Computed Tomography Screening for Lung Cancer

Phillip M. Boiselle, MD, Discussant

**Dr Tess:** Ms L is a 64-year-old woman considering screening for lung cancer. She began smoking 1 to 2 cigarettes a day at age 12 years. She eventually accumulated 30 pack-years of smoking before successfully quitting when her father was diagnosed as having lung cancer in 1990. In 2003, she enrolled in the National Lung Screening Trial (NLST) and was randomized into the computed tomography (CT) screening group of the study. Her baseline CT scan in 2003 showed numerous bilateral micronodules (<4 mm) that did not meet study criteria for a positive screening result (FIGURE 1). As part of the trial, she underwent 2 annual screening CT scans, which showed no change in the micronodules and no new findings to suggest the presence of lung cancer. Now that the trial has concluded, she is deciding whether to electively undergo continued CT screening.

Her medical history includes hypertension, restless legs syndrome, bilateral knee replacements, and anxiety. She is employed as a real estate agent and has health insurance. She has no history of drug or alcohol abuse and reports no history of occupational exposures. Her family history is remarkable for a mother who died of emphysema, a father who died of lung cancer, and a brother who died of a gastrointestinal stromal tumor. Her medications include hydrochlorothiazide, oxycodone, and escitalopram. On a recent physical examination, her blood pressure was 120/78 mm Hg and her pulse was 68/min. Her height is 5 ft 4 in and her weight is 165 lb. The remainder of her physical examination results were normal.

**Ms L: Her View**

My father was diagnosed with lung cancer on June 26, 1990, and he passed away 6 weeks later on August 15, 1990. It happened so fast, and I made up my mind that he was not going to die for nothing. So I quit smoking and I made my husband quit. I felt that if his cancer had been diagnosed earlier, then he may not have died. So, I volunteered for the screening study because I thought it could help in understanding the disease.

The screening test the first year indicated that I had nodules, but they were very small, and consistently for the 2 years of smoking before successfully quitting when her father was diagnosed as having lung cancer in 1990. In 2003, she enrolled in the National Lung Screening Trial (NLST) and was randomized into the computed tomography (CT) screening group of the study. Her baseline CT scan in 2003 showed numerous bilateral micronodules (<4 mm) that did not meet study criteria for a positive screening result (FIGURE 1). As part of the trial, she underwent 2 annual screening CT scans, which showed no change in the micronodules and no new findings to suggest the presence of lung cancer. Now that the trial has concluded, she is deciding whether to electively undergo continued CT screening.

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**Importance** Low-dose computed tomography (CT) screening was shown to reduce lung cancer–specific mortality in a large randomized trial of a high-risk population. The decision to pursue CT screening for lung cancer is a timely question raised by individuals at risk of lung cancer and by their health care practitioners.

**Objectives** To discuss the evidence for use of chest x-rays and low-dose CT in screening for lung cancer; to describe potential benefits, harms, and uncertainties of CT screening; and to review current guidelines for CT screening.

**Evidence Review** MEDLINE and the Cochrane Library were searched from 1984 to 2012. Additional citations were obtained from lists of references from select research and review articles on this topic. Evidence was graded using the American Hospital Association level of evidence guidelines.

**Findings** Low-dose CT screening has been associated with a 20% reduction in lung cancer mortality in a large randomized controlled trial (National Lung Screening Trial [NLST]) of a high-risk population. Mortality data have not yet been reported for 5 other randomized controlled trials, and the sample sizes were too small to detect a meaningful difference in 2 other completed trials. A major risk of CT screening is a high false-positive rate, with associated risks and costs associated with follow-up CT scans and the potential for more invasive diagnostic procedures. Published guidelines for screening indicate a consensus that screening may be indicated for individuals who meet entry criteria for the NLST, but some guidelines expand their recommendations for screening beyond these criteria.

**Conclusions and Relevance** Individuals at high risk of lung cancer who meet the criteria for CT screening in published guidelines should participate in an informed and shared decision-making process by discussing the potential benefits, harms, and uncertainties of screening with their physicians.
years after that there was no change in them. Since the study has been over, I have been thinking about going back and having another screening scan done. As a diagnostic tool, I thought it was very good. It offers peace of mind. I am not anxious at all about it. No matter what the diagnosis is, early is much better than late.

I think there are probably some downsides. There are hoops to go through because of society and the insurance companies. I have 2 daughters who work in the health care field, so I know the cost is exorbitant. My insurance won’t pay for it. I am in a position where I can pay. It is not okay for other people who can’t afford it. It is a double-edged sword. You want to know if you have cancer at an early stage because there is more hope, and yet there is a cost to it. My question for my primary care doctor and for Dr Boiselle is, do they think it prudent for me to go forward and have another screening done?

**AT THE CROSSROADS: QUESTIONS FOR DR BOISELLE**

What are the risk factors for lung cancer? What is the evidence for use of chest x-ray in the screening for lung cancer? What is the evidence for use of CT in the screening for lung cancer? What are the associated risks and costs? What do current guidelines recommend? What do you recommend for Ms L?

**DR BOISELLE: Ms L is a healthy woman with 2 major risk factors for lung cancer—a history of cigarette smoking and a positive family history of lung cancer. She has undergone low-dose CT screening in the past as part of a randomized control trial, and her CT scans did not show evidence of lung cancer. Her decision as to whether to pursue further lung cancer screening with CT is a timely question that is being raised by an increasing number of individuals at risk of lung cancer and by their health care practitioners.**

**LUNG CANCER PREVALENCE AND RISK FACTORS**

Lung cancer remains the leading cause of cancer deaths in the United States and the world. In 2012, it was estimated that there were more than 225,000 new cases of lung cancer and more than 160,000 deaths due to lung cancer in the United States. The number of estimated lung cancer deaths for 2012 surpassed the combined total of estimated deaths from cancers of the breast, prostate, and colon.

Although these numbers are relatively bleak, longitudinal US cancer statistics show some progress. Between 2004 and 2008, the overall US cancer death rate declined by 2%. Among men, 40% of this reduction can be attributed to the decline in lung cancer mortality related to smoking reduction over the last 50 years. A decline in lung cancer mortality among women has also been observed, but this trend began more than a decade later among women than in men. This lag reflects historical differences in tobacco use, with cigarette smoking peaking among women 2 decades later than in men.

The positive relationship between smoking trends and lung cancer deaths relates to the fact that tobacco use is by far the most important risk factor for lung cancer. It is estimated that at least 85% of all lung cancers can be attributed to cigarette smoking. Tobacco use remains the major modifiable risk factor for lung cancer, with an associated 20-fold relative increase in risk of lung cancer. It is estimated that there are 94 million current and former smokers in the United States alone. In fact, 45 million people (approximately 20% of the US population) are thought to be active smokers. Prolonged smoking cessation markedly reduces the future rate of increase in risk of developing lung cancer over time; however, the level of risk never declines to that of a lifetime nonsmoker. For example, a study from the United Kingdom showed that the cumulative risk of lung cancer by age 75 years among continuing women smokers was 9.5% compared with 5.3% for women who stopped smoking at age 60 years and 2.2% among those who stopped at age 50 years. Thus, the most important advice for current smokers is to stop smoking.

Other risk factors for lung cancer include occupational exposures, residential radon exposure, personal cancer history (particularly smoking-related cancers such as head and neck cancer), family history of lung cancer, and chronic lung diseases, including chronic obstructive pulmonary disease and chronic interstitial lung disease (such as idiopathic pulmonary fibrosis).
shown a benefit in reducing lung cancer mortality.9-16 For example, the Mayo Lung Project included 10,933 men who were aged 45 years or older and smoked more than 1 pack of cigarettes daily who were randomized to 1 of 2 study groups.10,11 The control group was assigned to yearly chest radiograph and sputum cytology, which was the standard of care at that time. The study group was assigned to receive the same tests more frequently (every 4 months). Compared with the controls, the study group had more cancers detected (206 vs 160), a higher resectability rate (46% vs 32%), and a 5-year survival benefit. However, the death rates for the 2 groups were statistically similar (3.2 per 1000 person-years vs 3.0 per 1000 person-years), and there was no mortality benefit either at the end of the trial or 15 years after completion of the study.10,11

Reexamination of the data from the Mayo Lung Project and other similar trials has raised issues regarding their methods and low power.17 Because of the concern that a positive effect of chest radiographic screening may have been missed because of the small size of the study populations in prior trials, this topic was reexamined in the 1990s in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.18 In this population-based study of men and women aged 55 to 74 years, 154,901 participants were randomly assigned to receive either annual chest radiographs for 4 years or standard of care (no chest radiograph) and were followed up for approximately 12 years. Participants in the 2 study groups were similar in terms of smoking status, sex distribution, and age. At the end of the study, the 2 groups demonstrated similar cumulative lung cancer incidences (20.1 vs 19.2 per 10,000 person-years), similar cumulative lung cancer mortality (n=1213 vs n=1230), and similar stage and histologic findings of detected lung cancers.

Relevant to Ms L, the PLCO study also included an ancillary analysis that compared annual chest radiographs with standard of care in a subset of 15,183 participants who met entry criteria for the NLST (Box 1). Cumulative lung cancer incidence and mortality rates were similar between the 2 groups in this ancillary analysis, showing no benefit of chest radiographic screening in this high-risk cohort.18

The results of the PLCO trial, which was sufficiently powered to detect a 10% reduction in lung cancer mortality in the intervention group, provide high-quality evidence that screening with an annual chest radiograph for 4 years does not reduce lung cancer mortality. Thus, there is no role for chest radiography in screening for lung cancer.

**SCREENING FOR LUNG CANCER WITH LOW-DOSE CT**

In the 1990s, researchers in the United States and Japan independently began looking at low-dose CT as a screening tool for lung cancer. These studies were designed as single-group studies in which low-dose CT was compared with chest radiography in the same cohort.19-21 Despite differences in study entry criteria, all 3 single-group cohort studies found a strikingly high percentage (84%-93%) of CT screening-detected stage 1 lung cancers (Table I) among all screening-detected cancers and a consistent superiority of CT over chest radiography in the detection of cancers.19-21

Because these studies were not designed as randomized clinical trials, they were unable to assess the influence of CT screening on lung cancer mortality, the gold-standard measure of a screening test. However, these and other early studies22-24 effectively placed CT screening on the map and laid the groundwork for the NLST, the largest randomized controlled lung cancer screening trial ever performed.25 This study was designed to answer the question of whether lung cancer screening using low-dose helical CT can reduce lung cancer–specific mortality relative to screening with chest radiographs in a high-risk cohort.

As a participant in the NLST, Ms L was randomized to the CT group of the trial and underwent low-dose CT at baseline and annually thereafter for 4 years. Particularly relevant to Ms L’s experience in the study, the NLST defined a positive screening study result as a nodule measuring at least 4 mm in diameter.25,26 This criterion was based on a growing body of evidence that suggested that nodules less than 4 mm in diameter are very likely benign, even when detected in a patient at high risk for lung cancer.27,28 Based on this criterion, Ms L’s scans were interpreted as negative for lung cancer.

<table>
<thead>
<tr>
<th><strong>Box 1. Entry Criteria for National Lung Screening Trial</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> 55-74 years</td>
</tr>
<tr>
<td><strong>Smoking history</strong> ≥30 Pack-years*</td>
</tr>
<tr>
<td>Former smokers must have quit within past 15 years</td>
</tr>
<tr>
<td><strong>Exclusions</strong></td>
</tr>
<tr>
<td>Previous lung cancer</td>
</tr>
<tr>
<td>Other prior cancer (except nonmelanoma skin cancer) in past 5 years</td>
</tr>
<tr>
<td>Chest computed tomography within past 18 months</td>
</tr>
<tr>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Unexplained weight loss &gt;15 lb in past year</td>
</tr>
<tr>
<td>Metallic implants or devices in chest or back</td>
</tr>
<tr>
<td>Requirement for home oxygen supplementation</td>
</tr>
<tr>
<td>Pneumonia or other acute respiratory tract infection treated with antibiotics in past 12 weeks</td>
</tr>
</tbody>
</table>

*Pack-years refers to number of cigarette packs smoked per day (20 cigarettes per pack) multiplied by the number of years of smoking.
The NLST results were officially announced in 2010 and published in 2011.26 A total of 1060 lung cancers were diagnosed in the CT group compared with 941 in the radiography group. There were nearly twice as many very early-stage (1A) cancers detected in the CT group (40%) compared with the chest radiography group (21%).26 It should be noted that the percentage of stage 1A and 1B lung cancers detected by CT in the NLST was substantially lower than that reported in the early lung screening trials highlighted in Table 1 (50% compared with 85%-93%).

With regard to lung cancer–specific mortality, among participants who underwent at least 1 screening test, there were 346 lung cancer deaths among 26,455 participants (1.3%) in the CT group compared with 425 deaths among 26,232 participants (1.6%) in the radiography group.26 The overall rates of lung cancer death were 247 and 309 deaths per 100,000 participants in the CT and radiography groups, respectively. This represents a 20% reduction in lung cancer mortality in the CT screening group (95% CI, 6.8%-26.7%; P=.004) and a number needed to screen of 320 patients to prevent 1 lung cancer death.26

What are the implications of the NLST? First, this study has shown that in selected individuals at high risk of lung cancer, CT screening reduces lung cancer mortality by 20%. Second, it has demonstrated that CT screening is relatively safe. However, before public policy decisions about widespread screening can be addressed, several important questions remain to be answered. First, how does CT screening influence utilization of medical resources? Second, what is the added monetary cost due to CT screening and what are the quality-adjusted life-years gained by screening? Third, how does the process of CT screening influence participants’ quality of life and smoking habits? These questions will be addressed by forthcoming publications from the NLST.

There are also several outstanding questions that the NLST was not designed to directly answer. These questions include (1) Will other populations at risk of lung cancer benefit from CT screening? (2) Will less frequent screening regimens be equally effective as annual screening? (3) How long should screening continue? and (4) Will the NLST results be reproducible in community hospital settings?26 Some of these questions will be addressed by computer modeling of the NLST data27 and others will be addressed by pooling of results of several ongoing screening trials in Europe.28-34 Table 2 provides an overview of enrollment, entry criteria, and available published mortality data for completed and ongoing randomized control trials of low-dose CT screening for lung cancer.

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Table 1. Early Low-Dose Computed Tomography Screening Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients</th>
<th>Enrollment Criteria</th>
<th>No. of Detected Lung Cancers</th>
<th>Lung Cancer Prevalence</th>
<th>Stage I Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaneko et al,19 1996</td>
<td>1369</td>
<td>&gt;20 Pack-years of smoking Aged &gt;50 y</td>
<td>15</td>
<td>15/1369 (1)</td>
<td>14/15 (93)</td>
</tr>
<tr>
<td>Sone et al,20 1998</td>
<td>5483</td>
<td>Smokers and nonsmokers enrolled Aged 40-74 y</td>
<td>19</td>
<td>19/5483 (0.5)</td>
<td>16/19 (84)</td>
</tr>
<tr>
<td>Herschke et al,21 1999</td>
<td>1000</td>
<td>&gt;10 Pack-years of smoking Aged &gt;60 y</td>
<td>27</td>
<td>27/1000 (2.7)</td>
<td>23/27 (85)</td>
</tr>
</tbody>
</table>

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Table 2. Randomized Controlled Trials of Computed Tomography Screening for Lung Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Computed Tomography</th>
<th>Control</th>
<th>Age Range, y</th>
<th>Smoking Pack-Yearsb</th>
<th>Years Since Quitting Smoking</th>
<th>Mortality Reduction, %c</th>
</tr>
</thead>
<tbody>
<tr>
<td>DANTE</td>
<td>1276</td>
<td>1196</td>
<td>60-74</td>
<td>≥20</td>
<td>&lt;10</td>
<td>NR</td>
</tr>
<tr>
<td>Dépiscan</td>
<td>385</td>
<td>380</td>
<td>47-76</td>
<td>≥15</td>
<td>&lt;15</td>
<td>NR</td>
</tr>
<tr>
<td>DLCST</td>
<td>2052</td>
<td>2052</td>
<td>50-70</td>
<td>≥20</td>
<td>&lt;10</td>
<td>NSDd</td>
</tr>
<tr>
<td>DVAFS</td>
<td>92</td>
<td>98</td>
<td>50-80</td>
<td>≥30</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>ITALUNG</td>
<td>1613</td>
<td>1593</td>
<td>55-69</td>
<td>≥20</td>
<td>&lt;10</td>
<td>NR</td>
</tr>
<tr>
<td>LSS</td>
<td>1660</td>
<td>1658</td>
<td>55-74</td>
<td>≥30</td>
<td>&lt;10</td>
<td>NR</td>
</tr>
<tr>
<td>NELSON</td>
<td>7907</td>
<td>7915</td>
<td>50-75</td>
<td>&gt;15</td>
<td>≤10</td>
<td>NR</td>
</tr>
<tr>
<td>NLST</td>
<td>26722</td>
<td>26732</td>
<td>55-74</td>
<td>≥30</td>
<td>≤15</td>
<td>20</td>
</tr>
</tbody>
</table>

Abbreviations: DANTE, Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST, Danish Lung Cancer Screening Trial; DVAFS, Denver Veterans Administration Feasibility Study; LSS, Lung Screening Study; NELSON, Dutch Belgian Randomized Lung Cancer Screening Trial; NLST, National Lung Screening Trial; NR, not reported; NSD, no significant difference.

aData are from Bach et al.7
bPack-years refers to number of cigarette packs smoked per day (20 cigarettes per pack) multiplied by the number of years of smoking.
cMortality reduction refers to reduction in lung cancer–specific mortality in the computed tomography group compared with the control group.
dAlthough no significant difference in lung cancer mortality was observed between the 2 study groups, the study size and length of follow-up were not sufficient to detect a clinically meaningful reduction in lung cancer mortality.
RISKS AND COSTS OF LOW-DOSE CT SCREENING FOR LUNG CANCER

The risks of low-dose CT screening for lung cancer are summarized in Box 2. First and foremost, a false-positive result (defined as a positive screening study result that was later found to not represent lung cancer) is the most common risk associated with CT screening for lung cancer. As described in detail later in this section, false-positive results are significant because of associated risks and costs associated with follow-up CT scans and the potential for more invasive diagnostic procedures.

In the NLST CT group, almost 40% of participants had at least 1 positive CT result during the study. Notably, more than 96% of the positive test results in the CT group of the NLST were false-positive for lung cancer. Most participants with positive study results were followed up invasively by CT, but a small percentage underwent more invasive diagnostic testing, including percutaneous needle biopsy, and bronchoscopic and surgical procedures (FIGURE 2). It is reassuring that complications related to diagnostic evaluation of positive screening results were uncommon (1.4% in the CT group and 1.6% in the radiography group) and that deaths were rare. Although surgery for benign disease was rare in the NLST, a higher frequency has been reported in other screening studies.

Although Ms L underwent a baseline and 2 annual screening CT scans without a positive screening result, she is still at risk of false-positive results should she undergo additional CT screening. Additionally, there is the possibility that a lung cancer may be missed by CT (false-negative result). Second, anxiety is an important consideration for individuals such as Ms L who are contemplating CT screening. For example, the period of waiting for results of screening studies has been shown to be a source of short-term anxiety for almost half of all low-dose CT screening participants in an ongoing European lung cancer CT screening trial (NELSON). Although the news of a “negative” scan result has the potential to bring relief or peace of mind to patients such as Ms L, indeterminate low-dose CT screening results have been associated with a short-term increase in lung cancer—specific distress in NELSON. In addition to anxiety, false-positive results from a variety of different cancer screening tests have been shown to be associated with depression and changes in the overall perception of one’s health status. Quantification of such psychological costs of CT screening is an important aspect of the NLST design, and this data will be shared in a future publication.

A third potential risk is radiation exposure. When considering this factor, it is important to keep in mind that the exposures associated with CT screening are very low and generally considered safe. For example, the mean effective dose per scan in the NLST was 1.4 mSv, which is less than half of annual background exposure from living in the United States and represents about one-fifth the dose of a diagnostic chest CT scan. Ms L’s cumulative exposure from participation in the NLST is estimated at 4.2 mSv, which is about half the estimated total exposure for all NLST participants (many of whom underwent ≥1 follow-up diagnostic CT or positron emission tomography—CT scans). For patients such as Ms L and others with similar lung cancer risk profiles, the potential benefits of CT screening outweigh the small risk of cancer deaths related to cumulative radiation exposure. However, the risk-benefit ratio is less favorable for persons at very low risk of lung cancer and those of relatively young age.

A fourth concern is the possibility of overdiagnosis, a term that refers to detection of indolent cancers that may never have become symptomatic and would not have been detected outside of a screening program. Because current technology does not allow for accurately distinguishing between cancers that a patient will die of and those that a patient is likely to die with, potentially curable lung cancers detected by screening are treated surgically, with the associated risks and morbidity.

For example, prior chest radiography screening studies for lung cancer have an estimated overdiagnosis rate of approximately 25%. Because the period of follow-up in the NLST was not sufficient to quantify overdiagnosis, further follow-up is needed to determine the magnitude of this issue. With regard to financial costs of CT screening, the Medicare reimbursement rate of $300 for a CT scan has been used as a benchmark rate for low-dose CT screening studies performed on a self-pay basis. The Medicare contract rates vary geographically but are much lower than the out-of-pocket charges for a self-pay diagnostic CT scan performed outside of the screening setting.

The cost of self-pay CT screening is reportedly not a significant barrier to Ms L, but as she notes, it could pose a significant challenge to other patients. Until broad coverage for CT screening is available by insurers and other payers, one of the greatest barriers to implementation of CT screening is the ability to provide it to individuals at risk across all socioeconomic strata.

The cost of the screening CT scan is only a small part of the overall costs related to screening, which has substantial

Box 2. Risks Associated With Low-Dose Computed Tomography Screening

- False-positive and false-negative results
- Anxiety
- Potential unnecessary testing
- Radiation exposure
- Financial costs
- Overdiagnosis

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downstream costs related to workup of positive screening results and treatment-related costs for detected cancers, among other economic factors. To date, estimates of the cost-effectiveness of low-dose CT screening have relied on decision analysis modeling, with varying estimates of costs ranging from less than $50,000 to more than $2,000,000 per quality-adjusted life-year gained.\textsuperscript{42-44} Such variability relates to different assumptions regarding the risk level of the population being screened, adherence to screening, smoking cessation efforts, and other measures.\textsuperscript{42-44} The eagerly awaited NLST cost-effectiveness analysis will provide a more realistic estimate of costs associated with CT screening.

### CURRENT GUIDELINES FOR CT SCREENING FOR LUNG CANCER

In 2011, following the publication of the NLST results, the American Cancer Society (ACS) issued interim guidelines for lung cancer screening, which have recently been published as formal guidelines.\textsuperscript{45} In these guidelines, the ACS recommends that physicians should initiate a discussion about lung cancer screening with patients who meet NLST criteria (Box 1). This discussion should include a review of the potential benefits and harms and current uncertainties about screening. These guidelines also state that CT screening is not recommended at this time for individuals who do not meet the NLST entry criteria. Similar recommendations have recently been put forth in a set of clinical practice guidelines developed by the American College of Chest Physicians (ACCP) and American Society of Clinical Oncology (ASCO) with input from the American Thoracic Society.\textsuperscript{35}

Two sets of practice guidelines expand the recommendations for screening beyond the NLST entry criteria. The first is a wide-ranging set of CT screening guidelines offered by the National Comprehensive Cancer Network (NCCN), a consortium of 21 cancer centers in the United States.\textsuperscript{3} The NCCN recommends CT screening for 2 groups of patients at high risk of lung cancer. The first group is individuals who meet the entry criteria for the NLST. For this

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### Table 3. Computed Tomography Screening Recommendations

<table>
<thead>
<tr>
<th>Organizations</th>
<th>Primary Population for Screening</th>
<th>Other Populations for Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Association for Thoracic Surgery (AATS)</td>
<td>Aged 55-79 y ≥30 Pack-years of smoking</td>
<td>Aged ≥50 y ≥20 Pack-years of smoking Additional risk factor(s)\textsuperscript{a} or Lung cancer survivor ≥5 y</td>
</tr>
<tr>
<td>American College of Chest Physicians (ACCP) and American Society of Clinical Oncology (ASCO)</td>
<td>Aged 55-74 y ≥30 Pack-years of smoking Former smokers must have quit within past 15 y</td>
<td>NR</td>
</tr>
<tr>
<td>American Cancer Society</td>
<td>Aged 55-74 y ≥30 Pack-years of smoking Former smokers must have quit within past 15 y</td>
<td>NA</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network (NCCN)</td>
<td>Aged 55-74 y ≥30 Pack-years of smoking Former smokers must have quit within past 15 y</td>
<td>Aged ≥50 y ≥20 Pack-years of smoking Additional risk factor(s)\textsuperscript{d}</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; NR, not recommended for other populations.

\textsuperscript{a}American Hospital Association (AHA) level of evidence: A, multiple populations evaluated; data derived from multiple randomized trials or meta-analysis; B, limited populations evaluated; data derived from single randomized trial or nonrandomized studies; C, very limited populations evaluated; only consensus opinion of experts, case studies, or standard of care.

\textsuperscript{b}Additional risk factors for lung cancer defined by AATS include chronic obstructive pulmonary disease, environmental and occupational exposures, any prior cancer or thoracic radiation, and genetic or family history.

\textsuperscript{c}Although ACCP and ASCO evaluated more than 1 randomized trial, their recommendations are graded B because they were based on a single randomized trial (other studies were deemed “too small, too preliminary, or too poorly designed to support meaningful conclusions”).\textsuperscript{45}

\textsuperscript{d}Additional risk factors for lung cancer defined by NCCN include cancer history, lung disease history, family history of lung cancer, radon exposure, and occupational exposure.
group, there is uniform NCCN consensus that intervention (CT screening) is appropriate. The second group is individuals aged 50 years or older with at least a 20-pack-year smoking history plus 1 other defined risk factor (cancer history, lung disease history, family history of lung cancer, radon exposure, or occupational exposure). For this group, there is nonuniform NCCN consensus that intervention (CT screening) is appropriate.

The second is a set of guidelines by the American Association of Thoracic Surgeons (AATS). This group has modified the NLST entry criteria by removing the stipulation about duration of smoking cessation from the NLST entry criteria to focus solely on age and overall tobacco exposure, which the group considers to be the primary risk generators. Computed tomography screening guidelines from the AATS and other organizations are summarized in Table 3.

RECOMMENDATIONS FOR MS L

Because of Ms L’s long-standing success at smoking cessation, she no longer meets strict entry criteria for the NLST. Thus, if consideration is given only to clinical practice guidelines that rely solely on NLST entry criteria, such as those issued by the ACS, ACCP, and ASCO, Ms L is no longer considered a candidate for screening.

Notably, because the NLST criteria were not originally designed for the purpose of clinical guidelines, they do not allow for a consideration of the contribution of increased risk based on her advancing age since the time she entered that study. In the future, it is likely that individualized lung cancer risk prediction will allow for a more personalized decision-making approach when weighing the potential benefits and risks of screening.

Currently, however, based on Ms L’s age, cumulative smoking history, and family history of lung cancer, CT screening is still considered an appropriate, albeit less strong, recommendation under the NCCN guidelines. Moreover, her age and cumulative smoking history also qualify her for screening based on guidelines from the AATS.

Given that Ms L meets CT screening criteria for some but not all available guidelines for screening, and in the absence of current recommendations from the US Preventive Services Task Force (USPSTF), I believe that it is appropriate for her to carefully consider CT screening after cautiously weighing the risks and benefits with her primary care physician. In this conversation, it should also be emphasized that the most effective frequency and duration of screening are currently unknown.

If she chooses to undergo screening, she should select a site with experience in CT screening using a low-dose protocol and with access to a multidisciplinary team of lung cancer specialists. Because it is uncertain whether the results of the NLST can be replicated in the community, screening should ideally be performed in academic centers similar to those where the NLST was conducted.

QUESTIONS AND DISCUSSION

QUESTION: What is the degree of agreement among CT radiologists when reading screening CT scans?

DR BOISELLE: Although there is substantial interreader variability in the detection of small nodules, there is less variability for larger nodules. Two studies addressing various aspects of interobserver agreement in the interpretation of screening CT scans from the Lung Screening Study and the NLST have shown moderate to substantial agreement at baseline and annual screening. Several new technologies offer the opportunity to improve reader agreement in the future, including computer-aided detection programs and volumetric nodule measurement software programs, among others.

QUESTION: Many primary care clinicians look to the USPSTF to answer screening questions. Have they weighed in yet?

DR BOISELLE: The most recent USPSTF guidelines from 2004 state that there is insufficient evidence to recommend for or against screening for lung cancer with low-dose CT, radiography, sputum cytology, or a combination of these tests. An updated recommendation is anticipated, but the evidence review process for this recommendation is currently ongoing. Public policy decisions about widespread screening such as the USPSTF guidelines will await the publication of NLST data regarding cost-effectiveness of CT screening and its effect on quality of life. These publications are anticipated later in 2013.

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REFERENCES

13. Tockman MS. Survival and mortality from lung cancer in a screened popula-


15. Kubik A, Haerting J. Survival and mortality in a randomized study of lung can-

16. Ebeling K, Nischen P. Screening for lung cancer—results from a case-control

17. Straus GS, Gleason RE, Sugarbaker DJ. Chest x-ray screening improves out-
come in lung cancer: a reappraisal of randomized trials on lung cancer screening.

18. Oken MM, Hocking WG, Kvale PA, et al; PLCO Project team. Screening by
chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and

detection with low-dose spiral CT vs radiography. Radiology. 1996;201(3):
796-802.


Project: overall design and findings from baseline screening. Chest. 1999;


cancer screening using low-dose spiral CT: results of baseline and 1-year fol-

with low-dose spiral CT: prevalence in 817 asymptomatic smokers. Radiology.

25. Aberle DR, Berg CD, Black WC, et al; National Lung Screening Trial Research
Team. The National Lung Screening Trial: overview and study design. Radiology.

26. Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Re-
search Team. Reduced lung-cancer mortality with low-dose computed tomo-

27. Henschke CI, Yankelevitz DF, Naidich DP, et al. CT screening for lung cancer:
suspicousness of nodules according to size on baseline scans. Radiology. 2004;

management of small pulmonary nodules detected on CT scans: a statement

29. van Iersel CA, van den Bergh KA, Essink-Bot ML, Bunge EM, et al. Impact of computed tomo-
graphic screening for lung cancer among participants in a randomized controlled

screening trial—overall design and results of the prevalence round. J Thorac

randomized screening trial for lung cancer in smokers. Thorax. 2009;
64(1):34-40.

Project: overall design and findings from baseline screening. Chest. 1999;

33. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the

Guidelines for the Dutch-Belgian randomised lung cancer multi-slice CT screen-
ing program. J Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomo-
graphic scans for lung cancer survivors and other high-risk groups. J Thorac

35. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for

36. Infante M, Chiesa G, Solomon D, et al; DANTE Study Group. Surgical proc-
duress in the DANTE trial, a randomized study of lung cancer early detection with
spiral computed tomography: comparative analysis in the screening and control

37. Li F, Sone S, Abe H, MacMahon H, Armato SG III, Doi K. Lung cancers
missed at low-dose helical CT screening in a general population: comparison of
clinical, histopathologic, and imaging findings. Radiology. 2002;225(3):673-
683.

detection with low-dose spiral CT vs radiography. Radiology. 1996;201(3):
796-802.

39. Crosswell JM, Ransohoff DF, Kramer BS. Principles of cancer screening: les-

40. White CS. National Lung Screening Trial: a breakthrough in lung cancer

41. Aberle DR, Henschke CI, McLaughlin CT, Boiselle PM. Expert opinion: barriers to

42. Wisnivesky JP, Mushlin AI, Schereman N, Henschke C. The cost-effectiveness
of low-dose CT screening for lung cancer: preliminary results of baseline screen-

43. Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung
cancer screening with helical computed tomography in older adult smokers: a de-

44. Chirikos TN, Hazelton T, Tomcock M, Clark R. Screening for lung cancer with

45. Johnson R, Fontham ET, Barrera E, et al. American Cancer Society lung can-

46. Rakitin BM, Jacobson FL, Austin JM, et al. The American Association for
Thoracic Surgery guidelines for lung cancer screening using low-dose computed
tomography scans for lung cancer survivors and other high-risk groups. J Thorac

Guidelines for management of small pulmonary nodules detected on CT scans: a statement


49. Bach PB, Gould MK. When the average applies to no one: personalized de-

50. Donnelly EF. Technical parameters and interpretive issues in screening com-

51. Wood DE. Maximizing the benefit and minimizing the risks of lung cancer

on interpretation of pulmonary findings at low-dose CT screening. Radiology.

interpretation of follow-up CT scans at lung cancer screening. Radiology. 2011;
259(1):263-270.

54. van Klaveren RJ. CT screening for lung cancer ready for prime time? J Tho-

55. Armato SG III, Li F, Giger ML, MacMahon H, Sone S, Doi K. Lung cancer:
performance of automated lung nodule detection applied to cancers missed in a