Lung Cancer Screening

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NCCN Lung Cancer Screening Panel Members

**Risk Assessment and Screening Modality (LCS-1)**

**Solid or Part Solid Nodule: Evaluation and Follow-up of Screening Findings (LCS-2)**

**Ground Glass Opacity (GGO)/Ground Glass Nodule (GGN)/Nonsolid Nodule (NS): Evaluation and Follow-up of Screening Findings (LCS-3)**

**New Nodule: Evaluation and Follow-up of Screening Findings (LCS-4)**

**Risks/Benefits of Lung Cancer Screening (LCS-A)**

**Table 1. Comparison of the I-ELCAP and NLST Lung Screening Protocols (MS-19)**

**Table 2. Low-Dose Computed Tomography Acquisition, Storage, Interpretation, and Nodule Reporting (MS-20)**

**Clinical Trials:** The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

**NCCN Categories of Evidence and Consensus:** All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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### Risk Assessment

**High risk:**
- Age 55-74 y and
  - ≥ 30 pack year history of smoking and
  - Smoking cessation < 15 y (category 1)
- Age ≥ 50 y and
  - ≥ 20 pack year history of smoking and
  - One additional risk factor (other than second-hand smoke) (category 2B)

**Moderate risk:**
- Age ≥ 50 y and
  - ≥ 20 pack year history of smoking or second-hand smoke exposure
- No additional risk factors

**Low risk:**
- Age < 50 y and/or
  - < 20 pack year history of smoking

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### Screening Modality

**Baseline low-dose computed tomography (LDCT)**

**Findings**
- **Solid or part solid nodule**
- **Lung nodule(s) on LDCT**
- **Ground glass opacity (GGO)**
- **Ground glass nodule (GGN)**

### Screening Findings

- **No lung nodule(s) on LDCT**
- **Routine lung cancer screening not recommended**

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**Note:** All recommendations are category 2A unless otherwise indicated.

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EVALUATION OF SCREENING FINDINGS

Solid or part solid nodule

- ≤ 4 mm
- > 4-6 mm
- > 6-8 mm
- > 8 mm

FOLLOW-UP OF SCREENING FINDINGS

- Annual LDCT screening for 3 years and until age 74
- LDCT in 6 mo
- LDCT in 3 mo
- Consider PET/CT
- LDCT in 1 mo
- Biopsy or Surgical excision
- Bronchoscopy
- Annual LDCT screening for at least 2 years and until age 74

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**EVALUATION OF SCREENING FINDINGS**

- **< 5 mm**
  - LDCT in 12 mo
  - Stable → Annual LDCT screening for at least 2 years and until age 74
  - Increase in size and/or become solid or part solid → LDCT in 3-6 mo
  - Surgical excision

- **5-10 mm**
  - LDCT in 6 mo
  - Stable → Annual LDCT screening for at least 2 years and until age 74
  - Increase in size and/or become solid or part solid → Surgical excision

- **> 10 mm**
  - LDCT in 3-6 mo
  - Stable → Annual LDCT screening for at least 2 years and until age 74
  - Increase in size and/or become solid or part solid → Surgical excision

**FOLLOW-UP OF SCREENING FINDINGS**

- **No cancer** → Annual LDCT screening for at least 2 years and until age 74
- **Cancer confirmed** → See NCCN Non-small Cell Lung Cancer Guidelines

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1. All screening and follow-up CT scans should be performed at low dose (100-120 kVp & 40-60 mAs or less), unless evaluating mediastinal abnormalities or lymph nodes, where standard dose CT with IV contrast might be appropriate.

2. Without benign pattern of calcification, fat in nodule as in hamartoma, or features suggesting inflammatory etiology. When multiple nodules are present and occult infection or inflammation is a possibility, an added option is a course of a broad spectrum antibiotic with anaerobic coverage, followed by low-dose CT 1-2 months later.

3. If new nodule at annual or follow-up LDCT, see LCS-4. New nodule is defined as ≥ 3 mm in mean diameter.

4. There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.

5. Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter when compared to the baseline scan.

6. For nodules ≤ 15 mm: increase in mean diameter ≥ 2 mm in any nodule or in the solid portion of a part solid nodule compared to baseline scan. For nodules ≥ 15 mm: increase in mean diameter of ≥ 15% compared to baseline scan.

7. Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than NSCLC.

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EVALUATION OF SCREENING FINDINGS

FOLLOW-UP OF SCREENING FINDINGS

New nodule at annual or follow-up LDCT

- Suspected infection/inflammation
  - Treat with antimicrobials
  - Repeat LDCT in 1-2 mo

- Resolved
  - Radiologic follow-up to resolution or stability
  - Annual LDCT screening (see LCS-1)

- Persistent or enlarging
  - PET/CT
  - PET-CT for lesions greater than 8 mm.

- Solid or part solid nodule
  - See Evaluation of Screening Findings (LCS-2)
  - Ground glass opacity (GGO)
  - Ground glass nodule (GGN)
  - Nonsolid nodule (NS)

- No suspected infection/inflammation
  - Resolving Radiologic follow-up to resolution or stability
  - Annual LDCT screening (see LCS-1)

LDCT in 3 mo (See LCS-2 or LCS-3)

Low suspicion of lung cancer

- Suspicion of lung cancer
  - Biopsy or Surgical excision

No lung cancer

Lung cancer confirmed

See NCCN Non-small Cell Lung Cancer Guidelines

No lung cancer

Annual LDCT screening (see LCS-1)

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
RISKS/BENEFITS OF LUNG CANCER SCREENING

**RISKS**
- Futile detection of small aggressive tumors or indolent disease
- Quality of life
  - Anxiety of test findings
- Physical complications from diagnostic work-up
- False-positive results
- False-negative results
- Unnecessary testing
- Radiation exposure
- Cost

**BENEFITS**
- Decreased lung cancer mortality
- Quality of life
  - Reduction in disease-related morbidity
  - Reduction in treatment-related morbidity
  - Improvement in healthy lifestyles
  - Reduction in anxiety/psychosocial burden
- Cost effectiveness

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Discussion

NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Lung cancer is the leading cause of cancer-related mortality in the United States and the rest of the world. In 2011, it is estimated that 156,900 deaths (85,600 in men, 71,300 in women) from lung cancer will occur in the United States. Five-year survival rates for lung cancer are only about 15.6%, in part because most patients have advanced stage lung cancer at the time of initial diagnosis.

These facts—combined with the success of screening to improve outcomes in cervical, colon, and breast cancers—have been the impetus for studies to develop an effective lung cancer screening test. Ideally, effective screening will lead to earlier detection of lung cancer (before patients have symptoms and when treatment is more likely to be effective) and will decrease mortality. Currently, most lung cancer is diagnosed clinically when patients present with symptoms (such as cough, chest pain, weight loss); unfortunately, patients with these symptoms usually have advanced lung cancer.

Early detection of lung cancer is an important opportunity for decreasing mortality. There has been considerable interest in developing screening tools to detect early stage lung cancer. Recent data support using spiral (helical) low-dose computed tomography (LDCT) of the chest to screen select patients who are at high risk for lung cancer. The NCCN Lung Cancer Screening Panel developed this new screening guideline in 2011 based on the current body of evidence.

This NCCN guideline on lung cancer screening: 1) describes risk factors for lung cancer; 2) recommends criteria for selecting high-risk individuals for screening; 3) provides recommendations for evaluation and follow-up of nodules found during screening; 4) discusses the accuracy of LDCT screening protocols and imaging modalities; and 5) discusses the benefits and risks of screening.

Screening for Non-Small Cell Lung Cancer (NSCLC)

Most lung cancers (85%) are classified as NSCLC; small cell lung cancer occurs in about 13%-15% of patients (see the NCCN NSCLC and Small Cell Lung Cancer guidelines). Thus, this NCCN Lung Cancer Screening guideline mainly refers to detection of NSCLC. Other types of cancer can metastasize to the lungs (e.g., breast cancer), and there are also less common cancers of the lung or chest (e.g., malignant pleural mesothelioma, thymic carcinoma). Lung cancer screening may also detect other noncancerous conditions of the thorax (e.g., aortic aneurysm, coronary artery calcification) and tumors or benign disease outside of the chest (e.g., renal cell carcinoma, adrenal adenoma).
The goal of screening is to detect disease at a stage when it is not causing symptoms and when treatment is most successful. Screening should benefit the individual by increasing life expectancy and increasing quality of life. The rate of false-positive results should be low to prevent unnecessary additional testing. The large fraction of the population without the disease should not be harmed (low risk), and the screening test should not be so expensive that it places an onerous burden on the health care system. Thus, the screening test should: 1) improve outcome; 2) be scientifically validated (e.g., have acceptable levels of sensitivity and specificity); and 3) be low risk, reproducible, accessible, and cost effective.

Perhaps the most difficult aspect of lung cancer screening is addressing the moral obligation. As part of the Hippocratic oath, physicians promise to first “do no harm.” The dilemma is that if lung cancer screening is beneficial but physicians do not use it, they are denying patients effective care. However, if lung cancer screening is not effective, then patients may be harmed by overdiagnosis, increased testing, invasive testing or procedures, and the anxiety of a potential cancer diagnosis. Debates from mammography and prostate cancer screening may provide additional insight for lung cancer screening, especially regarding the problem of overdiagnosis (see next section on “Randomized Trials” in this manuscript).

**Computed Tomography (CT) as Part of a Screening Program**

Lung cancer screening with CT should be part of a program of care and should not be performed in isolation as a free standing test. Given the high percentage of false-positive results and the downstream management that ensues for many patients, the risks and benefits of lung cancer screening should be discussed with the individual before doing a screening LDCT scan. It is recommended that institutions performing lung cancer screening use a multidisciplinary approach that may include specialties such as radiology, pulmonary medicine, internal medicine, thoracic oncology, and thoracic surgery. Management of downstream testing and follow-up of small nodules is imperative and may require establishment of administrative processes to ensure the adequacy of follow-up.

**Randomized Trials**

Disease-specific mortality (number of cancer deaths relative to number of individuals screened) is considered the ultimate test of screening effectiveness and the only test that is without bias. Randomized controlled screening trials are essential for determining whether cancer screening decreases disease-specific mortality. Non-randomized trials are subject to biases that may cause an apparent increase in survival (e.g., lead-time bias, length-time bias) (http://www.cancer.gov/newscenter/qa/2002/nlstqaQA).

If lung cancer is detected by screening before symptoms occur, then the lead time in diagnosis equals the length of time between screening detection and when the diagnosis otherwise would have occurred, either due to symptoms or other imaging. Even if early treatment had no benefit, the survival of the screened person is increased simply by the addition of the lead time. Length-time bias refers to the tendency of the screening test to detect cancers that take longer to become symptomatic possibly because they are slower growing and perhaps indolent cancers. Survival (the number of individuals who are alive after detection and treatment of disease relative to number of individuals diagnosed with the disease) has often been reported but is subject to these biases. For further discussion of randomized and non-randomized screening trials, see the section on “Benefits of Lung Cancer Screening” in this manuscript.
In the 1960’s and 1970’s, several randomized trials assessed whether chest x-rays could improve lung cancer survival. Many of these studies were flawed in their design or power, and all were negative. More recently, studies have focused on the more sensitive modality of helical LDCT–based lung cancer screening studies (see also section on “Benefits of Lung Cancer Screening” in this manuscript). However, analyses of some lung cancer screening studies using LDCT scans suggest that overdiagnosis (i.e., diagnosis of “cancer” that would never be life threatening) and false-positive screening tests are significant. Thus, although LDCT scanning may be a better screening test for lung cancer, it also has limitations (see section on "Risks of Lung Cancer Screening" in this manuscript).

Multiple ongoing randomized trials are assessing LDCT screening for lung cancer among high-risk groups. Two randomized trials are 1) the National Lung Screening Trial (NLST), sponsored by the National Cancer Institute (NCI); and 2) the Dutch-Belgian screening trial known as NELSON. In November 2010, preliminary results from the NLST were reported suggesting that LDCT screening decreases disease-specific mortality. The results of the NLST trial have recently been published and show that LDCT yields a decrease in lung cancer specific mortality of 20% (95% CI, 6.8-26.7; \( P = .004 \)) and a decrease in all-cause mortality of 7% (95% CI, 1.2-13.6; \( P = .02 \)) when compared with chest x-ray alone.

**High-Risk Individuals**

An essential goal of any lung cancer screening protocol is to identify the populations that are at a high risk for developing the disease. Although smoking tobacco is a well-established risk factor for lung cancer, other environmental and genetic factors also appear to increase the risk. This section reviews the currently known risk factors for the development of lung cancer to identify high-risk populations that should be targeted for screening. Note that high-risk individuals who are recommended for screening do not have any symptoms suggestive of lung cancer (e.g., cough, chest pain, weight loss).

**Tobacco Smoke**

**Active Tobacco Use**

Tobacco smoking is a major modifiable risk factor in the development of lung cancer, and it accounts for 85% of all lung cancer related deaths. The causal relationship between tobacco smoking and lung cancer was first reported in 1939. Since then, the risk of developing lung cancer from smoking tobacco has been firmly established. There are more than 4,500 compounds in tobacco smoke; more than 50 of them are known carcinogens that increase the risk of cancerous mutations at the cellular level, especially among individuals with a genetic predisposition. There is a dose-response relationship between smoking tobacco and the risk of developing lung cancer; however, there is no risk-free level of tobacco exposure. The relative risk (RR) for lung cancer is approximately 20-fold higher for smokers when compared to non-smokers. Cessation of tobacco smoking decreases the risk of lung cancer. However, even reformed former smokers have a higher risk of lung cancer when compared to never smokers.

In the NCCN Lung Cancer Screening algorithm, individuals (age 55-74 years) with a 30 pack-year or more history of smoking tobacco are selected as the highest-risk group for lung cancer and are
recommended for screening (category 1) based on criteria for entry into the NLST.\textsuperscript{7,8} \textit{Pack-years of smoking history} is defined as the number of packs of cigarettes smoked every day multiplied by the number of years of smoking. Individuals with a 30 pack-year smoking history who quit smoking less than 15 years ago are still in this highest risk group.

**Exposure to Second-Hand Smoke**

The relationship between lung cancer and exposure to second-hand smoke (also known as, environmental tobacco smoke, “passive smoke,” involuntary smoke) was first suggested in epidemiologic studies published in 1981.\textsuperscript{19} Since then, several studies and pooled RR estimates suggest that second-hand smoke causally increases the risk for lung cancer among non-smokers

http://www.surgeongeneral.gov/library/secondhandsmoke/factsheets/factsheet6.html\textsuperscript{20}

However, the NCCN panel does not consider second-hand smoke as an independent risk factor, because the association is either weak or variable. Thus, second-hand smoke does not confer a great enough risk for exposed individuals to be considered for lung cancer screening in this NCCN guideline.

A pooled analysis of 37 published studies found an estimated RR of 1.24 (95% CI, 1.13 - 1.36) for adult non-smokers who live with a smoker.\textsuperscript{21} A pooled estimate from 25 studies found an RR of 1.22 (95% CI, 1.13 - 1.33) for lung cancer risk for exposure to second-hand smoke at the workplace.\textsuperscript{20} The pooled estimate for 6 studies suggests a dose-response relationship for number of years of second-hand smoke exposure and lung cancer risk.\textsuperscript{20} The data are inconsistent for second-hand smoke exposure during childhood and subsequent lung cancer risk in adulthood. For childhood tobacco smoke exposure, pooled RR estimates for development of lung cancer were 0.93 (95% CI, 0.81 - 1.07) for studies conducted in the United States, 0.81 (95% CI, 0.71 - 0.92) for studies conducted in European countries, and 1.59 (95% CI, 1.18 - 2.15) for studies conducted in Asian countries.\textsuperscript{20}

**Occupational Exposure**

Approximately 150 agents are classified as known or probable human carcinogens (IARC 2002). The 8 agents that are identified specifically as carcinogens targeting the lungs are arsenic, chromium, asbestos, nickel, cadmium, beryllium, silica, and diesel fumes.\textsuperscript{22-25} These agents are listed in order of their presumed risk.\textsuperscript{22} The calculated mean RR for development of lung cancer is 1.59 for individuals in the United States with a known occupational exposure to these agents.\textsuperscript{22,25} For those who are exposed to these carcinogens, smokers have a greater risk for lung cancer than nonsmokers.\textsuperscript{26}

**Residential Radon Exposure**

Radon (a gaseous decay product of Uranium-238 and Radium 226) has been implicated in the development of lung cancer.\textsuperscript{27} The risk of lung cancer from occupational exposure among uranium miners is well established.\textsuperscript{28} However, the risk associated with residential radon is uncertain. A meta-analysis in 1997 of 8 studies yielded an estimated RR of 1.14 (95% CI, 1.0-1.3).\textsuperscript{29} However, a 2005 meta-analysis of 13 studies (using individual patient data) reported a linear relationship between the amount of radon detected in a home and the risk of developing lung cancer.\textsuperscript{30} For those who are exposed to radon, smokers have a greater risk for lung cancer than nonsmokers.\textsuperscript{30}

**Cancer History**

There is evidence of an increased risk of new primary cancers among patients who survive lung cancer, lymphomas, cancers of the head and neck, or smoking-related cancers (e.g., esophageal cancer). Among patients who survive small cell lung cancer, there is a 3.5-fold increase
in the risk for developing a new primary cancer (predominantly NSCLC).\textsuperscript{31} The risk for subsequent lung cancers is increased in patients who continue to smoke and who have been previously treated with either chest irradiation or alkylating agents. There is a 13-fold increase in risk for developing new primary lung cancer in patients previously treated with chest irradiation and an estimated RR of 9.4 for patients previously treated with alkylating agents. In patients previously treated for Hodgkin’s lymphoma, the RR is 4.2 for new primary lung cancer if previously treated with alkylating agents and the RR is 5.9 if previously treated with 5 Gy or more of radiation therapy.\textsuperscript{32} In patients with head and neck cancers, subsequent new primary lung cancer may occur synchronously or metachronously. New primary tumors are seen in approximately 9% of patients. Most of these tend to be squamous cell cancers and a third of them occur in the lung. However, data do not suggest that previous treatment for head and neck cancers increases the risk of subsequent new primary lung cancer independent of tobacco exposure.\textsuperscript{33,34} Evidence suggests that patients who are successfully treated (i.e., cured) of an initial smoking-related lung cancer and who stop smoking will have a decreased risk of a subsequent smoking-related cancer than those who continue smoking.\textsuperscript{35} 

Family History of Lung Cancer

Several studies have suggested an increased risk for lung cancer among first-degree relatives of patients with lung cancer, even after adjustment for age, gender, and smoking habits.\textsuperscript{36,37} A meta-analysis of 28 case-control studies and 17 observational cohort studies showed a RR of 1.8 (95% CI, 1.6 - 2.0) for individuals with a sibling/parent or a first-degree relative with lung cancer.\textsuperscript{38} The risk is greater in individuals with multiple affected family members or with a diagnosis of cancer at a young age. While no high penetrance inherited syndrome has been described for lung cancer (either small cell lung cancer or NSCLC), a number of groups have identified genetic loci that may be associated with an increased risk of developing lung cancer. The Genetic Epidemiology of Lung Cancer Consortium (GELCC) conducted a genome wide linkage analysis of 52 families who had several first-degree relatives with lung cancer. Linkage disequilibrium was shown on chromosome 6, localizing a susceptibility locus influencing lung cancer risk to 6q23-25.\textsuperscript{39} Subsequently, 3 groups performed genome-wide association studies in patients with lung cancer and matched controls. They found a locus at 15q24-25 associated with an increased risk of lung cancer as well as nicotine dependence and peripheral artery disease.\textsuperscript{40-42} Interestingly, it was noted that subunits of the nicotinic acetylcholine receptor genes are localized to this area (CHRNA5, CHRNA3 and CHRN8B). Other investigators have recently found that a variant at 15q24/25 is associated with spirometric bronchial obstruction and emphysema as assessed by CT.\textsuperscript{43} In patients with classic familial cancer susceptibility syndromes (such as retinoblastoma, Li-Fraumeni syndrome), their risk for lung cancer is substantially increased if they also smoke tobacco.\textsuperscript{44-46}

History of Lung Disease in the Patient

Chronic Obstructive Pulmonary Disease (COPD)

A history of COPD is associated with lung cancer risk.\textsuperscript{47-53} This association may be largely due to smoking; Yang and colleagues\textsuperscript{54} found that COPD accounts for 12% of lung cancer cases among heavy smokers. However, even after statistical adjustment, evidence suggests that the association between COPD and lung cancer may not be
entirely due to smoking. For example, 1) family history of chronic bronchitis and emphysema is associated with increased risk of lung cancer, and 2) COPD is associated with lung cancer among never smokers. Yang and colleagues found that COPD accounts for 10% of lung cancer cases among never smokers. Koshiol and colleagues found that when they restricted their analyses to adenocarcinoma (which is more common among non-smokers, particularly women), COPD was still associated with an increased risk of lung cancer.

**Pulmonary Fibrosis**
Patients with diffuse pulmonary fibrosis appear to be at a higher risk for lung cancer even after age, gender, and a history of smoking are taken into consideration (RR = 8.25, 95% CI, 4.7 - 11.48). Among patients with a history of exposure to asbestos, those who develop interstitial fibrosis are at a higher risk of developing lung cancer when compared to those without fibrosis.

**Hormone Replacement Therapy (HRT)**
At this time, it is not clear whether HRT use affects the risk of lung cancer in women. More than 20 studies have been published, and the results have been inconsistent. Most of the currently available information comes from case-control and cohort studies. Cumulatively, these studies are variable; they have found associations demonstrating an increased risk of lung cancer, no effect, and a protective effect of HRT on lung cancer risk. However, in a large randomized controlled study, no increase in the incidence of lung cancer was found among postmenopausal women treated with estrogen plus progestin HRT, but deaths from lung cancer (especially NSCLC) were higher among patients receiving HRT.

**Selection of High-Risk Individuals for Screening**
As previously described, there are well-known risk factors for the development of lung cancer, especially smoking tobacco. Results from the recently concluded NLST support screening select individuals who are at high risk for lung cancer. The NCCN panel recommends that high-risk individuals should be screened; however, moderate and low-risk individuals should not be screened at this time (see the NCCN Lung Cancer Screening algorithm). Patients are selected for the different risk categories using the NLST inclusion criteria, non-randomized studies, and/or observational studies. Based on the available data, the NCCN Lung Cancer Screening panel recommends using the following criteria to determine whether individuals are at high, moderate, or low risk for lung cancer.

**High-Risk Individuals**
The NCCN panel recommends lung cancer screening using helical LDCT for individuals with the following high-risk factors (see the NCCN Lung Cancer Screening algorithm).

1. Screening is recommended (category 1) for high-risk individuals: age 55-74 years; ≥30 pack-year history of smoking tobacco; and if former smoker, have quit within 15 years. Some high-risk individuals in the NLST also had COPD and other risk factors. This is a category 1 recommendation, because these individuals are selected based on the NLST inclusion criteria. As previously described (see beginning of this Discussion), an NCCN category 1 recommendation is based on high-level evidence (i.e., randomized controlled trial) and uniform consensus among NCCN panel members.

Annual screening is recommended for these high-risk individuals until they are 74 years old based on the NLST.
However, there is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.

2) Screening is also recommended (category 2B) for high-risk individuals: age $\geq 50$ years, $\geq 20$ pack-year history of smoking tobacco, and one additional risk factor.\(^{61}\) This is a category 2B recommendation from the NCCN panel, because these individuals are selected based on non-randomized studies and observational data.\(^{61}\) These additional risk factors were previously described and include: cancer history, lung disease history, family history of lung cancer, radon exposure, and occupational exposure (see the NCCN Lung Cancer Screening algorithm). Note that the NCCN panel does not currently feel that exposure to second-hand smoke is an independent risk factor, because the data are either weak or variable (see earlier section on “Exposure to Second-Hand Smoke” in this Discussion).

**Moderate-Risk Individuals**

NCCN defines moderate-risk individuals as those: age $\geq 50$ years and $\geq 20$ pack-year history of smoking tobacco or second-hand smoke exposure, but no additional lung cancer risk factors.\(^{61}\) The NCCN Lung Cancer Screening panel does not recommend lung cancer screening for these moderate-risk individuals. This is a category 2A recommendation, based on non-randomized studies and observational data.

**Low-Risk Individuals**

NCCN defines low-risk individuals as those: age $< 50$ years and/or smoking history $< 20$ pack-years.\(^{61}\) The NCCN Lung Cancer Screening panel does not recommend lung cancer screening for these low-risk individuals. This is a category 2A recommendation, based on non-randomized studies and observational data.

**Accuracy of LDCT Protocols and Imaging Modalities**

As shown in the NCCN Lung Cancer Screening algorithm, LDCT is recommended for detecting noncalcified nodules that may be suspicious for lung cancer depending on their type and size (e.g., solid, part solid, and ground glass nodules). Li and colleagues found that the prevalence of malignancy was as follows: ground glass opacities (GGOs) (59%), mixed GGO and solid (48%), and solid (11%).\(^{62}\) GGOs have the highest incidence of malignancy; 75% of persistent GGO are cancer.\(^{63}\) However, the GGOs are mainly adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA), formerly known as bronchioloalveolar carcinoma (BAC), which have 100% 5-year disease-free survival if completely resected.\(^{63,64}\) Solid and part-solid nodules are more likely to be invasive and faster growing cancers, which are reflected in the increased suspicion and follow-up of these nodules.\(^{14}\)

Helical multidetector CT (MDCT) of the chest has made it possible to detect very small lung nodules, both benign and malignant. The ability to acquire thinner slices, the use of maximum intensity projection (MIP) or volume rendered (VR) images, and computer-aided diagnosis (CAD) software have increased the sensitivity of small nodule detection.\(^{65-74}\) The use of thinner images has also improved the characterization of small lung nodules.\(^{75}\)

For lung cancer screening, LDCT without intravenous contrast is currently recommended instead of standard-dose CT to decrease the dose of radiation. Although there is no strict definition of LDCT of the chest (see Table 2), it is usually considered to be approximately 10%-30% of standard-dose CT. In most cases, LDCT has been shown to be as accurate as standard-dose CT for the detection of solid...
pulmonary nodules, although nodule detection with LDCT may be limited in larger patients. However, LDCT appears to be less sensitive for detection of very low-density nonsolid nodules or GGOs. Decreasing the radiation dose does not significantly affect the measurement of nodule size when using 1-mm thick slices. These low-dose scans require radiologists to assess images that are much noisier than they are currently used to seeing. Studies suggest that some variation occurs in interpretation of LDCT scans among radiologists.

Recent LDCT lung cancer screening studies using MDCT have reported that lung cancer mortality is decreased when compared with unscreened cohorts or those receiving chest x-rays. However, studies using multi-detector LDCT screening for lung cancer in high-risk patients have applied various different protocol algorithms for detection and follow-up of pulmonary nodules/lesions. These protocols have been based on the positive relationships between 1) nodule size and/or nodule consistency/density and likelihood of malignancy; 2) nodule size and tumor stage; and 3) tumor stage and survival. They also take into account the average growth rate of lung cancer (i.e., doubling time). Most of these protocols have recommended consideration of the use of dynamic contrast-enhanced CT and/or PET/CT for nodules that are at least 7-10 mm, because these technologies have been shown to increase specificity for malignancy. In the workup of pulmonary nodules detected by CT in a high-risk lung cancer screening population, the roles of contrast-enhanced CT and PET/CT are still in evolution.

Optimally, these lung cancer screening methods will maximize detection of early stage lung cancer and minimize false-positive results, unnecessary invasive procedures, radiation exposure, and cost. In at least one medical center, improvement in CT equipment and change in screening protocol have been shown to increase early lung cancer detection, decrease the surgery rate, and improve cancer specific survival. Strict adherence to a screening protocol may also significantly reduce unnecessary biopsies.

Currently, it is difficult to determine the most accurate protocol for lung cancer detection by LDCT because of differing patient populations, methodologies, lengths of follow-up, and statistical analyses between lung cancer screening studies. Recent LDCT screening programs (with multiple years of follow-up) report that 65%-85% of their detected lung cancers are stage I. The I-ELCAP (International Early Lung Cancer Action Program) and the NLST are the 2 largest recent series examining lung cancer detection by LDCT in high-risk patients (see section on “Benefits of Lung Cancer Screening” in this manuscript).

Differences in screening algorithms or recommended diagnostic pathways between these 2 studies are summarized in Table 1. In 2005, the Fleischner Society published guidelines for the management of small pulmonary nodules detected on LDCT scans. Most radiologists in the United States are aware of these guidelines and/or work in a practice that uses these guidelines. However, these recommendations do not specifically address the management of part solid or nonsolid pulmonary nodules. Although our understanding of the histology and behavior of nonsolid and part solid nodules has changed in recent years, interim guidelines for assessment and management of subsolid nodules were recently proposed.

Because of the familiarity and/or acceptance of the Fleischner Society guidelines among radiologists, pulmonologists, and thoracic surgeons,
these same principles have been incorporated into the NCCN recommendations for lung cancer screening. The NCCN recommendations in the Lung Cancer Screening algorithm are an adaptation of the Fleischner Society guidelines, proposed guidelines for subsolid nodules by Godoy, NLST data, and the I-ELCAP protocol guidelines (http://www.ielcap.org/professionals/docs/ielcap.pdf).14,106 The currently proposed NCCN recommendations are less aggressive (i.e., less frequent LDCT) than the I-ELCAP protocol for the workup of baseline, and new solid and part solid nodules ≤6 mm. However, the NCCN recommendations are slightly different (i.e., consider PET/CT and/or contrast-enhanced CT) than the I-ELCAP protocol (see Table 1) in the evaluation of solid and part solid nodules greater than 8 mm, because the NCCN guidelines recommend considering short-term assessment with PET/CT (to increase nodule specificity) rather than longer term assessment with LDCT.

The NCCN definition of nodule growth is 1) an increase in mean diameter of 2 mm or more for nodules ≤15 mm or in the solid portion of a part solid nodule when compared to the baseline scan, or 2) an increase of 15% in mean diameter if the nodule is 15 mm or more when compared to the baseline scan. Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter when compared to the baseline scan. This definition of nodule growth is based on intraobserver and interobserver variability when measuring small pulmonary nodules, and on the minimum change in diameter that can be reliably detected by conventional methods (excluding volumetric analysis software).108 This definition of nodule growth is simplified compared with the formula used by I-ELCAP (see Table 1), which requires nodule growth of 1.5-3.0 mm in mean diameter for nodules 3-15 mm, depending on their diameter. The NCCN definition of nodule growth should also result in fewer false-positive diagnoses compared with the NLST suggested definition of nodule growth (≥10% increase in nodule diameter).8

Currently, the NCCN recommendations do not take into consideration other possibly relevant nodule features, such as proximity to the pleura or fissure.109-111 At this time, the topics of nodule volumetric analysis and/or calculations of tumor doubling time have not been addressed. In some cases, it may be appropriate to perform standard-dose CT with or without IV contrast for follow-up or further evaluation of lung or mediastinal abnormalities detected on screening LDCT.

The recommended LDCT acquisition parameters in this NCCN Lung Screening guideline (see Table 2) are similar to many of the recent and ongoing lung cancer screening studies using low-dose MDCT. Use of MIP, VR, and/or CAD software is highly recommended in addition to evaluation of conventional axial images for increased sensitivity of small nodule detection. A detector collimation of ≤1.5 mm is necessary for optimal use of these 3D applications. For accurate nodule volumetric analysis, some radiologists feel that a detector collimation of ≤1 mm is needed. Measurement and evaluation of small nodules are more accurate and consistent on 1-mm thick images compared with 5-mm images.75 There may be a similar, but less pronounced benefit, in evaluating nodules on 1-mm reconstructed images, after detecting them on 2.5-3.0 mm thick slices. Because slice thickness, reconstruction algorithms, and postprocessing filters affect nodule size measurement, the same technical parameters should be used for each screening LDCT. “Ultra-low-dose” chest CT currently produces lower sensitivity for nodule detection, especially in larger patients.77 However, new LDCT technologies may soon make it possible to significantly decrease the radiation dose without compromising nodule detection and evaluation.112-115
Benefits of Lung Cancer Screening

In this section, current information is summarized about the possible or projected benefits of screening for lung cancer using helical LDCT scans, including: 1) decreased lung cancer mortality, or improvement in other oncologic outcomes, 2) quality of life benefits from screening and from early detection (compared to standard clinical detection), 3) cost-effectiveness of screening, and 4) detection of disease, other than lung cancer, but requiring treatment.

Oncology Outcomes

After a clinical diagnosis of NSCLC, survival is directly related to stage at the time of diagnosis. Although the earliest stage patients (IA) may have a 5-year survival of about 75% with surgery, the outcomes quickly decrease with increasing stage (e.g., 5-year survival is 71% with stage IB, 58% with IIA, 49% with IIB, and less than 25% for stages III and IV). Note that staging for NSCLC was recently revised in January 2010 (see the NCCN Non-Small Cell Lung Cancer Guideline). While intuitively appealing to conclude that earlier detection of disease will improve outcome, screen-detected lung cancers may have a different natural history than clinically detected cancers and an apparent improvement in survival due to early detection itself (lead-time bias). Pathology results of resected lung cancers ... that screening increases the detection of indolent cancer. However, randomized trial data from the NLST show that LDCT screening decreases lung cancer mortality.

Non-Randomized Trials

Of the single-armed screening studies (i.e., non-randomized), the I-ELCAP study is the largest. It included 31,567 high-risk patients from around the world, all of whom were to be screened with baseline and annual LDCT scans analyzed centrally in New York. In the I-ELCAP study, Henschke and colleagues reported that a high percentage of stage I cancers (85%) were detected using LDCT, with an estimated 92% actuarial 10-year survival for stage I cancers resected within 1 month of diagnosis (62% of all cancers detected). The authors noted that 8 participants with clinical stage I cancer who opted not to receive treatment all died within 5 years, similar to published medical literature examining the natural history of stage I NSCLC. They concluded that annual helical LDCT screening can detect lung cancer that is curable. Important caveats about I-ELCAP include that it was not randomized, median follow-up time was only 40 months, and less than 20% of the subjects were observed for more than 5 years. Given the limited follow-up, the estimates of 10-year survival may have been overstated.

A study by Bach and colleagues raised concern that LDCT screening may lead to overdiagnosis of indolent cases without substantially decreasing the number of advanced cases or the overall attributable deaths from lung cancer. However, although overdiagnosis did occur with LDCT in the NLST, the magnitude was not large when compared with radiographic screening (83 versus 17 stage IA BAC [also known as AIS or MIA]). Data from the ELCAP suggest that baseline CT scans find more indolent cancers and subsequent annual scans find more rapidly growing cancers.

Another recent analysis of 7,995 participants in the NY-ELCAP single arm screening trial (the precursor to the I-ELCAP) compared the observed death rate from lung cancer among ELCAP subjects to that seen in participants in large cancer prevention cohort studies who were not undergoing prescribed lung cancer screening with LDCT scans. The analysis was adjusted for age, gender, and smoking status and suggested a significant reduction in deaths from lung cancer among the screened cohort, on the order of 40%-60%.
Randomized Trials

To try to address the concerns of bias and overdiagnosis from single-arm screening (i.e., non-randomized) studies, the NCI launched the NLST in 2002. The NLST was a prospective, randomized lung cancer screening trial comparing annual LDCT scan to annual chest x-ray for 3 years; this trial was designed to have 90% power to detect a 21% decrease in the primary end-point, lung cancer-specific mortality in the screened group. The investigators enrolled 53,454 high-risk participants age 55-74 years who had at least a 30-pack-year smoking history. If subjects were no longer smoking tobacco, they had to have quit within the previous 15 years. All screening exams were completed by mid-2007, and the study mandated a Data Safety Monitoring Board (DSMB) that met twice annually to evaluate follow-up information. In October 2010, the DSMB concluded that sufficient information was available to assess the primary outcome of the study. A NCI press release about the NLST findings was provided in November 2010. The NLST results were recently published and showed a substantial reduction in lung cancer specific mortality and a reduction in all-cause mortality (http://www.cancer.gov/newscenter/pressreleases/2011/NLSTprimaryNEJM).

The NLST participants were similar to a US census population of heavy smokers in terms of gender, but the NLST population was generally younger, better educated, and less likely to be current smokers. Subjects in both the LDCT screening and chest x-ray screening arms were very compliant (>90%) with their designated screening tests. The screening tests were deemed positive if there was a finding that was suspicious for lung cancer (i.e., suspicious nodule). Overall 24% of the LDCT scans and 7% of the chest x-rays performed were positive screens, an imbalance that was expected based on prior data. In each of the 3 years of screening, positive LDCT scan screens were determined to actually be lung cancer cases (i.e., true positive) 4%, 2%, and 5% of the time. The chest x-ray true positive rates were 6%, 4%, and 7% over the 3 screening exams.

Based on the published NLST results, 356 participants died of lung cancer in the LDCT arm and 443 participants died of lung cancer in the chest x-ray arm. Thus, LDCT screening yielded a 20% reduction in lung-cancer specific mortality. In addition, there was a 7% improvement in all-cause mortality. These results are impressive, and the NLST represents the first randomized study to demonstrate an improvement in either disease-specific or overall mortality when using a lung cancer screening program. The NLST results indicate that to prevent one death from lung cancer, 320 high-risk individuals need to be screened with LDCT. The NLST results will likely change medical practice in the United States. Results of the NELSON trial are anxiously awaited to ensure the NLST findings are validated in a separate cohort; further analysis of the NLST, including comparative effectiveness modeling, is underway.

The 20% reduction in mortality from LDCT screening (when compared with chest x-ray) may actually be greater in clinical practice, because chest x-rays are not currently recommended for lung cancer screening as standard practice (by either the American Thoracic Society or the American College of Chest Physicians). In addition, if annual lung screening is continued for more than 3 years, this increased screening may yield mortality reductions of more than 20% (which was reported by the NLST after annual lung screening for only 3 years). Recent findings suggest that evaluating the impact of breast cancer screening requires follow-up of at least 20 years to demonstrate the benefits of screening.
Quality of Life

The NLST assessed quality of life among participants at the time of each annual screening study, but these results are not yet available. Possible quality-of-life benefits from early lung cancer detection (as opposed to detection at the time of clinical symptoms) include: 1) reduction in disease-related morbidity, 2) reduction in treatment-related morbidity, 3) alterations in health affecting lifestyles, and 4) reduction in anxiety and psychological burden.

Reduction in Disease-Related Morbidity

It is a reasonable assumption that the disease-related symptom burden would be decreased in patients whose lung cancer is detected early (via screening) compared to late (via clinical presentation). Most patients whose lung cancer is detected early are asymptomatic, and detection is often either incidental or part of a screening protocol. Historically, most patients with lung cancer have presented with symptoms of the disease (including cough, dyspnea, hemoptysis, pain, weight loss, and cachexia), and thus their lung cancer was detected clinically. An important analysis of the NLST quality of life data will be to assess the 2 cohorts for differences in the types of symptoms experienced at the time of diagnosis of lung cancer to see if screening truly can decrease the lung cancer symptom burden.

Reduction in Treatment-Related Morbidity

Patients with early stage lung cancer are primarily treated surgically, sometimes with adjuvant chemotherapy, while those with more advanced disease are treated with a combination of chemotherapy and radiation, or chemotherapy alone (see the NCCN NSCLC guidelines). Patients with early stage lung cancer who have an R0 resection have increased survival when compared to those with more advanced disease who have definitive chemoradiation therapy. However, few data have been published comparing the treatment burden of surgery versus chemoradiation therapy. It seems reasonable to assume that a patient with stage I lung cancer requiring a lobectomy alone probably has less treatment-related morbidity than a patient with stage III lung cancer requiring combined-modality therapy (i.e., chemotherapy, radiation, and a possible lung resection). However, this has not been shown.

The NLST found that 40% of the cancers detected in the CT-screening group were stage IA, 12% were stage IIIB, and 22% were stage IV. Conversely, 21% of the cancers detected in the chest x-ray group were stage IA, 13% were stage IIIB, and 36% were stage IV. These results suggest that LDCT screening decreases the number of cases of advanced lung cancer, and therefore, may decrease treatment-related morbidity. Lung cancer screening may reduce the number of patients who require pneumonectomy for treatment of lung cancer, which will reduce treatment-related morbidity and mortality. Several series have shown that pneumonectomy is performed in only 1% of cases of lung cancer diagnosed in CT screening programs in contrast to the 20%-30% rate of pneumonectomy in symptom detected cases.

Alterations in Health that Affect Lifestyles

It has been suggested that the process of lung cancer screening itself may increase smoking cessation rates. Conversely, it has also been suggested that negative results on a lung cancer screening test may provide a false sense of security to smokers and result in higher smoking rates. Neither hypothesis has been supported by any substantial evidence. A non-randomized screening study reported that smoking cessation rates were higher when more follow-up LDCT scans were ordered for abnormal findings, regardless of ultimate diagnosis of cancer, suggesting that patients became “scared” into quitting. In a controlled study, however, smoking abstinence rates were similarly higher than expected in both screened and unscreened arms. This
result suggests that the positive effect on smoking cessation was likely unrelated to the screening test results and may reflect a higher desire to be healthy among volunteers participating in screening clinical trials.\textsuperscript{135}

Smokers—including those undergoing lung cancer screening—should always be encouraged to quit smoking tobacco (http://www.smokefree.gov/).\textsuperscript{136} Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the Food and Drug Administration) can be very useful (see \textit{Treating Tobacco Use and Dependence: Quick Reference Guide for Clinicians} (http://www.surgeongeneral.gov/tobacco/tobaqrg.htm).

\textbf{Reduction in Anxiety and Psychological Burden}

As with mammogram screening for breast cancer, there has been discussion of whether lung cancer screening causes anxiety or improves overall quality of life. The randomized NELSON screening study recently published health-related quality of life data from 733 participants. In the short term, recipients of an indeterminate result from the LDCT scan experienced increased distress, while there was relief after a negative baseline screening exam.\textsuperscript{137} After 2 years of follow-up, data from the NELSON trial suggest that lung screening did not adversely affect quality of life.\textsuperscript{138} However, further longitudinal studies will need to be conducted to determine the long-term effect. Patients’ attitudes toward risk in their life (risk perception) also affect greatly their anxiety when undertaking cancer screening examinations.\textsuperscript{139} There is little definitive research to support or refute effects on quality of life from lung cancer screening.

\textbf{Cost-Effectiveness}

Only a small number of preliminary cost-benefit analyses have been performed with respect to lung cancer screening, and many are based on modeled predictive systems because randomized clinical trials have only recently been completed.\textsuperscript{140} In fact, a current fundamental flaw with cost-benefit analyses for lung cancer screening is that because the true benefit of screening requires more years of follow-up and more years of screening to realize the full potential, this crucial factor in prior analyses has been arbitrarily assigned or assumed.\textsuperscript{125} The types of assumptions made can significantly affect the conclusions of the analysis. Furthermore, many cost-benefit analyses do not adequately represent the detrimental effects of false-positive test results on screening. For a person undergoing lung cancer screening with 2 sequential annual exams, the cumulative risk of a false-positive test result was 33%.\textsuperscript{141} The economic effect of false-positive cancer screening results has been estimated to be at least $1000 per incident.\textsuperscript{142}

The original ELCAP study constructed a decision analysis model from their data.\textsuperscript{143} They documented that diagnostic procedure costs and hospital/physician costs in the first year after the diagnosis of lung cancer proportionally increased with increasing stage. Because they detected primarily early stage cancers, they estimated that a baseline screening LDCT scan could increase survival by 0.1 year at an incremental cost of about $230 (this study was published in 2003). The incremental cost per life-year gained ratio is also very sensitive to the fraction of the patients screened and found to have early stage disease; the higher the percentage of patients found with early stage disease, the lower the incremental cost ratio.\textsuperscript{144} The emerging NSLT data will need to be carefully examined in order to ascertain the proportion of patients diagnosed with early stage disease, their comparative mortality and morbidity, and the associated costs. Additional studies to examine other cohorts at risk will also be helpful in future cost-effectiveness analysis models.
Risks of Lung Cancer Screening

Lung cancer screening with LDCT has inherent risks and benefits. The risks of lung cancer screening need to be understood to determine whether screening is beneficial. The possible or projected risks of screening for lung cancer using LDCT scans include: 1) false-positive results, leading to unnecessary testing, unnecessary invasive procedures (including surgery), increased cost, and decreased quality of life because of mental anguish; 2) false-negative results, which may delay or prevent diagnosis and treatment because of a false sense of good health; 3) futile detection of small aggressive tumors (which have already metastasized, preventing meaningful survival benefit from screening); 4) futile detection of indolent disease (i.e., overdiagnosis), which would never have harmed the patient who receives unnecessary therapy; 5) indeterminate results, leading to additional testing; 6) radiation exposure; and 7) physical complications from diagnostic workup. Patients with several co-morbid conditions may be at greater risk than those with few or none.

False-Positive Results

Lung cancer screening studies (which have included only high-risk populations) have found a high rate of non-calcified nodules >4 mm on LDCT screening, with false-positive rates ranging from 10%-43%. In the NLST, the false-positive rate was 96.4% for the CT screening group. The cumulative risk of a false-positive result was 33% for a person undergoing lung cancer screening with 2 sequential annual exams. These “positive” results then require follow-up, which may include surveillance with chest LDCT scans, percutaneous needle biopsy, or even surgical biopsy. Each one of these procedures has their own risks and potential harms. About 7% of individuals with a false-positive result will have an invasive procedure (typically bronchoscopy). However, in the NLST, the rate of major complications after an invasive procedure was very low (only 0.06%) after workup for a false-positive result in the CT screening group.

The NCCN Lung Cancer Screening protocol may avoid much of the most invasive follow-up for noncalcified nodules that are detected on baseline screening with LDCT (see the NCCN algorithm). The NCCN protocol utilizes the NLST and I-ELCAP protocols/recommendations (see Table 1) and the Fleischner Society guidelines and is based on expert opinion from the NCCN panel members. However, even repeat chest LDCT scanning carries the risks of: 1) increased radiation exposure; 2) increased cost of follow-up scans and clinic visits; and 3) ongoing anxiety to the individual who must wait for the results of repeat chest LDCT scans. Bach and colleagues also provide insight into the potential harms of LDCT screening, which results in a 3-fold increase in lung cancer diagnosis and a 10-fold increase in lung cancer surgery; this represent substantial psychological and physical burdens. Although the I-ELCAP investigators reported a surgical mortality rate of only 0.5% (when surgery is done by board certified thoracic surgeons at cancer centers), the average surgical mortality rate for major lung surgery across the United States is 5%, and the frequency of serious complications is greater than 20%. These potential harms of thoracic surgery mandate that the effectiveness of LDCT screening be accurately assessed.

False-Negative Results

Sone and colleagues published 2 reports on lung cancers missed at screening. Of the 88 lung cancers diagnosed, 32 were missed on 39 LDCT scans; 23 were due to detection errors (with a mean size of 9.8 mm) and 16 were due to interpretation errors (with a mean size of 15.9 mm). Detection errors included 1) subtle lesions (91%) appearing as GGOs; and 2) lesions (83%) that were overlapped with, obscured by, or similar in appearance to normal structures (such as blood
vessels). Interpretation errors (87%) were seen in patients who had underlying lung disease such as tuberculosis, emphysema, or fibrosis.

The second report revealed that 84% of missed cancers in that database were subsequently detected using an automated lung nodule detection method. The CAD method involved the use of gray-level thresholding techniques to identify 3-dimensionally contiguous structures with the lungs, which were possible nodule candidates. The problem is that CAD systems are not universally deployed, and the “success” of detecting disease can vary greatly among radiologists. The variability and success of CAD and volumetric analysis systems may also affect the success of screening trials. While these issues are partly being addressed through NCI sponsored programs (such as the RIDER and PAR 08-225 programs), the range in variability at various centers, particularly outside of academic institutions, may lead to significant differences in results compared to the published results in clinical trials. It is possible that false-negative results for a screening test may provide an individual patient with a false sense of security, leading a patient to perhaps ignore symptoms that may have previously led to more evaluation.

**Futile Detection of Small Aggressive Tumors**

Early detection using lung cancer screening may not be beneficial if a small tumor is very aggressive and has already metastasized, with a loss of opportunity for effective treatment. Studies show that a 5-mm lung cancer has undergone approximately 20 doublings yielding $10^{8}$ cells, while patient death typically occurs with a tumor burden of $10^{12}$ cells. Even small tumors may have already metastasized. Studies have also shown that metastases can occur at the time of angiogenesis, when lesions are approximately 1-2 mm. Human tumors grown in nude mouse models can shed 3-6 million cells per gram of tissue every 24 hours, setting up the potential for early metastasis.

However, the NLST trial results show that lung cancer screening is effective in select high-risk patients. The data from this trial show that detecting and treating lung lesions leads to a reduction in lung cancer specific mortality. Therefore, the likelihood of futile therapy in patients with screen detected tumors is much less, albeit not zero. However, because the natural history of lung cancer is heterogeneous and not completely predictable or linear, there remains the potential for futile treatment in those patients with an aggressive tumor that is already incurable at the time of screening diagnosis.

**Futile Detection of Indolent Disease**

Although lung cancer specialists generally have a strong opinion of the uniform fatality of untreated lung cancer, recent studies of some low-grade lung cancers (i.e., BAC) demonstrate a potential for prolonged survival in some patients with NSCLC, even without therapy. Note that a new lung adenocarcinoma classification has recommended that the term “BAC” should not be used anymore. Newly defined entities of AIS and MIA, which are likely to present as GGN, should have 100% 5-year disease-free survival if completely resected. A greater percentage of the lepidic pattern (formerly BAC pattern), which corresponds with the ground glass component in a part solid nodule, is correlated with more favorable prognosis.

Furthermore, experience in lung cancer screening has raised the question of an increased identification of indolent tumors in the screened population. These indolent tumors may not cause symptoms or cancer mortality; therefore, patients are not benefited by screening and subsequent workup and treatment. A percentage of these patients will undergo the risk, morbidity, and mortality of surgical...
resection that, in retrospect, will not increase their life expectancy. As the newly defined entities of AIS and MIA (formerly BAC) with excellent survival have been separated from overtly invasive adenocarcinomas, there is potential to learn how to minimize surgical intervention for pure GGN through CT screening studies and long-term follow-up.\(^6\)

Bach and colleagues found an increase in the number of lung cancer patients detected among screened patients, yet no evidence of a decline in the number of deaths from lung cancer.\(^{12}\) Their non-randomized study raised concern that LDCT screening may lead to overdiagnosis of indolent cases and to the morbidity of treatment, without a survival benefit. However, the recent randomized NLST found that LDCT does decrease lung cancer mortality.\(^8\)

**Quality of Life**

It is not fully known what effect a lung cancer screening trial will have on the quality of life (see “Benefits of Lung Cancer Screening” in this manuscript). In a study by van den Bergh and colleagues, there were no measured adverse affects, although there was discomfort of waiting for the results, which was reported by approximately half of the participants.\(^{16}\) However, others have reported significant personal and physical quality of life issues from screening tests (http://health.usnews.com/usnews/health/articles/030519/19diagnosis.htm). Several studies (including the NLST and NELSON trial) will be measuring quality of life issues.\(^{137,138}\) Recent data from the NELSON trial suggest that lung screening did not adversely affect quality of life due to mental anguish and additional testing.\(^{138}\) False-positive and indeterminate results may decrease quality of life due to mental anguish and additional testing.

**Unnecessary Testing**

Any lung cancer screening program will result in additional testing. In a report by Croswell and colleagues (from the Prostate, Lung, Colorectal, and Ovarian [PLCO] trial), the cumulative risk of having one false-positive result was 60% for men and 49% for women. The cumulative risk of undergoing an invasive diagnostic procedure prompted by the false-positive test was 29% for men and 22% for women.\(^{16}\) The NLST is a carefully supervised randomized controlled trial. In a less controlled environment, the rate of additive studies may be higher. Sistrom and coauthors reviewed the recommendations for additional imaging in more than 5.9 million radiology reports; they reported additional imaging of 35.8% for chest LDCT.\(^{16}\) The issue of incidental findings on screening examinations is problematic, and there are some organizations attempting to address the issue, but regional and physician variations remain.\(^{167}\)

**Radiation Exposure With LDCT**

Current MDCT scanners provide a significantly enhanced capability for detecting small nodules by allowing thinner slice images. Using low-dose techniques, the effective radiation dose is 0.65 mSv compared to 5.8 mSv for conventional CT. However, the radiation dose of LDCT is 10 times that of chest radiography.

There may be even more reason to be concerned about utilization of chest LDCT scans for lung cancer screening, because there may be adverse effects of increased radiation exposure to these individuals who are already at high risk for lung cancer. In fact, the effects of repeated exposure to radiation at regular intervals are not known. Brenner has estimated a 1.8% increase in lung cancer cases if 50% of all current and former smokers in the United States between the ages of 50-75 years were to undergo annual LDCT scans for lung cancer screening.\(^{168}\) However, lower doses of radiation are now used for LDCT scans and these lower doses may be less dangerous.\(^{169}\) The risk of radiation exposure over long periods will have to be considered when...
screening guidelines are developed, especially when recommending how frequently the scans should be done.

**Increased Cost**

Many are concerned about the effect of lung cancer screening on medical resources including the cost of LDCT screening and additional testing. For each LDCT screen for lung cancer, the Medicare reimbursement rate is about $300 in the United States [http://www.cancer.gov/newscenter/pressreleases/2011/NLSTFastFacts](http://www.cancer.gov/newscenter/pressreleases/2011/NLSTFastFacts). The number of high-risk individuals eligible for lung cancer screening is about 7 million (using NLST data). Thus, the annual cost in the United States would be about $2.1 billion.¹⁸

Helical LDCT screening will lead to false-positive results, detection of indeterminate nodules, and detection of potential disease other than lung cancer. In the NLST, 24.2% of the LDCT scans were “positive”; however, most of these were false positive (96.4%). In 2004, the economic effect of false-positive cancer screening results was estimated to be at least $1000 per incident.¹⁴² Therefore, a conservative estimate of the costs of workup of only the false-positive results after 1 year would be (7 million × 24.2% = 1.694 million × 96.4% = 1.633 × $1000 = $1.63 billion). This estimate does not include costs of workup of other potential abnormalities detected during screening, such as cardiac and upper abdominal pathology. Of individuals with a false-positive result, about 7% will have an invasive procedure (typically bronchoscopy).¹⁴¹

Limiting screening to only high-risk patients not only helps to avoid unnecessary risks in individuals with a lower risk of cancer but also is important so that the screening program is cost effective. "Pre-screening"—using age, smoking history, appropriate medical history, family history, and occupational history—is important to determine which patients are high risk (see the NCCN Lung Cancer Screening algorithm).

Lack of well-defined guidelines can lead to over utilization of screening. Excessive screening and/or interpretations of studies by unskilled individuals may occur without strict guidelines (as with mammography). Other factors, such as the interval at which screening should be performed, will also affect calculations of cost. In the recent screening studies using helical LDCT, 23% of the ELCAP and 69% of the 1999 Mayo Clinic study had at least one indeterminate nodule. Depending on the size and characteristics of the indeterminate nodule, further evaluation may include serial follow-up LDCT, dynamic contrast-enhanced nodule densitometry, positron emission tomography (PET), or biopsy. In addition, false-positive results also lead to additional unnecessary testing and increased cost as previously described. The financial burden, potential complications from invasive procedures, and psychological effect of investigating these indeterminate and false-positive lesions are not fully understood.

Lung screening also leads to detection of disease other than lung cancer such as infection; coronary artery calcification; and renal, adrenal, and liver lesions. Although detection of other diseases may frequently provide a clinical benefit to the patient, certainly costs will be further increased with additional testing and treatment.

**Cost-Effectiveness**

It is also important to consider the cost-effectiveness of lung cancer screening. LDCT imaging is more expensive than many other screening programs, and it is therefore important to validate the effectiveness first. Each LDCT screen for lung cancer costs about $300 [http://www.cancer.gov/newscenter/pressreleases/2011/NLSTFastFacts](http://www.cancer.gov/newscenter/pressreleases/2011/NLSTFastFacts). In contrast, a mammogram costs about $80-$150. Several cost
analyses of LDCT lung cancer screening have been undertaken, but all have some limitations because they used simulation modeling.\textsuperscript{144,170,171} The Mahadevia study concluded that false-positive results are a major obstacle to LDCT screening and may prevent it from being cost effective.\textsuperscript{170} However, Wisnivesky and colleagues have argued that LDCT lung cancer screening is potentially highly cost effective and not different to cost-effectiveness ratios of other screening programs.\textsuperscript{143} The NLST cost-effectiveness evaluation will be extremely beneficial in understanding this issue.

**Summary**

Lung cancer screening with LDCT is a complex and controversial topic with inherent risks and benefits. Results from the large, prospective, randomized NLST show that lung cancer screening with LDCT can decrease lung cancer specific mortality by 20\% and even decrease all-cause mortality by 7\%.\textsuperscript{6} The NLST results indicate that to prevent one death from lung cancer, 320 high-risk individuals need to be screened with LDCT. However, the NLST findings have not been replicated yet in a separate cohort. Further analysis of the NLST is underway, including comparative effectiveness modeling. The cost-effectiveness and true benefit-to-risk ratio for lung cancer screening still need to be determined. At some point, an acceptable level of risk will have to be deemed appropriate for the benefits of screening.

The NCCN Lung Cancer Screening panel recommends helical LDCT screening for select patients at high risk for lung cancer based on the NLST results, non-randomized studies, and observational data. Criteria for determining which patients are at high risk are described in detail in the NCCN Lung Cancer Screening algorithm and this Discussion. In addition, the NCCN algorithm provides recommendations for evaluating and following-up nodules detected on LDCT screening (e.g., solid and part solid nodules).

Smokers should always be encouraged to quit smoking tobacco (http://www.smokefree.gov/). Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the Food and Drug Administration) can be very useful (see *Treating Tobacco Use and Dependence: Quick Reference Guide for Clinicians*) (http://www.surgeongeneral.gov/tobacco/tobagrg.htm).

When considering lung cancer screening, it is important to have a full understanding of all risks and benefits related to screening with LDCT. As policies for implementing lung screening programs are designed, a focus on multidisciplinary programs (incorporating primary care doctors, pulmonologists, radiologists, thoracic surgeons, medical oncologists, and pathologists) will be helpful to optimize decision making and to minimize interventions for patients with benign lung disease.
# Table 1 Comparison of the I-ELCAP and NLST Lung Screening Protocols

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<th>Definition of Positive Nodule*</th>
<th>I-ELCAP</th>
<th>NLST†</th>
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<tr>
<td>Baseline</td>
<td>Solid and PS nodule ≥5mm‡</td>
<td>Nodule ≥4mm</td>
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<td>NS nodule ≥8mm‡</td>
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<table>
<thead>
<tr>
<th>Recommendations for Positive Nodule</th>
<th>I-ELCAP</th>
<th>NLST†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>LDCT in 3 mo, then resume annual LDCT if stable. Consider PET if solid component &gt;10mm. Biopsy if PET positive; annual LDCT if PET negative. If nodule ≥15mm, treat with antibiotics and LDCT at 1 mo, or biopsy. LDCT in 1 mo for solid endobronchial nodule.</td>
<td>Solid or PS nodule 4-10mm, then LDCT 3-6 mo. NS nodule 4-10mm, then LDCT 6-12 mo. If growth but nodule &lt;7mm, then LDCT in 3-6 mo. If growth and nodule ≥7mm, then follow recommendations of nodules &gt;10mm. Any nodule &gt; 10mm consider biopsy, CECT, PET/CT; or LDCT in 3-6 mo if low suspicion.</td>
</tr>
<tr>
<td>Annual</td>
<td>Annual LDCT if NS nodule &lt;8mm. LDCT in 6 mo if new solid/PS nodule. Antibiotics and 1 mo LDCT if solid/PS nodule ≥5mm or NS nodule ≥8mm, then LDCT at 3 mo if nodule stable.</td>
<td>Same as Baseline</td>
</tr>
</tbody>
</table>

| Definition of Nodule Growth | ≥50% increase in mean diameter if nodule <5mm | ≥10% increase in nodule diameter |
|                            | ≥30% increase in mean diameter if nodule 5-9mm |        |
|                            | ≥20% increase in mean diameter if nodule >10mm |        |

CECT = contrast-enhanced CT; CT = computed tomography; I-ELCAP = International Early Lung Cancer Action Program; LDCT = low-dose CT; NLST = National Lung Screening Trial; NS = nonsolid; PET = positron-emission tomography; PS = part solid.


*Requiring imaging or workup in addition to annual LDCT. †Guidelines rather than a strict study regimen. ‡Mean diameter of nodule.
## Table 2 Low-Dose Computed Tomography Acquisition, Storage, Interpretation, and Nodule Reporting

<table>
<thead>
<tr>
<th>Acquisition</th>
<th>Small Patient (BMI ≤30)</th>
<th>Large Patient (BMI &gt;30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total radiation exposure</td>
<td>≤3 mSv</td>
<td>≤5 mSv</td>
</tr>
<tr>
<td>kVp</td>
<td>100-120</td>
<td>120</td>
</tr>
<tr>
<td>mAs</td>
<td>≤40</td>
<td>≤60</td>
</tr>
<tr>
<td>Gantry rotation speed</td>
<td>≤0.5</td>
<td></td>
</tr>
<tr>
<td>Detector collimation</td>
<td>≤1.5 mm</td>
<td></td>
</tr>
<tr>
<td>Slice width</td>
<td>≤3 mm; ≤1.5 mm preferred</td>
<td></td>
</tr>
<tr>
<td>Slice interval</td>
<td>≤ slice width; 50% overlap preferred for 3D and CAD applications</td>
<td></td>
</tr>
<tr>
<td>Scan acquisition time</td>
<td>≤10 seconds (single breath hold)</td>
<td></td>
</tr>
<tr>
<td>Breathing</td>
<td>Maximum inspiration</td>
<td></td>
</tr>
<tr>
<td>Contrast</td>
<td>No oral or intravenous contrast</td>
<td></td>
</tr>
<tr>
<td>CT scanner detectors</td>
<td>≥16</td>
<td></td>
</tr>
<tr>
<td>Storage</td>
<td>All acquired images, including thin sections; MIPs and CAD renderings if used</td>
<td></td>
</tr>
<tr>
<td>Interpretation Tools</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platform</td>
<td>Computer workstation review</td>
<td></td>
</tr>
<tr>
<td>Image type</td>
<td>Standard and MIP images</td>
<td></td>
</tr>
<tr>
<td>Comparison studies</td>
<td>Comparison with prior chest CT images (not reports) is essential to evaluate change in size, morphology, and density of nodules; review of serial chest CT exams is important to detect slow growth</td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index; CAD = computer aided diagnostics; CT = computed tomography; MIP = maximum intensity projection.
### Table 2 Continued
Low-Dose Computed Tomography Acquisition, Storage, Interpretation, and Nodule Reporting

<table>
<thead>
<tr>
<th>Nodule Parameters</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Largest mean diameter on a single image*</td>
</tr>
<tr>
<td>Density</td>
<td>Solid, ground glass, or mixed†</td>
</tr>
<tr>
<td>Calcification</td>
<td>Present/absent; if present: solid, central vs eccentric, concentric rings, popcorn, stippled, amorphous</td>
</tr>
<tr>
<td>Fat</td>
<td>Report if present</td>
</tr>
<tr>
<td>Shape</td>
<td>Round/ovoid, triangular</td>
</tr>
<tr>
<td>Margin</td>
<td>Smooth, lobulated, spiculated</td>
</tr>
<tr>
<td>Lung location</td>
<td>By lobe of the lung, preferably by segment, and if subpleural</td>
</tr>
<tr>
<td>Location in dataset</td>
<td>Specify series and image number for future comparison</td>
</tr>
<tr>
<td>Temporal comparison</td>
<td>If unchanged, include the longest duration of no change as directly viewed by the interpreter on the images (not by report); if changed, report current and prior size</td>
</tr>
</tbody>
</table>

BMI = body mass index; CAD = computer-aided diagnosis; CT = computed tomography; MIP = maximum intensity projection.

*Mean of the longest diameter of the nodule and its perpendicular diameter, when compared to the baseline scan.

†Mixed, otherwise referred to as part solid.
References


107. Eisenberg RL, Bankier AA, Boiselle PM. Compliance with Fleischner Society guidelines for management of small lung nodules: a


138. van den Bergh KA, Essink-Bot ML, Borsboom GJ, et al. Long-term effects of lung cancer computed tomography screening on health-


