

# Management of lung nodules on LDCT screening

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# NLST

- Annual LDCT vs. CXR x 3
- Eligibility
  - 55-74 y/o
  - Smoking  $\geq$  30 PY, had not quit within the previous 15 yrs
- Definition of “positive”
  - any noncalcified nodule measuring at least 4 mm in any diameter
  - other abnormalities such as adenopathy or effusion
- Results
  - 20% relative risk reduction in lung cancer mortality
  - Positive screening tests = 24.2%; false positive results = 96.4%

## Recommendations for Follow-up and Management of Nodules Smaller than 8 mm Detected Incidentally at Nonscreening CT

Nodule Size (mm)*	Low-Risk Patient†	High-Risk Patient‡
≤4	No follow-up needed§	Follow-up CT at 12 mo; if unchanged, no further follow-up
>4–6	Follow-up CT at 12 mo; if unchanged, no further follow-up	Initial follow-up CT at 6–12 mo then at 18–24 mo if no change
>6–8	Initial follow-up CT at 6–12 mo then at 18–24 mo if no change	Initial follow-up CT at 3–6 mo then at 9–12 and 24 mo if no change
>8	Follow-up CT at around 3, 9, and 24 mo, dynamic contrast-enhanced CT, PET, and/or biopsy	Same as for low-risk patient

Note.—Newly detected indeterminate nodule in persons 35 years of age or older.

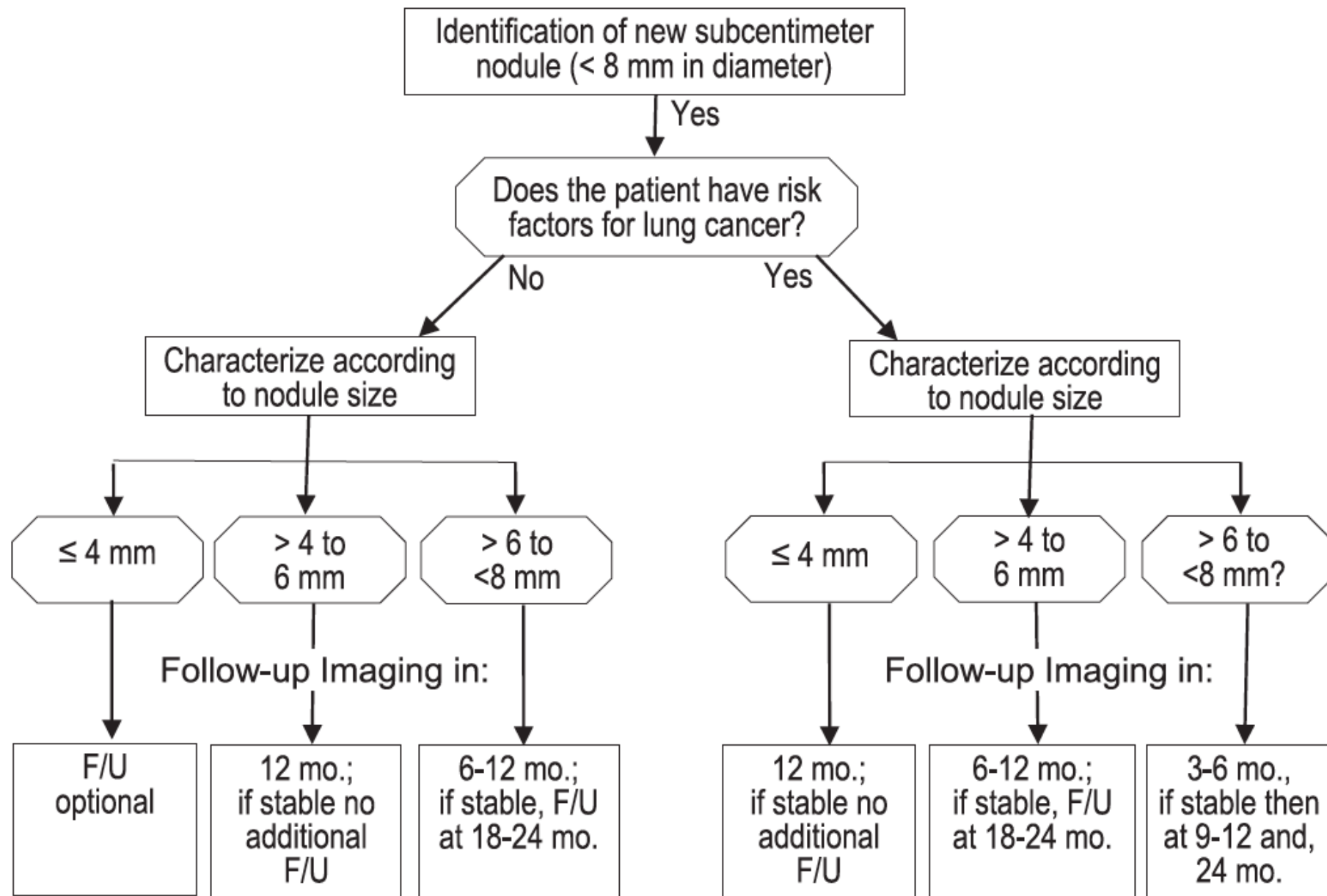
\* Average of length and width.

† Minimal or absent history of smoking and of other known risk factors.

‡ History of smoking or of other known risk factors.

§ The risk of malignancy in this category (<1%) is substantially less than that in a baseline CT scan of an asymptomatic smoker.

|| Nonsolid (ground-glass) or partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma.

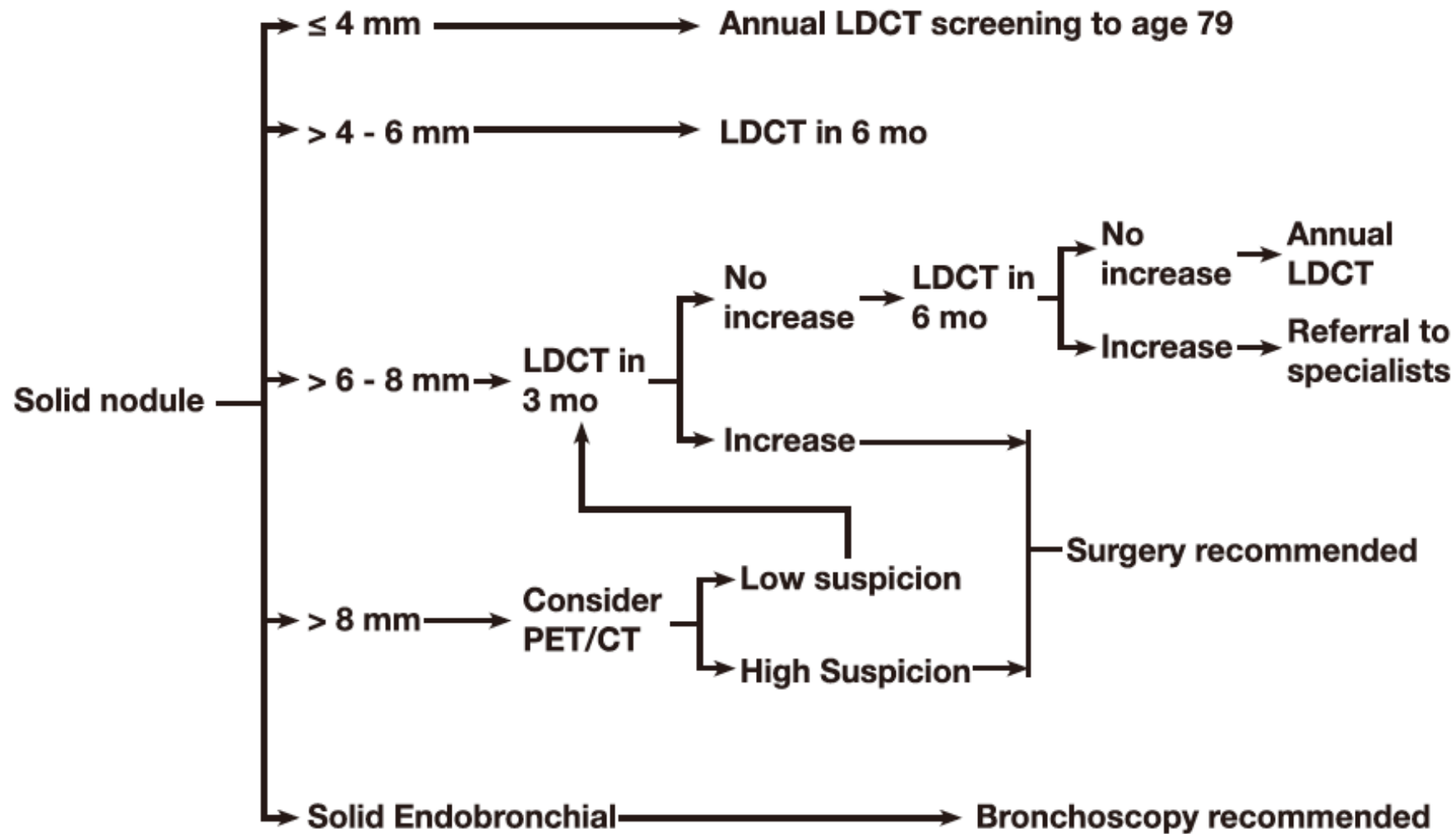


# Subsolid nodule management plan

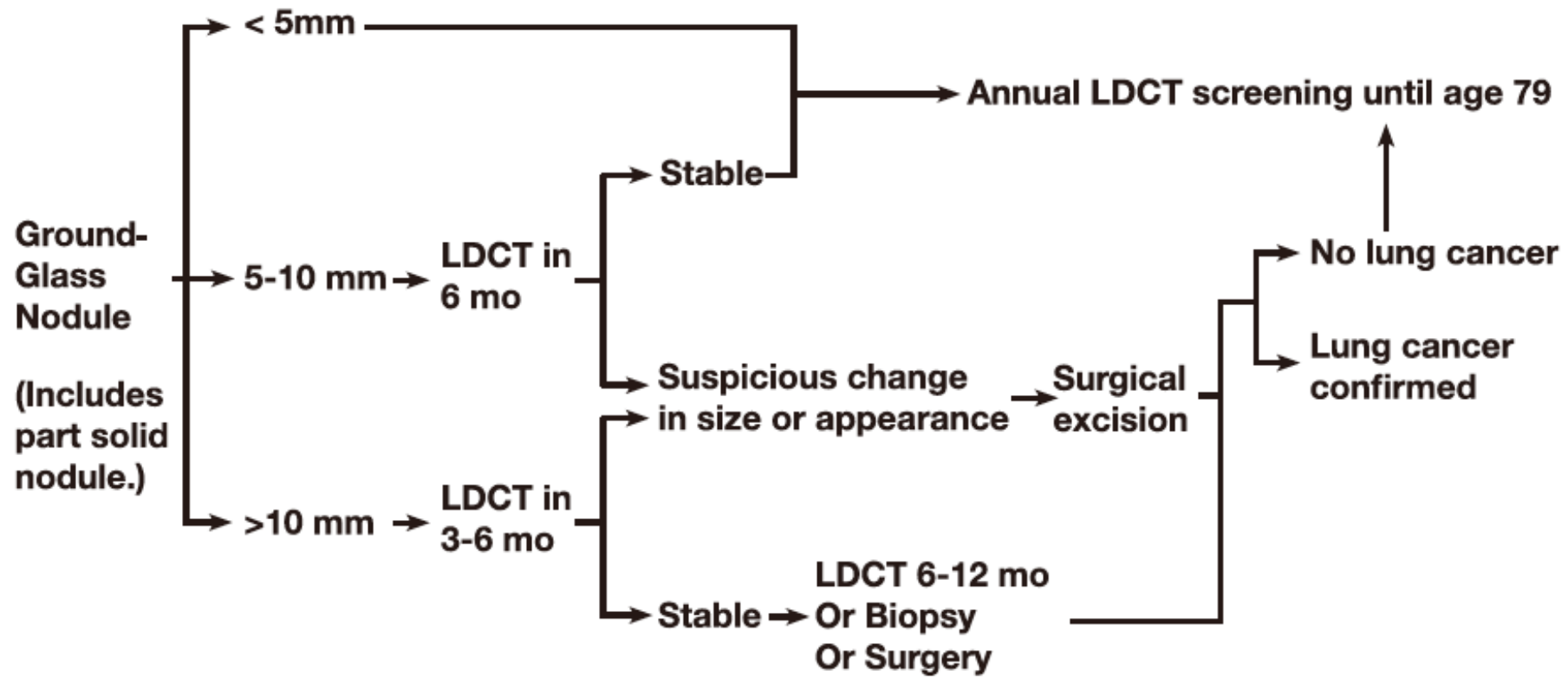
## Recommendations for the Management of Subsolid Pulmonary Nodules Detected at CT: A Statement from the Fleischner Society

Nodule Type	Management Recommendations	Additional Remarks
Solitary pure GGNs		
≤5 mm	No CT follow-up required	Obtain contiguous 1-mm-thick sections to confirm that nodule is truly a pure GGN
>5 mm	Initial follow-up CT at 3 months to confirm persistence then annual surveillance CT for a minimum of 3 years	FDG PET is of limited value, potentially misleading, and therefore not recommended
Solitary part-solid nodules	Initial follow-up CT at 3 months to confirm persistence. If persistent and solid component <5 mm, then yearly surveillance CT for a minimum of 3 years. If persistent and solid component ≥5 mm, then biopsy or surgical resection	Consider PET/CT for part-solid nodules >10 mm
Multiple subsolid nodules		
Pure GGNs ≤5 mm	Obtain follow-up CT at 2 and 4 years	Consider alternate causes for multiple GGNs ≤5 mm
Pure GGNs >5 mm without a dominant lesion(s)	Initial follow-up CT at 3 months to confirm persistence and then annual surveillance CT for a minimum of 3 years	FDG PET is of limited value, potentially misleading, and therefore not recommended
Dominant nodule(s) with part-solid or solid component	Initial follow-up CT at 3 months to confirm persistence. If persistent, biopsy or surgical resection is recommended, especially for lesions with >5 mm solid component	Consider lung-sparing surgery for patients with dominant lesion(s) suspicious for lung cancer

Note.—These guidelines assume meticulous evaluation, optimally with contiguous thin sections (1 mm) reconstructed with narrow and/or mediastinal windows to evaluate the solid component and wide and/or lung windows to evaluate the nonsolid component of nodules, if indicated. When electronic calipers are used, bidimensional measurements of both the solid and ground-glass components of lesions should be obtained as necessary. The use of a consistent low-dose technique is recommended, especially in cases for which prolonged follow-up is recommended, particularly in younger patients. With serial scans, always compare with the original baseline study to detect subtle indolent growth.



**FIGURE 3.** AATS lung cancer screening guidelines for solid nodules on low-dose computed tomography (*LDCT*).

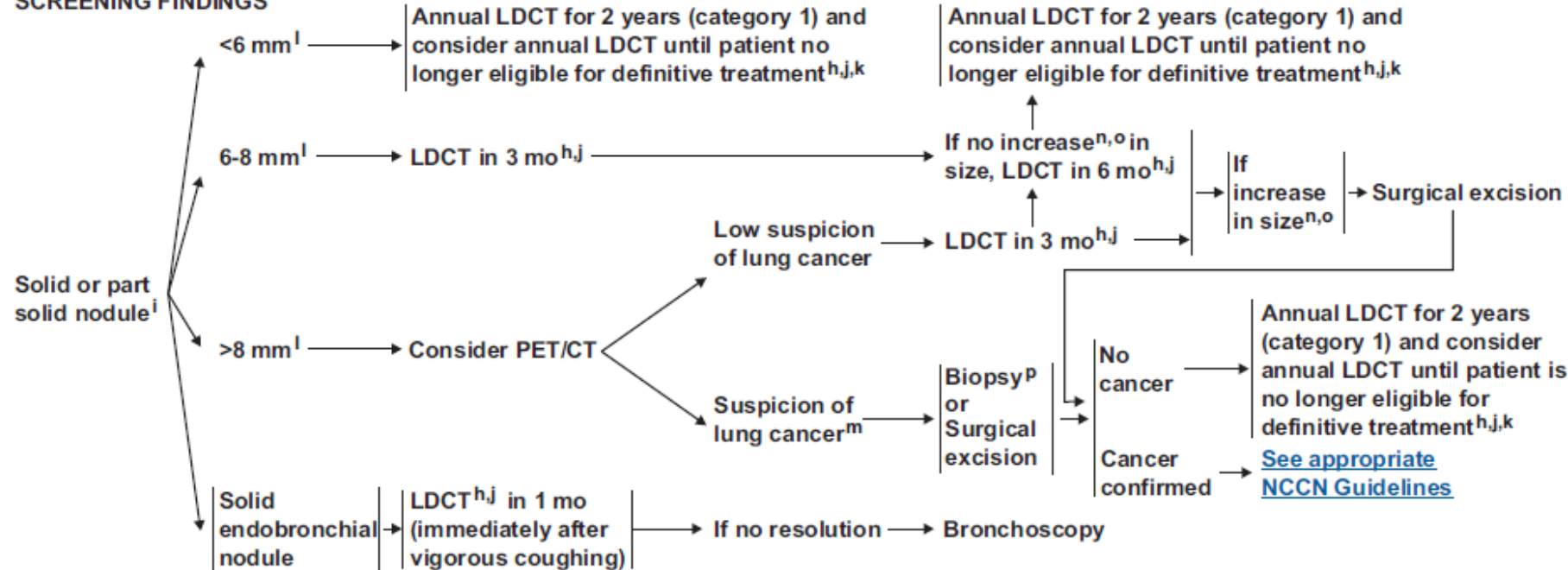


**FIGURE 4.** AATS lung cancer screening guidelines for ground-glass nodule.



**EVALUATION OF  
SCREENING FINDINGS**

**FOLLOW-UP OF SCREENING FINDINGS**



<sup>h</sup>All screening and follow-up CT scans should be performed at low dose (100-120 kVp & 40-60 mAs or less), unless evaluating mediastinal abnormalities or lymph nodes, where standard dose CT with IV contrast might be appropriate. (See Table 2). There should be a systematic process for appropriate follow-up.

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

<sup>j</sup>If new nodule at annual or follow-up LDCT, see LCS-6. New nodule is defined as  $\geq 3$  mm in mean diameter.

<sup>k</sup>There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.

<sup>l</sup>Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter.

<sup>m</sup>Criteria for suspicion of malignancy: hypermetabolism higher than the background of surrounding lung parenchyma, regardless of absolute SUV.

<sup>n</sup>For nodules  $<15$  mm: increase in mean diameter  $\geq 2$  mm in any nodule or in the solid portion of a part solid nodule compared to baseline scan. For nodules  $\geq 15$  mm: increase in mean diameter of  $\geq 15\%$  compared to baseline scan.

<sup>o</sup>Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer.

<sup>p</sup>Tissue samples need to be adequate for both histology and molecular testing. Travis WD, et al. Diagnosis of lung cancer in small biopsies and cytology: Implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Classification. Arch Pathol Lab Med 2013;137:668-684.

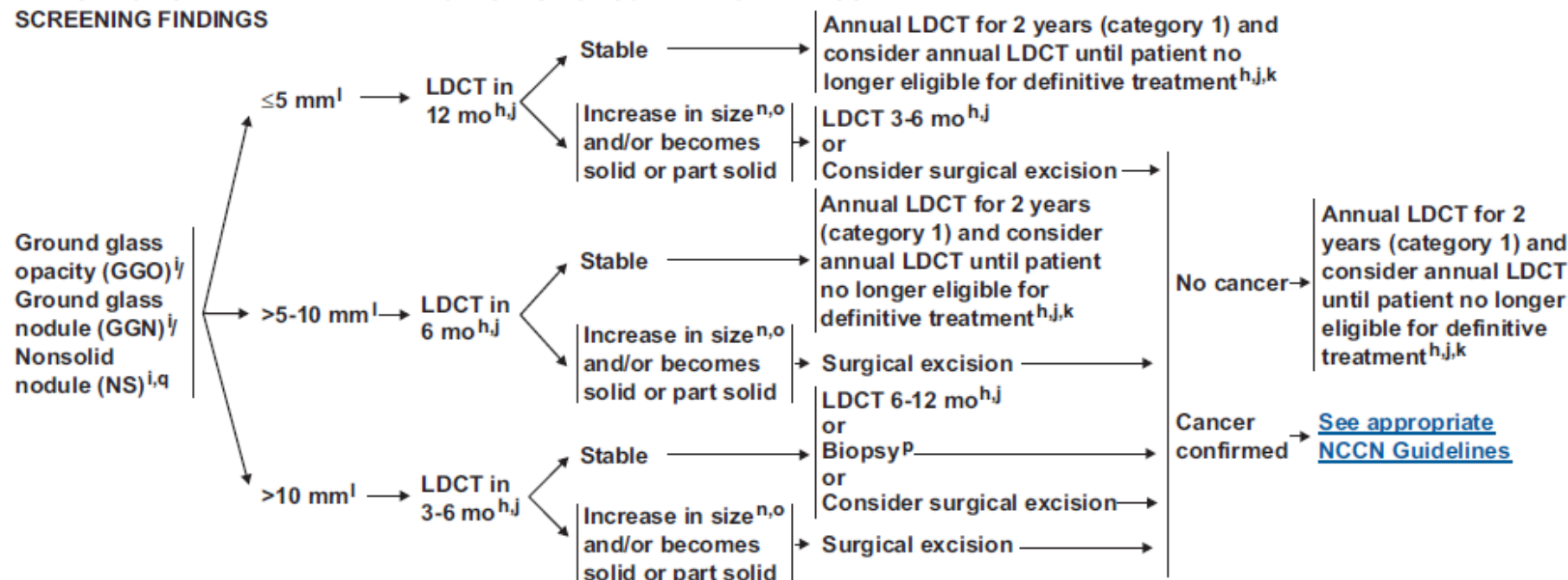
**Note:** All recommendations are category 2A unless otherwise indicated.

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



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<sup>o</sup>Rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than NSCLC.

<sup>p</sup>Tissue samples need to be adequate for both histology and molecular testing. Travis WD, et al. Diagnosis of lung cancer in small biopsies and cytology: Implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Classification. Arch Pathol Lab Med 2013;137:668-684.

<sup>q</sup>It is crucial that all GGO/GGN/nonsolid lesions must be reviewed at thin ( $<1.5$  mm) slices to exclude any solid components. Any solid component in the nodule requires management of the lesion with the part-solid recommendations (see LCS-3).

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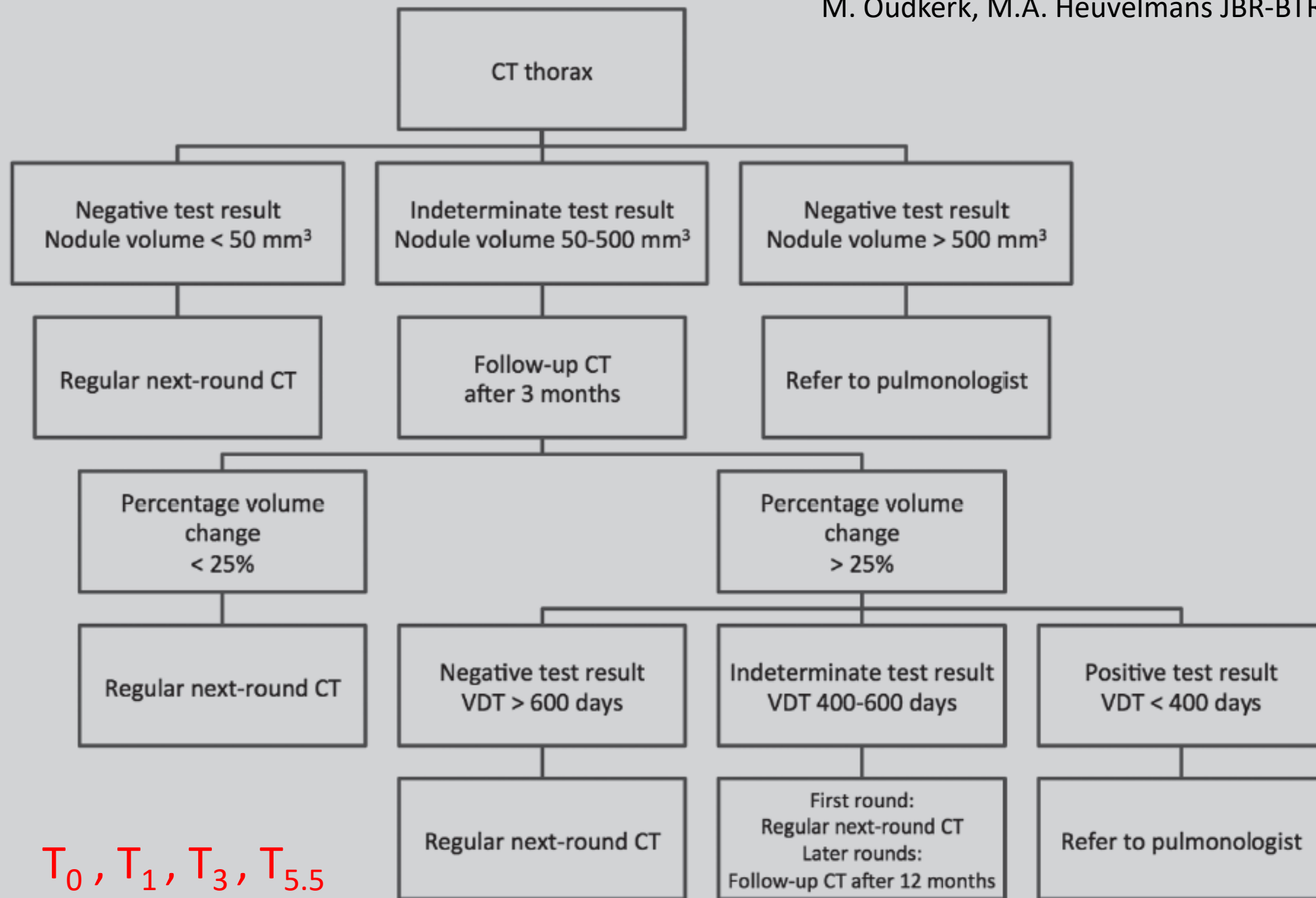
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# NELSON (Dutch-Belgian lung cancer screening trial)

- Launched in 2003
- Questionnaire: 106,931 (32%) of the 335,441 responded.
- Primary object: whether LDCT screening in year 1, 2, 4 and 6.5 will decrease lung cancer mortality by  $\geq 25\%$  in high-risk smokers between 50-75 y/o compared to a control group receiving no screening.
  - Current and former smokers ( $\leq 10$  yrs of cessation), who smoked  $> 15$  pieces/day for  $> 25$  yrs or  $> 10$  pieces/day for  $> 30$  yrs
- Nodule management: nodule volume and VDT

# Nodule management plan

- First round
  - Positive
    - any non-calcified nodule  $> 500 \text{ mm}^3$  ( $> 9.8 \text{ mm}$ )
    - VDT of an indeterminate nodule  $< 400$  days
  - Indeterminate
    - solid nodule or the solid component of a part-solid nodule was 50-500  $\text{mm}^3$  (4.6-9.8 mm)
    - A 3-month FU to determine the VDT
  - Negative



$T_0, T_1, T_3, T_{5.5}$

# Baseline (first round, $T_0$ )

- 1.6% had a nodule with volume  $> 500\text{mm}^3$ .
- 19.2% had at least one indeterminate nodule ( $50 - 500\text{mm}^3$ )
  - 5.3% had tumor growth at a three-month follow-up CT ( $19.2\% \times 5.3\% = 1\%$ )
- In total, 196/7,557 (2.6%) participants tested positive.
- In 70/196 (35.7%) participants, malignancy was confirmed
- The lung cancer detection rate was 0.9%.
- Sensitivity of the baseline round screening was 94.6%, the negative predictive value was 99.7%.

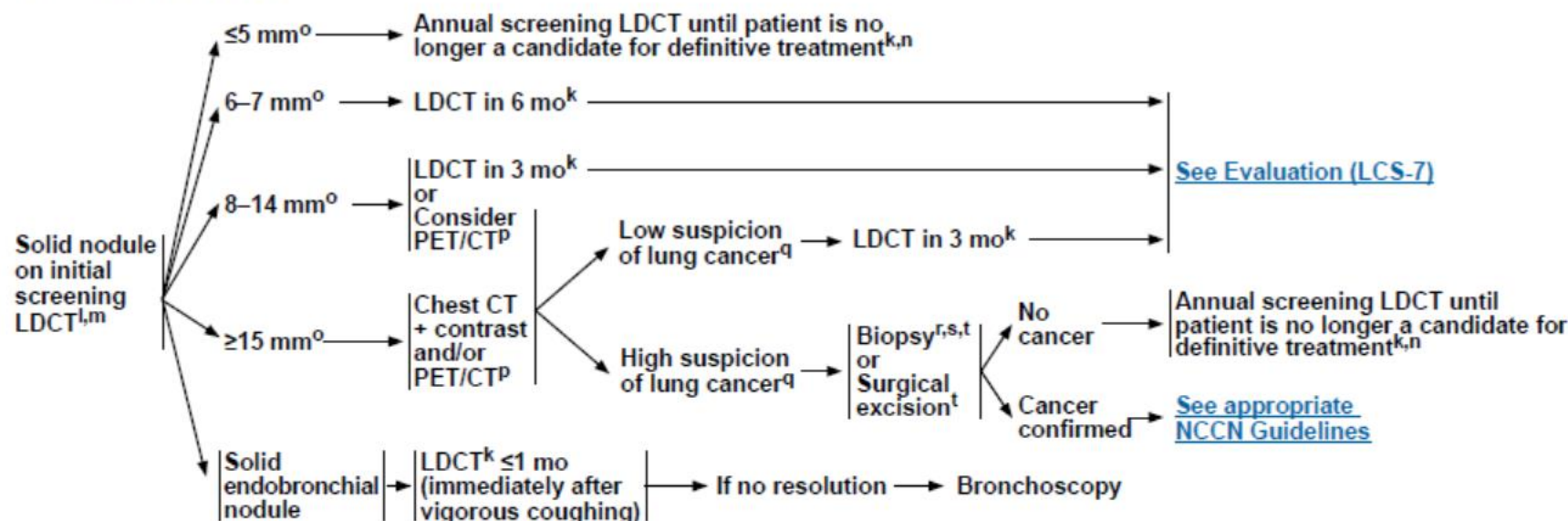
2019





### EVALUATION OF SCREENING FINDINGS

### FOLLOW-UP OF SCREENING FINDINGS



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<sup>l</sup>The NCCN Guidelines for Lung Cancer Screening are harmonized with Lung-RADS (<http://www.acr.org/Quality-Safety/Resources/LungRADS>). Pinsky PF, Gierada DS, Black W, et al. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. *Ann Intern Med* 2015;162:485-491.

<sup>m</sup>Without benign pattern of calcification, fat in nodule suggestive of hamartoma, or features suggesting inflammatory etiology. When multiple nodules or other findings are present that suggest occult infection or inflammation is a possibility, suggest follow-up LDCT in 1–3 months.

<sup>n</sup>There is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate.

<sup>o</sup>Nodules should be measured on lung windows and reported as the average diameter rounded to the nearest whole number; for round nodules only a single diameter measurement is necessary. Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter.

<sup>p</sup>PET has a low sensitivity for nodules with less than 8 mm of solid component and for small nodules near the diaphragm. PET/CT is only one consideration of multiple criteria for determining whether a nodule has a high risk of being lung cancer. In areas endemic for fungal disease, the false-positive rate for PET/CT is higher.

<sup>q</sup>The evaluation for the suspicion of lung cancer requires a multidisciplinary approach with expertise in lung nodule management (thoracic radiology, pulmonary medicine, and thoracic surgery). This may include use of a lung nodule risk calculator to assist with probability determination. Examples of lung nodule risk calculators: [Mayo risk model](#); [Brock university model](#); [model by Herder, GJ et al. Chest 2005;128:2490-2496](#). The use of risk calculators does not replace multidisciplinary nodule management. Geographic and other factors can substantially influence the accuracy of nodule calculators.

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

<sup>s</sup>If biopsy is non-diagnostic and a strong suspicion for cancer persists, suggest repeat biopsy or surgical excision or short-interval follow-up (3 months).

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

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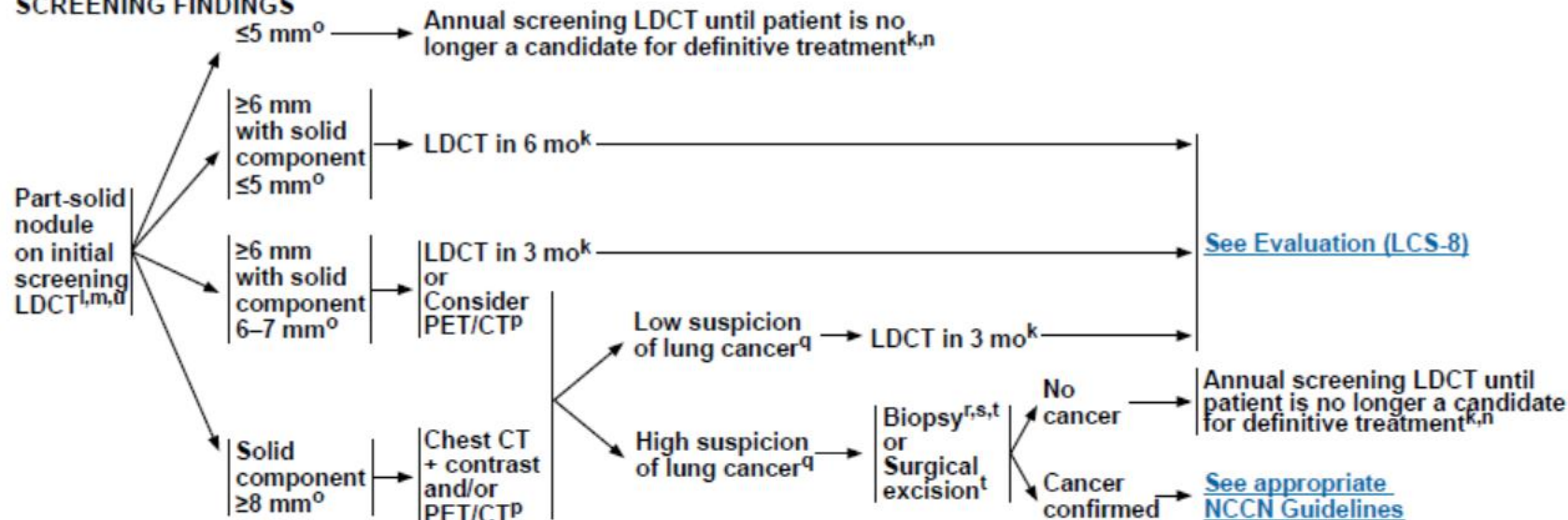
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<sup>u</sup>It is crucial that all nonsolid lesions be reviewed at thin (<1.5 mm) slices to exclude any solid components. Any solid component in the nodule requires management of the lesion with the part-solid recommendations ([LCS-8](#)).

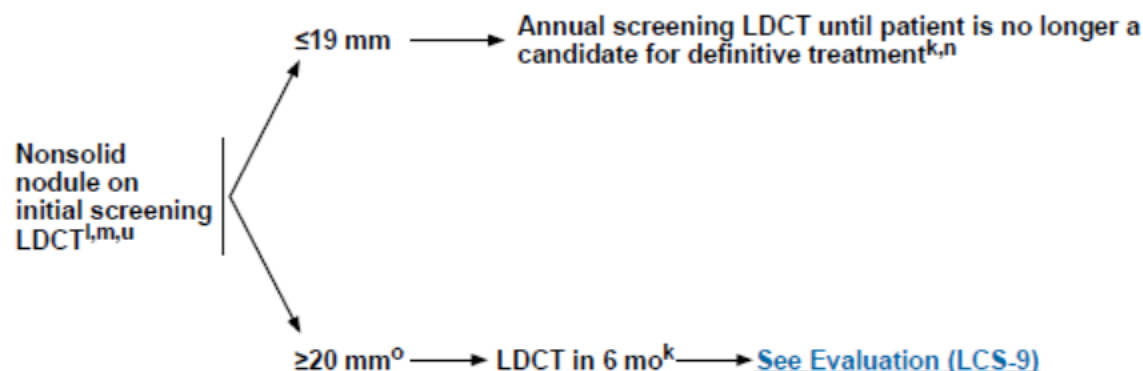
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**A: Solid Nodules\***

Nodule Type	Size			Comments
	<6 mm (<100 mm <sup>3</sup> )	6–8 mm (100–250 mm <sup>3</sup> )	>8 mm (>250 mm <sup>3</sup> )	
Single				
Low risk <sup>†</sup>	No routine follow-up	CT at 6–12 months, then consider CT at 18–24 months	Consider CT at 3 months, PET/CT, or tissue sampling	Nodules <6 mm do not require routine follow-up in low-risk patients (recommendation 1A).
High risk <sup>†</sup>	Optional CT at 12 months	CT at 6–12 months, then CT at 18–24 months	Consider CT at 3 months, PET/CT, or tissue sampling	Certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up (recommendation 1A).
Multiple				
Low risk <sup>†</sup>	No routine follow-up	CT at 3–6 months, then consider CT at 18–24 months	CT at 3–6 months, then consider CT at 18–24 months	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).
High risk <sup>†</sup>	Optional CT at 12 months	CT at 3–6 months, then at 18–24 months	CT at 3–6 months, then at 18–24 months	Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (recommendation 2A).



**B: Subsolid Nodules\***

Nodule Type	Size		Comments
	<6 mm (<100 mm <sup>3</sup> )	≥6 mm (>100 mm <sup>3</sup> )	
Single			
Ground glass	No routine follow-up	CT at 6–12 months to confirm persistence, then CT every 2 years until 5 years	In certain suspicious nodules < 6 mm, consider follow-up at 2 and 4 years. If solid component(s) or growth develops, consider resection. (Recommendations 3A and 4A).
Part solid	No routine follow-up	CT at 3–6 months to confirm persistence. If unchanged and solid component remains <6 mm, annual CT should be performed for 5 years.	In practice, part-solid nodules cannot be defined as such until ≥6 mm, and nodules <6 mm do not usually require follow-up. Persistent part-solid nodules with solid components ≥6 mm should be considered highly suspicious (recommendations 4A-4C)
Multiple	CT at 3–6 months. If stable, consider CT at 2 and 4 years.	CT at 3–6 months. Subsequent management based on the most suspicious nodule(s).	Multiple <6 mm pure ground-glass nodules are usually benign, but consider follow-up in selected patients at high risk at 2 and 4 years (recommendation 5A).

# Lung-RADS Version 1.0 (2014.4.28)

Category	Category Descriptor	Category	Findings	Management	Probability of Malignancy	Estimated Population Prevalence
Incomplete	-	0	prior chest CT examination(s) being located for comparison part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed	n/a	1%
Negative	No nodules and definitely benign nodules	1	no lung nodules nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules	Continue annual screening with LDCT in 12 months	< 1%	90%
Benign Appearance or Behavior	Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	solid nodule(s): < 6 mm new < 4 mm			
			part solid nodule(s): < 6 mm total diameter on baseline screening			
			non solid nodule(s) (GGN): < 20 mm OR ≥ 20 mm and unchanged or slowly growing category 3 or 4 nodules unchanged for ≥ 3 months			

- 
- Size: 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
  - Growth: an increase in size of > 1.5 mm

<http://www.acr.org/Quality-Safety/Resources/LungRADS>

Reporting and Data System

# Lung-RADS Version 1.0 (2014.4.28)

Category	Category Descriptor	Category	Findings	Management	Probability of Malignancy	Estimated Population Prevalence
Probably Benign	Probably benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	solid nodule(s): ≥ 6 to < 8 mm at baseline OR new 4 mm to < 6 mm	6 month LDCT	1-2%	5%
			part solid nodule(s) ≥ 6 mm total diameter with solid component < 6 mm OR new < 6 mm total diameter			
			non solid nodule(s) (GGN) ≥ 20 mm on baseline CT or new			
Suspicious	Findings for which additional diagnostic testing and/or tissue sampling is recommended	4A	solid nodule(s): ≥ 8 to < 15 mm at baseline OR growing < 8 mm OR new 6 to < 8 mm	3 month LDCT; PET/CT may be used when there is a ≥ 8 mm solid component	5-15%	2%
			part solid nodule(s): ≥ 6 mm with solid component ≥ 6 mm to < 8 mm OR with a new or growing < 4 mm solid component			
			endobronchial nodule			
		4B	solid nodule(s) ≥ 15 mm OR new or growing, and ≥ 8 mm	chest CT with or without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a ≥ 8 mm solid component.	> 15%	2%
			part solid nodule(s) with: a solid component ≥ 8 mm OR a new or growing ≥ 4 mm solid component			
		4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy			

# Lung-RADS® Version 1.1

Assessment Categories Release date: 2019

Category Descriptor	Lung-RADS Score	Findings	Management	Risk of Malignancy	Est. Population Prevalence
Incomplete	0	Prior chest CT examination(s) being located for comparison Part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed	n/a	1%
Negative  No nodules and definitely benign nodules	1	No lung nodules Nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules	Continue annual screening with LDCT in 12 months	< 1%	90%
Benign Appearance or Behavior  Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	Perifissural nodule(s) (See Footnote 11) < 10 mm (524 mm <sup>3</sup> )			
		Solid nodule(s): < 6 mm (< 113 mm <sup>3</sup> ) new < 4 mm (< 34 mm <sup>3</sup> )			
		Part solid nodule(s): < 6 mm total diameter (< 113 mm <sup>3</sup> ) on baseline screening			
		Non solid nodule(s) (GGN): <30 mm (<14137 mm <sup>3</sup> ) OR ≥ 30 mm (≥ 14137 mm <sup>3</sup> ) and unchanged or slowly growing			
		Category 3 or 4 nodules unchanged for ≥ 3 months			













<b>Probably Benign</b>  Probably benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	<b>Solid nodule(s):</b> $\geq 6$ to $< 8$ mm ( $\geq 113$ to $< 268$ mm <sup>3</sup> ) at baseline <b>OR</b> new 4 mm to $< 6$ mm (34 to $< 113$ mm <sup>3</sup> ) <b>Part solid nodule(s)</b> $\geq 6$ mm total diameter ( $\geq 113$ mm <sup>3</sup> ) with solid component $< 6$ mm ( $< 113$ mm <sup>3</sup> ) <b>OR</b> new $< 6$ mm total diameter ( $< 113$ mm <sup>3</sup> ) <b>Non solid nodule(s)</b> (GGN) $\geq 30$ mm ( $\geq 14137$ mm <sup>3</sup> ) on baseline CT or new	6 month LDCT	1-2%	5%
<b>Suspicious</b>  Findings for which additional diagnostic testing is recommended	4A	<b>Solid nodule(s):</b> $\geq 8$ to $< 15$ mm ( $\geq 268$ to $< 1767$ mm <sup>3</sup> ) at baseline <b>OR</b> growing $< 8$ mm ( $< 268$ mm <sup>3</sup> ) <b>OR</b> new 6 to $< 8$ mm (113 to $< 268$ mm <sup>3</sup> ) <b>Part solid nodule(s):</b> $\geq 6$ mm ( $\geq 113$ mm <sup>3</sup> ) with solid component $\geq 6$ mm to $< 8$ mm ( $\geq 113$ to $< 268$ mm <sup>3</sup> ) <b>OR</b> with a new or growing $< 4$ mm ( $< 34$ mm <sup>3</sup> ) solid component <b>Endobronchial nodule</b>	3 month LDCT; PET/CT may be used when there is a $\geq 8$ mm ( $\geq 268$ mm <sup>3</sup> ) solid component	5-15%	2%
<b>Very Suspicious</b>  Findings for which additional diagnostic testing and/or tissue sampling is recommended	4B	<b>Solid nodule(s)</b> $\geq 15$ mm ( $\geq 1767$ mm <sup>3</sup> ) <b>OR</b> new or growing, and $\geq 8$ mm ( $\geq 268$ mm <sup>3</sup> ) <b>Part solid nodule(s) with:</b> a solid component $\geq 8$ mm ( $\geq 268$ mm <sup>3</sup> ) <b>OR</b> a new or growing $\geq 4$ mm ( $\geq 34$ mm <sup>3</sup> ) solid component	Chest CT with or without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a $\geq 8$ mm ( $\geq 268$ mm <sup>3</sup> ) solid component. <i>For new large nodules that develop on an annual repeat screening CT, a 1 month LDCT may be recommended to address potentially infectious or inflammatory conditions</i>	> 15%	2%
	4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy			
<b>Other</b> Clinically Significant or Potentially Clinically Significant Findings (non lung cancer)	S	<b>Modifier - may add on to category 0-4 coding</b>	As appropriate to the specific finding	n/a	10%









# Lung RADS 1.1

- Perifissural nodule < 10 mm
  - category 2 (annual FU)
- Pure GGN
  - cutoff 20 mm → 30 mm (annual FU)
- Category 4B management for a *New* large nodule on annual repeat LDCT
  - Chest CT, PET/CT, and/or biopsy → LDCT CT FU at 1 m
- Volumetric measurement

# Lung-RADS 1.1 (baseline)

	Solid	Part-solid	GGN	cancer risk	
1					1 Y
2	 < 6	 Total < 6	 < 30	< 1%	1 Y
3	 6-8	 Total ≥ 6 Solid c. < 6	 ≥ 30	1-2%	6 M
4A	 8-15	 Solid c. 6-8		5-15%	3M or PET
4B	 ≥ 15	 Solid c. ≥ 8		> 15%	PET or Bx

# Lung-RADS 1.1 (repeat)

	Solid	Part-solid	GGN	cancer risk	
1					1 Y
2	 < 4		 ≥ 30	< 1%	1 Y
3	 4-6	 Total < 6		1-2%	6 M
4A	 < 8 (growing) 6-8 (new)	 Solid c. < 4		5-15%	3M or PET
4B	 ≥ 8	 Solid c. ≥ 4		> 15%	PET or Bx

# EU statement

Oudkerk M, et al. Lancet Oncol. 2017 Dec;18(12):e754-e766.

A round nodule of 6 mm in diameter  
= 113 mm<sup>3</sup>

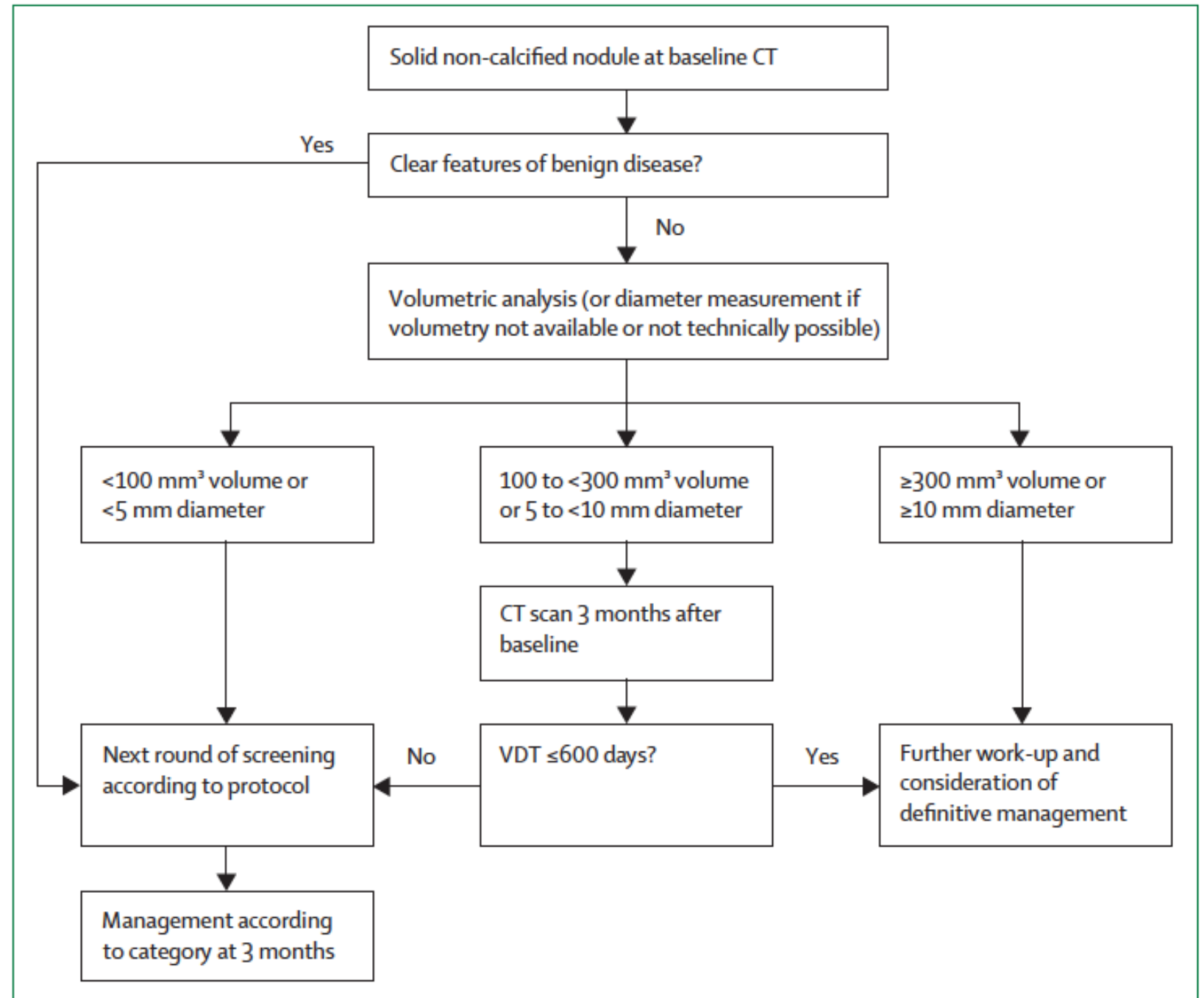
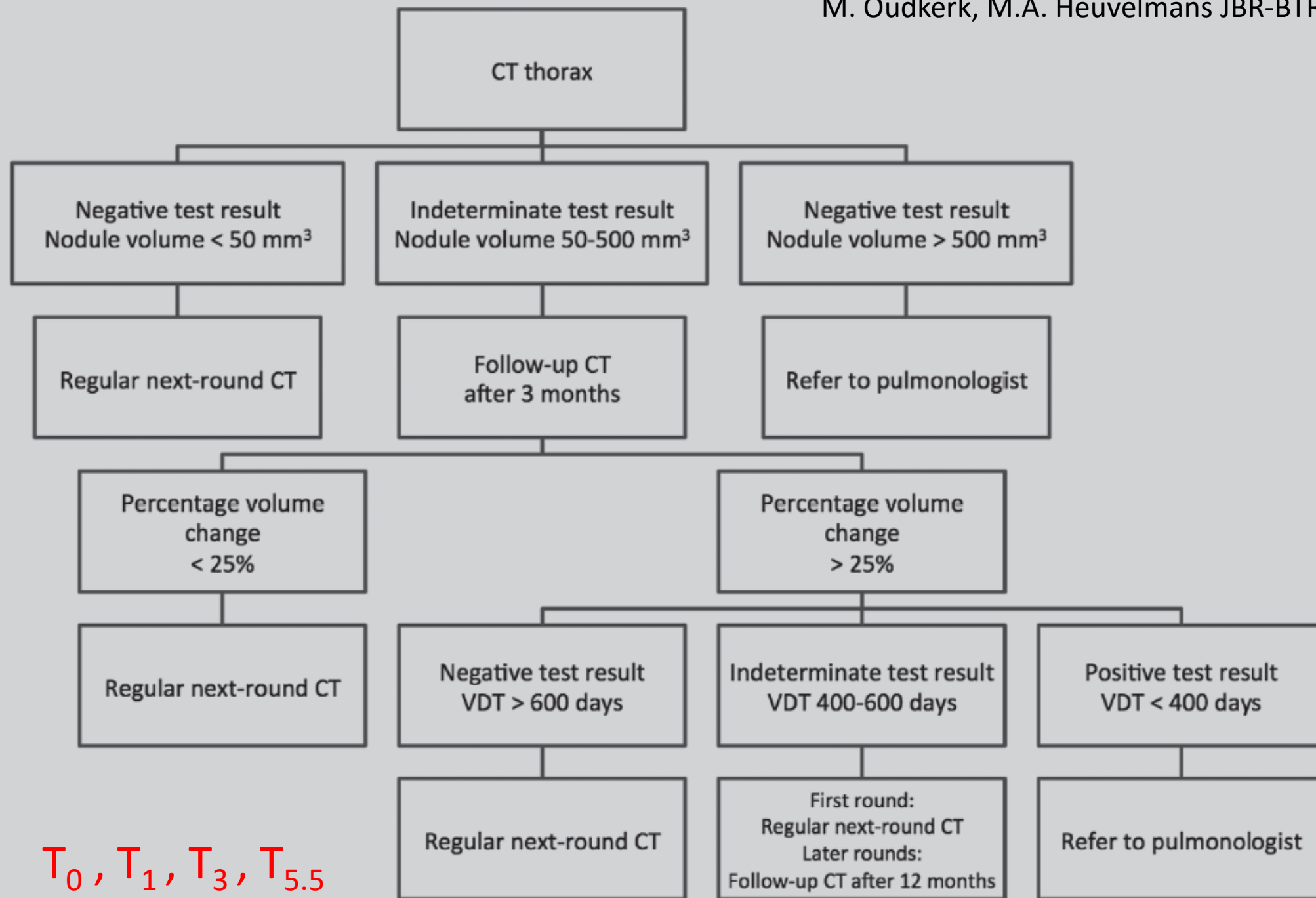


Figure 3: Nodule management protocol for screen-detected solid nodules at baseline



$T_0, T_1, T_3, T_{5.5}$

# KEY numbers for daily practice

- In an annual repeat LDCT (~400 days)
  - 25% increase of a diameter roughly equals to a double of volume  
i.e. a  $> 25\%$  increase of a nodule should warrant a diagnostic investigation
  - 15-25% increase suggests a VDT of 400-600 days, follow-up at 1 yr interval
  - $< 15\%$  increase suggests a VDT larger than 600, follow-up at 2 yr interval
- In a 3-month follow-up LDCT
  - A  $> 5\%$  increase of a diameter suggests a VDT of 400 days or less, need diagnostic work-up  
(it is far beyond the limitation of manual measurement)



# Summary

- Multidisciplinary team discussion (MTD)
- Shared decision making (SDM)
- Biomarkers other than CT images

# Conclusions

- Subjects with high risks for lung cancer should take LDCT screening. LDCT should not be offered to subjects without lung cancer risks.
- Lung cancer screening program should be undertaken at qualified institutes, with screening experience, and a multidisciplinary team.
- The best strategy for nodule management is undetermined.
  - Both CT features, size, and growth rate should be considered
  - Semi-automatically volumetric measurement is preferred
  - Trend towards to conservative management for non-solid nodules
- An urgent need for identification of the risk factors for lung cancer in never smokers; determination of the usefulness of LDCT and the best strategy for subsolid nodule management in this subjects.

Thanks for your attention