National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Lung Cancer Screening

Version 2.2018 — August 8, 2017

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NCCN Guidelines Version 2.2018 Panel Members
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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 indicated.

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 2.2018 Updates
Lung Cancer Screening

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Updates in Version 2.2018 of the NCCN Guidelines for Lung Cancer Screening from Version 1.2018 include:

MS-1

- **The Discussion section has been updated to reflect the changes in the algorithm**

Updates in Version 1.2018 of the NCCN Guidelines for Lung Cancer Screening from Version 1.2017 include:

Global changes

- **Symbols used in numerical ranges made consistent and based on rounding to whole numbers.**

LCS-1

- **Risk Status; High risk; bullet 6 modified: "Additional risk factors (other than second-hand smoke) *that increase the risk of lung cancer to ≥1.3% (see footnote i)"***
- **Footnote i, third sentence modified: 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 (Tammemägi 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).**

LCS-3

- **Footnote r modified: "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."* (also applies to LCS-4, LCS-7, LCS-8)**

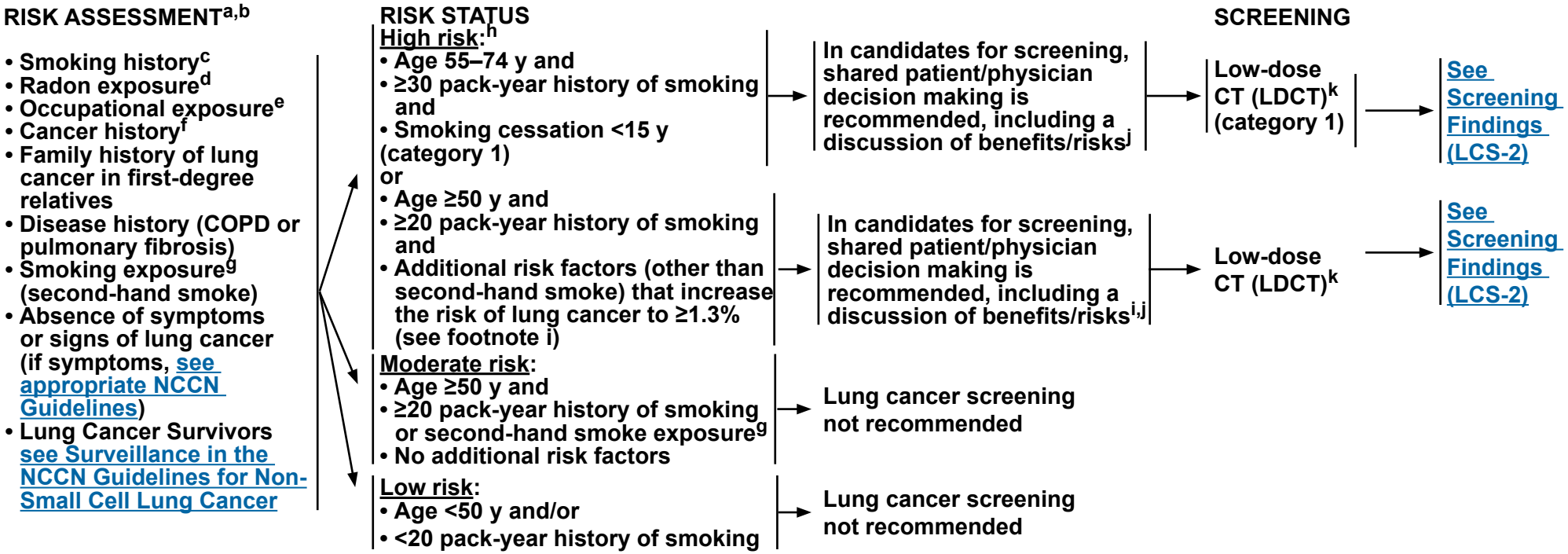
LCS-10

- **Link added to the NCCN Guidelines for Non-Small Cell Lung Cancer.**

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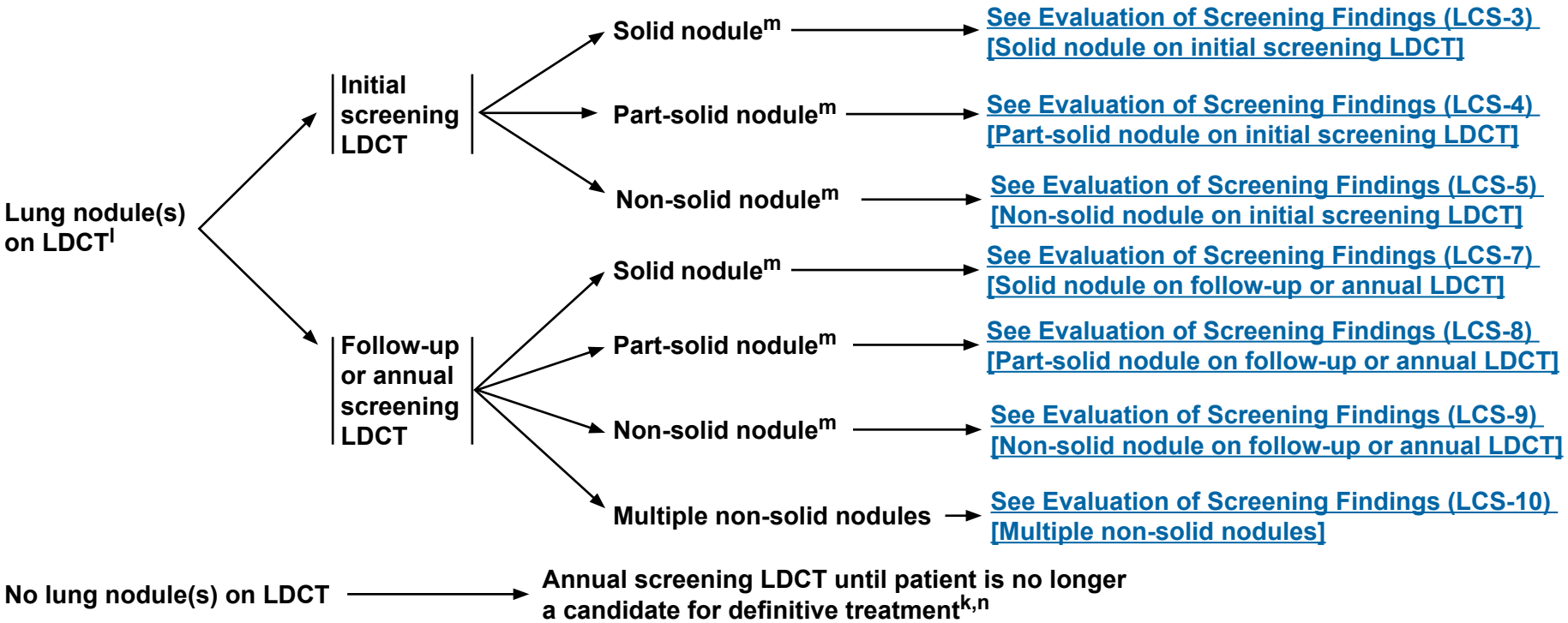


[a]It is recommended that institutions performing lung cancer screening use a multidisciplinary approach that includes the specialties of thoracic radiology, pulmonary medicine, and thoracic surgery.
[b]Lung cancer screening is appropriate to consider for high-risk patients who are potential candidates for definitive treatment. Chest x-ray is not recommended for lung cancer screening.
[c]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.
[d]Documented sustained and substantially elevated radon exposure.
[e]Agents that are identified specifically as carcinogens targeting the lungs: silica, cadmium, asbestos, arsenic, beryllium, chromium, diesel fumes, nickel, coal smoke, and soot.
[f]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.
[g]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.
[h]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.
[i]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 (Tammemägi 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).
[j]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.shouldiscreen.com/benefits-and-harms-screening, and https://www.mskcc.org/cancer-care/types/lung/screening/lung-screening-decision-tool.
[k]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.

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SCREENING FINDINGS



No lung nodule(s) on LDCT → **Annual screening LDCT until patient is no longer a candidate for definitive treatment[k,n]**

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

[k]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.

[l]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.

[m]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.

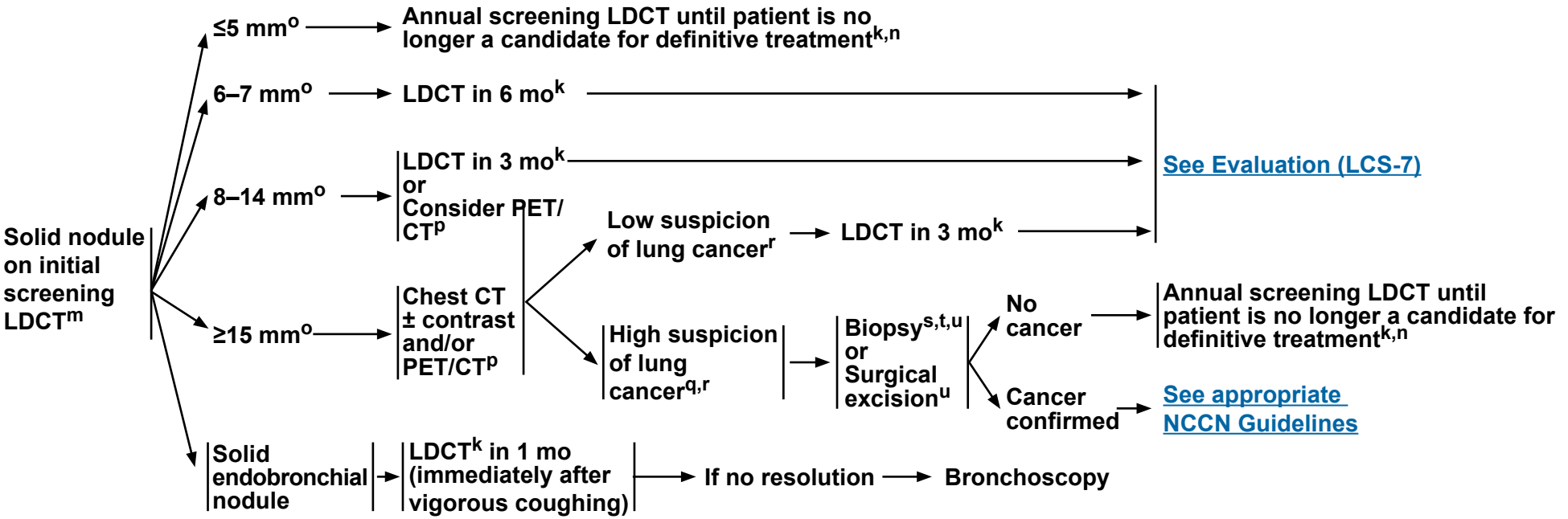
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EVALUATION OF SCREENING FINDINGS

FOLLOW-UP OF SCREENING FINDINGS



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

[o]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.

[p]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.

[q]Criteria for suspicion of malignancy: hypermetabolism higher than the background of surrounding lung parenchyma, regardless of absolute SUV.

[r]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.

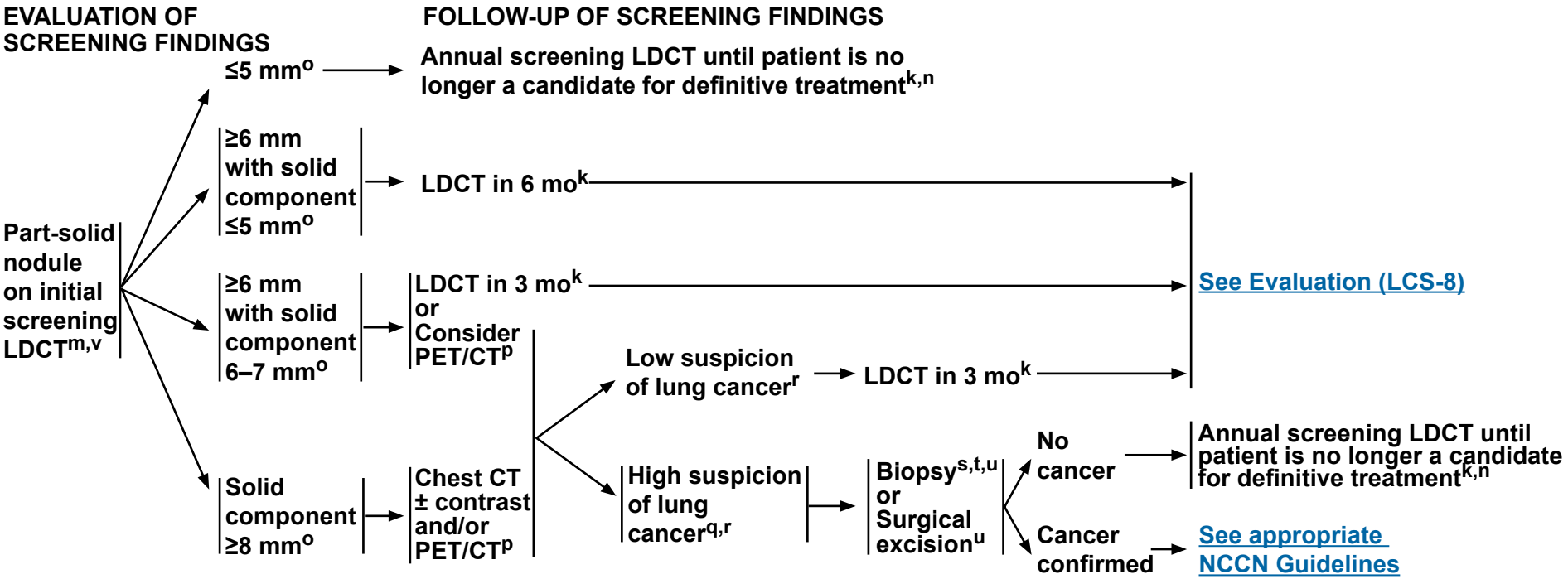
[s]Tissue samples need to be adequate for both histology and molecular testing. Travis WD, et al. Rationale for classification in small biopsies and cytology. In, WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, 4th Ed. Lyon:International Agency for Research on Cancer;2015:16-17.

[t]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).

[u]See the diagnostic evaluation of a lung nodule (DIAG-1 through DIAG-A) in the NCCN Guidelines for Non-Small Cell Lung Cancer.

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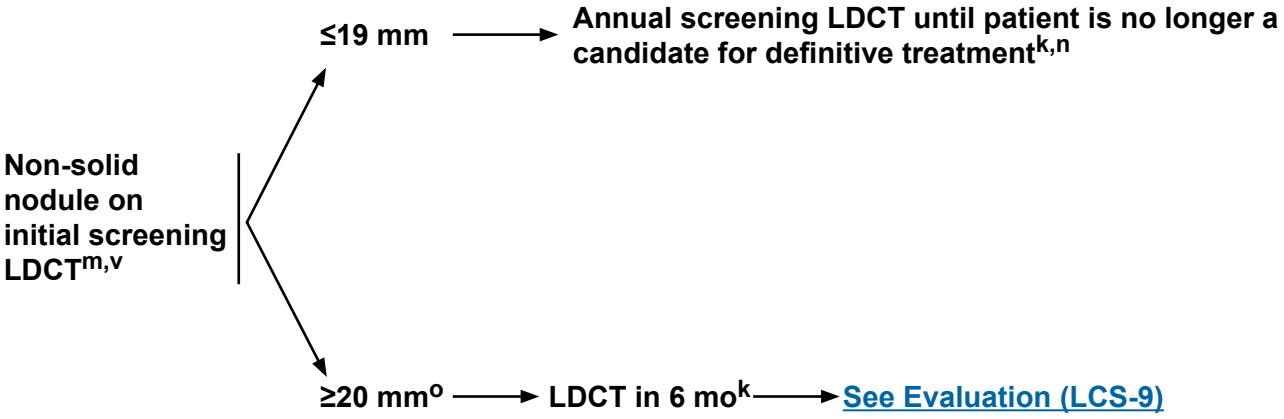
[v]It is crucial that all nonsolid lesions be reviewed at thin (<1.5 mm) slices to exclude any solid components. Any solid component in the nodule requires management of the lesion with the part-solid recommendations (LCS-8).

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EVALUATION OF SCREENING FINDINGS

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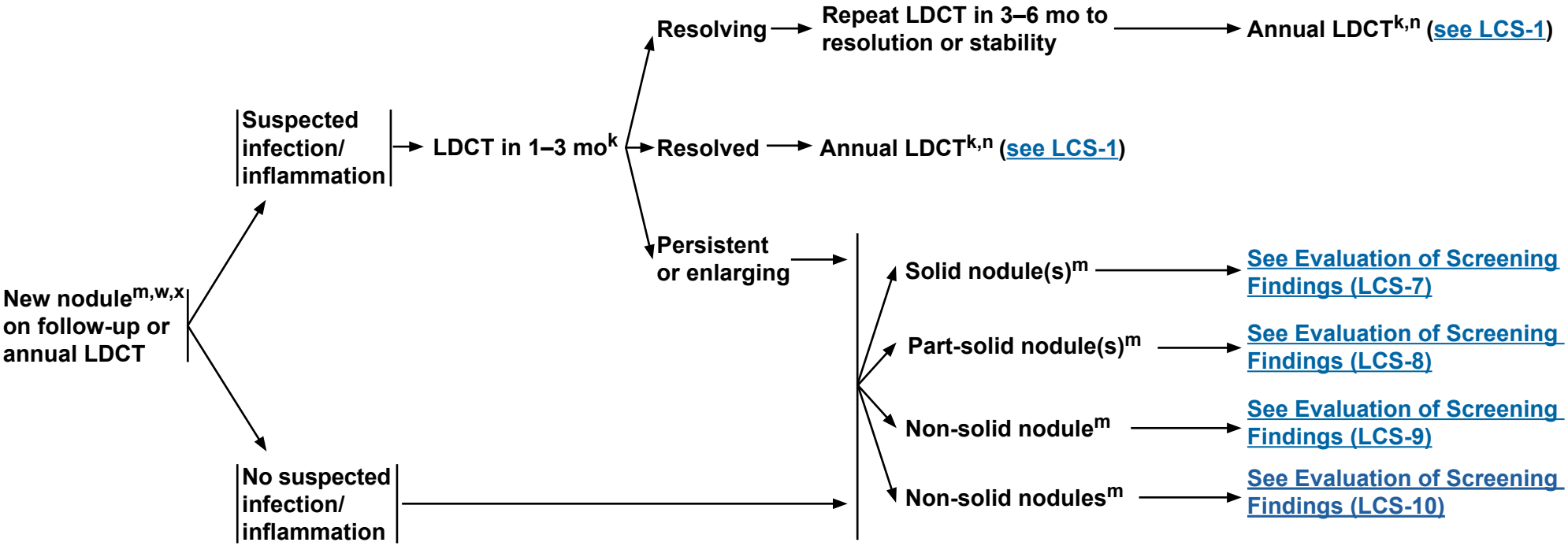
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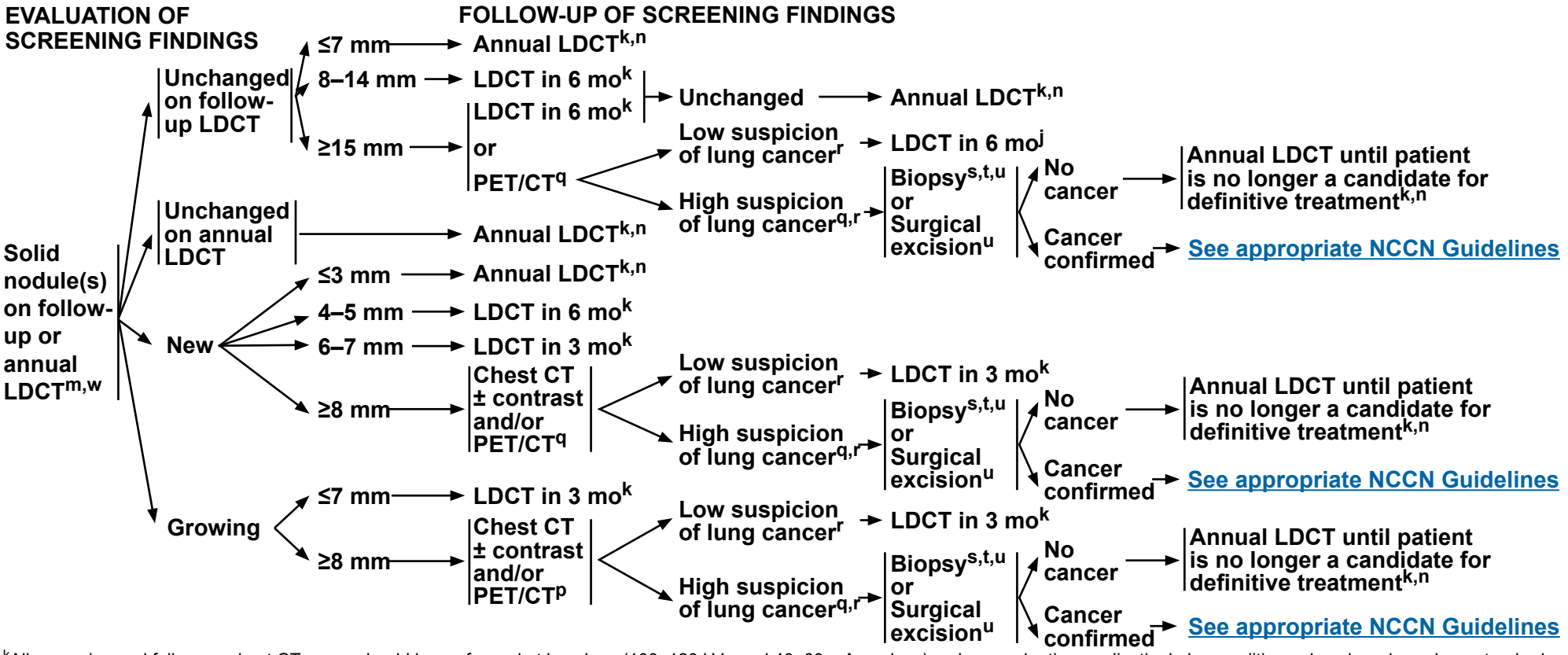
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[w]Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer.
[x]New nodule is defined as ≥3 mm in mean diameter.

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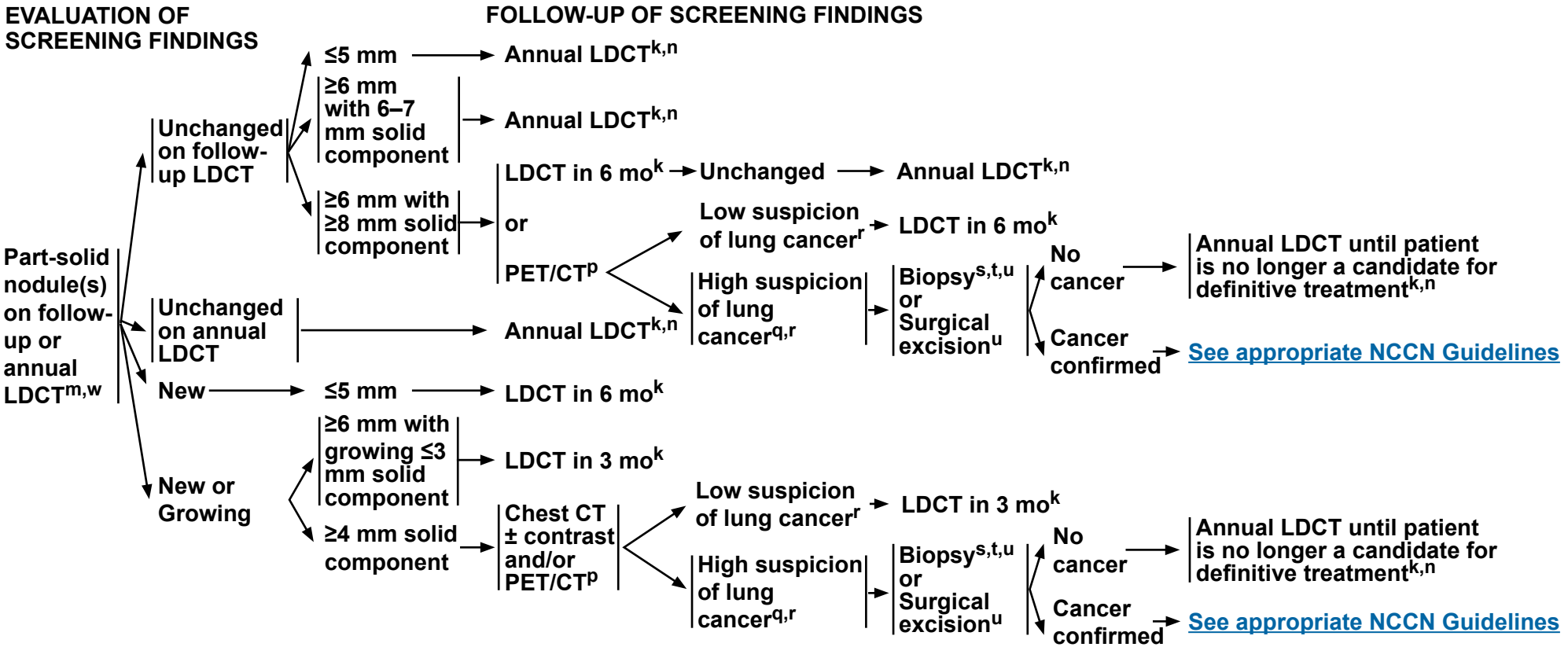
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[w]Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer (See LCS-6).

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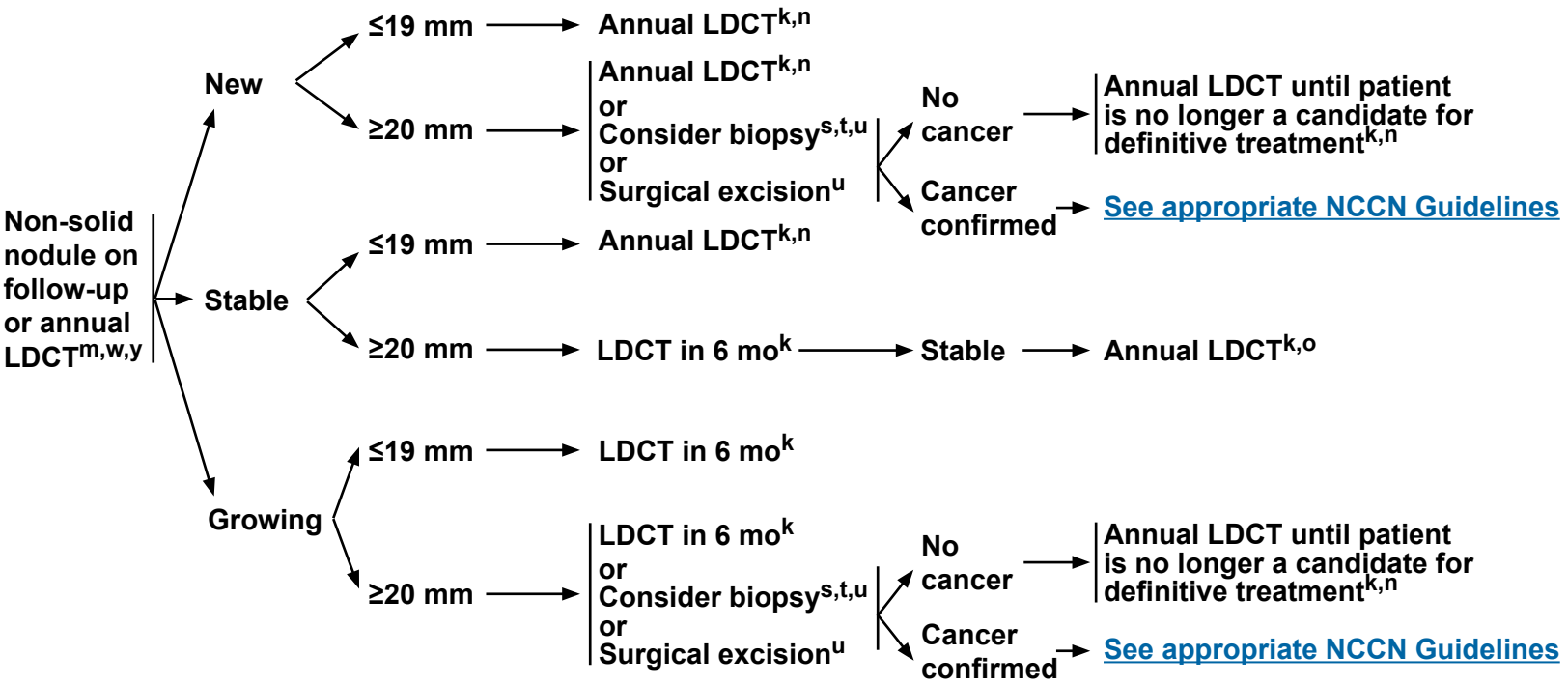
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EVALUATION OF SCREENING FINDINGS

FOLLOW-UP OF SCREENING FINDINGS



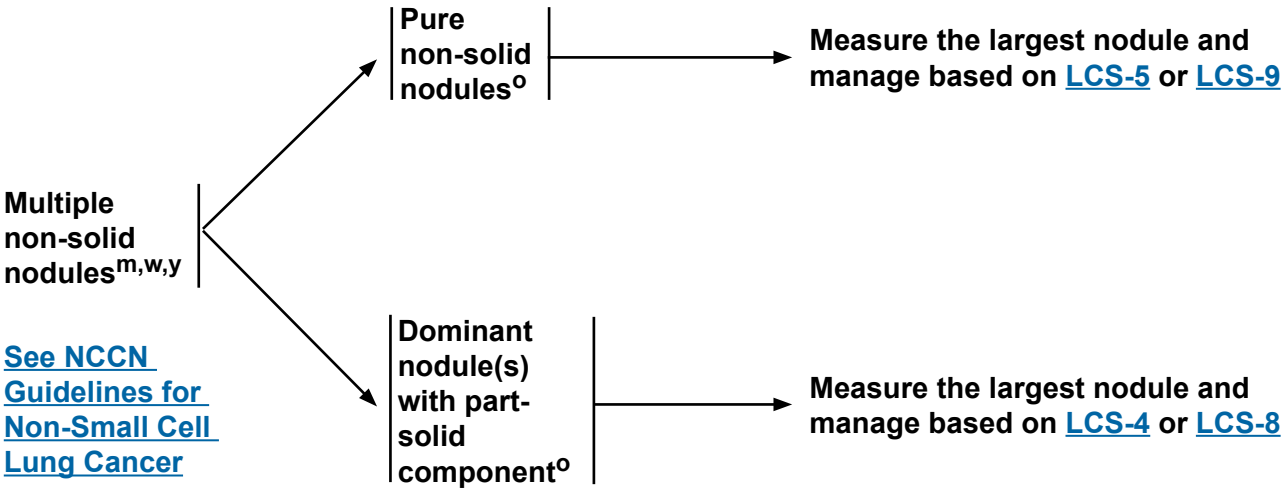
[k]All screening and follow-up chest CT scans should be performed at low dose (100–120 kVp and 40–60 mAs or less), unless evaluating mediastinal abnormalities or lymph nodes, where standard dose CT with IV contrast might be appropriate. (See LCS-A). There should be a systematic process for appropriate follow-up.
[m]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.
[n]There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.
[s]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.
[t]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).
[u]See the diagnostic evaluation of a lung nodule (DIAG-1 through DIAG-A) in the NCCN Guidelines for Non-Small Cell Lung Cancer.
[w]Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer (See LCS-6).
[y]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).

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

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[m]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.
[o]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.
[w]Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer. (see LCS-6)
[y]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).

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Low-Dose Computed Tomography Acquisition, Storage, Interpretation, and Nodule Reporting[1,2]

Acquisition	**Small Patient (BMI ≤30)**	**Large Patient (BMI >30)**
Total radiation exposure	≤3 mSv	≤5 mSv
kVp	100–120	120
mAs	≤40	≤60
	All Patients	
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	
Storage	All acquired images, including thin sections; MIPs and CAD renderings if used	
Interpretation Tools		
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	
Nodule Parameters		
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.

[1]Protocol information: http://www.aapm.org/pubs/CTProtocols/documents/LungCancerScreeningCT.pdf

[2]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.

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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[1]
- 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.

[1]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.

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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.

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Overview

Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide.[1-5] In 2017, it is estimated that 155,870 deaths (84,590 in men and 71,280 in women) from lung cancer will occur in the United States.[6] Five-year survival rates for lung cancer are only 18%, partly because most patients have advanced-stage lung cancer at initial diagnosis.[7] These facts—combined with the success of screening in improving outcomes in patients with cervical, colon, and breast cancers—have been the impetus for studies to develop an effective lung cancer screening test.[8-10] 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.[11] 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. Early detection of lung cancer is an important opportunity for decreasing mortality. Considerable interest has been shown in developing screening tools to detect early-stage lung cancer. Data support using low-dose computed tomography (LDCT) of the chest to screen select patients who are at high risk for lung cancer.[11-15] Chest x-ray is not recommended for lung cancer screening.[11,16,17]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Lung Cancer Screening were developed in 2011 and have been subsequently updated at least once every year.[11,18,19] These 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 protocols and imaging modalities; and 5) discuss the benefits and risks of LDCT screening. The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for Version 1.2018 (see the NCCN Guidelines for Lung Cancer Screening). For example, the NCCN cutoff thresholds for solid, part solid, and nonsolid nodules have been rounded to the nearest whole number to harmonize with the Lung Imaging Reporting and Data System (Lung-RADS) cutoffs.[20-22]

Adenocarcinoma is the most common type of non-small cell lung cancer (NSCLC).[7,23] Thus, these NCCN Guidelines for Lung Cancer Screening mainly refer to detection of adenocarcinoma. Other types of cancer can metastasize to the lungs, such as breast cancer. There are also less common cancers of the lung or chest, such as malignant pleural mesothelioma and thymic carcinoma. Lung screening may also detect noncancerous conditions of the thorax (eg, aortic aneurysm, coronary artery calcification), tumors or benign disease outside of the chest (eg, renal cell carcinoma, adrenal adenoma), and infections (eg, tuberculosis, sarcoidosis).[24,25]

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. 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 outcomes; 2) be scientifically validated (eg, 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

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to first *do no harm*.[26] The dilemma is that if lung cancer screening is beneficial but physicians do not use it, they are denying patients effective care. If lung cancer screening is not effective, then patients may be harmed from overdiagnosis, increased testing, invasive testing or procedures, and the anxiety of a potential cancer diagnosis.[27-30]

Literature Search Criteria and Guidelines Update Methodology

Before the update of this version of the NCCN Guidelines for Lung Cancer Screening, an electronic search of the PubMed database was performed to obtain key literature in lung cancer screening, published between April 1, 2016 and April 1, 2017 using the following search terms: lung cancer screening computed tomography, low-dose computed tomography, low-dose CT screening, and LungRADS. The PubMed database was chosen, because it is the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature. 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 PubMed search resulted in 91 citations and their potential relevance was examined. The data from key PubMed articles selected by the NCCN Panel for review during the NCCN Guidelines update meeting, as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the NCCN Panel, have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). 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 webpage.

LDCT as Part of a Lung Screening Program

Lung cancer screening with LDCT should be part of a program of care and should not be performed in isolation as a free-standing test.[20,31-33] Trained personnel and an organized administrative system to contact patients to achieve compliance with recommended follow-up studies are required for an effective lung screening program.[32,34,35] 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 from LDCT lung examinations.[20,36] The Lung-RADS protocol has been shown to improve the detection of lung cancer and to decrease the false-positive rate.[22,32,34,36,37]

When assessing scans, the most important radiologic factor is change or stability of nodules when compared with a previous imaging study. 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 a screening LDCT scan is performed.[28,29,38,39] Shared patient/physician decision-making may be the best approach before deciding whether to do LDCT lung screening, especially for patients with comorbid conditions.[16,40,41] It is recommended that institutions performing lung cancer screening use a multidisciplinary approach that may include specialties such as chest radiology, pulmonary medicine, and thoracic surgery.[42] Guidelines from the American College of Chest Physicians

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(ACCP) and ASCO state that only centers with considerable expertise in lung cancer screening should do LDCT.[43]

Randomized Trials

Disease-specific mortality, which is the number of cancer deaths relative to the number of individuals screened, is considered the ultimate test of screening effectiveness and is the only test that is without bias.[44] Randomized controlled screening trials are essential for determining whether cancer screening decreases disease-specific mortality. Nonrandomized trials are subject to biases that may cause an apparent increase in survival (eg, lead-time bias, length-time bias).[45]

If lung cancer is detected through 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 as a result of 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 are indolent cancers. Survival (the number of individuals who are alive after detection and treatment of disease relative to the number of individuals diagnosed with the disease) has often been reported but is subject to these biases.[10] For further discussion of randomized and nonrandomized screening trials, see *Benefits of Lung Cancer Screening* in this Discussion.

Several randomized trials have assessed whether screening with chest radiography could improve lung cancer survival. Many of these studies were flawed in their design or power, and all were negative.[29,46-49] A phase 3 randomized trial (The Prostate, Lung, Colorectal, and Ovarian [PLCO]) reported that annual screening with chest radiography is not useful for lung cancer screening in individuals at low risk for lung cancer.[50] Other studies have focused on the more sensitive modality of LDCT–based lung cancer screening (see *Benefits of Lung Cancer Screening* in this Discussion). Analyses of some lung cancer screening studies using LDCT scans suggest that overdiagnosis (ie, diagnosis of cancer that would never be life-threatening) and false-positive screening tests are significant concerns.[30,51,52] Although LDCT scanning may be a better screening test for lung cancer, it also has limitations (see *Benefits of Lung Cancer Screening* and *Risks of Lung Cancer Screening* in this Discussion).[29]

Multiple randomized trials are assessing LDCT screening for lung cancer among high-risk groups, including: 1) the National Lung Screening Trial (NLST), sponsored by the NCI;[10] 2) the Dutch-Belgian randomized lung cancer screening trial (NELSON); 3) the UK Lung Screen (UKLS); 4) the Danish Lung Cancer Screening Trial; and 5) Detection And screening of early lung cancer with Novel imaging Technology (DANTE) trial.[12,53-67] The published results from the NLST show 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.[11] 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. Several smaller trials have reported that screening with LDCT did not decrease mortality.[57,68]

Lung Cancer Screening Guidelines

NCCN was the first major organization to develop lung cancer screening guidelines using LDCT based on the NLST data.[18] The International Association for the Study of Lung Cancer (IASLC) supports the NCCN Guidelines by emphasizing the need for guidelines, a

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multidisciplinary team approach, and integrated smoking cessation programs.[42] 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.[16] 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. ACCP and ASCO also recommend lung cancer screening 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);[43] this recommendation has also been approved by the American Thoracic Society. Several organizations also emphasize the need for a multidisciplinary team approach and smoking cessation.[69] The American Cancer Society, American Association for Thoracic Surgery, and USPSTF have also developed guidelines for lung cancer screening with LDCT.[16,70-72]

Risk Factors for Lung Cancer

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 seem to increase risk.[36,73-76] 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. Note that 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.[3,8,9] Approximately 36.5 million U.S. adults currently smoke cigarettes.[77] Smoking tobacco is also associated with other cancers and diseases, such as kidney, bladder, pancreatic, gastric, or cervical cancer or acute myeloid leukemia.[3]. It is estimated that about 443,000 U.S. adults die from smoking-related illnesses each year; cigarette smoking is estimated to cause about 30% of deaths due to cancer.[78,79] Globally, it is estimated that deaths from smoking tobacco will increase to 10 million by 2020.[80] 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. Tobacco smoke contains more than 7000 compounds, and more than 50 of these are known carcinogens that increase the risk of cancerous mutations at the cellular level, especially among individuals with a genetic predisposition.[81-84] The FDA has defined a list of 93 chemicals that are considered harmful and potentially harmful constituents (HPHCs) in tobacco products or tobacco smoke.

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[3,85] for smokers than for nonsmokers. Cessation of tobacco smoking decreases the risk for lung cancer.[81,86-89] But, even former smokers have a higher risk for lung cancer compared with never-smokers. As a result, 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

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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 criteria for entry into the NLST (see *Risk Status* in the NCCN Guidelines for Lung Cancer Screening).[10,11] 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. Note that data for determining whether patients are at high risk for cancer are based on cigarette smoking and not on other kinds of tobacco products, which may also put patients at risk for cancer.[90,91] For those who smoke cigars, information is available that may be useful for determining the risk for cancer.[92,93]

Exposure to Second-Hand Smoke

The relationship between lung cancer and exposure to second-hand smoke (also known as *environmental tobacco smoke*, *passive smoke*, and *involuntary smoke*) was first suggested in epidemiologic studies published in 1981.[94] Since then, several studies and pooled RR estimates have suggested that second-hand smoke causally increases the risk for lung cancer among nonsmokers.[95] The NCCN Panel does not feel that second-hand smoke is an independent risk factor, because the association is either weak or variable (see the NCCN Guidelines for Lung Cancer Screening). Second-hand smoke does not confer a great enough risk for exposed individuals to be candidates for lung cancer screening in the NCCN Guidelines.

A pooled analysis of 37 published studies found an estimated RR of 1.24 (95% CI, 1.13–1.36) for adult nonsmokers who live with a smoker.[96] A pooled 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 workplace.[95] The pooled estimate for 6 studies suggests a dose–response relationship between number of years of second-hand smoke exposure and lung cancer risk.[95] 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 the 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.[95]

Occupational Exposure to Carcinogens

Approximately 150 agents are classified as known or probable human carcinogens (IARC 2002). Agents that are identified specifically as carcinogens targeting the lungs include arsenic, chromium, asbestos, nickel, cadmium, beryllium, silica, diesel fumes, coal smoke, and soot.[74,97-102] 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 agents.[74,102] Among those who are exposed to these carcinogens, data suggest that smokers have a greater risk for lung cancer than nonsmokers.[97,99,103-105]

Residential Radon Exposure

Radon (a gaseous decay product of uranium-238 and radium-226) has been implicated in the development of lung cancer.[106] The risk for lung cancer from occupational exposure among uranium miners is well established.[107] 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).[108] 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.[109] Among those exposed to radon, smokers have a greater risk for lung cancer than nonsmokers.[109] The NCCN Panel feels that radon

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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.[110] Patients who survive small cell lung cancer have a 3.5-fold increase in the risk for developing a new primary cancer, predominantly NSCLC.[111] Risk for second lung cancers is increased if survivors continue smoking.[112]

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. 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's 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.[113]

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.[114] Most of these tend to be squamous cell cancers and a third of them occur in the lung. In patients with laryngeal or hypopharyngeal cancer, the lung is the most common site of second primary cancers.[115] 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.[116,117]

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.[81,118,119] 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.[120] 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.[121] The Genetic Epidemiology of Lung Cancer Consortium 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.[122] 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 for lung cancer, nicotine dependence, and peripheral artery disease.[123-125] It was noted that subunits of the nicotinic acetylcholine receptor genes are localized to this area (*CHRNA5*, *CHRNA3*, and *CHRNB4*). Other investigators found that a variant at 15q24-25 is associated with spirometric bronchial obstruction and emphysema as assessed with CT.[126,127] 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.[128-130]

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History of Lung Disease

Chronic Obstructive Pulmonary Disease

A history of chronic obstructive pulmonary disease (COPD) is associated with lung cancer risk,[131-137] and this association may be largely caused by smoking.[121] Yang et al[138] found that COPD is associated with 12% of lung cancer cases among heavy smokers. Data suggest that lower pack-year thresholds may be useful to trigger LDCT screening in individuals with COPD.[139] Even after statistical adjustment, evidence suggests that the association between COPD and lung cancer may not be entirely caused by smoking.[140-142] 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.[138,142-144] Yang et al[138] found that COPD accounts for 10% of lung cancer cases among never-smokers. Koshiol et al[142] found that when they restricted their analyses to adenocarcinoma (which is more common among nonsmokers, particularly women), COPD was still associated with an increased risk for lung cancer.

Pulmonary Fibrosis

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).[145,146] 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.[147]

Hormone Replacement Therapy

Whether use of hormone replacement therapy (HRT) affects the risk for lung cancer in women is currently unclear. 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 ranging from an increased risk of lung cancer, no effect on risk, and a protective effect against lung cancer risk. In a large randomized controlled study,[148] 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 Individuals for Lung Screening

Well-known risk factors exist for the development of lung cancer, especially smoking tobacco.[3,8,9] Results from the NLST support screening select individuals who are at high risk for lung cancer.[11] 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. Patients are selected for the different risk categories using the NLST inclusion criteria, nonrandomized studies, and/or observational studies. 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 lung cancer screening.[11,17]

Based on the available data, 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

The NCCN Panel recommends lung cancer screening using LDCT for individuals with high-risk factors (see *Risk Status* in the NCCN Guidelines for Lung Cancer Screening). There are 2 groups of individuals who qualify as high risk:

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- Group 1: Individuals age 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).[10,11] Initial screening with LDCT is a category 1 recommendation for group 1, because these individuals are selected based on the NLST inclusion criteria.[10,11] An NCCN category 1 recommendation is based on high-level evidence (eg, randomized controlled trial) and uniform consensus among panel members. Annual screening LDCT is recommended for these individuals with high-risk factors based on the NLST.[11] Annual screening LDCT is also recommended for those at high risk with negative LDCT scans or for those whose nodules do not meet the size cutoff for more frequent scanning or other intervention until individuals are no longer candidates for definitive treatment. Uncertainty exists about the appropriate duration of screening and the age at which screening is no longer appropriate.[29,149]

- Group 2: Individuals age 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, which is described in greater detail in this section. LDCT screening is a category 2A recommendation for group 2 based on lower level evidence (eg, nonrandomized studies, observational data, ongoing randomized trials).[150] These additional risk factors were previously described and include personal history of cancer or lung disease, family history of lung cancer, radon exposure, and occupational exposure to carcinogens.[73,74,76,109,113,120,142] Note that the NCCN Panel does not currently believe that exposure to second-hand smoke is an independent risk factor, because the data are either weak or variable (see *Exposure to Second-Hand Smoke* in this Discussion).

NCCN Panel Members feel 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 feels 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.[71,151,152] 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.[150,153] Using just the narrow NLST criteria—shown in group 1 of the NCCN high-risk categories (eg, individuals age 55–74 years with a 30 or more pack-year smoking history)—only 27% of patients currently being diagnosed with lung cancer would be candidates for LDCT screening.[153] 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.[154] Expanding the groups at high risk who are candidates for screening—for example, including individuals age 50 or more years with a 20 or more pack-year smoking history and one additional risk factor (other than second-hand smoke)—may save thousands of additional lives.[21,150,155-157]

It is important to note that the NLST included both low- and high-risk individuals.[151,156] 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%.[151] 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.[156,158,159] Individuals in group 2 may be considered at high risk if they have additional risk factors (other than

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second-hand smoke) that increase the lung cancer risk above a threshold of 1.3%.[158]

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. NCCN Panel Members feel 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.[54,55,58,59,61,62,64,67,160] The Danish Lung Cancer Screening Trial (DLCST) screened individuals 50 to 70 years of age.[57,161,162] Several studies have assessed LDCT using an extended age range of 50 to 85 years.[163-165]

It is uncertain what the age cutoff should be, where screening is no longer appropriate.[43] The NCCN Guidelines acknowledge that select individuals with high-risk factors who are older than 74 years are also candidates for LDCT. At diagnosis of lung cancer, the median age of patients is 70 years.[7] 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.[7,166] Screening may benefit older patients who are 75 to 84 years.[167] The USPSTF recommends LDCT for individuals aged 55 to 80 years with high-risk factors.[16] Similarly, the American Association for Thoracic Surgery recommends LDCT for individuals aged 55 to 79 years with high-risk factors.[71] Annual screening LDCT seems reasonable 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 (see *Risk Status* in the NCCN Guidelines for Lung Cancer Screening). The appropriate duration of screening is uncertain.[43] 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).[11,168] The NLST data show that lung cancer continues to occur over time in individuals with high-risk factors. In addition, the incidence of lung cancer and the death rate from lung cancer did not change during the 7 years of the NLST.[169] Thus, 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

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 lung cancer screening for these individuals at moderate risk for lung cancer. This is a category 2A recommendation based on nonrandomized studies and observational data.[43,170] Of interest, data show that some patients in the moderate-risk group would benefit from lung cancer screening.[171]

Individuals with Low-Risk Factors

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 lung cancer screening for these individuals at low risk for lung cancer. This is a category 2A

recommendation based on nonrandomized studies and observational data.[43,170]

Accuracy of LDCT Protocols and Imaging Modalities

As shown in the NCCN algorithm, 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.[45] Solid and subsolid nodules are the 2 main types of pulmonary nodules. Subsolid nodules include: 1) nonsolid nodules, also known as ground-glass opacities (GGOs) or ground-glass nodules (GGNs); and 2) part-solid nodules (also known as mixed nodules), which contain both ground-glass and solid components.[172-176] 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.[23,173-175,177-179] Data also suggest that many nonsolid nodules can resolve, although they need to be followed.[45,180,181] 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.[24,182-184] Recent data suggest that long-term survival is excellent if part-solid nodules are resected.[172] 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 (VR) images, and computer-aided diagnosis (CAD) software have increased the sensitivity of small-nodule detection.[185-199] The use of thinner images has also improved the characterization of small lung nodules.[200]

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, it is usually approximately 10% to 30% of standard-dose CT. In most cases, 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.[201,202] LDCT seems to be less sensitive for detecting very low-density nonsolid nodules or nonsolid nodules.[203] Decreasing the radiation dose does not significantly affect the measurement of nodule size when using 1-mm thick slices.[204] These low-dose scans require radiologists to assess images that are much noisier than typical scans.[205] Studies suggest that some variation occurs in interpretation of LDCT scans among radiologists.[206-212]

LDCT lung cancer screening studies using MDCT have reported that lung cancer mortality is decreased when compared with unscreened cohorts or those receiving chest radiographs.[11,213] Studies using multidetector LDCT screening for lung cancer in individuals with high-risk factors have applied various different protocol algorithms for detection and follow-up of pulmonary nodules/lesions.[10,162,163,214-218] These protocols have been based on the positive relationships among: 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).[219-226] 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.[25,227-233] PET has low sensitivity for nodules with less than 8 mm of solid component and for

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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.[234-236]

If lung nodules have higher uptake on PET compared to surrounding lung parenchyma (ie, hypermetabolism in the lung nodules), then the nodules are suspicious for lung cancer, regardless of the standardized uptake value (SUV) analysis.[231,237] In the workup of pulmonary nodules detected with CT in a high-risk lung cancer screening population, the roles of contrast-enhanced CT and PET/CT are still in evolution.[238,239] Solitary pulmonary nodules pose unique challenges.[227,240-244] Nodule risk calculators have been published, which may be helpful when assessing solitary pulmonary nodules.[241,245] There is an increased risk of cancer if a nodule is located in the upper lobes.[240] Geographic and other risk factors can influence the accuracy of nodule risk calculators.

Optimally, these lung cancer screening methods will increase detection of early-stage lung cancer and decrease 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.[246] Strict adherence to a screening protocol may also significantly reduce unnecessary biopsies.[247] When a biopsy is recommended, tissue samples need to be adequate for both histology and molecular testing.[178,248,249]

Currently, the most accurate protocol for lung cancer detection using LDCT is difficult to determine because of differing patient populations, methodologies, lengths of follow-up, and statistical analyses among lung cancer screening studies. LDCT screening programs (with multiple years of follow-up) report that 65% to 85% of their detected lung cancers are stage I.[61,68,155,217,233] 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 (see *Benefits of Lung Cancer Screening* in this Discussion).[10,221] Differences in screening algorithms or recommended diagnostic pathways between these studies are summarized in Table 1.[10,221] To help ensure good image quality, all LDCT screening programs should use CT scanners that meet quality standards equivalent to or exceeding the accreditation standards of the ACR.[20]

The Fleischner Society has published guidelines for the management of small pulmonary nodules detected on LDCT scans.[184] Most radiologists in the United States are aware of these guidelines and/or work in a practice that uses them.[250] The Fleischner Society has also published guidelines for the management of part-solid or nonsolid pulmonary nodules.[174] Because of the familiarity and/or acceptance of the Fleischner 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 algorithm are an adaptation of the Fleischner guidelines for solid and subsolid nodules, NLST data, I-ELCAP protocol guidelines, and LungRADS guidelines.[20,36,174,184] 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-positive results.[11,58,251,252] In Version 1.2014 of the NCCN Guidelines, the cutoff sizes for assessing solid and part-solid lung nodules on initial LDCT screening recommended by NCCN and the ACR 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 Lung Cancer Screening.[18,36,252,253]

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The NCCN-recommended cutoff sizes for solid, part-solid, and nonsolid nodules detected on LDCT scans are shown in the algorithm (see the NCCN Guidelines for Lung Cancer Screening). 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. There is a higher degree of suspicion for new or growing nodules and hence lower cutoff sizes are used.[53] 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.[20,36,254] Lung-RADS has been shown to improve the detection of lung cancer and to decrease the false-positive results to approximately 1 in 10 screened individuals compared with more than 1 in 4 in NLST.[22,32,36,37] For subsequent LDCT scans after baseline, the false-positive result for LungRADS was also decreased when compared with NLST (5.3% [95% CI, 5.1%–5.5%] vs. 21.8% [95% CI, 21.4%–22.2%]).[22] The NCCN Panel has harmonized Lung-RADS with the NCCN Guidelines for Lung Cancer Screening by revising the definitions of positive scans for initial screening, follow-up, and annual screening LDCT.[22] For the Version 1.2018 update, the NCCN threshold cutoffs for solid, part-solid, and nonsolid nodules have been rounded to the nearest whole number to harmonize with the LungRADS cutoffs.[20,21]

For solid or part-solid nodules, the NCCN definition of a positive initial screening scan is a nodule measuring *6 mm* in mean diameter (see the NCCN Guidelines for Lung Cancer Screening).[12,22,24,61,255] 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. For example, an immediate chest CT with or without contrast and/or PET/CT is recommended to assess for malignancy for the following nodules detected on an initial screening LDCT: 1) solid nodules of 15 mm or more; and 2) part-solid nodules with a solid component of 8 mm or more.

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.[53] If a new solid nodule is detected on follow-up or subsequent annual screening LDCT scans, the cutoff threshold is decreased to 4 mm (see the NCCN Guidelines for Lung Cancer Screening). 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 (see the NCCN Guidelines for Lung Cancer Screening). 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.[173,174,190,191,200]

In LungRads, growth is defined as an increase in size of >1.5 mm.[19,208] *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

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be reliably detected using conventional methods (excluding volumetric analysis software).[256] 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 to 3.0 mm in mean diameter for nodules 3 to 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).[11]

Currently, the NCCN recommendations for lung screening do not include other possibly relevant nodule features, such as proximity to the pleura or fissure.[257-260] The topics of nodule volumetric analysis and/or calculations of tumor doubling time have not been addressed either.[152,261] The NELSON trial is using volumetric analysis, which has decreased the false-positive rate to 64%; the NLST had a false-positive rate of 96%.[42,61,64,214] Only 2.6% of individuals had a positive initial test result in the NELSON trial compared with 24% in the NLST. In some cases, it may be appropriate to perform standard-dose CT with or without intravenous contrast for follow-up or further evaluation of lung or mediastinal abnormalities detected on screening LDCT. Note that if endobronchial nodules are suspected, then LDCT is recommended after 1 month (see *Follow-up of Screening Findings* in the NCCN Guidelines for Lung Cancer Screening). 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 *Low-Dose Computed Tomography Acquisition, Storage, Interpretation, and Nodule Reporting* in the NCCN Guidelines for Lung Cancer Screening). 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 or less is necessary for optimal use of these 3-dimensional applications. For accurate nodule volumetric analysis, some radiologists feel that a detector collimation of 1 mm or less is needed. Measurement and evaluation of small nodules are more accurate and consistent on 1-mm thick images compared with 5-mm images.[200] There may be a similar but less-pronounced benefit in evaluating nodules on 1-mm reconstructed images after detecting them on 2.5- to 3.0-mm thick slices.

The preferred slice width is 1 mm or less, and the acceptable slice width is 2.5 mm or less based on Lung-RADS.[22,36,174,190] Nonsolid lesions must be evaluated at thin slices (<1.5 mm) to exclude solid components.[174] Part-solid nodules have higher malignancy rates than either solid nodules or pure nonsolid nodules and, therefore, require rigorous evaluation.[174] 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).[205,262] Ultra-low-dose chest CT currently produces lower sensitivity for nodule detection, especially in larger patients.[202] New LDCT technologies may make it possible to significantly decrease the radiation dose without compromising nodule detection and evaluation.[263-266] Some organizations, including the ACR, recommend using CT dose tracking for all CT screening programs to ensure that screening facilities are adhering to acceptable radiation limits (eg, reporting the dose-length product [DLP] for each CT).[267]

Multiple Nonsolid Nodules

As previously mentioned, subsolid nodules include 1) nonsolid nodules (also known as GGOs or GGNs); and 2) part-solid nodules (also known

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as mixed nodules), which contain both ground-glass and solid components.[173-176] 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.[24] 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.[268] Multiple nodules may also be due to inflammation or infection, especially if they are rapidly expanding in size.[24]

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.[174,182,240] All nonsolid nodules should be reviewed at thin (<1.5 mm) slices to exclude any solid components.[174] If the nodule contains any solid components, then the nodule should be managed using the recommendations from the NCCN Panel for part-solid nodules (see *Follow-up of Screening Findings* in the NCCN Guidelines for Lung Cancer Screening).[227,269]

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 lung cancer screening include a reduction in mortality and improvement in quality of life.[28,270] The risks of lung screening include false-negative and false-positive results, radiation exposure, overdiagnosis of incidental findings, futile detection of aggressive disease, anxiety, unnecessary testing, complications from diagnostic workup, and financial costs.[27,270-275] 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.[273,276] The risks and benefits of lung cancer screening should be discussed with the individual before an LDCT scan is done (see *Shared Decision-Making* in this Discussion).

Benefits of Lung Cancer Screening

This section summarizes current information about the possible or projected benefits of screening for lung cancer using LDCT scans, including: 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.[14,29,39,43,169] Effective lung screening may prevent more than 12,000 premature lung cancer deaths per year.[277] Other occult health risks may be identified such as thyroid nodules, COPD, moderate to severe coronary artery calcification, aortic aneurysm, other cancers (eg, breast cancer, renal cancer), and other conditions.[278]

Oncology Outcomes

After a clinical diagnosis of NSCLC, survival is directly related to stage at diagnosis.[279] 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 (eg, 5-year survival is 71% for stage IB; 58% for IIA; 49% for IIB; and <25% for stages III and IV).[280] Note that current staging for NSCLC uses the 2010 AJCC staging system (7th edition) (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at NCCN.org).[281] A new edition of the AJCC Cancer Staging Manual (8th edition) was published in late 2016 and will be effective for all cancer cases recorded on or after January 1, 2018.[282,283]

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The NCCN Guidelines will use the AJCC (7th edition) staging system for lung cancer until January 1, 2018.[281] 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[284,285] 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.[11]

Nonrandomized Trials

Of the nonrandomized screening studies, the I-ELCAP study is the largest.[47] It included 31,567 individuals with high-risk factors from around the world, all of whom were screened with baseline and annual screening LDCT scans analyzed centrally in New York.[221] In the I-ELCAP study, Henschke et al[221] reported that a high percentage of stage I cancers (85%) were detected using LDCT, with an estimated 92% actuarial 10-year survival rate for stage I cancers resected within 1 month of diagnosis (62% of all cancers detected). Three participants with clinical stage I cancer—who opted not to undergo treatment—all died within 5 years, similar to other data examining the natural history of stage I NSCLC.[286,287] The authors concluded that annual screening LDCT can detect lung cancer that is curable. Important caveats about the I-ELCAP study include that it was not randomized, the median follow-up time was only 40 months, and fewer than 20% of the subjects were observed for more than 5 years. Given the limited follow-up, the 10-year survival estimates may have been overstated.

A study by Bach et al[288] 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. Although overdiagnosis did occur with LDCT in the NLST, the magnitude was not large when compared with radiographic screening (83 vs. 17 stage IA BAC, also known as AIS or MIA).[11,23,168] An analysis of the NLST data stated that 18% of all lung cancers detected by LDCT seemed to be indolent.[30] Data suggest that baseline CT scans find more indolent cancers, and subsequent annual scans find more rapidly growing cancers.[12,13,53,289]

Randomized Trials

To address the concerns of bias and overdiagnosis from nonrandomized screening studies, the NCI launched the NLST in 2002.[10] The NLST was a prospective, randomized lung cancer screening trial comparing annual screening LDCT scans with annual chest radiographs for 2 years; this trial was designed to have 90% power to detect a 21% decrease in the primary endpoint of lung cancer–specific mortality in the screened group. The investigators enrolled 53,454 individuals aged 55 to 74 years who had smoking history of at least 30 pack-years. If subjects were no longer smoking tobacco, they had to have quit within the previous 15 years. The NLST results showed that annual screening LDCT decreased the RR of death from lung cancer by 20%.[11]

Overall, 24% of the LDCT scans and 7% of the chest radiographs performed were positive screens, an imbalance that was expected based on prior data. In each of the 3 rounds of screening, positive LDCT scan screens were determined to be actual lung cancer cases (ie, true-positive) 4%, 2%, and 5% of the time, compared with 6%, 4%, and 7% of the time for positive chest radiographs.

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 radiograph arm.[11] Thus, annual screening LDCT decreased the

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RR of death by 20%. These results are impressive, and the NLST represents the first randomized study showing an improvement in disease-specific mortality when using a lung cancer screening program.[12] The NLST results indicate that to prevent one death from lung cancer, 320 individuals with high-risk factors must be screened with LDCT. The NLST results will likely change medical practice in the United States. A combined analysis of the NELSON and other European trials may confirm the NLST findings.[55,61,62]

Some feel that the 20% reduction in mortality from LDCT screening (compared with chest radiography) may actually be greater in clinical practice, because the observed mortality reduction underestimates the true reduction and because chest radiographs are not currently recommended for lung cancer screening as standard practice.[242,290,291] In stop screening trials, such as the NLST, deaths during prolonged follow-up may have been prevented if screening had been continued.[290] Thus, if annual lung screening is continued for more than 2 years, this increased screening may yield mortality reductions of more than 20% (which was reported by the NLST after annual lung screening for only 2 years). Findings suggest that showing the benefit of breast cancer screening requires follow-up of at least 20 years.[292] Others feel that the mortality benefit from screening for lung cancer with LDCT will vary substantially across patients who differ in their baseline risk of developing lung cancer.[293] Smaller randomized trials, such as the MILD and DLSCT trials, have not reported that LDCT screening decreases mortality.[161,294] The MILD trial was underpowered to detect a difference in mortality.[45,294]

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.[277] 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 3000 deaths would be averted.[150]

Quality of Life

The NLST assessed quality of life among participants at the time of each annual screening study.[295] 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.

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 with 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.[10] Historically, most patients with lung cancer 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 lung cancer diagnosis to see if screening truly can decrease the lung cancer symptom burden. In addition, lung cancer screening 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.[11,24,296-299]

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Reduction in Treatment-Related Morbidity

Patients with early-stage lung cancer primarily are treated surgically, sometimes with adjuvant chemotherapy, whereas those with more advanced disease are treated with a combination of chemotherapy and radiation, or chemotherapy alone (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at NCCN.org).[300,301] Patients with early-stage lung cancer who undergo an R0 resection have increased survival compared with those with more advanced disease who undergo definitive chemoradiation therapy.[302] 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 (or SBRT, also known as stereotactic ablative radiotherapy [SABR]) probably has less treatment-related morbidity than a patient with stage III lung cancer requiring combined-modality therapy (ie, chemotherapy, radiation, possible lung resection).[303,304] However, a difference in morbidity 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.[11] Conversely, 21% of the cancers detected in the chest radiograph 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.[55,61] 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% to 30% rate of pneumonectomy in symptom-detected cases.[305-308]

Patients with early-stage lung cancer may be candidates for treatment that would not be appropriate for those with advanced stage disease. Video-assisted thorascopic surgery (VATS) is an option for patients with early-stage NSCLC (eg, those who may not tolerate or may refuse an open lobectomy).[309-312] VATS lobectomy is associated with less morbidity than open lobectomy. Data suggest that SBRT is also a reasonable option for patients with early-stage lung cancer who are not candidates for surgery.[303,313-315]

Alterations in Health That Affect Lifestyles

The process of lung cancer screening itself has been suggested to 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.[316] Neither hypothesis has been supported by any substantial evidence.[317-319] Studies suggest 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.[317,320] In a controlled study, 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.[321] A study in more than 1400 individuals reported that relapse rates were lower in patients with positive scans who had stopped smoking for 2 years or less.[322]

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Smokers, including those undergoing lung cancer screening, should always be encouraged to quit smoking tobacco (see the NCCN Guidelines for Smoking Cessation, available at NCCN.org).[69,323,324] Likewise, former smokers should be encouraged to remain abstinent. Lung cancer screening is not a substitute for smoking cessation.[325] Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful in helping individuals to quit smoking.[325-327]

Reduction in Anxiety and Psychological Burden

Whether lung cancer screening causes anxiety or improves overall quality of life has been assessed in the NLST and NELSON trials. 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.[295] In the NELSON trial, recipients of an indeterminate result from the LDCT scan experienced increased distress in the short term, whereas relief was experienced after a negative baseline screening examination.[328] After 2 years of follow-up, data from the NELSON trial suggest that lung screening did not adversely affect quality of life.[329] In the UKLS trial, screening was not associated with clinically significant long-term anxiety, depression, or distress in individuals at high risk for cancer.[330] Further longitudinal studies are needed to determine the long-term effect. Patients' attitudes toward risk in their life (risk perception) also greatly affect their anxiety when undertaking cancer screening examinations.[331] Little definitive research is available to support or refute effects on quality of life from lung cancer screening.

Risks of Lung Cancer Screening

Lung cancer screening with LDCT has inherent risks and benefits.[28,29,43,168,332] These 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 comorbid 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 noncalcified nodules larger than 4 mm on LDCT screening, with false-positive rates ranging from 10% to 43%.[164,307,333-336] In the NLST, the false-positive rate was 96.4% for the CT screening group.[11] The cumulative risk of a false-positive result was 33% for a person undergoing lung cancer screening with 2 sequential annual examinations.[333] 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.[11,25] Data from the NELSON trial show that using volumetric analysis decreases the false-positive rate.[64,214] Use of the LungRADS protocol has been shown to decrease the false-positive rate and increase the detection of lung cancer.[21,22,36]

False-positive and indeterminate results require follow-up, which may include surveillance with chest LDCT scans, percutaneous needle

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biopsy, or even surgical biopsy. Each of these procedures has its own risks and potential harms.[337] Approximately 7% of individuals with a false-positive result will undergo an invasive procedure (typically bronchoscopy).[333] 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.[11]

The NCCN recommendations for lung cancer screening may avoid much of the most invasive follow-up for noncalcified nodules that are detected on baseline screening with LDCT (see *Screening Findings* in the NCCN Guidelines for Lung Cancer Screening). The NCCN recommendations use the NLST and I-ELCAP protocols/recommendations (see Table 1) and the Fleischner Society guidelines and are based on expert opinion from NCCN Panel Members.[11,174,184,338] 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.[38,339]

Bach et al[288] 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%.[340] These potential harms associated with thoracic surgery[340-342] 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 experienced, dedicated, multidisciplinary teams to minimize unnecessary testing and procedures and the morbidity of those procedures.

False-Negative Results

Sone et al[343] published 2 reports on lung cancers missed at screening.[344,345] Of the 88 lung cancers diagnosed, 32 were missed on 38 LDCT scans: 23 from detection errors (with a mean size of 9.8 mm) and 16 from interpretation errors (with a mean size of 15.9 mm). 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.[242]

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 within 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. 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.[187]

Although 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

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compared with those published from clinical trials. Variability occurs when assessing subsolid nodules.[206-208] False-negative results from a screening test may provide an individual patient with a false sense of security, causing a patient to perhaps ignore symptoms that may have otherwise 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, whereas patient death typically occurs with a tumor burden of 10^{12} cells.[346] 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.[347]

The NLST trial results show that lung cancer screening is effective in select individuals with high-risk factors.[11] The data from this trial show that detecting and treating lung lesions lead 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. Because the natural history of lung cancer is heterogeneous and not completely predictable or linear,[348] 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.[349,350] AIS and MIA, which are likely to present as nonsolid nodules, have a 100% 5-year disease-free survival rate if completely resected.[23,349] 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.[23,349,350]

Furthermore, experience in lung cancer screening has raised the question of increased identification of indolent tumors in the screened population, which is termed *overdiagnosis*.[288,351] 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 (formerly BAC) with excellent survival have been separated from overtly invasive adenocarcinomas, the potential exists to learn how to minimize surgical intervention for pure nonsolid nodules through CT screening studies and long-term follow-up.[23]

Overdiagnosis is difficult to measure; initial estimates from the NLST suggested that it was 13%, but others suggested it may have been as high as 25%.[45,352] An analysis of the NLST data reported that 18% of all lung cancers detected by LDCT seemed to be indolent.[30] Bach et al[288] 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.[11]

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Quality of Life

The effect of lung cancer screening on the quality of life (see *Benefits of Lung Cancer Screening* in this Discussion) is not fully known. A study by van den Bergh et al[353] 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.[328,329] Data from the NLST and NELSON trials suggest that lung screening did not adversely affect quality of life.[295,329] False-positive and indeterminate results may decrease quality of life because of mental anguish and additional testing.[27]

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.[11,354] Thus, individuals should be cautioned that LDCT may not identify all lung cancers or prevent death from lung cancer.[11] In addition, they should be informed that a positive test result does not mean they have lung cancer because many false-positive results occur with LDCT.[38]

Unnecessary Testing

Any lung cancer screening program will result in additional testing. In a report by Croswell et al[355] (from the 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. The NLST was a carefully supervised randomized controlled trial. In a less-controlled environment, the rate of additive studies may be higher. Sistrom et al[356] reviewed the recommendations for additional imaging in more than 5.9 million radiology reports; they reported additional imaging of 35.8% for chest LDCT. The issue of incidental findings on screening examinations is problematic, and some organizations are attempting to address the issue, but regional and physician variations remain.[357]

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 (SD, 0.5 mSv) compared with an average of 7 mSv for conventional CT.[11,14,45,358] The radiation dose of LDCT is 10 times that of chest radiography.

There may be even more reason to be concerned about use of chest LDCT scans for lung cancer screening, because these individuals, who are already at high risk for lung cancer, may experience adverse effects from increased radiation exposure. In fact, the effects of repeated exposure to radiation at regular intervals are not known. Brenner[359] 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.[360,361] The risk of radiation exposure over long periods will have to be taken into account when screening guidelines are developed, especially when recommending how frequently the scans should be performed.[339] Radiation exposure from lung cancer screening using LDCT and PET/CT is greater for woman than for men.[271] 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).

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Increased Cost

Many are concerned about the effect of lung cancer screening 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).[362] Approximately 15% of the U.S. adult population (about 36.5 million people) are active smokers; approximately 11% are daily smokers.[77,79,363] In 2015, the number of individuals at high risk who were candidates for lung cancer screening was approximately 6 million (using NLST criteria).[11,364] Depending on the screening rate (50% or 75%), the annual cost in the United States is estimated to be about $1.7 to $3.4 billion.[362,364] If 75% of the eligible population has screening, it is estimated that it will cost $240,000 to prevent one lung cancer death.[39] About $12.1 billion is spent each year on lung cancer care in the United States.[362]

LDCT screening will lead to false-positive results, detection of indeterminate nodules, and detection of potential disease other than lung cancer.[295] In the NLST, although 24.2% of the LDCT scans were positive, most of these were false-positive (96.4%).[11] Follow-up for positive nodules typically involves further imaging.[11] 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 × 23% × $1000). Use of LungRADS 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 a false-positive result, approximately 7% will undergo an invasive procedure (typically bronchoscopy).[333] 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. *Pre-screening* based on age, smoking history, appropriate medical history, family history, and occupational history is important to determine which patients are at high risk (see *Risk Assessment* in the NCCN Guidelines for Lung Cancer Screening).

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 (as with mammography). 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 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, PET, or biopsy. False-positive results also lead to additional unnecessary testing and increased cost. 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; COPD; and renal, adrenal, and liver lesions.[24,242,297-299,365,366] 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 (see *Follow-up of Screening Findings for Infection/Inflammation* in the NCCN Guidelines for Lung Cancer Screening); however, antimicrobials are not indicated for chronic lesions.[242] 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,

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noncalcified granulomas, thyroid incidentalomas, upper abdominal lesions).[11,278]

Cost-Effectiveness and Cost-Benefit Analyses

The cost-effectiveness of lung cancer screening is also important to take into account.[367] LDCT imaging is more expensive than many other screening programs, and therefore it is important to validate the effectiveness of screening.[368] Currently, Medicare reimburses $285 for a CT scan.[362,367] 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 (QALYs) gained for LDCT, which indicates that screening is cost effective.[369] A threshold level of $100,000 per QALY gained is what some experts consider to be a reasonable value in the United States.

A fundamental flaw with cost–benefit analyses for lung cancer screening is that the true benefit of screening requires more years of follow-up and more years of screening to realize the full potential; therefore, this crucial factor has been arbitrarily assigned or assumed in prior analyses.[292] 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 examinations, the cumulative risk of a false-positive test result was 33%.[333] The cost of false-positive cancer screening results has been estimated to be at least $1000 per incident.[370]

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.[371] 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.[372] The emerging NLST data must be carefully examined 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.

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 lung cancer screening should be discussed with the individual before a screening LDCT scan is performed.[28,29,38,39,251,373,374] Individuals should be cautioned that LDCT may not identify all lung cancers or prevent death from lung cancer.[11] In addition, they should be informed that a positive test result does not mean they have lung cancer because false-positive results occur with LDCT.[38] Shared patient/physician decision-making may be the best approach before deciding whether to do LDCT lung screening, especially for elderly patients with comorbid conditions.[16,40,41,375] Smoking cessation counseling is recommended.[69,376] Lung screening is not recommended for patients who are not able or willing to have curative therapy, because of health problems or other major concerns.[16] It is recommended that institutions performing lung cancer screening use a multidisciplinary approach that may include specialties such as chest radiology, pulmonary medicine, and thoracic surgery.[42] Guidelines from the ACCP and ASCO state that only centers with considerable expertise in lung cancer screening should do LDCT.[32,43]

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Shared decision-making aids may assist when determining if screening should be recommended (see the NCCN Guidelines for Lung Cancer Screening). In addition, risk calculators may be used to assist with decision-making for group 2 in the NCCN Guidelines (ie, individuals ≥50 years with a ≥20 pack-year smoking history).[158] For example, the Tammemagi risk calculator includes additional variables that can be used to help determine whether individuals in group 2 are candidates for screening. The additional 7 variables include age, race/ethnicity, socioeconomic status, body mass index, COPD, personal history of cancer, and family history of lung cancer. Using this risk calculator, the threshold for screening is 1.3%. Previous lung cancer screening results can also be used for risk stratification.[160]

Summary

Lung cancer screening with LDCT is a complex and controversial topic, with inherent risks and benefits. Results from the large, prospective, randomized NLST showed that screening with LDCT decreased the RR of death from lung cancer by 20% in a select group of individuals with high-risk factors.[11] The NLST results indicate that to prevent one death from lung cancer, 320 individuals at high risk must be screened with LDCT. The NLST findings have not yet been replicated in a separate cohort, although the other randomized trials assessing the efficacy of lung screening with LDCT have been underpowered. Seven analyses have reported a cost effectiveness ratio of $100,000 (in U.S. dollars) or less per QALYs gained for LDCT, which indicates that screening is cost effective.[369] A threshold level of $100,000 per QALY gained is what some experts consider to be a reasonable value in the United States. At some point, an acceptable level of risk will have to be deemed appropriate for the benefits of screening.

The NCCN Panel recommends LDCT screening for select individuals at high risk for lung cancer based on the NLST results, nonrandomized studies, and observational data. These NCCN Guidelines discuss in detail the criteria for determining which patients are at high risk, and the algorithm provides recommendations for evaluating and following up nodules detected on LDCT screening (eg, solid, part-solid, and nonsolid nodules). The cutoffs for assessing suspicious nodules were revised to decrease the false-positive rate in Version 1.2014 of the NCCN Guidelines. For solid or part-solid nodules, the NCCN definition of a positive screening scan is a solid nodule measuring 6 mm. For nonsolid lesions, the NCCN-recommended cutoff is 20 mm. The ACR has developed Lung-RADS to standardize the reporting and management from LDCT lung examinations.[36,254] Lung-RADS has been reported to improve the detection of lung cancer and to decrease the false-positive rate.[22,32,36,37] For the Version 1.2018 update, the NCCN cutoff thresholds for solid, part solid, and nonsolid nodules have been rounded to the nearest whole number to harmonize with the LungRADS cutoffs.[22]

Lung cancer screening is recommended (category 2A) for group 2 of the high-risk groups that are candidates for lung cancer screening (those ≥50 years with a ≥20 pack-year smoking history and one additional risk factor other than second-hand smoke). The NCCN Panel feels it is important to expand screening beyond the narrow NLST criteria to a larger group of individuals at high risk.[150] Using just the narrow NLST criteria, only 27% of patients currently being diagnosed with lung cancer will be covered. For LDCT of the lung, the preferred slice width is 1.0 mm or less and the acceptable slice width is 2.5 mm or less based on Lung-RADS.

Before recommending lung cancer screening, shared patient/physician decision-making is recommended so that patients have a full understanding of all risks and benefits related to screening with

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LDCT.[150,373] Shared decision-making aids may assist when determining if screening should be recommended. Smokers should always be advised to quit smoking tobacco (see the NCCN Guidelines for Smoking Cessation, available at NCCN.org). Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful. Former smokers should be encouraged to remain abstinent. As policies for implementing lung screening programs are designed, a focus on multidisciplinary programs (incorporating chest radiology, pulmonary medicine, and thoracic surgery) will be helpful to optimize decision-making and minimize interventions for patients with benign lung disease.

The USPSTF recommends lung screening; 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. CMS covers annual screening LDCT for appropriate Medicare beneficiaries at high risk for lung cancer based on the NLST criteria if they also receive counseling and shared decision-making before screening.

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Table 1: Comparison of the I-ELCAP and NLST Lung Screening Protocols

Definition of Positive Nodule*	**I-ELCAP**	**NLST†**
Baseline	Solid and PS nodule ≥5 mm‡	Nodule ≥4 mm
	NS nodule ≥8 mm‡	
Annual	New solid or PS nodule	Same as Baseline
	New NS nodule ≥8 mm‡	
Recommendations for Positive Nodule		
Baseline	LDCT in 3 mo, then resume annual LDCT if stable. Consider PET if solid component >10 mm. Biopsy if PET positive; annual LDCT if PET negative. If nodule ≥15 mm, treat with antibiotics and LDCT at 1 mo, or biopsy. LDCT in 1 mo for solid endobronchial nodule.	Solid or PS nodule 4–10 mm, then LDCT 3–6 mo. NS nodule 4–10 mm, then LDCT 6–12 mo. If growth but nodule <7 mm, then LDCT in 3–6 mo. If growth and nodule ≥7 mm, then follow recommendations of nodules >10 mm. Any nodule >10 mm consider biopsy, CECT, PET/CT, or LDCT in 3–6 mo if low suspicion.
Annual	Annual LDCT if NS nodule <8 mm. LDCT in 6 mo if new solid/PS nodule. Antibiotics and 1 mo LDCT if solid/PS nodule ≥5 mm or NS nodule ≥8 mm, then LDCT at 3 mo if nodule stable.	Same as Baseline
Definition of Nodule Growth	≥50% increase in mean diameter if nodule <5 mm	≥10% increase in nodule diameter
	≥30% increase in mean diameter if nodule 5–9 mm	
	≥20% increase in mean diameter if nodule >10 mm	

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.

I-ELCAP protocol. Available at (http://www.ielcap.org/protocols). Accessed June 1, 2017.

NLST protocol. Available at (http://www.acrin.org/TabID/145/Default.aspx). Accessed June 1, 2017.

*Requiring imaging or workup in addition to annual LDCT. †Guidelines rather than a strict study regimen. ‡Mean diameter of nodule.

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References

1. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends--an update. Cancer Epidemiol Biomarkers Prev 2016;25:16-27. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26667886.

2. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25651787.

3. The Health Consequences of Smoking: A Report of the Surgeon General (ed 2010/07/30). Atlanta: US Department of Health and Human Services; 2004.

4. Thun MJ, Henley SJ, Burns D, et al. Lung cancer death rates in lifelong nonsmokers. J Natl Cancer Inst 2006;98:691-699. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16705123.

5. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21296855.

6. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28055103.

7. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, based on November 2016 SEER data submission, posted to the SEER web site, April 2017. Bethesda, MD: National Cancer Institute; 2017. Available at: https://seer.cancer.gov/csr/1975_2014/.

8. Jemal A, Ward EM, Johnson CJ, et al. Annual report to the nation on the status of cancer, 1975-2014, featuring survival. J Natl Cancer Inst 2017;109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28376154.

9. Jemal A, Thun MJ, Ries LA, et al. Annual report to the nation on the status of cancer, 1975-2005, featuring trends in lung cancer, tobacco use, and tobacco control. J Natl Cancer Inst 2008;100:1672-1694. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19033571.

10. National Lung Screening Trial Research T, Aberle DR, Berg CD, et al. The National Lung Screening Trial: overview and study design. Radiology 2011;258:243-253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21045183.

11. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21714641.

12. Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med 2013;369:920-931. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24004119.

13. National Lung Screening Trial Research T, Church TR, Black WC, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med 2013;368:1980-1991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23697514.

14. Kramer BS, Berg CD, Aberle DR, Prorok PC. Lung cancer screening with low-dose helical CT: results from the National Lung Screening Trial (NLST). J Med Screen 2011;18:109-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22045816.

15. Midthun DE. Screening for lung cancer. Clin Chest Med 2011;32:659-668. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22054878.

16. Moyer VA, Force USPST. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;160:330-338. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24378917.

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17. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e78S-92S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23649455.

18. Wood DE, Eapen GA, Ettinger DS, et al. Lung cancer screening. J Natl Compr Canc Netw 2012;10:240-265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22308518.

19. Wood DE. Lung cancer screening: the last 10 years. J Natl Compr Canc Netw 2012;10:1323-1325. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23138161.

20. Kazerooni EA, Armstrong MR, Amorosa JK, et al. ACR CT accreditation program and the lung cancer screening program designation. J Am Coll Radiol 2016;13:R30-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26846533.

21. McKee BJ, Regis SM, McKee AB, et al. Performance of ACR Lung-RADS in a clinical CT lung screening program. J Am Coll Radiol 2016;13:R25-29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26846532.

22. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25664444.

23. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21252716.

24. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e93S-120S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23649456.

25. Murrmann GB, van Vollenhoven FH, Moodley L. Approach to a solid solitary pulmonary nodule in two different settings-"Common is common, rare is rare". J Thorac Dis 2014;6:237-248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24624288.

26. Lee CI, Forman HP. CT screening for lung cancer: implications on social responsibility. AJR Am J Roentgenol 2007;188:297-298. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17242233.

27. Slatore CG, Sullivan DR, Pappas M, Humphrey LL. Patient-centered outcomes among lung cancer screening recipients with computed tomography: a systematic review. J Thorac Oncol 2014;9:927-934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24922011.

28. Aberle DR, Abtin F, Brown K. Computed tomography screening for lung cancer: has it finally arrived? Implications of the national lung screening trial. J Clin Oncol 2013;31:1002-1008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23401434.

29. de Koning HJ, Meza R, Plevritis SK, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. Ann Intern Med 2014;160:311-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24379002.

30. Patz EF, Jr., Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med 2014;174:269-274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24322569.

31. Wiener RS, Gould MK, Arenberg DA, et al. An official American Thoracic Society/American College of Chest Physicians policy statement: implementation of low-dose computed tomography lung

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cancer screening programs in clinical practice. Am J Respir Crit Care Med 2015;192:881-891. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26426785.

32. Mazzone P, Powell CA, Arenberg D, et al. Components necessary for high-quality lung cancer screening: American College of Chest Physicians and American Thoracic Society Policy Statement. Chest 2015;147:295-303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25356819.

33. Davis AM, Cifu AS. Lung cancer screening. JAMA 2014;312:1248-1249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25247521.

34. Fintelmann FJ, Bernheim A, Digumarthy SR, et al. The 10 pillars of lung cancer screening: rationale and logistics of a lung cancer screening program. Radiographics 2015;35:1893-1908. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26495797.

35. Armstrong K, Kim JJ, Halm EA, et al. Using lessons from breast, cervical, and colorectal cancer screening to inform the development of lung cancer screening programs. Cancer 2016;122:1338-1342. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26929386.

36. Kazerooni EA, Austin JH, Black WC, et al. ACR-STR practice parameter for the performance and reporting of lung cancer screening thoracic computed tomography (CT): 2014 (Resolution 4). J Thorac Imaging 2014;29:310-316. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24992501.

37. McKee BJ, Regis SM, McKee AB, et al. Performance of ACR Lung-RADS in a Clinical CT Lung Screening Program. J Am Coll Radiol 2015;12:273-276. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25176499.

38. Wiener RS, Gould MK, Woloshin S, et al. What do you mean, a spot?: A qualitative analysis of patients' reactions to discussions with their physicians about pulmonary nodules. Chest 2013;143:672-677. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22814873.

39. Goulart BH, Ramsey SD. Moving beyond the national lung screening trial: discussing strategies for implementation of lung cancer screening programs. Oncologist 2013;18:941-946. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23873718.

40. Sox HC. Implementing lung cancer screening under Medicare: the last chance to get it right? JAMA 2014;312:1206-1207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25247515.

41. Volk RJ, Hawk E, Bevers TB. Should CMS cover lung cancer screening for the fully informed patient? JAMA 2014;312:1193-1194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25247511.

42. Field JK, Smith RA, Aberle DR, et al. International Association for the Study of Lung Cancer Computed Tomography Screening Workshop 2011 report. J Thorac Oncol 2012;7:10-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22173661.

43. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA 2012;307:2418-2429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22610500.

44. Hulka BS. Cancer screening. Degrees of proof and practical application. Cancer 1988;62:1776-1780. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3048638.

45. Marshall HM, Bowman RV, Yang IA, et al. Screening for lung cancer with low-dose computed tomography: a review of current status. J Thorac Dis 2013;5 Suppl 5:S524-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24163745.

46. Humphrey LL, Deffebach M, Pappas M, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive services task force recommendation. Ann

Version 2.2018, 08/08/17 © National Comprehensive Cancer Network, Inc. 2017, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Intern Med 2013;159:411-420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23897166.

47. Midthun DE, Jett JR. Screening for lung cancer: the US studies. J Surg Oncol 2013;108:275-279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23918530.

48. Humphrey LL, Johnson M, Teutsch S. Lung cancer screening: An update for the U.S. Preventive Services Task Force [Internet] (ed 2010/08/20); 2004.

49. Humphrey LL, Teutsch S, Johnson M, Force USPST. Lung cancer screening with sputum cytologic examination, chest radiography, and computed tomography: an update for the U.S. Preventive Services Task Force. Ann Intern Med 2004;140:740-753. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15126259.

50. Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA 2011;306:1865-1873. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22031728.

51. Reich JM. A critical appraisal of overdiagnosis: estimates of its magnitude and implications for lung cancer screening. Thorax 2008;63:377-383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18364449.

52. Black WC. Computed tomography screening for lung cancer: review of screening principles and update on current status. Cancer 2007;110:2370-2384. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17941031.

53. Walter JE, Heuvelmans MA, de Jong PA, et al. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. Lancet Oncol 2016;17:907-916. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27283862.

54. Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technol Assess 2016;20:1-146. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27224642.

55. Field JK, Duffy SW, Baldwin DR, et al. UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. Thorax 2016;71:161-170. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26645413.

56. Patz EF, Jr., Greco E, Gatsonis C, et al. Lung cancer incidence and mortality in National Lung Screening Trial participants who underwent low-dose CT prevalence screening: a retrospective cohort analysis of a randomised, multicentre, diagnostic screening trial. Lancet Oncol 2016;17:590-599. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27009070.

57. Wille MM, Dirksen A, Ashraf H, et al. Results of the randomized Danish Lung Cancer Screening Trial with focus on high-risk profiling. Am J Respir Crit Care Med 2016;193:542-551. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26485620.

58. Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol 2014;15:1332-1341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25282285.

59. Horeweg N, Scholten ET, de Jong PA, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. Lancet Oncol 2014;15:1342-1350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25282284.

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60. Prosch H, Schaefer-Prokop C. Screening for lung cancer. Curr Opin Oncol 2014;26:131-137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24441507.

61. Horeweg N, van der Aalst CM, Thunnissen E, et al. Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial. Am J Respir Crit Care Med 2013;187:848-854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23348977.

62. McRonald FE, Yadegarfar G, Baldwin DR, et al. The UK Lung Screen (UKLS): demographic profile of first 88,897 approaches provides recommendations for population screening. Cancer Prev Res (Phila) 2014;7:362-371. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24441672.

63. Field JK, van Klaveren R, Pedersen JH, et al. European randomized lung cancer screening trials: Post NLST. J Surg Oncol 2013;108:280-286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23893464.

64. Ru Zhao Y, Xie X, de Koning HJ, et al. NELSON lung cancer screening study. Cancer Imaging 2011;11 Spec No A:S79-84. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22185865.

65. Xu DM, Gietema H, de Koning H, et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. Lung Cancer 2006;54:177-184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16989922.

66. Nair A, Hansell DM. European and North American lung cancer screening experience and implications for pulmonary nodule management. Eur Radiol 2011;21:2445-2454. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21830100.

67. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). Int J Cancer 2007;120:868-874. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17131307.

68. Infante M, Cavuto S, Lutman FR, et al. Long-term follow-up results of the DANTE trial, a randomized study of lung cancer screening with spiral computed tomography. Am J Respir Crit Care Med 2015;191:1166-1175. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25760561.

69. Fucito LM, Czabafy S, Hendricks PS, et al. Pairing smoking-cessation services with lung cancer screening: A clinical guideline from the Association for the Treatment of Tobacco Use and Dependence and the Society for Research on Nicotine and Tobacco. Cancer 2016;122:1150-1159. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26916412.

70. Wender R, Fontham ET, Barrera E, Jr., et al. American Cancer Society lung cancer screening guidelines. CA Cancer J Clin 2013;63:107-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23315954.

71. Jaklitsch MT, Jacobson FL, Austin JH, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg 2012;144:33-38. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22710039.

72. Roberts H, Walker-Dilks C, Sivjee K, et al. Screening high-risk populations for lung cancer: guideline recommendations. J Thorac Oncol 2013;8:1232-1237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24457233.

73. Alberg AJ, Brock MV, Ford JG, et al. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest

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2013;143:e1S-29S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23649439.

74. Driscoll T, Nelson DI, Steenland K, et al. The global burden of disease due to occupational carcinogens. Am J Ind Med 2005;48:419-431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16299703.

75. de Groot P, Munden RF. Lung cancer epidemiology, risk factors, and prevention. Radiol Clin North Am 2012;50:863-876. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22974775.

76. Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. J Thorac Oncol 2008;3:819-831. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18670299.

77. Jamal A, King BA, Neff LJ, et al. Current cigarette smoking among adults - United States, 2005-2015. MMWR Morb Mortal Wkly Rep 2016;65:1205-1211. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27832052.

78. Jacobs EJ, Newton CC, Carter BD, et al. What proportion of cancer deaths in the contemporary United States is attributable to cigarette smoking? Ann Epidemiol 2015;25:179-182 e171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25487970.

79. Centers for Disease C, Prevention. Current cigarette smoking among adults - United States, 2011. MMWR Morb Mortal Wkly Rep 2012;61:889-894. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23134971.

80. Jha P, Peto R. Global effects of smoking, of quitting, and of taxing tobacco. N Engl J Med 2014;370:60-68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24382066.

81. Chen LS, Baker T, Hung RJ, et al. Genetic risk can be decreased: quitting smoking decreases and delays lung cancer for smokers with high and low CHRNA5 risk genotypes - a meta-analysis. EBioMedicine 2016;11:219-226. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27543155.

82. Hecht SS. Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 1999;91:1194-1210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10413421.

83. Secretan B, Straif K, Baan R, et al. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 2009;10:1033-1034. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19891056.

84. Sakoda LC, Loomis MM, Doherty JA, et al. Germ line variation in nucleotide excision repair genes and lung cancer risk in smokers. Int J Mol Epidemiol Genet 2012;3:1-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22493747.

85. Centers for Disease C, Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses--United States, 2000-2004. MMWR Morb Mortal Wkly Rep 2008;57:1226-1228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19008791.

86. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med 2013;368:341-350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23343063.

87. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004;328:1519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15213107.

88. Moolgavkar SH, Holford TR, Levy DT, et al. Impact of reduced tobacco smoking on lung cancer mortality in the United States during 1975-2000. J Natl Cancer Inst 2012;104:541-548. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22423009.

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89. Peto R, Darby S, Deo H, et al. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. BMJ 2000;321:323-329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10926586.

90. Kasza KA, Ambrose BK, Conway KP, et al. Tobacco-product use by adults and youths in the United States in 2013 and 2014. N Engl J Med 2017;376:342-353. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28121512.

91. Hu SS, Neff L, Agaku IT, et al. Tobacco product use among adults - United States, 2013-2014. MMWR Morb Mortal Wkly Rep 2016;65:685-691. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27416365.

92. CDC. Fast facts: cigars. Accessed: June 7, 2017: Centers for Disease Control and Prevention; 2016. Available at: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/tobacco_industry/cigars/.

93. Smoking and Tobacco Control Monograph 9: Cigars: Health Effects and Trends. Bethesda, MD: National Cancer Institute; 1998. Available at: http://www.cancercontrol.cancer.gov/tcrb/monographs/9/index.html.

94. Garfinkel L. Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J Natl Cancer Inst 1981;66:1061-1066. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6941041.

95. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General (ed 2010/07/30). Atlanta; 2006.

96. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1997;315:980-988. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9365295.

97. Delva F, Margery J, Laurent F, et al. Medical follow-up of workers exposed to lung carcinogens: French evidence-based and pragmatic recommendations. BMC Public Health 2017;17:191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28193266.

98. Straif K, Benbrahim-Tallaa L, Baan R, et al. A review of human carcinogens--part C: metals, arsenic, dusts, and fibres. Lancet Oncol 2009;10:453-454. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19418618.

99. Silverman DT, Samanic CM, Lubin JH, et al. The Diesel Exhaust in Miners study: a nested case-control study of lung cancer and diesel exhaust. J Natl Cancer Inst 2012;104:855-868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22393209.

100. Nelson DI, Concha-Barrientos M, Driscoll T, et al. The global burden of selected occupational diseases and injury risks: Methodology and summary. Am J Ind Med 2005;48:400-418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16299700.

101. Nurminen M, Karjalainen A. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland. Scand J Work Environ Health 2001;27:161-213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11444413.

102. Steenland K, Loomis D, Shy C, Simonsen N. Review of occupational lung carcinogens. Am J Ind Med 1996;29:474-490. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8732921.

103. Markowitz SB, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer. New findings from the North American insulator cohort. Am J Respir Crit Care Med 2013;188:90-96. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23590275.

104. Frost G, Darnton A, Harding AH. The effect of smoking on the risk of lung cancer mortality for asbestos workers in Great Britain

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(1971-2005). Ann Occup Hyg 2011;55:239-247. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21252055.

105. Reid A, de Klerk NH, Ambrosini GL, et al. The risk of lung cancer with increasing time since ceasing exposure to asbestos and quitting smoking. Occup Environ Med 2006;63:509-512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16849527.

106. El Ghissassi F, Baan R, Straif K, et al. A review of human carcinogens--part D: radiation. Lancet Oncol 2009;10:751-752. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19655431.

107. Leuraud K, Schnelzer M, Tomasek L, et al. Radon, smoking and lung cancer risk: results of a joint analysis of three European case-control studies among uranium miners. Radiat Res 2011;176:375-387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21714633.

108. Lubin JH, Boice JD, Jr. Lung cancer risk from residential radon: meta-analysis of eight epidemiologic studies. J Natl Cancer Inst 1997;89:49-57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8978406.

109. Darby S, Hill D, Auvinen A, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 2005;330:223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15613366.

110. Wu GX, Nelson RA, Kim JY, Raz DJ. Non-small cell lung cancer as a second primary among patients with previous malignancy: who is at risk? Clin Lung Cancer 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28412093.

111. Tucker MA, Murray N, Shaw EG, et al. Second primary cancers related to smoking and treatment of small-cell lung cancer. Lung Cancer Working Cadre. J Natl Cancer Inst 1997;89:1782-1788. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9392619.

112. Shiels MS, Gibson T, Sampson J, et al. Cigarette smoking prior to first cancer and risk of second smoking-associated cancers among survivors of bladder, kidney, head and neck, and stage I lung cancers. J Clin Oncol 2014;32:3989-3995. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25385740.

113. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002;94:182-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11830608.

114. Spector JG, Sessions DG, Haughey BH, et al. Delayed regional metastases, distant metastases, and second primary malignancies in squamous cell carcinomas of the larynx and hypopharynx. Laryngoscope 2001;111:1079-1087. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11404625.

115. Morris LG, Sikora AG, Patel SG, et al. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol 2011;29:739-746. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21189382.

116. Kawaguchi T, Matsumura A, Iuchi K, et al. Second primary cancers in patients with stage III non-small cell lung cancer successfully treated with chemo-radiotherapy. Jpn J Clin Oncol 2006;36:7-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16368713.

117. Richardson GE, Tucker MA, Venzon DJ, et al. Smoking cessation after successful treatment of small-cell lung cancer is associated with fewer smoking-related second primary cancers. Ann Intern Med 1993;119:383-390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8393311.

118. Jonsson S, Thorsteinsdottir U, Gudbjartsson DF, et al. Familial risk of lung carcinoma in the Icelandic population. JAMA

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2004;292:2977-2983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15613665.

119. Li X, Hemminki K. Familial multiple primary lung cancers: a population-based analysis from Sweden. Lung Cancer 2005;47:301-307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15713513.

120. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. Br J Cancer 2005;93:825-833. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16160696.

121. Yang IA, Holloway JW, Fong KM. Genetic susceptibility to lung cancer and co-morbidities. J Thorac Dis 2013;5 Suppl 5:S454-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24163739.

122. Bailey-Wilson JE, Amos CI, Pinney SM, et al. A major lung cancer susceptibility locus maps to chromosome 6q23-25. Am J Hum Genet 2004;75:460-474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15272417.

123. Thorgeirsson TE, Geller F, Sulem P, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature 2008;452:638-642. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18385739.

124. Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature 2008;452:633-637. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18385738.

125. Amos CI, Wu X, Broderick P, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet 2008;40:616-622. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18385676.

126. Bierut LJ. Convergence of genetic findings for nicotine dependence and smoking related diseases with chromosome 15q24-25. Trends Pharmacol Sci 2010;31:46-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19896728.

127. Lambrechts D, Buysschaert I, Zanen P, et al. The 15q24/25 susceptibility variant for lung cancer and chronic obstructive pulmonary disease is associated with emphysema. Am J Respir Crit Care Med 2010;181:486-493. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20007924.

128. Hwang SJ, Cheng LS, Lozano G, et al. Lung cancer risk in germline p53 mutation carriers: association between an inherited cancer predisposition, cigarette smoking, and cancer risk. Hum Genet 2003;113:238-243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12802680.

129. Sanders BM, Jay M, Draper GJ, Roberts EM. Non-ocular cancer in relatives of retinoblastoma patients. Br J Cancer 1989;60:358-365. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2789942.

130. Fletcher O, Easton D, Anderson K, et al. Lifetime risks of common cancers among retinoblastoma survivors. J Natl Cancer Inst 2004;96:357-363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14996857.

131. Mayne ST, Buenconsejo J, Janerich DT. Previous lung disease and risk of lung cancer among men and women nonsmokers. Am J Epidemiol 1999;149:13-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9883789.

132. Samet JM, Humble CG, Pathak DR. Personal and family history of respiratory disease and lung cancer risk. Am Rev Respir Dis 1986;134:466-470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3752703.

133. Alavanja MC, Brownson RC, Boice JD, Jr., Hock E. Preexisting lung disease and lung cancer among nonsmoking women. Am J

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Epidemiol 1992;136:623-632. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1442729.

134. Wu-Williams AH, Dai XD, Blot W, et al. Lung cancer among women in north-east China. Br J Cancer 1990;62:982-987. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2257230.

135. Gao YT, Blot WJ, Zheng W, et al. Lung cancer among Chinese women. Int J Cancer 1987;40:604-609. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2824385.

136. Brenner AV, Wang Z, Kleinerman RA, et al. Previous pulmonary diseases and risk of lung cancer in Gansu Province, China. Int J Epidemiol 2001;30:118-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11171871.

137. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. Ann Intern Med 1986;105:503-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3752756.

138. Yang P, Sun Z, Krowka MJ, et al. Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk. Arch Intern Med 2008;168:1097-1103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18504338.

139. Lowry KP, Gazelle GS, Gilmore ME, et al. Personalizing annual lung cancer screening for patients with chronic obstructive pulmonary disease: A decision analysis. Cancer 2015;121:1556-1562. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25652107.

140. Young RP, Hopkins RJ. How the genetics of lung cancer may overlap with COPD. Respirology 2011;16:1047-1055. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21749550.

141. El-Zein RA, Young RP, Hopkins RJ, Etzel CJ. Genetic predisposition to chronic obstructive pulmonary disease and/or lung cancer: important considerations when evaluating risk. Cancer Prev Res (Phila) 2012;5:522-527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22491518.

142. Koshiol J, Rotunno M, Consonni D, et al. Chronic obstructive pulmonary disease and altered risk of lung cancer in a population-based case-control study. PLoS One 2009;4:e7380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19812684.

143. Young RP, Hopkins RJ, Christmas T, et al. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur Respir J 2009;34:380-386. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19196816.

144. Turner MC, Chen Y, Krewski D, et al. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. Am J Respir Crit Care Med 2007;176:285-290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17478615.

145. Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. Thorax 1980;35:496-499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7434310.

146. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Am J Respir Crit Care Med 2000;161:5-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10619790.

147. Hughes JM, Weill H. Asbestosis as a precursor of asbestos related lung cancer: results of a prospective mortality study. Br J Ind Med 1991;48:229-233. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2025587.

148. Chlebowski RT, Schwartz AG, Wakelee H, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled

 © National Comprehensive Cancer Network, Inc. 2017, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

trial. Lancet 2009;374:1243-1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19767090.

149. Han SS, Ten Haaf K, Hazelton WD, et al. The impact of overdiagnosis on the selection of efficient lung cancer screening strategies. Int J Cancer 2017;140:2436-2443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28073150.

150. McKee BJ, Hashim JA, French RJ, et al. Experience with a CT screening program for individuals at high risk for developing lung cancer. J Am Coll Radiol 2015;12:192-197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25176498.

151. Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med 2013;369:245-254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23863051.

152. Berg CD. Formidable challenges ahead for lung cancer screening. Oncology (Williston Park) 2012;26:182, 185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22489354.

153. Pinsky PF, Berg CD. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? J Med Screen 2012;19:154-156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23060474.

154. Pinsky PF, Kramer BS. Lung cancer risk and demographic characteristics of current 20-29 pack-year smokers: implications for screening. J Natl Cancer Inst 2015;107. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26483244.

155. Miller DL, Mayfield WR, Luu TD, et al. Community-based multidisciplinary computed tomography screening program improves lung cancer survival. Ann Thorac Surg 2016;101:1864-1869. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26876342.

156. Katki HA, Kovalchik SA, Berg CD, et al. Development and validation of risk models to select ever-smokers for CT lung cancer screening. JAMA 2016;315:2300-2311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27179989.

157. Li K, Husing A, Sookthai D, et al. Selecting high-risk individuals for lung cancer screening: a prospective evaluation of existing risk models and eligibility criteria in the German EPIC cohort. Cancer Prev Res (Phila) 2015;8:777-785. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26076698.

158. 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:e1001764. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25460915.

159. Ten Haaf K, Jeon J, Tammemagi MC, et al. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. PLoS Med 2017;14:e1002277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28376113.

160. Yousaf-Khan U, van der Aalst C, de Jong PA, et al. Risk stratification based on screening history: the NELSON lung cancer screening study. Thorax 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28360223.

161. Saghir Z, Dirksen A, Ashraf H, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. Thorax 2012;67:296-301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22286927.

162. Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. J Thorac Oncol 2009;4:608-614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19357536.

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163. Menezes RJ, Roberts HC, Paul NS, et al. Lung cancer screening using low-dose computed tomography in at-risk individuals: the Toronto experience. Lung Cancer 2010;67:177-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19427055.

164. Swensen SJ, Jett JR, Hartman TE, et al. CT screening for lung cancer: five-year prospective experience. Radiology 2005;235:259-265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15695622.

165. Wilson DO, Weissfeld JL, Fuhrman CR, et al. The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. Am J Respir Crit Care Med 2008;178:956-961. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18635890.

166. Pinsky PF, Gierada DS, Hocking W, et al. National Lung Screening Trial findings by age: Medicare-eligible versus under-65 population. Ann Intern Med 2014;161:627-633. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25199624.

167. Varlotto JM, Decamp MM, Flickinger JC, et al. Would screening for lung cancer benefit 75- to 84-year-old residents of the United States? Front Oncol 2014;4:37. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24639950.

168. Sox HC. Better evidence about screening for lung cancer. N Engl J Med 2011;365:455-457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21714644.

169. Jett JR, Midthun DE. Screening for lung cancer: for patients at increased risk for lung cancer, it works. Ann Intern Med 2011;155:540-542. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21893615.

170. Berrington de Gonzalez A, Kim KP, Berg CD. Low-dose lung computed tomography screening before age 55: estimates of the mortality reduction required to outweigh the radiation-induced cancer risk. J Med Screen 2008;15:153-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18927099.

171. Farjah F, Wood DE, Zadworny ME, et al. Resected lung cancer patients who would and would not have met screening criteria. Ann Thorac Surg 2016;101:274-279. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26298169.

172. Yip R, Henschke CI, Xu DM, et al. Lung cancers manifesting as part-solid nodules in the National Lung Screening Trial. AJR Am J Roentgenol 2017;208:1011-1021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28245151.

173. Gardiner N, Jogai S, Wallis A. The revised lung adenocarcinoma classification-an imaging guide. J Thorac Dis 2014;6:S537-546. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25349704.

174. Naidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. Radiology 2013;266:304-317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23070270.

175. Seidelman JL, Myers JL, Quint LE. Incidental, subsolid pulmonary nodules at CT: etiology and management. Cancer Imaging 2013;13:365-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24061063.

176. Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246:697-722. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18195376.

177. Travis WD, Asamura H, Bankier AA, et al. The IASLC lung cancer staging project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. J Thorac Oncol 2016;11:1204-1223. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27107787.

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178. Travis WD, Brambilla E, Noguchi M, et al. Diagnosis of lung cancer in small biopsies and cytology: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med 2013;137:668-684. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22970842.

179. Kim HY, Shim YM, Lee KS, et al. Persistent pulmonary nodular ground-glass opacity at thin-section CT: histopathologic comparisons. Radiology 2007;245:267-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17885195.

180. Yip R, Yankelevitz DF, Hu M, et al. Lung cancer deaths in the National Lung Screening Trial attributed to nonsolid nodules. Radiology 2016;281:589-596. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27378239.

181. Fukui M, Suzuki K, Matsunaga T, et al. Surgical intervention for ground glass dominant lesions: observation or outright resection? Jpn J Clin Oncol 2017:1-6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28431123.

182. Chang B, Hwang JH, Choi YH, et al. Natural history of pure ground-glass opacity lung nodules detected by low-dose CT scan. Chest 2013;143:172-178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22797081.

183. Lindell RM, Hartman TE, Swensen SJ, et al. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. Radiology 2007;242:555-562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17255425.

184. MacMahon H, Austin JH, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. Radiology 2005;237:395-400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16244247.

185. Jacobs C, van Rikxoort EM, Murphy K, et al. Computer-aided detection of pulmonary nodules: a comparative study using the public LIDC/IDRI database. Eur Radiol 2016;26:2139-2147. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26443601.

186. Zhao Y, de Bock GH, Vliegenthart R, et al. Performance of computer-aided detection of pulmonary nodules in low-dose CT: comparison with double reading by nodule volume. Eur Radiol 2012;22:2076-2084. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22814824.

187. Armato SG, 3rd, McLennan G, Bidaut L, et al. The Lung Image Database Consortium (LIDC) and Image Database Resource Initiative (IDRI): a completed reference database of lung nodules on CT scans. Med Phys 2011;38:915-931. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21452728.

188. Clark TJ, Flood TF, Maximin ST, Sachs PB. Lung CT screening reporting and data system speed and accuracy are increased with the use of a semiautomated computer application. J Am Coll Radiol 2015;12:f1301-1306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26507823.

189. Jacobs C, van Rikxoort EM, Scholten ET, et al. Solid, part-solid, or non-solid?: classification of pulmonary nodules in low-dose chest computed tomography by a computer-aided diagnosis system. Invest Radiol 2015;50:168-173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25478740.

190. Valencia R, Denecke T, Lehmkuhl L, et al. Value of axial and coronal maximum intensity projection (MIP) images in the detection of pulmonary nodules by multislice spiral CT: comparison with axial 1-mm and 5-mm slices. Eur Radiol 2006;16:325-332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16086181.

191. Fischbach F, Knollmann F, Griesshaber V, et al. Detection of pulmonary nodules by multislice computed tomography: improved detection rate with reduced slice thickness. Eur Radiol

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2003;13:2378-2383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12743736.

192. Kawel N, Seifert B, Luetolf M, Boehm T. Effect of slab thickness on the CT detection of pulmonary nodules: use of sliding thin-slab maximum intensity projection and volume rendering. AJR Am J Roentgenol 2009;192:1324-1329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19380557.

193. Peloschek P, Sailer J, Weber M, et al. Pulmonary nodules: sensitivity of maximum intensity projection versus that of volume rendering of 3D multidetector CT data. Radiology 2007;243:561-569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17456878.

194. Park EA, Goo JM, Lee JW, et al. Efficacy of computer-aided detection system and thin-slab maximum intensity projection technique in the detection of pulmonary nodules in patients with resected metastases. Invest Radiol 2009;44:105-113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19034026.

195. Jankowski A, Martinelli T, Timsit JF, et al. Pulmonary nodule detection on MDCT images: evaluation of diagnostic performance using thin axial images, maximum intensity projections, and computer-assisted detection. Eur Radiol 2007;17:3148-3156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17763856.

196. Rubin GD, Lyo JK, Paik DS, et al. Pulmonary nodules on multi-detector row CT scans: performance comparison of radiologists and computer-aided detection. Radiology 2005;234:274-283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15537839.

197. Fraioli F, Bertoletti L, Napoli A, et al. Computer-aided detection (CAD) in lung cancer screening at chest MDCT: ROC analysis of CAD versus radiologist performance. J Thorac Imaging 2007;22:241-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17721333.

198. Sahiner B, Chan HP, Hadjiiski LM, et al. Effect of CAD on radiologists' detection of lung nodules on thoracic CT scans: analysis of an observer performance study by nodule size. Acad Radiol 2009;16:1518-1530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19896069.

199. Das M, Muhlenbruch G, Heinen S, et al. Performance evaluation of a computer-aided detection algorithm for solid pulmonary nodules in low-dose and standard-dose MDCT chest examinations and its influence on radiologists. Br J Radiol 2008;81:841-847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18941043.

200. Lee HY, Goo JM, Lee HJ, et al. Usefulness of concurrent reading using thin-section and thick-section CT images in subcentimetre solitary pulmonary nodules. Clin Radiol 2009;64:127-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19103341.

201. Kubo T, Lin PJ, Stiller W, et al. Radiation dose reduction in chest CT: a review. AJR Am J Roentgenol 2008;190:335-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18212218.

202. Lee JY, Chung MJ, Yi CA, Lee KS. Ultra-low-dose MDCT of the chest: influence on automated lung nodule detection. Korean J Radiol 2008;9:95-101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18385555.

203. Funama Y, Awai K, Liu D, et al. Detection of nodules showing ground-glass opacity in the lungs at low-dose multidetector computed tomography: phantom and clinical study. J Comput Assist Tomogr 2009;33:49-53. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188784.

204. Hein PA, Romano VC, Rogalla P, et al. Linear and volume measurements of pulmonary nodules at different CT dose levels - intrascan and interscan analysis. Rofo 2009;181:24-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19085687.

205. Donnelly EF. Technical parameters and interpretive issues in screening computed tomography scans for lung cancer. J Thorac

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Imaging 2012;27:224-229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22847590.

206. van Riel SJ, Sanchez CI, Bankier AA, et al. Observer variability for classification of pulmonary nodules on low-dose CT images and its effect on nodule management. Radiology 2015;277:863-871. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26020438.

207. Ridge CA, Yildirim A, Boiselle PM, et al. Differentiating between subsolid and solid pulmonary nodules at CT: inter- and intraobserver agreement between experienced thoracic radiologists. Radiology 2016;278:888-896. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26458208.

208. Kim H, Park CM, Song YS, et al. Measurement variability of persistent pulmonary subsolid nodules on same-day repeat CT: what is the threshold to determine true nodule growth during follow-up? PLoS One 2016;11:e0148853. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26859665.

209. Penn A, Ma M, Chou BB, et al. Inter-reader variability when applying the 2013 Fleischner guidelines for potential solitary subsolid lung nodules. Acta Radiol 2015;56:1180-1186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25293951.

210. Pinsky PF, Gierada DS, Nath PH, et al. National lung screening trial: variability in nodule detection rates in chest CT studies. Radiology 2013;268:865-873. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23592767.

211. Singh S, Pinsky P, Fineberg NS, et al. Evaluation of reader variability in the interpretation of follow-up CT scans at lung cancer screening. Radiology 2011;259:263-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21248232.

212. Gierada DS, Pilgram TK, Ford M, et al. Lung cancer: interobserver agreement on interpretation of pulmonary findings at low-dose CT screening. Radiology 2008;246:265-272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024436.

213. Henschke CI, Boffetta P, Gorlova O, et al. Assessment of lung-cancer mortality reduction from CT Screening. Lung Cancer 2011;71:328-332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21168236.

214. van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009;361:2221-2229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19955524.

215. Lopes Pegna A, Picozzi G, Mascalchi M, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. Lung Cancer 2009;64:34-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18723240.

216. Veronesi G, Bellomi M, Scanagatta P, et al. Difficulties encountered managing nodules detected during a computed tomography lung cancer screening program. J Thorac Cardiovasc Surg 2008;136:611-617. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18805261.

217. Infante M, Cavuto S, Lutman FR, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med 2009;180:445-453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19520905.

218. Swensen SJ, Jett JR, Hartman TE, et al. Lung cancer screening with CT: Mayo Clinic experience. Radiology 2003;226:756-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12601181.

219. Henschke CI, Yankelevitz DF, Naidich DP, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. Radiology 2004;231:164-168. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14990809.

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220. Henschke CI, Yankelevitz DF, Miettinen OS, International Early Lung Cancer Action Program I. Computed tomographic screening for lung cancer: the relationship of disease stage to tumor size. Arch Intern Med 2006;166:321-325. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16476872.

221. International Early Lung Cancer Action Program I, Henschke CI, Yankelevitz DF, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-1771. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17065637.

222. Steele JD, Buell P. Asymptomatic solitary pulmonary nodules. Host survival, tumor size, and growth rate. J Thorac Cardiovasc Surg 1973;65:140-151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4682461.

223. Galante E, Reduzzi D, Gallus G, et al. The growth rate in the interpretation of the natural history of lung cancer. Tumori 1984;70:427-432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6506228.

224. Usuda K, Saito Y, Sagawa M, et al. Tumor doubling time and prognostic assessment of patients with primary lung cancer. Cancer 1994;74:2239-2244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7922975.

225. Arai T, Kuroishi T, Saito Y, et al. Tumor doubling time and prognosis in lung cancer patients: evaluation from chest films and clinical follow-up study. Japanese Lung Cancer Screening Research Group. Jpn J Clin Oncol 1994;24:199-204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8072198.

226. Weiss W, Boucot KR, Cooper DA. The histopathology of bronchogenic carcinoma and its relation to growth rate, metastasis, and prognosis. Cancer 1970;26:965-970. Available at: http://www.ncbi.nlm.nih.gov/pubmed/5476797.

227. Patel VK, Naik SK, Naidich DP, et al. A practical algorithmic approach to the diagnosis and management of solitary pulmonary nodules: part 2: pretest probability and algorithm. Chest 2013;143:840-846. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23460161.

228. Allen TL, Kendi AT, Mitiek MO, Maddaus MA. Combined contrast-enhanced computed tomography and 18-fluoro-2-deoxy-D-glucose-positron emission tomography in the diagnosis and staging of non-small cell lung cancer. Semin Thorac Cardiovasc Surg 2011;23:43-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21807298.

229. Swensen SJ, Viggiano RW, Midthun DE, et al. Lung nodule enhancement at CT: multicenter study. Radiology 2000;214:73-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10644104.

230. Yi CA, Lee KS, Kim BT, et al. Tissue characterization of solitary pulmonary nodule: comparative study between helical dynamic CT and integrated PET/CT. J Nucl Med 2006;47:443-450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16513614.

231. Christensen JA, Nathan MA, Mullan BP, et al. Characterization of the solitary pulmonary nodule: 18F-FDG PET versus nodule-enhancement CT. AJR Am J Roentgenol 2006;187:1361-1367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17056930.

232. Schillaci O, Travascio L, Bolacchi F, et al. Accuracy of early and delayed FDG PET-CT and of contrast-enhanced CT in the evaluation of lung nodules: a preliminary study on 30 patients. Radiol Med 2009;114:890-906. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19579015.

233. Bastarrika G, Garcia-Velloso MJ, Lozano MD, et al. Early lung cancer detection using spiral computed tomography and positron emission tomography. Am J Respir Crit Care Med 2005;171:1378-1383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15790860.

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234. Sebro R, Aparici CM, Hernandez-Pampaloni M. FDG PET/CT evaluation of pathologically proven pulmonary lesions in an area of high endemic granulomatous disease. Ann Nucl Med 2013;27:400-405. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23400394.

235. Reyes N, Onadeko OO, Luraschi-Monjagatta Mdel C, et al. Positron emission tomography in the evaluation of pulmonary nodules among patients living in a coccidioidal endemic region. Lung 2014;192:589-593. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24801058.

236. Huber H, Hodolic M, Stelzmuller I, et al. Malignant disease as an incidental finding at (1)(8)F-FDG-PET/CT scanning in patients with granulomatous lung disease. Nucl Med Commun 2015;36:430-437. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25646704.

237. Fletcher JW, Kymes SM, Gould M, et al. A comparison of the diagnostic accuracy of 18F-FDG PET and CT in the characterization of solitary pulmonary nodules. J Nucl Med 2008;49:179-185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18199626.

238. Ashraf H, Dirksen A, Loft A, et al. Combined use of positron emission tomography and volume doubling time in lung cancer screening with low-dose CT scanning. Thorax 2011;66:315-319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21169285.

239. Ohno Y, Koyama H, Matsumoto K, et al. Differentiation of malignant and benign pulmonary nodules with quantitative first-pass 320-detector row perfusion CT versus FDG PET/CT. Radiology 2011;258:599-609. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21273522.

240. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med 2013;369:910-919. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24004118.

241. Herder GJ, van Tinteren H, Golding RP, et al. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography. Chest 2005;128:2490-2496. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16236914.

242. Patel VK, Naik SK, Naidich DP, et al. A practical algorithmic approach to the diagnosis and management of solitary pulmonary nodules: part 1: radiologic characteristics and imaging modalities. Chest 2013;143:825-839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23460160.

243. Gould MK, Fletcher J, Iannettoni MD, et al. Evaluation of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:108S-130S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17873164.

244. Madsen PH, Holdgaard PC, Christensen JB, Hoilund-Carlsen PF. Clinical utility of F-18 FDG PET-CT in the initial evaluation of lung cancer. Eur J Nucl Med Mol Imaging 2016;43:2084-2097. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27164899.

245. Al-Ameri A, Malhotra P, Thygesen H, et al. Risk of malignancy in pulmonary nodules: A validation study of four prediction models. Lung Cancer 2015;89:27-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25864782.

246. Liu X, Liang M, Wang Y, et al. The outcome differences of CT screening for lung cancer pre and post following an algorithm in Zhuhai, China. Lung Cancer 2011;73:230-236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21168238.

247. New York Early Lung Cancer Action Project I. CT Screening for lung cancer: diagnoses resulting from the New York Early Lung Cancer Action Project. Radiology 2007;243:239-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17392256.

Version 2.2018, 08/08/17 © National Comprehensive Cancer Network, Inc. 2017, All rights reserved. **The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

248. Ray CE, Jr., English B, Funaki BS, et al. ACR appropriateness criteria(R) radiologic management of thoracic nodules and masses. J Am Coll Radiol 2012;9:13-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22221631.

249. Ray CE, Jr., Mohammed TL. Review of ACR Appropriateness Criteria(R) Radiologic Management of Thoracic Nodules and Masses. J Thorac Imaging 2012;27:W85-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22847592.

250. Eisenberg RL, Bankier AA, Boiselle PM. Compliance with Fleischner Society guidelines for management of small lung nodules: a survey of 834 radiologists. Radiology 2010;255:218-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20308458.

251. Gierada DS, Pinsky P, Nath H, et al. Projected outcomes using different nodule sizes to define a positive CT lung cancer screening examination. J Natl Cancer Inst 2014;106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25326638.

252. Yip R, Henschke CI, Yankelevitz DF, Smith JP. CT screening for lung cancer: Alternative definitions of positive test result based on the National Lung Screening Trial and International Early Lung Cancer Action Program databases. Radiology 2014;273:591-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24955929.

253. Wood DE, Kazerooni E, Baum SL, et al. Lung cancer screening, version 1.2015: featured updates to the NCCN guidelines. J Natl Compr Canc Netw 2015;13:23-34; quiz 34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25583767.

254. Kazerooni EA, Armstrong MR, Amorosa JK, et al. ACR CT accreditation program and the lung cancer screening program designation. J Am Coll Radiol 2015;12:38-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25455196.

255. Henschke CI, Yip R, Yankelevitz DF, et al. Definition of a positive test result in computed tomography screening for lung cancer: a cohort study. Ann Intern Med 2013;158:246-252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23420233.

256. Revel MP, Bissery A, Bienvenu M, et al. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? Radiology 2004;231:453-458. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15128990.

257. Ahn MI, Gleeson TG, Chan IH, et al. Perifissural nodules seen at CT screening for lung cancer. Radiology 2010;254:949-956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20177105.

258. de Hoop B, van Ginneken B, Gietema H, Prokop M. Pulmonary perifissural nodules on CT scans: rapid growth is not a predictor of malignancy. Radiology 2012;265:611-616. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22929331.

259. Hanaoka T, Sone S, Takayama F, et al. Presence of local pleural adhesion in CT screening-detected small nodule in the lung periphery suggests noncancerous, inflammatory nature of the lesion. Clin Imaging 2007;31:385-389. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17996600.

260. Xu DM, van der Zaag-Loonen HJ, Oudkerk M, et al. Smooth or attached solid indeterminate nodules detected at baseline CT screening in the NELSON study: cancer risk during 1 year of follow-up. Radiology 2009;250:264-272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18984780.

261. Heuvelmans MA, Oudkerk M, de Bock GH, et al. Optimisation of volume-doubling time cutoff for fast-growing lung nodules in CT lung cancer screening reduces false-positive referrals. Eur Radiol 2013;23:1836-1845. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23508275.

262. Rampinelli C, Origgi D, Bellomi M. Low-dose CT: technique, reading methods and image interpretation. Cancer Imaging

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2013;12:548-556. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23400217.

263. Bankier AA, Tack D. Dose reduction strategies for thoracic multidetector computed tomography: background, current issues, and recommendations. J Thorac Imaging 2010;25:278-288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21042066.

264. Lee TY, Chhem RK. Impact of new technologies on dose reduction in CT. Eur J Radiol 2010;76:28-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20643522.

265. Pontana F, Pagniez J, Flohr T, et al. Chest computed tomography using iterative reconstruction vs filtered back projection (Part 1): Evaluation of image noise reduction in 32 patients. Eur Radiol 2011;21:627-635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21053003.

266. Pontana F, Duhamel A, Pagniez J, et al. Chest computed tomography using iterative reconstruction vs filtered back projection (Part 2): image quality of low-dose CT examinations in 80 patients. Eur Radiol 2011;21:636-643. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21080171.

267. Christner JA, Kofler JM, McCollough CH. Estimating effective dose for CT using dose-length product compared with using organ doses: consequences of adopting International Commission on Radiological Protection publication 103 or dual-energy scanning. AJR Am J Roentgenol 2010;194:881-889. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20308486.

268. Kozower BD, Larner JM, Detterbeck FC, Jones DR. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e369S-399S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23649447.

269. Kim H, Park CM, Koh JM, et al. Pulmonary subsolid nodules: what radiologists need to know about the imaging features and management strategy. Diagn Interv Radiol 2014;20:47-57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24100062.

270. Detterbeck FC. Overdiagnosis during lung cancer screening: is it an overemphasised, underappreciated, or tangential issue? Thorax 2014;69:407-408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24646660.

271. Rampinelli C, De Marco P, Origgi D, et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. BMJ 2017;356:j347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28179230.

272. Wiener RS. Balancing the benefits and harms of low-dose computed tomography screening for lung cancer: Medicare's options for coverage. Ann Intern Med 2014;161:445-446. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24957566.

273. Ettinger DS. Lung cancer screening: has its time come? Oncology (Williston Park) 2014;28:342, 448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25004646.

274. Braillon A. Bronchioalveolar lung cancer: screening and overdiagnosis. J Clin Oncol 2014;32:3575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25225426.

275. Johnson DH, Schiller JH, Bunn PA. Reply to A. Braillon. J Clin Oncol 2014;32:3575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25225428.

276. Brawley OW, Flenaugh EL. Low-dose spiral CT screening and evaluation of the solitary pulmonary nodule. Oncology (Williston Park) 2014;28:441-446. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25004661.

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277. Ma J, Ward EM, Smith R, Jemal A. Annual number of lung cancer deaths potentially avertable by screening in the United States. Cancer 2013;119:1381-1385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23440730.

278. Morgan L, Choi H, Reid M, et al. The frequency of incidental findings and subsequent evaluation in low-dose CT scans for lung cancer screening. Ann Am Thorac Soc 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28421812.

279. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706-714. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17762336.

280. Rami-Porta R, Ball D, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 2007;2:593-602. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17607114.

281. Edge SB, Byrd DR, Compton CC. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010.

282. Amin MB, Greene FL, Edge SB, et al. AJCC Staging Manual, 8th ed: Springer International Publishing; 2017:1-1024.

283. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:138-155. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28140453.

284. Flieder DB, Vazquez M, Carter D, et al. Pathologic findings of lung tumors diagnosed on baseline CT screening. Am J Surg Pathol 2006;30:606-613. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16699315.

285. Hall FM. Identification, biopsy, and treatment of poorly understood premalignant, in situ, and indolent low-grade cancers: are we becoming victims of our own success? Radiology 2010;254:655-659. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20177083.

286. Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 2007;132:193-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17505036.

287. McGarry RC, Song G, des Rosiers P, Timmerman R. Observation-only management of early stage, medically inoperable lung cancer: poor outcome. Chest 2002;121:1155-1158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11948046.

288. Bach PB, Jett JR, Pastorino U, et al. Computed tomography screening and lung cancer outcomes. JAMA 2007;297:953-961. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17341709.

289. Carter D, Vazquez M, Flieder DB, et al. Comparison of pathologic findings of baseline and annual repeat cancers diagnosed on CT screening. Lung Cancer 2007;56:193-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17239983.

290. Yankelevitz DF, Smith JP. Understanding the core result of the National Lung Screening Trial. N Engl J Med 2013;368:1460-1461. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23574139.

291. Foy M, Yip R, Chen X, et al. Modeling the mortality reduction due to computed tomography screening for lung cancer. Cancer 2011;117:2703-2708. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21656748.

292. Tabar L, Vitak B, Chen TH, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. Radiology 2011;260:658-663. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21712474.

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293. Bach PB, Gould MK. When the average applies to no one: personalized decision making about potential benefits of lung cancer screening. Ann Intern Med 2012;157:571-573. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22893040.

294. Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev 2012;21:308-315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22465911.

295. Gareen IF, Duan F, Greco EM, et al. Impact of lung cancer screening results on participant health-related quality of life and state anxiety in the National Lung Screening Trial. Cancer 2014;120:3401-3409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25065710.

296. Mets OM, de Jong PA, Prokop M. Computed tomographic screening for lung cancer: an opportunity to evaluate other diseases. JAMA 2012;308:1433-1434. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23047354.

297. Mets OM, Buckens CF, Zanen P, et al. Identification of chronic obstructive pulmonary disease in lung cancer screening computed tomographic scans. JAMA 2011;306:1775-1781. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22028353.

298. Jacobs PC, Gondrie MJ, Mali WP, et al. Unrequested information from routine diagnostic chest CT predicts future cardiovascular events. Eur Radiol 2011;21:1577-1585. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21603881.

299. Sekikawa A, Curb JD, Edmundowicz D, et al. Coronary artery calcification by computed tomography in epidemiologic research and cardiovascular disease prevention. J Epidemiol 2012;22:188-198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22485011.

300. Molina JR, Yang P, Cassivi SD, et al. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83:584-594. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18452692.

301. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. N Engl J Med 2004;350:379-392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14736930.

302. Manser R, Wright G, Hart D, et al. Surgery for early stage non-small cell lung cancer. Cochrane Database Syst Rev 2005:CD004699. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15674959.

303. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-1076. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20233825.

304. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19632716.

305. Crestanello JA, Allen MS, Jett JR, et al. Thoracic surgical operations in patients enrolled in a computed tomographic screening trial. J Thorac Cardiovasc Surg 2004;128:254-259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15282462.

306. Grannis FW. Can we avert the need for pneumonectomy by screening for lung cancer? Eur J Cardiothorac Surg 2004;25:296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14747135.

307. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354:99-9105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10408484.

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308. Sone S, Nakayama T, Honda T, et al. Long-term follow-up study of a population-based 1996-1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography. Lung Cancer 2007;58:329-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17675180.

309. Flores RM, Park BJ, Dycoco J, et al. Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. J Thorac Cardiovasc Surg 2009;138:11-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19577048.

310. Whitson BA, Groth SS, Duval SJ, et al. Surgery for early-stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. Ann Thorac Surg 2008;86:2008-2016; discussion 2016-2008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19022040.

311. Cheng D, Downey RJ, Kernstine K, et al. Video-assisted thoracic surgery in lung cancer resection: a meta-analysis and systematic review of controlled trials. Innovations (Phila) 2007;2:261-292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22437196.

312. Detterbeck F. Thoracoscopic versus open lobectomy debate: the pro argument. Thorac Surg Sci 2009;6:Doc04. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21289905.

313. Chang JY, Li QQ, Xu QY, et al. Stereotactic ablative radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small cell lung cancer: how to fly in a "no fly zone". Int J Radiat Oncol Biol Phys 2014;88:1120-1128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24661665.

314. Senan S, Palma DA, Lagerwaard FJ. Stereotactic ablative radiotherapy for stage I NSCLC: Recent advances and controversies. J Thorac Dis 2011;3:189-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22263087.

315. Guckenberger M. What is the current status of Stereotactic body radiotherapy for stage I non-small cell lung cancer? J Thorac Dis 2011;3:147-149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22263080.

316. Anderson CM, Yip R, Henschke CI, et al. Smoking cessation and relapse during a lung cancer screening program. Cancer Epidemiol Biomarkers Prev 2009;18:3476-3483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19959698.

317. Clark MA, Gorelick JJ, Sicks JD, et al. The relations between false positive and negative screens and smoking cessation and relapse in the National Lung Screening Trial: implications for public health. Nicotine Tob Res 2016;18:17-24. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25746779.

318. Park ER, Gareen IF, Jain A, et al. Examining whether lung screening changes risk perceptions: National Lung Screening Trial participants at 1-year follow-up. Cancer 2013;119:1306-1313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23280348.

319. Slatore CG, Baumann C, Pappas M, Humphrey LL. Smoking behaviors among patients receiving computed tomography for lung cancer screening. Systematic review in support of the U.S. preventive services task force. Ann Am Thorac Soc 2014;11:619-627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24701999.

320. Townsend CO, Clark MM, Jett JR, et al. Relation between smoking cessation and receiving results from three annual spiral chest computed tomography scans for lung carcinoma screening. Cancer 2005;103:2154-2162. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15825210.

321. Ashraf H, Tonnesen P, Holst Pedersen J, et al. Effect of CT screening on smoking habits at 1-year follow-up in the Danish Lung Cancer Screening Trial (DLCST). Thorax 2009;64:388-392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19052048.

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322. Borondy Kitts AK, McKee AB, Regis SM, et al. Smoking cessation results in a clinical lung cancer screening program. J Thorac Dis 2016;8:S481-487. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27606076.

323. Sitas F, Weber MF, Egger S, et al. Smoking cessation after cancer. J Clin Oncol 2014;32:3593-3595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25267760.

324. Taylor KL, Cox LS, Zincke N, et al. Lung cancer screening as a teachable moment for smoking cessation. Lung Cancer 2007;56:125-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17196298.

325. Leone FT, Evers-Casey S, Toll BA, Vachani A. Treatment of tobacco use in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e61S-77S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23649454.

326. Cataldo JK, Dubey S, Prochaska JJ. Smoking cessation: an integral part of lung cancer treatment. Oncology 2010;78:289-301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20699622.

327. Hays JT, McFadden DD, Ebbert JO. Pharmacologic agents for tobacco dependence treatment: 2011 update. Curr Atheroscler Rep 2012;14:85-92. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22002681.

328. van den Bergh KA, Essink-Bot ML, Borsboom GJ, et al. Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). Br J Cancer 2010;102:27-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19935789.

329. van den Bergh KA, Essink-Bot ML, Borsboom GJ, et al. Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial. Eur Respir J 2011;38:154-161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21148229.

330. Brain K, Lifford KJ, Carter B, et al. Long-term psychosocial outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised controlled trial. Thorax 2016;71:996-1005. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27471048.

331. Bunge EM, van den Bergh KAM, Essink-Bot M-L, et al. High affective risk perception is associated with more lung cancer-specific distress in CT screening for lung cancer. Lung Cancer 2008;62:385-390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18468717.

332. Silvestri GA. Screening for lung cancer: it works, but does it really work? Ann Intern Med 2011;155:537-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21893614.

333. Croswell JM, Baker SG, Marcus PM, et al. Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial. Ann Intern Med 2010;152:505-512, W176-580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20404381.

334. Diederich S, Wormanns D, Semik M, et al. Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. Radiology 2002;222:773-781. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11867800.

335. Gohagan JK, Marcus PM, Fagerstrom RM, et al. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. Lung Cancer 2005;47:9-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15603850.

336. Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology 1996;201:798-802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8939234.

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337. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. Ann Intern Med 2011;155:137-144. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21810706.

338. Henschke CI, Yip R, Yankelevitz DF, Miettinen OS. Computed tomography screening for lung cancer: prospects of surviving competing causes of death. Clin Lung Cancer 2006;7:323-325. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16640803.

339. McCunney RJ, Li J. Radiation risks in lung cancer screening programs: a comparison with nuclear industry workers and atomic bomb survivors. Chest 2014;145:618-624. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24590022.

340. Bach PB, Cramer LD, Schrag D, et al. The influence of hospital volume on survival after resection for lung cancer. N Engl J Med 2001;345:181-188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11463014.

341. Silvestri GA, Handy J, Lackland D, et al. Specialists achieve better outcomes than generalists for lung cancer surgery. Chest 1998;114:675-680. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9743149.

342. Stephan F, Boucheseiche S, Hollande J, et al. Pulmonary complications following lung resection: a comprehensive analysis of incidence and possible risk factors. Chest 2000;118:1263-1270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11083673.

343. Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998;351:1242-1245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9643744.

344. Li F, Sone S, Abe H, et al. Lung cancers missed at low-dose helical CT screening in a general population: comparison of clinical, histopathologic, and imaging findings. Radiology 2002;225:673-683. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12461245.

345. Armato SG, 3rd, Li F, Giger ML, et al. Lung cancer: performance of automated lung nodule detection applied to cancers missed in a CT screening program. Radiology 2002;225:685-692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12461246.

346. DeVita VT, Jr., Young RC, Canellos GP. Combination versus single agent chemotherapy: a review of the basis for selection of drug treatment of cancer. Cancer 1975;35:98-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/162854.

347. Folkman J. Seminars in Medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. N Engl J Med 1995;333:1757-1763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7491141.

348. Patz EF, Black WC, Goodman PC. CT screening for lung cancer: not ready for routine practice. Radiology 2001;221:587-591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11719648.

349. Yoshizawa A, Motoi N, Riely GJ, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Mod Pathol 2011;24:653-664. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21252858.

350. Russell PA, Wainer Z, Wright GM, et al. Does lung adenocarcinoma subtype predict patient survival?: A clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol 2011;6:1496-1504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21642859.

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351. Jett JR, Midthun DE. Commentary: CT screening for lung cancer--caveat emptor. Oncologist 2008;13:439-444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18448559.

352. Bach PB. Reduced lung-cancer mortality with CT screening. N Engl J Med 2011;365:2036; author reply 2037-2038. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22111730.

353. van den Bergh KA, Essink-Bot ML, Bunge EM, et al. Impact of computed tomography screening for lung cancer on participants in a randomized controlled trial (NELSON trial). Cancer 2008;113:396-404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18484588.

354. Gierada DS, Pinsky PF, Duan F, et al. Interval lung cancer after a negative CT screening examination: CT findings and outcomes in National Lung Screening Trial participants. Eur Radiol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28050695.

355. Croswell JM, Kramer BS, Kreimer AR, et al. Cumulative incidence of false-positive results in repeated, multimodal cancer screening. Ann Fam Med 2009;7:212-222. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19433838.

356. Sistrom CL, Dreyer KJ, Dang PP, et al. Recommendations for additional imaging in radiology reports: multifactorial analysis of 5.9 million examinations. Radiology 2009;253:453-461. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19710005.

357. Berland LL, Silverman SG, Gore RM, et al. Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee. J Am Coll Radiol 2010;7:754-773. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20889105.

358. Larke FJ, Kruger RL, Cagnon CH, et al. Estimated radiation dose associated with low-dose chest CT of average-size participants in the National Lung Screening Trial. AJR Am J Roentgenol 2011;197:1165-1169. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22021510.

359. Brenner DJ. Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. Radiology 2004;231:440-445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15128988.

360. Frank L, Christodoulou E, Kazerooni EA. Radiation risk of lung cancer screening. Semin Respir Crit Care Med 2013;34:738-747. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24258564.

361. Mascalchi M, Belli G, Zappa M, et al. Risk-benefit analysis of X-ray exposure associated with lung cancer screening in the Italung-CT trial. AJR Am J Roentgenol 2006;187:421-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16861547.

362. Goulart BH, Bensink ME, Mummy DG, Ramsey SD. Lung cancer screening with low-dose computed tomography: costs, national expenditures, and cost-effectiveness. J Natl Compr Canc Netw 2012;10:267-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22308519.

363. Centers for Disease C, Prevention. Vital signs: current cigarette smoking among adults aged ≥18 years--United States, 2005-2010. MMWR Morb Mortal Wkly Rep 2011;60:1207-1212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21900875.

364. Mauchley DC, Mitchell JD. Current estimate of costs of lung cancer screening in the United States. Thorac Surg Clin 2015;25:205-215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25901564.

365. Schweigert M, Dubecz A, Beron M, et al. Pulmonary infections imitating lung cancer: clinical presentation and therapeutical approach. Ir J Med Sci 2013;182:73-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22592566.

366. Jacobs PC, Gondrie MJ, van der Graaf Y, et al. Coronary artery calcium can predict all-cause mortality and cardiovascular events on low-dose CT screening for lung cancer. AJR Am J Roentgenol

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2012;198:505-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22357989.

367. Black WC, Gareen IF, Soneji SS, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. N Engl J Med 2014;371:1793-1802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25372087.

368. Duke SL, Eisen T. Finding needles in a haystack: annual low-dose computed tomography screening reduces lung cancer mortality in a high-risk group. Expert Rev Anticancer Ther 2011;11:1833-1836. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22117150.

369. Puggina A, Broumas A, Ricciardi W, Boccia S. Cost-effectiveness of screening for lung cancer with low-dose computed tomography: a systematic literature review. Eur J Public Health 2016;26:168-175. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26370440.

370. Lafata JE, Simpkins J, Lamerato L, et al. The economic impact of false-positive cancer screens. Cancer Epidemiol Biomarkers Prev 2004;13:2126-2132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15598770.

371. Wisnivesky JP, Mushlin AI, Sicherman N, Henschke C. The cost-effectiveness of low-dose CT screening for lung cancer: preliminary results of baseline screening. Chest 2003;124:614-621. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12907551.

372. Chirikos TN, Hazelton T, Tockman M, Clark R. Screening for lung cancer with CT: a preliminary cost-effectiveness analysis. Chest 2002;121:1507-1514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12006436.

373. Lillie SE, Fu SS, Fabbrini AE, et al. What factors do patients consider most important in making lung cancer screening decisions? Findings from a demonstration project conducted in the Veterans Health Administration. Lung Cancer 2017;104:38-44. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28212998.

374. Woloshin S, Schwartz LM, Black WC, Kramer BS. Cancer screening campaigns--getting past uninformative persuasion. N Engl J Med 2012;367:1677-1679. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23113476.

375. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2017: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2017;67:100-121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28170086.

376. Tammemagi MC, Berg CD, Riley TL, et al. Impact of lung cancer screening results on smoking cessation. J Natl Cancer Inst 2014;106:dju084. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24872540.

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