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# Setting Up a Lung Cancer Screening Program

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## Key Words

Screening, risk assessment, prevention, tobacco, lung cancer, CT scan

## Abstract

This article summarizes what is known about the best practices of lung cancer screening and provides suggestions for the proper structure for institutions considering offering lung cancer screening services. Important points of emphasis include the need to confine screening to patients at highest risk, the presence of multidisciplinary teams capable of managing the high number of false-positive findings, the need for additional research on biomarkers and risk models for lung cancer, and the currently unknown cost-effectiveness of lung cancer screening on a societal level. (*JNCCN* 2012;10:277–285)

In November 2010, the National Lung Cancer Screening Trial (NLST) was halted by the NIH, with the compelling news that CT reduced lung cancer mortality by 20% and all-cause mortality by 7% when 3 annual low-dose helical CT scans were performed in heavy ( $\geq 30$  pack-years) current or former (within 15 years) smokers between 55 and 75 years of age.<sup>1</sup> Since that time, many academic and private facilities either have begun to offer or are considering offering lung cancer screening with CT, either in isolation or as part of a collaborative pro-

gram, despite the absence of recommendations for it in guidelines from authoritative bodies typically entrusted with establishing guidelines for screening (e.g., U.S. Preventive Services Task Force, American Cancer Society) and the lack of third-party payor coverage. In October 2011, NCCN published the first lung cancer screening guidelines recommending the use of CT for lung cancer screening. These guidelines provide a detailed description of the rationale and extensive references for screening with CT for anyone wishing to read further (see the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Lung Cancer Screening, available in this issue and online at [www.NCCN.org](http://www.NCCN.org)).<sup>2</sup>

This article provides guidance for clinicians who are embarking on a CT-based lung cancer screening program. The rationale for and evidence supporting screening are covered briefly,<sup>3,4</sup> with the main focus on what the authors believe are the necessary components of a program to provide the maximum benefit from lung cancer screening while minimizing the potential for harm inherent in screening asymptomatic individuals. Anyone starting a lung cancer screening program should understand the risks and benefits of screening, including the false-positive rate and downstream diagnostic pathways, to assist patients in making an informed decision about whether to pursue screening and how to manage the test results. In addition to the potential for physical harm and psychological distress, data yet unpublished from the NLST will provide important insights into the costs associated with CT lung cancer screening, its cost-effectiveness, and the impact on quality of life and smoking status.

CT screening for lung cancer is a process, not a test performed in isolation. Currently, no information has been published on the optimum structure of a comprehensive lung cancer screening program, and therefore the authors' recommendations are based on the design,

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execution, and results of the NLST; published data from clinical trials (NLST, DANTE, NELSON); available guidelines (Fleischner Society guidelines<sup>5</sup>); and, where the existing literature leaves holes, expert opinion. These recommendations are intended to offer a framework on which a screening program might be built and achieve best practices. The authors offer suggested answers to several questions, such as:

- Who should be screened?
- What information should individuals considering lung cancer screening with CT be made aware of when making a decision to be screened?
- Should smoking cessation be part of a lung cancer screening program?
- In what environment should screening occur and test results be managed?
- How should CT examinations be performed and interpreted for screening?
- What is the proper approach to patients with an abnormal screen?
- What is the proper approach to patients with a negative screen?
- What data should lung cancer screening programs collect?

## Who Should Be Screened?

Individuals who meet the criteria used for enrollment in the NLST (age 55–74 years, with a current or recent [within 15 years] history of heavy tobacco use [ $\geq 30$  pack-years]) represent the only cohort in which a mortality reduction from lung cancer has been shown, and should form the core of patients for whom screening is recommended. Individuals outside of this population should not be offered screening unless it is within the confines of a clinical research trial, or if they can be determined to have a similar risk of lung cancer as individuals enrolled in the NLST, as discussed in the NCCN Guidelines for Lung Cancer Screening (available in this issue; for the most recent version, visit the NCCN Web site at [www.NCCN.org](http://www.NCCN.org)).<sup>2</sup>

The NLST was designed to enroll people at high risk for lung cancer, and established an age range of 55 to 74 years based on epidemiologic data showing the high incidence of lung cancer in this range, while aiming to maximize the benefit of screening through reducing the (unmeasurable) factor of competing

mortality in a higher age group. Smoking history was also critical, and the NLST investigators used 2 factors to focus the trial on those with the highest identifiable risk: 30 pack-years or more of either current or recent (within the past 15 years) tobacco use.<sup>6–8</sup> The strictest interpretation of the results of this trial should lead to the conclusion that only current or recent former smokers meeting these criteria for tobacco use and age range should be considered for a screening program.

Other populations may be at similar risk for lung cancer and may benefit from screening. Reasonable individuals could argue that a 54-year-old with a 50 pack-year tobacco history is at greater risk for lung cancer than a 55-year-old with a 30 pack-year history. Why then would lung cancer screening not be offered to the former person who might inquire about it? Suppose that this person is 50 years of age and has 2 older siblings who had lung cancer? These are compelling questions that should continue to drive research agendas, particularly proposals aimed at defining lung cancer risk more precisely. The NCCN Guidelines extend screening to other high-risk populations based on the assumption that these populations have a similar lung cancer risk and will derive a similar benefit from CT screening.<sup>2</sup> To validate this plausible assumption, entering patients into a lung cancer screening registry in the future may be useful.

Several models have been proposed as clinical tools to predict lung cancer risk<sup>9–13</sup> (Table 1). However, they all require further validation and refinement before they can be routinely applied in clinical practice. In addition to clinical and demographic variables, any future clinically useful risk model would likely eventually include molecular or genetic indicators of risk. These biomarkers of risk ideally would reflect the underlying biologic predisposition to lung cancer susceptibility, and several have been published.<sup>14–17</sup> It is unlikely that any single biomarker will supplant all others, and a model that includes genetic risk, molecular indicators of susceptibility, age, medical history, and environmental or lifestyle exposures is expected to have the greatest predictive accuracy for lung cancer risk.<sup>18–20</sup> The effectiveness of screening in any given group could be benchmarked to the average risk for lung cancer among NLST participants, with any risk model that predicts risk at or greater than the level of risk observed in NLST potentially justifying extending screening to

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**Table 1 Examples of Published Models Aimed at Identifying Individuals at Greatest Risk for Lung Cancer**

Model	Variables Used	Accuracy/Utility	Training Set	External Validation
Bach et al. <sup>11</sup>	<ul style="list-style-type: none"> <li>• Age</li> <li>• Gender</li> <li>• Asbestos exposure</li> <li>• Average cigarettes smoked per day</li> <li>• Smoking duration</li> <li>• Duration of abstinence</li> </ul>	Reported only on the variation in 10-year lung cancer risk among smokers	CARET trial participants	Compared predicted and observed rates of cancer across deciles of risk
Spitz et al. <sup>12</sup>	<ul style="list-style-type: none"> <li>• Secondhand smoke</li> <li>• Dust</li> <li>• Prior respiratory disease*</li> <li>• Smoking history (current, former, and never)</li> <li>• Age at smoking cessation</li> <li>• Asbestos</li> <li>• Family history of tobacco-related malignancy</li> </ul>	69% and 70% true-positive rate in current and former smokers, respectively	<p>1851 patients and 2001 controls matched by age, gender, ethnicity, and smoking status (current, former, never)</p> <p>Three-fourths of subjects were used for training set</p>	One-fourth of the participants were used for validation of the training set data
Cassidy et al. <sup>9</sup>	<ul style="list-style-type: none"> <li>• Age</li> <li>• Smoking duration</li> <li>• Prior diagnosis of pneumonia</li> <li>• Asbestos (occupational exposure)</li> <li>• Prior malignancy</li> <li>• Family history of lung cancer (none, before, and after 60 years of age)</li> </ul>	AUC of 0.7	579 lung cancer cases and 1157 age- and gender-matched controls	Subsequent validation by D'Amelio et al. <sup>10</sup> in a cohort recruited in Boston, Massachusetts area
Tammemagi et al. <sup>13</sup>	<ul style="list-style-type: none"> <li>• Age</li> <li>• Socioeconomic status (educational level)</li> <li>• Body mass index</li> <li>• Family history</li> <li>• COPD (yes/no)</li> <li>• Recent (within 3 years) CXR</li> <li>• Smoking history (current, former, and never)</li> <li>• Pack-years</li> <li>• Smoking duration</li> <li>• Duration of abstinence†</li> </ul>	AUC of 0.841 and 0.784 in validation sets, with models 1 and 2, respectively	PLCO participants (n = 70,962 for model 1, and n = 38,254 smokers for model 2)	44,223 PLCO intervention-arm participants

Abbreviations: AUC, area under the curve; CARET,  $\beta$ -Carotene and Retinol Efficacy Trial; COPD, chronic obstructive pulmonary disease; CXR, chest radiographic images; PLCO, Prostate, Lung, Colorectal And Ovarian Cancer Screening Trial.

\*Emphysema, hay fever (protective), and dust exposure (only significant in smokers).

†Only 1 of 2 models used this variable, and it did not strengthen predictive ability.

those individuals. Cost-effectiveness analyses can be modeled to estimate cost per years of life gained in a given risk group, further informing the decision whether to pursue screening.

### Important Information for Considering Lung Cancer Screening With CT

Most primary health care providers are comfortable discussing screening tests that have been in practice for decades, such as mammography and colonoscopy. With the more recent advent of CT screening for lung cancer, providers may be less well prepared to discuss the screening process and answer questions patients may have. This section provides information on the common questions that health care providers and patients may have about lung cancer screening with CT.

Individuals seeking screening should be counseled not only on the benefit of lung cancer screening with CT with respect to reducing lung cancer mortality but also on the likelihood of a positive screen, the subsequent management of a positive screen, the possibility that a significant abnormality may be detected that is not related to lung cancer, and the implications of a negative screen. Radiation exposure should also be discussed to mitigate patient concerns. The nature of screening and the implications of false-positive findings are difficult for many people to comprehend. Patients should be counseled on the notion that screening for lung cancer is not a test but rather a process, and one that has measureable associated risks.

The following are important elements of the screening discussion and answers to the questions that many patients considering screening may have:

- What constitutes a positive CT screen?  
Lung nodules 4 mm and larger that do not have specific benign features (e.g., certain patterns of calcification or fat), new nodules, or growing nodules.
- What is the likelihood of a positive screen?  
In NLST, 27% of individuals had an abnormal screen on their first screening CT examination. In other screening trials, most of which are single-arm screened cohort studies, up to 50% of subjects had an abnormal first screening CT examination. In the Mayo Clinic single-arm cohort study, after 5 an-

nual CT screening examinations, at least 1 noncalcified lung nodule was found in 74% of participants.<sup>21</sup>

- What is the likelihood that a positive screen represents lung cancer?  
In NLST, only 4% of patients with a positive screen had lung cancer; 96% of the abnormal findings were false-positives.
- What is the most common finding and how is it usually managed?

Most abnormal screens are small lung nodules, 4 to 8 mm in size, for which management involves additional low-dose nodule CT examinations. Nodules smaller than 4 mm are not considered a positive screen, and individuals with these findings should undergo no additional testing but should continue to the next annual screening CT.

- What is the likelihood that a new nodule will be detected on a subsequent annual screening CT and that the new nodule is cancer?  
In a report from I-ELCAP (International Early Lung Cancer Action Program), of 27,500 individuals who had a negative baseline screening CT, 5.3% (n = 1460) developed a new lung nodule 1 year later. Of these new nodules, only 5% (n = 70) were lung cancer.<sup>22</sup>
- What is the likelihood that an invasive procedure will be required to evaluate an abnormal screen?

Fortunately, as shown in NLST, invasive procedures were performed in a very small number of individuals, and the rate of at least one complication was 1.4% in CT-screened individuals. Among those who did not have cancer, fewer than 0.1% of the positive results led to a major complication after an invasive procedure. For individuals with cancer, the rate of major complications resulting from an invasive procedure was 11.2%. Of the more than 26,000 subjects in the CT arm of NLST, 16 participants (< 0.03%), 10 of whom had lung cancer, died within 60 days after an invasive diagnostic procedure.<sup>6</sup> Therefore, 10 invasive procedures were performed per life saved,



but also 640 imaging studies were performed per life saved, most of which were CT examinations driven by the large number of small nodules detected.

- What is the likelihood that clinically significant abnormalities other than lung cancer will be detected on a lung cancer screening CT?

In a systematic review of incidental findings on lung cancer screening CT examinations, 14.2% of individuals (CI, 13.2%–15.2%;  $n = 4531$ ) had clinically significant incidental findings requiring additional investigation. These abnormalities range from lung disease, such as pulmonary fibrosis or bronchiectasis, to aortic aneurysm, mediastinal tumors, and upper abdominal malignancies.<sup>23</sup> In a recent study of more than 5200 individuals undergoing annual lung cancer screening with CT, 0.5% were diagnosed with an unsuspected extrapulmonary malignancy, most of which were renal cell carcinomas (44%), followed by lymphoma (26%).<sup>24</sup>

## Smoking Cessation

Both smoking reduction and smoking cessation reduce the risk of lung cancer.<sup>25,26</sup> Because the purpose of a lung cancer screening program is to reduce the likelihood of dying from lung cancer, and this goal is most efficiently achieved through smoking cessation, this is an essential element of any lung cancer screening program. All patients seen in a screening setting should be offered counseling and pharmacotherapy options for smoking cessation. Follow-up phone calls to encourage continued abstinence may also be effective.<sup>27</sup>

## Environment for Screening and Management of Test Results

Screening in general is one of the many critical roles of primary care physicians. This is true, for example, for hyperlipidemia, diabetes, hypertension, domestic violence, and breast, colon, and prostate cancers. Therefore, it is natural to assume that lung cancer screening, if and when it becomes widely accepted, would also be the responsibility of primary care providers. This is likely to be the most efficient way to bring at-risk patients into contact with a CT for lung cancer screening,

and this may ultimately be possible with well-defined guidelines for managing positive screening test results.

However, important differences exist between current cancer screening strategies and those for lung cancer screening. First, the rate of false-positives for lung cancer screening is higher than for breast, colon, or prostate cancer screening,<sup>28</sup> necessitating further testing in a high percentage of patients to determine the likelihood of cancer. Until widely accepted algorithm-based strategies are established, this further testing should occur within a multidisciplinary group with experience detecting lung cancer in incidental lung nodules. As noted by the authors of the NLST study, the low incidence of complications from investigating screen-detected abnormalities may not be achievable if the follow-up is performed outside of high-volume centers.<sup>27</sup> Second, because screening for lung cancer should be offered to high-risk individuals and not to the general population, this places considerable emphasis on identifying individuals at high risk for lung cancer, particularly those who meet the age and smoking criteria used in NLST. Estimating risk is not a standardized or precise practice, even in highly specialized tertiary care research centers.<sup>9,11–13,29</sup>

These caveats are not meant to steer the responsibility for lung cancer screening away from well-qualified primary care providers. Rather, the purpose of emphasizing these differences is to suggest that the responsibility of those specializing in lung cancer diagnosis is to 1) develop and provide educational tools to assess risk and manage abnormal CT screening results for primary care physicians, and 2) serve as a consultant for abnormal findings suggesting malignancy when additional interventions may be needed (e.g., PET scan, bronchoscopy, percutaneous biopsy, surgical resection). The authors' center is working with their primary care network to facilitate recognition of high-risk individuals using electronic medical record prompts and a single phone call referral process when abnormalities are discovered on CT screening examinations. Many centers have developed or are developing screening clinics, where individuals seeking screening can call the clinic coordinator, who will question the individual for screening eligibility and then offer low-dose screening CT scans if eligibility criteria are met. Those who are not eligible are offered counseling on smoking cessation and participation in biomarker studies.

Currently, self-referral for screening CT by patients directly is strongly discouraged, because patients will be incompletely prepared for the test results and, without a responsible provider, may not receive the necessary follow-up to act on detected abnormalities. In addition, although the entry criteria for many other screening tests are straightforward, such as age only, the entry into lung cancer CT screening includes age, calculation of smoking exposure in pack-years, and integration of other factors for lung cancer, making self-referral challenging. As public understanding of the role of CT in lung cancer screening increases and greater clarity of eligible populations emerges, self-referral with a physician of record, as often occurs with screening mammography, will likely be possible.

## Performance and Interpretation of CT Scans

CT examinations for lung cancer screening are not the same as routine chest CTs performed for other purposes. Among the most important differences are radiation exposure and slice thickness. NLST used a low-radiation exposure protocol. Although the term *low-dose* has no standardized definition, the parameters used in NLST included a voltage of 120 to 140 kVp, and a tube current–time product of 40 to 80 mAs, dependent on the body habitus of the screened subject. The resulting radiation exposure was approximately 1.5 millisievert (mSv), whereas a conventional chest CT results in an exposure of approximately 5 to 8 mSv. Slice thickness should be 3 mm or smaller, with overlapping reconstructions at 50% of the slice thickness, which allows for improved detection and characterization of nodules, particularly important for nodule volume calculations and computer-aided diagnosis. Thicker slices are not appropriate for lung cancer screening. Sliding-slab maximum-intensity projections should be used during interpretation whenever possible to improve nodule detection.

The CT reports should be structured and include the following information: 1) for each indeterminate nodule, the size, shape, morphology, and lobar/segmental location should be reported; 2) the series and slice number should also be reported for each nodule to facilitate comparison on future examinations; 3) examinations should always be compared directly with previous ones, and not simply with prior reports,

and any change in nodule size, shape, or composition should be described; and 4) the CT reports should include standard guidelines for further evaluation of positive test results, as developed by multidisciplinary groups, such as the Fleischner Society.

Looking to the future, as techniques are developed for standard, reproducible volume measurement of lung nodules, management may be determined by volume and not simply diameter. For example, investigators in the Dutch Belgian randomized lung cancer screening trial (NELSON) recommended short-term follow-up for indeterminate nodules based on a volume of 50 to 500 mm<sup>3</sup> (or approximately 4–10 mm in diameter), with a repeat CT examination obtained 3 months later to assess doubling time.<sup>30</sup> If the lesion had a volume-doubling time of fewer than 400 days, subjects were referred to a chest physician for workup and diagnosis.<sup>30</sup>

## Approach to Patients With an Abnormal Screen

Although an in-depth discussion on the management of pulmonary nodules is beyond the scope of this article, some general points about screen-detected nodules are relevant. With the purpose of screening being to detect lung cancer at an early, asymptomatic, and ideally curable stage, one strategy is to approach abnormal findings with the notion that they are lung cancer until proven otherwise. This may sound extreme in light of data from the NLST (and, coincidentally, other nonrandomized trials<sup>22</sup>) showing that only approximately 4% of screen-detected abnormalities are cancer. It becomes less extreme, however, when recognizing that the urgency with which “proof of benignity” is pursued varies from person to person and from nodule to nodule. There are essentially 3 ways to prove a nodule is benign:

1. The nodule has a benign pattern of calcium, fat, or morphology that suggests an arteriovenous malformation.
2. The nodule exhibits benign biologic behavior (no growth or shrinks) on serial follow-up low-dose CT examinations for at least 2 years.<sup>31</sup>
3. The nodule is surgically removed and histologically confirmed to be benign.

The higher the pretest probability of malignancy in a nodule, the greater the degree of certainty is required to prove it is benign. Although a biopsy

(transbronchial or CT-guided) uncommonly provides a definitively benign result, a “benign” diagnosis such as granuloma or organizing pneumonia is usually not cause to ignore the nodule. Some degree of follow-up to exclude a false-negative biopsy result is needed to ensure resolution or lack of growth. Regarding biopsy, a rule of thumb is that the negative predictive value of a biopsy is of greatest use when the pretest probability for malignancy is already low. Patients with nodules highly suspicious for cancer who are at very high risk for resection can be referred for tissue biopsy so that all treatment options (surgery, radiotherapy) can be discussed appropriately. Similarly, when an indeterminate nodule is large enough to be characterized on PET scan (generally when it is  $\geq 8$  mm), this scan, or preferably a CT/PET scan, should be performed.<sup>31</sup> When negative, again this is not cause to cease evaluation of the nodule, but to perform follow-up of the nodule using low-dose CT. In an otherwise healthy individual, a nodule highly likely to be malignant (e.g., based on size, patient age, and nodule characteristics for example<sup>31–33</sup>; see <http://www.chestx-ray.com/SPN/SPNProb.html>) should undergo surgical resection.<sup>31,33</sup>

When approaching a patient with a nodule of low probability for lung cancer, the Fleischner Society guidelines<sup>5</sup> have performed very well for both patients and physicians in detecting malignancy, while minimizing the number of CT scans required to reach proof of benignity. The authors recommend adhering to these guidelines when selecting the interval of follow-up CT scans on indeterminate pulmonary nodules. One common problem not directly addressed by the Fleischner Society guidelines is the management of pure ground glass nodules, which are often associated with adenocarcinoma in situ, formerly known as *pure bronchioloalveolar carcinoma*.<sup>34,35</sup> Clearly, the “2-year” rule for radiologic follow-up is not always sufficient to establish a benign etiology, particularly for pure ground glass and mixed solid/ground glass nodules, each of which carries a higher likelihood of malignancy than do solid nodules. The Fleischner Society guidelines do contain a footnote acknowledging this fact, but no consensus exists on the appropriate length of follow-up for pure ground glass lesions, and this is largely because of the poor understanding of the natural history of these lesions.

One point that should be stressed is that the management of patients with pulmonary nodules is best performed within the context of a multidisciplinary

team, comprising radiologists, nuclear medicine specialists, surgeons, pulmonologists, and cancer specialists, all of whom preferably have a significant proportion of their practice focused on the management of patients with known or suspected lung cancer.<sup>36,37</sup> Radiologists practicing in teaching hospitals or in a practice with at least one fellowship-trained thoracic radiologist are more likely to be aware of and follow the Fleischner Society guidelines than other radiologists.<sup>38</sup>

### Proper Approach to a Negative Screen

Many feared that normal screening results would result in lesser rates of tobacco cessation, and that patients would not return for follow-up screens. Neither of these fears seemed to have been realized in the NLST.<sup>27</sup> Patients with normal screening results should be reminded that screening for lung cancer is a process over time, not a single test, and that the mortality benefit of screening seen in NLST was achieved through yearly CT scans for 3 years. Although no data currently support screening beyond 3 years, extrapolation of the NLST results suggests that continued screens beyond 3 annual scans may yield greater mortality benefit than the 20% reduction in lung cancer-specific mortality observed in this trial.<sup>27,39</sup> Further data, projected modeling of mortality, and cost-effectiveness analyses from published screening studies will likely inform the decision regarding whether to screen beyond 3 annual CT scans. Currently, the NCCN Guidelines recommend screening until 74 years of age. To understand whether continued screening beyond the 3-year time frame is warranted, patients should be enrolled into a lung cancer screening registry.

### Data Collection

Establishing a lung cancer screening program in the current health care environment should come with a responsibility to establish a standardized database or registry of screened subjects, and a commitment to working in multidisciplinary groups to develop and/or prospectively validate a model that measures risk at the individual level. Ideally, when infrastructure permits, a biospecimen repository to facilitate development and/or validation of biomarkers would further enhance understanding of who



should be screened and which patients with positive CT screening examinations require more intensive follow-up.

## Conclusions

Lung cancer screening with 3 yearly CT scans (a baseline CT and 2 subsequent CTs annually thereafter) using a low-dose protocol has been shown to reduce lung cancer–specific mortality by 20% in a population of older heavy smokers.<sup>1</sup> The importance of this achievement by the NLST investigators cannot be overstated, but this should be viewed as an important first step, not a final destination. Many major questions remain about how to best realize this mortality reduction in a practical real-world context. Screening for lung cancer can and should be performed, but it will be most effective if it is accompanied by continued research on modeling risk and seeking biomarkers along the full spectrum, from molecular predictors of risk to diagnostic and prognostic biomarkers. For clinicians seeking to establish a program of lung cancer screening, the authors encourage that this be done in a responsible fashion, and with as much attention given to proper management of screen-detected abnormalities as is given to the initial screening process.

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