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## Lung Cancer Screening, Version 3.2018:

### Clinical Practice Guidelines in Oncology

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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.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. The full NCCN Guidelines for Lung Cancer Screening are not printed in this issue of *JNCCN* but can be accessed online at [NCCN.org](http://NCCN.org).

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Disclosures for the NCCN Lung Cancer Screening Panel

Individual disclosures for the NCCN Lung Cancer Screening Panel members can be found on page 441. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at [NCCN.org](http://NCCN.org).)

These guidelines are also available on the Internet. For the latest update, visit [NCCN.org](http://NCCN.org).

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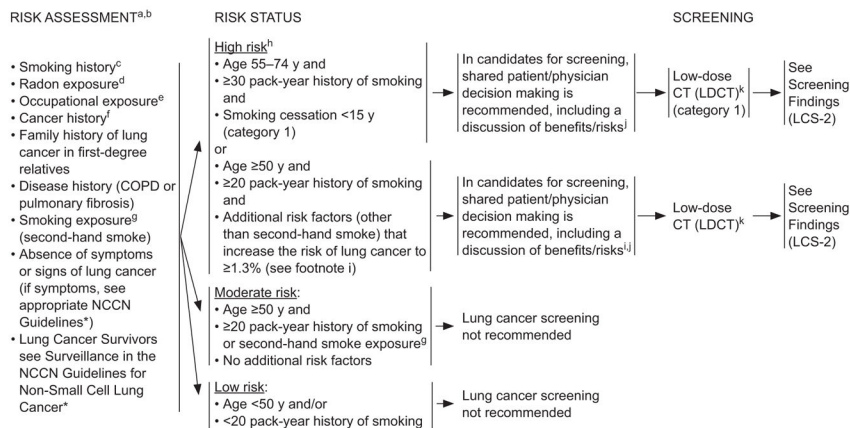
## **Abstract**

Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide. Early detection of lung cancer is an important opportunity for decreasing mortality. Data support using low-dose computed tomography (LDCT) of the chest to screen select patients who are at high risk for lung cancer. Lung screening is covered under the Affordable Care Act for individuals with high-risk factors. The Centers for Medicare & Medicaid Services (CMS) covers annual screening LDCT for appropriate Medicare beneficiaries at high risk for lung cancer if they also receive counseling and participate in shared decision-making before screening. The complete version of the NCCN Guidelines for Lung Cancer Screening provides recommendations for initial and subsequent LDCT screening and provides more detail about LDCT screening. This manuscript focuses on identifying patients at high risk for lung cancer who are candidates for LDCT of the chest and on evaluating initial screening findings.

## **Overview**

Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide.<sup>1–5</sup> In 2018, it is estimated that 154,050 deaths from lung cancer will occur in the United States.<sup>6</sup> Five-year survival rates for lung cancer are only 18%, partly because most patients have advanced-stage lung cancer at initial diagnosis.<sup>7</sup> Currently, most lung cancer is diagnosed clinically when patients present with symptoms such as persistent cough, pain, and weight loss; unfortunately, patients with these symptoms usually have advanced lung cancer. These facts—combined with the success of cervical, colon, and breast cancer screening—have been the impetus for developing an effective lung cancer screening (LCS) test.<sup>8–10</sup> 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.<sup>11</sup> Data support using low-dose computed tomography (LDCT) of the chest to screen select patients who are at high risk for lung cancer.<sup>11–15</sup> Chest x-ray is not recommended for LCS.<sup>11,16,17</sup>

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for LCS were developed in 2011 and have been updated every year.<sup>11,18,19</sup> The NCCN Guidelines 1) describe risk factors for lung cancer; 2) recommend criteria for selecting individuals with high-risk factors for screening; 3) provide recommendations for evaluation and follow-up of lung nodules found during screening; 4) discuss the accuracy of chest LDCT screening; and 5) discuss the benefits and risks of LDCT screening. The “Summary of the Guidelines Updates” section in the algorithm (available at [NCCN.org](https://www.nccn.org)) briefly describes the new changes for 2018. For example, the NCCN cutoff thresholds for lung nodules have been revised to harmonize with the Lung Imaging Reporting and Data System (Lung-RADS) cutoffs.<sup>20–22</sup> The complete version of the NCCN Guidelines for Lung Cancer Screening provides recommendations for initial and subsequent LDCT screening and provides more detail about LDCT screening than this manuscript (see the complete version of the NCCN Guidelines for Lung Cancer Screening, available at [NCCN.org](https://www.nccn.org)). This manuscript focuses on identifying patients at high risk for lung cancer who are candidates for LDCT of the chest and on evaluating initial screening findings.



<sup>\*</sup>To view the most recent version of these guidelines, visit NCCN.org.

<sup>a</sup>It is recommended that institutions performing lung cancer screening use a multidisciplinary approach that includes the specialties of thoracic radiology, pulmonary medicine, and thoracic surgery.

<sup>b</sup>Lung cancer screening is appropriate to consider for high-risk patients who are potential candidates for definitive treatment. Chest x-ray is not recommended for lung cancer screening.

<sup>c</sup>All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support and resources, smokers can be referred to <http://www.smokefree.gov>. Lung cancer screening should not be considered a substitute for smoking cessation. Smoking history should document both extent of exposure in pack-years and the amount of time since smoking cessation in former smokers. See also the NCCN Guidelines for Smoking Cessation<sup>h</sup>.

<sup>d</sup>Documented sustained and substantially elevated radon exposure.

<sup>e</sup>Agents that are identified specifically as carcinogens targeting the lungs: silica, cadmium, asbestos, arsenic, beryllium, chromium, diesel fumes, nickel, coal smoke, and soot.

<sup>f</sup>There is increased risk of developing new primary lung cancer among survivors of lung cancer, lymphomas, cancers of the head and neck, or smoking-related cancers.

<sup>g</sup>Individuals exposed to second-hand smoke have a highly variable exposure to the carcinogens, with varying evidence for increased risk after this variable exposure. Therefore, second-hand smoke is not independently considered a risk factor for lung cancer screening.

<sup>h</sup>Although randomized trial evidence supports screening to age 74 years, there is uncertainty about the upper age limit to initiate or continue screening. One can consider screening beyond age 74 years as long as patient functional status and comorbidity allow consideration for curative intent therapy.

<sup>i</sup>The NCCN panel recognizes there are individuals who would not have met the NLST criteria but are at similar risk to the NLST cohort and recommends lung cancer screening for these individuals. However, substantial uncertainty exists about the true benefits and harms of screening these individuals. It is reasonable to consider using the Tammemagi lung cancer risk calculator to assist in quantifying risk for individuals in this group, considering a 1.3% threshold of lung cancer risk over a 6 year timeframe was considered similar to that of the USPSTF (Tammemagi MC, Church TR, Hocking WG, et al. Evaluation of the lung cancer risks at which to screen ever- and never-smokers: screening rules applied to the PLCO and NLST cohorts. PLOS Med 2014;11:1-13).

<sup>j</sup>Shared decision-making aids may assist in determining if screening should be performed. Examples of decision-making aids: <https://brocku.ca/lung-cancer-risk-calculator>, <http://www.shouldscreen.com/benefits-and-harms-screening>, and <https://www.mskcc.org/cancer-care/types/lung/screening/lung-screening-decision-tool>.

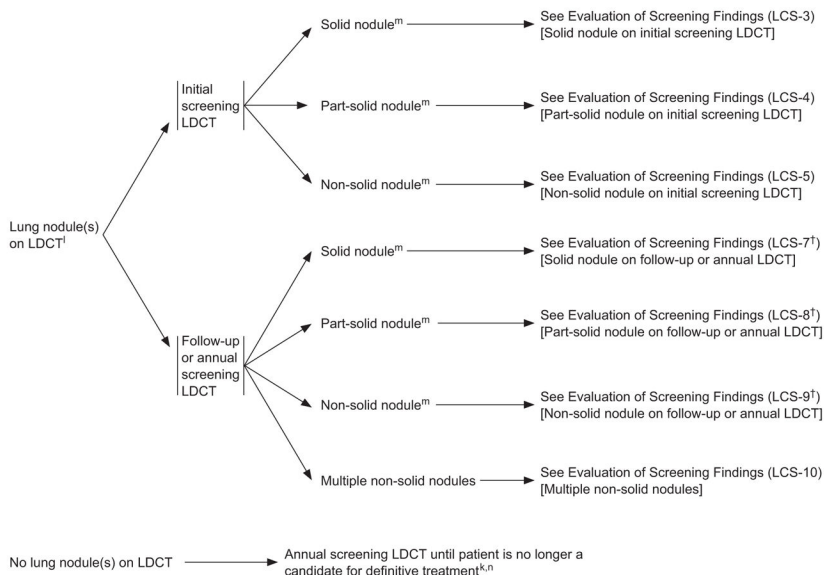
<sup>k</sup>All screening and follow-up chest CT scans should be performed at low dose (100–120 kVp and 40–60 mAs or less), unless evaluating mediastinal abnormalities or lymph nodes, where standard-dose CT with IV contrast might be appropriate (see LCS-A). There should be a systematic process for appropriate follow-up.

LCS-1

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SCREENING FINDINGS

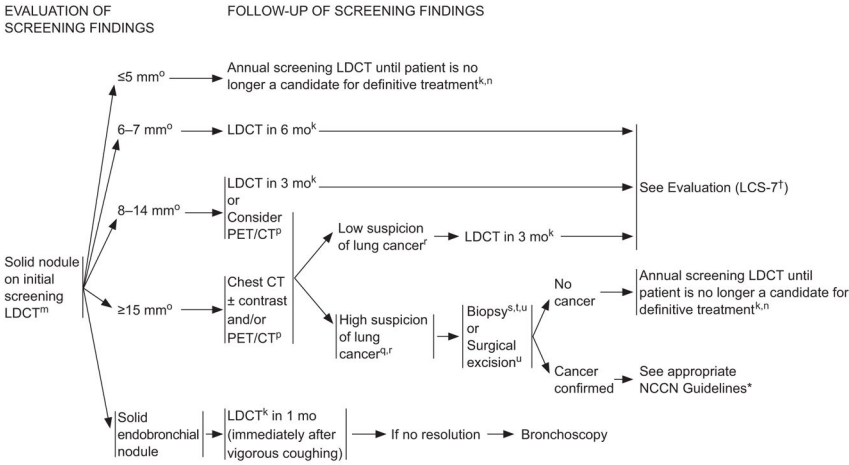


Findings requiring follow-up for diseases other than lung cancer (eg, suspicious for other cancers, COPD, moderate to severe coronary artery calcification, aortic aneurysm)

†Available online, in these guidelines, at NCCN.org.

<sup>k</sup>All screening and follow-up chest CT scans should be performed at low dose (100–120 kVp and 40–60 mAs or less), unless evaluating mediastinal abnormalities or lymph nodes, where standard-dose CT with IV contrast might be appropriate (see LCS-A). There should be a systematic process for appropriate follow-up.  
<sup>l</sup>The NCCN Guidelines for Lung Cancer Screening are harmonized with LungRADS (<http://www.acr.org/Quality-Safety/Resources/LungRADS>). Pinsky PF, Gierada DS, Black W, et al. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. *Ann Intern Med* 2015;162:485-491.  
<sup>m</sup>Without benign pattern of calcification, fat in nodule suggestive of hamartoma, or features suggesting inflammatory etiology. When multiple nodules or other findings are present that suggest occult infection or inflammation is a possibility, suggest follow-up LDCT in 1–3 months.  
<sup>n</sup>There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.

LCS-2

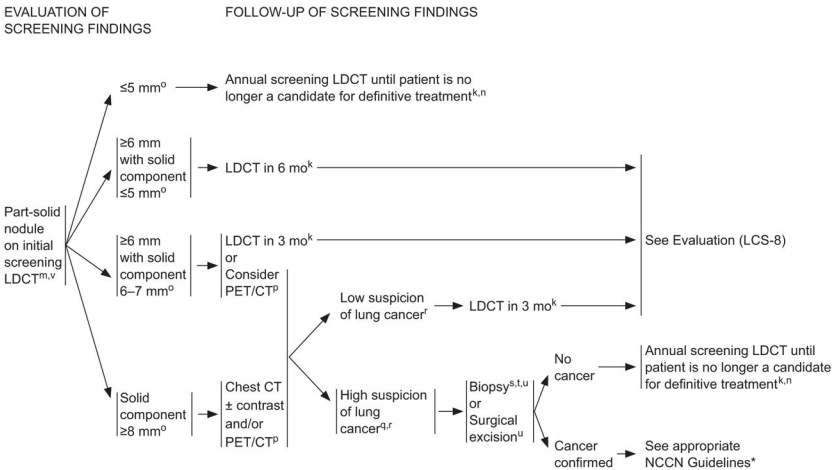


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<sup>n</sup>There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.  
<sup>o</sup>Nodules should be measured on lung windows and reported as the average diameter rounded to the nearest whole number; for round nodules only a single diameter measurement is necessary. Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter.  
<sup>p</sup>PET has a low sensitivity for nodules with less than 8 mm of solid component and for small nodules near the diaphragm. PET/CT is only one consideration of multiple criteria for determining whether a nodule has a high risk of being lung cancer. In areas endemic for fungal disease, the false-positive rate for PET/CT is higher.  
<sup>q</sup>Criteria for suspicion of malignancy: hypermetabolism greater than the adjacent mediastinal blood pool, regardless of absolute SUV.  
<sup>r</sup>The evaluation for the suspicion of lung cancer requires a multidisciplinary approach with expertise in lung nodule management (thoracic radiology, pulmonary medicine, and thoracic surgery). This may include use of a lung nodule risk calculator to assist with probability determination. Examples of lung nodule risk calculators: Mayo risk model; Brock university model; model by Herder, GJ et al. Chest 2005;128:2490-2496. The use of risk calculators does not replace multidisciplinary nodule management. Geographic and other factors can substantially influence the accuracy of nodule calculators.  
<sup>s</sup>Tissue samples need to be adequate for both histology and molecular testing. Travis WD, et al. Rationale for classification in small biopsies and cytology. In: WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, 4th Ed. Lyon:International Agency for Research on Cancer;2015:16-17.  
<sup>t</sup>If biopsy is non-diagnostic and a strong suspicion for cancer persists, suggest repeat biopsy or surgical excision or short-interval follow-up (3 months).  
<sup>u</sup>See the diagnostic evaluation of a lung nodule (DIAG-1 through DIAG-A<sup>†</sup>) in the NCCN Guidelines for Non-Small Cell Lung Cancer\*.



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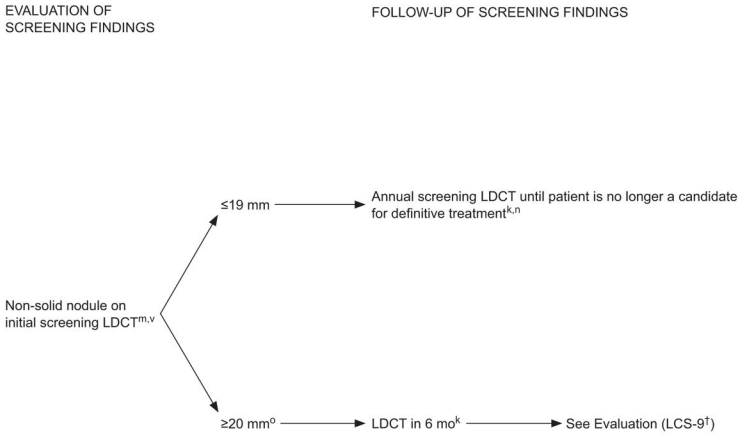
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<sup>u</sup>See the diagnostic evaluation of a lung nodule (DIAG-1 through DIAG-A<sup>†</sup>) in the NCCN Guidelines for Non-Small Cell Lung Cancer\*.

<sup>v</sup>It is crucial that all nonsolid lesions be reviewed at thin (<1.5 mm) slices to exclude any solid components. Any solid component in the nodule requires management of the lesion with the part-solid recommendations (LCS-B<sup>†</sup>).





<sup>†</sup>Available online, in these guidelines, at NCCN.org.

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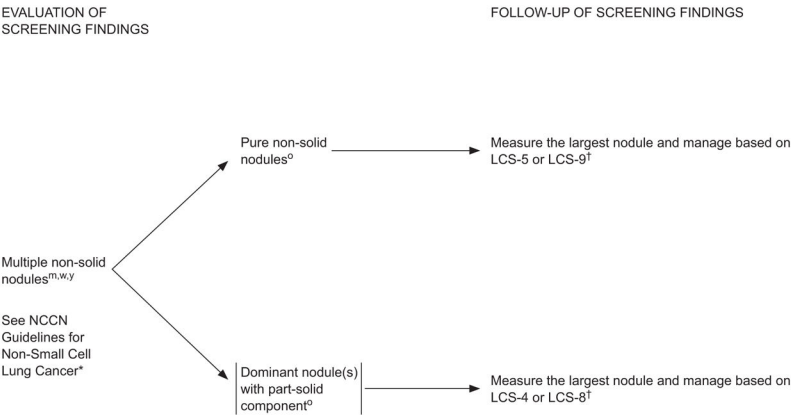
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<sup>v</sup>It is crucial that all nonsolid lesions be reviewed at thin (<1.5 mm) slices to exclude any solid components. Any solid component in the nodule requires management of the lesion with the part-solid recommendations (LCS-8<sup>†</sup>).

Lung Cancer Screening, Version 3.2018



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<sup>m</sup>Without benign pattern of calcification, fat in nodule suggestive of hamartoma, or features suggesting inflammatory etiology. When multiple nodules or other findings are present that suggest occult infection or inflammation is a possibility, suggest follow-up LDCT in 1–3 months.  
<sup>o</sup>Nodules should be measured on lung windows and reported as the average diameter rounded to the nearest whole number; for round nodules only a single diameter measurement is necessary. Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter.  
<sup>w</sup>Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer. (see LCS-6<sup>†</sup>)  
<sup>y</sup>It is crucial that all nonsolid lesions be reviewed at thin (<1.5 mm) slices to exclude any solid components. Any solid component in the nodule requires management of the lesion with the part-solid recommendations (see LCS-4 or LCS-8<sup>†</sup>).

Low-Dose Computed Tomography Acquisition, Storage, Interpretation, and Nodule Reporting<sup>1,2</sup>

Acquisition	Small Patient (BMI ≤30)	Large Patient (BMI >30)
Total radiation exposure	≤3 mSv	≤5 mSv
kVp	100–120	120
mAs	≤40	≤60
<b>All Patients</b>		
Gantry rotation speed	≤0.5	
Detector collimation	≤1.5 mm	
Slice width	≤2.5 mm; ≤1.0 mm preferred	
Slice interval	≤slice width; 50% overlap preferred for 3D and CAD applications	
Scan acquisition time	≤10 seconds (single breath hold)	
Breathing	Maximum inspiration	
Contrast	No oral or intravenous contrast	
CT scanner detectors	≥16	
<b>Storage</b>	All acquired images, including thin sections; MIPs and CAD renderings if used	
<b>Interpretation Tools</b>		
Platform	Computer workstation review	
Image type	Standard and MIP images	
Comparison studies	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	
<b>Nodule Parameters</b>		
Size	Largest mean diameter on a single image*	
Density	Solid, ground-glass, or mixed†	
Calcification	Present/absent; if present: solid, central vs. eccentric, concentric rings, popcorn, stippled, amorphous	
Fat	Report if present	
Shape	Round/ovoid, triangular	
Margin	Smooth, lobulated, spiculated	
Lung location	By lobe of the lung, preferably by segment, and if subpleural	
Location in dataset	Specify series and image number for future comparison	
Temporal comparison	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	

\*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.

<sup>1</sup>Protocol information: <http://www.aapm.org/pubs/CTProtocols/documents/LungCancerScreeningCT.pdf>

<sup>2</sup>The LDCT acquisition parameters should be used both for annual screening LDCT exams and for interim LDCTs recommended to evaluate positive screens. The former are considered screening CTs by CPT code, and the latter are considered diagnostic CTs by CPT code.

LCS-A

## Lung Cancer Screening, Version 3.2018

## 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 workup
- False-positive results
- False-negative results
- Unnecessary testing and procedures
- Radiation exposure
- Cost
- Incidental lesions

## BENEFITS

- Decreased lung cancer mortality<sup>1</sup>
- Quality of life
  - ▶ Reduction in disease-related morbidity
  - ▶ Reduction in treatment-related morbidity
  - ▶ Improvement in healthy lifestyles
  - ▶ Reduction in anxiety/psychosocial burden
- Discovery of other significant occult health risks (eg, thyroid nodule, severe but silent coronary artery disease, early renal cancer in upper pole of kidney, aortic aneurysm, breast cancer)

\*See Discussion for more detailed information.

<sup>1</sup>National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395-409.

LCS-B

The goal of screening is to detect disease at a stage when it is not causing symptoms and when treatment will be most successful. Screening should benefit the individual by increasing life expectancy and increasing quality of life. False-positive results should be low to prevent unnecessary additional testing. The screening test should 1) improve outcomes; 2) be scientifically validated; and 3) be low risk, reproducible, accessible, and cost-effective. LCS is not a substitute for smoking cessation.<sup>23</sup> Smokers, including those undergoing LCS, should always be encouraged to quit smoking tobacco (see the NCCN Guidelines for Smoking Cessation, available at [NCCN.org](http://NCCN.org)).<sup>24-26</sup> Likewise, former smokers should be

encouraged to remain abstinent. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can help individuals to quit smoking.<sup>23,27,28</sup>

### Literature Search Criteria and Guidelines Update Methodology

An electronic search of the PubMed database was performed to obtain key literature in LCS. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: clinical trial, phase 2; clinical trial, phase 3; clinical trial, phase 4; guideline; meta-analysis; randomized controlled trial; systematic reviews; and validation studies. The data from key PubMed articles have been included in this discussion. If high-level evidence is lacking, recommendations are based on the panel's review of lower-level evidence and expert opinion. The complete details of the development and update of the NCCN Guidelines are available on the NCCN web-page ([NCCN.org](http://NCCN.org)).

### LDCT as Part of a Lung Screening Program

LCS with LDCT should be part of a program of care and should not be performed in isolation as a free-standing test.<sup>20,29–31</sup> Trained personnel and a system to contact patients to achieve compliance with recommended follow-up studies are required for an effective lung screening program.<sup>30,32,33</sup> The NCCN-recommended follow-up intervals assume compliance with follow-up recommendations. To help ensure good image quality, all chest LDCT screening programs should use CT scanners that meet the standards of the American College of Radiology (ACR). The ACR has developed Lung-RADS to standardize the reporting and management of LDCT lung examinations.<sup>20,34</sup> The Lung-RADS protocol has been shown to improve the detection of lung cancer and to decrease the false-positive rate.<sup>22,30,32,34,35</sup>

When assessing scans, the most important radiologic factor is change or stability of nodules when compared with a previous imaging study. The risks and benefits of LCS should be discussed with the individual before a screening LDCT scan is performed.<sup>36–39</sup> Shared patient/physician decision-making is recommended before LDCT lung screening, especially for patients with comorbid conditions.<sup>16,40,41</sup> Institutions performing LCS should use a multidisciplinary approach, such as chest radiology, pulmonary medicine, and thoracic surgery.<sup>42</sup> Only centers with considerable expertise in LCS should perform LDCT.<sup>43</sup>

### Randomized Trials

Multiple randomized trials have assessed LDCT screening for lung cancer among high-risk groups.<sup>10,12,44–58</sup> The National Lung Screening Trial (NLST) showed that LDCT decreased the relative risk (RR) of death from lung cancer by 20% (95% CI, 6.8–26.7;  $P=.004$ ) when compared with chest radiography alone.<sup>11</sup> Although the NLST also reported a significant decrease in all-cause mortality of 7%, the apparent decrease is not significant after lung cancer mortality has been subtracted. Analyses of some LCS studies using LDCT scans suggest that overdiagnosis (ie, diagnosis of cancer that would never be life-threatening) and false-positive results are significant concerns.<sup>59–61</sup> A phase 3 randomized trial (The Prostate,

Lung, Colorectal, and Ovarian [PLCO] trial) reported that annual screening with chest radiography is not useful for LCS in individuals at low risk for lung cancer.<sup>62</sup>

### Lung Cancer Screening Guidelines

NCCN was the first major organization to develop LCS guidelines using LDCT based on the NLST data.<sup>18</sup> The U.S. Preventive Services Task Force (USPSTF) recommends lung screening with LDCT; their B recommendation means that lung screening is covered under the Affordable Care Act for individuals with high-risk factors who are 55 to 80 years of age.<sup>16</sup> The Centers for Medicare & Medicaid Services (CMS) covers annual screening LDCT for appropriate Medicare beneficiaries at high risk for lung cancer (ie, smokers and former smokers ages 55–77 years with a 30 pack-year smoking history) if they also receive counseling and participate in shared decision-making before screening. The American College of Chest Physicians and ASCO also recommend LCS with LDCT for individuals at high risk if they meet the criteria of the NLST (ie, smokers and former smokers ages 55–74 years with a 30 pack-year smoking history).<sup>43</sup> Other organizations have also developed guidelines for LCS with LDCT.<sup>16,63–65</sup>

### Risk Factors for Lung Cancer

An essential goal of any LCS 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 seem to increase risk.<sup>34,66–69</sup> This section reviews the currently known risk factors for the development of lung cancer to identify populations with high-risk factors that should be targeted for screening. Individuals with high-risk factors who are candidates for screening should not have any symptoms suggestive of lung cancer (eg, cough, pain, weight loss).

### Tobacco Smoke

**Active Tobacco Use:** Tobacco smoking is a major modifiable risk factor in the development of lung cancer and accounts for 85% of all lung cancer-related deaths.<sup>3,8,9</sup> Approximately 36.5 million adults in the United States smoke cigarettes.<sup>70</sup> Smoking tobacco is also associated with other cancers and diseases, such as kidney, bladder, pancreatic, gastric, or cervical cancer or acute myeloid leukemia.<sup>3</sup> It is estimated that about 443,000 United States adults die from smoking-related illnesses each year; cigarette smoking is estimated to cause about 30% of deaths due to cancer.<sup>71,72</sup> Globally, experts estimate that deaths from smoking tobacco will increase to 10 million by 2020.<sup>73</sup> The risk of developing lung cancer from smoking tobacco has been firmly established. Tobacco smoke contains more than 50 known carcinogens.<sup>74–77</sup>

A dose–response relationship exists between smoking tobacco and the risk of developing lung cancer; however, there is no risk-free level of tobacco exposure. The RR for lung cancer is approximately 20-fold higher for smokers than for nonsmokers.<sup>3,78</sup> Cessation of tobacco smoking decreases the risk for lung cancer.<sup>74,79–82</sup> Former smokers have a higher risk for lung cancer compared with never-smokers. Current or past history of tobacco smoking is considered a risk factor for the development of lung cancer, irrespective of the magnitude of

exposure and the time since smoking cessation. In the NCCN Guidelines, individuals aged 55 to 74 years with a 30 or more pack-year history of smoking tobacco are selected as the highest-risk group for lung cancer and are recommended for LDCT screening (category 1) based on NLST criteria.<sup>10,11</sup> Individuals with a 30 pack-year smoking history who quit smoking fewer than 15 years ago are still in this highest-risk group. *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. Data for determining whether patients are at high risk for cancer are based on cigarette smoking and not on other kinds of tobacco products.<sup>83,84</sup>

**Exposure to Second-Hand Smoke:** Studies have suggested that second-hand smoke (also known as *environmental tobacco smoke*, *passive smoke*, and *involuntary smoke*) causally increases the risk for lung cancer among nonsmokers.<sup>85,86</sup> The NCCN Panel does not feel that second-hand smoke is an independent risk factor, because the association is either weak or variable. Second-hand smoke does not confer a great enough risk for exposed individuals to be candidates for LCS. An analysis of 37 studies found an RR of 1.24 (95% CI, 1.13–1.36) for adult nonsmokers who live with a smoker.<sup>87</sup> An estimate from 25 studies found an RR of 1.22 (95% CI, 1.13–1.33) for lung cancer risk from exposure to second-hand smoke at the work-place.<sup>85</sup> The pooled estimate for 6 studies suggests a dose–response relationship between number of years of second-hand smoke exposure and lung cancer risk.<sup>85</sup> Data are inconsistent for second-hand smoke exposure during childhood and subsequent lung cancer risk in adulthood.<sup>85</sup>

### Occupational Exposure to Carcinogens

Carcinogens targeting the lungs include arsenic, chromium, asbestos, nickel, cadmium, beryllium, silica, diesel fumes, coal smoke, and soot.<sup>67,88–93</sup> The calculated mean RR for development of lung cancer is 1.59 for individuals in the United States who have a known occupational exposure to these carcinogens.<sup>67,93</sup> Among those who are exposed to these carcinogens, data suggest that smokers have a greater risk for lung cancer than nonsmokers.<sup>88,90,94–96</sup>

### Residential Radon Exposure

Radon (a gaseous decay product of uranium-238 and radium-226) has been implicated in the development of lung cancer.<sup>97</sup> The risk for lung cancer from occupational exposure among uranium miners is well established.<sup>98</sup> 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).<sup>99</sup> A 2005 meta-analysis of 13 studies (using individual data from patients) reported a linear relationship between the amount of radon detected in a home and the risk of developing lung cancer.<sup>100</sup> Among those exposed to radon, smokers have a greater risk for lung cancer than nonsmokers.<sup>100</sup> The NCCN Panel feels that radon is a risk factor if there is a documented sustained and substantially elevated radon exposure.

### History of Cancer

Evidence shows an increased risk for new primary lung cancers among patients who survive lung cancer, lymphomas, cancers of the head and neck, or smoking-related cancers, such as bladder cancer.<sup>101</sup> Patients who survive small cell lung cancer have a 3.5-fold increase in the



risk for developing a new primary cancer, predominantly non-small cell lung cancer (NSCLC).<sup>102</sup> Risk for second lung cancers is increased if survivors continue smoking.<sup>103</sup> Patients previously treated with chest irradiation have a 13-fold increase in risk for developing new primary lung cancer, and those previously treated with alkylating agents have an estimated RR of 9.4. In patients previously treated for Hodgkin lymphoma, the RR for new primary lung cancer is 4.2 if previously treated with alkylating agents and 5.9 if previously treated with 5 Gy or more of radiation therapy.<sup>104</sup> In patients with laryngeal or hypopharyngeal cancer, the lung is the most common site of second primary cancers.<sup>105</sup> Evidence suggests that patients who are successfully treated (ie, cured) for an initial smoking-related lung cancer and who stop smoking will have a decreased risk for a subsequent smoking-related cancer compared with those who continue smoking.<sup>106,107</sup>

### 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.<sup>74,108,109</sup> A meta-analysis of 28 case-control studies and 17 observational cohort studies showed an RR of 1.8 (95% CI, 1.6–2.0) for individuals with a sibling/parents or a first-degree relative with lung cancer.<sup>110</sup> The risk is greater in individuals with multiple affected family members or who had a cancer diagnosis at a young age. Although no high-penetrance inherited syndrome has been described for lung cancer (either small cell lung cancer or NSCLC), several groups have identified genetic loci that may be associated with an increased risk of developing lung cancer.<sup>111–115</sup> Patients with classic familial cancer susceptibility syndromes (such as retinoblastoma and Li-Fraumeni syndrome) have a substantially increased risk for lung cancer if they also smoke tobacco.<sup>116–118</sup>

### History of Lung Disease

A history of chronic obstructive pulmonary disease (COPD) is associated with lung cancer risk,<sup>119–125</sup> which may be largely caused by smoking.<sup>115</sup> COPD is associated with 12% of lung cancer cases among heavy smokers.<sup>126</sup> Data suggest that lower pack-year thresholds may be useful to trigger LDCT screening in individuals with COPD.<sup>127</sup> Evidence suggests that the association between COPD and lung cancer may not be entirely caused by smoking.<sup>128–130</sup> For example, 1) family history of chronic bronchitis and emphysema is associated with increased risk for lung cancer; 2) COPD is associated with lung cancer among never-smokers; and 3) COPD appears to be an independent risk factor for lung cancer.<sup>126,130–132</sup> COPD accounts for 10% of lung cancer cases among never-smokers.<sup>126</sup> When analyses are restricted to adenocarcinoma (which is more common among nonsmokers, particularly women), COPD was still associated with an increased risk for lung cancer.<sup>130</sup> Patients with diffuse pulmonary fibrosis seem 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).<sup>133,134</sup> Among patients with a history of exposure to asbestos, those who develop interstitial fibrosis are at a higher risk of developing lung cancer than those without fibrosis.<sup>135</sup>

## Selection of Individuals for Lung Screening

Well-known risk factors exist for the development of lung cancer, especially smoking tobacco.<sup>3,8,9</sup> Results from the NLST support screening select individuals who are at high risk for lung cancer.<sup>11</sup> The NCCN Panel recommends that individuals at high risk for lung cancer should be screened using LDCT; individuals at moderate or low risk should not be screened. Screening with LDCT should only be recommended for select individuals at high risk if they are potential candidates for definitive treatment (ie, curative intent therapy). Chest radiography is not recommended for LCS.<sup>11,17</sup>

The NCCN Panel recommends using the following criteria to determine whether individuals are at high, moderate, or low risk for lung cancer.

### Individuals with High-Risk Factors

There are 2 groups of individuals who qualify as high risk:

- Group 1: Individuals aged 55 to 74 years with a 30 or more pack-year history of smoking tobacco who currently smoke or, if former smoker, have quit within 15 years (category 1).<sup>10,11</sup> Initial screening with LDCT is a category 1 recommendation for group 1, because these individuals are selected based on the NLST inclusion criteria.<sup>10,11</sup> Annual screening LDCT is recommended until individuals are no longer candidates for definitive treatment. The appropriate duration of screening and the age at which screening is no longer appropriate are uncertain.<sup>36,136</sup>
- Group 2: Individuals aged 50 years or older with a 20 or more pack-year history of smoking tobacco and with one additional risk factor (category 2A). Panel members expanded screening beyond the NLST criteria to a larger group of individuals at risk for lung cancer. LDCT screening is a category 2A recommendation for group 2 based on lower level evidence (eg, nonrandomized studies, observational data).<sup>137</sup> These additional risk factors include personal history of cancer or lung disease, family history of lung cancer, radon exposure, and occupational exposure to carcinogens.<sup>66,67,69,100,104,110,130</sup> Exposure to second-hand smoke is not an independent risk factor.

Panel members believe that individuals in group 2 are also at high risk for lung cancer based on data from the NLST and other studies. The NCCN Panel believes that limiting use to the NLST criteria is arbitrary and naïve, because the NLST only used age and smoking history for inclusion criteria and did not consider other well-known risk factors for lung cancer. Others share this opinion.<sup>64,138,139</sup> The NCCN Panel feels that it is important to expand screening beyond the NLST criteria to a larger group of individuals at risk for lung cancer.<sup>137,140</sup> Using just the narrow NLST criteria, only 27% of patients currently being diagnosed with lung cancer would be candidates for LDCT screening.<sup>140</sup> Data suggest that the lung cancer risk for individuals with a 20 to 29 pack-year smoking history is similar to that of individuals with a 30 or more pack-year history.<sup>141</sup> Expanding the groups at high risk who are candidates for screening—by including individuals aged 50 or more years with a 20 or

more pack-year smoking history and one additional risk factor—may save thousands of additional lives.<sup>21,137,142–144</sup>

The NLST included both low-risk and high-risk individuals.<sup>138,143</sup> Only 1% of the prevented deaths occurred among individuals whose risk was 0.55% or less; almost 90% of prevented deaths were observed among individuals with a baseline risk of at least 1.24%.<sup>138</sup> The true risks and benefits of screening these group 2 individuals are uncertain. A risk calculator may be useful to assist in quantifying the risk for individuals in group 2 for use in a shared decision-making process.<sup>143,145,146</sup> Individuals in group 2 may be considered at high risk if they have additional risk factors that increase the lung cancer risk above a threshold of 1.3%.<sup>145</sup>

In the NCCN Guidelines, the age range for LDCT was extended for individuals in group 2 (ie, 50 years and >74 years) for several reasons. Panel Members believe that younger and older individuals in group 2 are also at high risk for lung cancer based on data from the NLST and other studies. Three phase 3 randomized trials assessed screening in younger patients ages 50 to 55 years of age. The NELSON screening and UKLS trials assessed LDCT in individuals 50 to 75 years of age.<sup>45,46,49,50,52,53,55,58,147</sup> The Danish Lung Cancer Screening Trial screened individuals 50 to 70 years of age.<sup>48,148,149</sup> Several studies have assessed LDCT using an extended age range of 50 to 85 years.<sup>150–152</sup>

What the age cutoff should be, at which screening is no longer appropriate, is uncertain.<sup>43</sup> At diagnosis of lung cancer, the median age of patients is 70 years.<sup>7</sup> Approximately 54% of lung cancer is diagnosed in patients aged 55 to 74 years; about 27% of lung cancer is diagnosed in older patients aged 75 to 84 years.<sup>7,153</sup> Screening may benefit older patients who are 75 to 84 years.<sup>154</sup> The USPSTF recommends LDCT for individuals aged 55 to 80 years with high-risk factors.<sup>16</sup> The American Association for Thoracic Surgery recommends LDCT for individuals aged 55 to 79 years with high-risk factors.<sup>64</sup> Annual screening LDCT is recommended in the NCCN Guidelines for individuals older than 74 years with high-risk factors who are candidates for definitive treatment, generally defined as curative intent therapy (eg, surgery, chemoradiation, stereotactic body radiation therapy [SBRT]). Screening can be considered for individuals older than 74 years if they have good functional status, do not have serious comorbidities that would impede curative treatment, and are willing to undergo treatment.

For individuals at high risk with negative LDCT scans or those whose nodules do not meet the size cutoff for more frequent scanning or other intervention, the NCCN Guidelines suggest annual screening LDCT until individuals are no longer candidates for definitive treatment. The appropriate duration of screening is uncertain.<sup>43</sup> After the 3 rounds of LDCT in the NLST, new cases (367 cases) of lung cancer were frequently diagnosed during the 3.5 years of follow-up (median of 6.5 years).<sup>11,155</sup> The NLST data show that lung cancer continues to occur over time in individuals with high-risk factors. The incidence of lung cancer and the death rate from lung cancer did not change during the 7 years of the NLST.<sup>156</sup> The NLST data support annual screening LDCT for at least 2 years but do not define a time limit on efficacy.

### Individuals with Moderate-Risk Factors and Low-Risk Factors

NCCN defines individuals with moderate-risk factors as those aged 50 years or older and with a 20 or more pack-year history of smoking tobacco or second-hand smoke exposure but no additional lung cancer risk factors. The NCCN Panel does not recommend (category 2A) LCS for individuals at moderate risk for lung cancer based on nonrandomized studies and observational data.<sup>43,157</sup> NCCN defines individuals with low-risk factors as those younger than 50 years and/or with a smoking history of fewer than 20 pack-years. The NCCN Panel does not recommend (category 2A) LCS for individuals at low risk for lung cancer based on nonrandomized studies and observational data.<sup>43,157</sup>

### Accuracy of LDCT Protocols and Imaging Modalities

LDCT is recommended for detecting noncalcified nodules that may be suspicious for lung cancer depending on their type and size (eg, solid, part-solid, and nonsolid nodules). Most noncalcified nodules are solid.<sup>158</sup> Solid and subsolid nodules are the 2 main types of pulmonary nodules. Subsolid nodules include 1) nonsolid nodules, also known as ground-glass opacities or ground-glass nodules; and 2) part-solid nodules (also known as mixed nodules), which contain both ground-glass and solid components.<sup>159–163</sup> Nonsolid nodules are mainly adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA), formerly known as bronchioloalveolar carcinoma (BAC); patients have 5-year disease-free survival rates of 100% if these nonsolid nodules are completely resected.<sup>160–162,164–167</sup> Data suggest that many nonsolid nodules can resolve, although they need to be followed.<sup>158,168,169</sup> Solid and part-solid nodules are more likely to be invasive and faster-growing cancers, factors that are reflected in the increased suspicion and follow-up of these nodules.<sup>170–173</sup> Data suggest that long-term survival is excellent if part-solid nodules are resected.<sup>159</sup> When assessing subsequent LDCT scans, the most important radiologic factor is change or stability of nodules compared with a previous imaging study.

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 images, and computer-aided diagnosis (CAD) software have increased the sensitivity of small-nodule detection.<sup>174–188</sup> The use of thinner images has also improved the characterization of small lung nodules.<sup>189</sup> For LCS, LDCT without intravenous contrast is currently recommended (instead of standard-dose CT) to decrease the dose of radiation. LDCT of the chest is usually approximately 10% to 30% of standard-dose CT. LDCT has been shown to be as accurate as standard-dose CT for detecting solid pulmonary nodules, although nodule detection with LDCT may be limited in larger patients.<sup>190,191</sup> LDCT seems to be less sensitive for detecting very low-density nonsolid nodules or nonsolid nodules.<sup>192</sup> Decreasing the radiation dose does not significantly affect the measurement of nodule size when using 1-mm thick slices.<sup>193</sup> Studies suggest that some variation occurs in interpretation of LDCT scans among radiologists.<sup>194–200</sup>

Studies using MDCT have reported that lung cancer mortality is decreased when compared with unscreened cohorts or those receiving chest radiographs.<sup>11,201</sup> Studies using multidetector LDCT screening for lung cancer in individuals with high-risk factors have

used different protocol algorithms for detection and follow-up of pulmonary nodules/lesions.<sup>10,149,150,202–206</sup> These protocols are based on 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 (ie, doubling time).<sup>207–214</sup> Most of these protocols recommend that dynamic contrast-enhanced CT and/ or PET/CT be considered for nodules that are at least 7 to 10 mm, because these technologies have been shown to increase specificity for malignancy.<sup>215–222</sup> PET has low sensitivity for nodules with less than 8 mm of solid component and for small nodules near the diaphragm.

Patients who live in areas endemic for fungal disease may have granulomatous disease; the false-positive rate for PET/CT is higher for granulomas.<sup>223–225</sup> Solitary pulmonary nodules pose unique challenges.<sup>215,226–230</sup> Nodule risk calculators have been published, which may be helpful when assessing solitary pulmonary nodules.<sup>227,231</sup> The risk of cancer is increased if a nodule is located in the upper lobes.<sup>226</sup> Geographic and other risk factors can influence the accuracy of nodule risk calculators. LDCT screening programs (with multiple years of follow-up) report that 65% to 85% of their detected lung cancers are stage I.<sup>52,142,205,222,232</sup> The I-ELCAP (International Early Lung Cancer Action Program) and NLST are the largest series examining lung cancer detection using LDCT in individuals with high-risk factors.<sup>10,209</sup>

The NCCN recommendations are an adaptation of the Fleischner guidelines for solid and sub-solid nodules, NLST data, I-ELCAP protocol guidelines, and LungRADS guidelines.<sup>20,34,161,173</sup> Studies suggested that the definition of a positive result from an LDCT scan should be revised, because the original definition from the NLST was associated with a high percentage of false-positives.<sup>11,49,233,234</sup> In Version 1.2014 of the NCCN Guidelines, the recommended cutoff sizes for assessing solid and part-solid lung nodules on initial LDCT screening were increased to 6 mm in diameter rather than the 4 mm originally used in the NLST and in earlier versions of the NCCN Guidelines for LCS.<sup>18,34,234,235</sup> The NCCN-recommended cutoff sizes for solid, part-solid, and nonsolid nodules detected on LDCT scans are shown in the algorithm (LSC-3–LSC-5, pages 416–418; also online, in these guidelines, at [NCCN.org](http://NCCN.org)). The cutoff sizes differ for nodules detected on initial screening LDCT when compared with new or growing nodules detected on follow-up and annual screening LDCT scans (see the complete version of the NCCN Guidelines for Lung Cancer Screening, available at [NCCN.org](http://NCCN.org)). There is a higher degree of suspicion for new or growing nodules and hence lower cutoff sizes are used.<sup>44</sup> If there is a high suspicion of lung cancer, recommendations include biopsy or surgical excision. For nodules of borderline concern, assessment with interval LDCT scans is often recommended to determine if the nodule is changing to a suspicious form by increasing in size and/or by having a new or growing solid component.

The ACR developed Lung-RADS to standardize LDCT lung examinations.<sup>20,34,236</sup> Lung-RADS has been shown to improve the detection of lung cancer and to decrease false-positives to approximately 1 in 10 screened individuals compared with more than 1 in 4 in NLST.<sup>22,30,34,35</sup> For subsequent LDCT scans after baseline, the false-positive result for Lung-RADS was also decreased when compared with NLST (5.3% [95% CI, 5.1%–5.5%])

vs 21.8% [95% CI, 21.4%–22.2%]).<sup>22</sup> The NCCN Panel has harmonized Lung-RADS with the NCCN Guidelines by revising the definitions of positive scans for initial screening, follow-up, and annual screening LDCT.<sup>22</sup> For the 2018 update, the NCCN threshold cutoffs for solid, part-solid, and nonsolid nodules have been rounded to the nearest whole number to harmonize with the Lung-RADS cutoffs.<sup>20,21</sup> For solid or part-solid nodules, the NCCN definition of a positive initial screening scan is a nodule measuring 6 mm in mean diameter.<sup>12,22,52,170,237</sup> For nonsolid nodules, the NCCN definition of a positive initial screening scan is 20 mm in diameter; nodules of this size require a short-term follow-up LDCT scan in 6 months to assess for malignancy. Specific recommendations for other types of nodules, other size ranges, and different types of LDCT scans (ie, initial, follow-up, annual) are provided in the NCCN Guidelines (available at [NCCN.org](https://www.nccn.org)).

If a new or growing nodule is detected on follow-up interim scans or subsequent annual screening LDCT scans, the definition of a positive scan is different because these nodules are associated with higher risk.<sup>44</sup> If a new solid nodule is detected on follow-up or subsequent annual screening LDCT scans, the cutoff threshold is decreased to 4 mm. For new part-solid nodules with a solid component of 4 mm, an immediate chest CT with or without contrast and/or PET/CT is recommended to assess for malignancy. Again, if a new or growing nonsolid nodule is detected on follow-up interim scans or subsequent annual LDCT scans, follow-up recommendations are different. Nodules should be measured on lung windows and reported as the average diameter rounded to the nearest whole number; only a single diameter measurement is necessary for round nodules. The NCCN Guidelines emphasize that nonsolid lesions must be evaluated using thin slices (<1.5 mm) to increase the sensitivity for a solid component and to detect subtle changes over time.<sup>160,161,179,180,189</sup>

In Lung-Rads, growth is defined as an increase in size of more than 1.5 mm.<sup>19,196</sup> Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter. 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 using conventional methods (excluding volumetric analysis software).<sup>238</sup> If endobronchial nodules are suspected, then LDCT is recommended after 1 month. The technician should ask the patient to cough vigorously, then the LDCT should be immediately done. If findings suggest infection or inflammation, a follow-up LDCT is suggested in 1 to 3 months.

A table on recommended LDCT acquisition parameters is included in the algorithm (see LCSA, page 420). Use of MIP, volume rendered, 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 or less is necessary for optimal use of these 3-dimensional applications. Measurement and evaluation of small nodules are more accurate and consistent on 1-mm thick images compared with 5-mm images.<sup>189</sup>

The preferred slice width is 1 mm or less, and the acceptable slice width is 2.5 mm or less based on Lung-RADS.<sup>22,34,161,179</sup> Nonsolid lesions must be evaluated at thin slices (<1.5 mm) to exclude solid components.<sup>161</sup> Part-solid nodules have higher malignancy rates than either solid nodules or pure non-solid nodules and, therefore, require rigorous evaluation.<sup>161</sup>



Because slice thickness, reconstruction algorithms, and postprocessing filters affect nodule size measurement, the same technical parameters should be used for each screening LDCT (eg, the same window/width and window/level settings).<sup>239,240</sup> Ultra-low-dose chest CT currently produces lower sensitivity for nodule detection, especially in larger patients.<sup>191</sup>

## Multiple Nonsolid Nodules

Subsolid nodules may contain part-solid or solid components, which increase the possibility of malignancy. When multiple subsolid nodules occur, the dominant lesion should be assessed.<sup>170</sup> Careful assessment is needed to determine whether patients have 1) a malignant nodule and several benign nodules, 2) several synchronous lung cancers, or 3) dominant malignant nodule with metastases.<sup>241</sup> Multiple nodules may also be due to inflammation or infection, especially if they are rapidly expanding in size.<sup>170</sup>

The following increase the degree of suspicion that nonsolid or part-solid nodules may be malignant: 1) part-solid nodules with solid components larger than 5 mm; 2) pure nonsolid nodules larger than 10 mm; 3) atypical subsolid nodules with spiculated contours, bubbly appearance, or reticulation; 4) pure nonsolid nodules or part-solid nodules with solid components smaller than 5 mm that show interval change in size or attenuation; or 5) solid lesions with characteristics that are suspicious for invasive carcinoma.<sup>161,171,226</sup> All nonsolid nodules should be reviewed at thin (<1.5 mm) slices to exclude any solid components.<sup>161</sup> If the nodule contains any solid components, then the nodule should be managed using the recommendations from the NCCN Panel for part-solid nodules.<sup>215,242</sup>

## Benefits and Risks of Lung Cancer Screening

The goal of screening is to identify disease at an early stage while it is still treatable and curable. The potential huge benefits of LCS include a reduction in mortality and improvement in quality of life.<sup>38,243</sup> The risks of lung screening include false-negatives and false-positives, radiation exposure, overdiagnosis of incidental findings, futile detection of aggressive disease, anxiety, unnecessary testing, complications from diagnostic workup, and financial costs.<sup>243–249</sup> Most lung nodules found on LDCT are benign; if possible, these nodules should be assessed using noninvasive procedures to avoid the morbidity of invasive procedures in patients who may not have cancer.<sup>246,250</sup> The risks and benefits of LCS should be discussed with the individual before an LDCT scan is done.

### Benefits

Benefits of screening for lung cancer using LDCT scans include 1) decreased lung cancer mortality, or improvement in other oncologic outcomes; 2) quality-of life benefits from screening and early detection of cancer (compared with standard clinical detection); and 3) detection of disease, other than lung cancer, that requires treatment.<sup>14,36,39,43,156</sup> Effective lung screening may prevent more than 12,000 premature deaths due to lung cancer per year.<sup>251</sup>

**Oncology Outcomes:** After a clinical diagnosis of NSCLC, survival is directly related to stage at diagnosis.<sup>252</sup> Although patients with earliest-stage disease (IA) may have a 5-year



survival rate of approximately 75% with surgery, the outcomes quickly decrease with increasing stage.<sup>253</sup> A new edition of the AJCC Cancer Staging Manual (8th edition) will be effective for all cancer cases recorded on or after January 1, 2018.<sup>254,255</sup> Although it is intuitively appealing to conclude that earlier detection of disease will improve outcome, screen-detected lung cancers may have a different natural history from that of clinically detected cancers,<sup>256,257</sup> and an apparent improvement in survival from early detection itself (lead-time bias). Pathology results of resected lung cancers detected through prior screening trials suggest that screening increases the detection of indolent cancer. Randomized trial data from the NLST show that LDCT screening decreases lung cancer mortality.<sup>11</sup>

To address the concerns of bias and overdiagnosis from nonrandomized screening studies, the NCI launched the NLST in 2002.<sup>10</sup> The NLST was a prospective, randomized LCS trial comparing annual screening LDCT scans with annual chest radiographs for 2 years. The NLST results showed that annual screening LDCT decreased the RR of death from lung cancer by 20%.<sup>11</sup> In the NLST, 356 participants died of lung cancer in the LDCT arm and 443 participants died of lung cancer in the chest radiograph arm.<sup>11</sup> Thus, annual screening LDCT decreased the RR of death by 20%. The NLST results indicate that to prevent 1 death from lung cancer, 320 individuals with high-risk factors must be screened with LDCT. Approximately 8.6 million individuals were eligible for LDCT lung screening in 2010 using the NLST definitions of high risk. It was estimated that 12,250 deaths would be averted if these high-risk individuals received LDCT screening.<sup>251</sup> If NCCN group 2 criteria were also used to identify high-risk individuals, then an additional 2 million individuals would also receive lung screening. An additional 3,000 deaths would be averted.<sup>137</sup>

**Quality of Life:** The NLST assessed quality of life among participants at the time of each annual screening study.<sup>258</sup> 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. Presumably, quality of life is also improved with negative LDCT findings, although the need for continued follow-up may increase anxiety. In the NLST trial, patients with either a false-positive result or significant incidental finding did not report increased anxiety or differences in quality of life at 1 or 6 months after screening.<sup>258</sup> LCS may identify other clinical conditions unrelated to lung cancer that require follow-up (eg, coronary artery calcification, COPD, other cancers); presumably, treatment of these other conditions will decrease the overall disease burden.<sup>11,170,259–262</sup>

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.<sup>11</sup> Conversely, 21% of the cancers detected in the chest radio-graph 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. Data from the NELSON and UKLS trials also suggest that CT screening detects more early-stage lung cancer.<sup>46,52</sup>

## Risks

LCS with LDCT has inherent risks and benefits.<sup>36,38,43,155,263</sup> The risks must 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 (ie, overdiagnosis), which would never have harmed the patient who subsequently undergoes 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:** LCS studies (which have included only high-risk populations) have found a high rate of noncalcified nodules larger than 4 mm on LDCT screening, with false-positives ranging from 10% to 43%.<sup>151,264–268</sup> In the NLST, the false-positive rate was 96.4% for the CT screening group.<sup>11</sup> The cumulative risk of a false-positive result was 33% for a person undergoing LCS with 2 sequential annual examinations.<sup>264</sup> Thus, LDCT had a high rate of sensitivity but a low rate of specificity in the NLST. These false-positive results in the NLST were probably due to benign intrapulmonary lymph nodes and noncalcified granulomas.<sup>11,216</sup> Use of the Lung-RADS protocol has been shown to decrease false-positive results and increase the detection of lung cancer.<sup>21,22,34</sup> False-positive and indeterminate results require follow-up, which may include surveillance with chest LDCT scans, percutaneous needle biopsy, or even surgical biopsy. Each of these procedures has its own risks and potential harms.<sup>269</sup> Approximately 7% of individuals with a false-positive result will undergo an invasive procedure (typically bronchoscopy).<sup>264</sup> 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.<sup>11</sup>

The NCCN recommendations for LCS may avoid much of the most invasive follow-up for noncalcified nodules that are detected on baseline screening with LDCT. The NCCN recommendations use the Lung-RADS, NLST, and I-ELCAP protocols/ recommendations and the Fleischner Society guidelines and are based on expert opinion from NCCN Panel Members.<sup>11,161,173,270</sup> Repeat chest LDCT scanning is associated with risk for 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.<sup>37,271</sup>

Bach et al<sup>272</sup> 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 represents substantial psychological and physical burdens. Although the I-ELCAP investigators reported a surgical mortality rate of only 0.5% (when surgery is performed 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%.<sup>273</sup> These potential harms associated with thoracic

surgery<sup>273–275</sup> mandate that the effectiveness of LDCT screening be accurately assessed. Methods of decreasing potential harms with thoracic surgery include using treatment with less morbidity (eg, sublobar resection, VATS lobectomy, SBRT), using minimally invasive diagnostics (endobronchial ultrasound and navigational bronchoscopy), and using multidisciplinary teams to minimize unnecessary testing and morbidity.

**False-Negative Results:** Sone et al<sup>276</sup> reported on lung cancers missed at screening.<sup>277,278</sup> Of 88 lung cancers diagnosed, 32 were missed on 38 LDCT scans: 23 from detection errors and 16 from interpretation errors. Detection errors included 1) subtle lesions (91%) appearing as nonsolid nodules; 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.<sup>228</sup> The second report revealed that 84% of missed cancers 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 within the lungs, which were possible nodule candidates. A database of lung nodules on CT scans provides an imaging resource for radiologists, which may help to decrease false-negative and false-positive results.<sup>176</sup>

**Futile Detection of Small Aggressive Tumors:** Early detection using LCS 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, whereas patient death typically occurs with a tumor burden of  $10^{12}$  cells.<sup>279</sup> 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 to 2 mm.<sup>280</sup>

The NLST trial results show that LCS is effective in select individuals with high-risk factors.<sup>11</sup> The data 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. Because the natural history of lung cancer is heterogeneous,<sup>281</sup> the potential remains for futile treatment in 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, studies of some low-grade lung cancers (ie, AIS or MIA, formerly known as BAC) show a potential for prolonged survival in some patients with NSCLC, even without therapy.<sup>282,283</sup> AIS and MIA, which are likely to present as nonsolid nodules, have a 100% 5-year disease-free survival rate if completely resected.<sup>166,282</sup> A greater percentage of the lepidic pattern (formerly BAC pattern), which corresponds with the nonsolid component in a part-solid nodule, is correlated with a more favorable prognosis.<sup>166,282,283</sup>

Furthermore, experience in LCS has raised the question of increased identification of indolent tumors in the screened population, which is termed *overdiagnosis*.<sup>272,284</sup> These indolent tumors may not cause symptoms or cancer mortality; therefore, patients do not

benefit from screening and subsequent workup and treatment. A percentage of these patients will be exposed to the risk, morbidity, and mortality of surgical resection that, in retrospect, will not increase their life expectancy. As the entities of AIS and MIA, with excellent survival, have been separated from overtly invasive adenocarcinomas, the potential exists to minimize surgical intervention for pure nonsolid nodules through CT screening studies and long-term follow-up.<sup>166</sup> Overdiagnosis is difficult to measure.<sup>158,285</sup> An analysis of the NLST data reported that 18% of all lung cancers detected by LDCT seemed to be indolent.<sup>59</sup> Bach et al<sup>272</sup> found an increase in the number of patients with lung cancer detected through screening, yet found no evidence of a decline in the number of deaths from lung cancer. Their nonrandomized 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 randomized NLST found that LDCT does decrease lung cancer mortality.<sup>11</sup>

**Quality of Life:** The effect of LCS on the quality of life is not fully known. van den Bergh et al<sup>286</sup> found no measured adverse effects, although approximately half of the participants reported discomfort while waiting for the results. Several studies (including the NLST and NELSON trial) have measured quality-of-life issues.<sup>287,288</sup> Data from the NLST and NELSON trials suggest that lung screening did not adversely affect quality of life.<sup>258,288</sup> False-positive and indeterminate results may decrease quality of life because of mental anguish and additional testing.<sup>249</sup> During the NLST, 3 rounds of LDCT screening were done (ie, baseline, year 1, year 2) and then individuals were followed for an additional 3.5 years. Lung cancer was diagnosed between annual screens in some patients (ie, interval cancers); lung cancer was also diagnosed during follow-up.<sup>11,289</sup> Thus, individuals should be cautioned that LDCT may not identify all lung cancers or prevent death from lung cancer.<sup>11</sup> They should be informed that a positive test result does not mean they have lung cancer because many false-positive results occur with LDCT.<sup>37</sup>

**Unnecessary Testing:** Any LCS program will result in additional testing. The NLST was a carefully supervised randomized controlled trial. In a less-controlled environment, the rate of additive studies may be higher. Siström et al<sup>290</sup> reviewed the recommendations for additional imaging in more than 5.9 million radiology reports; they reported an additional imaging rate of 35.8% for chest LDCT. The issue of incidental findings on screening examinations is problematic.<sup>291</sup>

**Radiation Exposure with LDCT:** Current MDCT scanners provide a significantly enhanced capability for detecting small nodules through allowing thinner slice images. Using low-dose techniques, the mean effective radiation dose is 1.5 mSv (standard deviation [SD], 0.5 mSv) compared with an average of 7 mSv for conventional CT.<sup>11,14,158,292</sup> The radiation dose of LDCT is 10 times that of chest radiography. Brenner<sup>293</sup> estimated a 1.8% increase in lung cancer cases if 50% of all current and former smokers in the United States between 50 and 75 years of age were to undergo annual screening LDCT. Lower doses of radiation are now used for LDCT scans, and these lower doses may be less dangerous.<sup>294,295</sup> 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 performed.<sup>271</sup> Radiation exposure from LCS using LDCT and PET/CT is greater for

woman than for men.<sup>244</sup> For men, the median cumulative effective dose was 9.3 mSv after 10 years of screening; the dose was 13.0 mSv for women. These doses are equivalent to one standard CT of the chest (7–8 mSv).

**Increased Cost:** Many experts are concerned about the effect of LCS on medical resources, including the cost of LDCT screening and additional testing. The cost of an LDCT scan was estimated to be about \$527 (in 2011 U.S. dollars).<sup>296</sup> Approximately 15% of the adult population in the United States (about 36.5 million people) are active smokers; approximately 11% are daily smokers.<sup>70,72,297</sup> In 2015, the number of individuals at high risk who were candidates for LCS was approximately 6 million (using NLST criteria).<sup>11,298</sup> Depending on the screening rate (50% or 75%), the annual cost in the United States is estimated at \$1.7 to \$3.4 billion.<sup>296,298</sup> If 75% of the eligible population has screening, it is estimated that it will cost \$240,000 to prevent one lung cancer death.<sup>39</sup> About \$12.1 billion is spent each year on lung cancer care in the United States.<sup>296</sup>

LDCT screening will lead to false-positive results, detection of indeterminate nodules, and detection of potential disease other than lung cancer.<sup>258</sup> In the NLST, although 24.2% of the LDCT scans were positive, most of these were false-positive (96.4%).<sup>11</sup> Follow-up for positive nodules typically involves further imaging.<sup>11</sup> Assuming a 50% screening rate, a conservative estimate of the annual cost of working up false-positive nodules is about \$800 million (3.5 million  $\times$  23%  $\times$  \$1,000). Use of Lung-RADS will probably decrease this cost because the false-positive rate will decrease. This estimate does not include costs of workup for other potential abnormalities detected during screening, such as cardiac and upper abdominal pathology. Of individuals with false-positives, approximately 7% will undergo an invasive procedure (typically bronchoscopy).<sup>264</sup> Limiting screening to only individuals with high-risk factors not only helps avoid unnecessary risks in individuals with a lower risk for cancer but also is important for decreasing the costs of the screening program. Prescreening based on age, smoking history, appropriate medical history, family history, and occupational history is important to determine which patients are at high risk.

Lack of well-defined guidelines can lead to overuse of screening. Excessive screening and/or interpretations of studies by unskilled individuals may occur without strict guidelines. Other factors, such as the interval at which screening should be performed, will also affect calculations of cost. In screening studies using LDCT, 23% of the ELCAP and 69% of the 1999 Mayo Clinic study had at least 1 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, PET, or biopsy. False-positives also lead to additional unnecessary testing and increased cost.

Lung screening also leads to detection of disease other than lung cancer, such as infection; coronary artery calcification; COPD; and renal, adrenal, and liver lesions.<sup>170,228,260–262,299,300</sup> Although detection of other diseases may frequently provide a clinical benefit to the patient, costs will be further increased with additional testing and treatment. It is important to rule out infection; however, antimicrobials are not indicated for chronic lesions.<sup>228</sup> Inappropriate use of antimicrobials may cause adverse side effects and will increase cost. Incidental lesions may also be detected, which may require further testing (eg,

intrapulmonary lymph nodes, noncalcified granulomas, thyroid incidentalomas, upper abdominal lesions).<sup>11,301</sup>

## Cost-Effectiveness and Cost-Benefit Analyses

The cost-effectiveness of LCS is also important to consider.<sup>302</sup> LDCT imaging is more expensive than many other screening programs, and therefore it is important to validate the effectiveness of screening.<sup>303</sup> Currently, Medicare reimburses \$285 for a CT scan.<sup>296,302</sup> Note that cost-benefit analysis provides dollar values for the outcomes, whereas cost-effectiveness analysis provides cost per health outcome (eg, cost per life-year gained). Seven analyses have reported a cost effectiveness ratio of \$100,000 (in U.S. dollars) or less per quality adjusted life years gained for LDCT, which indicates that screening is cost effective.<sup>304</sup> A threshold level of \$100,000 per quality-adjusted life year gained is what some experts consider to be a reasonable value in the United States.

A fundamental flaw with cost-benefit analyses for LCS is that the true benefit of screening requires more years of follow-up and more years of screening to realize the full potential; this crucial factor has been arbitrarily assigned or assumed in prior analyses.<sup>305</sup> The types of assumptions made can significantly affect the conclusions of the analysis. Many cost-benefit analyses do not adequately represent the detrimental effects of false-positives on screening. For a person undergoing LCS with 2 sequential annual examinations, the cumulative risk of a false-positive was 33%.<sup>264</sup> The cost of false-positives has been estimated to be at least \$1,000 per incident.<sup>306</sup> The ELCAP investigators documented that diagnostic procedure costs and hospital/physician costs in the first year after the diagnosis of lung cancer proportionally increased with increasing stage.<sup>307</sup>

## Shared Decision-Making

Given the high percentage of false-positive results and the downstream management that ensues for many patients, the risks and benefits of LCS should be discussed with the individual before a screening LDCT scan is performed.<sup>36–39,233,308,309</sup> Individuals should be cautioned that LDCT may not identify all lung cancers or prevent death from lung cancer.<sup>11</sup> They should be informed that a positive test result does not mean they have lung cancer because false-positives occur with LDCT.<sup>37</sup> Shared patient/physician decision-making may be the best approach before deciding whether to perform LDCT lung screening, especially for elderly patients with comorbid conditions.<sup>16,40,41,310</sup> Smoking cessation counseling is recommended.<sup>24,311</sup>

Lung screening is not recommended for patients who are not able or willing to undergo curative therapy, because of health problems or other major concerns.<sup>16</sup> Shared decision-making aids may assist when determining if screening should be recommended. Risk calculators may assist with decision-making for group 2 in the NCCN Guidelines (ie, individuals 50 years with a 20 pack-year smoking history).<sup>145</sup> The Tammemagi risk calculator includes additional variables that can be used to help determine whether individuals in group 2 are candidates for screening. Using this risk calculator, the threshold for screening is 1.3%. Previous LCS results can also be used for risk stratification.<sup>147</sup>



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## Individual Disclosures for Lung Cancer Screening Panel

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Pierre P. Massion, MD	None	None	None	4/21/17
Peter Mazzone, MD, MPH	Oncoocyte Corporation; and Veracyte, Inc.	Exact Sciences Corporation; GRAIL, Inc.; Nucleix Ltd.; Oncimmune USA, LLC; Oncoocyte Corporation; and Owlstone, Inc.	None	2/7/18
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