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National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Lung Cancer Screening

Version 1.2025 — October 14, 2024

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**NCCN recognizes the importance of clinical trials and encourages participation when applicable and available.
Trials should be designed to maximize inclusiveness and broad representative enrollment.**

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¥ Patient advocacy

Ξ Pulmonary medicine

§ Radiotherapy/Radiation

φ Surgical oncology
£ Supportive care

including palliative, pain
management, pastoral
care, and oncology
social work

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See [NCCN Categories of Evidence and Consensus](#).

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Updates in Version 1.2025 of the NCCN Guidelines for Lung Cancer Screening from Version 2.2024 include:

LCS-1

- Risk Assessment, Patients not eligible for lung cancer screening, third bullet revised: Functional status and/or comorbidity that would prohibit curative intent treatment (see Principles of Surgery in the NCCN Guidelines for Non-Small Cell Lung Cancer and *Principles of Radiation Therapy in the NCCN Guidelines for Non-Small Cell Lung Cancer*)
- Risk Status:
 - ▶ High risk, second bullet revised: ≥ 20 pack-year history of smoking cigarettes (category 1) or ≥ 20 year history of smoking cigarettes (category 2B).
 - ▶ Low risk, second bullet revised: ≥ 20 pack-year history of smoking cigarettes or < 20 year history of smoking cigarettes (category 2B).

LCS-1A

- Footnotes revised:
 - ▶ Footnote e: Documented sustained and substantially elevated radon exposure increases the risk for lung cancer in patients ~~who also have a history of heavy smoking~~ . . .
 - ▶ Footnote k: Curative intent treatment includes surgery and stereotactic *ablative radiotherapy (SABR)*, also known as stereotactic body radiation therapy (SBRT), ~~also known as stereotactic ablative body radiotherapy (SABR)~~. Ablative *image-guided thermal ablation (IGTA)* techniques, such as radiofrequency ablation (RFA), *microwave ablation*, and *cryoablation* are additional alternatives for curative intent treatment. ~~SBRT or ablation SABR or IGTA may be used for patients with advanced age and medically inoperable patients with cardiac disease or severe COPD who are unable to have surgery, which themselves do not preclude eligibility for screening.~~ See also the NCCN Guidelines for Non-Small Cell Lung Cancer.
 - ▶ Footnote m: Black and African American individuals with less cigarette smoking exposure have a similar risk for lung cancer as white individuals with more cigarette smoking exposure. . .

LCS-2A

- Footnote r revised: A nodule is a *3-dimensional rounded opacity*, measuring up to 3 cm in diameter. A solid nodule has a homogeneous soft-tissue attenuation, a nonsolid nodule (also known as a ground-glass nodule) has hazy increased attenuation that does not obliterate bronchial and vascular margins, and a part-solid nodule has elements of both solid and nonsolid nodules. Nodules should be evaluated and measured on the LDCT using lung windows. . . (Also pages LCS-3A, LCS-4A, LCS-5, LCS-6, LCS-7A, LCS-8A, LCS-9A, LCS-10A, and LCS-11)

LCS-3A

- Footnotes revised:
 - ▶ Footnote z: Patients with a strong ~~clinical suspicion probability~~ of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery. . .
 - ▶ Footnote aa: If ~~nonsurgical therapy is contemplated without tissue confirmation, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with therapy without tissue confirmation.~~ IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595. ~~Prior to treatment, multidisciplinary evaluation that includes treating physicians and specialists in obtaining tissue diagnosis (thoracic surgery, interventional pulmonology, and interventional radiology) is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult, that a clinical diagnosis of lung cancer is appropriate, and that treatment is warranted.~~ (Also pages LCS-4A, LCS-7A, LCS-8A, LCS-9A, and LCS-10A)

LCS-10A

- Footnote hh revised: Patient preferences should be taken into account when deciding whether to follow-up with LDCT in 6 months or use invasive procedures *in consultation with expert recommendations*.



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RISK ASSESSMENT^{a,b,c}

- Cigarette smoking history^d
- Radon exposure^e
- Occupational exposure^f
- Cancer history^g
- Family history of lung cancer in first-degree relatives
- Disease history (chronic obstructive pulmonary disease [COPD] or pulmonary fibrosis)
- Cigarette smoking exposure^h (second-hand smoke)
- Risk calculator to enhance determination of risk status^{i,j}

Patients not eligible for lung cancer screening:

- Symptoms of lung cancer (see [NCCN Guidelines for Non-Small Cell Lung Cancer](#))
- Previous lung cancer (see [Surveillance in the NCCN Guidelines for Non-Small Cell Lung Cancer](#))
- Functional status and/or comorbidity that would prohibit curative intent treatment^k (see [Principles of Surgery in the NCCN Guidelines for Non-Small Cell Lung Cancer and Principles of Radiation Therapy in the NCCN Guidelines for Non-Small Cell Lung Cancer](#))

RISK STATUS

High risk^{i,l,m}

- Age ≥ 50 y (category 1) and
- ≥ 20 pack-year history of smoking cigarettes (category 1) or ≥ 20 year history of smoking cigarettes (category 2B)

In candidates for screening, shared patient/provider decision-making is recommended, including a discussion of benefits/risks^{c,j}

Low-dose CT (LDCT)ⁿ
(category 1)

Screening Findings ([LCS-2](#))

Low risk

- Age < 50 y and/or
- < 20 pack-year history of smoking cigarettes or < 20 year history of smoking cigarettes (category 2B)

Lung cancer screening not recommended

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

[Footnotes on LCS-1A](#)



FOOTNOTES

- ^a It is recommended that institutions performing lung cancer screening use a multidisciplinary approach for nodule management that includes the specialties of thoracic radiology, pulmonary medicine, and thoracic surgery. Some institutions also include medical oncology, radiation oncology, and/or pathology.
- ^b Lung cancer screening with LDCT is appropriate to consider for patients at high risk for cancer who are potential candidates for definitive treatment. Chest x-ray is not recommended for lung cancer screening.
- ^c Although age and smoking history are used for risk assessment, other potential risk factors for lung cancer (eg, occupational exposure, radon exposure, cancer history, family history, lung disease history) may be discussed during shared decision-making.
- ^d All individuals who currently smoke cigarettes should be advised to quit smoking, and all individuals who formerly smoked should be advised to remain abstinent from smoking. For additional cessation support and resources, individuals who smoke can be referred to <https://www.smokefree.gov>. Lung cancer screening should not be considered a substitute for smoking cessation. Cigarette smoking history should document both extent of exposure in pack-years (number of packs smoked every day multiplied by the number of years) and the amount of time since smoking cessation in individuals who previously smoked. See also the [NCCN Guidelines for Smoking Cessation](#).
- ^e Documented sustained and substantially elevated radon exposure increases the risk for lung cancer in patients. Many state websites have information more specific to local areas, including areas of known elevated radon.
- ^f Agents that are identified specifically as carcinogens targeting the lungs include: arsenic, asbestos, beryllium, cadmium, chromium, coal smoke, diesel fumes, nickel, silica, soot, and uranium.
- ^g There is increased risk of developing new primary lung cancer among survivors of lymphomas, cancers of the head and neck, or smoking-related cancers.
- ^h 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 sufficient for recommending lung cancer screening.
- ⁱ NCCN encourages providers to consider using risk calculators, if possible, because additional candidates at high risk for lung cancer may be identified for lung screening. See [Tammemagi lung cancer risk calculator](#). Sands J, et al. J Thorac Oncol 2021;16:37-53.
- ^j Shared decision-making aids may assist in counseling patients about the risks and benefits of screening. Examples of decision-making aids can be found at: <http://www.shouldiscreen.com/benefits-and-harms-screening>. Use of risk models may identify patients with a lower risk or higher risk within the current recommendations.
- ^k Curative intent treatment includes surgery and stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT). Ablative image-guided thermal ablation (IGTA) techniques, such as radiofrequency ablation (RFA), microwave ablation, and cryoablation are additional alternatives for curative intent treatment. SABR or IGTA may be used for patients with advanced age and patients with cardiac disease or severe COPD who are unable to have surgery, which themselves do not preclude eligibility for screening. See also the [NCCN Guidelines for Non-Small Cell Lung Cancer](#).
- ^l Although randomized trial evidence supports screening up to age 77 years, there is uncertainty about the upper age limit to initiate or continue screening. One can consider screening beyond age 77 years as long as patient functional status and comorbidity allow consideration for curative intent therapy.
- ^m Black and African American individuals with less cigarette smoking exposure have a similar risk for lung cancer as white individuals with more cigarette smoking exposure. This increased risk for Black/African Americans should be considered in shared decision-making and risk assessment. Aldrich M, et al. JAMA Oncol 2019;5:1318-1324.
- ⁿ All screening and follow-up chest CT scans should use a CT dose index volume (CTDI_{vol}) threshold of 3 mGy or less for a patient of average size, unless evaluating mediastinal abnormalities or lymph nodes, where standard-dose CT with IV contrast might be appropriate ([LCS-A](#)). Parameters should be adjusted for patients of smaller or larger size. There should be a systematic process for appropriate follow-up. See [ACR-STR Practice Parameter for the Performance and Reporting of Lung Cancer Screening Thoracic Computed Tomography \(CT\)](#).

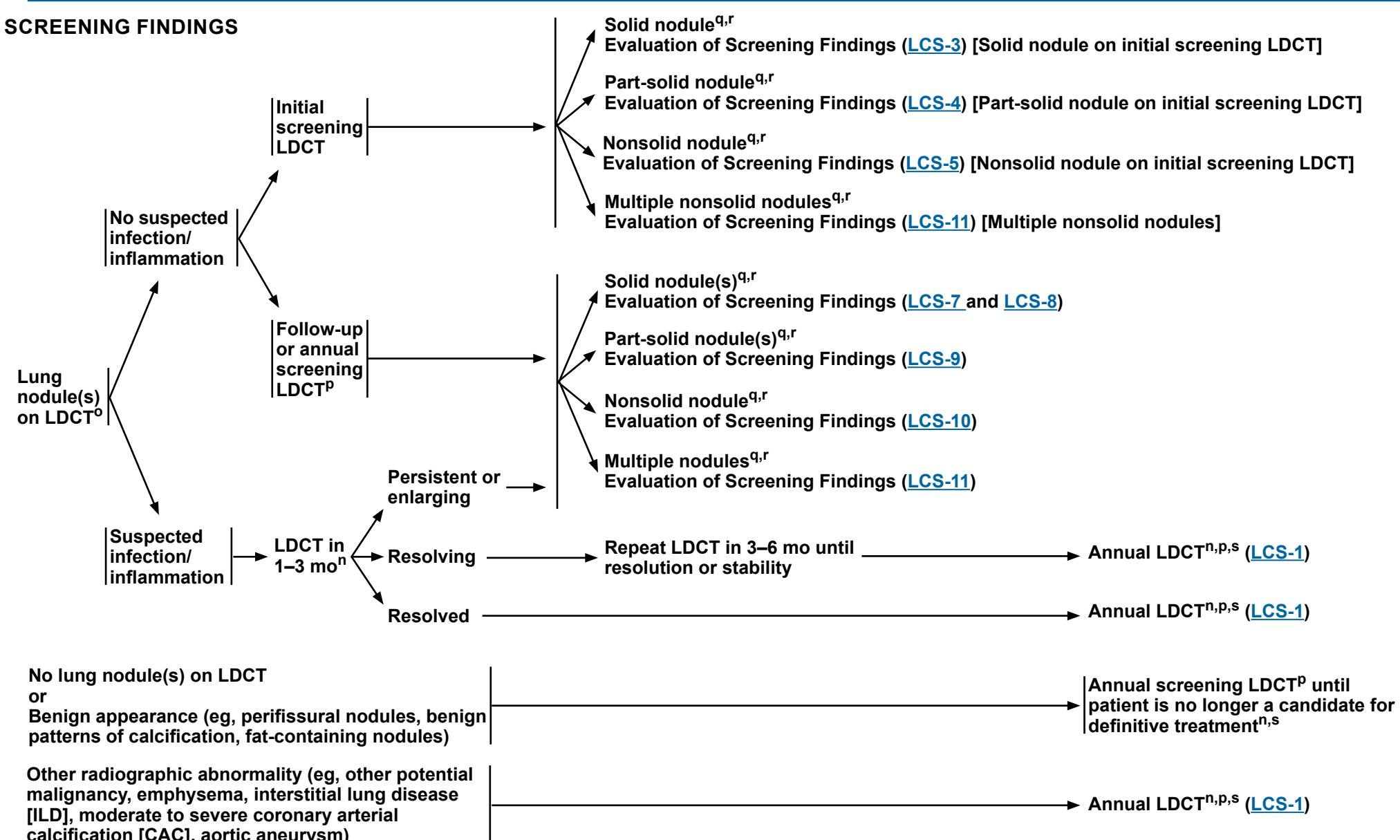
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SCREENING FINDINGS


[Footnotes on LCS-2A](#)

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



FOOTNOTES

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- ^o The NCCN Guidelines for Lung Cancer Screening are harmonized with [Lung-RADS](#) with rounding of mean measurement to the nearest whole number (mm).
- ^P Ideally, the annual LDCT is performed 12 months from the initial or interval scan.
- ^q 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.
- ^r A nodule is a 3-dimensional opacity, measuring up to 3 cm in diameter. A solid nodule has a homogeneous soft-tissue attenuation, a nonsolid nodule (also known as a ground-glass nodule) has hazy increased attenuation that does not obliterate bronchial and vascular margins, and a part-solid nodule has elements of both solid and nonsolid nodules. Nodules should be evaluated and measured on the LDCT lung windows. The size of all nodules is underestimated when viewed on soft-tissue windows, and some nodules may not even be visible, particularly nonsolid nodules and small nodules. Bankier AA, et al. Radiology 2017;285:584-600.
- ^s There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.

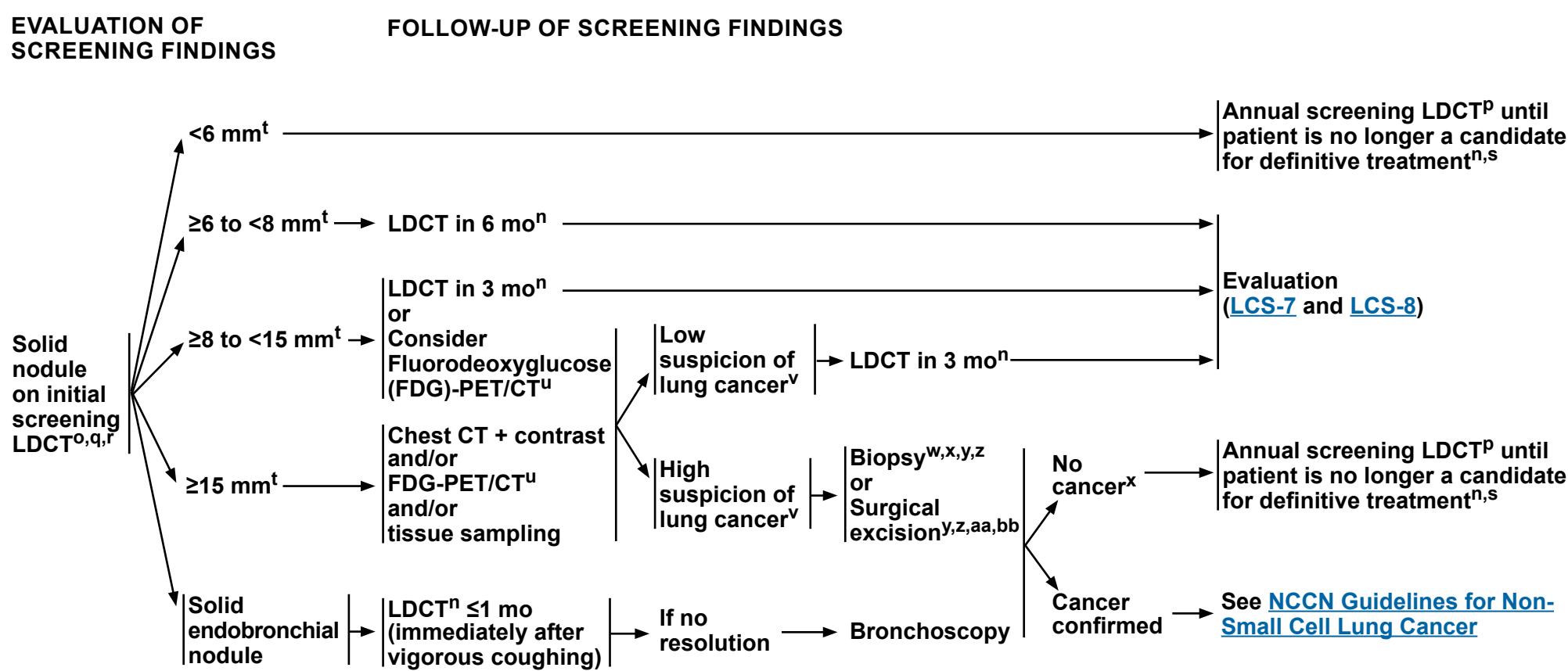
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EVALUATION OF SCREENING FINDINGS



[Footnotes on LCS-3A](#)

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



FOOTNOTES

ⁿ All screening and follow-up chest CT scans should use a CTDI_{vol} threshold of 3 mGy or less for a patient of average size, unless evaluating mediastinal abnormalities or lymph nodes, where standard-dose CT with IV contrast might be appropriate ([LCS-A](#)). Parameters should be adjusted for patients of smaller or larger size. There should be a systematic process for appropriate follow-up. See [ACR-STR Practice Parameter for the Performance and Reporting of Lung Cancer Screening Thoracic Computed Tomography \(CT\)](#).

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

^t 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.

^u FDG-PET has a low sensitivity for nodules with <8 mm of solid component and for small nodules near the diaphragm. FDG-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 FDG-PET/CT is higher.

^v 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 include: [Mayo risk model](#); [Brock university model](#); and 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.

^w Tissue samples need to be adequate for both histology and molecular testing. Travis WD, et al. In: WHO Classification of Thoracic Tumors, 5th Ed. Lyon: International Agency for Research on Cancer; 2021:29-36.

^x If biopsy is non-diagnostic and a strong suspicion for cancer persists, suggest repeat biopsy, surgical excision, or short-interval LDCT follow-up (3 months).

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

^z Patients with a strong probability of stage I lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery. A biopsy adds time, cost, and procedural risk and may not be needed for treatment decisions. A preoperative biopsy may be appropriate if a non-lung cancer diagnosis is strongly suspected, which can be diagnosed by bronchoscopy, core biopsy, or fine-needle aspiration (FNA), or if an intraoperative diagnosis appears difficult or very risky. When a preoperative tissue diagnosis has not been obtained, an intraoperative diagnosis (ie, wedge resection or needle biopsy) is necessary before lobectomy, bilobectomy, or pneumonectomy. See [Principles of Diagnostic Evaluation in the NCCN Guidelines for Non-Small Cell Lung Cancer](#).

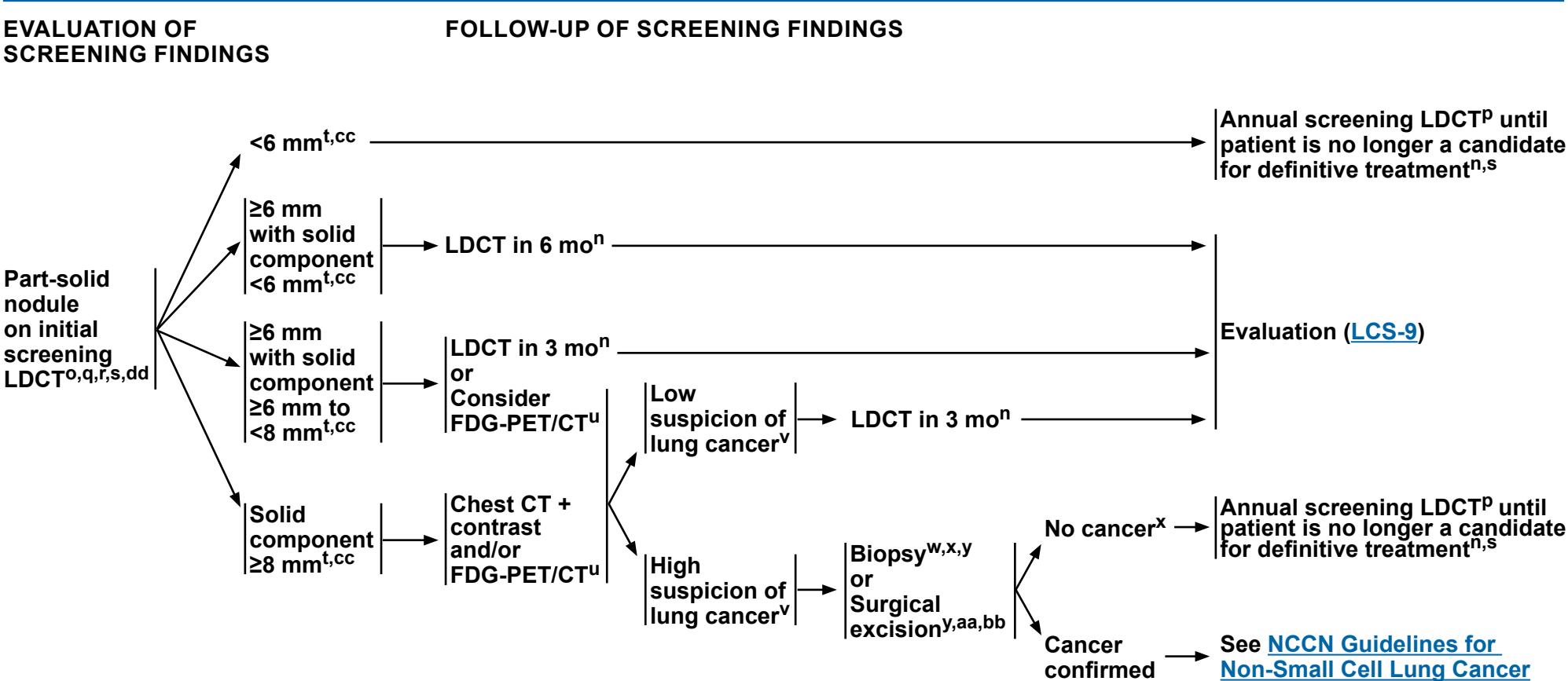
^{aa} Prior to treatment, multidisciplinary evaluation that includes treating physicians and specialists in obtaining tissue diagnosis (thoracic surgery, interventional pulmonology, and interventional radiology) is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult, that a clinical diagnosis of lung cancer is appropriate, and that treatment is warranted.

^{bb} SABR is also an appropriate option for patients with high surgical risk. This should include a multidisciplinary evaluation, including at least thoracic surgery and radiation oncology. See [Principles of Radiation Therapy in the NCCN Guidelines for Non-Small Cell Lung Cancer](#).

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



**EVALUATION OF
SCREENING FINDINGS**



[Footnotes on LCS-4A](#)

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



FOOTNOTES

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^o The NCCN Guidelines for Lung Cancer Screening are harmonized with [Lung-RADS](#) with rounding of mean measurement to the nearest whole number (mm).

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^{bb} SABR is also an appropriate option for patients with high surgical risk. This should include a multidisciplinary evaluation, including at least thoracic surgery and radiation oncology. See [Principles of Radiation Therapy in the NCCN Guidelines for Non-Small Cell Lung Cancer](#).

^{cc} All part-solid nodules ≥6 mm should be identified and solid areas should be measured.

^{dd} 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-9](#)).

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



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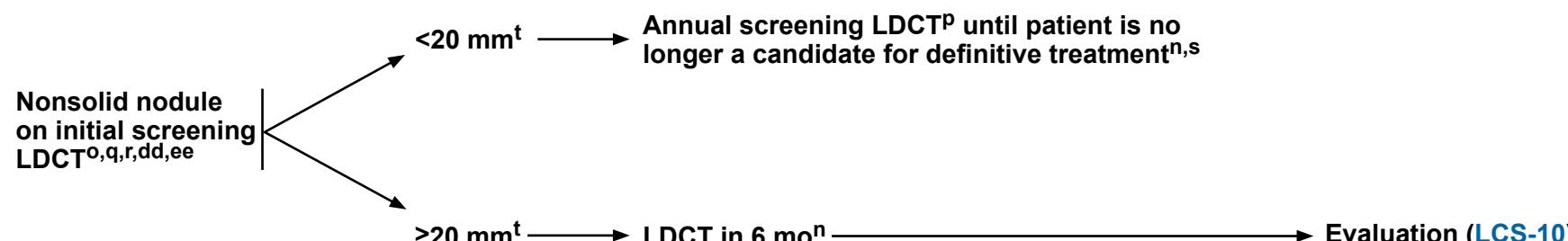
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EVALUATION OF SCREENING FINDINGS

FOLLOW-UP OF SCREENING FINDINGS



^h All screening and follow-up chest CT scans should use a CTDI_{vol} threshold of 3 mGy or less for a patient of average size, unless evaluating mediastinal abnormalities or lymph nodes, where standard-dose CT with IV contrast might be appropriate ([LCS-A](#)). Parameters should be adjusted for patients of smaller or larger size. There should be a systematic process for appropriate follow-up. See [ACR-STR Practice Parameter for the Performance and Reporting of Lung Cancer Screening Thoracic Computed Tomography \(CT\)](#).

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^{dd} 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-9](#)).

^{ee} Lung-RADS 1.1 has increased the size of a nonsolid nodule that can continue with annual screening to <30 mm, rather than <20 mm as recommended in the previous version. The NCCN Guidelines Panel has not harmonized this portion of the [Lung-RADS](#) update, as the consensus among panel members is that baseline or new nonsolid nodules ≥ 20 mm should have an earlier evaluation at 6 months.

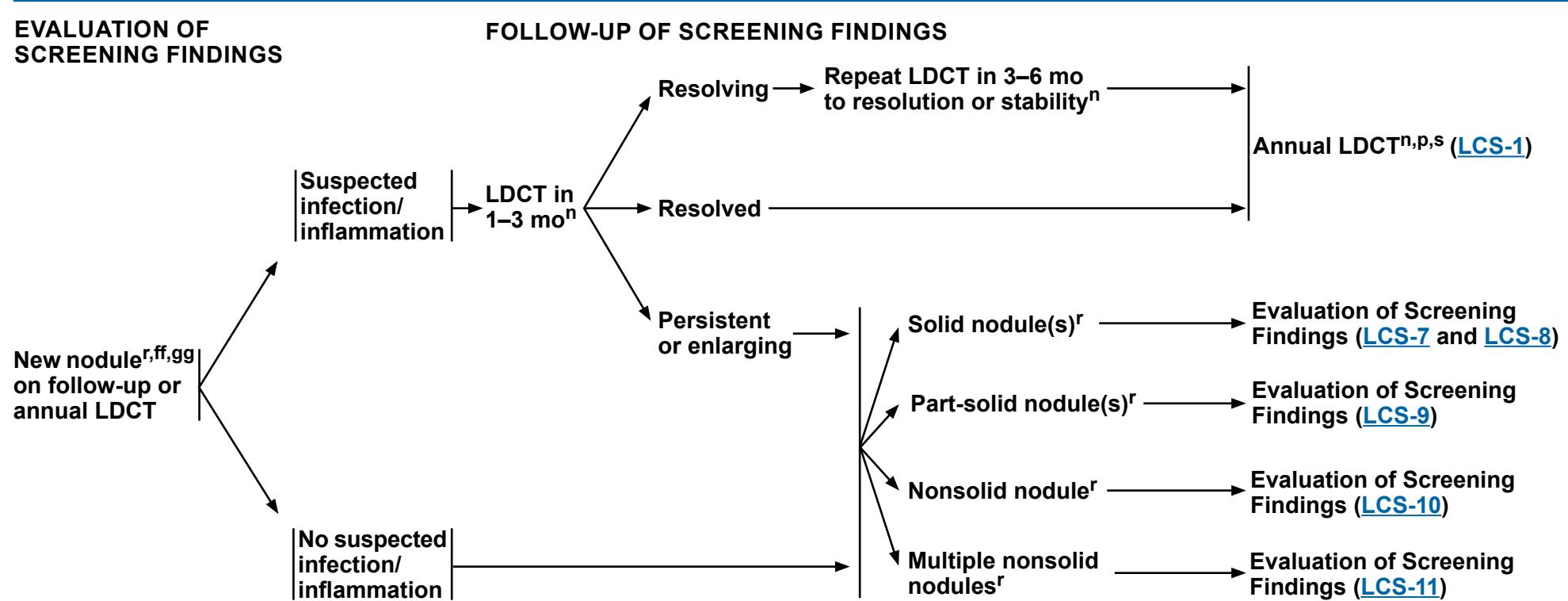
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EVALUATION OF SCREENING FINDINGS



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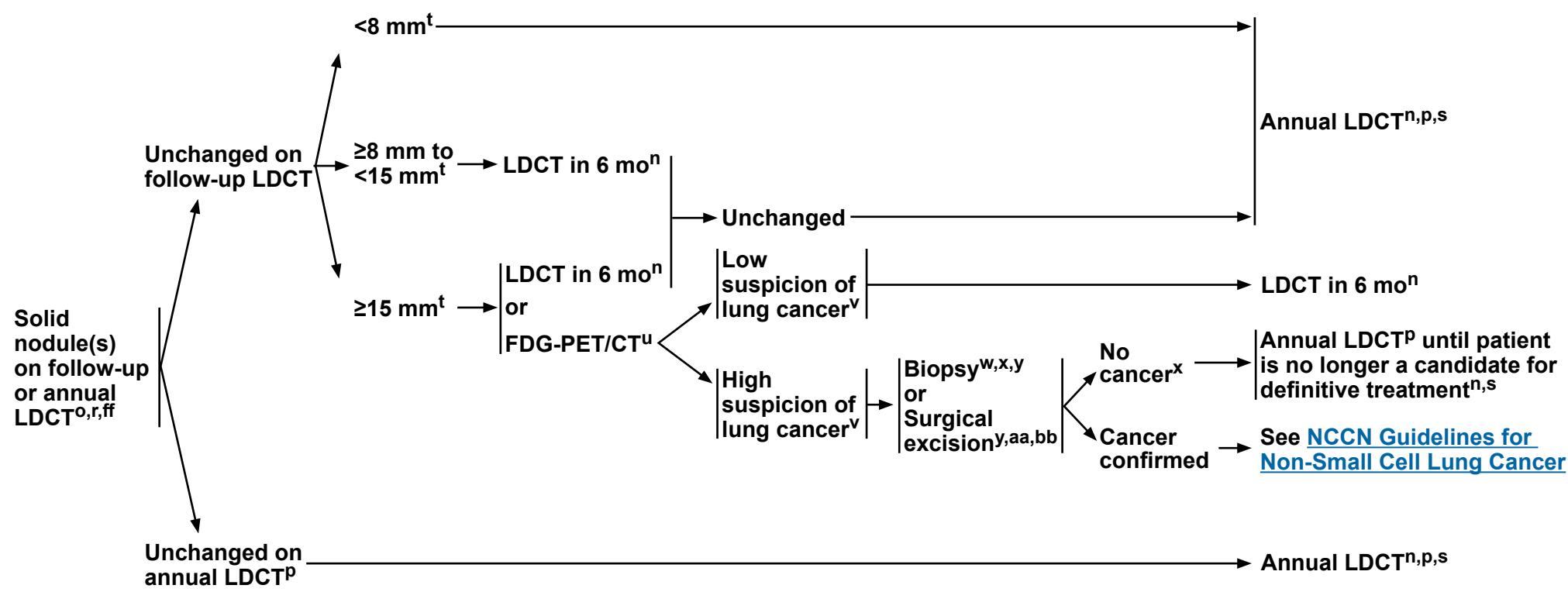
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[Footnotes on LCS-7A](#)

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



FOOTNOTES

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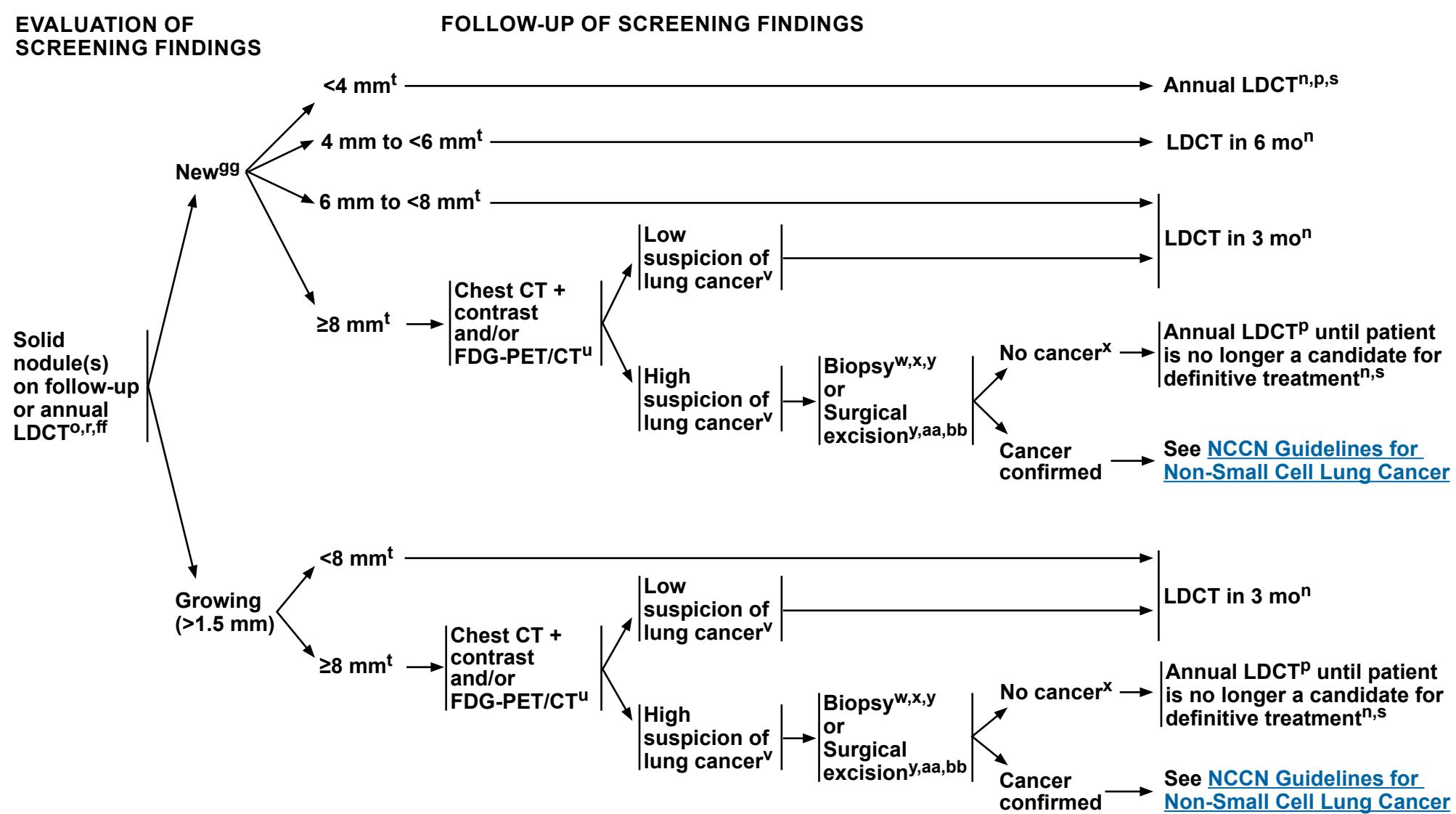
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Note: All recommendations are category 2A unless otherwise indicated.

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FOOTNOTES

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^{gg} New nodule is defined as ≥4 mm in mean diameter.

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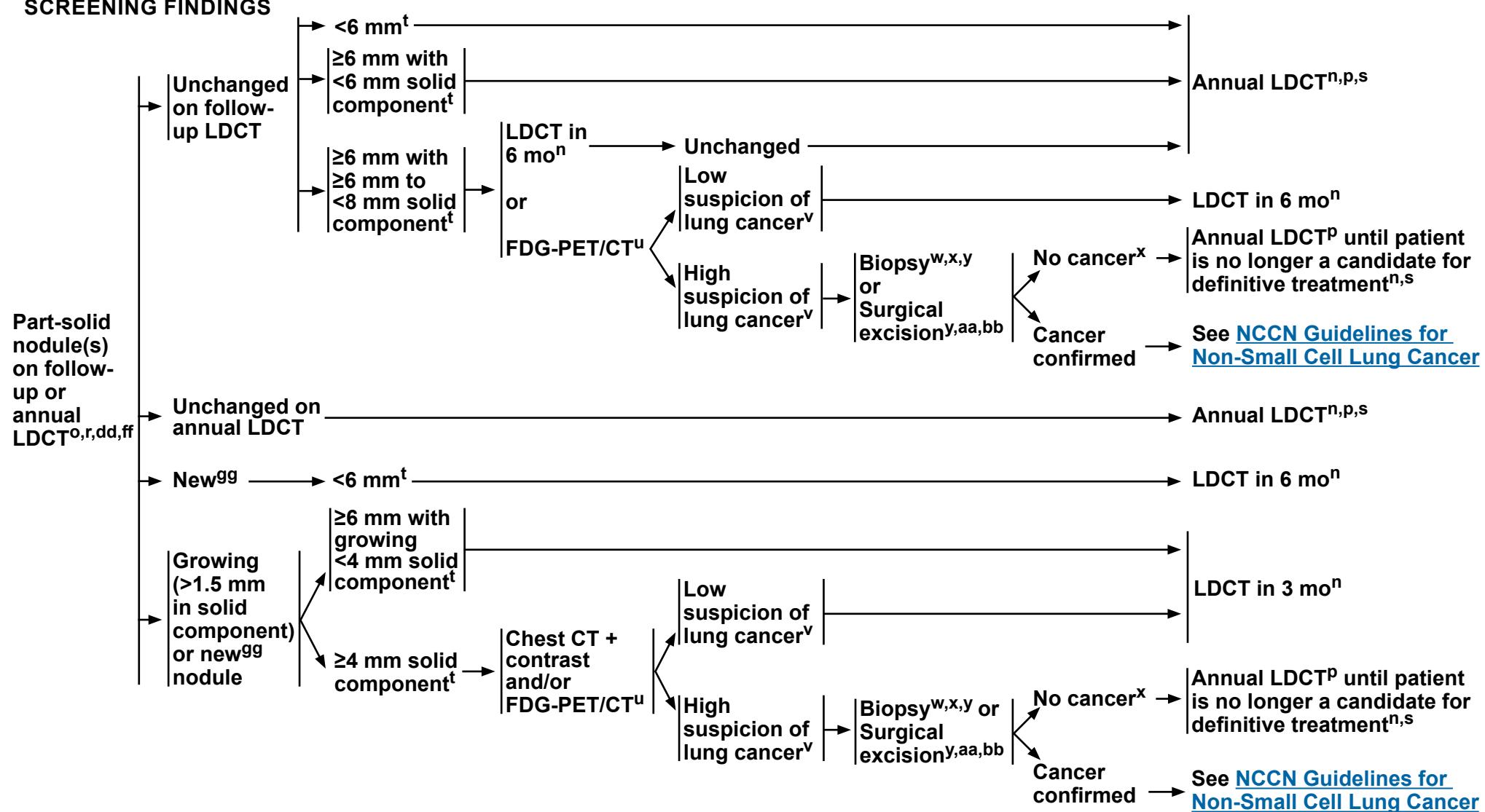


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Note: All recommendations are category 2A unless otherwise indicated.

[Footnotes on LCS-9A](#)



FOOTNOTES

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^{dd} 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-9](#)).

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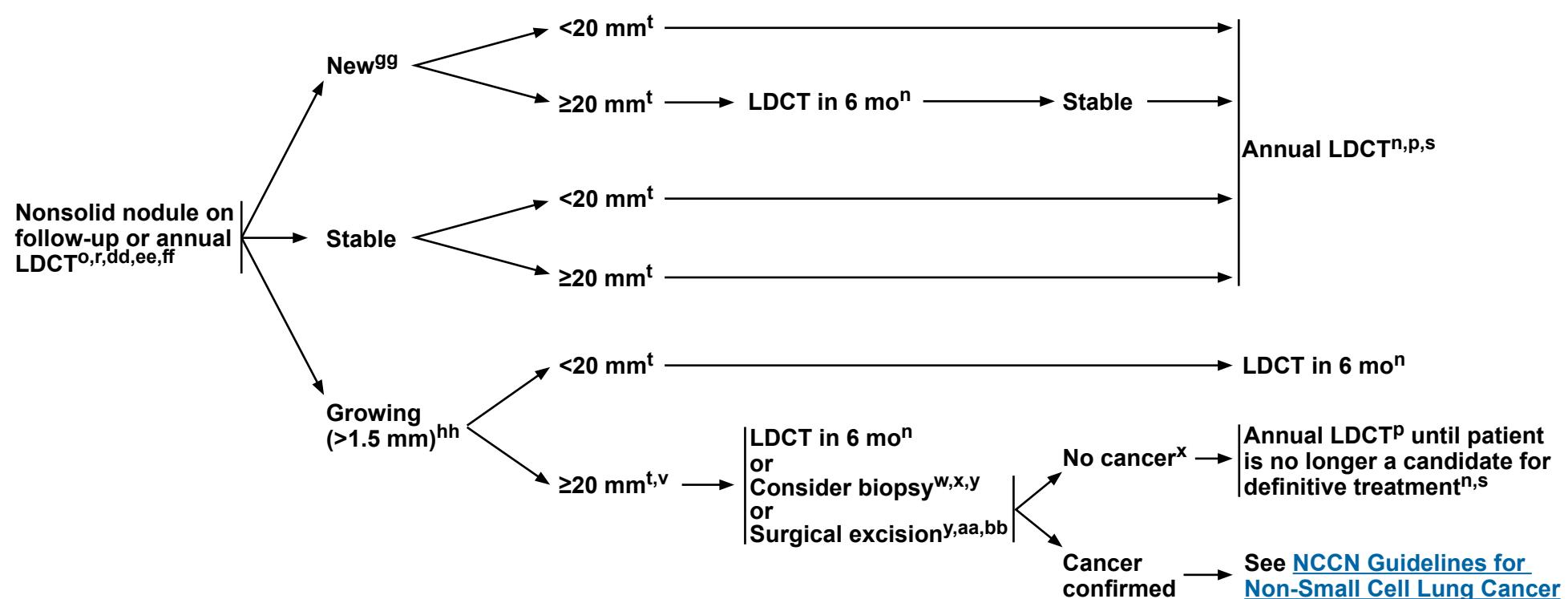
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^{dd} It is crucial that all nonsolid lesions be reviewed at thin (≤ 1.5 mm) slices to exclude any solid components. Any solid component in the nodule requires management of the lesion with the part-solid recommendations ([LCS-9](#)).

^{ee} Lung-RADS 1.1 has increased the size of a nonsolid nodule that can continue with annual screening to <30 mm, rather than <20 mm as recommended in the previous version. The NCCN Guidelines Panel has not harmonized this portion of the Lung-RADS update, as the consensus among panel members is that baseline or new nonsolid nodules ≥ 20 mm should have an earlier evaluation at 6 months.

^{ff} Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer ([LCS-6](#)).

^{gg} New nodule is defined as ≥ 4 mm in mean diameter.

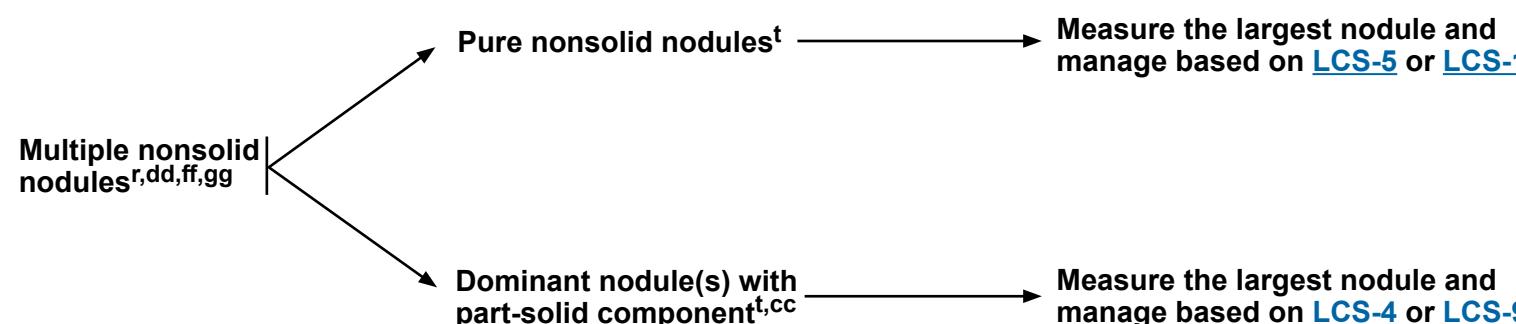
^{hh} Patient preferences should be taken into account when deciding whether to follow-up with LDCT in 6 months or use invasive procedures in consultation with expert recommendations.

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See [NCCN Guidelines for Non-Small Cell Lung Cancer](#)

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^{cc} All part-solid nodules ≥6 mm should be identified and solid areas should be measured.

^{dd} 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-9](#)).

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LOW-DOSE COMPUTED TOMOGRAPHY ACQUISITION, STORAGE, INTERPRETATION, AND NODULE REPORTING (Lung-RADS)^{a-e}

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	≤1.5 mm preferred for characterization of nodule consistency, particularly for small nodules ^e	
Slice interval	≤slice width; 50% overlap preferred for 3D and computer-aided detection (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; maximum intensity projections (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 (mean of the longest diameter of the nodule and its perpendicular diameter, when compared to the baseline scan)	
Density	Solid, nonsolid (also known as ground glass), or part solid (also known as mixed)	
Calcification	Present/absent; if present: solid, central vs. eccentric, concentric rings, popcorn, stippled, or amorphous	
Fat	Report if present	
Shape/Margin	Round/ovoid, triangular/smooth, lobulated, or 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	

[Footnotes on LCS-A 2 of 2](#)**Note:** All recommendations are category 2A unless otherwise indicated.**LCS-A
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FOOTNOTES

- ^a Protocol information: <http://www.aapm.org/pubs/CTProtocols/documents/LungCancerScreeningCT.pdf>
- ^b 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 current procedural terminology (CPT) code, and the latter are considered diagnostic CTs by CPT code.
- ^c Pinsky PF, et al. Ann Intern Med 2015;162:485-491.
- ^d Reporting the presence or absence of CAC detected on chest CT may be useful to the referring clinician and patient as a marker of atherosclerosis. CAC may be reported using either a visual score (none, mild, moderate, or severe) or quantitative score (such as the Agatston score). Further evaluation is recommended if CAC is severe. Munden RF, et al. J Am Coll Radiol 2018;15:1087-1096; Hecht HS, et al. J Thorac Imaging 2017;32:W54-W66.
- ^e 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-9](#)).

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RISKS/BENEFITS OF LUNG CANCER SCREENING^{1,2}

RISKS

- Futile detection of indolent disease
- Quality of life
 - ▶ Anxiety about 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 mortality³⁻⁵
- 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)

¹ See [Discussion](#) for more detailed information.

² Sands J, et al. J Thorac Oncol 2021;16:37-53.

³ National Lung Screening Trial Research Team; Aberle DR, et al. N Engl J Med 2011;365:395-409.

⁴ de Koning HJ, et al. N Engl J Med 2020;382:503-513.

⁵ Pastorino U, et al. Ann Oncol 2019;30:1162-1169.

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ABBREVIATIONS

BMI body mass index

CAC coronary arterial calcification

CAD computer-aided detection

COPD chronic obstructive pulmonary disease

CPT current procedural terminology

CTDI_{vol} CT dose index volume

FDG Fluorodeoxyglucose

ILD interstitial lung disease

LDCT low-dose computed tomography

Lung-RADS Lung Imaging Reporting and Data System

MIP maximum intensity projection

RFA radiofrequency ablation

SABR stereotactic ablative body radiotherapy

SBRT stereotactic body radiation therapy



NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence (≥ 1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus ($\geq 50\%$, but $< 85\%$ support of the Panel) 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 indicated.



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Discussion

This discussion corresponds to the NCCN Guidelines for Lung Cancer Screening.

Last updated: October 18, 2023

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Overview

Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide.¹⁻³ In 2023, an estimated 238,340 new cases (117,550 in males and 120,790 in females) of lung and bronchial cancer will be diagnosed, and 127,070 deaths (67,160 in males and 59,910 in females) are estimated to occur in the United States, which is about 21% of all U.S. deaths from cancer.⁴ Throughout the COVID-19 pandemic, the diagnosis and treatment of patients with lung cancer have been hampered⁵; however, this has not been reflected in the 2023 estimates for incidence and mortality because of the typical delays in collecting, calculating, and reporting of data.⁴ Five-year survival rates for lung cancer are only 22.9%, partly because most patients have advanced-stage lung cancer at initial diagnosis.⁶ These facts—combined with the success of screening in improving outcomes in patients with cervical, colon, and breast cancers—were the impetus for studies to develop an effective lung cancer screening test.⁷⁻¹⁰

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.^{3,10-13} Currently, most lung cancer is diagnosed clinically when patients present with symptoms such as persistent cough, hemoptysis, shortness of breath, bone and/or chest pain, hoarseness, headaches, and unintentional weight loss; unfortunately, patients with these symptoms usually have advanced lung cancer.^{14,15} Early detection of lung cancer is an important opportunity for decreasing mortality. Data support using low-dose CT (LDCT) of the chest to screen select individuals who are at high risk for lung cancer.^{10,11,13,16-19} Only about 5.7% to 12.8% of eligible individuals at high risk for lung cancer actually undergo LDCT lung cancer screening using the 2013 U.S. Preventive Services Task Force (USPSTF) eligibility criteria.²⁰⁻²² Chest radiography is not recommended for lung cancer screening.^{11,23-25} Recent

evidence is starting to show a stage shift in lung cancer from advanced cancer to early-stage cancer, with lung cancer screening attributed to this change.²⁶⁻³⁰

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.^{11,31,32} 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 initial and subsequent 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 the 2024 update, which are described in greater detail in this revised Discussion text. For v.1.2024, the NCCN Lung Cancer Screening Panel clarified that stereotactic ablative body radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT), and ablative techniques, such as radiofrequency ablation (RFA), are appropriate options for medically inoperable patients with cardiac disease or severe chronic obstructive pulmonary disease (COPD) as well as for patients with high risk for complications from surgery (also, refer to NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).^{33,34} The NCCN Panel recommends multidisciplinary evaluation before deciding whether to use SABR, especially if a biopsy will not be done because it is deemed too risky or difficult for a patient to undergo.^{33,35}

In December 2022, a revised version of the Lung Imaging Reporting and Data System (Lung-RADS) was published (v2022). Changes for Lung-RADS v2022 include new recommendations for airway nodules, nodules with a cystic component, and inflammatory or infectious findings. They also include a stepped-down management approach. For example, a



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patient with a LungRADS 4A result undergoing a 3-month follow-up LDCT would step down to a LungRADS 3 with a 6-month follow-up LDCT if no growth; if that LDCT also showed no growth, the patient would step down to a LungRADS 2 with the recommendation to continue annual screening in 12 months. The NCCN Panel will review v2022 of Lung-RADS and revise the NCCN Guidelines® accordingly.

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer.^{6,36,37} Thus, these NCCN Guidelines for Lung Cancer Screening mainly refer to detection of NSCLC. Other types of cancer can metastasize to the lungs, such as breast cancer. There are also fewer common cancers of the lung or chest, such as small cell lung cancer (SCLC), malignant pleural mesothelioma, thymoma, thymic carcinoma, and esophageal carcinoma. Lung cancer screening may also detect other cancers or noncancerous conditions in the thorax, lower neck, or upper abdomen, including infections and inflammatory conditions like sarcoidosis.³⁸⁻⁴² In the first 1.6 million screening LDCT scans noted in the ACR Lung Cancer Screening Registry, 18.7% had one or more clinically significant or potentially significant findings, with the most common being moderate or severe coronary arterial calcification (11.6%), a mass that could be cancer outside the lungs (2.8%, with recommended follow-up), interstitial lung disease (ILD) (2.2%), and moderate or severe emphysema (1.2%).⁴³⁻⁴⁵

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 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 to first *do no harm*.⁴⁶ 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.⁴⁷⁻⁵⁰

LDCT as Part of a Lung Cancer Screening Program

Lung cancer screening with LDCT should be part of an organized program of care and not be performed in isolation as a free-standing test.⁵¹⁻⁵⁷ Trained personnel and an organized administrative system to contact individuals to achieve adherence with recommended follow-up studies are required for an effective lung cancer screening program.^{53,56,58} The NCCN-recommended follow-up interval scans assume adherence with follow-up recommendations. Individuals who currently smoke, in addition to other factors, are less likely to be adherent than those who have quit smoking.^{30,59-62} Data show that adherence rates to LDCT follow-up testing recommendations and to subsequent annual lung cancer LDCT screening remain low and can be improved.^{30,60,63-65}

To help ensure good image quality, all lung cancer screening programs should use CT scanners that meet the standards of the ACR.⁶⁶ The ACR developed Lung-RADS to standardize the reporting and management of LDCT lung cancer screening examinations, which has improved lung cancer detection and decreased false-positive rates.^{51,53,55,56,67-77} When assessing subsequent scans, the most important radiologic factors are resolution, stability, growth of previous nodules, or appearance of a new nodule(s). As with any screening test, the risks and benefits of lung cancer



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screening should be discussed with the individual before an initial screening LDCT scan is performed.^{48,49,51,78,79} Shared patient/provider decision-making may be the best approach before deciding whether to do lung cancer screening, especially for individuals with comorbid conditions (see shouldiscreen.com).^{24,51,80-82} It is recommended that institutions use a multidisciplinary approach for the management of screen-detected abnormalities that might be lung cancer, which may include specialties such as cardiothoracic radiology, pulmonary medicine, and thoracic surgery. For v.1.2024, the NCCN Panel added a caveat that some institutions also include medical oncology, radiation oncology, and/or pathology. If these specialties are not available locally, the institutions should collaborate with programs that offer them.

Randomized Trials

Several randomized trials have studied whether screening with chest radiography improves lung cancer survival or mortality; however, many were flawed in design or power, and all were negative.^{49,83-87} The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a phase 3 randomized trial, reported that annual screening with chest radiography is not useful for lung cancer screening in individuals at low risk for lung cancer.²³ Other studies have focused on the more sensitive modality of LDCT-based lung cancer screening; some studies suggest that overdiagnosis (ie, cancer diagnosis that would never be life-threatening) and false-positive screening tests are concerns.^{50,88-92} Although LDCT scanning may be a better screening test for lung cancer, it also has limitations. See *Benefits and Risks of Lung Cancer Screening* in this Discussion.⁴⁹

Multiple randomized trials have assessed LDCT screening among individuals at risk for lung cancer.^{9-11,13,83,93-98} Data from the larger clinical trials—the National Lung Screening Trial (NLST) and the NELSON trial—support screening individuals at high risk for lung cancer based on age

and smoking history criteria.^{10,11,13} Several smaller trials have reported that LDCT screening did not decrease mortality; however, these trials were not adequately powered to detect significant differences in mortality.^{83,94,95,97,98} The Danish Lung Cancer Screening Trial (DLCST) included individuals at lower risk compared with the NLST and NELSON trials.^{10,11,98}

The NCI-sponsored NLST assessed LDCT versus chest radiography in 53,454 individuals at high risk for lung cancer based on age and smoking history using three rounds of annual screening; 51% were males.^{11,13} The individuals were aged 55 to 74 years with a ≥30 pack-year smoking history who either currently smoked or had quit smoking within 15 years. LDCT decreased the relative risk (RR) of death from lung cancer by 20% (95% CI, 6.8%–26.7%; $P = .004$) compared with radiography.¹¹ The number needed to screen (NNS) to prevent one lung cancer death was 323 over 6.5 years of follow-up.⁹⁶ With extended follow-up, the NNS was 303 with a reduction in lung cancer mortality of 16% (per 100,000 person years).¹³ Although the NLST also reported a significant decrease in all-cause mortality, this decrease was largely attributable to lower lung cancer mortality.

The NELSON trial assessed LDCT screening in four rounds versus no screening in 15,789 individuals at high risk for lung cancer based on age and smoking history; 85% were men. The individuals were aged 50 to 74 years and currently smoked or quit smoking within the last 10 years.^{10,99} At 10-year follow-up, NELSON demonstrated a reduction in lung cancer mortality of 24% in men (cumulative rate ratio for death from lung cancer: 0.76; 95% CI, 0.61–0.94; $P = .01$) and 33% in women (rate ratio, 0.67; 95% CI, 0.38–1.14).¹⁰ The NNS to prevent one lung cancer death was 130 over 10 years of follow-up.⁹⁶

The MILD trial assessed LDCT screening (annual or biennial) versus no screening in 4099 individuals aged 49 to 75 years with a ≥20 pack-year smoking history.⁹³ After 10 years of screening, the LDCT arm yielded a



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39% decreased risk of lung cancer mortality (hazard ratio [HR], 0.61; 95% CI, 0.39–0.95). The benefit of screening was greater after the fifth year, with a 58% decreased risk of lung cancer mortality (HR, 0.42; 95% CI, 0.22–0.79).

Lung Cancer Screening Guidelines

NCCN was the first major organization to develop lung cancer screening guidelines using LDCT based on the NLST data.³¹ The International Association for the Study of Lung Cancer (IASLC) supports the NCCN Guidelines by emphasizing the need for guidelines, a multidisciplinary team approach, and integrated smoking cessation programs.¹⁰⁰ The USPSTF recommends lung cancer screening with LDCT; their grade B recommendation means that lung cancer screening is covered under the Affordable Care Act for individuals at high risk for lung cancer, defined as those 50 to 80 years of age with a ≥20 pack-year cigarette smoking history who currently smoke or have quit smoking during the past 15 years.^{24,101} The Centers for Medicare & Medicaid Services (CMS) covers annual LDCT lung cancer screening of Medicare beneficiaries with these risk factors ≤77 years of age if they participate in shared decision-making before their first screening LDCT.¹⁰² An estimated 15 million individuals in the United States meet these criteria.¹⁰³ Most professional organizations in the United States also recommend LDCT screening for individuals at high risk for lung cancer as defined by age and smoking history, including the ACR, American Cancer Society (ACS), American Lung Association, and American College of Chest Physicians (ACCP).⁵¹ Although age and smoking history are used for risk assessment, other potential risk factors for lung cancer—including personal history of cancer or lung disease, family history of lung cancer, radon exposure, and occupational exposure to lung carcinogens—may be discussed during shared decision-making (see shouldiscreen.com).^{51,104-112}

Guidelines Update Methodology

The complete details of the development and update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update 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 since the previous Guidelines update, using the search terms: “lung cancer” AND (screening OR computed tomography OR low-dose computed tomography OR LungRADS OR low-dose CT screening). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes 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; Practice Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies. The data from key PubMed articles and additional sources deemed as relevant to these guidelines by the panel during the Guidelines update meeting have been included in the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel’s review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.¹¹³ NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing



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on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Risk Factors for Lung Cancer

An essential goal of any screening protocol is to identify the populations that are at a high risk for developing the disease. Although smoking cigarettes is a well-established risk factor for lung cancer, other environmental and genetic factors also increase risk.^{72,106,107,112,114} This section reviews the currently known risk factors for the development of lung cancer to identify populations with high risk that should be considered for screening. For those who do not have risk factors or are at low risk, lung cancer screening is not recommended because: 1) the chance of finding lung cancer is less than 1%; and 2) the risks from workup outweigh the benefits of screening.¹¹⁵ Note that individuals who are candidates for screening should not have any symptoms suggestive of lung cancer, such as cough, pain, or weight loss, and should undergo a clinical diagnostic evaluation.

Cigarette Smoke

Active Cigarette Use

The causal relationship between smoking tobacco and lung cancer was first reported in 1950.^{116,117} Since then the risk of developing lung cancer

from smoking tobacco has been firmly established.¹¹⁸ Cigarette smoke contains >7000 compounds, and ≥69 of these are known carcinogens that increase the risk of cancerous mutations at the cellular level, especially among individuals with a genetic predisposition.¹¹⁹⁻¹²⁴ The FDA has defined a list of 93 chemicals that are considered harmful and potentially harmful constituents (PHPCs) in tobacco products or tobacco smoke. Cigarette smoking is a major modifiable risk factor in the development of lung cancer, directly accounting for 81% of all lung cancer-related deaths in the United States.⁴ Approximately 35 million or 1 in 9 individuals ≥ 18 years of age in the United States currently smoke cigarettes, the lowest prevalence since 1965. Smoking cigarettes is also associated with other cancers, including head and neck, kidney, bladder, pancreatic, gastric, and cervical cancer and acute myeloid leukemia, as well as cardiovascular disease and COPD.¹¹⁸ In the United States, an estimated 480,000 individuals die from smoking-related illnesses annually representing 1 in 5 deaths, with cigarette smoking estimated to cause about 30% of all cancer-related deaths.¹²⁵⁻¹²⁷ Globally, nearly 1 in 5 of the 1.8 million cancer deaths are attributable to smoking tobacco.^{128,129} The WHO estimates that 8 million people globally die from tobacco use every year.¹³⁰

A dose-response relationship exists between cigarette smoking and the risk of developing lung cancer; however, there is no risk-free level of cigarette exposure. The RR for lung cancer is approximately 20-fold higher for individuals who currently smoke than for those who never smoked.^{118,131} While cigarette smoking cessation decreases the risk for lung cancer (with a greater magnitude with each incremental year since quitting), individuals who quit smoking still have a higher risk for lung cancer compared to those who never smoked.^{120,132-138} As a result, current or past history of cigarette smoking is considered a risk factor for developing lung cancer, irrespective of the magnitude of exposure and the time since smoking cessation.



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In the NCCN Guidelines, individuals aged ≥ 50 years with a ≥ 20 pack-year history of cigarette smoking are the high-risk group for lung cancer. LDCT screening of the chest (category 1) is recommended for these individuals at high risk based on data from the NLST and NELSON trials, with the extended upper age based on Cancer Intervention and Surveillance Modeling Network (CISNET) modeling included in the USPSTF recommendation analyses (see *Risk Status* in the algorithm).^{9-11,13,24,101} 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. Determining whether an individual is at high risk for cancer is based on cigarette smoking and not on the use of other tobacco products, which may also put individuals at risk for cancer.¹³⁹⁻¹⁴² For those who smoke cigars, information is available that may be useful for determining the risk for cancer.^{143,144}

Exposure to Second-Hand Smoke

The relationship between lung cancer and exposure to second-hand smoke (also known as environmental tobacco smoke, passive smoke, or involuntary smoke [ie, smoke created by others who are smoking]) was first suggested in epidemiologic studies published in 1981.¹⁴⁵ Since then, several studies and pooled RR estimates have suggested that second-hand smoke causally increases the risk for lung cancer among individuals who never smoked.¹⁴⁶

A pooled analysis of 37 published studies found an estimated RR of 1.24 (95% CI, 1.13–1.36) for individuals who do not smoke but live with someone who smokes.¹⁴⁷ 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.¹⁴⁶ The pooled estimate for six studies suggests a dose-response relationship between number of years of second-hand smoke exposure and lung cancer risk.¹⁴⁶ 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.¹⁴⁶

The NCCN Lung Cancer Screening Panel discussions concluded that second-hand smoke is not an independent risk factor sufficient for recommending screening, because the association is either weak, variable, or difficult to measure. Second-hand smoke does not confer a great enough risk for exposed individuals to be recommended for lung cancer screening in the NCCN Guidelines.

Occupational Exposure to Carcinogens

Lung carcinogens include arsenic, asbestos, beryllium, cadmium, chromium, coal smoke, diesel fumes, nickel, silica, soot, and uranium.^{112,148-156} 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.^{112,154} Among those who are exposed to these carcinogens, data suggest that individuals who also smoke tobacco have a greater risk for lung cancer than those who do not smoke.^{149,151,157-159}

Residential Radon Exposure

Radon (a gaseous decay product of uranium-238 and radium-226) has been implicated in the development of lung cancer; however, the individual risk associated with residential radon is uncertain.¹⁶⁰ According to the Environmental Protection Agency (EPA), radon exposure is the leading cause of lung cancer in individuals who have never smoked, and the WHO notes that radon exposure causes up to 15% of lung cancers worldwide.^{161,162} 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.¹⁰⁸ Among



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those exposed to radon, individuals who smoke have a greater risk for lung cancer than those who do not smoke.¹⁰⁸ For v.1.2024, the NCCN Lung Cancer Screening Panel clarified that documented sustained and substantially elevated radon exposure increases the risk for lung cancer in patients who also have a history of heavy cigarette smoking. Many state websites have information more specific to local areas, including areas of known elevated radon. Challenges in using radon exposure as an indication for lung cancer screening include difficulty in measuring individual exposure, and lack of clinical trials.

History of Cancer

Evidence shows that individuals who survive lymphomas or smoking-related cancers have an increased risk for subsequent primary lung cancers.^{163,164} Patients who survive SCLC have a 3.5-fold increase in the risk of developing a subsequent primary cancer, predominantly NSCLC.¹⁶⁵ The risk for second lung cancers increases if survivors continue to smoke tobacco.^{166,167}

Patients previously treated with chest irradiation have a 13-fold increase in risk for developing new primary lung cancer, and those previously treated with alkylating agents have an estimated RR of 9.4. In patients previously treated for Hodgkin lymphoma, the RR for new primary lung cancer is 4.2 and 5.9 if previously treated with alkylating agents and ≥5 Gy of radiation therapy, respectively.¹⁰⁹

In patients with head and neck cancers, subsequent new primary lung cancer may occur synchronously or metachronously, with new primary tumors in approximately 9% of patients.¹⁶⁸ Most are 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.¹⁶⁹ Patients who are successfully treated (ie, cured) for an initial smoking-related lung cancer and stop smoking will have a

decreased risk for a subsequent smoking-related cancer compared to those who continue smoking.^{170,171}

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 adjusting for age, gender, and smoking habits.^{120,172,173} A meta-analysis of 28 case-control studies and 17 observational cohort studies showed a RR of 1.8 (95% CI, 1.6–2.0) for individuals with a sibling/parents or a first-degree relative with lung cancer.¹¹⁰ The risk is greater in individuals with multiple affected family members or who had a cancer diagnosis at a young age. A meta-analysis from the International Lung Cancer Consortium reported the risk for lung cancer is increased in individuals who have a sibling with lung cancer (odds ratio [OR], 1.8; 95% CI, 1.6–2.0).¹⁷⁴

Although no high-penetrance inherited syndrome has been described for either SCLC or NSCLC, several groups have identified genetic loci that may be associated with an increased risk of developing lung cancer.¹²⁴ A susceptibility locus influencing lung cancer risk on 6q23-25 was found by the Genetic Epidemiology of Lung Cancer Consortium, which conducted a genome-wide linkage analysis of 52 families with several first-degree relatives with lung cancer.¹⁷⁵ Subsequently, three 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.¹⁷⁶⁻¹⁷⁸ It was noted that subunits of the nicotinic acetylcholine receptor genes are localized to this area (*CHRNA5*, *CHRNA3*, and *CHRN4*). Other investigators found that a variant at 15q24-25 is associated with spirometric bronchial obstruction and emphysema as assessed with CT.^{179,180} Individuals with classic familial cancer susceptibility syndromes (such as retinoblastoma and Li-Fraumeni



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syndrome) have a substantially increased risk for lung cancer if they also smoke cigarettes.¹⁸¹⁻¹⁸³

History of Lung Disease

Chronic Obstructive Pulmonary Disease

A history of COPD is associated with lung cancer risk, and this association may be largely caused by cigarette smoking.^{124,184-190} Yang et al found that COPD is associated with 12% of lung cancer cases among individuals with a history of heavy smoking.¹⁹¹ A large prospective study of individuals from the NLST showed a linear relationship between the severity of airflow limitation and risk for lung cancer.¹⁹² Importantly, LDCT screening was not associated with a mortality benefit in patients with severe or very severe COPD; therefore, comorbidity should be considered when discussing LDCT screening with these patients.¹⁹³ Data suggest that lower pack-year thresholds may be useful to trigger LDCT screening in individuals with COPD.¹⁹⁴ Even after statistical adjustment, evidence suggests that the association between COPD and lung cancer may not be entirely caused by cigarette smoking.^{111,195,196} 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 individuals who have never smoked; and 3) COPD appears to be an independent risk factor for lung cancer.^{111,191,197,198} Yang et al found that COPD accounts for 10% of lung cancer cases among individuals who have never smoked.¹⁹¹

Koshiol et al found that when they restricted their analyses to adenocarcinoma (which is more common among those who do not smoke, particularly females), COPD was still associated with an increased risk for lung cancer.¹¹¹ In the Bergen COPD Cohort Study of 433 patients with COPD and 279 healthy control patients, 28 patients with COPD developed lung cancer versus 3 patients without COPD (HR, 5.0; CI, 1.7–10.6; $P < .01$).¹⁹⁹ The study also reported that smoking status did not affect the rate of lung cancer in patients with COPD.

Pulmonary Fibrosis

Studies show that patients with pulmonary fibrosis are 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).^{200,201} Among individuals 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.²⁰²

Hormone Replacement Therapy

It is currently unclear whether use of hormone replacement therapy (HRT) affects the risk for lung cancer. More than 20 studies have been published, with inconsistent results in predominantly case-control and cohort studies. In a post-hoc analysis of one large randomized controlled study, more deaths from lung cancer (especially NSCLC) were observed among women who were postmenopausal who were receiving estrogen plus progestin HRT, although it did not increase the incidence of lung cancer.²⁰³ No increase in the incidence of or death from lung cancer was found among women who were postmenopausal who were treated with estrogen alone versus placebo.²⁰⁴

Selection of Individuals for Lung Cancer Screening

The NCCN Lung Cancer Screening Panel recommends that:

- 1) Individuals at high risk for lung cancer, including those with previously treated cancers other than lung cancer, should be screened using LDCT if they are potential candidates for curative-intent therapy and have participated in, or been offered, shared decision-making (see shouldiscreen.com).⁵¹ The NCCN Panel defines *curative-intent* treatment as including surgery, SABR (also known as SBRT), or ablation (such as RFA). SABR or ablation may be used for patients who are medically inoperable (see



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the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).^{33,34}

- 2) Individuals at lower risk should not be screened.
- 3) LDCT screening is not recommended for individuals with symptoms of lung cancer, or functional status or comorbidity that would prohibit curative-intent therapy.
- 4) Patients previously treated for lung cancer are under surveillance indefinitely until they are also no longer eligible for treatment (see *Surveillance* in the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org). Surveillance after treatment for lung cancer, although similar, is distinct from lung cancer screening and not addressed in the NCCN Guidelines for Lung Cancer Screening.
- 5) Chest radiography is not recommended for lung cancer screening.^{11,23,25}

Individuals with High-Risk Factors

The NCCN Lung Cancer Screening Panel recommends LDCT lung cancer screening (category 1) for individuals at high risk for lung cancer based on phase 3 randomized trials and data from modeling studies such as CISNET and Agency for Healthcare Research and Quality (AHRQ) that can be found in USPSTF research summaries.^{10,11,13,96}

In the first NCCN Guidelines for Lung Cancer Screening (v.1.2012), the NCCN Guidelines Panel recommended LDCT screening for two high-risk groups. Group 1 included individuals aged 55 to 77 years with a ≥30 pack-year history of cigarette smoking who currently smoked or had quit within the past 15 years (category 1) based on the NLST inclusion criteria.^{11,31} Group 2 included individuals aged ≥50 years with a ≥20

pack-year history of cigarette smoking (who either currently smoked or had quit smoking) and had at least one additional risk factor, such as occupational exposure to lung carcinogens.³¹ Group 2 was included because the NCCN Panel considered that limiting screening to the NLST inclusion criteria alone was arbitrary and incomplete, because the NLST only used age and smoking history for inclusion criteria for purposes of conducting a trial and being able to collect longer term mortality data, and did not consider other risk factors for lung cancer. Others share this opinion.²⁰⁵⁻²¹¹ Using the narrow NLST criteria—individuals aged 55 to 77 years with a ≥30 pack-year smoking history (who currently smoked or had quit smoking within the past 15 years)—only 27% of patients being diagnosed with lung cancer would be candidates for LDCT screening.²¹²

In 2020, the NCCN Lung Cancer Screening Panel consolidated the previous two groups and levels of recommendations into a simplified and expanded age range for screening to ≥50 years and smoking history of ≥20 pack-years (category 1), which may result in thousands of additional lives being saved.^{70,212-216} The pack-year threshold was lowered based on data from the NELSON and MILD trials that suggests the lung cancer risk for individuals with a 20 to 29 pack-year smoking history is similar to individuals with a ≥30 pack-year history.^{10,217,218} The age range was lowered to 50 years for several reasons. Approximately 5.6% of lung cancer diagnoses are in patients aged 45 to 54 years.⁶ Younger individuals may be at high risk for lung cancer based on data from phase 3 randomized trials including NELSON, UK Lung Cancer Screening Trial (UKLS), and DLCST screening trials that evaluated LDCT screening in individuals ≥50 years of age.^{10,98,219-221} Similarly, several non-randomized prospective cohort studies included individuals ≥50 years of age.²²²⁻²²⁴ Furthermore, data suggest that decreasing the age and smoking history cutoffs will help reduce disparities in LDCT screening for African Americans and to a lesser degree in women.²²⁵⁻²²⁷ These two changes



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increased the eligible individuals for screening from approximately 8 million people to 15 million people.¹⁰³

In 2020, the NCCN Screening Guideline Panel decided not to include an upper age cutoff for lung cancer screening. Eligibility for screening is contingent on eligibility for curative-intent treatment on an individual basis until a patient is no longer a candidate for definitive treatment, rather than on an arbitrary chronological age cutoff.^{216,228,229} This decision was made for several reasons. The median patient age at the time of lung cancer diagnosis is 71 years, with approximately 27% of lung cancer diagnosed in patients aged 75 to 84 years, and 9.4% in patients ≥ 84 years.^{6,213,230} Although randomized trial data support screening in patients ≤ 77 years of age, uncertainty exists about the appropriate duration of screening and the age at which screening is no longer appropriate.^{10,231,232} Determining factors to consider include functional status, comorbidities that could impede curative treatment, and an individual's interest and willingness to undergo treatment.

In removing the time since quitting smoking, the NCCN Guidelines differ from the lung cancer screening recommendations from USPSTF and CMS national coverage decision that continue to restrict screening for lung cancer in individuals who quit smoking >15 years ago.^{101,102} While acknowledging that the cessation of cigarette smoking decreases the risk for lung cancer, the NCCN Panel does not agree with this 15-year restriction. Individuals who previously smoked have a higher risk for lung cancer compared with those who have never smoked, and there is no substantive drop off in that risk after 15 years since quitting (YSQ). An analysis of the Framingham Heart Study found that lung cancer risk remains more than threefold higher in individuals who previously smoked after 25 YSQ than in those who had never smoked, and 40% of lung cancers occurred in individuals who previously smoked with >15 YSQ.¹³⁶ Another study reported that individuals who previously smoked had an

elevated lung cancer risk (RR, 6.6; 95% CI, 5.0–8.7) ≤ 30 years after smoking cessation.¹³⁷ In a prospective study that evaluated patients with lung cancer who would have “missed out” on lung cancer screening, by far the largest percentage not eligible for screening using the 2013 USPSTF criteria were due solely to having quit smoking for >15 years.¹³⁸ The NCCN Panel has not placed a time limit for screening eligibility after smoking cessation, because the 15-year restriction is not based on or justified by evidence. Further, this restriction creates unintended consequences and a paradox of incentives for individuals who previously smoked who wish to undergo or continue lung cancer screening. As a consequence of this 15-year restriction, individuals may be unintentionally encouraged to resume smoking, or to lie about their smoking history, in order to remain eligible for screening.

The NCCN Panel reviewed the USPSTF recommendations and their research summaries from the 2013 and 2021 statements that both included LDCT. In 2013, the USPSTF recommended lung cancer screening for individuals aged 55 to 80 years with a 30 pack-year smoking history who currently smoked or had quit within the last 15 years.²⁴ In 2021, the USPSTF reduced the age of eligibility to 50 years and pack-year smoking history to 20 years.¹⁰¹ In both iterations, the USPSTF recommendations became more closely aligned with the earlier 2011 and 2020 NCCN Guidelines.^{31,216}

For individuals at high risk for lung cancer with a negative screening LDCT or those whose nodules do not meet the size cutoff for more frequent scanning or other intervention, the NCCN Guidelines recommend annual screening LDCT until individuals are no longer candidates for definitive treatment (see *Risk Status* in the algorithm). While the appropriate duration of screening has some uncertainty, in part because fewer individuals who have been screened have been followed past their eighth decade of life, data support continued screening. After the 3 rounds of



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LDCT in the NLST, 367 new cases of lung cancer were frequently diagnosed during the 3.5 years of follow-up (median of 6.5 years).^{11,233} The NLST and NELSON data show that lung cancer continues to occur over time in individuals with high-risk factors.^{13,234} In addition, the incidence of lung cancer and the death rate from lung cancer did not change during the 7 years of the NLST.²³⁵ Thus, the NLST data support annual screening LDCT for at least 2 years but do not define a time limit on efficacy. Data from the NELSON trial indicate that with a longer screening interval, there is a higher percentage of non-resolving new nodules and thus a higher percentage of lung cancers, strengthening the evidence of benefit for continued screening beyond 3 years.^{10,236} Data from a recent modeling study suggest that annual screening is better than biennial or even longer intervals between scans.^{103,237}

Individuals with Low-Risk Factors

The NCCN Lung Cancer Screening Panel defines individuals at low risk for lung cancer as <50 years of age and/or with a smoking history of <20 pack-years. The NCCN Panel, the USPSTF, the ACR, and the ACS do not recommend lung cancer screening for these individuals.^{66,101} This is a category 2A recommendation based on nonrandomized studies and observational data.^{238,239}

Management of Abnormalities Found on LDCT Screening Scans

NCCN Recommendations

Findings on LDCT include 1) no lung nodules or definitely benign nodules, such as benign patterns of calcification, fat-containing nodules, and/or perifissural nodules (ie, negative LDCT screening result); 2) nodules with a benign appearance or low likelihood of being cancer that would impact the patient due to small size or lack of growth (ie, negative LDCT screening result); 3) nodules that could be cancer warranting interim follow-up testing between screens or a diagnostic assessment due to their high risk of

cancer (positive or abnormal LDCT screening result); and 4) other CT abnormalities that are clinically significant or potentially significant for which clinical evaluation and/or additional diagnostic testing may be warranted.

For positive screening results, the next step in management is based primarily on assessing both nodule size and consistency (solid, part solid, or nonsolid [also known as ground glass]). Among those, the nodules are categorized by risk of malignancy, with the lower-risk positive screens undergoing an interval LDCT at 3 or 6 months to understand its biologic behavior by looking for growth or lack thereof. When no growth occurs, these nodules are downgraded to being negative screens and a patient continues annual screening; these could be considered false positives. However, they could also be indolent cancers that have not yet grown, and attention should be paid to them on the next annual screening CT.²⁴⁰ Among the highest risk nodules—based on larger size, growth, or additional imaging findings (such as spiculation or enlarged lymph nodes)—the next steps are directed into a diagnostic pathway that may include an fluorodeoxyglucose (FDG)-PET/CT or tissue sampling. Some of the nodules will be diagnosed as lung cancer. Most of these patients will have NSCLC (approximately 85%); a very small percentage of patients will have SCLC. The appropriate guidelines can then be used to manage the cancer (see NCCN Guidelines for Non-Small Cell Lung Cancer and NCCN Guidelines for Small Cell Lung Cancer, available at www.NCCN.org).

Assessing Risk for Malignancy in Nodules

LDCT is recommended for detecting noncalcified pulmonary nodules that may be suspicious for lung cancer depending on their size and type. Solid and subsolid nodules are the two main types of nodules.²⁴¹ 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 nonsolid and



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solid components.²⁴²⁻²⁴⁷ A solid nodule has a homogeneous soft tissue attenuation, while a nonsolid nodule has increased attenuation that does not obliterate bronchial and vascular margins.

Nonsolid nodules that do not resolve or slowly grow on subsequent scans are mainly adenocarcinomas with a lepidic component.^{36,244-246,248-250} These nodules mostly consist of adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and lepidic-predominant adenocarcinomas. Individuals with AIS and MIA have 5-year disease-free survival rates of 100% or near 100%, respectively, if their lesions are completely resected.³⁶ Lepidic-predominant adenocarcinomas have favorable outcomes ranging from 70% to 90% if completely resected, depending on the size and histologic patterns in the invasive components. 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.^{41,55,251-253} If a solid component develops in a nonsolid nodule, then the guidelines for part-solid nodules need to be used. Data suggest that long-term survival is excellent if part-solid nodules are resected.^{243,254,255}

Several other radiologic factors are associated with increased suspicion of lung cancer, including shape and irregular or spiculated margins.²⁵¹ Location in the upper lobes, especially the right lobe, also has an increased risk for lung cancer.^{256,257} On PET/CT, nodules with higher FDG uptake compared to mediastinal blood pool are at greater suspicion for lung cancer, regardless of the standardized uptake value (SUV) analysis.^{258,259} As previously mentioned, clinical risk factors associated with increased suspicion of lung cancer include age, smoking history, exposure to other carcinogens, COPD, pulmonary fibrosis, and family history of lung cancer.

When assessing subsequent LDCTs, the most important radiologic factors are resolution, stability, or growth of a previous nodule(s) or the

development of a new nodule(s). A new nodule is defined as ≥4 mm in mean diameter. Rapid increase in nodule size suggests an inflammatory etiology or rare malignancy other than NSCLC. Data from the NELSON trial indicate that new solid nodules found during subsequent LDCT screening are more likely to be lung cancer than solid nodules found at baseline screening.²³⁴ Approximately 44% of new solid nodules (50–500 mm³) did not resolve, of which 10% were cancer, whereas only 3% of non-resolving solid nodules at baseline were lung cancer.²³⁴ Thus, new solid nodules need to be followed more aggressively than baseline solid nodules.²³⁴

In summary, the following factors on LDCT screening increase the suspicion that nodules may be malignant: 1) part-solid type; 2) nonsolid type ≥20 mm; 3) subsolid type with spiculated contours, *bubbly* cystic lucencies, or reticulation; 4) part-solid type with overall growth and/or growth of the solid component; or 5) solid type with growth or characteristics suspicious for invasive carcinoma.^{245,252,257} All nonsolid nodules should be reviewed at thin (≤1.5 mm) slices to detect any solid components, which if found should be managed using the recommendations for part-solid nodules (see *Follow-up of Screening Findings* in the algorithm).^{245,260,261} Pure nonsolid nodules <20 mm are usually AIS or MIA and may be followed with annual LDCT screening until they develop a change in morphology such as developing a new solid component.²⁴⁵ The NCCN Panel recommends using a cutoff of 20 mm for nonsolid nodules and not using the Lung-RADS 1.1 cutoff of 30 mm.^{68,69,262-264} The panel also recommends doing an earlier interim LDCT evaluation at 6 months for baseline or new nonsolid nodules of ≥20 mm. Data suggest that many nonsolid nodules that resolve on subsequent scans are not adenocarcinomas, but benign inflammatory lesions, although they need to be followed.^{241,265,266} Pure nonsolid nodules smaller than 5 mm are usually atypical adenomatous hyperplasia.



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Solitary pulmonary nodules pose unique management challenges.^{242,257,261,267-270} Published nodule risk calculators may be helpful when assessing solitary pulmonary nodules; however, geographic location and other risk factors can influence the accuracy of these calculators.^{267,271} Patients who live in areas endemic for fungal disease may have granulomatous disease associated with a higher false-positive rate on FDG-PET/CT for granulomas.^{39,272-275} The NCCN Panel encourages providers to consider using a risk calculator that may identify additional candidates at high risk for lung cancer.^{12,276}

LDCT Screening and Screen-Detected Imaging Protocols

The ability to acquire thinner slices with multidetector CT (MDCT), the use of maximum intensity projection (MIP) or volume-rendered (VR) images, and computer-aided detection (CAD) software have increased the sensitivity of small-nodule detection.²⁷⁷⁻²⁹¹ The use of thinner images has also improved the characterization of small lung nodules.²⁹² The recommended CT technique for lung cancer screening is LDCT without IV contrast, which is sufficient for the task of detecting lung nodules and follows the principle of As Low as Reasonably Achievable (ALARA).^{66,293,294} Although there is no strict definition of LDCT of the chest, it is usually approximately 30% to 70% or less radiation exposure than a standard-chest CT.

Patient radiation exposure should be based on patient size as measured by body mass index (BMI), which is broken into categories from severely underweight to several categories of obesity.²⁹⁵ For example, patients with ≤ 30 BMI should generally receive lower radiation exposure than those with >30 BMI to generate similar lung image quality for nodule detection, minimizing radiation dose in smaller patients and not sacrificing image quality in larger patients. Iterations of LDCT using the same dose across all patients contributed to more image noise in larger patients, leading to difficulties in interpreting images scans, with studies suggesting variation

occurs in interpretation of LDCT scans among radiologists.²⁹⁶⁻³⁰⁵ Decreasing radiation exposure has been shown to not significantly affect the measurement of nodule size when using 1-mm-thick slices.³⁰⁶ For v.1.2024, the NCCN Panel clarified that all screening and follow-up interval chest CT scans for screen-detected nodules requiring further evaluation should use a CT dose index volume (CTDIvol) threshold of ≤ 3 mGy and slice width of ≤ 1.5 mm for a patient with average BMI (see Lung Cancer Screening Protocols from the American Association of Physicists in Medicine [AAPM]).^{72,307,308} Parameters should be adjusted for patients with a BMI of ≤ 30 and >30 .

Nodules should be evaluated and measured on LDCT using 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 size of nodules is underestimated on soft tissue windows, and some nodules may not even be visible, particularly nonsolid and small nodules.³⁰⁹ *Mean diameter* is the mean of the longest diameter of the nodule and its perpendicular diameter. Inter-reader variability can occur when using manual diameter measurement for assessing nodule growth, especially for nodules with spiculated and irregular margins and small nodules, which can lead to misinterpretation of nodule growth.^{297,298} Semiautomated diameter and volume measurements are more accurate for determining size and growth of pulmonary nodules.^{251,297,298}

Optimally, these lung cancer screening protocols 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.³¹⁰ A study reported that tagging suspicious nodules found on LDCT appeared to improve follow-up for pulmonary findings.⁵⁴ Strict adherence to a screen-detected



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management protocol may also significantly reduce unnecessary biopsies.³¹¹

Currently, the NCCN recommendations for lung cancer screening do not include other possibly relevant nodule features, such as proximity to the pleura or fissure.³¹²⁻³¹⁵ The topics of nodule volumetric analysis and/or calculations of tumor doubling time have also not been addressed.^{210,316} The NLST had a false-discovery rate of 96.4% and a false-positive rate of 23.5%.^{100,317,318} The NELSON trial used volumetric analysis and an “indeterminate” classification and reported a false-positive rate of 1.2%; this decrease in the false-positive rate is due to classification and not to scan metrics (see *False-Positive Results* in this Discussion).¹⁰ Approximately 2% of individuals had a positive initial test result in the NELSON trial compared with 24% in the NLST.¹⁰

In some cases, it may be appropriate to perform standard-dose CT with IV contrast for follow-up or further evaluation of lung or mediastinal abnormalities detected on screening LDCT. If endobronchial nodules are suspected, then LDCT is recommended in ≤1 month (see *Follow-up of Screening Findings* in the algorithm). If there is no resolution, then bronchoscopy is recommended. The technician should ask the patient to cough vigorously right before LDCT is performed. For the v.1.2024 update, the NCCN Panel added a new pathway following bronchoscopy: 1) if no cancer is detected, annual LDCT screening is recommended if the patient remains eligible for screening and a candidate for definitive treatment, and 2) if cancer is confirmed, refer to NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org.

A table on recommended LDCT acquisition parameters is included in the algorithm, which includes Lung-RADS [see *Low-Dose Computed Tomography Acquisition, Storage, Interpretation, and Nodule Reporting (Lung-RADS)*].⁷¹ This table also includes information about coronary artery calcium (CAC) scoring.^{45,319,320} 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. The preferred slice width is ≤1.5 mm for characterization of nodule consistency, particularly for small nodules.^{69,71,72,245,282} A detector collimation of ≤1.5 mm is necessary for optimal use of these 3-dimensional (3-D) applications. For accurate nodule volumetric analysis, some radiologists have decided that a detector collimation of ≤1 mm is needed. Measurement and evaluation of small nodules are more accurate and consistent on 1-mm-thick images compared with 5-mm images.²⁹² 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 NCCN Guidelines emphasize that nonsolid lesions must be evaluated at thin slices (≤1.5 mm) to exclude solid components.²⁴⁵

Part-solid nodules have higher malignancy rates than either solid nodules or pure nonsolid nodules and, therefore, require rigorous evaluation.²⁴⁵ All part-solid nodules of ≥6 mm should be identified and the solid areas should be measured. 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).^{296,321} Ultra-low-dose chest CT currently produces lower sensitivity for nodule detection, especially in patients with BMI >25.²⁹⁴ LDCT technologies may make it possible to significantly decrease the radiation dose without compromising nodule detection and evaluation.^{309,322-325} 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 and adjusting radiation dose (eg, reporting the dose-length product [DLP] for each CT).³²⁶



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Clinical Management Protocols for LDCT Screening

LDCT lung cancer screening studies using MDCT scanners have decreased lung cancer mortality in subjects at high risk for lung cancer compared with unscreened or chest radiography-screened cohorts, but have applied varying clinical and imaging management algorithms for defining abnormal screens and the follow-up of nodules or other findings concerning for lung cancer.^{9,11,221,222,318,327-331} These algorithms are based on the positive relationships among: 1) nodule size and/or nodule consistency 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, volume doubling time).³³²⁻³³⁹ Most of these algorithms recommend FDG-PET/CT be considered for nodules that are at least 7 to 10 mm, or dynamic contrast-enhanced CT if FDG-PET/CT is not available, because these technologies have been shown to increase specificity for malignancy.^{42,258,261,340-344} FDG-PET has low sensitivity for nodules with <8-mm solid component and for small nodules near the diaphragm or heart where there is motion artifact. In the workup of nodules detected with CT in a lung cancer screening population at high risk for lung cancer, most nodules requiring follow-up undergo interval LDCT, with the roles of contrast-enhanced CT and FDG-PET/CT in evolution, and the latter limited to larger nodules.^{345,346}

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 detected lung cancers are stage I.^{10,97,214,317,330,344} The NELSON trial, 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).^{9,10,334,347,348} 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.⁵⁵ The original definition of a positive LDCT scan used in NLST was a nodule size of ≥4 mm, which was associated with a high percentage of false-positive results; studies suggest the need for alternate size thresholds and revision.^{11,99,349,350} In v.1.2014 of the NCCN Guidelines for Lung Cancer Screening, the nodule size cutoff—to assign a positive result for solid and part-solid lung nodules on the initial LDCT screening—was increased to 6 mm from 4 mm used in earlier versions of the Guidelines.^{31,72,350,351} Solid and part-solid lung nodules <6 mm on the initial LDCT screening scan are considered very low risk for lung cancer.

The Fleischner Society published guidelines for the management of incidentally detected solid pulmonary nodules on CT scans in 2005 followed by subsequent guidelines for subsolid nodules in 2013, which were harmonized into one guideline in 2017.^{245,251,352} These guidelines are specifically for incidentally detected nodules and not for use in the lung cancer screening settings.³⁵³ However, because of the familiarity and/or acceptance of Fleischner Society Guidelines among radiologists, pulmonologists, and thoracic surgeons, some of the principles were incorporated into the original NCCN recommendations for lung cancer screening.³¹

The ACR developed Lung-RADS specifically for the lung cancer screening population to provide a standardized reporting and management tool for clinicians.^{55,69,72,354} Lung-RADS (and not Fleischner Society Guidelines) is recommended by the NCCN Guidelines, when interpreting CT findings in an individual who has undergone lung cancer screening, and for interval LDCTs performed for the management of screen-detected nodules.^{55,70,71} 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 >1 in 4 in NLST.^{56,67,71,72,76} For subsequent



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LDCT scans after baseline, the false-positive result for Lung-RADS is also lower than NLST (5.3%; 95% CI, 5.1%–5.5% vs. 21.8%; 95% CI, 21.4%–22.2%).⁷¹ The NELSON trial used volume-metric nodule measurement of screen-detected nodules and classified the screening result as “indeterminate” until after a short-term follow-up LDCT was completed, at which time the growth behavior was used to classify the screens as “positive” or “negative” (see *False-Positive Results* in this Discussion).¹⁰ Although this method reduced false positives, this reduction is based on classification of the initial and follow-up CT together rather than any actual differences in scan metrics.

The NCCN Lung Cancer Screening Panel harmonized the recommendations in Lung-RADS and the NCCN Guidelines for Lung Cancer Screening by revising the nodule management algorithms for screen-detected lung nodules.^{69,71} The NCCN threshold cutoffs for solid, part-solid, and nonsolid nodules have been harmonized with the Lung-RADS 1.1 cutoffs by rounding of the mean measurement to the nearest whole number (mm).^{55,70} The exception is that the NCCN Panel recommends a size cutoff of 20 mm for nonsolid nodules for defining a positive screen and not the Lung-RADS 1.1 cutoff of 30 mm.^{68,69}

The current NCCN recommendations for assessment of pulmonary nodules are an adaptation of the Lung-RADS guidelines. The NCCN-recommended size cutoffs for solid, part-solid, and nonsolid nodules detected on LDCT scans are shown in the algorithm. The size cutoffs differ for nodules detected on initial screening LDCT when compared with new or growing nodules detected on follow-up and subsequent annual screening LDCT scans. With the higher degree of suspicion for new or growing nodules, lower size cutoffs are used.²³⁴ The NCCN Panel recommends that annual LDCT scans are performed 12 months from the initial or interval scans.

For solid or part-solid nodules, the current NCCN definition of a positive initial screening scan is a nodule measuring $\geq 6\text{ mm}$ in mean diameter.^{16,41,71,317,355} For nonsolid nodules, the NCCN definition of a positive initial screening scan is $\geq 20\text{ mm}$ in diameter; nodules of this size require a short-term follow-up LDCT scan in 6 months to assess for malignancy. The panel decided that baseline or new nonsolid nodules of $\geq 20\text{ mm}$ should have an earlier evaluation at 6 months.^{262–264} For positive-screen nodules of low to intermediate risk for lung cancer, assessment with an interval LDCT scan is recommended to determine if the nodule is increasing in size or shape or developing a new or growing solid component, features that increase the risk of lung cancer.

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.^{234,356} If a new solid nodule is detected on follow-up or subsequent annual screening LDCT scans, the cutoff threshold is decreased to 4 mm (LCS-8 in the algorithm). For new part-solid nodules with a *solid component of $\geq 4\text{ mm}$* , an immediate chest CT with contrast and/or FDG-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 (LCS-10 in the algorithm). LDCT after 6 months is recommended for new nonsolid nodules of $\geq 20\text{ mm}$ followed by annual LDCT if no cancer is found.³⁵⁶ Biopsy and surgical excision are not recommended for new nodules, because these nonsolid nodules are often caused by pneumonia or are AIS with little malignant potential. However, biopsy or surgical excision are recommended for enlarging nodules and/or those developing part-solid components. The NCCN Panel recommends considering patient preferences when deciding between follow-up with LDCT within 6 months or invasive procedure. As previously mentioned, rapid increase in size and/or multiple nodules suggest an inflammatory etiology or malignancy.



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other than NSCLC. If findings suggest infection or inflammation, a follow-up LDCT is suggested within 1 to 3 months.

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 contrast and/or FDG-PET/CT is recommended to assess for malignancy for the following nodules detected on an initial screening LDCT: 1) solid nodules of ≥ 15 mm; and 2) part-solid nodules with a solid component of ≥ 8 mm. For both solid and part-solid nodules, smaller nodules not near the diaphragm are recommended to be assessed by FDG-PET/CT. For patients with solid nodules of ≥ 15 mm, tissue sampling is a recommended option in addition to or instead of imaging with an immediate chest CT with contrast and/or FDG-PET/CT.

For any nodules with the highest risk of lung cancer, recommendations include biopsy or surgical excision; tissue samples need to be sufficient and adequate to enable histology and molecular testing.^{249,357-359} If a biopsy is negative but there is a strong suspicion of cancer, the NCCN Panel recommends repeating the biopsy, surgical excision, or short-interval LDCT follow-up in 3 months. Many patients with a strong clinical suspicion of stage I or II lung cancer do not require a biopsy before surgery. However, a preoperative biopsy may be appropriate if a non-cancer diagnosis is strongly suspected—which can be diagnosed by bronchoscopy, core biopsy, or fine-needle aspiration (FNA)—or if an intraoperative diagnosis appears difficult or risky. If a preoperative tissue diagnosis has not been obtained, then an intraoperative diagnosis (ie, wedge resection or needle biopsy) is necessary before proceeding with a lobectomy, bilobectomy, or pneumonectomy. The NCCN Panel maintains that SABR (also known as SBRT) is an appropriate option for patients with high risk for complications from surgery.^{33,34} However, the panel recommends multidisciplinary evaluation before deciding whether to use

SABR, especially if a biopsy will not be done because it is deemed too risky or difficult.³⁵

In the NCCN Guidelines, nodule growth is defined as an increase in size of >1.5 mm based on Lung-RADS 1.1.^{32,69,301} Part-solid nodule growth was defined as an increase in size of >1.5 mm in the solid component in the NCCN algorithm. However, the NCCN Lung Cancer Screening Panel decided that they could not provide guidance for an increase in the nonsolid component of part-solid nodules because nonsolid nodules are difficult to measure.^{55,251} This definition of nodule growth is based on intra- and inter-observer variability when measuring small pulmonary nodules, and on the minimum change in diameter that can be reliably detected using conventional methods (excluding volumetric analysis software).³⁶⁰ This definition of nodule growth is simplified compared with the formula used by I-ELCAP, 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 Lung-RADS and NCCN definitions of nodule growth should also result in fewer false-positive diagnoses compared with the NLST-suggested definition of nodule growth ($\geq 10\%$ increase in nodule diameter).¹¹

Multiple Nonsolid Nodules

When multiple subsolid nodules are found, their management is based on whether: 1) all nodules are nonsolid; and 2) there are part-solid components in which case the largest or fastest-growing nodule should be assessed.⁴¹ All part-solid nodules of ≥ 6 mm should be identified, and solid areas should be measured. Careful assessment is needed to determine whether patients have: 1) a lung cancer with several benign nodules; 2) several synchronous lung cancers; or 3) a lung cancer with metastases.³⁶¹ Multiple nodules may also be due to inflammation or infection, especially if they are rapidly expanding in size.⁴¹ The NCCN Panel strongly recommends that all nonsolid lesions be reviewed at thin (≤ 1.5 mm) slices to exclude any solid components



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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.^{10,12,13,48,51,94,362,363} The risks of lung cancer screening include false-negative and false-positive results, radiation exposure, overdiagnosis of incidental findings, futile detection of indolent disease, anxiety about test findings, unnecessary testing and procedures, physical complications from diagnostic workup, and financial costs.^{47,51,362-371} 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.^{369,372} The risks and benefits of lung cancer screening should be discussed with the individual before LDCT screening is initiated (see *Shared Decision-Making* in this Discussion).

Benefits of Lung Cancer Screening

This section summarizes 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.^{12,18,49,51,79,235,238,362} Effective lung cancer screening may prevent an estimated 48,000 lung cancer deaths per year in the United States.¹² Other occult health risks may be identified such as thyroid nodules, COPD, moderate to severe CAC, aortic aneurysm, other cancers (eg, breast cancer, renal cancer), and other conditions.^{104,373-378}

Oncology Outcomes

After a clinical diagnosis of NSCLC, survival is directly related to stage at diagnosis.³⁷⁹ The outcomes for patients with adenocarcinoma quickly

decrease with increasing stage: 5-year survival is 72% for localized, 45% for regional, and 9.5% for distant.^{6,380} Current staging for NSCLC uses the 2017 AJCC staging system (8th edition) (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).³⁸¹ 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 and an apparent increase in survival from early detection itself (lead-time bias).^{382,383} Pathology results of resected lung cancers detected through prior screening trials suggest that screening increases the detection of indolent cancer. Instead, LDCT screening decreases lung cancer mortality as shown by randomized data from the NLST and the NELSON trial.^{10,11,13}

Nonrandomized Trials

Of the nonrandomized screening studies, the I-ELCAP study is the largest.^{85,348} 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.³³⁴ The I-ELCAP study reported that a high percentage of stage I cancers (85%) were detected using LDCT, with an estimated 92% (95% CI, 88%–95%) actuarial 10-year survival rate for stage I cancers resected within 2 months of diagnosis.^{333,348} 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.^{384,385} The authors concluded that annual LDCT screening 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 <20% of the individuals were observed for >5 years. Given the limited follow-up, the 10-year survival estimates may have been overstated.

A study by Bach et al raised concern that LDCT screening may lead to overdiagnosis of indolent cases without substantially decreasing the



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number of advanced cases or the overall attributable deaths from lung cancer.³⁸⁶ Although overdiagnosis occurred with LDCT in the NLST, the magnitude was not large when compared with radiographic screening (83 vs. 17 stage IA bronchioloalveolar carcinoma).^{11,36,233} An analysis of the NLST data stated that 18% of all lung cancers detected by LDCT seemed to be indolent.⁵⁰ Data suggest that baseline LDCT scans find more indolent cancers, and subsequent annual scans find more rapidly growing cancers.^{16,17,234,387} Data from the NELSON trial indicate that new solid nodules found during subsequent LDCT screening are more likely to be lung cancer than solid nodules found at baseline screening.²³⁴

Randomized Trials

To address the concerns of bias and overdiagnosis from nonrandomized screening studies, the NCI launched the NLST in 2002.⁹ As previously mentioned, the NLST was a prospective, phase 3 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 a smoking history of at least 30 pack-years. If individuals were no longer smoking cigarettes, 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%.^{11,13} Overall, 24% of the LDCT scans and 7% of the chest radiographs were positive screens, an imbalance that was expected based on prior data. In each of the three 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.^{11,13} Thus, annual LDCT screening decreased the RR of lung cancer death by 20% in the NLST. These results are impressive, and the NLST represented the first randomized study showing an improvement in disease-specific mortality when using a lung cancer screening program.^{13,16} The NNS to prevent one lung cancer death was 323 over 6.5 years of follow-up.⁹⁶ Extended follow-up of the NLST showed an NNS of 303.¹³ Although the NLST also reported a significant decrease in all-cause mortality, this decrease was largely attributable to lower lung cancer mortality. The NLST results have changed medical practice in the United States.

The NELSON trial evaluated four rounds of LDCT screening versus no screening in 13,195 men and 2594 women ages 50 to 74 years at high risk for lung cancer who currently or previously smoked, demonstrating lung cancer mortality reduction with screening of 26% in men and 39% in women at 10 years compared to the no screening group.¹⁰ The NNS to prevent one lung cancer death was 130 over 10 years of follow-up.⁹⁶

Some clinicians believe the 20% reduction in lung cancer mortality from LDCT screening (compared with chest radiography) in the NLST may actually be greater in clinical practice, because the observed mortality reduction underestimates the true reduction obtained with continued annual screening and because chest radiographs are not currently recommended for lung cancer screening.^{268,388,389} In limited duration screening trials, such as the NLST, deaths during prolonged follow-up may have been prevented if screening had been continued.^{388,390} Thus, if annual lung cancer screening is continued after three annual screens, the increased screening may yield greater lung cancer mortality reduction than reported in NLST. Data from the NELSON trial—which screened at baseline and years 1, 3, and 5.5—support this hypothesis. Data from the MILD trial demonstrated a 39% overall decreased risk of lung cancer mortality (HR, 0.61; 95% CI, 0.39–0.95) after 10 years of screening in the



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LDCT arm, with the benefit of screening improving beyond the fifth year to a 58% decreased risk of lung cancer mortality (HR, 0.42; 95% CI, 0.22–0.79).⁹³ Smaller randomized trials have not reported a mortality reduction with LDCT screening, primarily because they were underpowered for this outcome measure.²²⁰

Approximately 8.6 million individuals were eligible for LDCT lung cancer screening in 2010 using the NLST definitions of high risk. It was estimated that 12,250 deaths would be averted if these individuals at high risk for lung cancer received LDCT screening.³⁹¹ If NCCN group 2 criteria were also used to identify individuals at high risk for lung cancer, then an additional 2 million individuals would also have been eligible to receive lung cancer screening and an additional 3000 deaths would be averted.²¹²

Quality of Life

The NLST assessed quality of life among participants at the time of each annual LDCT screening study.³⁹² The NELSON trial also assessed quality of life in individuals undergoing screening.³⁹³ 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

Historically, most patients with lung cancer exhibited symptoms of the disease (including cough, dyspnea, hemoptysis, pain, weight loss, and cachexia), and thus their lung cancer was detected clinically. It is a reasonable assumption that the disease-related symptom burden would be decreased in patients whose lung cancer is detected early (by screening) compared with late detection (by clinical presentation). Most patients whose lung cancer is detected early are asymptomatic, and

detection is often either incidental or part of a screening protocol.^{9,10,13,251} In addition, lung cancer screening may identify other abnormalities unrelated to lung cancer that require follow-up; presumably, treatment of these other conditions will decrease the overall disease burden.^{11,41,394-397}

Lung-RADS 1.1 includes a modifier “S” for significant or potentially significant findings that is entered into the ACR Lung Cancer Screening Registry (LCSR). In a review of 1,695,746 consecutive LDCT screening exams in the LCSR from 2015 to 2019, 18.8% of LDCTs had one or more significant or potentially clinically significant findings, of which 15.6% had one finding, 2.2% had two findings, and 0.4% had three or more findings.⁴³ The most common findings were moderate or severe CAC on 11.6% of examinations, a mass concerning for cancer (other than lung cancer) in 2.8%, ILD in 2.2%, emphysema (moderate or severe) in 1.2%, and an aortic aneurysm in 0.9%.⁴³ The ACR white papers on incidental findings provide primarily consensus opinion combined with evidence review to provide structured recommendations for management recommendations, with a summary quick guide created to specifically address the types of incidental findings found on screening LDCTs.^{43,44} Reporting the presence of CAC detected on LDCT is a useful marker of atherosclerosis and future cardiovascular risk, and may be reported using either a visual score (ie, none, mild, moderate, severe) or a quantitative score (such as the Agatston score).^{45,319} Further clinical evaluation is recommended if CAC is severe.

Reduction in Treatment-Related Morbidity

Patients with early-stage NSCLC are treated surgically, and sometimes with neoadjuvant or adjuvant therapy, or with SABR, whereas those with more advanced disease are treated with a combination of systemic therapy and radiation, or systemic therapy alone (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org). Patients with early-stage NSCLC who undergo an R0 resection have



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increased survival compared with those with more advanced disease who undergo definitive chemoradiation therapy.³⁹⁸ Few data have been published comparing the treatment burden of surgery versus chemoradiation therapy. While it seems reasonable to assume that patients with stage I NSCLC requiring a lobectomy alone or SABR (also known as SBRT) probably have less treatment-related morbidity than patients with stage III NSCLC requiring combined-modality therapy (chemotherapy, radiation, and possibly lung resection), a difference in morbidity has not been shown.^{34,399}

The NLST found that 40% of the cancers detected in the LDCT screening group were stage IA, 12% were stage IIIB, and 22% were stage IV.^{11,13} Conversely, 21% of the cancers detected in the chest radiograph group were stage IA, 13% were stage IIIB, and 36% were stage IV. Data from the NELSON and UKLS trials also suggest that LDCT screening detects more early-stage lung cancer.^{10,219,317} These results suggest that LDCT screening decreases the number of cases of advanced lung cancer and the patients who require pneumonectomy, both decreasing treatment-related morbidity and mortality. Several series have shown that pneumonectomy is performed in only 1% of patients with lung cancer diagnosed by LDCT screening programs, in contrast to the 20% to 30% rate of pneumonectomy in symptom-detected cases.⁴⁰⁰⁻⁴⁰³

Patients with early-stage NSCLC may be candidates for treatment that is not appropriate for those with advanced-stage disease such as video-assisted thoracoscopic surgery (VATS), especially for those who may not tolerate or refuse an open lobectomy.⁴⁰⁴⁻⁴⁰⁷ VATS lobectomy is associated with less morbidity than open lobectomy. SABR or percutaneous ablation treatment are recommended options for patients with early-stage NSCLC who are not candidates for surgery (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).^{34,408-410}

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 individuals who currently smoke and result in higher smoking rates.⁴¹¹ Neither hypothesis has been supported by any substantial evidence.⁴¹²⁻⁴¹⁴ Studies suggest that smoking cessation rates were higher when more follow-up LDCT scans were ordered for abnormal findings, regardless of ultimate cancer diagnosis, suggesting that screenings were catalysts for patients to quit smoking.^{412,415} 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.⁴¹⁶ A study in >1400 individuals reported that relapse rates were lower in patients with positive LDCT scans who had stopped smoking for ≤2 years.⁴¹⁷

Individuals who currently smoke, including those undergoing lung cancer screening, should always be encouraged to quit smoking tobacco (see the NCCN Guidelines for Smoking Cessation, available at www.NCCN.org).⁴¹⁸⁻⁴²⁰ Likewise, individuals who quit smoking should be encouraged to remain abstinent. Lung cancer screening is not a substitute for smoking cessation.⁴²¹ Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) are recommended to help individuals quit smoking.⁴²¹⁻⁴²³

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.^{392,393} In NLST, 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



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months after screening.³⁹² In NELSON, recipients of an indeterminate result from the initial LDCT scan experienced increased distress in the short term, whereas relief was experienced after a negative baseline screening examination.⁴²⁴ After 2 years of follow-up, data from the NELSON trial suggest that lung cancer screening did not adversely affect quality of life.³⁹³ In the UKLS trial, screening was not associated with clinically significant long-term anxiety, depression, or distress in individuals at high risk for cancer.⁴²⁵ Further longitudinal studies are needed to determine the long-term effect of lung cancer screening. Patients' attitudes toward risk in their life (risk perception) also greatly affect their anxiety when undertaking cancer screening examinations.⁴²⁶ 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.^{48,49,233,238,427} These risks must be understood to determine whether screening is beneficial. The possible or projected risks of baseline and annual repeat 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 indolent disease (ie, overdiagnosis), which would never have harmed the patient who subsequently undergoes unnecessary therapy; 4) indeterminate results, leading to additional testing; 5) radiation exposure; 6) physical complications from diagnostic workup; 7) incidental lesions; and 8) impact on quality of life due to anxiety about test findings. Patients with several comorbid conditions may be at greater risk than those with few or none. Therefore, the initial risk assessment before screening needs to include an assessment of functional status to determine whether patients can tolerate curative-intent

treatment if they are found to have lung cancer. Patients with extensive comorbidity may not be candidates for lung cancer screening, because treatment for lung cancer might not prolong survival and could cause potential morbidity and mortality.

False-Positive Results

Lung cancer screening studies of populations at high risk for lung cancer have found a high rate of noncalcified nodules 4 mm and larger on LDCT screening, with false-positive rates ranging from 1% to 43%.^{10,223,402,428-431} In the NELSON trial, the false-positive rate was 1.2% using a combined LDCT screen and 3-month follow-up CT for indeterminate screens.¹⁰ In NLST, the false-discovery rate was 96.4% and the false-positive rate was 23.5% for the LDCT screening group.^{11,13} The cumulative risk of a false-positive result was 33% over three annual screening LDCTs, meaning that LDCT screening had a high sensitivity but low rate of specificity, which is a common characteristic of screening tests in general.⁴²⁸ The false-positive results were probably due to benign intrapulmonary lymph nodes and noncalcified granulomas coupled with the 4-mm nodule size cutoff to define a positive test.^{11,42} False-positive reporting overestimates the risk of unintended harm because only a percentage of patients with a positive LDCT screening result are considered for invasive tissue diagnosis.^{73,366,432} The rate of invasive procedures in NLST was 4.2% over the 3 years of LDCT screening.¹³ The invasive procedure rate in real-world settings has been reported to be 3.1% to 7% in 1 year, postulated in part to be related to selection of patients with the highest risk for cancer for lung cancer screening, and to confounding of patients with lung cancer symptoms as lung cancer screening rolls out in the United States.^{366,432}

The NELSON trial classified some LDCT screening results as "indeterminate," deferring the classification as "positive" or "negative" screening results until after a short-term follow-up LDCT scan.¹⁰ While this



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strategy of combining the screening and follow-up LDCT reduced the number of false-positive results compared to NLST and other screening trials, it resulted in similar metrics to the Lung-RADS reporting system, which reports the first screen as positive or negative, and updates the result after the short-term follow-up LDCT.^{10,13}

Use of the Lung-RADS protocol has been shown to decrease the false-positive rate and increase the detection of lung cancer.⁷⁰⁻⁷² A review of the first 1.2 million screening CTs in the ACR LCSR demonstrated a positive screen rate of 17.3% for baseline screens and 10.1% for subsequent annual screens, compared to the NLST of 27.3% on baseline screens and 16.8% on the second annual screening round. A lung cancer screening study in 2106 veterans reported a high false-positive rate in lower-risk veterans but a lower false-positive rate in higher-risk veterans, although this was confounded by identifying a majority of positive nodules that would have been considered negative by current Lung-RADS criteria.^{69,433,434}

False-positive and indeterminate results require follow-up, which may include surveillance with chest LDCT scans, FDG-PET/CT, percutaneous needle biopsy, bronchoscopic biopsy, or even surgical biopsy. Each of these procedures has its own risks and potential harms.⁴³⁵ Approximately 7% of individuals with a false-positive result will undergo an invasive procedure, most commonly bronchoscopy.⁴²⁸ The rate of major complications in NLST after an invasive procedure was very low at 0.06% after workup for a false-positive result in the LDCT screened group.¹¹ The complication rate in the real-world setting is higher than reported in clinical trials.^{364,365}

Although the I-ELCAP investigators reported a surgical mortality rate of only 0.5% when 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%.⁴³⁶ These potential harms mandate that the effectiveness of LDCT screening be accurately assessed.⁴³⁶⁻⁴³⁸ Methods of decreasing potential harms with thoracic surgery include using 1) approaches with less morbidity such as sublobar resection, VATS lobectomy, SABR, or percutaneous ablation; 2) minimally invasive diagnostics such as endobronchial US and navigational bronchoscopy; and 3) experienced, dedicated, multidisciplinary teams to minimize unnecessary testing and procedures and the morbidity of those procedures.

Patient perspectives and both the psychological and physical impact of the workup of screen-detected findings are important to consider in the balance of benefit and harm in lung cancer screening. Patients should be informed that a positive screening test result is not definitive for lung cancer but indicates that the abnormalities found require further evaluation.⁵¹ In a study of veterans, they were less concerned about health risks from lung cancer screening and more concerned about their personal risk for cancer.⁴³⁹ Bach et al 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 with associated psychological and physical burdens.³⁸⁶

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 and annual repeat screening with LDCT (see *Screening Findings* in the algorithm). The NCCN screening recommendations use the NELSON, NLST, Lung-RADS, and I-ELCAP protocols/recommendations, and relevant content from the Fleischner Society Guidelines for incidentally detected nodule management, and are based on expert opinion from NCCN Lung Cancer Screening Panel members.^{10,11,13,69,71,245,251,352,440}



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False-Negative Results

Sone et al published two reports on lung cancers missed at screening.⁴⁴¹⁻⁴⁴³ 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.²⁶⁸

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-D 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.^{297,298} 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.²⁷⁹

The range in variability at various centers, particularly outside of academic institutions, may lead to significant differences in results compared with those published from clinical trials. Variability occurs when assessing subsolid nodules.²⁹⁹⁻³⁰¹ 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.

While most lung cancers in NLST were diagnosed based on screen-detected findings, additional lung cancers were diagnosed between annual

screens (ie, interval cancers) in some patients who either clinically presented with concerning symptoms or were imaged for other reasons, and were also diagnosed during the 3- to 5-year follow-up period after the three rounds of screening were completed.^{11,13,444} Thus, individuals undergoing or considering screening should be cautioned that LDCT may not identify all lung cancers or prevent death from lung cancer.^{11,13}

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, lepidic adenocarcinoma) show a potential for prolonged survival in some patients with NSCLC, even without therapy.^{445,446} AIS and MIA, which are likely to present as nonsolid nodules, have 5-year disease-free survival rates of 100% or near 100%, respectively, if completely resected.^{36,445} Lepidic-predominant adenocarcinomas have favorable outcomes ranging from 70% to 90%, if completely resected. A greater percentage of the lepidic pattern, which corresponds with the nonsolid component in a part-solid nodule, is correlated with a more favorable prognosis.^{36,445,446}

Furthermore, experience in lung cancer screening has raised the question of increased identification of indolent tumors in the screened population, which is termed *overdiagnosis*.^{386,447} 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. AIS and MIA have excellent survival and should be separated from overtly invasive adenocarcinomas; therefore, surgical intervention for pure nonsolid nodules should be minimized by using CT screening protocols and multidisciplinary decision-making.^{36,71}



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Overdiagnosis is difficult to measure; initial estimates from the NLST suggested that it was 13%, but others suggest it may have been as high as 25%.^{241,448} An analysis of the NLST data reported that 18% of all lung cancers detected by LDCT seemed to be indolent.⁵⁰ Bach et al 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.³⁸⁶ Their nonrandomized study raised concern that screening may lead to overdiagnosis of indolent cases and diagnosis and treatment-related morbidity, without a mortality benefit. However, the randomized NLST and NELSON trials found that LDCT does decrease lung cancer mortality.^{10,11,13}

Incidental Findings

Examinations performed for lung cancer screening will detect other findings in the lungs, chest, lower neck, or upper abdomen that are clinically significant or potentially clinically significant, and that may require additional testing or medical management.^{44,45,367} 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.^{44,449} Given the high frequency of these findings, 18.7% in over 1.6 million screens in the first 5 years of the ACR LCSR, it is important that patients are made aware, as part of shared decision-making, that incidental findings may occur.⁴³

Quality of Life

The effect of lung cancer screening on quality of life (see *Benefits of Lung Cancer Screening* in this Discussion) is not fully known. A study by van den Bergh et al found no measured adverse effects, although approximately half of the participants reported discomfort while waiting for the results.⁴⁵⁰ Several studies (including the NLST and NELSON trial) have measured quality-of-life issues.^{393,424} Data from the NLST and NELSON trials suggest that lung cancer screening did not adversely affect

quality of life.^{392,393} False-positive and indeterminate results may decrease quality of life because of mental anguish and additional testing.⁴⁷

Radiation Exposure with LDCT

Current MDCT scanners provide a significantly enhanced capability for detecting small nodules through allowing thinner slice images, shorter scan times, and improved image reconstruction techniques. Using low-dose techniques, the mean effective radiation dose is 1.5 millisievert (mSv) (standard deviation [SD], 0.5 mSv) compared with an average of 7 mSv for conventional CT.^{11,18,241,451} The radiation dose of LDCT is 10 times that of chest radiography. Advances in image reconstruction algorithms, such as iterative reconstruction, provide better image quality at lower radiation exposures than was used in trials like the NLST that performed LDCT screening starting in the year 2000.

The effects of repeated exposure to radiation at regular intervals are not known and are controversial, with most models of radiation exposure and cancer risk extrapolated using various models from major radiation events, such as the atomic bomb exposures in Japan. Cancer risk from radiation decreases with age, being highest in children. The radiation exposure from annual LDCT screening annually beginning at age 50, in addition to interval CT scans to evaluate concerning nodules, raises concern about the adverse effects of this radiation exposure and any additional cancer risk, because these individuals are already at high risk for lung cancer. Brenner estimated a 1.8% increase in lung cancer cases if half of all individuals who currently smoke or quit smoking in the United States between 50 and 75 years of age were to undergo annual screening LDCT, using atomic bomb survivor cohort data as the basis for predicting radiation-related lung cancer risks in a general population.⁴⁵² Looking at the balance of benefits and harms in the more recent COSMOS study, radiation exposure is considered acceptable when put in the context of substantial mortality reduction from screening and competing



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comorbidities in this population.³⁶⁷ Radiation exposure from LDCT is greater for women than for men.³⁶⁷ The MILD trial found that the median cumulative effective dose was 13.0 mSv for females and 9.3 mSv for males after 10 years of annual screening.²¹⁷ In that trial, the numbers of lung cancer reported as induced by 10 years of screening corresponded to an additional risk of induced major cancers of 0.05%. These doses approximate that of one standard CT of the chest (7–8 mSv). LDCT scans currently used for lung cancer screening are performed with lower radiation exposure, which should be associated with a lower risk.^{453,454}

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 estimated cost of an LDCT scan is about \$332 (U.S. national average).^{366,455} CMS increased the reimbursement rate for hospital outpatient LDCT to \$111.19 in 2022.⁴⁵⁶ Approximately 30.8 million U.S. individuals currently smoke cigarettes.⁴⁵⁷ In 2015, the number of individuals at high risk who were candidates for lung cancer screening was approximately 6 million (using NLST criteria).^{11,458} Depending on the screening rate (50% or 75%), the annual cost in the United States was estimated to be about \$1.7 to \$3.4 billion in 2015 if fully implemented.^{455,458} If 75% of the eligible population at high risk for lung cancer has screening, it is estimated that it will cost \$240,000 to prevent one lung cancer death.⁷⁹ It is estimated that \$18 billion will be spent in 2020 on lung cancer care in the United States.^{455,459} However, the potential cost savings of shifting to lung cancer therapy for an earlier stage of disease (ie, the cost of surgical therapy for early-stage disease versus the cost of systemic therapy for advanced disease) and having an increased productive life span without loss of work years have not been factored in. Estimates of the cost of lung cancer care for Medicare patients do not include newer immunotherapy regimens.⁴⁶⁰

LDCT screening will lead to false-positive results, detection of indeterminate nodules, and detection of potential disease other than lung cancer.³⁹² Follow-up for positive LDCT screens 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 Lung-RADS has decreased follow-up CTs because of larger nodule size cutoffs for positive screens, which reduces the false-positive rate.⁶⁹ 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).⁴²⁸ Thus, false-positive reporting overestimates the risk of unintended harm because only a percentage of positive findings are considered for invasive tissue diagnosis (see *False-Positive Results* in this Discussion).^{73,366,432} 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. A pre-screening risk assessment—based on age, smoking history, appropriate medical history, family history, and occupational history—is important to determine which patients are at high risk for lung cancer (see *Risk Assessment* in the algorithm).

Lack of adherence to screening guidelines can lead to overuse of screening. A recent study reported that 21% (538/2567) of individuals who had LDCT screening did not meet any of the USPSTF eligibility criteria for screening.²⁰ 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



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serial follow-up LDCT, dynamic contrast-enhanced nodule densitometry, FDG-PET, or biopsy. False-positive results also lead to additional unnecessary testing and increased cost.

Lung cancer screening also leads to detection of disease other than lung cancer.^{11,41,45,104,268,319,373-378,395-397,433,461,462} 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 and inflammation (see *New Nodule on Follow-Up or Annual LDCT* in the algorithm); however, antimicrobials are not indicated for chronic lesions.²⁶⁸ Inappropriate use of antimicrobials may cause adverse side effects and will increase cost.

Cost-Effectiveness and Cost-Benefit Analyses

The cost-effectiveness of lung cancer screening is also important to take into account.⁴⁶³ LDCT imaging is more expensive than many other screening tests, and therefore it is important to validate the effectiveness of screening.⁴⁶⁴ LDCT is considered to be cost-effective using current standards.⁵¹ The estimated cost of an LDCT scan is about \$332 (U.S. national average).³⁶⁶ CMS increased the reimbursement rate for hospital outpatient LDCT to \$111.19 in 2022.⁴⁵⁶ 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.⁴⁶⁵ 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.⁴⁶⁶ 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 two sequential annual examinations in the NLST, the cumulative risk of a false-positive test result was 33%.⁴²⁸ The cost of false-positive cancer screening results has been estimated to be at least \$1000 per incident.⁴⁶⁷ 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.⁴⁶⁸ An analysis using SEER-Medicare data also found that costs increase with increasing stage.⁴⁶⁰ 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.⁴⁶⁹

Shared Decision-Making

The risks and benefits of lung cancer screening should be discussed with the individual before a screening LDCT scan is performed, as done for other screening tests.^{48,49,51,78,79,349,439,470} Although age and smoking history are used for risk assessment, other potential risk factors for lung cancer—including personal history of cancer or lung disease, family history of lung cancer, radon exposure, and occupational exposure to lung carcinogens—may be discussed during shared decision-making (see shouldiscreen.com).^{51,104-112} Individuals should be cautioned that LDCT may not identify all lung cancers or prevent death from lung cancer. In addition, a positive screening test result is not definitive for lung cancer but only indicates that their nodule(s) require further evaluation; >90% of positive LDCT findings are found to be benign.^{10,11,13,51,78} To obtain the mortality benefits of screening, individuals should be aware that LDCT screening is an ongoing process that involves annual (or more frequent)



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screening for many years with the possibility of additional interval tests to evaluate screen-detected findings. Smoking cessation counseling is recommended.^{418,471}

Shared patient/provider decision-making may be the best approach before deciding whether to do LDCT lung cancer screening, especially for older individuals with comorbid conditions.^{24,51,80,81,472} Lung cancer screening is not recommended for individuals who are not able or willing to have curative therapy because of health problems or other major concerns.²⁴ Thus, the initial risk assessment should include an assessment of functional status to determine whether patients can tolerate curative-intent treatment if they are found to have lung cancer. The NCCN Panel defines *curative-intent* treatment as including surgery, SABR (also known as SBRT), or ablation. SABR or ablation may be used for patients who are medically inoperable because of cardiac disease or severe COPD (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).³⁴

Risk calculators may be used to assist with decision-making.^{267,473} It is well established that risk calculators can identify patients who are actually low risk and should not be screened and can identify individuals who are high risk and should be screened. For example, the Tammemagi risk calculator includes additional variables that can be used to help determine whether individuals are candidates for screening.²⁷⁶ The additional variables include BMI, history of COPD, education level, chest radiography in the last 3 years, and family history of lung cancer. Using this risk calculator, the threshold for screening is 1.34% to 1.51%.^{276,473} Previous lung cancer screening results can also be used for risk stratification.^{229,474} The Tammemagi risk calculator was used to assess 7044 individuals (PanCan study), and an increased incidence of early-stage lung cancer was observed when compared with the NLST (Tammemagi: 133/172 [77%] vs. NLST: 593/1040 [57%]; $P < .0001$).²⁷⁶ For the v.1.2024 update, the NCCN

Panel added a caveat that providers should consider using risk calculators, if possible, because additional candidates at high risk for lung cancer may be identified for lung cancer screening.^{12,276} Use of risk models may identify patients with a lower risk or higher risk within the current recommendations.

Summary

The NCCN Lung Cancer Screening Panel recommends criteria for selecting individuals at high risk for lung cancer for LDCT screening of the chest and provides recommendations for evaluation and follow-up of lung nodules found during initial and subsequent screening. The guidelines include recommendations for a multidisciplinary approach, shared decision-making, utilization of risk calculators, and nodule management for initial lung cancer screening and follow-up evaluations. The panel plans to review the revised and published v2022 of Lung-RADS and modify the NCCN Guidelines where appropriate.



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