Supplementary Appendix

Persisting new nodules in incidence rounds of the NELSON CT lung cancer screening study

Table of content

Supplementary Methods

CT scan procedure

The four screening sites used 16-MDCT scanners or 64-MDCT scanners (Sensation-16, Siemens Medical Solutions, Forchheim, Germany; or Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Best, Netherlands). Datasets were derived from images of the thorax with 1.0mm slice width and a 0.7mm reconstruction interval. In the first two rounds, two independent radiologists evaluated each CT scan individually, and a third reader decided ultimately in case of discrepancy.[1,2] In the third and fourth screening round, single reading was performed. It was shown before that double reading consensus has no benefit with the use of semiautomated software.[3] CT data analysis was performed on digital workstations (Leonardo, Siemens Medical Solutions) using software for semiautomated volume measurements (LungCare, version Somaris/5 VA70C-W, Siemens Medical Solutions). Based on the three-dimensional nodule volume, this software also simulated longest and perpendicular nodule diameter in the axial plane. Radiologists were allowed to overrule protocol-based screening result (done for 195 [6%] of 3,318 participants at the baseline screening round) and manually adjust the volume measurement in case of inappropriate segmentation.[4] Manual adjustments occurred in case of high suspicion of malignancy (eg, enlarged mediastinal lymph nodes) or benignity (eg, benign calcification patterns)[4]. Individual matching of nodules on subsequent LDCT scans was based on the software's matching algorithm (depending on consistency, size and location) and the radiologist's visual confirmation of the matching. Data generated during CT evaluation were uploaded to the NELSON management system.[1]

Volume Doubling Time

$$VDT(days) = \frac{[ln2 \times \Delta t]}{[ln(V2/V1)]}$$

in which Δt represents the time between scans in days, V1 represents the volume of the new solid nodule at initial new nodule detection, and V2 represents the volume of the new solid nodule at first-follow up scan.

Calculations on Participant-level

Based on the fastest growing nodule or largest nodule respectively, receiver operating characteristic analysis showed an area under the curve for the volume doubling time (VDT) of 0.901 (95% confidence interval [95% CI]: 0.846, 0.956, P<0.0001) and for nodule volume of 0.849 (95% confidence interval [95% CI]: 0.790, 0.908, P<0.0001). The identified cutoffs correspond to those found in the nodule-based analysis and the lung cancer probabilities as well as the cutoff performance are shown in Supplementary Table 3 and 4.

Supplementary Figures

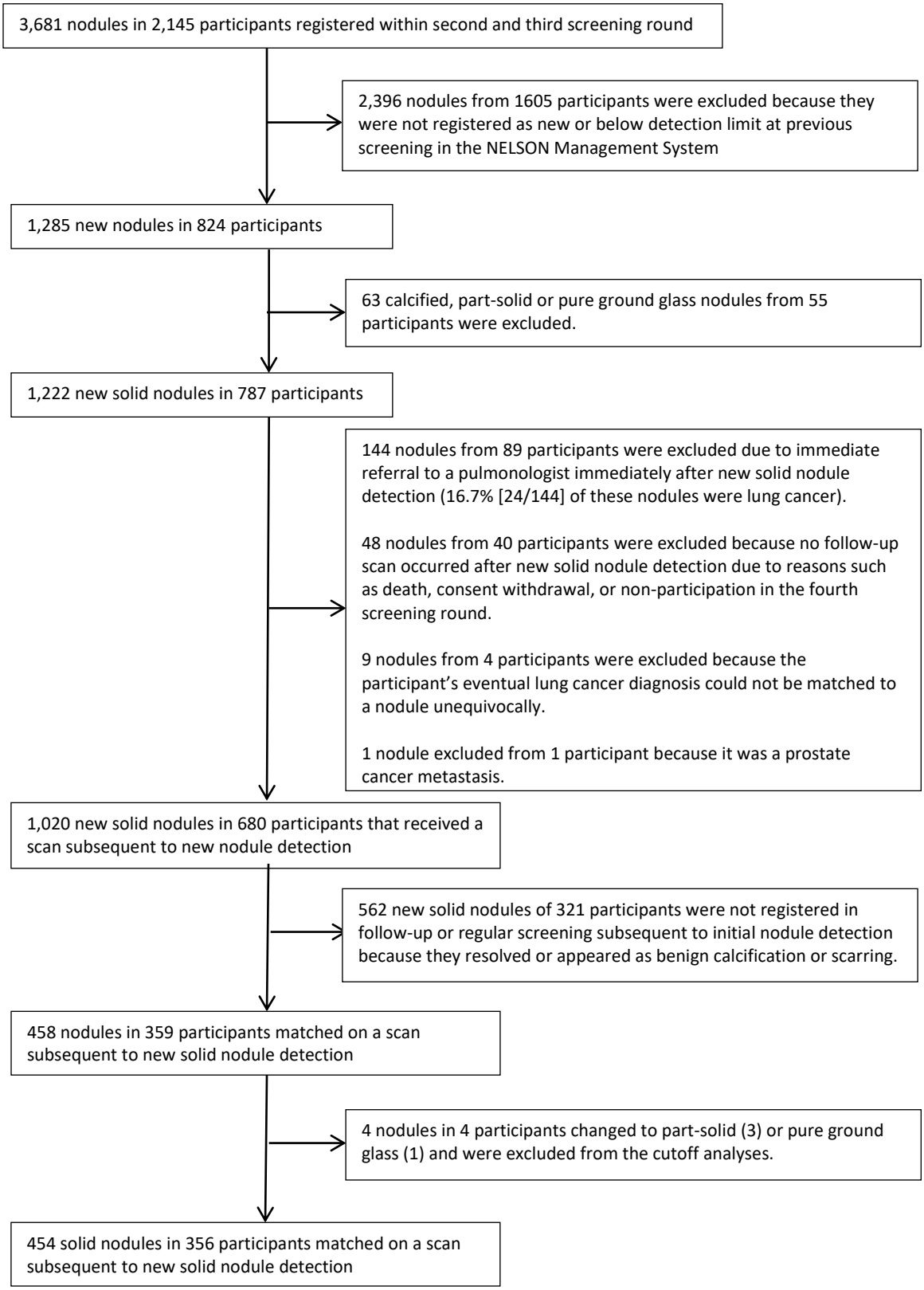

Figure S1: Flowchart of new solid nodules detected within second and third screening round
Some participants had a new nodule and, for example, a previously missed nodule. Whereas the missed nodule was excluded, the new nodule (and therefore the participant) was included.

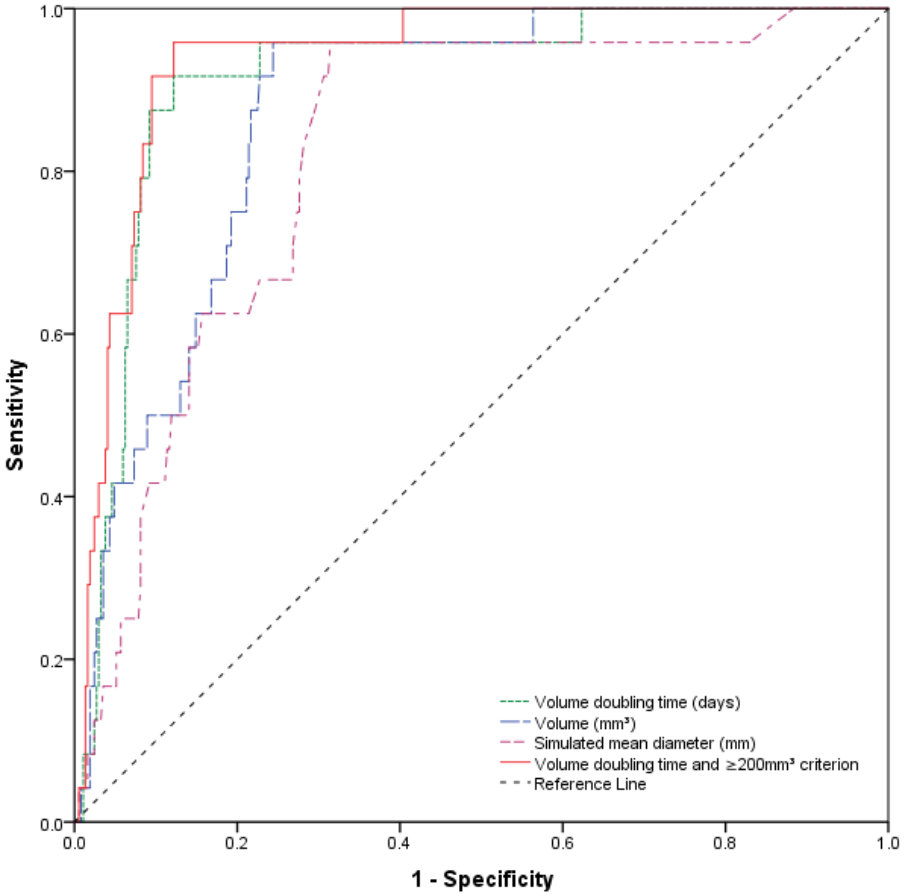

Figure S2: Receiver operating characteristic curves* of volume doubling time, nodule volume, simulated mean diameter and the combination of volume doubling time and ≥200mm^3 at first follow-up or regular screening after initial detection for discrimination of lung cancer. Volume doubling time (AUC: 0.915, 95%CI 0.862-0.967, P<0.0001); Volume (AUC: 0.871, 95%CI 0.818-0.925, P<0.0001); Simulated mean diameter (AUC: 0.822, 95%CI 0.748-0.897, P<0.0001); Volume doubling time and ≥200mm^3 criterion (AUC: 0.939, 95%CI 0.903-0.975, P<0.0001). AUC=area under the curve.

* Exact volume measurement or simulated mean diameter was not available for 60 benign nodules and one lung cancer, and they were not included in the calculations. Diameters were simulated from computer generated volume measurements, based on three-dimensional voxels.

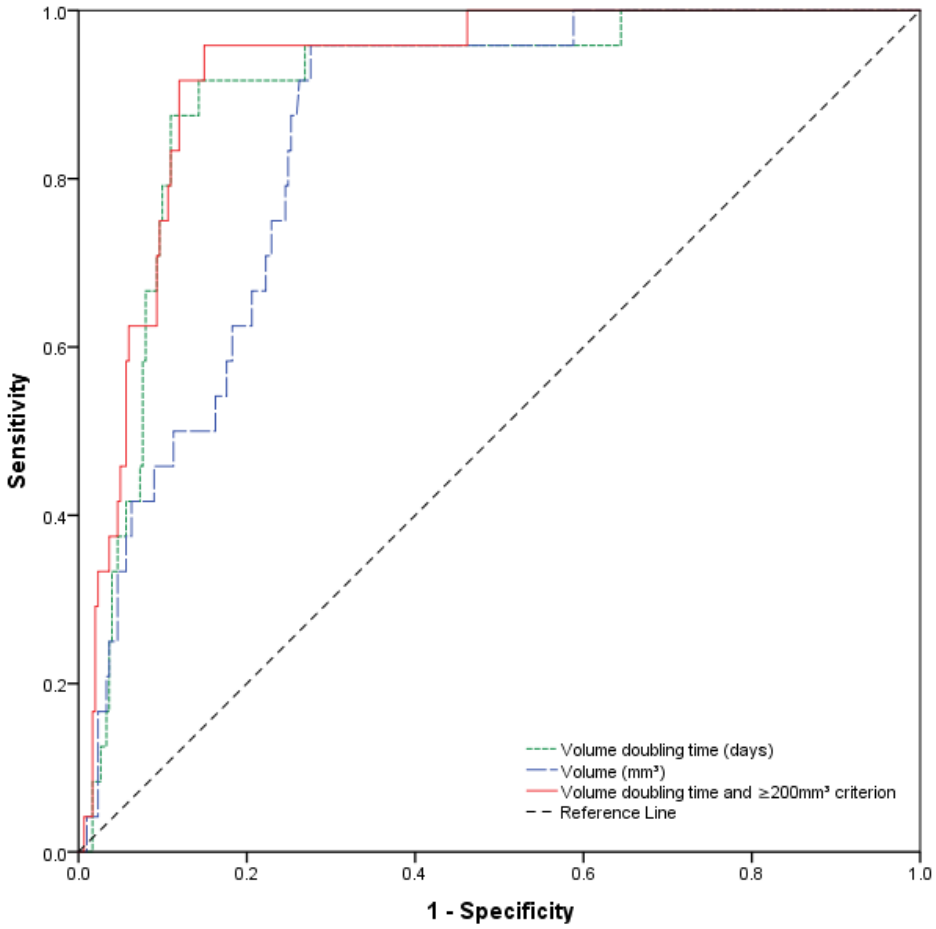

Figure S3: Participant level: Receiver operating characteristic curves* of fastest volume doubling time, largest nodule volume, and the combination of fastest volume doubling time and ≥200mm^3 largest nodule volume criterion at first follow-up or regular screening after initial detection for discrimination of lung cancer. Volume doubling time (AUC: 0.901, 95%CI 0.846-0.956, P<0.0001); Volume (AUC: 0.849, 95%CI 0.790-0.908, P<0.0001); Volume doubling time and ≥200mm^3 (AUC: 0.923, 95%CI 0.881-0.965, P<0.0001). AUC=area under the curve.

* Exact volume measurement was not available for 34 benign nodules and one cancer, and they were not included in the calculations.

Supplementary Tables

Table S1: Characteristics of included participants with at least one new solid nodule during second or third screening round and subsequent follow-up or regular screening (n=680)

		At least one new nodule persisted at follow-up		
	Overall Population, n=680 (100%)	**Yes, n=359[*] (52.8%)**	**No, n=321 (47.2%)**	**P-Value**
Sex				0.246
Female	166/680 (24.4)	81/359 (22.6)	84/321 (26.3)	
Male	514/680 (75.6)	278/359 (77.4)	236/321 (73.8)	
Age (years)				
50 - 54	158/680 (23.2)	87/359 (24.2)	71/321 (22.1)	
55 - 59	209/680 (30.7)	111/359 (30.9)	98/321 (30.5)	
60 - 64	185/680 (27.2)	92/359 (25.6)	93/321 (29.0)	
65 - 69	91/680 (13.4)	47/359 (13.1)	44/321 (13.7)	
≥70	37/680 (5.4)	22/359 (6.1)	15/321 (4.7)	
Median (IQR)	59 (55-63)	59 (55-63)	59 (55-63)	0.811
Smoking pack-years[‡]				
<20	2/679 (0.3)	1/358 (0.3)	1/321 (0.3)	
20 - 39	380/679 (56.0)	208/358 (57.9)	172/321 (53.6)	
40 - 59	208/678 (30.6)	102/358 (28.5)	106/321 (33.0)	
60 - 79	57/679 (8.4)	28/358 (7.8)	29/321 (9.0)	
≥80	32/679 (4.7)	19/358 (5.3)	13/321 (4.0)	
Median (IQR)	39 (30-49)	39 (30-49)	39 (30-49)	0.482

Abbreviations: IQR - Interquartile range.

[*] In four participants a benign new solid nodule changed to part-solid (n=3) or pure ground-glass nodules (n=1) at follow-up. In three participants the respective nodule was the only new solid nodule detected.

[‡] Pack-Year information was missing for one participant.

Table S2: New solid nodules at initial detection stratified by volume (N=1020; 995 benign nodules and 25 lung cancer nodules)

	All new solid nodules, n=1020 (100%)	**New solid not visible in retrospect, n=788 (77%)**	**New solid nodules below the trial's detection limit in retrospect, n=232 (33%)**
<50mm^3			
All nodules	618/1020 (61%)	394/788 (50%)	224/232 (97%)
% Lung cancer	9/618 (2%)	6/394 (2%)	3/224 (1%)
Nonresolving nodules	284/618 (46%)	108/394 (27%)	176/224 (79%)
% Lung cancers	9/284 (3%)	6/108 (6%)	3/176 (2%)
50-<500mm^3			
All nodules	361/1020 (35%)	354/788 (45%)	7/232 (3%)
% Lung cancer	16/361 (4%)	15/354 (4%)	1/7 (14%)
Nonresolving nodules	158/361 (44%)	153/354 (43%)	5/7 (71%)
% Lung cancers	16/158 (10%)	15/153 (10%)	1/5 (20%)
≥500mm^3			
All nodules	38/1020 (4%)	37/788 (5%)	1/232(<1%)
% Lung cancer	0/38 (0%)	0/37 (0%)	0/1 (0%)
Nonresolving nodules	15/38 (34%)	14/37 (38%)	1/1 (100)
% Lung cancers	0/15 (0%)	0/37 (0%)	0/1 (0%)

Table S3: Characteristics of included participants with at least one new solid nodule during second or third screening round that persisted as solid nodule after initial detection.*

	Overall Population, n=356 (100%)	Lung Cancer		P-Value
		Yes, n=25 (7.0%)	No, n=331 (93.0%)	
Sex				0.999
Female	80/356 (22.5)	5/25 (20.0)	75/331 (22.7)	
Male	276/356 (77.5)	20/25 (80.0)	256/331 (77.3)	
Age (years)				
50 - 54	87/356 (24.2)	7/25 (28.0)	79/331 (23.9)	
55 - 59	110/356 (30.9)	5/25 (20.0)	105/331 (31.7)	
60 - 64	92/356 (25.8)	5/25 (20.0)	87/331 (26.3)	
65 - 69	46/356 (12.9)	6/25 (24.4)	40/331 (12.1)	
≥70	22/356 (6.2)	2/25 (8.0)	20/331 (6.0)	
Median (IQR)	59 (55-63)	60 (54-65)	58 (55-63)	0.393
Smoking pack-years†				
<20	1/355 (0.3)	0	1/330 (0.3)	
20 - 39	208/355 (58.4)	12/25 (48.0)	196/330 (59.4)	
40 - 59	101/355 (28.4)	9/25 (36.0)	92/330 (27.9)	
60 - 79	27/355 (7.6)	3/25 (12.0)	24/330 (7.3)	
≥80	18/355 (5.1)	1/25 (4.0)	17/330 (5.2)	
Median (IQR)	39 (30-49)	44 (30-55)	38 (30-49)	0.350

Abbreviations: IQR - Interquartile range.

* In three (<1% [3/359]) of the participants the new nodule did not persist as solid nodule and they were excluded from the calculations.
† Pack-Year information was missing for one participant.

Table S4: Histology and staging of the 25 lung cancers

	Adenocarcinoma, 16/25 (64%)	Large cell carcinoma, 3/25 (12%)	Squamous cell carcinoma, 2/25 (8%)	Others*, 4/25 (16%)
Stage				
I	15 (94%)	2 (67%)	2 (100%)	4 (100%)
III	1 (6%)	1 (33%)	0	0

***** Others included one large cell neuro-endocrine carcinoma, one non-small-cell lung carcinoma not otherwise specified, and two lung cancers where the histological diagnosis could not be established.

Table S5: Performance of predefined VDT cutoffs at first follow-up or regular screening after initial detection (N=437; 412 benign nodules and 25 lung cancer nodules)

	All new solid nodules that persisted on the first LDCT after detection	Subsequent LDCT within 120 days	Subsequent LDCT after 120 days
Lung cancer probability			
VDT >600 days (95% CI)	2/361, 0.6% (0-2.1)	2/139, 1.4% (0.1-5.4)	0/222, 0 % (0-2.0)
VDT 400-600 days (95% CI)	1/12, 8.3% (0-37.5)	0/3, 0% (0-61.7)	1/9, 11.1% (0-45.7)
VDT <400 days (95% CI)	22/64, 34.4% (23.9-46.6)	15/53, 28.3% (17.9-41.7)	7/11, 63.6% (35.2-85.0)
VDT <400 days			
Sensitivity (95% CI)	22/25, 88.0% (69.2-96.7)	15/17, 88.2% (64.4-98.0)	7/8, 87.5% (50.8-99.9)
Specificity (95% CI)	370/412, 89.8% (86.5-92.4)	140/178, 78.7% (72.0-84.1)	230/234, 98.3% (95.5-99.5)
PPV (95% CI)	22/64, 34.4% (23.9-46.6)	15/53, 28.3% (17.9-41.7)	7/11, 63.6% (35.2-85.0)
NPV (95% CI)	370/373, 99.2% (97.5-99.8)	140/142, 98.6% (94.7-99.9)	230/231, 100% (97.3-100)
VDT <600 days			
Sensitivity (95% CI)	23/25, 92.0% (73.9-98.9)	15/17, 88.2% (64.4-98.0)	8/8, 100% (62.8-100)
Specificity (95% CI)	359/412, 87.1 % (83.5-90.0)	137/178, 77.0% (70.2-82.6)	222/234, 94.9% (91.7-97.4)
PPV (95% CI)	23/76, 30.3% (21.0-41.4)	15/56, 26.8% (17.5-41.0)	8/20, 40.0% (21.8-61.4)
NPV (95% CI)	359/361, 99.4% (97.9-100)	137/139, 98.6% (94.6-99.9)	222/222, 100% (98.0-100)
VDT ≤590 days or volume ≥200mm^3			
Sensitivity (95% CI)	25/25, 100.0% (84.2-100)	17/17, 100.0% (78.4-100)	8/8, 100% (62.8-100)
Specificity (95% CI)	345/412, 83.7% (79.9-87.0)	124/178, 69.7% (62.5-76.0)	221/234, 94.4% (90.6-96.8)
PPV (95% CI)	25/92, 27.2% (19.1-37.1)	17/71, 24.6% (15.9-36.0)	8/21, 38.1% (20.7-59.2)
NPV (95% CI)	345/345, 100.0% (98.7-100)	124/124, 100.0% (96.4-100)	221/221, 100.0% (97.9-100)

Abbreviations: IQR - Interquartile range, LDCT – Low-dose computed tomography, NPV - Negative predictive value, PPV - Positive predictive value, VDT - Volume doubling time.
Exact volume measurement was not available or classification based on radiologist's size categorization was unattainable for 17 benign nodules, and they were not included in the calculations.

Table S6: Performance of identified cutoffs for new solid nodules stratified by their visibility in retrospect (N=437; 412 benign nodules and 25 lung cancer nodules)

	New solid nodules at initial detection not visible in retrospect	New solid nodules at initial detection visible in retrospect as minuscule nodule below the trial's detection limit
VDT ≤590 days		
Sensitivity (95% CI)	19/21, 90.5 (69.9-98.6)	4/4, 100% (44.4-100)
Specificity (95% CI)	191/236, 80.9% (75.4-85.5)	169/176, 96.0% (91.9-98.2)
PPV (95% CI)	19/64, 29.7% (19.8-41.8)	4/11, 36.4% (15.0-64.8)
NPV (95% CI)	191/193, 99.0% (96.1-100)	169/169, 100% (97.3-100)
VDT ≤590 days or volume ≥200mm^3		
Sensitivity (95% CI)	21/21, 100% (81.8-100)	4/4, 100% (44.4-100)
Specificity (95% CI)	174/232, 74.6% (68.6-79.7)	169/176, 96.0% (91.9-98.2)
PPV (95% CI)	21/79, 25.9% (17.6-36.5)	4/11, 36.4% (15.0-64.8)
NPV (95% CI)	176/176, 100.0% (97.4-100)	169/169, 100% (97.3-100)
Volume ≥65mm^3		
Sensitivity (95% CI)	21/21, 100% (81.8-100)	3/4, 75% (28.9-96.6)
Specificity (95% CI)	141/236, 59.7% (53.4-65.8)	172/176, 97.7% (94.1-99.3)
PPV (95% CI)	21/116, 18.1% (12.1-26.2)	3/7, 42.9% (15.8-75.0)
NPV (95% CI)	141/141, 100% (96.8-100)	172/173, 99.4% (96.5-100)

Abbreviations: IQR - Interquartile range, NPV - Negative predictive value, PPV - Positive predictive value, VDT - Volume doubling time.
Exact volume measurement or simulated mean diameter was not available and classification based on the radiologist's size categorization was unattainable for 17 benign nodules, and they were not included in the calculations.

Table S7: Performance of identified cutoffs at first follow-up or regular screening after initial detection for nodules with simulated mean diameter classification available (N=432; 407 benign nodules and 25 lung cancer nodules)

	All new solid nodules that persisted on the first LDCT after detection	Subsequent LDCT within 120 days	Subsequent LDCT after 120 days
VDT ≤590 days			
Sensitivity (95% CI)	23/25, 92.0% (73.9-98.9)	15/17, 88.2% (64.4-98.0)	8/8, 100% (62.8-100)
Specificity (95% CI)	357/407, 87.7% (84.1-90.6)	135/174, 77.6% (70.8-83.2)	222/233, 95.3% (91.7 -97.4)
PPV (95% CI)	23/73, 31.5% (22.0-42.9)	15/54, 27.8% (17.5-41.0)	8/19, 42.1% (23.1-63.8)
NPV (95% CI)	357/359, 99.4% (97.9-100)	135/137, 98.5% (94.5-99.9)	222/222, 100% (98.0-100)
VDT ≤590 days or volume ≥200mm^3			
Sensitivity (95% CI)	25/25, 100.0% (84.2-100)	17/17, 100.0% (78.4-100)	8/8, 100% (62.8-100)
Specificity (95% CI)	342/407, 84.0% (80.1-87.3)	122/174, 70.1% (62.9-76.4)	220/233, 94.4% (90.6-96.8)
PPV (95% CI)	25/75, 27.8% (19.5-37.8)	17/69, 24.6% (15.9-36.0)	8/21, 38.1% (20.7-59.2)
NPV (95% CI)	342/342, 100.0% (98.7-100)	122/122, 100.0% (96.3-100)	220/220, 100.0% (97.9-100)
Volume ≥65mm^3			
Sensitivity (95% CI)	24/25, 96.0% (78.9-100)	16/17, 94.1% (71.1-100)	8/8, 100% (62.8-100)
Specificity (95% CI)	311/407, 76.4% (72.0-80.3)	93/174, 53.4% (46.0-60.7)	218/233, 93.6% (89.6-96.1)
PPV (95% CI)	24/120, 20.0% (13.8-28.1)	16/97, 16.5% (10.3-25.2)	8/23, 34.8% (18.7-55.2)
NPV (95% CI)	311/312, 99.7% (98.0-100)	93/94, 98.9% (93.6-100)	218/218, 100% (97.9-100)
Simulated mean diameter ≥5mm			
Sensitivity (95% CI)	24/25, 96.0% (78.9-100)	16/17, 94.1% (71.1-100)	8/8, 100% (62.8-100)
Specificity (95% CI)	284/407, 69.8% (65.1-74.0)	76/174, 43.7% (36.5-51.1)	208/233, 89.3% (84.6-92.7)
PPV (95% CI)	24/147, 16.3% (11.2-23.2)	16/114, 14.0% (8.7-21.7)	8/33, 24.2% (12.6-41.3)
NPV (95% CI)	284/285, 99.6% (97.8-100)	76/77, 98.7% (92.3-100)	208/208, 100% (97.8-100)

Abbreviations: IQR - Interquartile range, LDCT – Low-dose computed tomography, NPV - Negative predictive value, PPV - Positive predictive value, VDT - Volume doubling time.
Exact volume measurement or simulated mean diameter was not available and classification based on the radiologist's size categorization was unattainable for 22 benign nodules, and they were not included in the calculations.

Table S8: Lung cancer probability for participants with at least one persisting new solid nodule stratified by volume doubling time and volume at of the largest or fastest-growing new solid nodule at first follow-up of regular screening after initial detection

	Participants with lung cancer/participants meeting criterion	Lung cancer probability (95% CI)
VDT		
>590 days	2/269	0.7% (0.0-2.8)
≤590 days	23/71	32.4% (22.6-44.0)
Volume		
<65mm^3	1/228	0.4% (0.0-2.7)
≥65mm^3	24/112	24/112, 21.4% (14.8-30.0)
VDT and volume		
>590 days and <200mm^3	0/253	0.0% (0.0-1.8)
≤590 days or ≥200mm^3	25/91	27.5% (19.3-37.5)

Abbreviations: CI - Confidence interval, IQR - Interquartile range, VDT - Volume doubling time.
In 14 participants without lung cancer insufficient nodule size data led to their exclusion from the analysis.

Table S9: Performance of identified cutoffs in participants based on the largest or fastest-growing new solid nodule at first follow-up or regular screening after initial detection

	All new solid nodules that persisted on the first LDCT after detection
VDT ≤590 days	
Sensitivity (95% CI)	23/25, 92.0% (73.9-98.9)
Specificity (95% CI)	267/315, 84.8% (80.4-88.3)
PPV (95% CI)	23/71, 32.4% (22.6-44.0)
NPV (95% CI)	267/269, 99.3% (97.2-100)
VDT ≤590 days or volume ≥200mm^3	
Sensitivity (95% CI)	25/25, 100.0% (84.2-100)
Specificity (95% CI)	253/315, 80.3% (75.6-84.3)
PPV (95% CI)	25/87, 28.7% (20.2-39.0)
NPV (95% CI)	253/253, 100.0% (98.2 -100)
Volume ≥65mm^3	
Sensitivity (95% CI)	24/25, 96.0% (78.9-100)
Specificity (95% CI)	227/315, 72.1% (66.9-76.7)
PPV (95% CI)	24/112, 21.4% (14.8-30.0)
NPV (95% CI)	313/314, 99.6% (97.4-100)

Abbreviations: IQR - Interquartile range, LDCT – Low-dose computed tomography, NPV - Negative predictive value, PPV - Positive predictive value, VDT - Volume doubling time.
In 14 participants without lung cancer insufficient nodule size data led to their exclusion from the analysis.

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