Chapter 2
Lung Cancer Screening

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The History of Lung Cancer Screening

A successful screening test requires a significant disease with identifiable risk factors and a preclinical period. Screening might meaningfully impact disease outcomes if the disease can be identified before developing symptoms, and early treatment can reduce mortality. Lung cancer as we know it today meets these criteria. In the mid-twentieth century, the burden of lung cancer grew swiftly from a rare disease to surpassing all other cancer-related causes of death [1]. British scientists reported the association between cigarette smoking and lung cancer in 1950, reporting a 15-fold increase in lung cancer mortality from 1922 to 1947 in the United Kingdom [2]. This report was followed by the US Surgeon General, and Royal College of Physicians reports firmly linking cigarette smoking to lung cancer [3].

Sputum Cytology and Chest Radiography

For decades, clinicians and researchers sought effective lung cancer screening (LCS) tests. Early in the lung cancer epidemic, sputum cytology and chest radiographs were investigated as potential screening tests. When periodic chest radiographs alone [4] appeared inadequate for early detection and improved lung cancer mortality, a large collaborative trial between the Mayo Clinic, Johns Hopkins, and Memorial Sloan-Kettering enrolled men over 45 years of age who smoked at least one package of cigarettes daily for either chest radiograph with or without sputum cytology [5]. Over 30,000 patients were enrolled in the early 1980s and followed for

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10 years, but the study failed to show significant benefit for sputum cytology and chest radiography to reduce lung cancer mortality. In 1996, the United States Preventive Services Task Force (USPSTF) issued its first recommendation about LCS, with a Grade D recommendation against using chest radiography or sputum cytology to screen asymptomatic individuals.

In the late 1990s, at the peak of lung cancer mortality, screening again gained interest, especially as reexamining prior trials demonstrated they might have been inadequately powered to detect an effect. Enter the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. With its 150,000-plus participants, the Prostate, Lung, Colon, and Ovarian (PLCO) trial was powered to detect a 10% difference in lung cancer mortality [6]. However, this trial definitively asserted the futility of annual chest radiographs for LCS, showing no mortality benefit for the 75,000 participants randomized to annual chest radiographs, compared to no lung screening. Furthermore, large studies in the United Kingdom and the United States failed to show a mortality benefit for LCS with the available diagnostic technologies at the time: sputum cytology in combination with chest radiography.

The United States Preventive Services Task Force is an independent national organization whose volunteer members review published literature about preventive care services. They evaluate the available evidence and recommend preventive services, including cancer screening. In 2004, the USPSTF issued a Grade I recommendation on LCS, a designation signifying insufficient evidence to recommend for or against screening [7]. Specifically, the recommendations stated: "Current data do not support screening for lung cancer with any method. These data, however, are also insufficient to conclude that screening does not work, particularly in women." The evidence reviewed to make this recommendation included some early small studies of low-dose chest computed tomography for LCS, and the broader availability of chest computed tomography offered new promise for an effective LCS modality.

Chest Computed Tomography for Lung Cancer Screening

In 2013, following the results of the landmark National Lung Screening Trial (NLST), [8] the USPSTF updated the LCS guidelines [9]. For the first time, LCS with low-dose computed tomography (LDCT) received a favorable Grade B recommendation meaning "high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial" Screening was recommended for those "55–80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery." The Cancer Intervention and Surveillance Modeling Network (CISNET) conducted extensive scenario modeling of risk factor-based lung cancer screening patient selection strategies. The models, which included different thresholds for age at screening initiation, age at screening discontinuation, pack-years, and quit time,

showed that the USPSTF 2013 guidelines were often the most efficient combination of risk factor thresholds [10].

Most major professional societies (including the American Cancer Society, American Thoracic Society, American College of Chest Physicians, Society for Thoracic Surgeons, and National Comprehensive Cancer Network) endorsed lung cancer screening with LDCT. The notable exception was the American Academy of Family Physicians (AAFP), whose recommendation remained ambivalent based on "insufficient evidence" [11]. Considering that Family Physicians comprise the largest proportion of primary care clinicians, this failure to endorse LCS with LDCT no doubt impacted the initial uptake of the service [12].

Preventative Care Coverage Policy in the United States

In 2010, a significant policy change conferred particular importance on the Grade B recommendation. The Affordable Care Act was passed into law in 2010 and required private insurers to cover preventive services recommended by the USPSTF with a grade of A or B and to cover these services with no cost-sharing (i.e., no deductible and no co-pay) [13, 14]. Furthermore, the Affordable Care Act authorizes Medicare to expand coverage of preventive services to include USPSTF recommendations and requires Medicaid to cover preventive services recommended by the USPSTF with a grade of A or B.

Coverage of preventive services under Medicare or Medicaid is codified using national coverage determinations. In 2014, the Centers for Medicare and Medicaid services (CMS) conducted a national coverage analysis of lung cancer screening at the request of lung cancer advocates [15]. The resulting coverage determination confirmed eligibility for individuals aged 55–77 who had smoked at least 30 pack-years with additional stipulations and unprecedented conditions for coverage [16]. One major condition of coverage was a shared decision-making visit to be performed by a credentialed independent clinician (physician or advanced practitioner) in person to confirm eligibility and discuss risks and benefits. Critics of this requirement saw it as an unnecessary barrier to receiving care, but others recognized that for a preventive service like LCS with LDCT, the risks and benefits vary based on individual patient factors, including lung cancer risk, medical comorbidities, and personal values.

Evidence for Lung Cancer Screening

The National Lung Screening Trial (NLST)

The NLST enrolled 53,454 individuals between the ages of 55–74 at randomization who had at minimum a 30-pack-year smoking history and who were currently smoking or had quit within the past 15 years. Individuals were randomized to single

view (posteroanterior projection) chest radiography or LDCT, with an initial screening at the time of randomization, and annual screenings for 2 years, totaling three screening exams. Median follow-up was 6.5 years. Results were reported to participants without a specific study procedure mandated to work up suspicious findings.

The LDCT group had a higher rate of lung cancer diagnosis, 645 per 100,000 person-years, as opposed to 572 per 100,000 person-years in the chest radiography group. Of key clinical significance, the LDCT group had a higher stage I identification rate and a lower rate for stage III and IV non-small cell lung cancers (NSCLC). The rate of positive screenings was also higher in the LDCT group, which had a three times higher rate of identification of non-lung cancer abnormalities. Ultimately 96.4% of the positive results in the low-dose CT group and 94.5% in the radiography group were false positives.

The NLST was stopped when it reached the predetermined endpoint of a 20% reduction in lung cancer mortality in the LDCT screening group compared to the radiography group. For LDCT, the number needed to screen to prevent one lung cancer death was 320. For its 2013 recommendations, the USPSTF reviewed evidence from the NLST in making the recommendation for LCS, with further information provided by the CISNET models [10, 17].

Global Lung Cancer Screening Trials

In the years before and after the NLST, numerous LCS trials were conducted across Europe, including the German LCS Intervention (LUSI), Danish LCS Trial (DLCST), Multicentric Italian Lung Detection (MILD), and UK Lung Cancer Screening Trial (UKLS), each of which looked at the effect of screening CT vs. usual care [18–21]. While relatively similar in the study participants' age and smoking exposure inclusion criteria, the trials utilized various methods for identifying and recruiting participants, screening intervals, nodule management, and length of follow-up. Compared to the NLST, these trials had much smaller study populations and follow-up person-years and thus did not have the statistical power to show a mortality benefit for LCS [22, 23].

In 2020, the results of the second largest screening study, the Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON), were published [24]. The trial randomized 15,789 participants (13,195 men and 2594 women) aged 50–74 with a smoking history of 10 cigarettes daily for at least 30 years (15 pack-years) or 15 cigarettes daily for at least 25 years (18.75 pack-years). Those who formerly smoked needed to meet the required smoking history and have a quit date within the previous 10 years. For the intervention group, screening occurred at baseline, then at intervals of 1, 2, and 2.5 years for a total of four screening exams. Individuals were followed for a minimum of 10 years.

Among male participants, the LDCT screening group had a higher rate of lung cancer diagnosis, 5.58 cases per 1000 person-years, compared to 4.91 cases per 1000 person-years in the control group. Of the screen-detected cancers in the

intervention group, 58.6% were stage I compared to 13.8% in the control group. Similarly, stage IV lung cancers comprised only 9.4% of screen-detected cancers in the intervention group but 45.7% in the control group. At 10 years, there was a 24% reduction in lung cancer mortality among men and a 33% reduction among women.

Notable aspects of the NELSON results that have prompted further interest and discussion include its finding of a mortality benefit despite conducting screening on less-than-annual basis and the lower rate of positive scans and follow-up studies required compared to the NLST. The NELSON trial reported an overall false-positive scan rate of 1.2%, with a baseline "indeterminate" scan rate of 19.7%. Most of these were later adjudicated as negative scans based on volume doubling time calculated at exam follow-up. By comparison, the NLST reported a baseline positive scan rate of 27.3% with an overall false-positive rate of 23.3%. The number of positive or indeterminate scans is of particular interest given the ramifications of a false-positive screening result, such as the psychological impact and potential need for invasive testing. The use of volume-based low-dose CT, with its focus on volumetric measurements and volume doubling time as opposed to the diameter-based estimates of standard LDCT, may have contributed to the lower percentage of positive or indeterminate scans, especially in later stages of screening.

Limitations in LCS Evidence

Both NELSON and the NLST have shown a mortality benefit from LCS. However, both trials have generalizability limitations, particularly regarding the study populations. The NLST population was 59% male and over 90% white, while the primary analyses in the NELSON study were conducted in a male population with race not reported but assumed to be white. The NELSON study was not powered to detect mortality benefits for women [25], but results suggest women would benefit even more than men. Furthermore, the NLST study sample was relatively young and healthy [26] and disproportionately comprised of individuals who no longer smoked and had higher educational attainment, compared to real-world screening [27, 28] populations. Studies have shown that participants and settings in the NLST and NELSON trials did not represent the general US population [29]. Small studies suggest the benefits of LCS may be even greater for participants with lower educational attainment [30], and Black individuals [31]. Analysis of lung cancer cases in the Southern Community Cohort Study [32] demonstrated that USPSTF 2013 criteria were less sensitive for Black individuals, with 67% of the lung cancer cases diagnosed in Black individuals who would not meet 2013 LCS eligibility due to insufficient smoking history. Lung cancer and screening are not unique in the disparities between the type of individuals included in large clinical trials and those most burdened by the disease [33, 34].

Beyond differences in participant characteristics, the NLST and NELSON also had study protocols that are not replicated in most real-world screening programs. For example, the NLST had more stringent requirements [35] for interpreting

radiologists (LDCT interpretation experience and training) than are currently required in for interpretation of LDCT for LCS. The NELSON trial radiologists had computer-assisted detection [36] of nodules including volumetric measurement. In both the NLST and NELSON, screening was conducted primarily at highly respected academic medical centers, whose outcomes may not be achievable in all clinical settings.

2021 USPSTF LCS Recommendations

Since the 2013 LCS guidelines were published, several important trials warranted consideration when creating the revised 2021 USPSTF guidelines. Key evidence questions focused on patient selection, specifically, whether the NLST participants and settings were representative of the United States as a whole and whether the use of individualized risk calculation (risk model-based strategy) improved patient selection compared to age and pack-year smoking history (risk factor-based strategy). Synthesizing the evidence [37] from the largest RCTs powered to detect a mortality benefit for LDCT (NLST and NELSON trials) and modeling studies [38] supported expanded recommendations lowering the screening eligibility threshold to 50 years of age and smoking exposure to 20 pack-years. Women and individuals who identify as Black, Hispanic, and American Indian/Alaska Native stand to benefit from the lowered smoke exposure thresholds for screening. The 2021 recommendations remain Grade B, with a moderate certainty of moderate net benefit. The AAFP endorsed the new guidelines shortly after the 2021 USPSTF updated recommendations. Again, lung cancer advocates requested a reconsideration of national CMS coverage, prompting a new coverage determination [39]. In 2022, CMS issued its final decision to expand coverage for LCS using the new eligibility criteria while removing some of the previous conditions [40].

Lung Cancer Screening Methods

Low-Dose CT Screening Exam Technique

Per the National Comprehensive Cancer Network (NCCN) guidelines [41], LDCT screening exams should have a total radiation exposure less than or equal to 3 millisieverts (mSv), with 1 mSv being the annual average background radiation for an individual in the United States, and the worldwide average being 2–4 mSv (based on average size patient). The American College of Radiology (ACR) designates LCS Centers [42, 43] based on adherence to a similar set of technical guidelines, including the radiation dose from the CT scanner ($CTDI_{vol}$), slice thickness, and image acquisition time. The radiation exposure from LDCT scans is approximately

one-fifth the amount of a conventional CT scan and may decrease further in the future as clinicians experiment with ultralow-dose CT scanning (ULDCT) [44].

The LDCT technique as described assumes patient BMI is less than 30, so total radiation dose is adjusted for body weight. The slice width should be less than or equal to 2.5 mm (1.0 mm preferred), with an acquisition time of less than or equal to 10 s or a single breath hold. No contrast agent of any kind is used for LDCT.

Nodule size is reported as the average two measurements: the longest nodule diameter and its perpendicular length on a single image. An alternative approach is volumetric analysis and volume doubling time, conducted using automated or semi-automated computer programs used in the recent NELSON trial [24]. Volumetric analysis may ultimately provide a lower rate of false-positive findings by giving more sensitive information on nodule growth over time. There are limitations as irregular nodules can still be hard to measure [45]. While commonly used in Europe, Volume CTs are not used in routine practice in the United States.

Interpretation

In the NLST, scans with 4 mm or greater diameter nodules were considered positive, and the study was marked by a high rate of false-positive scans, with 90% of positive scans not resulting in a lung cancer diagnosis [46]. To standardize reporting of screening exams and reduce the false-positive rate reported in the NLST, the ACR created the Lung Reporting and Data System (Lung-RADS) [47]. An analysis of NLST nodules in the 4–6 mm range and results from the International Early Lung Cancer Action Program (I-ELCAP) were considered when formulating the Lung-RADS criteria [48]. By using size criteria of 6 mm in diameter for solid nodules and greater than or equal to 20 mm for subsolid or ground-glass nodules as a positive LDCT, the Lung-RADS criteria showed a decrease in false-positive screenings with an increase in positive predictive value when applied retroactively to the participants included in the NLST [49, 50].

Two updates to Lung-RADS have been released by the ACR at the time of this publication. Lung-RADS Version 1.1 was published in 2019 and increased the threshold for classifying nonsolid nodules as probably benign from 20 to 30 mm and for likely benign perifissural nodules from 6 to 10 mm, recommended measurement of mean nodule diameter to one decimal point and included volumetric measurements in addition to diametric measurements to help facilitate future use of volumetric technology [51]. Lung-RADS version 2022, released in November 2022, included additional guidance on cystic pulmonary lesions and airway nodules. Although the British Thoracic Society has recommended volumetric measurement, the impact on clinical decision-making is unclear, and there are practical limitations to widespread use of volumetric analysis [52].

Lung-RADS v2022 categories are shown in Table 2.1.

Table 2.1 Lung-RADS v2022. Reprinted under Creative Commons Attribution-NoDerivatives 4.0 International Public License, from the American College of Radiology. https://creativecommons.org/licenses/by-nd/4.0/legalcode

American College of Radiology™

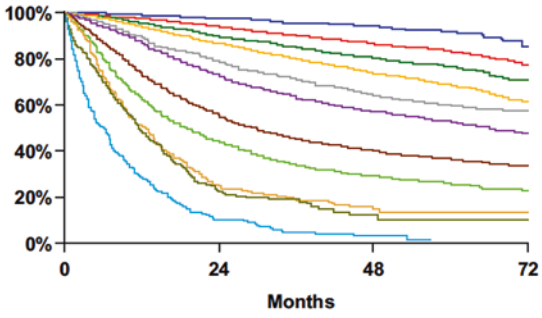
Lung-RADS® v2022

Release Date: November 2022

Lung-RADS	Category Descriptor	Findings	Management
0	**Incomplete** Estimated Population Prevalence: ~ 1%	Prior chest CT examination being located for comparison (see note 9)	Comparison to prior chest CT;
		Part or all of lungs cannot be evaluated	Additional lung cancer screening CT imaging needed;
		Findings suggestive of an inflammatory or infectious process (see note 10)	1-3 month LDCT
1	**Negative** Estimated Population Prevalence: 39%	**No lung nodules OR**	12-month screening LDCT
		Nodule with benign features: • Complete, central, popcorn, or concentric ring calcifications **OR** • Fat-containing	
2	**Benign** - Based on imaging features or indolent behavior Estimated Population Prevalence: 45%	**Juxtapleural nodule:** • < 10 mm (524 mm^3) mean diameter at baseline or new **AND** • Solid; smooth margins; and oval, lentiform, or triangular shape	
		Solid nodule: • < 6 mm (< 113 mm^3) at baseline **OR** • New < 4 mm (< 34 mm^3)	
		Part solid nodule: • < 6 mm total mean diameter (< 113 mm^3) at baseline	
		Non solid nodule (GGN): • < 30 mm (< 14,137 mm^3) at baseline, new, or growing **OR** • ≥ 30 mm (≥ 14,137 mm^3) stable or slowly growing (see note 7)	
		Airway nodule, subsegmental - at baseline, new, or stable (see note 11)	
		Category 3 lesion that is stable or decreased in size at 6-month follow-up CT **OR** Category 4B lesion proven to be benign in etiology following appropriate diagnostic workup	
3	**Probably Benign** - Based on imaging features or behavior Estimated Population Prevalence: 9%	**Solid nodule:** • ≥ 6 to < 8 mm (≥ 113 to < 268 mm^3) at baseline **OR** • New 4 mm to < 6 mm (34 to < 113 mm^3)	6-month LDCT
		Part solid nodule: • ≥ 6 mm total mean diameter (≥ 113 mm^3) with solid component < 6 mm (< 113 mm^3) at baseline **OR** • New < 6 mm total mean diameter (< 113 mm^3)	
		Non solid nodule (GGN): • ≥ 30 mm (≥ 14,137 mm^3) at baseline or new	
		Atypical pulmonary cyst: (see note 12) • Growing cystic component (mean diameter) of a thick-walled cyst	
		Category 4A lesion that is stable or decreased in size at 3-month follow-up CT (excluding airway nodules)	
4A	**Suspicious** Estimated Population Prevalence: 4%	**Solid nodule:** • ≥ 8 to < 15 mm (≥ 268 to < 1,767 mm^3) at baseline **OR** • Growing < 8 mm (< 268 mm^3) **OR** • New 6 to < 8 mm (113 to < 268 mm^3)	3-month LDCT; PET/CT may be considered if there is a ≥ 8 mm (≥ 268 mm^3) solid nodule or solid component
		Part solid nodule: • ≥ 6 mm total mean diameter (≥ 113 mm^3) with solid component ≥ 6 mm to < 8 mm (≥ 113 to < 268 mm^3) at baseline **OR** • New or growing < 4 mm (< 34 mm^3) solid component	
		Airway nodule, segmental or more proximal - at baseline (see note 11)	
		Atypical pulmonary cyst: (see note 12) • Thick-walled cyst **OR** • Multilocular cyst at baseline **OR** • Thin- or thick-walled cyst that becomes multilocular	
4B	**Very Suspicious** Estimated Population Prevalence: 2%	**Airway nodule**, segmental or more proximal - stable or growing (see note 11)	Referral for further clinical evaluation
		Solid nodule: • ≥ 15 mm (≥ 1767 mm^3) at baseline **OR** • New or growing ≥ 8 mm (≥ 268 mm^3)	Diagnostic chest CT with or without contrast; PET/CT may be considered if there is a ≥ 8 mm (≥ 268 mm^3) solid nodule or solid component; tissue sampling; and/or referral for further clinical evaluation Management depends on clinical evaluation, patient preference, and the probability of malignancy (see note 13)
		Part solid nodule: • Solid component ≥ 8 mm (≥ 268 mm^3) at baseline **OR** • New or growing ≥ 4 mm (≥ 34 mm^3) solid component	
		Atypical pulmonary cyst: (see note 12) • Thick-walled cyst with growing wall thickness/nodularity **OR** • Growing multilocular cyst (mean diameter) **OR** • Multilocular cyst with increased loculation or new/increased opacity (nodular, ground glass, or consolidation)	
		Slow growing solid or part solid nodule that demonstrates growth over multiple screening exams (see note 8)	
4X	Estimated Population Prevalence: < 1%	Category 3 or 4 nodules with additional features or imaging findings that increase suspicion for lung cancer (see note 14)	
S	**Significant or Potentially Significant** Estimated Population Prevalence: 10%	**Modifier:** May add to category 0-4 for clinically significant or potentially clinically significant findings unrelated to lung cancer (see note 15)	As appropriate to the specific finding

Risks and Benefits

As with any clinical procedure, the risks and benefits of LCS need to be considered for each individual. The purpose of LCS, and therefore the primary benefit, is the potential to identify asymptomatic lung cancer early through stage shift instead of an advanced lung cancer presenting due to symptoms. The largest determinant of lung cancer survival is the stage at diagnosis. The current stage groupings (eighth edition) of the TNM Classification for Lung Cancer set forth by the International Association for the Study of Lung Cancer (IASLC) distinguishes between a 1 cm (stage IA1) and 2 cm (stage IA2) lung nodule [53], as shown in Fig. 2.1. This illustrates the impact of early detection through LCS.



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Fig. 2.1 Two- and 5-year survival by clinical stage in the eighth edition of the TNM classification for lung cancer. (Reprinted with permission from publisher)

Does Lung Cancer Screening Result in Stage Shift?

Early-stage cancer rates varied considerably among the randomized LDCT trials (Table 2.2). In all cases, LDCT screening resulted in higher earlier stage cancer rates compared to control and to average stage at diagnosis in the Surveillance, Epidemiology, and End Results (SEER) registry [58] during the same years. SEER registry reported stage at diagnosis of non-small cell lung cancer increasing from 26% to 31% stage I or II between 2006 and 2016. These findings are likely partly due to early effects of screening and partly due to incidentally detected cancers on chest CT.

Any form of cancer screening can appear beneficial when viewed through the lens of the number of cancers found or years from diagnosis to death. One must consider the possibility of lead time bias when screening leads to an earlier diagnosis and creates the appearance of a longer survival when death still occurs at the same point as it would have after a symptom-based diagnosis [59]. Overdiagnosis, the discovery of indolent cancers that will never be clinically significant, or cancer diagnosed in an individual with a life-limiting comorbid condition that causes their death before the cancer becomes clinically significant, can also impact perceptions on the effectiveness of screening [60].

The decision to pursue LCS is not without potential risk to the individual and requires discussion and consideration of these risks [60]. Annual radiation exposure, however low, potentially for decades can accumulate to significant levels [61] and increase the risk of radiation-induced cancer. Finding a suspicious nodule raises

Table 2.2 Randomized LDCT trials demonstrated stage shift to early stage lung cancer

Randomized LDCT trial (year screening concluded)	Reported proportion of early stage lung cancer (LDCT/control)
National Lung Screening Trial (NLST) [46] 2007	50%/31% Stage I
	57%/39% Stages I + II
Italian Lung Cancer Screening Trial (ITALUNG) [54] 2009	36%/11% Stage I
	43%/18% Stages I + II
Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE) [55] 2010	45%/22% Stage I
	61%/41% Stages I + II
Danish Lung Cancer Screening Trial (DLST) [56] 2010	68%/21% Stage I
	68%/29% Stages I + II
Multicentric Italian Lung Detection (MILD) [57] 2011	63%/[a] Stage I
	71%/[a] Stages I + II
German Lung cancer Screening Intervention (LUSI) [18] 2011	67%/8% Stage I
	73%/22% Stages I + II
Dutch–Belgian lung-cancer screening trial (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON]) [24] 2012	40%/13% Stage I
	49%/23% Stages I + II

[a] Group not reported

the likelihood of needing invasive diagnostic procedures such as biopsies or surgical resection, which could be curative but, for some may result in the diagnosis of a benign nodule. Incidental findings unrelated to lung cancer are also very common on LDCT, with most exams having at least one. While the NLST [62] reported 20% rate of incidental findings, real-world screening programs have reported more than half of exams to "virtually all" having incidental findings. Currently, there is no standard reporting strategy [63] for incidental findings on LDCT, leading to wide variability in reporting rates. While most of these are not clinically significant, they have the potential to impact the individual and clinician LCS experience.

Screening Strategy

A key element for maximizing LCS benefit is patient selection, individuals at high risk of lung cancer who can benefit from early detection and the possibility of surgical cure. Significant discussion and research have focused on the best way to identify these "high-risk individuals." Thus far, most lung cancer screening studies and guidelines have been based on selecting individuals for screening based on age and smoking history. So-called risk factor-based screening currently serves as the basis for screening within the United States, with individuals qualifying based on age, pack-years, or time since quitting cigarettes.

Because age and personal smoking history are not the sole determinants of lung cancer risk, considering only these factors ignores the impact of other factors (like social determinants of health and family history). Some of the NLST participants were at relatively lower risk for lung cancer but still met eligibility criteria based on risk factors, while other individuals who didn't meet the risk factor eligibility criteria are at increased risk for lung cancer. Only half of the people with lung cancer [64] in a small cohort study met the NLST or USPSTF 2013 eligibility for LCS. One approach to rectify this discordance is the use of risk model-based screening, where individuals are selected for cancer screening based on the results of risk prediction models that incorporate a variety of demographic and historical variables [65].

One example of lung cancer risk model is the $PLCOm_{2012}$, which estimates an individual's risk of developing lung cancer in the next 6 years and includes other factors that contribute to lung cancer risk besides age and smoke exposure intensity, such as family history, educational attainment, and other medical conditions [66]. Low-quality evidence including post hoc analyses and modeling studies did show that a risk model-based approach to patient selection improves performance of LCS including number needed to screen and false positives. Currently, risk prediction models are an area of active investigation, with some studies such as UK lung cancer screening trial and the International Lung Screening Trial using risk prediction models to select study populations [21, 67]. However, LCS has been difficult to implement effectively with more straightforward risk factor-based eligibility, so using a risk model-based approach requiring multiple additional pieces of information would almost certainly increase barriers to lung screening uptake.

Implementation of Lung Cancer Screening

State of Implementation

Although the recommendation and approval of LCS were heralded by many as a giant step in reducing lung cancer mortality, implementation has proved challenging. In the decade since annual low-dose chest CT scan for LCS has been demonstrated to reduce all-cause and disease-specific mortality, the proportion of eligible persons screened has progressed very slowly. Only 6% of the 8.5 million eligible persons in the United States have been screened for lung cancer [68, 69]. Compare this with breast cancer, where screening rates rose steeply just 3 years after the first USPSTF recommendation [70].

Breast cancer screening, which employs another imaging test—the mammogram–has occurred at rates consistently above 70% of eligible people since 1999 [70]. The Department of Health and Human Services Healthy People 2030 goals aim for 77% of women receiving breast cancer screening with mammograms but only 7.5% of people eligible for LCS receiving LDCT [70, 71], despite the two tests having comparable performance—the number of persons screened to save one life [72, 73]. Important distinctions between the two cancers are the public perception of the diseases and the policies governing the tests' conduct. While lessons learned from other cancer screening tests may apply to LCS, lung cancer is unique because there are additional system-level policy barriers and individual-level psychological barriers not pertinent to other cancers. Nihilism about lung cancer treatment and stigma associated with a disease attributed to a behavioral risk (cigarette smoking) are both patient- and provider-level individual barriers. Systemic barriers related to regulatory requirements of LCS coverage by payors also contribute to low LCS uptake.

System-Level Barriers

Unlike other cancers, LCS eligibility is based on historical behavior/exposure related to cigarette smoking. Estimating (and documenting) a person's "pack-year history" is time-consuming and not easily stored in most electronic health records (EHR). Recall bias and stigma toward cigarette smoking may also impact an individual's ability to accurately report their smoking history. Furthermore, the complexity of the stipulations for LCS coverage established by the CMS in their 2015 coverage determination memo was a major source of system-level barriers [16]. Identifying LCS-eligible persons is difficult because EHRs do not provide accurate estimates of smoking pack-year history [74]. As a new screening test with more complex eligibility requirements than age and/or sex, many clinicians report lack of EHR notification to aid identification of eligible candidates for LCS as a barrier [75].

The Centers for Medicare and Medicaid Services (CMS) is part of the Department of Health and Human Services and oversees the public health insurance programs Medicare and Medicaid, which cover older Americans, Americans with disabilities, and lower income, among others. CMS imposed unprecedented additional requirements for reimbursement of LCS, with implications for the ordering clinician, the screening exam order itself, the technical specifications of the images, the radiologists interpreting images, and the imaging centers conducting the exams. The most impactful of these requirements was the requirement for a face-to-face visit where shared decision-making (SDM) was conducted and documented by a physician or advanced practice provider. SDM proved to be quite a challenge for individuals eligible for LCS and healthcare systems. This contrasts with mammography for breast cancer screening, where an ordering clinician is not required—women can self-refer for mammography. A minor variation in the upper age cutoff for CMS (compared to USPSTF) also added to confusion about differing eligibility based on individual insurance coverage. Based on the NLST protocol, where participants aged 55–74 underwent three annual LDCT scans and were followed several additional years to a maximum age of 77, CMS adopted this age range [54–57, 59–77] for screening eligibility [15]. However, based on modeling data, USPSTF adopted the age range of 55–80 years for eligibility [16]. An additional CMS requirement was participation in a LCS registry. The only approved registry is hosted by the ACR in their National Radiology Data Registry. While the ACR hosts multiple imaging registries, including mammography, participation is not required for imaging centers to be reimbursed by CMS for screening mammography [76]. When CMS revisited the LCS coverage in 2021, these requirements were lightened, such that the SDM is no longer mandated to be face-to-face or conducted by a physician or advanced practice provider. Registry participation is no longer required, but the upper age limit of eligibility remains divergent from USPSTF, leading to uncertainty about eligibility for people aged 78–80 years, depending on their insurance plan.

Clinician-Level Barriers

The unprecedented complexity of eligibility and coverage for LCS contributes to clinician-level barriers. Clinicians report uncertainty about insurance coverage, lack of time, and lack of expertise to manage findings [77, 78]. Many primary care providers are family physicians, and their leading organization failed to endorse LCS until 2021, so skepticism and conflicting messages also contributed to clinician-level barriers.

Shared Decision-Making Visit and Decision Aids

Although the concept of shared decision-making (SDM) is patient-centered, the requirement to do so in a face-to-face visit places a burden on patients and clinicians alike [79, 80]. The content and quality of SDM vary widely [81]. Many decision aids have been developed to facilitate this process, with variable outcomes in terms of patient knowledge, decision conflict, and decision regret [82, 83]. The largest study to investigate the effect of decision aids on LCS uptake showed no difference in intent to screen or receipt of LDCT for LCS but did show reduced decision conflict [84]. One study showed that robust SDM, including discussion of risks, impacted patients' confidence in making the same decision again and returning for annual follow-up exams [85]. This study also demonstrated that some patients prefer to defer the decision to their healthcare provider. Other studies have shown low levels of decisional conflict when LCS knowledge was lower and no decision aid was used [80]. Most decision aids rely upon individual risk calculators based on one of two risk models, Bach or $PLCO_{m2012}$ [66, 86] and provide the user with a comparison of the risks and benefits for someone with their level of lung cancer risk. Another decision aid provides projections of how many screened persons will experience certain benefits and harms while encouraging patients to consider their own values [87].

LCS Program Structure

LCS programs can be described as centralized, decentralized, or hybrid [88]. Centralized programs accept referrals for potentially eligible patients, conduct SDM, order LDCT if appropriate, and manage follow-up of abnormal findings. Centralized programs have been shown to have higher annual adherence and concordance with screening eligibility guidelines [89, 90]. Presumably, decentralized programs increase patient access by avoiding the additional barrier of referral to another clinician and/or clinic. One hybrid program offered screening by PCPs or referral to specialists and found that most PCPs habitually behaved in consistent ways, either doing all the screening or referring all their patients for specialist-driven screening [91].

Adherence to Screening

While rates of baseline LCS exams are dismally low, with a national average [68] of 5%, annual adherence has proven to be equally challenging. A pooled analysis found 55% annual adherence rate, which is much lower than what was seen in the NLST [92]. In one study, program structure (centralized) was the greatest

independent predictor of annual adherence [89]. In that study, the centralized program's annual adherence rate was 70%, compared with 41% of decentralized programs. Another study [93] reported similar findings of lower annual adherence in decentralized programs and among Black persons with normal baseline LCS. A systematic review and meta-analysis [92] concluded that patient factors like educational attainment, White race, and former smoking status also predicted higher annual adherence rates. However, to realize the full benefit of LCS, annual adherence must be higher than has been seen thus far. Microsimulation modeling showed [94] that the benefit of screening is reduced directly as adherence to annual screening is reduced.

In addition to annual adherence to LCS, adherence to recommended follow-up of abnormal LDCT is certainly required to realize the benefit of screening. A recent cohort study [95] showed that less than half of positive screening exams resulted in follow-up adherence to recommendations. More suspicious findings were associated with higher rates of positive screen adherence, but even after extending follow-up timelines, 20% of suspicious exams did not appear to have appropriate follow-up. Adherence to follow-up for positive screens appears to be higher [93] in centralized LCS programs.

Patient-Level Barriers

Some barriers at the patient level are associated with social determinants of health. That is, individuals who have smoked heavily and might benefit most from LCS are also more likely to have lower levels of educational attainment and experience systemic racism [96]. Patient access barriers include tangible considerations like insurance coverage and transportation [97]. Transportation is particularly relevant because there has been an inverse relationship between where most LCS-eligible persons are and where LCS is available, especially under 2015 CMS requirements [98]. Psychological barriers like fear, stigma, and nihilism also impact patients because of the historically low survival of lung cancer and internal and external stigma experienced by people who smoke [77].

Lung Cancer Screening and Smoking Cessation

Cigarette smoking remains the most significant risk factor for lung cancer. LCS mortality benefit is magnified to the extent that the process also leads to smoking cessation. Some studies have shown a positive effect of LCS on efforts at smoking cessation. The Italian Lung Cancer Screening Trial (ITALUNG) found higher smoking quit rates among patients in the screening arm than usual care arm [99]. A cross-sectional study using Behavioral Risk Factor Surveillance System (BRFSS)

data found participants receiving lung cancer screening were less likely to be current smokers and more likely to have attempted quitting in the prior year [100].

Counseling and interventions to promote smoking cessation are included in the USPSTF recommendations and CMS decision memo on lung cancer screening [40, 101]. While the importance of smoking cessation is widely recognized, counseling on smoking cessation is often limited during the shared decision-making process. Even less often are patients referred for specific services or provided with prescriptions for pharmacologic therapy [102, 103]. Several NIH-funded studies are underway to understand how LCS can be used to maximize smoking cessation [104].

Emerging Issues in Lung Cancer Screening

Future Directions for Lung Cancer Screening Tests

A screening test for lung cancer that doesn't involve the harm of ionizing radiation or the requirement for going to an imaging center would help to improve risks of and access to LCS. A screening test with fewer false positives and incidental findings might make screening feasible for people with lower risk for lung cancer, such as people who quit smoking long ago or never smoked cigarettes but have radon exposure or a family history of lung cancer. One might imagine population screening with such a test that, if abnormal, could be followed up with a LDCT. As of 2022, no such tests LCS are available, but some new technologies being tested may hold promise.

Blood tests are available to improve risk stratification in people with indeterminate lung nodules, including techniques such as proteomics or DNA methylation. A commercially available blood test measuring relative quantities of two plasma proteins was shown to perform better than positron emission tomography (PET) for indeterminate lung nodules [105]. Another blood test is in multisite clinical trials for early detection of lung cancer among high-risk individuals, looking at methylation patterns in circulating DNA. Emerging technologies of metabolomic analysis of blood samples are being tested as well [106]. Multiple reports of dogs detecting lung cancer likely demonstrate that volatile organic compounds are emitted from people with the disease [107]. Thus, several clinical trials are underway to test exhaled breath analysis with machine learning analysis of exhaled compounds for early and noninvasive detection of lung cancer. At least one has been published with promising results [108]. These technologies are not ready for routine screening use but expand the possibilities for future screening approaches.

Lung Cancer Screening for Other High-Risk individuals

While cigarette smoking is the dominant cause of lung cancer [109], there are other environmental or occupational exposures known to cause lung cancer for which the guidelines are less clear. In addition, studies of certain high-risk groups, such as individuals with proven environmental or occupational exposure to asbestos, show a benefit from early implementation of lung cancer screening [110, 111].

The NCCN guidelines, noting that risk assessment is based on age and smoking history, suggest considering other possible risk factors for lung cancer, such as occupational exposures, radon exposure, family history of lung cancer, and personal history of lung disease (chronic obstructive pulmonary disease or pulmonary fibrosis) during the shared decision-making process [41]. However, most insurance does not routinely cover LCS for individuals who do not meet USPSTF criteria. Discussions to ascertain whether an individual meets the criteria for LCS based on age and smoking history provide an opportunity to assess and educate about other causes of lung cancer, such as possible radon exposure. In addition, it can be a significant opportunity to counsel on smoking cessation given the known synergistic effect of smoking and radon or asbestos exposure [109].

Lung Cancer Screening During the COVID-19 Pandemic

At the start of the COVID-19 pandemic in March 2020, enrollment in lung, breast, and other routine cancer screenings was deferred based on expert recommendations [112, 113]. Many screening programs resumed operations in 2020, with some reporting an increase in suspicious nodules that required further invasive workup [114]. The rate of lung cancer screening nationally appears to have remained stable from 2019 to 2020, with some significant differences at the state level, perhaps driven by lockdown procedures, infection rates, or differences in screening infrastructure [69]. The low use of LCS before the pandemic is thought to have led to smaller changes in LCS utilization compared to other types of cancer screening, such as breast or colon [115]. In the case of lung cancer, many patients at highest risk of lung cancer are also at highest risk for severe complications from COVID-19 due to their underlying lung health.

Concerns that COVID-19 may cause an exacerbation of disparities within LCS have prompted studies examining rates of LCS by sex, race, and other demographic factors. Screening rates did not differ by race or urban/rural status in one state-wide study [116]; another study did note differences by race and gender when examining "no-show" rates [114]. Ongoing attention to lung cancer incidence and mortality rates will provide additional insight into the effect of the pandemic on lung cancer screening behaviors over time.

Conclusions

Lung cancer is the deadliest cancer in the world. Screening with LDCT has shown promise in reducing lung cancer mortality. However, implementation of LCS in the United States has been relatively slow, likely due to many factors including system-level barriers such as inequitable access to health care, complicated Centers for Medicare and Medicaid reimbursement stipulations, and psychological factors like stigma and nihilism about lung cancer. Groups who potentially stand to gain the most from LCS like Black Americans, those with lower educational attainment, people who still smoke cigarettes, and women, are disproportionately behind in the race to offer screening to all eligible persons. In the future, other screening tests for lung cancer might expand access without increasing harm and cost, but these have yet to be identified. The most significant risk factor for lung cancer is cigarette smoke exposure, but there are other known risk factors, including radon, air pollution and asbestos exposure and family history. Furthermore, individuals without identifiable risk factors do develop lung cancer, so this remains an important area of study.

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