trial, and 33% decrease in women (RR = 0.67, 95% CI = 0.38–1.14) compared to 24% in men (RR = 0.76, 95% CI = 0.61–0.94, p = 0.01) in the NELSON trial [27••, 28]. The extended NLST follow-up data also confirmed a lower LC mortality for women compared to men [26].

**Screening Guidelines**

Appropriate patient selection is essential in order to balance the benefits of screening in at-risk patients, while minimizing the adverse effects.

Table 2 summarizes the current inclusion and exclusion criteria for screening as recommended by various groups [2, 17, 19, 28–32, 33••, 34, 35, 36••, 37, 38]. The ACCP guidelines were in turn endorsed by multiple other societies [33••]. Most groups have additional recommendations regarding the clinical setting for LC screening, use of risk calculators, use of shared decision making, and/or smoking cessation counseling.

The USPSTF has recently announced the finalized updates to its prior recommendations, by lowering the age to start screening to 50 years and decreasing the pack-year smoking eligibility to > 20 years [39], a grade “B” recommendation, based on evidence favoring moderate benefit by expanding the eligibility criteria. Further review by various professional societies and formal adoption of these recommendations by CMS and other healthcare payors, leading to more widespread implementation, is awaited.

**Role of Prediction Models for Risk Assessment**

The NLST study used fixed criteria (age, pack-years of smoking, and years since smoking cessation) to select high-risk patients for enrollment. However, there are additional risk factors that either individually or in combination increase LC risk, such as personal history of cancer, family history of LC, ethnicity, education, BMI, socioeconomic status, intensity of smoking (actual number of daily cigarettes instead of collective grouping as pack years), occupational/asbestos/radon exposures, and imaging in the past 3 years. Several risk prediction models have been developed to improve patient selection based on individual risk factors instead of subgroups based on risk factors (such as NLST criteria).

Tammemagi et al. compared PLCO and NLST criteria in development and validation cohorts, and the PLCO risk prediction model improved patient selection and LC detection compared to NLST criteria [40]. The PanCan model, a...
### Table 1
Summary of randomized-controlled trials on LDCT screening with extended follow-up and lung cancer-specific mortality results published within last 5 years

| Name of study     | Country | Year of publication/update | Inclusion criteria                                                                                                                                                                                                 | Number of patients in randomized arm | Follow-up period (median years) | Comparison | Number of annual screens | Lung cancer mortality events | Conclusion                                                                                                      | Comments                                                                                               |
|-------------------|---------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|---------------------------------|------------|---------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| NLST (baseline reference) [16••] | USA     | 2011                      | ▪ 55–74 years of age  
▪ ≥ 30 pack years smoking  
▪ Current smoker or quit < 15 years  
▪ Males and females | 26,722                               | 6.5                | CXR         | 3                       | 356 (1.3) 443 (1.7)                  | ReR 20% 95% CI 6.8–26.7          | 0.004 • Screening with LDCT decreased mortality by 20%, NNS 320                                               | Conducted in centers with expertise, unsure if generalizable Only 3 rounds of screening                   |
| DANTE [20]        | Italy   | 2015                      | ▪ 60–74 years of age  
▪ ≥ 20 pack years smoking  
▪ Current smoker or quit < 10 years  
▪ Only males | 1264                                | 8.35               | Clinical review | Baseline+4  | 59 (4.7) 55 (4.6)                  | HR 0.99 (95% CI 0.688–1.433)     | NR • Unable to make conclusions re: efficacy of LDCT screening  
▪ No significant mortality difference | Insufficient sample size, limited power, single site, low sensitivity of screening protocol               |
| DLCST [21]        | Denmark | 2016                      | ▪ 50–70 years  
▪ ≥ 20 pack years smoking  
▪ Current smoker or quit < 10 years and after age of 50  
▪ FEV1 ≥ 30%  
▪ Can climb 2 flights of stairs (36 steps) without pause  
▪ Males and females | 2052                                | 9.8                | Usual care  | Baseline+4  | 39 (1.9) 38 (1.9)                  | HR 1.03 (95% CI 0.66–1.6)        | 0.888 • No significant all-cause or LC mortality difference noted with screening | Underpowered, single site                                                                                   |
| Name of study | Country | Year of publication/update | Inclusion criteria | Number of patients in randomized arm | Follow-up period (median years) | Comparison | Number of annual screens | Lung cancer mortality events | Conclusion | Comments |
|--------------|---------|---------------------------|-------------------|-------------------------------------|-------------------------------|------------|--------------------------|-----------------------------|------------|---------|
| ITALUNG [22] | Italy   | 2017                      | ▪ 55–69 years of age ▪ ≥ 20 pack years smoking ▪ Current smoker or quit < 10 years ▪ Males and females | 1613 | 9.3 | Usual care | 4 | 43 (3) 60 (3.8) | RR =0.70 (95% CI: NR 0.47–1.03) | • 30% reduction in LC-specific and 17% reduction in all-cause mortality noted in LDCT group • This was not statistically significant • This trend suggests that screening with LDCT could decrease mortality | Insufficient power |
| MILD [23, 24] | Italy   | 2019                      | ▪ 49–75 years of age ▪ ≥ 20 pack years smoking ▪ Current smoker or quit < 10 years ▪ No history of cancer in ≤ 5 years ▪ Males and females | 2376 1190 annual arm 1186 biennial arm | 10 | No intervention 7 in annual 4 in biennial | 40 (1.7) 40 (2.3) | HR 0.61 (95% CI: 0.39–0.95) | 0.14 | • 39% decrease in 10-year risk of LC mortality with screening • No significant 10-year overall or LC-specific mortality difference between annual and biennial screening • Long-term screening with biennial screening is effective | There was insufficient power in trial at 5 years of follow-up but adequate power was achieved after 10 years of screening follow-up |
| Name of study | Country | Year of publication/update | Inclusion criteria | Number of patients in randomized arm | Follow-up period (median years) | Comparison | Number of annual screens | Lung cancer mortality events | Conclusion | Comments |
|--------------|---------|---------------------------|-------------------|-------------------------------------|-------------------------------|------------|-------------------------|--------------------------------|----------|---------|
| LUSI [25]    | Germany | 2019                      | ● 50–69 years of age  
● ≥ 1/2 pack for ≥ 30 years  
● ≥ 3/4 pack for ≥ 25 years  
● Current smoker or quit < 10 years  
● Males and females | 2029 | 8.8 | Usual care | Baseline + 4 | 29 (1.4) | 40 (2.0) | HR 0.74 (95% CI: 0.46–1.19) | 0.21 • No significant all-cause or LC mortality difference noted with screening  
• Significant decrease in LC mortality in subgroup of women as compared with men | Insufficient sample size |
| NLST [26]    | USA     | 2019                      | ● 55–74 years of age  
● ≥ 30 pack years smoking  
● Current smoker or quit < 15 years  
● Males and females | 26,722 | 12.3 | CXR | 3 | 1147 (4.3) | 1236 (4.6) | 0.92 (95% CI: 0.85–1.00) | 0.06 • Screening with LDCT decreased mortality by 8%, NNS 303 |
| NELSON [27••] | Netherlands, Belgium | 2020 | ● 50–74 years of age  
● ≥ 1/2 pack for ≥ 30 years  
● ≥ 3/4 pack for ≥ 25 years  
● Current smoker or quit < 10 years  
● Males and females | 7900 | 10 | Usual care | Baseline + 3 (years 1, 3, and 5.5) | 186 (2.4) | 248 (3.2) | RR 0.76 (95 CI: 0.61–0.94) | 0.01 • LC screening with volume CT significantly decreased mortality  
• Significant decrease in LC-specific mortality in women compared to men | |

DANTE Detection of Early Lung Cancer by Novel Imaging Technology and Molecular Essays, DLCST Danish Lung Cancer Screening Trial, ITALUNG Italian Lung Cancer Screening Trial, HR hazard ratio, LDCT low-dose computed tomography, LC lung cancer, LUSI German Lung Cancer Screening Intervention, MILD Multi-centric Italian Lung Detection Trial, NELSON Nederlands-Leuvens Longkanker Screenings Onderzoek Study, NLST National Lung Cancer Screening Trial, NR not reported, RR rate ratio, ReR relative reduction
forerunner to the PLCoM2012 validated model, was studied prospectively in 2537 ever-smokers, and approximately 133 (77%) of detected LCs were early stage (stages I and II) and potentially curable [41]. Wider use of risk prediction models was recommended for improving patient selection.

Katki et al. compared absolute risk models with USPSTF recommendations to determine effective screening strategies [42]. In the risk-based fixed population size model, 36% of lower risk screen-eligible smokers were replaced by a similar number of high-risk smokers, either low-intensity longer term smokers or higher intensity smokers who quit >15 years ago. There was improved screening efficacy, with decreased number needed to screen (NNS) to prevent one death, i.e., 162 (95% CI, 157–166) compared to 194 (95% CI, 128–137) and a decrease in false-positive CT examinations. In the risk-based fixed effectiveness strategy, the relative modeled preventable death was 34% higher. Overall, their study showed that application of risk-based models prevented more deaths at 5 years and improved effectiveness of screening by decreasing NNS to prevent one death.

### Table 2  Lung cancer screening criteria recommendations by specialty societies, institution, NLST, and CMS

| Society          | Age (years) | Current or former smoking (pack years) | Quit period for former smokers (years) | Additional criteria for inclusion | Who should not be screened (exclusion or discontinuation) |
|------------------|-------------|----------------------------------------|----------------------------------------|----------------------------------|----------------------------------------------------------|
| NLST [16••]      | 55–74       | ≥ 30                                   | <15                                    | Asymptomatic                     | Exclusion:                                               |
|                  |             |                                        |                                        |                                  | - History of LC                                         |
|                  |             |                                        |                                        |                                  | - Chest CT within 18 months                             |
|                  |             |                                        |                                        |                                  | - Hemoptysis                                             |
|                  |             |                                        |                                        |                                  | - Unexplained weight loss of >15 lb in last year        |
| USPSTF [17, 39]  | 50–80       | ≥ 20                                   | <15                                    | Asymptomatic                     | - Life-limiting health condition                        |
|                  |             |                                        |                                        |                                  | - Unable or unwilling to have curative surgery           |
| CMS [19]         | 55–77       | ≥ 30                                   | <15                                    | Asymptomatic                     | - Life-limiting health condition                        |
|                  |             |                                        |                                        |                                  | - Unable or unwilling to have screening/curative treatment |
| NCCN [2]         | Gp 1: 55–74 | Gp 1: ≥ 30                             | <15                                    | Gp 1: Asymptomatic               | Gp 1: One of the following:                             |
|                  | Gp 2: ≥ 50  | Gp 2: ≥ 20                             |                                        |                                  | personal history of cancer or certain chronic lung      |
|                  |             |                                        |                                        |                                  | diseases (COPD, pulmonary fibrosis), family history of  |
|                  |             |                                        |                                        |                                  | LC, radon/occupational exposures                        |
| ACCP [29–32, 33••] | 55–74     | ≥ 30                                   | <15                                    | Asymptomatic                     |                                                          |
| ATS              |             |                                        |                                        |                                  |                                                          |
| IASCLC           |             |                                        |                                        |                                  |                                                          |
| ACS              |             |                                        |                                        |                                  |                                                          |
| ASCO             |             |                                        |                                        |                                  |                                                          |
| AATS [34]        | Gp 1: 55–79 | Gp 1: ≥ 30                             | Gp 1: <15                              | Gp 1: Asymptomatic               | Gp 2: Prior history of LC                               |
|                  | Gp 3: 50–79 | Gp 3: ≥ 20                             |                                        |                                  | without recurrence ×4 years, starting 5 years post-      |
|                  |             |                                        |                                        |                                  | treatment                                              |
|                  |             |                                        |                                        |                                  | Gp 3: Comorbidities which confer ≥ 5% cumulative risk   |
|                  |             |                                        |                                        |                                  | of LC within 5 years                                     |
| ALA [35]         | 55–80       | ≥ 30                                   | <15                                    |                                  |                                                          |
| AAFP [36••]      |             |                                        |                                        |                                  | LC screening with LDCT not supported currently due to    |
|                  |             |                                        |                                        |                                  | initial concerns about relying on one study alone       |

AATS American Association of Thoracic Surgery, AAFP American Academy of Family Physicians, ACS American Cancer Society, ACCP American College of Chest Physicians, ALA American Lung Association, ASCO American Society of Clinical Oncology, ATS American Thoracic Society, CMS Centers for Medicare and Medicaid Services, IASCLC International Association for the Study of Lung Cancer, NCCN National Comprehensive Cancer Network, NLST National Lung Screening Trial, USPSTF United States Preventive Services Task Force.
Risk prediction models generally predict either LC incidence or mortality. Nine of these models with broad applicability [Bach model, Liverpool Lung Project (LLP) model, PLCOm2012 model, the Two-Stage Clonal Expansion (TSCE) model for incidence, two versions of TSCE model for death, Knoke model and simplified versions of PLCOm2012 and LLP models] were reviewed and validated by Ten Haaf et al. [43] and applied to both NLST and PLCO cohorts. They found that with risk thresholds specific to each model, all had a higher sensitivity and specificity than currently used NLST criteria, which had a specificity of 62.2% (95% CI: 61.7–62.7%) and sensitivity of 71.4% (95% CI: 68–74.6%). Overall, however, the models which performed the best, with sensitivities >79.8% and specificities >62.3%, were the PLCOm2012 model, followed by the Bach and TSCE incidence models.

When combined with LDCT results, the use of the PLCOm2012 validated model in NLST data was able to help stratify patients into high- and low-risk groups, and improve prediction of LC risk [44].

In summary, risk prediction models can help improve patient risk stratification and screening efficacy. Prospective studies are needed for comparative analysis of various models in different populations to help determine optimal patient selection. The ongoing Yorkshire Lung Cancer Screening Trial [45], designed to evaluate three selection methods (USPSTF criteria, the PLCOm2012 and LLP models), will help further our understanding.

At times, models can be tedious, and determination of the best risk threshold to use is not always clear. To combat this, online calculators have been developed, such as the Brock model (https://brocku.ca/lung-cancer-risk-calculator), which includes PLCOm2012 risk calculator and LDCT results, and are more user-friendly.

**Components of a High-Quality Screening Program**

Less than 5% eligible Americans are currently undergoing screening [46]. There is a need for high-quality programs to improve screening effectiveness.

A combined policy statement released by the ACCP and ATS in 2015 outlined the recommendations for screening programs to help implement LC screening in clinical practice [47]. Nine main components were identified, as summarized in Fig. 1.

**Harms of Screening**

1. **False Positives** In NLST, a 4-mm threshold was used to classify nodules as positive, and the LDCT group had a false positive rate of 96.4% [16••]. Increasing the threshold for nodule detection can decrease false positives at the risk of decreasing sensitivity. The rate of adverse events associated with a diagnostic procedure as a result of a false positive screening test was noted to be low at 0.4% [28].

2. **False Negatives or “Missed” Diagnoses** This accounts for approximately 90% versus 5% of the presumed errors in CXR and CT scan screening, respectively [48].

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**Fig. 1** Components of a high-quality lung cancer screening program: combined ACCP and ATS policy statement
Occur due to observer error, characteristics of the lesion or technical error, and can have medicolegal consequences.

3. **Overdiagnosis** Overdiagnosis refers to detection of slow growing cancers that might not otherwise have caused symptoms or harm, and generally occur due to over-detection, i.e., decreasing the thresholds, or overdefinition, i.e., expanding the range of the definition for a diagnosis [49]. This can lead to unnecessary procedures, and contribute to morbidity, anxiety, and expense. There is significant variation in overdiagnosis reported in trials, and an extended follow-up period is helpful for estimation. The overdiagnosis rate in NLST was approximately 18.5% [50], although this decreased to 3% with increase in follow-up from 6.5 to 11 years [26]. Similarly, in the NELSON study, an overdiagnosis rate of 19.7% at 10 years decreased to 8.9% after extension of follow-up to 11 years [27••]. In the DLCST and ITALUNG trials, the rates of overdiagnoses were 67% and 0%, respectively. It is important that trials report overdiagnosis rates and that these are considered in clinical practice [51].

4. **Invasive Procedures and Complications** Screen-detected abnormalities often lead to additional diagnostic and therapeutic procedures. The invasive procedure rates are reported to be approximately 5.1% and 2.7% after screening with LDCT and CXR, respectively [34], with complication rates also higher in patients who were screen-positive by LDCT compared to CXR. In NLST, complications were higher in patients with malignancy (23.3%) versus false-positive benign disease (0.4%) [16••, 28]. Complications were higher after surgery compared to bronchoscopy in both malignant (32.4% vs 9.2%) and benign (15.9% vs 4.8%) diagnoses, with rates of complications of needle biopsies lying in between. The overall surgical perioperative mortality rate (within 60 days) was 1% for LDCT screened patients vs 0.2% for the control (CXR) patients [52].

5. **Radiation Exposure** The radiation exposure from a CXR is 0.1mSv and LDCT is 1.5 mSv. In contrast, the radiation from a full-dose CT scan and PET-CT are approximately 8 mSv and 14 mSv, respectively [52]. There is a cancer risk from exposure to ionizing radiation during scanning, which is cumulative throughout life [36••]. In NLST, the cumulative radiation dose per patient during 3 years of screening was approximately 8 mSv. It is predicted that for every 2500 patients undergoing LC screening, there would be 1 radiation-related cancer death [52]. For smokers undergoing LDCT screening from 50 to 75 years, annual screening is estimated to increase the baseline risk of cancer in males (15.8%) by 0.23% and females (16.9%) by 0.85%, representing a 1.5% and 5% increase in risk respectively [53]. In higher risk older patients, the benefits clearly outweigh the risks, but this is less certain in younger patients at lower risk who may face 20–30 years of annual LDCT screening. In such cases, spacing out of screening intervals may be important, and this warrants further prospective studies.

6. **Psychosocial Impact from Screening** Patients can develop anxiety, depression, and psychological distress over screening results, diagnosis of cancer, or related to complications. Distress briefly increases after an abnormal result, but returns back to baseline, without significant change in overall health-related quality of life (HRQOL) [54]. Distress is associated with smoking status, with ex-smokers reporting less worry compared to current smokers [55]. In NLST participants, there were no significant differences at 1 and 6 months in anxiety and HRQOL among patients with false positive or significant incidental findings (SIFs) compared to negative findings. However, physical and mental health scores were lower, and anxiety was higher, in those diagnosed with LC within 1 year of positive screens [56].

**Other Screening Considerations**

**Significant Incidental Findings (SIF)** This refers to abnormal findings unrelated to lung nodules, but requiring follow-up, specialist referrals, and/or additional workup. In a retrospective analysis of 320 LDCT-screened patients, at least one incidental finding occurred in all patients [57]. Incidental findings were most frequently of pulmonary (69.6%), cardiovascular (67.5%), or gastrointestinal (25.9%) etiology. Approximately 46.2% of total reimbursement related to screening was associated with workup of SIFs. Some authors [58, 59] have noted inconsistent radiologic reporting of SIFs. Patients should be counseled on the probability of SIFs and screening programs should standardize reporting and evaluation.

**Cost-Effectiveness** Approximately 8.6 million Americans are LC screen-eligible [60]. While this would significantly increase the costs of screening, studies suggest that the actual cost-effectiveness of screening was approximately $81,000 per quality adjusted life year (QALY) [61], and overall, there was economic benefit. A cost-effective analysis using 4 models studying annual LDCT using NLST, CMS, and USPSTF screening criteria found that incremental cost-effective ratios averaged $49,000, $68,600, and $96,700 per QALY, respectively, and that it was cost-effective to use these criteria [62].

**Shared Decision Making**

Shared decision making (SDM) refers to an evidence-based risk–benefit discussion with the patient about LDCT screening, with decisions made taking into account the
patient’s values and preferences. This is recommended by USPSTF and mandated with the use of decision aids by CMS as part of coverage requirements [19].

The goal of the SDM process is to promote patient-centered care [63]. Given risks, patients may opt not to proceed with LC screening. The success of the SDM encounter depends on the informed decision making process rather than the actual outcome of proceeding or not with screening [63].

Decision aids can be particularly helpful during SDM visits, and increase patients’ knowledge, especially related to screening risks [64]. They can be in the form of videos, pamphlets, or internet-based, and a variety of different media options may be required to cater to variations in literacy and comfort levels. There are several decision aids available online as links in websites of professional organizations [61].

SDM has not yet been widely adopted as intended [46, 65, 66]. Qualitative analyses of SDM conversations found that harms were not really explained, minimal time was spent on screening, and decision aids were likely not used [65, 67]. Several reasons for poor performance have been identified. Many patients and providers lack proper education about the nuances of the SDM process. Physician barriers include lack of time to integrate SDM with clinic visits, competing priorities, ambivalence towards screening, and concern over risks [67]. Patients were generally more accepting of screening, but often did not fully understand risks, and were guided by emotion, personal fears, and fatalism during decision making.

In summary, SDM is not optimally performed. Efforts at provider and patient education may help bridge barriers, and improve patient engagement, collaboration, and the overall quality of the encounter.

Smoking Cessation

Approximately 50% of patients enrolled in LC screening are current smokers [68]. There is a 20% mortality benefit after 7 years of smoking cessation, similar to that seen with LDCT screening in the NSLT trial [69]. There is even greater mortality benefit when smoking cessation is combined with lung cancer screening.

CMS has mandated that smoking cessation counseling services be integrated into LC screening programs, and the cost-effectiveness of screening may be improved by 20–45% with this integration [70]. However, there are knowledge gaps and challenges in the delivery of smoking cessation interventions in this setting [68].

LC screening is thought to represent a teachable moment for smoking cessation [71]. Enrolled patients are generally more interested in cessation and intervention [72]. During the screening process, patients have multiple scheduled interactions with the healthcare team, and each of these interactions represents an opportunity for counseling. Approximately 75% of patients enrolling in screening will have negative results [72], but there is no clear data suggesting that this provides false reassurance to continue smoking. However, patients with positive screening results have demonstrated higher quit rates at 1 year [73].

Only 12–20% of smokers are ready to quit within a month at any particular time [74]. All patients, regardless of motivation, should be offered intervention for smoking cessation, as quit rates are higher in those offered intervention [72]. Clinician training in motivational interviewing and smoking cessation counseling is important for success. Guidelines suggest using strategies such as the 5As (ask, advise, assess, assist, and arrange) to counsel patients motivated to quit, and the 5Rs (relevance, risks, rewards, roadblocks, and repetition) to improve future cessation in patients not yet ready to quit [75]. Counseling and medication are also recommended together, as the combination increases cessation success compared to either alone [75].

The Smoking Cessation within the Context of Lung Cancer Screening (SCALES) is an ongoing multi-institutional collaboration of 8 clinical trials [68]. Results generated from this group are awaited to further our understanding of design, implementation, practice, and outcomes of smoking cessation services within screening programs.

Radiology Considerations

A prerequisite of a successful screening program is the existence of structured reporting and standardized management algorithms [47].

Standardized Reporting: In NLST, a nodule threshold of ≥ 4 mm in largest transverse diameter was considered positive. The LUNG-RADS reporting system was developed by the American College of Radiology (ACR) to standardize classification and reporting of screen-detected lung nodules [76]. In LUNG-RADS, the positive threshold was increased to 6 mm as a transverse bi-dimensional average, and growth of pre-existing nodules was also considered [77]. The application of LUNG-RADS to the NLST cohort lowered the false positive rate at the expense of lower sensitivity [78]. The positive predictive value was improved by 2.5 [79]. There are some limitations with LUNG-RADS such as inconsistent reporting of certain significant abnormalities and increase in positive results due to rounding [79–81]. Prospective validation of LUNG-RADS and improvement in standardized reporting of significant abnormalities will be important for overall benefit.

Volumetric Analysis: The NELSON study [27••] focused on volumetric analysis of nodules instead of traditional two-dimensional measurements. Volumes and doubling times were used to determine positive, indeterminate, or negative results. A nodule size threshold of ≥ 27 mm³ had a 95% sensitivity for detecting malignancy, while volume doubling time of > 600 days...
had a very low probability of malignancy [82]. Use of volumetric analysis decreased false positive rates and unnecessary diagnostic interventions. The British Thoracic Society Guidelines for the management of pulmonary nodules has incorporated volumetric analysis in their recommendations [83].

**Disparities in Lung Cancer Screening**

There are several disparities in screening. Current LC screening criteria do not consider the specific differences within a population with regards to race, ethnicity, socioeconomic status, gender, specific comorbidities, geography, and access to healthcare. For example, compared to white patients, African-Americans have a higher LC risk at an earlier age and despite a lower pack-year smoking history, would benefit from liberalizing eligibility criteria [84]. Even when referred to LC screening programs, they had lower screening rates as well as delayed follow-up [85]. Women are at higher risk for LC than men despite variations in smoking practices, and patients with HIV have a higher independent LC risk [86]. Patients with lower literacy levels or from different cultures may not equally benefit from current SDM tools, which are not catered specifically towards this population.

The ATS recently issued an official statement to address disparities, so that care and resources can be more equitably provided [86]. The committee has proposed several strategies and recommendations to improve eligibility and access to screening and overcome multiple barriers. Continued, committed efforts at the individual, local, and national levels are required to bridge barriers and minimize disparities.

**Screening During COVID-19 Pandemic**

The current COVID-19 pandemic has presented unique screening challenges. Most screening programs were modified or put on hold during active hospital surges due to cancellations in imaging services and non-emergent procedures. The ACCP Expert Panel group put forth recommendations, endorsed by ATS and ACR, to address the management of screening and lung nodules during this time [87]. Clinicians should refer to these guidelines for details, with clinical application recommended based on individual patient appropriateness and availability or constraints in local resources.

**Biomarkers in Screening**

Multiple biomarkers are being studied in LC screening, either to improve risk-based patient selection pre-screening or to improve risk-stratification after nodule detection. Some of these include blood-based biomarkers such as autoantibodies, complement fragments, circulating proteins, circulating DNA and microRNA signature profiles, and exhaled breath condensates, metabolomics, and image analysis of sputum [88]. Airway gene expression is currently being utilized in patients with lung nodules to assist with lung cancer risk stratification [88–90], and is covered by Medicare. At this time, there is no sole approved biomarker in lung cancer screening, and research efforts continue to be underway.

**Conclusion: Challenges and Future Directions**

In conclusion, LC screening with LDCT has a proven significant mortality benefit. There are still significant knowledge and communication gaps in patient and physician understanding of screening nuances [66], requiring further education. The United States is currently still in the infancy stages in implementation of screening programs, and European countries have been issued a call for action to set up screening [91]. Multiple professional societies and experts have worked together to put forth guidelines and recommendations to improve the efficacy of screening programs, standardize screening eligibility and reporting, bridge healthcare disparities, and weather unique challenges during the COVID-19 pandemic. Multiple trials have been completed or are ongoing to refine our understanding about patient selection, nodule assessment and reporting, benefits and harms of screening, and integration of smoking cessation interventions. It is commendable that so much national and international work has been done just within the last decade. However, much work is still left to be done.

Future research should focus on patient selection based on individual risk, optimizing screening practices such as frequency of screening, radiation exposure and reporting practices to enhance benefits and minimize harms, and improve local and national advocacy to minimize racial disparities and improve access to screening for all. Exciting advances in biomarkers and genetic testing, in combination with current screening practices, may help herald the next phase of personalized screening and lung cancer prediction.

**Declarations**

**Conflict of Interest** Anuradha Ramaswamy declares no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.
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