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Issues With Implementing a High-Quality Lung Cancer Screening Program

James L. Mulshine, MD¹; Thomas A. D'Amico, MD²

After a comprehensive review of the evidence, the United States Preventive Services Task Force recently endorsed screening with low-dose computed tomography as an early detection approach that has the potential to significantly reduce deaths due to lung cancer. Prudent implementation of lung cancer screening as a high-quality preventive health service is a complex challenge. The clinical evaluation and management of high-risk cohorts in the absence of symptoms mandates an approach that differs significantly from that of symptom-detected lung cancer. As with other cancer screenings, it is essential to provide to informed at-risk individuals a safe, high-quality, cost-effective, and accessible service. In this review, the components of a successful screening program are discussed as we begin to disseminate lung cancer screening as a national resource to improve outcomes with this lethal cancer. This information about lung cancer screening will assist clinicians with communications about the potential benefits and harms of this service for high-risk individuals considering participation in the screening process. CA Cancer J Clin 2014;000:000-000. © 2014 American Cancer Society.

Keywords: American Academy of Family Physicians (AAFP), American Association of Physicists in Medicine (AAPM), Centers for Medicaid and Medicare Services (CMS), chest x-ray (CXR), low-dose computed tomography (LDCT), lung cancer screening, National Lung Screening Trial (NLST), Nederlands-Leuvens Longkanker Screenings ONderzoek (NELSON) trial, Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial, US Preventive Services Task Force (USPSTF).



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Introduction

The medical, economic, and social burden imposed by lung cancer, the most lethal cancer worldwide, is difficult to fully convey.¹ In the United States, lung cancer causes more than 160,000 deaths each year and accounts for nearly one-third of all cancer deaths.² The US Preventive Services Task Force (USPSTF) recently recommended the use of low-dose, helical computed tomography (LDCT) in annual screening for lung cancer in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. With this recommendation, lung cancer joins other types of cancer as a major site for which objective evidence supports the dissemination of screening on a national level.^{3,4} Population-level screening for breast and colorectal cancer has been associated with improved outcomes, and this experience provides an important precedent for the process of implementing national LDCT screening: the implementation of these earlier screening tools may facilitate the responsible dissemination of lung cancer screening.^{5–7} As we know from

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DISCLOSURES: This article discusses unlabeled use of spiral CT for early lung cancer detection, which is recommended by USPSTF but is not a formally approved use of CT scanning. Dr. Mulshine is the inventor on and has had patents issued for and received patent payments for the following 12 patents held by the National Institutes of Health that are unrelated to the current study: 1) monoclonal antibody against non-small cell lung cancer (US Patent No. 4,569,788); 2) intrabronchial injection of monoclonal antibody conjugates for the detection of lung cancer (US Patent No. 4,911,690); 3) technique for early detection of lung cancer (US Patent No. 5,455,159); 4) lipoxygenase as a target for treatment and prevention of epithelial cancer (US Patent No. 6,071,949); 5) an epithelial protein and DNA thereof for use in early cancer detection (US Patent No. 5,994,062); 6) divisional filing for an epithelial protein and DNA thereof for use in early cancer detection (US Patent No. 5,994,062); 6) divisional filing for an epithelial protein and DNA thereof for use in early cancer detection (US Patent No. 5,994,062); 6) divisional filing for an epithelial protein and DNA thereof for use in early cancer detection (US Patent No. 5,994,062); 6) divisional filing for an epithelial protein and DNA thereof for use in early cancer detection (US Patent No. 5,994,062); 6) divisional filing for an epithelial protein and DNA thereof for use in early cancer detection (use the approximation for aerosolization (patent submitted CIP: application no. 60/187,539); 9) retinoid formulation for aerosolization and inhalation (WO/2001066104); 10) method for diagnosing cancer or precancer based on hnRNP protein expression (US patent No. 6,756,399); and 12) use of differential oblique angle spectroscopy of oral epithelium (US Patent No. 6,990,369). Dr. A'Amico has acted as a paid consultant for Scanlan Instruments, for work outside of the current study.

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STUDY	ROUND 1 NO. OF CA/TOTAL SCREENED	ROUND 2 NO. OF CA/TOTAL SCREENED	ROUND 1 STAGE I/ALL DETECTED CA	ROUND 2 STAGE I/ALL DETECTED CA
NLST	168/24,715 (0.67%)	211/24,102 (0.87%)	104/165 (63%)	141/204 (69%)
NELSON	40/7289 (0.5%)	57/7289 (0.8%) ^a	42/57 (73.7%)	

TABLE 1.	Summary of NLST ¹⁸	and NELSON ¹⁷	Trials Cancer	Detection an	nd Stage I	Frequencies in	Follow-Up	Rounds
	of LDCT				-			

CA indicates cancer; LDCT, low-dose computed tomography; NLST, National Lung Screening Trial. ^aFor the NELSON trial, round 2/3 data were presented together, reflecting study design.

these previous efforts, a cancer screening service must be widely available to patients considering participation and be delivered in an efficient, economical, and culturally sensitive manner to optimize public health benefit.

The thoughtful development and disciplined implementation of lung cancer screening as a high-quality preventive health service involves multiple interactive steps that will undoubtedly continue to evolve over time. In particular, it is important to recognize that the clinical evaluation and management of high-risk cohorts, in the absence of symptoms, mandates a new approach that differs significantly from the standard clinical approach of managing a symptomdetected lung cancer.

The purpose of this article was to discuss the evidence supporting LDCT lung cancer screening, as well as other screening-related issues, including benefits and harms, current recommendations and guidelines, implementation strategies, and policy and payment considerations.

Evidence Supporting Lung Cancer Screening

After decades of disappointing results, there is now objective evidence that demonstrates the efficacy of an approach to detect and cure early lung cancer. The National Lung Screening Trial (NLST), the most expensive randomized screening trial of a single cancer ever conducted by the National Cancer Institute, found that the use of LDCT in at-risk populations was associated with a significant reduction in lung cancer mortality.8 Specifically, annual LDCT in smokers or recent former smokers aged 55 to 74 years was associated with a 20% decrease in the death rate from lung cancer. In addition, a comprehensive literature survey by the Agency for Healthcare Research and Quality (AHRQ) on lung cancer screening, which synthesized relevant data from 8149 papers published on the topic between 2000 and the last quarter of 2012, supports screening for lung cancer.⁴ Based on these findings, LDCT screening is now recommended by the USPSTF, the American Cancer Society (ACS), and a number of other medical organizations.^{3,7,9–12}

The NLST, which accrued 53,454 patients, is the only completed, fully powered, randomized, lung cancer screening trial reported to date. In contrast, 2 small, randomized, recently reported European trials with a combined accrual of 6576 patients did not report a mortality reduction benefit, but neither study was adequately powered to give a reliable assessment of mortality reduction.¹³⁻¹⁶ Although ongoing trials will generate interesting and important cost and other relevant data that are complementary to the NLST results, no existing trial will have sufficient study power to supersede the positive conclusion of the NLST relative to the mortality reduction endpoint. The largest of the ongoing trials is the Nederlands-Leuvens Longkanker Screenings ONderzoek (NELSON) Dutch-Belgian lung cancer screening trial. The NELSON is currently in final phase of follow-up prior to definitive analysis and reporting.¹⁷ Although the NELSON and NLST studies have important differences in study design, risk profiles, and diagnostic workup approach, preliminary data from NEL-SON indicate that the cancer detection rate is comparable and the stage I detection rate is similar (Table 1).^{17,18} Based on these findings, a major difference from the NLST regarding the estimate of benefit associated with LDCT is not expected in NELSON.¹⁸

Because NLST was budgeted to cost over \$200 million, the core design assumption was widely vetted prior to its implementation. The consensus that emerged was that a target mortality reduction of 20% with LDCT versus chest x-ray (CXR) would constitute compelling evidence of an objective screening benefit. An analysis of the full benefit of LDCT would have been much more expensive and required considerably more time to complete. Therefore, it is not surprising that a recent analysis of NLST outcomes with a rederived eligibility risk model constructed from Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial case outcomes resulted in a more efficient lung cancer case detection rate.¹⁹ Using that risk tool in a reanalysis of NLST data yielded more sensitive case detection estimates that could improve both the cost-effectiveness and the mortality reduction benefit of LDCT screening.¹⁹ This experience demonstrates how reanalysis of clinical outcome data derived from a screened cohort such as with the NLST represents an invaluable research resource. Our knowledge about many existing screening questions may be enhanced through reanalysis of the now broadly available NLST data set. Similarly, as lung screening programs are

developed and implemented, it will be essential to systematically analyze the outcomes from a reasonable sample of screening participants so that ongoing process and quality evaluations are possible.¹⁹ Such registry resources may enable continuous improvement in screening management and will be particularly valuable if cross-linked to death registries for the purpose of assessing long-term outcomes. Currently, a number of groups are collecting LDCT screening data, including the Society of Thoracic Surgeons, the Lung Cancer Alliance (LCA), and the International Early Lung Cancer Action Program (I-ELCAP).^{20–22} This rapidly growing data resource is critical in allowing continuous research in I-ELCAP digital image and screening process improvement.²²

An important point to clarify is what the definition of "low-dose" CT really means. In general, LDCT is usually considered to use doses of radiation that are 10% to 30% of the radiation dose exposure used in a standard, diagnostic, noncontrast CT. This very low amount of radiation is also sufficient for the reliable characterization of solid pulmonary nodules in follow-up screening examinations.¹⁸ Furthermore, the rapid refinement of CT scan resolution has resulted in the routine detection of progressively smaller primary lung cancers, an evolution that improves patient outcomes for 2 reasons. First, smaller tumors are associated with better cancer-specific outcomes.²³ Second, smaller tumors are likely to be amenable to treatment with minimally invasive thoracic surgery, a new approach associated with a better quality of life (QOL), better compliance with adjuvant therapy, and fewer postoperative complications.^{20,24} For the management of primary lung cancer, smaller is definitely better.

Issues to Consider With Benefits and Harms

Disparate views exist regarding the strength of the evidence supporting LDCT screening. The authors of one set of guidelines cautioned that "uncertainty exists about the potential harms of screening and the generalizability of results."25 This point of view is in contrast to the more optimistic perspective offered by the USPSTF or the more recent ACS review; both of these analyses judged the benefits to outweigh the potential harms.⁷ Humphrey et al, who performed the comprehensive USPSTF analysis as part of their data synthesis of this topic, outlined successful screening management innovations reported after the design of the NLST that markedly improved the efficiency and diagnostic precision of LDCT screening.3,26 The USPSTF did carefully outline potential harms of the LDCT screening process, including the frequency of unproductive diagnostic workup, exposure to medical radiation, anxiety about a cancer diagnosis, and the frequency of surgical complications.^{3,8} However, the final recommendation of the

USPSTF did reflect newer LDCT-related research published over the past decade (ie, since the start of the NLST), which outlines mitigation strategies that greatly reduce the frequency of harms occurring in the screening setting. The challenge with the national implementation of LDCT relates to ensuring that provisions to best mitigate potential harms are routinely embedded in the provision of screening services.

Unproductive Diagnostic Workup

Early pilot LDCT screening trials were challenged with the practical issue of managing the large number of small, noncalcified, pulmonary nodules routinely identified during LDCT screening.²⁷ In these earlier studies, there were no established algorithms regarding the diagnostic evaluation of subcentimeter nodules, and thus concern may exist that unnecessary biopsies or procedures would be performed. Since then, there has been considerable progress in mitigating harms by defining more efficient approaches to the diagnostic workup of suspected lung cancers based on the nodule growth rate. In such cases, an invasive workup would be restricted only to individuals with a pulmonary nodule of critical size and a growth rate consistent with a clinically aggressive cancer.^{4,28}

Published reports have been sharply critical of the LDCT process but these reports have largely overlooked the considerable refinement in the clinical management of the screening process. Given the importance of this issue, it is useful to outline the evolution of these improvements.²⁵ At the time of the initiation of the NLST in 2002, the NLST protocol did not mandate a specific nodule management process for all the patients in the study. Yankelevitz et al had reported that clinically important lung nodules could be successfully identified by restricting the diagnostic workup to suspicious nodules that showed significant growth over a defined period of time, but it was not feasible to incorporate this provision into the NLST.²⁹ This interval-growth diagnostic workup approach was integrated into the design of the NELSON trial and resulted in an invasive diagnostic workup rate of 12%, with a diagnostic sensitivity of 95% and a specificity of 99% for LDCT.¹⁷ By comparison, the screening positivity rate on the first round of annual screening from the NLST was 27.9%, with a diagnostic sensitivity of 93.8% and a diagnostic specificity of 73.4%.4,18 More recently, the interval-growth criterion for suspicious nodules was used prospectively in a cohort of 4700 screening patients cared for at the Princess Margaret Hospital. In that study, Wagnetz et al reported an overall false-positive recommendation rate of 0.42%, which translates into 20 falsepositive (or cases in which the diagnostic workup showed no evidence of a cancer) calls with the screening management of 4782 screening subjects.²⁸ These unproductive



FIGURE 1. National Comprehensive Cancer Network (NCCN) Algorithm for Low-Dose Computed Tomography (LDCT) Screening Management.³⁴ PET indicates positron emission tomography. Reproduced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Lung Cancer Screening V.2.2014. © 2014 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines[®] and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK[®], NCCN[®], NCCN GUIDELINES[®], and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

workups included 12.5% (16 of 128) of fine-needle aspiration biopsies and 3.9% (5 of 128) of benign nodules revealed by video-assisted thoracic surgery (VATS). The overall false-positive rate was 0.33% (16 of 4782) with fine-needle aspiration biopsy and 0.10% (5 of 4782) with VATS.²⁸

Overdiagnosis

Overdiagnosis is an important screening bias. As defined in the AHRQ Evidence Synthesis statement, overdiagnosis is the screening-related diagnosis and treatment of a cancer that would otherwise not have been important during an individual's lifetime.³⁰ CXR screening was the initial basis of concern for overdiagnosis in lung cancer screening.³¹ However, in the lung cancer evaluation arm of the PLCO Screening Trial, the cumulative incidence of lung cancer after 6 years of follow-up in screening participants at risk of lung cancer due to heavy tobacco exposure was the same in both the CXR and usual-care groups (606 vs 608 per 100,000 person-years, respectively; relative risk, 1.00 [95% confidence interval, 0.88 to 1.13]). Therefore, although the PLCO trial failed to show a benefit for the early detection of lung cancer with CXR, the results of this large early detection trial suggest that overdiagnosis may not be as significant a factor as previously thought in evaluating the benefit of lung cancer screening with CXR.²⁶

In a recent updated statement on the benefit of LDCT screening, the USPSTF cited their modeling exercise, which suggested that 10% to 12% of screen-identified lung cancer cases are overdiagnosed.⁴ In their prior analysis, the USPSTF had concurred with a consensus of international lung cancer screening experts in characterizing the data

from CXR studies in the United States as being not compelling as a major source of bias in lung cancer screening results related to overdiagnosis.^{32,33} An analysis of a large number of lung cancer outcomes in the California Cancer Registry also suggested that the degree of overdiagnosis in defining the early lung cancer screening mortality benefit is unlikely to be a major factor,³⁴ a position that is further supported by consideration of the ongoing results regarding LDCT from the NLST.³⁵ A recent analysis of the contribution to the reported results of the NLST suggested that there may be as much as an 18% rate of overdiagnosis. However, a large part of that was due to the number of bronchioalveolar carcinomas that were resected during the NLST.¹⁸ The recent revision to the pathological classification of lung cancer suggests that this form of stage I lung cancer, now termed adenocarcinoma in situ, is noninvasive and therefore it is no longer managed with surgical resection until it evolves into a more clinically aggressive cancer.⁹ The second limitation of that overdiagnosis analysis was actually pointed out by the authors. Because LDCT is known to detect lung cancer at an earlier stage, longer-term follow-up is required in a trial before a screened-detected lung cancer should be declared to be overdiagnosed. Going forward, with best practice surgical management and appropriate follow-up, a much reduced rate of overdiagnosis would be expected compared with the recent report.9 Therefore, perhaps a more productive focus for improving LDCT screening would not be overdiagnosis but rather to focus on minimizing harms with diagnostic and surgical interventions so as to reduce overtreatment by following established guidelines (Fig. 1).9,20,21,24,34

Radiation-Related Harms

Radiation exposure occurs due a range of naturally occurring sources from solar energy to uranium decay in the earth's crust and is a known carcinogen.³⁶ Current understanding of the contribution of radiation exposure to the development of cancer is based on limited data such as those from studies of the outcomes from atomic bomb exposures and from industrial exposures.36 Because these events are unusual and precise knowledge of actual radiation exposures is limited, the exact determination of the dose relationship of exposures causally related to the development of cancer has not yet been established. As already discussed, the medical radiation dose used in the NLST was modest (1.5 millisieverts [mSv]). An even lower radiation dose is now being widely used for LDCT in routine clinical care.4,26 With regard to the potential harms associated with such low doses, the considered position of the American Association of Physicists in Medicine (AAPM) is as follows: "Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged. These predictions are harmful because they lead to sensationalistic articles in the public media that cause some patients and parents to refuse medical imaging procedures, placing them at substantial risk by not receiving the clinical benefits of the prescribed procedures."37 The threshold radiation dose cited by the AAPM as being potentially associated with carcinogenesis is 50 mSv. More recently, an exposure model developed to consider the potential consequences of exposure to radiation doses in the range of current LDCT exposures found once again that the risk of cancer from radiation was hard to quantitate but was believed to be quite low.³⁶

The risk of low-dose radiation exposure should also be considered in the context of the screening setting. The relevant population for lung cancer screening is restricted to heavily tobacco-exposed individuals around the sixth decade of life. An individual participating in a lung cancer screening program as per the USPSTF recommendation would have had a considerable lifetime tobacco exposure and therefore a significant risk of developing lung cancer. Consequently, although careful quality control to minimize radiation exposure is essential, it should not constrain the use of LDCT in populations at high risk of lung cancer, especially since the dose of radiation exposure required in lung cancer screening continues to decrease. Clinicians, including radiologists, should follow the guidelines that specify the frequency of examinations and the focus on using LDCT, as opposed to diagnostic CT, in screening algorithms.

Providing LDCT imaging services safely and with consistent high quality could be greatly assisted by new resources introduced by the American College of Radiology (ACR), which is now certifying standards for the process of lung cancer screening that build on their previous role in monitoring the quality of the breast cancer screening process (acr.org/Quality-Safety/Lung-Cancer-Screening-Center).³⁸ This designation will require facilities seeking this certification to meet specific equipment, personnel, and imaging protocol requirements. Another aspect of the ACR's LDCT efforts is Lung Imaging Reporting and Data System (Lung-RADS), which the ACR characterizes as a quality assurance tool with which to standardize lung cancer screening, CT reporting, and management recommendations; reduce confusion in lung cancer screening CT interpretations; and facilitate outcome monitoring. Both of these programs are essential resources for clinicians in providing consistent, high-quality lung cancer screening care.

QOL and Harm Associated With LDCT

Concerns have been raised about accrued harm relative to QOL in the course of screening. NLST investigators reported that adverse events in the study were "few and minor,"⁸ a characterization that is consistent with the narratives in several other new guidelines.^{11,35,39,40} The conclusion from the final USPSTF recommendation on LDCT stated "Overall, LDCT screening did not seem to result in substantial long-term psychological distress, although assessment has been limited. No studies reported long-term differences in anxiety or distress levels associated with LDCT in participants."⁴ However, with any medical process, significant iatrogenic harms are possible, such as unnecessary biopsies or diagnostic procedures. Adherence to established guidelines will minimize the chance iatrogenic harm, and further research into this issue is necessary.⁹

Potential Evolution of Screening Criteria

Defining the optimal approach to the LDCT process with the greatest efficiency and quality, while minimizing costs and harms, is the fundamental challenge as we move toward the national implementation of lung cancer screening.

Current Screening Recommendations

The National Comprehensive Cancer Network[®] (NCCN[®]) in February 2012 became the first organization to publish guidelines that endorse LDCT screening as a screening tool, and serves as a useful source of information on the LDCT screening process.⁹ NCCN[®] recommendations specify that LDCT screening requires: 1) sophisticated multidetector CT scanners and analytic software; 2) professional physicists and staff who certify equipment and perform studies to a consistent standard at acceptable radiation exposures; 3) qualified radiologists who use

standardized terminology and standardized interpretation; 4) appropriate guidelines; 5) reliable communication requirements with primary care physicians; and 6) medical environments that can absorb patients who require ongoing management and handle the responsibility of tracking screened individuals and documenting outcomes.³⁹ Since then, a number of other organizations have addressed recommendations for lung cancer screening, including the American Association for Thoracic Surgery (AATS) and the ACS.^{11,35}

The most recent NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Lung Cancer Screening represent its third revision and attempt to synthesize USPSTF and ACS recommendations for LDCT screening.³⁹ These guidelines serve as an excellent source of objective information for the clinician to consider in the dialogue with potential screening candidates. The NCCN Guidelines[®] for Lung Cancer Screening for LDCT screening eligibility stratify candidates into 3 categories by risk (low, moderate, and high) (Table 2).³⁹ NCCN eligibility criteria for the highest risk group mirror those in the NLST trial; however, the lower risk strata still include patients who may develop lung cancer but in whom the benefit-to-harms ratio may be narrower. Over time, with the implementation of screening with continued process improvement research, we can better define the risk groups that would be expected to benefit (both in terms of health outcomes and expense) from undergoing the screening evaluation.

Although many professional organizations now endorse LDCT screening for individuals with the appropriate risk profile, the American Academy of Family Physicians (AAFP) on January 1, 2014 concluded that the current evidence is "insufficient to recommend for or against screening for lung cancer with low-dose computed tomography (LDCT)." A statement posted on the AAFP Web site went on to say: "There actually were four (randomized LDCT) studies; the one that was done in the United States is the largest and showed the most benefit." (aafp.org/ news/health-of-the-public/20140113aafplungcarec.html). The US study, the NLST, was a randomized, controlled trial that involved more than 50,000 participants. The 3 other studies were conducted in Europe and were not considered to be of the same quality or to demonstrate the same degree of benefit as the NLST.41 As already discussed, 2 of the European studies are extremely small and underpowered; the results of the third European study (NELSON) have not yet been fully reported. Therefore, the basis for the AAFP decision is not compelling. Although the NELSON study is not as large as the NLST, it has been well designed and executed. Published results to date in regard to diagnostic efficiency and harms with surgical intervention have been quite promising and at least as favorable

TABLE 2. NCCN Guidelines: LDCT Screening Eligibility



LDCT indicates low-dose computed tomography; NCCN, National Comprehensive Cancer Network. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Lung Cancer Screening V.2.2014. © 2014 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines[®] and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK[®], NCCN[®], NCCN GUIDELINES[®], and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

as those of the NLST.^{17,42} The final results of the NEL-SON study are expected to be reported in the next 2 years.

Implementation and Screening Quality

To date, definitive evidence-based guidance for implementing LDCT screening programs has not been defined. One strategic approach to delivering a complex clinical service with consistent high quality is to use a checklist to begin to systematize the screening process.⁴³ The checklist approach, which has been used successfully in organizing other processes of medical care, includes provisions for acquiring follow-up information.

The technology of lung cancer screening has improved substantially over time, and these improvements could facilitate the implementation of LDCT by reducing potential harms and cost. Although multidetector scanners were used in the NLST, recently developed CT scanners enable more rapid image acquisition and shorter scanning times, which may translate into technically higher-quality studies with less motion artifact. In addition to enhancing the quality of images, improved CT technology has also reduced exposure to medical radiation, thereby lowering imaging risks. These innovations have been supported by the imaging vendors, since the advantages of new scanners affect many more clinical services beyond LDCT screening. All of these factors are material in the national implementation of LDCT as a cancer screening resource.⁴⁴ Guidance on the imaging process for LDCT has been recently released by the ACR.³⁸ The Quantitative Imaging Biomarker Alliance of the Radiological Society of North America, whose focus is on reliable nodule measurement, is also releasing a document outlining best practice approaches to minimize variance in quantitative imaging measurements in the screening setting.⁴⁵

Risk Assessment and Screening Duration

The number of rounds of annual screening evaluated in the NLST was limited by study design and budget, and thus the optimal interval and duration of screening with LDCT could not be definitively established. Critics of LDCT have cited these uncertainties as a justification for delaying the national implementation of screening.⁴⁶ Similarly, there are concerns that the current risk assessment approach is not rigorous enough in defining the appropriate high-risk groups for screening.³⁹ However the number needed to screen for lung cancer is a more favorable rate of detection than other cancers.³ Self-reported tobacco exposure as a risk discriminant does suffer from a number of limitations but it does allow for a simple use and broad application.⁴⁷ While considerable research is underway to deepen our understanding of these issues, the current USPSTF recommendations on the implementation of LDCT are generally based on parameters embedded in the NLST.¹⁸

The context for lung cancer screening is unique in that tobacco exposure is such a powerful determinant of risk. Recently, a large British meta-analysis that included data from more than 250,000 individuals resulted in the development of a tool that was very robust in stratifying risks using only tobacco exposure history.48 This approach is consistent with a recent report by Tammemagi et al that did in fact model a more efficient risk stratification approach than was used in the NLST, taking into account more clinical variables.¹⁹ Although more comprehensive molecular or genetic models are being developed, the tobacco exposure history risk tool would be an attractive candidate with which to start the national screening process in evaluating the generalizable benefit of LDCT screening.^{39,40,49} The NCCN and the AATS have suggested that it would be logical to extend LDCT screening to other target cohorts whose level of risk is similar to that of the NLST target population.^{9,11} For example, screening could be recommended for individuals based on age, tobacco exposure histories, and other known risk factors for lung cancer as determined by that risk tool, to define a screening cohort equivalent to the validated risk strata observed in NLST participants. Perhaps further work with the PLCO risk model could help to define a tool that would prospectively classify the risk of lung cancer relative to the risk strata studied in the NLST.¹⁹ In the future, with research including validation studies, it will be responsible to define appropriate cohorts for LDCT screening more broadly and further reductions in cost and harms could be realized.

As mentioned above, the risk of lung cancer after heavy smoking persists, despite smoking cessation, and remains elevated as long as the former smoker lives.⁵⁰ Therefore, ongoing lung cancer screening beyond the 2 rounds of annual screening evaluated in the NLST might further improve the mortality benefit beyond the reported 20% threshold.⁸ Further research is also required to define how long and at what frequency LDCT screening should be performed. Two recent reports have suggested that sustained annual screening (more than the 2 rounds used in the NLST) may reduce lung cancer mortality between 40% and 60% under different screening scenarios,^{51,52} and therefore acquiring further clinical outcomes to establish the full magnitude of the mortality reduction benefit of LDCT merits further study.

Integration of Smoking Cessation

A critical opportunity to optimize screening benefit is to constitutively integrate smoking cessation with lung cancer screening.^{53–55} Although the integration of LDCT screening with smoking cessation has been reported with mixed success regarding the efficacy of smoking cessation counseling, medications, and recidivism, to date there has been little investment in research to optimize how smoking cessation would be approached in a recurrent screening setting. A recent review of lung cancer screening and smoking cessation reviewed the existing literature on this subject and concluded that there was no evidence of increased smoking related to participation in lung cancer screening.⁵⁶

The LDCT screening setting, which (for now) involves annual follow-up, provides an opportunity to manage tobacco cessation at each annual encounter. Some authors have characterized the screening encounter as a "teachable moment" for engaging the smoking cessation dialogue. The intensity of the character of the cessation strategy can be tailored to the persistent smoker, and this new screening management setting comprises a new platform in which to adaptively personalize efforts at smoking cessation.⁵⁷ The cost-efficiency of the routine integration of robust smoking cessation measures with LDCT screening is projected to be extremely favorable.54,58 Increasing success with smoking cessation would not only improve the inherent cost-efficiency of the LDCT screening process relative to lung cancer outcomes, but would also accrue the other well-validated health and economic benefits associated with successful smoking cessation.59

Role of Primary Care

As the LDCT screening service is disseminated, it will evolve to become an integrated component of preventive care medicine. Currently, the target population specified by the USPSTF includes current and recent former smokers between the ages of 55 and 80 years with an exposure to at least 30 pack-years of smoking.⁴ Estimates suggest that more than 50% of the US adult population is either a current or former smoker. Notably, approximately 7 million asymptomatic individuals will fall into the target eligibility window for LDCT screening consideration.8 Implementing a cancer service of this scope is an ambitious undertaking and the issue of ensuring responsible follow-up of at-risk individuals is a significant challenge for already overtaxed primary care providers. Both the ACR and the LCA are providing tools to help with this important challenge.^{21,38} This includes provisions to ensure the responsible follow-up of at-risk individuals since lung cancer risk is known to increase with age. Further research to define best practice with screening adherence is a critical area for the future.

For the purpose of informed decision-making, which is a consensus element of the lung cancer screening process that all the guidelines support, clinicians need to communicate with patients about the potential adverse consequences of tobacco exposure relative to lung cancer risk and overall health and then relate the potential for benefit both with tobacco cessation as well as LDCT screening. A balanced discussion of both the potential for benefit and the harms associated with lung cancer screening should take place prior to a referral to LDCT testing. The opportunity to provide not only access to LDCT but also integrated tobacco cessation services, when relevant, should not be missed because it is an ideal time for the primary care community to engage patients in a proactive and informed discussion about important options to adaptively manage their own health.^{44,57}

Currently, there are nearly 45 million former smokers in the United States,⁶⁰ and primary care clinicians must remain vigilant to the fact that lung cancer risk in former smokers remains elevated for life. In one recent study, lung cancer was diagnosed in individuals who had stopped smoking an average of 18 years earlier.⁶¹ Thus, despite having already heeded the Surgeon General's advice on smoking cessation, this group constitutes a critical target population for LDCT screening.⁵⁰

Other Potential Benefits of LDCT Screening

A related consideration with LDCT involves an unprecedented potential to evaluate the status of other tobaccorelated diseases. For example, recent reports have shown that coronary calcium analysis can be derived from an LDCT scan and could be a useful tool with which to stratify the risk of coronary artery disease.^{62,63} Furthermore, the integration of an LDCT assessment of lung injury as a metric of risk for chronic obstructive pulmonary disease (COPD) progression has also been reported.^{64,65} Indeed, tobacco-exposed populations participating in lung cancer screening are known to experience a significant comorbid risk of COPD and cardiovascular disease. With further research, the opportunity exists to simultaneously coevaluate for the 3 major host consequences of tobacco exposure (lung cancer, COPD, and cardiovascular disease) from a single LDCT scan. Notably, these diseases represent 3 of the leading causes of premature death in our society.⁶⁶ We are now fortunate to have an emerging setting in which the LDCT screening approach can provide a useful window into the preclinical phase of 3 major chronic diseases. The time is ripe to explore this critical opportunity so an understanding of the actual benefits and harms of these additional aspects of LDCT screening can be responsibly evaluated.

Managing Patients With Positive Screens

A more efficient approach to evaluating for potential screen-detected lung cancer than that used in the NLST was described in a recent retrospective analysis of baseline lung cancer cases accrued to the I-ELCAP.²² In the analysis, changing the nodule size threshold for a lung cancer diagnostic workup from 4 to 5 mm to 7 to 8 mm was associated with a timely diagnosis of early lung cancer, while significantly reducing the frequency of negative lung cancer diagnostic workups by 75%.²² The implementation of this approach could potentially improve the efficiency of LDCT screening by reducing the cost and harms of invasive diagnostic workups in the baseline screening process.

The NCCN has dynamically integrated evolving screening research information into its management recommendations. Figure 1 depicts their current (as of 2014) best practice recommendation in regard to the management of suspicious nodules.^{34,39} Use of a predictive model to improve workup efficiency is described in another recent report.⁶⁷ Continued research along these lines with other epidemiological, imaging, or molecular biomarkers, measured in either the serum or relevant specimen, may lead to further reductions in the frequency of false-positive diagnostic screening workups by more clearly elucidating the biological nature of suspicious lung nodules.^{5,67} The approach used in selecting the nodule size threshold for an invasive diagnostic workup is an example of continuous process improvement for lung cancer screening management, which may be an approach that could be used more generally in optimizing other aspects of the management of LDCT.²²

Standards of Care in Lung Cancer Surgery and the Impact of Surgical Quality on Screening Program Outcomes

In the NLST, surgical management was not specified by an optimized protocol and was typically not delivered in centers that have achieved recognition for excellence in thoracic surgical care. Definitive data regarding the optimal approach to surgical management in the screening setting do not exist; however, many centers of excellence have reported favorable surgical outcomes using minimally invasive approaches, generally VATS.^{20,24} Minimally invasive surgery was used in only a minority of the cancers detected in the NLST but limited thoracic surgical resection is an important opportunity with which to minimize surgical complications in the LDCT setting.⁶⁸

A recent retrospective review of 347 thoracic resections performed in a lung cancer screening cohort demonstrated that the long-term (10-year) effect of sublobar resection is equivalent to that of lobectomy in patients with clinical stage Ia lung cancers.^{23,40} Sublobar resection offers the additional benefit of preserving a larger amount of functioning lung tissue. For this reason, the LCA advocacy group proposed the Lung Cancer Screening framework,^{21,40} a mechanism that encourages institutions providing screening services to use "best practice" screening and treatment measures, including minimally invasive surgical techniques, so that the quality of screening services is maintained at a high level. Incorporation of such best practices into the protocols of developing LDCT screening programs could potentially help these programs meet or even exceed the favorable results reported in the NLST.

Measuring Outcomes of LDCT Screening Programs

In the wake of the publication of the NLST results, a critical correlate of LDCT screening success will be the increased frequency of early lung cancer detection, offset by a corresponding decrease in the frequency of advanced lung cancer diagnoses.^{8,18} The success of screening may be further evaluated by institutions with lung cancer screening registries or government agencies with registries of cancer deaths. The LCA encourages institutions that provide lung cancer screening services to report quality and outcomes data so that such trends can be reliably analyzed. To validate that institutions are successful in screening management services, the LCA screening framework also mandates that participating institutions routinely report relevant screening outcomes and complication rates. Using this information, potential screening candidates can make informed decisions about where they choose to receive their screening care.²¹ Relevant parameters to report may include

the number of 1) patients screened annually, 2) cases requiring diagnostic workups, 3) surgical patients, and 4) complication rates with invasive surgical procedures. In addition, it would be helpful for the AATS and the NCCN to provide recommendations concerning quality measures (in addition to compliance with guidelines), such as the complication rate for invasive procedures and the falsepositive rate among patients in whom an intervention is performed. In addition to the LCA, other organizations such as the AATS, ACR, and I-ELCAP are committed to proactively acquiring this kind of critical outcome data (AATS statement, acr.org/Quality-Safety/Lung-Cancer-Screening-Center accessed June 5, 2014).⁴⁰

Outcomes data must be collected because reanalysis of these data may help to address issues such as the limited existing QOL data and, over time, to develop more objectively validated approaches to address participant distress with the LDCT process.

Policy and Payment Issues

A key provision of the Patient Protection and Affordable Care Act requires that most insurers (including Medicare) provide coverage, without cost sharing (eg, coinsurance, deductible, or copayment), for preventive care services that receive an "A" or "B" recommendation from the USPSTF. As a "B"-rated service, lung cancer screening may fall under this mandate.^{30,69} The cost of comprehensive LDCT screening was not considered in the analysis performed by Humphrey et al for the USPSTF^{3,4}; however, cost-effectiveness information could potentially be considered in the evaluation of this service by the Centers for Medicare and Medicaid Services (CMS) in the development of Medicare payment policies. Using existing CMS mechanisms, there is an opportunity to require the reporting of outcomes from the conduct of CMS-supported screening to assess the quality and success of implementing this service, especially with regard to minimizing potential harms, cost, and suboptimal results in the diagnostic workup process. Some lung screening advocates have expressed concern that a requirement for continued evidence development associated with Medicare reimbursement for all LDCT screening would add the burden of funding to the registry mechanism, which would slow down the process of LDCT dissemination. Furthermore, the requirement may also create an unintentional problem of limiting access to LDCT screening services for some medically underserved populations.⁷⁰ Forty professional and lung cancer advocacy organizations have advocated that the CMS provide coverage for individuals identified in the final recommendation of the USPSTF so that screening will be accessible to an important population of significantly tobacco-exposed individuals.⁷⁰ Through new

CMS mechanisms, the implementation of reimbursement for LDCT screening services beyond the USPSTF recommended population could be linked to demonstrating comparable outcomes with those reported in the NLST.⁷⁰ Because tobacco use is known to have a strong correlation with socioeconomic status, reimbursement for lung cancer screening is essential for low-income smokers and former smokers who would benefit from screening but who are unlikely to be able to afford the service in the absence of third-party support. The decision by 26 states to forgo participation in Medicaid expansion will affect individuals aged younger than 65 years who may not be eligible for lung cancer screening services unless individual states make special provisions. This could lead to a new health care disparity, limiting access to LDCT screening services for many high-risk individuals, and result in a corresponding gap in favorable outcomes for a vulnerable population.

What Is on the Horizon for Lung Cancer Screening?

Going forward, a critical issue is whether the reported benefits of LDCT screening can be met or exceeded when LDCT is implemented in a wide variety of settings across the country as a routine clinical service. Responsibly initiating a national LDCT screening process is a logistical and financial challenge, because numerous variables can contribute to the magnitude of the actual mortality benefit associated with LDCT screening. Nonetheless, the United States has shown leadership in this arena by launching and completing the NLST, and the USPSTF has provided a timely recommendation for targeted screening. With each of these steps, the support for LDCT screening has grown, as is evident in a recent letter submitted to the CMS by a large consortium.⁷⁰ National implementation is another opportunity for the United States to provide leadership in improving lung cancer outcomes.

Conclusions

Based on the largest and most extensive single-organ cancer screening trial ever performed, we now know with certainty that some lung cancer deaths can be prevented with LDCT.⁸ We also know that lung cancer screening implemented in conjunction with smoking cessation measures can enhance the cost-effectiveness of this screening service.58 Furthermore, a growing body of research points to additional opportunities to improve aspects of the screening service. LDCT as a screening tool is quick (it takes several seconds), painless, and generally already available; it has also been reported to have favorable cost characteristics compared with other cancer screening tools.⁵⁸ In addition to the demonstrated value of screening with regard to lung cancer mortality reduction, further potential exists to screen for other major tobacco-related diseases in the same at-risk population and to mitigate the burden of screening.

Given identified opportunities for improvement in the diagnostic workup, more tailored surgical management of screen-detected lung cancers, and the potential to extend LDCT imaging to other major tobacco-related diseases, the case for implementing lung cancer screening is quite strong, as recently reported by the USPSTF.³ The CMS must now decide on reimbursement provisions for LDCT screening to enable full national access to this new screening service and this process is informed by both scientific as well as political considerations.^{21,59,71,72} A shared challenge in implementing LDCT screening for this lethal cancer will be to develop strategies to further minimize the occurrence of the known complications of lung cancer screening so that a continuously improving screening process can be realized nationally. Decisive action in promptly and thoughtfully implementing a new lung cancer screening service associated with measures to track quality and outcome is an urgent national priority.

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In The Lancet Oncology, Nanda Horeweg and colleagues publish two Articles from the NELSON trial (a randomised controlled trial of low-dose CT lung cancer screening) to explore management strategies in screened individuals. The first report¹ outlines the results of their diagnostic approach to suspicious nodule assessment within the screening management process. In the second report,² the NELSON investigators address two crucial issues with low-dose CT screening: frequency of interval-detected cancers, and the optimum frequency of follow-up interval screening. The NELSON consortium has implemented the largest randomised trial assessing the benefit of low-dose CT screening in Europe. This group has already demonstrated the quality of their research efforts in an important paper showing the use of volumetric CT imaging to reduce the incidents of false-positive screening results.3

In the first report, the investigators showed that the use of a two-step algorithm-together with threshold values to define further work-up of pulmonary nodules detected in CT screening—both reduced unnecessary work-up, and increased diagnoses of early lung cancer.¹ They used both volumetric and diametric assessment of nodules to assess the probability of malignant disease for small nodules; the risk for small nodules (<100 mm³ risk 0.6% [95% Cl 0.4–0.8]; <5 mm risk 0.4% [0.2-0.7]) was sufficiently low so that no further workup was needed in that round of screening, whereas immediate diagnostic work-up was recommended for nodules larger than 300 mm³ in volume (risk 16.9% [95% CI 14.1-20.0]) or 10 mm in diameter (risk 15.2% [12.7-18.1]). Only nodules of intermediate size in between these two thresholds had further volumetric assessment, and subsequent work-up was determined according to nodule growth as measured by volume doubling times. The investigators used these thresholds to create volume-based and diameter-based management protocols for screening-detected nodules, and found these protocols compared favourably with simulated American College of Chest Physicians quidelines.

Work-up of pulmonary nodules should be based on the probability of malignant disease, and use of threshold values to determine further work-up is

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important. The NELSON investigators adopted the 5 mm diameter threshold for the definition of positive results, although this measurement was estimated with volumetric tumour assessment.1 This size threshold was initially proposed by ELCAP and later adopted by the Fleischner Society guidelines. In their report, the NELSON investigators provide probabilities of malignant disease based on their analysis of lung cancer cases identified in the first 2 years of the screening programme. Nodules that were 5-9 mm in diameter and more than 10 mm in diameter were significantly associated with increased cancer probability compared with smaller nodules.

Other screening programmes have based work-up on nodule size and used threshold values to initiate diagnostic workup, including the NLST and I-ELCAP studies, although the threshold values were different in these studies.3-5 The NELSON results provide very useful European data for 188 cases of lung cancer. The findings generally confirm previously reported lung cancer risks based on nodule size-eq, in the US NLST trial, which had a larger sample size (232 cases of lung cancer diagnosed within 1 year of the baseline CT screen), and from the I-ELCAP study, including more than 31000 screening participants between 1994, and 2005, and 21000 between 2006, and 2010 (in whom 484 and 119 cases of lung cancer, respectively, were diagnosed within a year of the baseline CT).^{5,6} Continued accumulation of evidence will help to further refine the work-up algorithms for all screening programmes, and NELSON is leading the way by using three-dimensional assessment of the nodule volume, whereas other studies are typically approximating the nodule volume with use of either one-dimensional or two-dimensional assessment.³⁻⁵ To enhance the precision of these analyses it is essential to separately develop the probabilities and appropriate thresholds for the baseline prevalence round, and the following incidence repeat rounds. The NELSON trial focused on the first 2 years of screening, presumably to have sufficient numbers of cancers, but the data are dominated by the baseline round. Although this distinction is not crucial for the trial result, when outcome measures are derived the cancer probability associated with repeat rounds of screening should

be separately defined to optimise the efficiency of the screening process. Additionally, because the management of non-solid nodules is changing, volume doubling time needs to be reported separately for this subset of nodules to reduce the potential for overdiagnosis.7

The second paper underlines the crucial need for standardised definitions for major screening parameters. Interval cancers, also known as interim cancers, are important factors in the timing between screenings. The classic definition of an interval cancer is one diagnosed after symptoms prompt work-up before the next scheduled screening. For example, in the Mayo Lung Project (which provided chest radiographs every 4 months) the rate of 4-month interval cancers was about 33%.8

In previous reports of CT screening, interim diagnoses have been much less frequent (eq, <1% reported by Henschke and colleagues⁵) than in this study.³ In the NELSON study, one symptomprompted case was reported before the first annual screening. The next screening was 2 years later, with ten symptom-prompted cases in the intervening period (many more than in the previous 1-year interval). Some of these reported cases (ie, interval cancers) seem to be due to protocol non-compliance, protocol non-adherence, inadequacy of the protocol, or human errors of detection and interpretation. The classic definition of interval cancer is intended to measure test sensitivity, but in the NELSON report the number of interval cancers results represented the conduct of the screening process.² Relative to the sensitivity of low-dose CT screening, other studies reported that almost 75% of cancers identified could be retrospectively identified;9 isolation of these cases is crucial to enable further research into improvement of case detection with the imaging approach. Therefore, these two papers clarify important issues and add to the overall favourable outcomes emerging with this screening approach. However, these analyses also underscore how much more work is needed to standardise methodology and optimise results.

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Length of chemotherapy and use of bevacizumab for breast cancer

Many attempts have been made in the past decade to improve on the average progression-free survival of 11 months and overall survival of 30 months after firstline treatment of metastatic breast cancer-particularly with the concurrent use of biological drugs such as bevacizumab-but the results have been disappointing. Initial enthusiasm over the doubling of progression-free survival with the addition bevacizumab to paclitaxel in See Articles page 1351 ECOG 2100 was tempered by a lack of improvement in overall survival.1 Subsequent trials showed more modest improvements in progression-free survival without improvements to overall survival.²⁻⁵ In addition, no biomarker for response to bevacizumab could be established in these studies.