After the publication of the NLST (National Lung Screening Trial) results, physicians will be faced with whether to begin ordering low-dose computed tomography (LDCT) of the chest to screen for lung cancer in patients with a history of tobacco use. Despite the encouraging reduction in deaths observed by using LDCT in the NLST study population, recommending adoption of lung cancer screening in general practice is premature.

Lessons learned from prostate and breast cancer screening should remind us that the reductions in deaths expected with screening are unfortunately not as readily achievable as initially believed. Furthermore, the potential harms of false-positive findings on chest computed tomography are very real. The morbidity and even mortality associated with invasive diagnostic testing and surgical resection due to false- and true-positive findings on computed tomography are likely to increase when the approach taken in the NLST is applied in non-specialty care settings and among the population at highest risk, namely, those with smoking-related comorbid conditions. Although the NLST results are perhaps encouraging, they do not tell us enough that we can be sure that patients who undergo LDCT in an attempt to find early-stage lung cancer will have more benefit than harm.

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A 62-year-old woman with a history of well-controlled hypertension presents for routine follow-up. She is asymptomatic and feels well. She has jogged 3 miles 3 times weekly for years, with no recent change in exercise tolerance. She has a 30-pack-year history of cigarette smoking but stopped 10 years ago. There is no personal or family history of cancer.

Physical examination is normal. She read a recent study that found a benefit to screening for lung cancer with computed tomography and inquires whether you think screening is appropriate for her. What should you recommend?

The recently published NLST (National Lung Screening Trial) is the largest (53 454 participants) and most expensive (>$200 million) randomized trial of a single cancer screening test in the history of U.S. medicine (1). The study enrolled current and former heavy smokers aged 55 to 74 years and randomly assigned them to chest radiography or low-dose computed tomography (LDCT) of the chest yearly for 3 years and followed them for another 3.5 years. It showed a 20% reduction in lung cancer-specific deaths in the LDCT group, with 247 deaths due to lung cancer per 100 000 person-years in the LDCT group and 309 deaths per 100 000 person-years in the chest radiography group.

There will be a major push for primary care providers to incorporate screening for lung cancer by using LDCT into their practices. It seems like a straightforward recommendation given the burden of lung cancer in the United States (150 000 deaths each year), the high proportion of patients presenting with advanced disease, and the low 5-year survivorship (16%) that has not changed much over the past 30 years. Persons will draw analogies between the lack of a screening program for lung cancer and the presence of active screening programs for prostate and breast cancers, in which proponents of screening will cite the much higher 5-year cancer survivorship in screened persons.

The general public supports screening. In 1 study, 87% of persons interviewed believe that screening is almost always a good idea; 75% were sure that screening saved lives most or all of the time; a substantial proportion believed that an 80-year-old person choosing not to be screened was irresponsible; and nearly 75% would prefer total-body CT to $1000 in cash (2). Unfortunately, the story is more complicated than what opinion polls suggest. After peeling away the rhetoric, we see that the science of screening is far from exact.

Given the tantalizing data from this large study, the immediate public reaction will be to screen as many persons as quickly as possible. The precedent for premature, broad-based recommendations for other types of cancer has been a push to screen and a belief in the benefits of screening without a complete understanding of the risks. We have learned important lessons that can be applied to lung cancer screening.

Regarding benefit, after decades of study, controversy still remains over whether screening substantially reduces cancer-specific deaths. In 2009, investigators from the PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) reported that 7 years of follow-up of more than 76 000 randomly assigned participants from the prostate group of the study did not detect a reduction in deaths from prostate cancer in participants screened with prostate-specific antigen testing (3). As many as 60% of cases of prostate cancer detected by prostate-specific antigen screening are overdiagnosed, meaning that a patient would die with, rather than of, prostate cancer (4). This concept is critical, because management of an overdiagnosed case of cancer results in undergoing unnecessary and perhaps morbid procedures (for example, prostatectomy, which is associated with a 10% risk for incontinence and a 20% risk for erectile dysfunction), with no hope of achieving any benefit in longevity from the screening.

Even the magnitude of the benefit of breast cancer screening has been questioned (5–7). A recent observational study of screening mammography in Norway estimated that despite an absolute benefit of 1 death from...
breast cancer avoided for every 2500 women screened over a 10-year period, 1000 women would have had at least 1 false-positive result requiring further evaluation. Even if one believes that these studies are overly pessimistic, no data conclusively support major reductions in cancer-specific deaths from prostate or breast cancer screening. Overdiagnosis and the evaluation and management of false-positive results combined with lower-than-expected reductions in death cannot be trivialized.

The NLST has not yet sufficiently evaluated the potential harms of CT screening. One reason is that generalizing the results of the NLST to community practices may be problematic. Participants in the NLST were enrolled in urban, tertiary care hospitals with expertise in all aspects of cancer care. Low-dose computed tomography studies were interpreted by dedicated chest radiologists with expertise in characterizing nodules and providing appropriate recommendations for follow-up. As a result, few patients required invasive testing and radiographic follow-up was sufficient for many patients.

However, community radiologists without expertise in evaluating lung nodules may feel compelled to advise invasive testing for a screening-detected nodule. Of the 26 309 persons randomly assigned to chest CT screening in the NLST, 7191 (27%) had an abnormal finding. Most scans (96.4%) yielded false-positive results that were followed by serial radiography. Variation in how nodules are managed could lead to a substantial increase in transthoracic needle aspiration of lung nodules, unnecessary surgery, additional morbidity, and even mortality for some persons who never had cancer to begin with. In the NLST, 16 patients died within 60 days of undergoing an invasive test to evaluate an abnormality detected during screening, and 6 of those patients did not have lung cancer.

To illustrate the potential consequences of this point, Wiener and colleagues (8) recently explored the morbidity of transthoracic needle biopsy in 15 865 patients from 4 regions of the United States. In that cohort, the rate of hemorrhage was 1%, with 18% requiring blood transfusion. The rate of pneumothorax was 15%, with 6.6% requiring chest tube placement. Compared with those without complications, patients who had hemorrhage or pneumothorax requiring chest tube placement had longer stays and were more likely to develop respiratory failure that required mechanical ventilation. Furthermore, smokers, the population that will be targeted for screening, were more likely to have complications than nonsmokers.

Wiener and colleagues’ study also demonstrated a more than 2-fold variation among geographic regions in use of CT-guided biopsy, ranging from 14.7 to 36.2 per 100 000 adults. This variation suggests a lack of consensus among clinicians on how to manage solitary pulmonary nodules—variation that may not have been present in the NLST and could substantially increase the morbidity associated with population-based screening. Furthermore, although the NLST was designed to allow patients with abnormal findings to be managed in the community, follow-up for an abnormal finding also may have occurred in the same institutions where the patient was screened and under the direct care of persons with dedicated expertise in lung cancer.

Previous studies have shown that, among all stages of lung cancer, centers that perform a high volume of lung cancer surgery have nearly twice the 5-year survivorship of low-volume centers (9). This factor may be one reason that the mortality rate for lung cancer surgery in the NLST is so low (1%) compared with national data, which suggest a rate between 3% and 5%. A small increase in surgical deaths could vastly decrease the beneficial effect of screening.

Finally, the NLST enrolled a younger, healthier population: Only 8% of the study participants were in the oldest age category (70 to 74 years), which makes generalizing the study results to that age group suspect. This point cannot be overstated—as the average age of diagnosis of lung cancer is 70 years—and should make clinicians wary of applying the mortality statistics for surgery to persons in the oldest age group.

Lost among the questions about lung cancer screening is that a mass screening program for lung cancer advocated by the U.S. Preventive Services Task Force would be the first screening program to target persons with a poor health habit—namely, cigarette smoking—whose attitudes and beliefs about screening differ from those of the general public (10). In 1 study assessing beliefs about lung cancer screening, smokers reported that they undergo recommended screening for other types of cancer less often than their nonsmoking counterparts, have less comprehension of what effective screening means, were less likely to be able to identify a medical home (an attribute shown in other cancer screening programs to be a significant barrier to screening), and were less likely to be willing to pay for lung cancer screening (10).

Couple these findings with the fact that smokers constitute a portion of the population that has traditionally had poor access to screening services (11). Twenty percent of the U.S. adult population (43 million persons) currently smokes, and that percentage has not changed in 5 years. Hidden within that statistic is that 30% of persons without a high school degree, but only 6% of persons with a graduate degree, are smokers. Similarly, 31% of persons below the poverty line smoke compared with 20% of persons at or above the poverty line.

These groups have always used screening services substantially less than the rest of the population, but we should not give up: Quite the opposite, we must learn how to better reach and serve these persons at high risk for lung cancer, but how best to do so—smoking cessation, screening, or other preventive health programs—is unclear. It is one thing to fill a trial with motivated study participants and quite another to reach the 8 million Americans who meet the criteria of the persons studied in the NLST. To
implement an effective screening program, the public health community and physicians will need new and innovative approaches to reach the target population.

Policymakers will and should struggle with whether payment for screening services should supersede funding for programs that prevent initiation of smoking, fund smoking cessation programs and nicotine-replacement products, and research therapies to treat lung cancer. Cost-efficacy analyses from the NLST are under way for screening by using LDCT. Even if this technology were deemed cost-effective, it is hard to imagine that the cost saved per quality-adjusted life-year would be nearly as low as the less than $5000 per quality-adjusted life-year estimated to implement the clinical practice guidelines on smoking cessation from the Agency for Healthcare Research and Quality (12). Some persons have suggested that enrollment in smoking cessation programs at the time of screening (a teachable moment) may improve cessation rates. The only randomized study to assess this question (13) found no difference in smoking cessation rates between screened and nonscreened groups.

In summary, results from the NLST show that screening for lung cancer can save lives—a finding that should be neither minimized nor overstated. We have too much experience in screening for other types of cancer to ignore the warning signs of overly optimistic estimates of benefit and underappreciation of risk. Now, decades after the initial hype of prostate and breast cancer screening, little has changed in cancer-specific deaths from these diseases, despite “improvements” in 5-year survivorship statistics that may represent nothing more than the effect of overdiagnosis (14).

Extending screening to persons outside of the inclusion criteria of the NLST is not appropriate at this time. Representatives of most stakeholders in the cancer community are collectively assembling guidelines for appropriate screening and management of screening-detected abnormalities. Having a uniform, accepted approach to screening should improve the chances of saving lives from lung cancer without introducing harm to our patients. Patients offered screening for lung cancer must be given a truly informed consent, which involves physicians pointing out the risks as well as the benefits of screening before testing.

The patient presented in the scenario has already made all of the right choices. She has stopped smoking, which substantially reduces her risk for lung and cardiovascular disease, and has begun a regular exercise program. Her best bet may be to continue to run—as far and as fast away from a CT scanner as she can get.

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