

## Supplementary Methods

### *Nodule management protocol*

According to the protocol of the LUSI, participants with nodules newly-detected by means of LDCT, independently of the screening round, were assigned to groups according to the nodule's largest diameter: (I) no observed nodules or all observed nodules less than 5 mm, (II) 5–7 mm, (III) 8–<10 mm and (IV) 10 mm or larger. Depending on the group to which the participants were assigned, they were: (I) sent back to annual screening, invited for a follow-up LDCT-screen after (II) 6 or (III) 3 months, or (IV) sent to diagnostic work-up immediately. In further rounds (2–5), management of previously observed nodules was based on nodule growth: (I) no growth or volume doubling time (VDT) more than 600 days (back to annual screening), (II) VDT within 400–600 days (LDCT after 6 months) or (III) VDT 400 days or less (immediate confirmatory diagnostic work-up). Immediate work-up was done by a cooperating pulmonologist, who decided whether further diagnostic procedures [X-ray, CT, PET, bronchoscopy, video-assisted thoracoscopic surgery (VATS) or biopsy] or treatment (antibiotics, short-term follow-up) were to be indicated.

### *Conversion of the education level categories between the German and US systems for the LCRAT+CT model.*

The categories of the variable “highest education level” defined for the LCRAT+CT model according to the US education system were linked to the available categories from the LUSI questionnaires, which were created according to the German education system, according to the following table (*Table S1*):

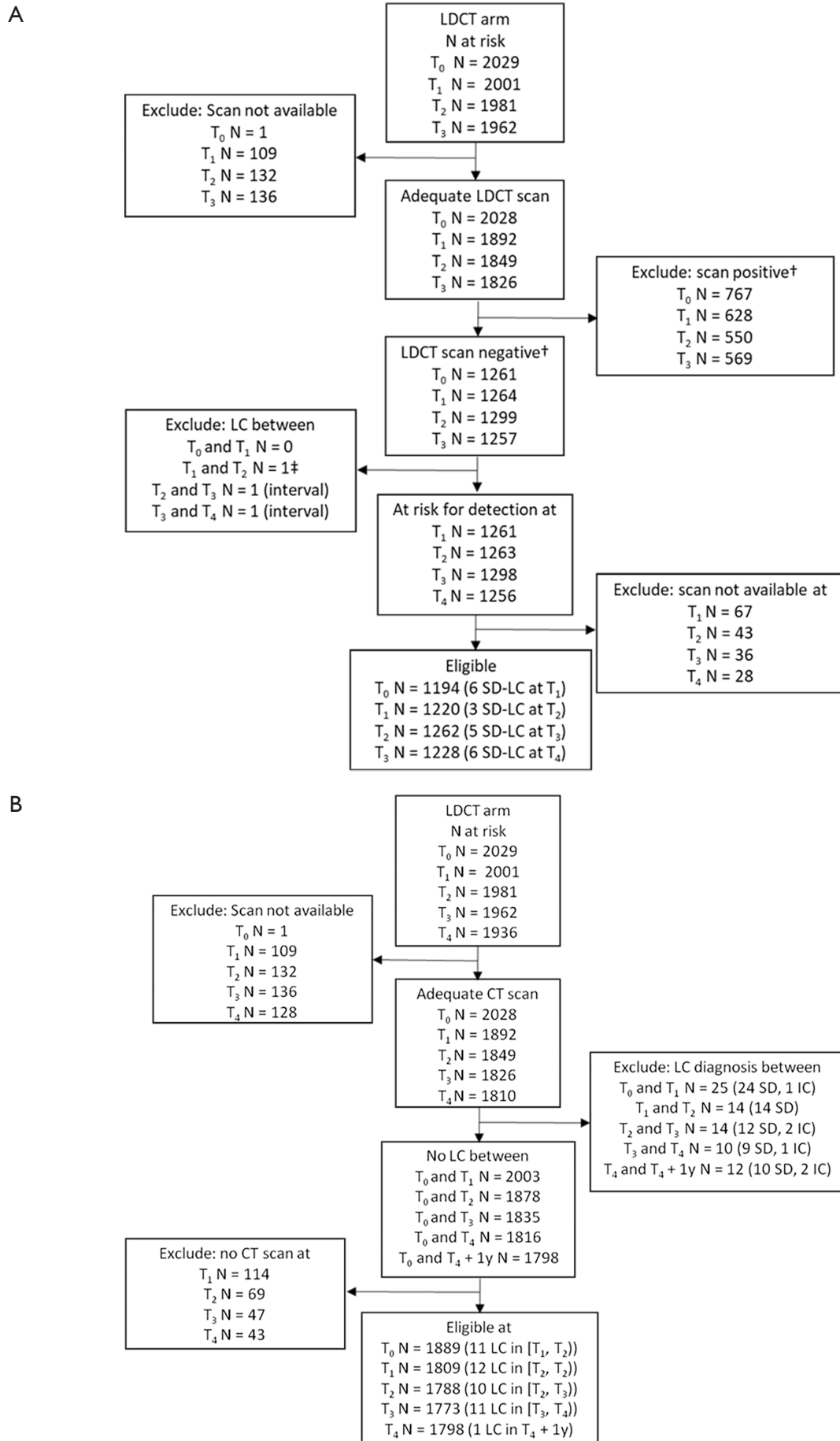
**Table S1** Conversion between German and US education level categories

US Education System	German Education System
1≤12 grade	kein Schulabschluss (no school certificate) Volksschulabschluss/Hauptschulabschluss (Certificate of Secondary Education) Mittlere Reife/Realschulabschluss (General Certificate of Secondary Education) keine berufliche Ausbildung und nicht in beruflicher Ausbildung (no vocational training and not currently in vocational training)
2=High school graduate	Noch in Ausbildung (Auszubildender, Student) (in vocational training, student)
3=Post high school, no college	Fachhochschulreife/Fachoberschulabschluss (high school diploma) Allgemeine Hochschulreife/Abitur (high school diploma/academic diploma) Lehre (kaufmännisch) [vocational training (commercial)] Lehre (gewerblich, technisch, landwirtschaftlich) [vocational training (industrial, technical, agricultural)]
4=Associate degree/some college	Berufsfach-/Handelsschulabschluss (technical school diploma) Fach-/Meister-/Technikerschule, Berufs-/Fachakademie (technical college/ university of cooperative education)
5=Bachelors degree	Bakkalaureus (bachelors degree)
6=Graduate school	Fachhochschule (Ingenieurschule) (university of applied sciences) Universität, Hochschule (university, college)

**Table S2** Nodule management protocol

Newly observed nodules (first screening round or new in subsequent rounds)		Known nodules (early recalls or subsequent screening rounds)	
Outcome by nodule size	Action	Outcome by nodule growth	Action
without abnormality or nodules <5 mm	back to routine screening (12 months)	–	–
nodules $\geq 5$ and <8 mm	early recall (6 months)	>600 VDT	back to routine screening
		400–600 VDT D <7.5 mm	early recall (6 months)
Nodules $\geq 8$ and $\leq 10$ mm	Early recall (3 months)	D $\geq 7.5$ –10 mm	Early recall (3 months)
Nodules >10 mm/Not highly suspicious		$\leq 400$ VDT or D >10 mm	Immediate recall
Highly suspicious	Immediate recall	Malignant	Treatment
		Non-malignant	Back to routine screening

mm: millimeters, VDT: volume doubling time; D: diameter.



**Figure S1** Participant selection flow charts for the validation of the selected models: (A) LCRAT + CT model, (B) Polynomial model. †NLSST criteria positive: at least one non-calcified nodule  $\geq 4$  mm in longest diameter; negative: absence of non-calcified nodules  $\geq 4$  mm in longest diameter. ‡The participant was excluded because of a lung cancer diagnosis based on additional findings in the absence of non-calcified nodules on LDCT scan images. LDCT: low-dose computed tomography; LC: lung cancer; SD: screen-detected; IC: interval cancer; y: year.

**Table S3** Coefficients of the LCRAT, LCRAT+CT and Polynomial models

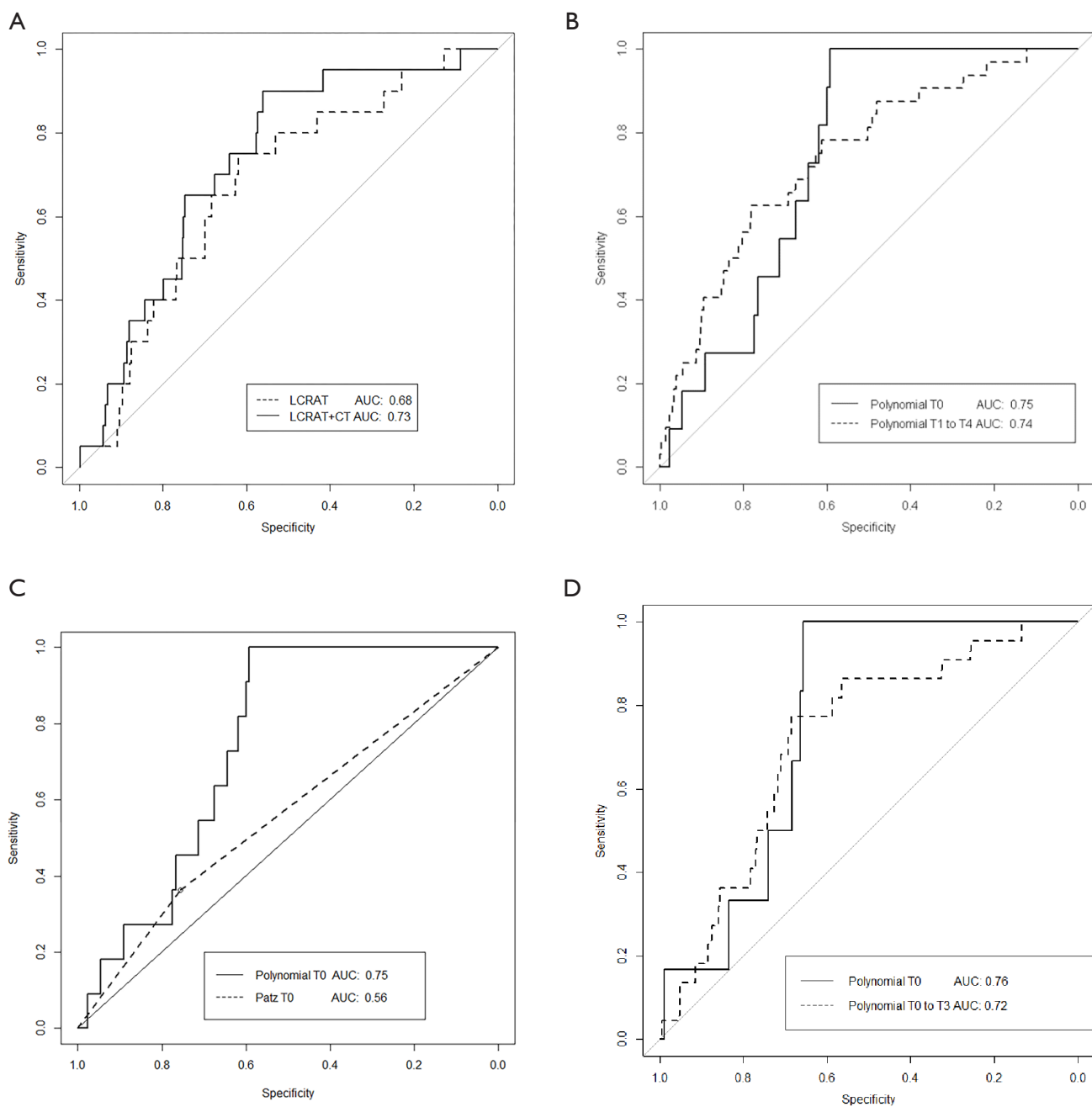
LCRAT		Polynomial model	
Predictor variable	$\beta$ coefficient	Predictor variable	$\beta$ coefficient
Sex (female)	-0.08057	Model constant	-28.15
Race (black/African-American)	0.217892	Age (y)	0.5845
Race (Hispanic)	-0.43413	Age <sup>2</sup> (y <sup>2</sup> )	-0.004026
Race (other ethnicity)	-0.39556	Prior diagnosis of cancer	0.5555
Education (trend)	-0.07143	Smoking status (active)	0.5046
Number of parents with lung cancer	0.4183	Pack-years (y)	0.03922
Lung disease (COPD or emphysema)	0.563422	Pack-years <sup>2</sup> (y <sup>2</sup> )	-0.0001632
BMI ( $\leq 18.5$ )	0.060925	Prior diagnosis of COPD	0.4144
CPD ( $>20$ )	0.310609	Longest perpendicular diameter (mm)	0.09962
Pack years [30, 40)	0.491254	Longest perpendicular diameter <sup>2</sup> (mm <sup>2</sup> )	-0.0006524
Pack years [40, 50)	0.562334	Presence of non-solid nodule	0.4217
Pack years ( $\geq 50$ )	0.715752	Presence of part solid nodule	0.9108
log(age)	4.386866	Presence of nodule in upper lobe	0.4685
log(BMI)	-0.72386	Presence of spiculated nodule	0.7512
log(years quit +1)	-0.3209	Nodule count per scan (per additional nodule)	0.5128
Years smoked	0.024002	Nodule count per scan <sup>2</sup> (per additional nodule <sup>2</sup> )	-0.1947
LCRAT + CT			
Predictor variable	Exponent		
Neither emphysema nor consolidation	1.08		
Emphysema	0.96		
Consolidation	0.77		

LCRAT: Lung Cancer Risk Assessment Tool; y: years; COPD: Chronic obstructive pulmonary disease; BMI: body mass index; CPD: cigarettes per day.

**Table S4** Baseline characteristics of eligible participants and their pulmonary nodules.

	Participants eligible for the LCRAT+CT model				Participants eligible for the Polynomial model			
	No Lung cancer	LC cancer in any round <sup>†</sup>	P	Total	No Lung cancer	Lung cancer at T <sub>1</sub> <sup>‡</sup>	P	Total
N	1482	24		1506	1878	11		1889
Sex (M/F)	942/540 (63.6/36.4)	18/6 (75.0/25.0)	0.346	960/546 (63.7/36.3)	1229/649 (65.4/34.6)	9/2 (81.8/18.2)	0.411	1238/651 (65.5/34.5)
Age [median, range]	56.70 [50.30, 71.80]	60.20 [54.60, 70.00]	<0.001	56.80 [50.30, 71.80]	56.80 [50.30, 71.90]	60.20 [54.60, 69.40]	0.013	56.80 [50.30, 71.90]
BMI (mean, (SD))	26.94 (4.20)	25.73 (3.69)	0.163	26.92 (4.19)	26.91 (4.14)	25.95 (3.28)	0.444	26.90 (4.14)
COPD or emphysema (no/yes)	1465/17 (98.9/1.1)	23/1 (95.8/4.2)	0.687	1488/18 (98.8/1.2)	1636/242 (87.1/12.9)	8/3 (72.7/27.3)	0.334	1644/245 (87.0/13.0)
Asbestos exposure (no/yes)	1390/92(93.8/6.2)	23/1 (95.8/4.2)	-	1413/93 (93.8/6.2)	1819/59 (96.9/3.1)	11 (100.0/0.0)	1.000	1830/59 (96.9/3.1)
Education			0.989				0.916	
< 12 grade	119 (8.0)	2 (8.3)		121 (8.0)	146 (7.8)	1 (9.1)		147 (7.8)
High school graduate	1 (0.1)	0 (0.0)		1 (0.1)	2 (0.1)	0 (0.0)		2 (0.1)
Post high school, no college	795 (53.6)	14 (58.3)		809 (53.7)	1014 (54.0)	7 (63.6)		1021 (54.0)
Associate degree/some college	305 (20.6)	4 (16.7)		309 (20.5)	392 (20.9)	1 (9.1)		393 (20.8)
Graduate school	262 (17.7)	4 (16.7)		266 (17.7)	324 (17.3)	2 (18.2)		326 (17.3)
Emphysema in scan (no/yes)	943/539 (63.6/36.4)	11/13 (45.8/54.2)	0.114	954/552 (63.3/36.7)	1159/719 (61.7/38.3)	5/6 (45.5/54.5)	0.427	1164/725 (61.6/38.4)
Consolidation in scan (no/yes)	1475/7 (99.5/0.5)	24/0 (100.0/0.0)	1.000	1499/7 (99.5/0.5)	1867/11 (99.4/0.6)	11/0 (100.0/0.0)	1.000	1878/11 (99.4/0.6)
Former smokers	574	6		580	714	3		717
Years of smoking [mean (SD)]	18.27 (4.37)	20.00 (2.74)	0.333	18.28 (4.36)	18.34 (4.40)	19.17 (2.89)	0.745	18.34 (4.39)
Years since quitting [mean (SD)]	4.90 (2.76)	4.33 (2.70)	0.620	4.89 (2.76)	4.85 (2.76)	5.50 (3.46)	0.684	4.85 (2.76)
Cigarettes per day [mean (SD)]	26.24 (12.13)	27.50 (17.32)	0.801	26.25 (12.17)	26.60 (12.29)	30.83 (7.64)	0.552	26.62 (12.27)
Pack-years [mean (SD)]	24.00 (13.07)	28.33 (20.81)	0.423	24.05 (13.15)	24.41 (13.14)	28.85 (3.77)	0.559	24.43 (13.11)
Current smokers	908	18		926	1164	8		1172
Years of smoking [mean (SD)]	34.87 (4.89)	37.50 (5.94)	0.025	34.92 (4.92)	35.03 (4.91)	38.75 (3.54)	0.033	35.05 (4.91)
Years since quitting [mean (SD)]	0.00 (0.00)	0.00 (0.00)	-	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	-	0.00 (0.00)
Cigarettes per day [mean (SD)]	20.40 (8.42)	21.94 (12.11)	0.444	20.43 (8.50)	20.55 (8.60)	25.62 (13.35)	0.098	20.59 (8.64)
Pack-years [mean (SD)]	35.85 (16.02)	41.56 (27.02)	0.141	35.96 (16.30)	36.24 (16.39)	50.55 (29.97)	0.015	36.34 (16.54)
With at least one NCN					895	6		901
Longest diameter [mean (SD)]					5.75 (3.62)	6.15 (2.40)	0.788	5.75 (3.62)
Perpendicular diameter [mean (SD)]					3.85 (1.75)	4.47 (1.53)	0.386	3.85 (1.74)
In upper lobe (%)					524 (58.5)	2 (33.3)	0.405	526 (58.4)
Solid (%)					853 (95.3)	6 (100.0)	1.000	859 (95.3)
Spiculated (%)					37 (4.1)	0 (0.0)	1.000	37 (4.1)

<sup>†</sup>Lung cancer screen-detected at any annual screening appointment. Not necessarily screen-detected at next-screen following a negative one. <sup>‡</sup> Lung cancer screen-detected at round 2 (T<sub>1</sub>) or diagnosed in between round 2 (T<sub>1</sub>) and round 3(T<sub>2</sub>). SD: standard deviation; BMI: body mass index; COPD: chronic obstructive pulmonary disease; LC: lung cancer.



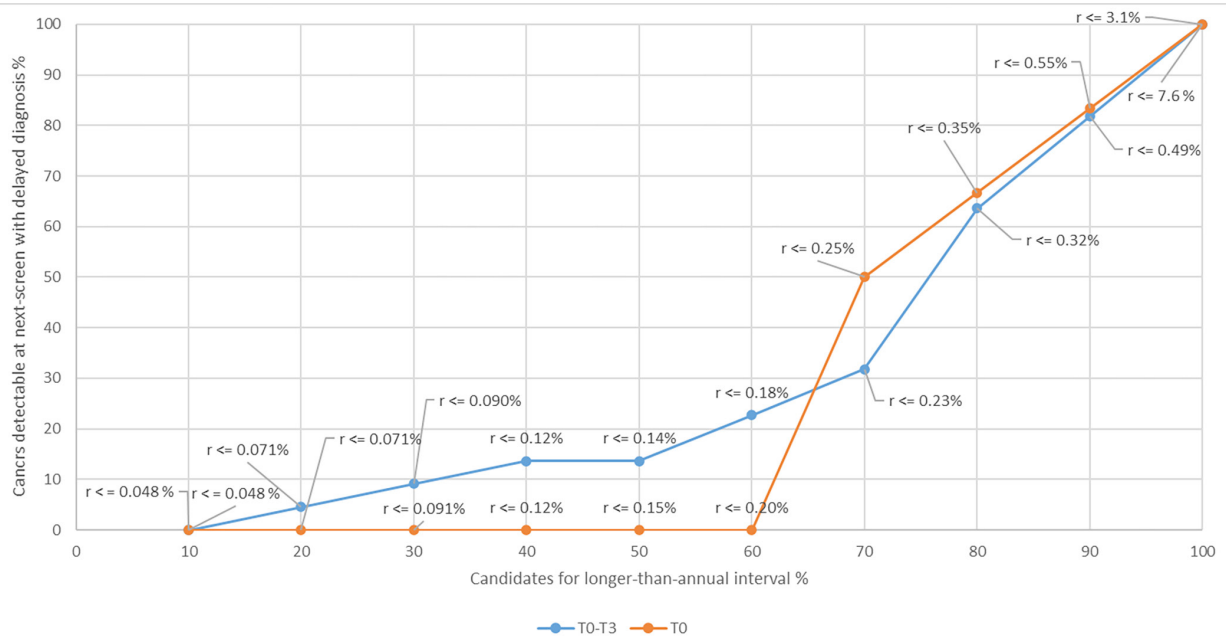
**Figure S2** ROC curves for the selected models: (A) LCRAT (1-year) and LCRAT+CT†, (B) Polynomial model‡, (C) Polynomial and Patz model applied to T0 data and d) Polynomial model applied to data from participants eligible for the LCRAT+CT model. LCRAT: Lung Cancer risk Assessment Tool; AUC: Area under the Curve. † Applied to data from LCRAT+CT-eligible participants from T0 to T3. ‡ Applied to data from Polynomial model eligible participants from T0 or T1 to T4.

**Table S5** Potential effect of risk thresholds from the Polynomial model in participants from all screening rounds of the LUSI Trial, eligible for the LCRAT+CT model

Percentile of risk	Polynomial risk	Candidates for Longer Interval, N (%; 95% CI)	Delayed cancer detections, N (%; 95% CI)	False positives avoided/delayed, N (%; 95% CI)	Indeterminates avoided/delayed, N (%; 95% CI)	Sens (%; 95% CI)	Spec (%; 95% CI)	PPV (PPV, 95% CI)	NPV (NPV, 95% CI)	PLR (PLR; 95% CI)	NLR (NLR; 95% CI)
<b>T<sub>0</sub></b>											
10 <sup>th</sup>	r ≤0.048 %	120 (10)	0 (0; 1.5, 48.3)	0 (0; 10.8, 94.5)	1 (33.3; 1.8, 87.5)	1.00 (0.54, 1.00)	0.10 (0.08, 0.12)	0.01 (0.00, 0.01)	1.00 (0.97, 1.00)	1.11 (1.09, 1.13)	0.00 (0.00, NaN)
20 <sup>th</sup>	r ≤0.071%	239 (20)	0 (0; 1.5, 48.3)	0 (0; 10.8, 94.5)	1 (33.3; 1.8, 87.5)	1.00 (0.54, 1.00)	0.20 (0.18, 0.23)	0.01 (0.00, 0.01)	1.00 (0.98, 1.00)	1.25 (1.22, 1.29)	0.00 (0.00, NaN)
30 <sup>th</sup>	r ≤0.091%	358 (30)	0 (0; 1.5, 48.3)	0 (0; 10.8, 94.5)	1 (33.3; 1.8, 87.5)	1.00 (0.54, 1.00)	0.30 (0.28, 0.33)	0.01 (0.00, 0.02)	1.00 (0.99, 1.00)	1.43 (1.38, 1.49)	0.00 (0.00, NaN)
40 <sup>th</sup>	r ≤0.12%	478 (40)	0 (0; 1.5, 48.3)	0 (0; 10.8, 94.5)	1 (33.3; 1.8, 87.5)	1.00 (0.54, 1.00)	0.40 (0.37, 0.43)	0.01 (0.00, 0.02)	1.00 (0.99, 1.00)	1.67 (1.60, 1.75)	0.00 (0.00, NaN)
50 <sup>th</sup>	r ≤0.15%	597 (50)	0 (0; 1.5, 48.3)	0 (0; 10.8, 94.5)	1 (33.3; 1.8, 87.5)	1.00 (0.54, 1.00)	0.50 (0.47, 0.53)	0.01 (0.00, 0.02)	1.00 (0.99, 1.00)	2.01 (1.90, 2.13)	0.00 (0.00, NaN)
60 <sup>th</sup>	r ≤0.20%	716 (60)	0 (0; 1.5, 48.3)	0 (0; 10.8, 94.5)	1 (33.3; 1.8, 87.5)	1.00 (0.54, 1.00)	0.60 (0.57, 0.63)	0.01 (0.00, 0.03)	1.00 (0.99, 1.00)	2.52 (2.35, 2.70)	0.00 (0.00, NaN)
70 <sup>th</sup>	r ≤0.25%	836 (70)	3 (50; 13.9, 86.1 )	0 (0; 10.8, 94.5)	2 (66.7; 12.5, 98.2)	0.50 (0.12, 0.88)	0.70 (0.67, 0.73)	0.01 (0.00, 0.02)	1.00 (0.99, 1.00)	1.67 (0.75, 3.74)	0.71 (0.32, 1.59)
80 <sup>th</sup>	r ≤0.35%	955 (80)	4 (66.7; 24.1, 94)	0 (0; 10.8, 94.5)	2 (66.7; 12.5, 98.2)	0.33 (0.04, 0.78)	0.80 (0.78, 0.82)	0.01 (0.00, 0.03)	1.00 (0.99, 1.00)	1.67 (0.54, 5.21)	0.83 (0.47, 1.47)
90 <sup>th</sup>	r ≤0.55%	1074 (90)	5 (83.3; 36.5, 99.1)	1 (100; 5.5, 100)	2 (66.7; 12.5, 98.2)	0.17 (0.00, 0.64)	0.90 (0.88, 0.92)	0.01 (0.00, 0.05)	1.00 (0.99, 1.00)	1.66 (0.28, 10.04)	0.93 (0.65, 1.33)
100 <sup>th</sup>	r ≤3.1%	1194 (100)	6 (100; 51.7, 100)	1 (100; 5.5, 100)	3 (100; 31, 100)						
<b>T<sub>0-3</sub></b>											
10 <sup>th</sup>	r ≤0.048	476 (10)	0 (0; 0.4,18.5)	0 (0; 3.2, 69)	1 (16.7; 0.9, 63.5)	1.00 (0.85, 1.00)	0.10 (0.09, 0.11)	0.01 (0.00, 0.01)	1.00 (0.99, 1.00)	1.11 (1.10, 1.12)	0.00 (0.00, NaN)
20 <sup>th</sup>	r ≤0.071	950 (20)	1 (4.5; 0.2, 24.9)	0 (0; 3.2, 69)	1 (16.7; 0.9, 63.5)	0.95 (0.77, 1.00)	0.20 (0.19, 0.21)	0.01 (0.00, 0.01)	1.00 (0.99, 1.00)	1.19 (1.09, 1.31)	0.23 (0.03, 1.54)
30 <sup>th</sup>	r ≤0.090	1428 (30)	2 (9.1; 1.6, 30.6)	0 (0; 3.2, 69)	1 (16.7; 0.9, 63.5)	0.91 (0.71, 0.99)	0.30 (0.29, 0.32)	0.01 (0.00, 0.01)	1.00 (0.99, 1.00)	1.30 (1.14, 1.49)	0.30 (0.08, 1.13)
40 <sup>th</sup>	r ≤0.12	1899 (40)	3 (13.6; 3.6, 36)	0 (0; 3.2, 69)	2 (33.3; 6, 75.9)	0.86 (0.65, 0.97)	0.40 (0.39, 0.42)	0.01 (0.00, 0.01)	1.00 (1.00, 1.00)	1.44 (1.22, 1.71)	0.34 (0.12, 0.97)
50 <sup>th</sup>	r ≤0.14	2378 (50)	3 (13.6; 3.6, 36)	0 (0; 3.2, 69)	2 (33.3; 6, 75.9)	0.86 (0.65, 0.97)	0.50 (0.49, 0.52)	0.01 (0.00, 0.01)	1.00 (1.00, 1.00)	1.73 (1.46, 2.05)	0.27 (0.10, 0.78)
60 <sup>th</sup>	r ≤0.18	2851 (60)	5 (22.7; 8.7, 45.8)	1 (33.3; 1.8, 87.5)	3 (50; 13.9, 86.1)	0.77 (0.55, 0.92)	0.60 (0.59, 0.62)	0.01 (0.01, 0.01)	1.00 (1.00, 1.00)	1.94 (1.54, 2.44)	0.38 (0.17, 0.82)
70 <sup>th</sup>	r ≤0.23	3325 (70)	7 (31.8; 14.7, 54.9)	1 (33.3; 1.8, 87.5)	4 (66.7; 24.1, 94)	0.68 (0.45, 0.86)	0.70 (0.69, 0.71)	0.01 (0.01, 0.02)	1.00 (1.00, 1.00)	2.28 (1.71, 3.05)	0.45 (0.25, 0.84)
80 <sup>th</sup>	r ≤0.32	3798 (80)	14 (63.6; 40.8, 82)	1 (33.3; 1.8, 87.5)	5 (83.3; 36.5, 99.1)	0.36 (0.17, 0.59)	0.80 (0.79, 0.81)	0.01 (0.00, 0.02)	1.00 (0.99, 1.00)	1.82 (1.05, 3.18)	0.79 (0.58, 1.09)
90 <sup>th</sup>	r ≤0.49	4273 (90)	18 (81.8; 59, 94)	2 (66.7; 12.5, 98.2)	6 (100; 51.7, 100)	0.18 (0.05, 0.40)	0.90 (0.89, 0.91)	0.01 (0.00, 0.02)	1.00 (0.99, 1.00)	1.82 (0.75, 4.45)	0.91 (0.75, 1.11)
100 <sup>th</sup>	r ≤7.6	4748 (100)	22 (100; 81.5, 99.6)	3 (100; 31, 96.8)	6 (100; 51.7, 100)						

LCRAT: Lung Cancer risk Assessment, Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, PLR: positive likelihood ratio, NLR: negative likelihood ratio.





**Figure S3** Potential effect of risk thresholds from the Polynomial model in participants from all screening rounds of the LUSI Trial, eligible for the LCRAT+CT model. LCRAT: Lung Cancer risk Assessment Tool.

**Table S6** Observed incidence and mean predicted risk from the LCRAT, LCRAT+CT models

Screening round	Observed incidence at next scan (%)	Mean predicted risk (%)		BS; Sp-Z (P value) <sup>†</sup>	
		LCRAT	LCRAT + CT	LCRAT	LCRAT + CT
T <sub>0</sub> to T <sub>3</sub>	20/4904 (0.41)	0.22	0.21	0.004; 2.88 (0.004)	0.004; 3.09 (0.002)
First round (T <sub>0</sub> )	6/1194 (0.50)	0.19	0.18	0.005; 2.44 (0.015)	0.005; 2.68 (0.007)
Second round (T <sub>1</sub> )	3/1220 (0.25)	0.21	0.20	0.002; 0.27 (0.787)	0.002; 0.39 (0.693)
Third round (T <sub>2</sub> )	5/1262 (0.40)	0.23	0.22	0.004; 1.28 (0.201)	0.004; 1.36 (0.175)
Fourth round (T <sub>3</sub> )	6/1228 (0.49)	0.24	0.24	0.005; 1.82 (0.069)	0.005; 1.82 (0.069)
T <sub>1</sub> to T <sub>3</sub>	14/3710 (0.38)	0.23	0.22	0.004; 1.97 (0.049)	0.004; 2.10 (0.036)

<sup>†</sup>Brier Score, Spiegelhalter's Z-Score and Spiegelhalter's test p-value. <sup>‡</sup> For the purpose of evaluating model calibration, the observed lung cancer incidence in the subset of participants eligible for the Polynomial model was calculated only among those with a valid prediction from the model (i.e. after removing those with NA for risks).

**Table S7** Observed incidence and mean predicted risk from the Polynomial models

Screening round	Observed incidence in [T <sub>n</sub> , T <sub>n+1</sub> ) <sup>‡</sup> (%)	Mean predicted risk (%)	BS; Sp-Z (P value) <sup>†</sup>
		Polynomial model	
First round (T <sub>0</sub> )	11/1889 (0.58)	0.31	0.006; 2.14 (0.032)
Second round (T <sub>1</sub> )	11/1737 (0.63)	0.33	0.006; 2.28 (0.023)
Third round (T <sub>2</sub> )	10/1728 (0.57)	0.32	0.006; 1.91 (0.055)
Fourth round (T <sub>3</sub> )	10/1726 (0.58)	0.36	0.006; 1.71 (0.088)
Fifth round (T <sub>4</sub> )	1/1754(0.057)	0.32	0.006; -1.95 (0.052)
T <sub>1</sub> to T <sub>4</sub>	32/6966 0.46	0.33	0.005; 1.98 (0.048)

<sup>†</sup>Brier Score, Spiegelhalter's Z-Score and Spiegelhalter's test p-value. <sup>‡</sup> For the purpose of evaluating model calibration, the observed lung cancer incidence in the subset of participants eligible for the Polynomial model was calculated only among those with a valid prediction from the model (i.e. after removing those with NA for risks).