OVERVIEW: The results of the National Lung Screening Trial (NLST) have provided the medical community and American public with considerable optimism about the potential to reduce lung cancer mortality with imaging-based screening. Designed as a randomized trial, the NLST has provided the first evidence of screening benefit by showing a 20% reduction in lung cancer mortality and a 6.7% reduction in all-cause mortality with low dose helical computed tomography (LDCT) screening relative to chest X-ray. The major harms of LDCT screening include the potential for radiation-induced carcinogenesis; high false-positivity rates in individuals without lung cancer, and overdiagnosis. Following the results of the NLST, the National Comprehensive Cancer Network (NCCN) published the first of multiple lung cancer screening guidelines under development by major medical organizations. These recommendations amalgamated screening cohorts, practices, interpretations, and diagnostic follow-up based on the NLST and other published studies to provide guidance for the implementation of LDCT screening. There are major areas of opportunity to optimize implementation. These include standardizing practices in the screening setting, optimizing risk profiles for screening and for managing diagnostic evaluation in individuals with indeterminate nodules, developing interdisciplinary screening programs in conjunction with smoking cessation, and approaching all stakeholders systematically to ensure the broadest education and dissemination of screening benefits relative to risks. The incorporation of validated biomarkers of risk and preclinical lung cancer can substantially enhance the effectiveness screening programs.

For decades, the early detection of common cancers has been advocated in an attempt to improve the chance for long-term survival and cure. Breast, colon, and prostate cancer all have established screening programs that are covered by insurers, embraced by physicians and the public, endorsed by professional societies and policy-makers, and touted as critical public-health measures as the U.S. health care system strives to prevent rather than treat disease. Lung cancer, the leading cause of cancer death in the United States and the world has lagged behind. There are many reasons, including that patients with lung cancer may suffer from the public's and policy-makers' perception of lung cancer as a "self-inflicted" disease. Also, the poor long term survivorships of lung cancer patients has compromised advocacy efforts. However, we are now at the beginning of a new and exciting era for patients with lung cancer. Revolutions in molecular genetics and modern technology have begun to have an effect on the course of this here-to-for highly lethal disease. For adenocarcinomas, in particular, several targeted therapies, such as the use of erlotinib, have emerged. Because of the National Lung Cancer Screening Trial (NLST), medical imaging advances have recently assessed the utilization of computerized tomographic scanning of the lung with a low radiation dose technique and provided the medical community and patients with optimism.1

Evidence for Benefit

Previously, trials that tested lung cancer screening with chest x-ray (CXR) showed disappointing results. Four randomized trials included one study in the Czech Republic and three National Cancer Institute (NCI)-sponsored trials that included sputum cytology in two trials that demonstrated no effect on lung-cancer specific mortality.2-55 The Mayo Lung Project (MLP), in particular, demonstrated a known problem with screening, i.e., of overdiagnosis—detecting lesions so indolent that they are not medically significant, with 17% more lung cancers detected in the screened arm, an excess that persisted for at least 20 years.6 Interestingly, a recent reanalysis of the MLP and the Johns Hopkins Lung Project shows some possible evidence of a very small beneficial mortality effect with sputum analysis.7 However, as a consequence of these studies, no major medical group recommended lung cancer screening until recently.

The Prostate, Lung, Colorectal, and Ovarian Cancer screening trial (PLCO) was launched in 1993 as a multimodal screening trial with ambitious goals. One was to assess with a large sample size the effect of CXR (postero-anterior only) screening (three rounds for nonsmokers and four rounds for current or former smokers) on lung cancer mortality. The trial enrolled 154, 901 individuals, 10% of whom were current smokers and 41.5% former smokers. The result unfortunately confirmed that this approach did not affect lung cancer mortality.8 There was perhaps some evidence of overdiagnosis—but not of the magnitude seen with the Mayo Lung Project.

Computed tomography (CT) has been clinically available in the United States for decades; however, image-acquisition time was slow until the advent of the helical CT. Also, until it was demonstrated that a low-dose technique could reliably image the lung parenchyma, valid concerns about radiation dose and subsequent carcinogenesis discouraged its use for screening a healthy population.9 With the advent of low-dose helical computed tomography (LDCT), several groups undertook screening of at-risk individuals and reported promising results. Among these was the Early Lung Cancer Action Program (ELCAP), in which 1000 individuals at risk of lung cancer underwent combined chest-x-ray and LDCT screening. A high proportion of early stage lung cancers were observed using LDCT, and the ELCAP was among the major studies to firmly introduce LDCT screening into the American consciousness. A number of downsides emerged from these various studies, including high false positivity rates and the challenges of distinguishing true mortality benefit from the well-known biases of lead-time, length, and overdiagnosis that arise from single arm screening studies.

From the Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD; Radiological Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA; Division of Cardiothoracic Surgery, University of Washington, Seattle, WA.

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Address reprint requests to Christine Berg, MD, National Cancer Institute, Early Detection Research Group, Division of Cancer Prevention, Executive Plaza North, Room 3112, 6130 Executive Boulevard, MSC 7346, Bethesda, MD 20892; email: bergec@mail.nih.gov.

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Lung Cancer Screening: Promise and Pitfalls

By Christine D. Berg, MD, Denise R. Aberle, MD, and Douglas E. Wood, MD
The concern in much of the scientific community was that given these limitations, as well as the highly aggressive and heterogeneous biology of lung cancer, the validity of LDCT screening would require demonstration of a mortality benefit in order to have great public health importance. Therefore, NCI decided that a randomized, controlled clinical trial should be designed and conducted to determine reliably the effect of LDCT on lung cancer-specific mortality.

The NLST was designed to answer one question in the shortest, most definitive manner: does screening with LDCT in an at-risk population lower lung cancer-specific mortality? A 20% mortality reduction was judged to be clinically important and feasible to assess. The entry criteria for the trial were set to bring a high-risk group into screening. These criteria included current or former smokers 55 to 74 years, 30 pack-years of smoking, if former smokers having quit within 15 years. The participants had to be asymptomatic and healthy enough to withstand surgery, and could not have had prior invasive cancers, and also not have had a CT within the last 18 months of enrollment. The trial was to compare three rounds of screening at 12 month intervals with LDCT compared to postero-anterior CXR. Consideration was given to having a third arm of no screening, but, as the PLCO was ongoing, it was decided to compare the NLST results to a matched cohort in the PLCO.12 Also, an analysis was done to assess whether or not adding rounds of screening would have any major, additional benefit; results showed that they did not. With these parameters, the needed sample size was 50,000 with 90% power and an α of 5% to determine a 20% mortality reduction (p > 0.05). The NCI launched the trial, which was managed by both the Lung Screening Study, under contract to the Division of Cancer Prevention, and the American College of Radiology Imaging Network, a cooperative group through the Division of Cancer Treatment and Diagnosis.

Accrual was rapid. Over 20 months from August 2002 to April 2004, 53,454 individuals were enrolled. Overall, the trial participants were younger, of higher educational status, and more likely to be former smokers than those who also matched the NLST entry criteria in the U. S. population.12 Screening was accomplished with a high degree of compliance in both arms—95% in LDCT and 93% in CXR. Follow-up continued after screening was completed. Regular assessments were done through questionnaires to participants and searches through tumor registries, National Death Index, and other sources to determine whether or not a participant developed lung cancer, whether he or she died, and the cause of death. A detailed endpoint verification process was undertaken to ensure the highest degree of accuracy and consistency in determining cause of death, particularly for lung cancer and deaths possibly from complications related to procedures done to evaluate for lung cancer. In October 2010, the Data and Safety Monitoring Board observed that a stopping boundary had been crossed and recommended that the trial cease. In November 2010, the initial findings from the NLST were released. On June 29, 2011, the primary results were published online in the New England Journal of Medicine and appeared in the print issue on August 4, 2011.1

Screening with LDCT resulted in a 20% decrease in lung-cancer specific mortality. A subset of the PLCO that matched the NLST was analyzed. There was no evidence that when compared with community care there was any mortality reduction with CXR, and the lung cancer–specific mortality in this cohort in the PLCO was the same as in the CXR arm of the NLST. The NLST was the first ever report from a randomized clinical trial documenting that lung cancer mortality could be reduced with a screening modality. Overall mortality was also lowered. However, when lung cancer deaths were removed, this difference was no longer statistically significant (p > 0.05). Compared with CXR, LDCT screening was associated with a stage shift towards earlier stages for all histologies of non-small cell lung cancer. There was no stage shift with small cell lung cancers. Unfortunately, the detection of limited small cell carcinoma was not enhanced with LDCT compared with CXR. During screening in the LDCT arm, 649 cases of lung cancer were diagnosed after a positive screen and 44 cases as interval cancer, whereas in the CXR arm, 279 cases were diagnosed after a positive screen, with 137 as interval cancer. A total of 1060 cases of lung cancer occurred in the LDCT arm compared with 941 in the CXR arm. Therefore, 129 additional cases of lung cancer were diagnosed in the LDCT arm than in the CXR arm; this absolute number is not an estimate of the amount of overdiagnosis. More follow-up would be helpful to determine precisely the numbers of excess cancers detected with LDCT compared with CXR that would not come to clinical detection during a participant’s life time. Alternatively, modeling can be done to better estimate the amount of overdiagnosis. Several approaches to determining overdiagnosis exist and further work is planned on this topic.

A positive result of suspected lung cancer was defined as a nodule ≥ 4 mm, or other findings potentially related to lung cancer. The average percentage of positive screens was high: 24.2% of LDCTs and 6.9% of CXRs. The chance for a participant overall after three screens to have one positive result was 39.1% in the LDCT arm and 16.0% in the CXR arm. Other significant abnormalities were also found more frequently in the LDCT arm than the CXR arm (7.5% compared with 2.1%, respectively). During the trial, there were guidelines for the evaluation of a positive screen both in the LDCT arm and the CXR arm. These were not mandatory, as it was judged important to leave follow-up

### KEY POINTS

- Screening with low dose computed tomography (LDCT) has been shown to reduce lung cancer by 20% relative to chest X-ray.
- Complication rates from screening and downstream diagnostic procedures are low in individuals with positive screens.
- The major harms of screening relate to high false positivity rates, the potential for radiation-induced carcinogenesis, and overdiagnosis.
- LDCT screening implementation should be interdisciplinary and integrated with smoking cessation programs to derive maximum benefit.
- Successful dissemination of LDCT screening will require a systematically approach to address the unique challenges of the screening centers, primary care environment, and population at risk.
in the hands of the radiologists and physicians caring for the individual patients, taking into account regional differences and patient-specific preferences. Fortunately, much of the evaluation of abnormalities could be conducted noninvasively. In general, a clinical evaluation and a diagnostic CT were performed. For a diagnosis of malignancy, invasive procedures were performed. The number of invasive procedures per malignancy diagnosed was relatively low. Complications were few (1.4% in the LDCT arm and 1.6% in the CXR arm). Major complications were primarily seen in individuals with underlying lung cancer, i.e., in the LDCT arm the rate of major complications in those with lung cancer was 11.2% compared to 0.06% in those without.

Reader variability studies done in the NLST reported that radiologists have a low level of agreement in detecting nodules and in measuring the growth of nodules. A panel of radiologists reviewed NLST baseline studies and reported the total number of abnormalities detected and classified as pulmonary nodules. There was up to a two-fold difference among radiologists. For cases classified as positive, consistency among recommendations for follow-up was poor. A similar study was done to assess changes in nodule morphology between two annual scans. Out of 95 nodules originally interpreted as present on both scans, 19 were judged by at least one of nine independent reviewers not to be present initially.

Another potential harm from an imaging test with ionizing radiation is that of radiation carcinogenesis. The medical physics group involved with the trial was diligent in setting image acquisition parameters to keep the dose low and to keep image quality high. Effective doses were estimated using volume CT dose index (CTDI) for the 97 scanners, and a whole-body mean effective dose was calculated. This was 1.4 millisievert (mSv). This compares with the average whole-body effective dose of 7 mSv from diagnostic CT. An estimate of radiation-induced cancers in an individual screened at 55, 56 and 57 years with the NLST LDCT technique is 1 to 3 lung cancer deaths per 10,000, and breast cancers induced is 0.3 per 10,000. This compares with 30 lung cancer deaths prevented per 10,000 screened three times. Of note, the cancers caused by radiation would occur many years after the screen whereas deaths prevented occurred within a few years.

A detailed assessment of cost-effectiveness is planned utilizing data from the NLST. This will take into account not only screening and diagnostic evaluation costs for positive screens but those evaluations undertaken in those screened who had other abnormalities or entered the medical system as a consequence of the screen. A preliminary report indicated that the incremental cost per year of life gained in the NLST was $38,000. Additionally, work with the Cancer Intervention and Surveillance Network (CISNET) is ongoing. The CISNET groups will validate and improve as needed their models using the NLST results. Other questions then that are very important when considering implementation of screening in the population, such as age at which to start screening, other smoking intensities, as well as other frequencies and durations of screening, will be addressed.

Concerns for Implementation

Clearly this is a major advance for patients at risk for lung cancer and will mean a major policy change by payers, policy-makers, guideline groups, and patient advocates. However, this enthusiasm, although deserved, must be tempered with caution. Another view of the NLST data reveals that it is necessary to screen 320 individuals every 12 months for three rounds for each lung cancer death avoided. Many patients will be exposed to the emotional and physical risks of lung-cancer screening to achieve the desired benefit. A careful, measured approach is important for the institution of lung cancer screening nationwide.

For the radiology community, the following considerations apply: the screening process itself should be standards-driven. Image-acquisition protocols must be consistent to ensure adequate image quality at the lowest reasonable radiation exposure, this is particularly important if computer-aided diagnosis (CAD) is incorporated into routine nodule detection and characterization. Imagery experienced in the management of lung nodules should provide interpretations and use consistent follow-up guidelines. Viable commercial solutions to track patients and nodules do not currently exist but would have a major beneficial effect on screening effectiveness and efficiencies; this critical need should be the basis for developing partnerships between screening centers and industry to understand how software technologies can facilitate workflow. There are several questions that remain to be addressed by the imaging community. Among them are the following:

Interpretation guidelines. Screening interpretations in the NLST were largely dichotomous, based on considerations of nodule size and morphology. The NELSON trial being conducted in the Netherlands and Denmark uses a two-tiered interpretation paradigm in which nodules falling between certain size thresholds are considered “indeterminate,” which mandate a 3-month follow-up LDCT to determine whether the screen is negative or positive. Using this algorithm, the positive predictive value of LDCT was substantially improved. Although it may be argued that medical resource utilization is not significantly different between the two interpretation paradigms, the implications of the screening result using the NELSON model more closely approximate lung cancer “risk” in individuals with indeterminate nodules, which has significant implications for both the individual patient and her/his provider.

Results communication. Screening centers should not only communicate results to the one being screened and his or her provider but have the necessary resources to follow up individuals with indeterminate nodules while keeping the primary provider fully informed.

Role of image analysis. Screening interpretation in the NLST was based on visual assessment. The European screening trials have predicated results interpretation on quantitative nodule volumetry. The incorporation of quantitative software into the screening process will impose modifications to workflow in imaging practice and will probably result in the expansion of trained allied personnel who can oversee software analysis before formal radiologist review.

The implications of lung cancer screening in the primary-care setting are substantial. Primary-care providers will need to be convinced that LDCT can be effective in reducing lung-cancer mortality and that the benefits of LDCT screening outweigh the potential harms of radiation exposure, high false positivity rates, and potential overdiagnosis. The in-
corporation of lung cancer screening adds additional complexity to a busy out-patient clinic, erodes already limited clinical time and resources, and disrupts workflow. The intent of screening and its importance must be communicated unambiguously to patients, screening exams must be scheduled, patients with significant findings on screens must be referred for additional testing, and patients counseled about likely outcomes and their implications. Finally, screening implementation will compete for attention with other validated and less costly health care measures like breast cancer or colon cancer screening, smoking cessation, weight loss, and exercise.

There are formidable challenges to the implementation of lung cancer screening from the community perspective. Successful implementation will require the diffusion of screening across all socioeconomic strata. Community engagement will be an important element of implementation in many cultural settings and requires trust and a successful dialogue in which community members can be informed about the health consequences of smoking, lung-cancer risk, and the balance of benefits versus risks of early detection, while also educating the medical profession regarding community priorities. The diffusion of screening and preventive services is particularly important in underserved and minority populations because these communities are disproportionately adversely affected by lung cancer; they are commonly diagnosed at advanced stages, less commonly undergo surgical resections, and, in particular, black men have a lower overall survival from lung cancer. If lung-cancer screening is to be equitably administered to all individuals at risk, the following barriers must be addressed: lack of awareness and low prioritization of lung-cancer prevention and early detection; cultural concerns of trust, fatalism, and stigmatization; financial constraints; and geographical barriers to access.

The NLST enrolled only patients at high risk of lung cancer. Although it would be naïve and narrow-minded to not recognize that additional patients, outside of the NLST criteria, may have substantial risk of lung cancer that warrants screening, one must be very cautious in extrapo-
lating the NLST results to other patient populations and recognize the unintended consequences of screening these patients. Second, the NLST centers included only programs with substantial experience and resources in radiology, pulmonary medicine, thoracic surgery, and pathology, along with a disciplined and multidisciplinary approach to nodule management. Ninety-six percent of lung nodules found were ultimately determined to be “false positives,” and 39% of patients had at least one positive result during the study. A highly organized and disciplined approach to management is the only way to mitigate the potential harms caused to patients by excessive and unnecessary testing and the morbidity of invasive procedures. The margin between net benefit and net harm in lung-cancer screening is likely small, and the benefit to patients could easily be lost if a higher percentage of the patients with false positive findings undergo unnecessary work-up and invasive testing. Successful implementation of lung-cancer screening will require the following: (1) pragmatic and thoughtful guidelines that define patients eligible for screening (not limited to NLST criteria yet reasonably narrow in scope); (2) experienced radiologists to interpret screening studies and minimize false positives; (3) a protocolized approach for the management of screen detected nodules; (4) diagnostic and therapeutic surgical procedures performed by board-certified thoracic surgeons in order to optimize staging and minimize morbidity; and (5) experienced multidisciplinary oncology management with thoracic surgery, medical, and radiation oncology to optimize oncology treatment and outcomes.

Guideline Development

The development of lung-cancer screening guidelines is underway, with the first being published by the National Comprehensive Cancer Network (NCCN) in October 2011.29 The NCCN has a strong history and experience in the development of cancer guidelines. The group assembled a panel of 26 professionals, representing thoracic surgery, radiology, pulmonary medicine, medical oncology, epidemiology, pathology, internal medicine, and patient advocacy, and worked together to produce the first lung cancer screening guidelines developed after the NLST. Most notable in the NCCN guidelines is the extrapolation of high-risk patients beyond the inclusion criteria of the NLST, to include patients 50 to 54 years (NLST included only 55 to 74 years), and patients with ≥ 20 pack per year smoking history (NLST required ≥ 30 pack-years) if the patient had another lung-cancer risk factor as well (chronic obstructive pulmonary disease, pulmonary fibrosis, radon or occupational exposure, cancer history, or family history). Another extrapolation was to recommend that screening continue annually until the individual reached 74 years. The NCCN also recommended a highly protocolized approach to the follow-up, work-up, and invasive testing of positive findings, similar to those recommended by the Fleischner Society24 and others.

The biggest challenge in lung-cancer screening is the thoughtful management of screen-detected nodules, the majority of which are benign. There are several variations on the management of screen-detected lung nodules, proposed by the Fleischner Society,24 the International Early Lung Cancer Action Program (I-ELCAP),30 the NLST,1 the NELSON Trial,23 and specific recommendations regarding nonsolid nodules by Godoy and colleagues.31 The NCCN Lung Screening Panel has amalgamated these recommendations into a pragmatic algorithm for nodule management (Fig. 1 and Fig. 2).29 The NCCN recommendations are less aggressive than the I-ELCAP for the work-up of baseline, new solid, and part solid nodules ≤ 6 mm. The NCCN recommendations are also slightly different in recommending a contrast enhanced CT or positron emission tomography (PET) in the evaluation of solid or part solid nodules > 8 mm. Finally, the NCCN defined nodule growth as either an increase in the mean diameter of 2 mm or more for nodules ≤ 15 mm or in the solid portion of a part-solid nodule, or an increase of 15% or more in the mean diameter for nodules > 15 mm. This definition of nodule growth is simplified compared with I-ELCAP and should result in fewer false positive results than seen in the NLST. Of note, surveys of compliance with the Fleischner Society guidelines have shown only 35% to 60% compliance by members of the Radiological Society of North America,32 and 27% compliance by members of the Society of Thoracic Radiology,33 with an overall trend toward over-management. It will be important for the successful application of screening programs to assure an algorithmic and disciplined approach to nodule work-up and follow-up in order to minimize the serious potential harms from excessive and invasive testing in these patients undergoing screening.

Once a nodule has been identified, the involvement of an experienced thoracic surgeon will help the multidisciplinary team refine a strategy for further work-up, including biopsy and/or resection. The Lung Cancer Early Detection and Prevention Clinic at the University of Washington incorporates a “Nodule Board,” consisting of specialists from thoracic radiology, pulmonary medicine, and thoracic surgery. This group reviews clinical details and imaging and develops a management plan based on a treatment algorithm and informed by the combined expertise of the involved specialists. The Non–Small Cell Lung Cancer Panel of the NCCN now recommends assessment and management of presumed or proven lung cancer by “board certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.”34 This recommendation is based on the data that as much as 50% of lung cancer surgery in the United States continues to be performed by general surgeons and that surgical outcomes (morbidity and mortality), as well as oncology outcomes (correct staging, extent of resection, and cancer survival) are better when performed by specialists in thoracic surgery.35,96 There are multiple potential adverse consequences of nonspecialist surgery, which are even more profound for recipients of lung-cancer screening: unnecessary surgery in cases where follow-up or other diagnostic testing may have been preferred, inadequate staging before and/or during lung cancer surgery, underutilization of minimally invasive surgery for both diagnostic and resection procedures, and a lack of advanced techniques (segmentectomy or sleeve resection) to minimize the extent of pulmonary resection. Specialist thoracic surgeons, working with a multidisciplinary lung cancer team, are best equipped to help maximize the benefit of early detection. They are an important part of avoiding the adverse consequences of unnecessary procedures or substandard cancer outcomes that potentially could result in more harm than good from lung-cancer screening programs applied without adherence to guidelines and necessary professional expertise.
Opportunities

There are major opportunities to be gained in the process of screening implementation. The NLST successfully addressed the critical endpoint of differential lung cancer mortality, and secondary analyses will inform the cost-effectiveness of LDCT in older, heavy smokers. However, broad-scale implementation of LDCT screening is predicated on several variables that the NLST does not directly address and for which further research is crucial. Among these are considerations of the optimal risk profile of those who are screened, and how risk profiles might be used to guide diagnostic strategies.

Morphologic features of indeterminate lung nodules on CT have been studied as potential predictors of lung cancer. Most analyses have relied on subjective visual assessment of nodule features such as: size (diameter), consistency (ground glass, part-solid, or solid), border definition, and internal features, such as reticulation, air bronchograms and bubble-like lucencies.\(^{37}\) Quantitative analysis of lung nodules using CAD seeks to characterize nodules by mathematical feature descriptors. We are at the cusp of validating analytic software that can reproducibly characterize lung nodules across a range of nodule types.\(^{38,39}\) Such nodule characterization could become standard in the diagnostic stratification of individuals with indeterminate nodules.

Between 80% and 90% of lung cancers occur in tobacco smokers, yet only 10% to 15% of chronic smokers develop lung cancer. Prospective studies have also shown that approximately 25% of smokers develop COPD as defined by spirometry, whereas 50% to 80% of patients with lung cancer have COPD.\(^{40,41}\) Relative to smokers with normal lung function, those with COPD have up to a six-fold increased risk of lung cancer, making COPD by far the greatest risk factor for lung cancer in ever smokers.\(^{41}\) These observations suggest an inherently greater risk of lung cancer among smokers with COPD than smokers with normal lung function. Although COPD and lung cancer have in common smoking exposure, several lines of evidence now support underlying shared genetic susceptibility that acts in
concern with the shared risk of smoking-related genetic and epigenetic effects. Genome-association studies have identified several heritable susceptibility or protective loci thought to affect both COPD and lung cancer development: single nucleotide polymorphisms on loci 15q25 that regulate cholinergic nicotine receptors (CHRNA3/5); several haplotypes involved in the xenobiotic metabolism of tobacco lung carcinogens, and; genes involved in cell-cycle control, apoptosis, airway inflammation, and repair.42,43

Emphysema has recently been found to be associated with lung cancer, independent of airflow obstruction on spirometry. Emphysema can be directly quantified on LDCT with high reproducibility, and commercial software is also available that can objectively quantify the severity of smoking-related airway remodeling.44 In patients with indeterminate nodules, such characterization could factor into diagnostic algorithms and may ultimately inform the determination of screening frequency at the individual patient level.

Finally, the peripheral blood serves as a repository of lung cancer-associated cytokines, soluble proteins, and microRNAs that derive from the tumor microenvironment and that exhibit molecular signatures similar to those in tumor tissues.45,46 Similarly, samples of airway epithelium obtained through bronchoscopy, sputum expectoration, or nasal cellular brushings express aberrant methylation and microRNA patterns observed in lung cancers.47,48 If validated, these lung cancer-specific molecular signatures from easily accessible tissues will enable their translation into clinical practice and will substantially alter how we define lung-cancer risk and screening in the future. At 15 of the NLST centers, sponsored by the American College of Radiology Imaging Network, participants volunteered to provide serial blood, sputum, and urine specimens. Lung cancer and other tissue specimens were collected across the trial and used to construct tissue-microarrays. These specimens, when combined with the voluminous data from the study, may be useful in enhancing this molecular-signature research. The biospecimens are available to the research community through a peer-reviewed process.49

As we begin to more systematically define lung-cancer risk through combinations of clinical, phenotypic, and molecular profiling, we will be better positioned to distinguish between individuals who have lung cancer versus no cancer. Such discrimination can significantly lower the harms of screening by reducing unnecessary interventions, minimizing anxiety, and lowering costs while promoting early diagnosis and intervention. Finally, the integration of biologic and imaging-based biomarkers to define risk provides significant opportunity to stimulate the motivational tension to stop smoking, which is most important in the prevention of lung cancer and all smoking-related diseases. The goal is to bring this epidemic of smoking-related disorders to an end.

### Authors’ Disclosures of Potential Conflicts of Interest

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*No relevant relationships to disclose.

### REFERENCES


