Lung Cancer Screening in the Post–National Lung Screening Trial Era: Applying Screening in the Real World

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Keywords

lung cancer; screening; low-dose computed tomography; National Lung Screening Trial

The National Lung Screening Trial (NLST) [1] was the first large randomized trial to demonstrate a survival advantage associated with screening high-risk patients for lung cancer using low-dose computed tomography (LDCT). The US Preventive Services Task Force designated a “B” rating for lung cancer screening with LDCT in 2013 [2], mandating private insurance coverage in 2015. Several international bodies have since issued guidelines supporting lung cancer screening, although their recommendations vary on who is eligible (Table 1). Furthermore, several important questions about how to apply screening in real-world populations were left unanswered by the NLST. To begin to address some of these questions, we provide an overview of the important randomized trials on lung cancer screening with LDCT (Table 2).

NLST

The NLST was conducted from 2002 to 2007 [1]. This was the first—and remains the only—large randomized trial to compare LDCT to chest radiography (CXR) for lung cancer screening. A total of 53,454 patients at 33 centers in the US were randomized to undergo either three annual LDCT scans or a single posteroanterior CXR. To be eligible, patients had to be 55 to 74 years old, have a smoking history of at least 30 pack-years, and be a current smoker or have quit within the last 15 years. Nearly 40% of patients in the LDCT arm had at least 1 positive screen (defined as a noncalcified nodule >4 mm), compared with 16% in the CXR group. More than 90% of positive screens in both groups were ultimately determined to be false-positives, but with a low rate of invasive procedures and few complications related to the workup of these lesions. More lung cancers were detected and fewer lung cancer deaths occurred in the LDCT group than in the CXR group, resulting in a 20%

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relative reduction in lung cancer–specific mortality and a nearly 7% reduction in overall mortality. The number of patients needed to screen to prevent 1 death from lung cancer was 320. A subsequent cost analysis [3] estimated that LDCT screening cost \$1631 per person over the course of the trial, corresponding to \$52,000 per life-year gained and \$81,000 per quality-adjusted life-year.

The NLST is not without limitations, and it left several questions unanswered, some of which were identified by the study’s authors. It is not possible, on the basis of this single study, to say whether populations with other risk profiles would benefit similarly from screening. Would expanding the eligibility criteria allow more people to benefit? Would excluding the lowest-risk patients in the study population increase the efficiency of screening? In addition, the optimal screening interval and duration were not addressed. Should patients continue to be screened past the three annual rounds used in the study? Is it safe to extend the screening interval to every 2 years? Or longer? In order for widespread screening to be optimally effective, three main questions—which are a focus of ongoing research in lung cancer screening—need to be addressed: Who to screen? How often to screen? How long to screen?

Who to Screen

One study that shed light on the issue of who should be offered screening is the Danish Lung Cancer Screening Trial (DLCST) [4]. This trial randomized 4104 patients to undergo either five annual LDCT screenings or no screening. To be eligible, patients had to be 50 to 70 years old, have a smoking history of at least 20 pack-years, have a predicted $FEV_1 > 30\%$, and be a current smoker, have quit within the last 10 years, or have quit after the age of 50. Compared with the NLST, the DLCST therefore included some younger patients with shorter smoking history. Despite the detection of more lung cancers in the screening group, as well as more early-stage lung cancers, there was no difference in mortality between arms. This may be related to overdiagnosis of cancers in the screening group, to the fact that patients in the screening group smoked more and had more-severe COPD than controls, or to the study being underpowered. However, interesting trends emerged when a post hoc subgroup analysis was performed by stratifying participants by lung cancer risk. The highest-risk subgroup—both COPD and > 35 pack-years—accounted for nearly half of the lung cancers detected, despite comprising less than one-quarter of the study population. Meanwhile, the lowest-risk subgroup—neither COPD nor > 35 pack-years—had only 13% of the lung cancer burden, despite being the largest of the three subgroups. Whereas the risk of lung cancer death was significantly higher in the highest-risk group, there was a nonsignificant 20% decrease in hazard ratio for lung cancer mortality in the screening arm, mirroring the benefit seen in the NLST. This suggests that screening had a potential benefit only for the group whose risk profile most closely matched that of the NLST participants, and not for lower-risk patients.

The finding of questionable value of screening for low-risk patients is supported by post hoc analysis of subgroups within the NLST [5]. In this study, published separately from the original trial, NLST participants were divided into quintiles on the basis of calculated risk of lung cancer. Although the relative mortality benefit did not differ significantly across

quintiles, there was a large absolute difference in the efficacy of screening among subgroups. The number of lung cancer deaths prevented increased with each quintile, and the rate of false-positive scans decreased. The 60% of participants within the three highest-risk quintiles accounted for 88% of the prevented lung cancer deaths in the screening arm, whereas the 20% of participants in the lowest-risk quintile accounted for only 1%. Accordingly, the number of patients needed to screen to prevent 1 death from lung cancer dropped from 5276 in the lowest-risk quintile to 161 in the highest-risk quintile. This study suggests that restricting eligibility to only high-risk populations—excluding some of the lowest-risk patients who were included in NLST—may improve efficacy and cost efficiency without significantly decreasing the number of cancer deaths prevented.

Conversely, restricting screening criteria to only those used in the NLST may fail to account for other higher-risk factors, such as being a current smoker with a history of <30 pack-years (as opposed to being a former smoker with >30 pack-years), ethnic and sex-related risks, history of COPD or smoking-related cancers, and family history. To address this, the National Comprehensive Cancer Network (NCCN) recommended a second high-risk group that should undergo screening (Table 1) [6]. This group includes patients 50 years old with a smoking history of at least 20 pack-years and at least one additional risk factor: personal history of a smoking-related cancer, a first-degree relative with a history of lung cancer, COPD, and exposure to other pulmonary carcinogens. There is no direct, randomized evidence for the inclusion of this group; however, one study did retrospectively compare the risks of lung cancer between the NLST study population (NCCN group 1) and NCCN group 2 at a single institution. There was no difference in lung cancer detection rates between the two groups, suggesting that a benefit similar to that seen in the NLST could be achieved by screening NCCN group 2. This should be confirmed by studying the lung cancer mortality benefit in this group; however, because group 2 patients are younger and have a shorter smoking history, their competing risk of death may actually be lower, suggesting a possibly increased benefit in this group. The authors of this study estimated that an additional 2 million people in the US would be eligible for screening by including NCCN group 2 in the criteria.

A similar study examined data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial [7], which randomized participants to yearly CXR or no screening [8]. Current smokers with a history of 20 to 29 pack-years were found to have a similar risk of lung cancer as former smokers within the NLST criteria. The authors estimated that an additional 1.6 million people in the US would meet these criteria and potentially benefit from screening. Furthermore, the people in this group were disproportionately nonwhite and women. Both of these demographic groups (nonwhites and women) have an increased risk of lung cancer and may be inappropriately barred from participating in screening otherwise.

It is important to note that the effects of lung cancer screening are difficult to predict. Just because a group of people has a similarly high risk of lung cancer as the NLST participants does not necessarily mean that they will benefit to the same degree from lung cancer screening. Other factors, such as competing risks of death and overdiagnosis, play an important role in the outcome of screening. For example, the same study that found an increased benefit of screening in the highest-risk quintile of NLST participants also found

that LDCT was likely to be effective in patients with no or one underlying pulmonary conditions (such as COPD, bronchiectasis, sarcoidosis) but not in patients with multiple pulmonary conditions—illustrating the sometimes seemingly contradictory effects of certain risk factors, possibly because of competing risks.

To improve the ability to select patients who will benefit the most from screening, several risk calculators have been developed, such as the $PLCO_{m2012}$ criteria [9]. This tool takes into account multiple factors, including demographic characteristics, medical history, and smoking exposure, to generate a risk of lung cancer. The $PLCO_{m2012}$ criteria were found to have a higher sensitivity and positive predictive value in selecting patients for lung cancer screening than the NLST criteria. However, what risk threshold should be used to select patients for screening remains a subject of debate.

How Often to Screen

The Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON) is the largest European randomized trial on lung screening with LDCT to date [10]. This study included 15,822 patients aged 55 to 75 who had smoked at least 15 cigarettes per day for 25 years or 10 per day for 30 years (equivalent to 18.75 and 15 pack-years, respectively) and were current smokers or had quit within 10 years. These patients were randomized to LDCT or no screening. The primary outcome—reduction in lung cancer mortality—has yet to be assessed, but multiple studies have been published on the basis of the early results of this trial. One unique aspect of this trial was the changing screening interval used. Participants were screened at baseline and again at 1, 3, and 5.5 years. This allowed for the investigation of different screening intervals (1, 2, and 2.5 years) within the same population. Comparison of the 1- and 2-year interval results showed no difference in lung cancer detection with the longer interval [11]. Even with a 2-year interval, lung cancer detection, positive predictive value, and specificity were superior to those in the NLST [12]. There was a <1% incidence of interval lung cancer detection (diagnosed between the screening scans), which was not different between the two screening intervals, although these interval cancers tended to be higher stage and were more likely to be small cell carcinomas, compared with screen-detected cancers. The final round of screening in the NELSON trial occurred at a 2.5-year interval [13]. The results of this round were inferior to the previous rounds with shorter intervals. There was an increase of nearly 150% in the incidence of interval cancer detection during the 2.5-year interval, compared with the 2-year interval, with most of these occurring during the last 6 months of the interval. Meanwhile, cancers detected in this final round were more likely to be higher stage than in the previous rounds. Taken together, these results suggest that, whereas a 2-year interval may be as safe and effective as a 1-year interval, increasing to 2.5 years may have a detrimental effect.

The Multicentric Italian Lung Detection (MILD) study also examined the effect of extending the screening interval [14]. In this study, 4099 patients aged >49 years with a smoking history of at least 20 pack-years who were current smokers or had quit within 10 years were randomized to screening with LDCT or no screening. The LDCT arm was then randomized again to either 1-year or 2-year screening intervals for 7 years. There were no differences in sensitivity, specificity, positive and negative predictive values, stage distribution of

screening-detected cancers, resectability of cancers, or rate of interval cancers between the 1- and 2-year intervals. There were also no differences in lung cancer-specific or overall mortality [15]. The authors did find a higher incidence of lung cancer detection in the 1-year interval group, without a corresponding increase in cancer stage in the 2-year interval group, which suggests an element of overdiagnosis in the shorter-interval group. However, there was also no difference in mortality between the LDCT group overall and the control group (no screening), which suggests that the study may have been underpowered.

How Long to Screen

The US Preventive Services Task Force, along with the American College of Chest Physicians and the American Thoracic Society, recommend continued yearly screening until the risks of screening are judged to outweigh the benefits or until the patient reaches 15 years since quitting smoking [16]. However, as screening duration increases, the risks of screening accumulate, as do competing mortality risks from other diseases.

As noted earlier, the NELSON and DLCST trials both screened patients for longer than the 3 years in the NLST; the German Lung Cancer Screening Intervention Trial (German acronym: LUSI) did as well [17]. Mature results from NELSON and LUSI are not available, but some information about the performance of screening >3 years can be gleaned from these studies. In the LUSI study, which involved yearly LDCT for 5 years, the rate of cancer detection decreased only slightly for the screens following the initial round: from 0.6% in the second year to 0.4% in the fifth year. Beginning in year 3, there was a trend toward a decrease in the number of advanced-stage cancers detected in the screening group, leading the authors to suggest a potential future benefit from screening, although this has not yet been demonstrated and cannot be definitively linked to the prolonged duration of screening in this trial.

The detrimental effect of extending the fourth screening interval to 2.5 years, as demonstrated in the NELSON trial, also suggests a need for continued screening. However, it is interesting to note that, in this study, participants with a negative result for their first LDCT had an 86.5% chance of having negative scans at both 1 and 3 years later. These participants had only a 1% chance of lung cancer, indicating the value of a single negative scan and calling into some question the benefit of repeated scans in this subgroup.

The authors of the MILD study compared their results with those from a pilot study where patients were screened annually for 10 years [14]. Their conclusion, based on steadily increasing mortality despite screening, was that prolonged screening may not be beneficial, although the study was not designed to answer this question.

Conclusion

In the wake of the NLST, nearly every major body that has weighed in on lung cancer screening with LDCT recommends its use. However, the data and conclusions from the NLST alone are not sufficient to fully guide practice. Other higher-risk groups that were not included in the NLST criteria may benefit from screening. On the other hand, eliminating some of the lowest-risk subgroups in the NLST would likely improve the efficiency of

screening. The annual scans performed in the NLST may be more frequent than is necessary, although extending the screening interval beyond 2 years may be detrimental. Finally, how long to continue screening patients remains an open question. Although the guidelines that do address this issue tend to recommend extended durations of screening, it may be inappropriate to extrapolate the NLST data past three annual screens, and the data from other, longer-duration studies are equivocal.

Perhaps most important to keep in mind when applying the results of the NLST to the general population is that screening and any necessary further evaluation and treatment must be done in a safe and effective manner. The operative mortality for lung resection in the NLST was 1%, which compares favorably to historical results. Invasive procedures were infrequent in the NLST; when they were required, they were done with very low morbidity, which substantially reduced the overall risk profile of screening. To achieve the same mortality benefit by screening the general population, it is critical that patients with positive screening results receive the same high level of care in their evaluation and treatment as was achieved in the relatively select group of institutions participating in the NLST. The importance of access to high-quality smoking cessation counselling can also not be overstated.

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References

1. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011; 365:395–409. [PubMed: 21714641]
2. Mayer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Int Med*. 2014; 160:330–41. [PubMed: 24378917]
3. Black WC, Gareen IF, Soneji SS, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. *N Engl J Med*. 2014; 371:1793–802. [PubMed: 25372087]
4. Wille MMW, Dirksen A, Ashraf H, et al. Results of the randomized Danish Lung Cancer Screening Trial with focus on high-risk profiling. *Am J Resp Crit Care Med*. 2016; 193:542–51. [PubMed: 26485620]
5. Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med*. 2013; 369:245–54. [PubMed: 23863051]
6. Wood, DE., Kazerooni, EA., Baum, SL., et al. [Accessed Aug 14, 2017] NCCN clinical practice guidelines in oncology: Lung Cancer Screening. National Comprehensive Cancer Network. 2018. https://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf
7. Gohagan JK, Prorok PC, Hayes RB, et al. The prostate, lung, colorectal and ovarian (PLCO) cancer screening trial of the National Cancer Institute: History, organization, and status. *Control Clin Trials*. 2000; 21:251S–72S. [PubMed: 11189683]
8. Pinsky PF, Kramer BS. Lung cancer risk and demographic characteristics of current 20–29 pack-year smokers: Implications for screening. *J Natl Cancer Inst*. 2015; 107:djv226. [PubMed: 26483244]
9. Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. *N Engl J Med*. 2013; 368:728–36. [PubMed: 23425165]
10. Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. *Lancet Oncol*. 2014; 15:1332–41. [PubMed: 25282285]

11. Horeweg N, van der Aalst CM, Vliegenthart R, et al. Volumetric computed tomography screening for lung cancer: Three rounds of the NELSON trial. *Eur Respir J*. 2013; 42:1659–67. [PubMed: 23845716]
12. Horeweg N, Scholten ET, de Jong PA, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. *Lancet Oncol*. 2014; 15:1342–50. [PubMed: 25282284]
13. Yousaf-Khan U, van der Aalst C, de Jong PA, et al. Final screening round of the NELSON lung cancer screening trial: The effect of a 2. 5-year screening interval. *Thorax*. 2016; 72:48–56. [PubMed: 27364640]
14. Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev*. 2012; 21:308–15. [PubMed: 22465911]
15. Sverzellati N, Silva M, Calareso G, et al. Low-dose computed tomography for lung cancer screening: Comparison of performance between annual and biennial screen. *Eur Radiol*. 2016; 26:3821–9. [PubMed: 26868497]
16. Wiener RS, Gould MK, Arenberg DA, et al. An official American Thoracic Society/American College of Chest Physicians policy statement: Implementation of low-dose computed tomography lung cancer screening programs in clinical practice. *Am J Respir Crit Care Med*. 2015; 192:881–891. [PubMed: 26426785]
17. Becker N, Motsch E, Gross ML, et al. Randomized study on early detection of lung cancer with MSCT in Germany: Results of the first 3 years of follow-up after randomization. *J Thorac Oncol*. 2015; 10:890–6. [PubMed: 25783198]
18. Centers for Medicare & Medicaid Services. [Accessed Aug 14, 2017] Decision memo for screening for lung cancer with low dose computed tomography (LDCT). <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274>
19. Zhou QH, Fan YG, Bu H, et al. China national lung cancer screening guideline with low-dose computed tomography (2015 version). *Thorac Cancer*. 2015; 6:812–8. [PubMed: 26557925]
20. Kauczor HU, Bonomo L, Gaga M, et al. ESR/ERS white paper on lung cancer screening. *Eur Resp J*. 2015; 46:28–39.
21. Lewin G, Morissette K, Dickinson J, et al. Recommendations on screening for lung cancer. *Can Med Assoc J*. 2016; 188:425–32. [PubMed: 26952527]
22. American Association of Family Practitioners. [Accessed Aug 14, 2017] Clinical preventive service recommendation: Lung Cancer. <http://www.aafp.org/patient-care/clinical-recommendations/all/lung-cancer.html>

Biography

Central Picture Legend

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Central Message

The National Lung Screening Trial established the utility of CT screening for lung cancer. We address the optimal population, interval, and duration of screening.

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Authors' Recommendations

On the basis of the above review, the authors offer their viewpoint on the three questions considered:

1. Who to screen: Strict adherence to NLST criteria likely excludes some high-risk patients who would benefit from screening, such as current smokers with a smoking history of <30 pack-years. Risk calculators such as PLCO_m2012 [8] should be used to aid in the identification of these patients. Conversely, expansion of inclusion criteria to patients with less risk than the NLST participants is not recommended.
2. How often to screen: The best evidence is for yearly screening, but it appears that biannual screening has a similar lung cancer detection rate and may be as effective. Intervals longer than 2 years are not recommended.
3. How long to screen: Screening beyond the three yearly scans performed in the NLST is reasonable as long as the risks and benefits to the patient are continually reevaluated. Competing risks of death, the results of previous screens, and the patient's goals of care should all be considered.

Table 1

Summary of Eligibility Criteria for Selected Lung Cancer Screening Guidelines

Recommending Body	Eligibility Criteria		
	Age	Tobacco Exposure	Smoking Status
USPSTF [2]	55–80	30 pack-years	Quit 15 years
NCCN group 1 [6]	55–74	30 pack-years	Quit 15 years
NCCN group 2 [6]	50	20 pack-years and 1 additional risk factor ^a	Any
CMS [18]	55–77	30 pack-years	Quit 15 years
CNHFPC [19]	50–74	20 pack-years	Quit 5 years
ERS [20]	55–80	30 pack-years	Quit 15 years
CTFPHC [21]	55–74	30 pack-years	Quit 15 years
AAFP [22]	Insufficient evidence to recommend for or against lung cancer screening		

AAFP = American Academy of Family Physicians; CMS = Centers for Medicare and Medicaid Services; CNHFPC = China National Health and Family Planning Commission; CTFPHC = Canadian Task Force on Preventive Health Care; ERS = European Respiratory Society; NCCN = National Comprehensive Cancer Network; USPSTF = US Preventive Services Task Force.

^aAdditional risk factors include history of smoking-related cancer, first-degree relative with lung cancer, COPD, and exposure to other pulmonary carcinogens.

Table 2

Summary of randomized controlled trials on low-dose computed tomography screening since the National Lung Screening Trial

Study	Sample Size (n)	Intervention	Control	Eligibility (age, smoking history)	Overall Mortality Benefit	Lung Cancer Mortality Benefit
NLST [1]	53,454	Annual LDCT x 3	Single CXR	55–74, 30 pack-years, quit within 15 yrs	20%	6.7%
NELSON [9]	15,822	LDCT at 0, 1, 3, and 5.5 yrs	No screening	55–75, 15 cig/day for 25 yrs or quit within 10 years	Pending	Pending
DLCST [3]	4104	Annual LDCT x 5	No screening	50–70, 20 pack-years, quit within 10 yrs or after age 50	No difference	No difference
LUSI [16]	4052	Annual LDCT x 5	No screening	50–69, 15 cig/day for 25 yrs or 10 cig/day for 30 yrs	Pending	Pending
MILD [13]	4099	Annual LDCT x 7 or biennial LDCT x 4	No screening	>49, 20 pack-years, quit within 10 yrs	No difference	No difference

CXR, chest radiography; DLCST, Danish Lung Cancer Screening Trial; LDCT, low-dose computed tomography; LUSI, German Lung Cancer Screening Intervention Trial; MILD, Multicentric Italian Lung Detection; NELSON, Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST, National Lung Screening Trial.