Erasmus MC
University Medical Center Rotterdam

What target sensitivity and specificity might confer clinical utility?

Example of lung cancer CT-screening

Harry J. de Koning, MD PhD
Professor & Deputy Chair of Public Health
Erasmus MC, Rotterdam
The Netherlands

Acknowledgements & Disclosures

Erasmus MC University Medical Center Rotterdam

University Medical Center Groningen

UMC Utrecht

Spaarne Gasthuis

UZ LEUVEN

Belgian Cancer Registry

CBG

IKNL integraal kankercentrum Nederland

ZonMw

Innovatiefonds Zorgverzekeraars

DUTCH CANCER SOCIETY

ROTS group

VLK Vlaamse Liga tegen Kanker

LOGO Leuven

G.Ph.Verhagen-Stichting

ERASMUS TRUSTFONDS

Research Grant

Roche Diagnostics: proteomics side-study

Perceptronix: sputum side-study

Workstations

Siemens Germany (nodule software)

Personal

Speaker fees LC screening symposia MSD/Teva

Reviewer IPSOS Mori TLHC NHS England

Erasmus MC

Test characteristics low-dose CT (AHRQ 2020)

Trial	Sensitivity	Specificity	PPV
DANTE	79.5	75.5	19
ITALUNG	95	26.4	4
LUSI	93.5	62.0	7
MILD	71	99.2	41
NELSON	59	95.8	44
NLST	93	76.5	3
median	80	76.4	21
range	(59-95)	(26.4-99.2)	(3-44)

Erasmus MC

Test characteristics low-dose CT (AHRQ 2020)

Trial	Sensitivity	Specificity	PPV
DANTE	79.5	75.5	19
ITALUNG	95	26.4	4
LUSI	93.5	62.0	7
MILD	71	99.2	41
NELSON	59	95.8	44
NLST	93	76.5	3
median	**80**	**76.4**	**21**
range	(59-95)	(26.4-99.2)	(3-44)

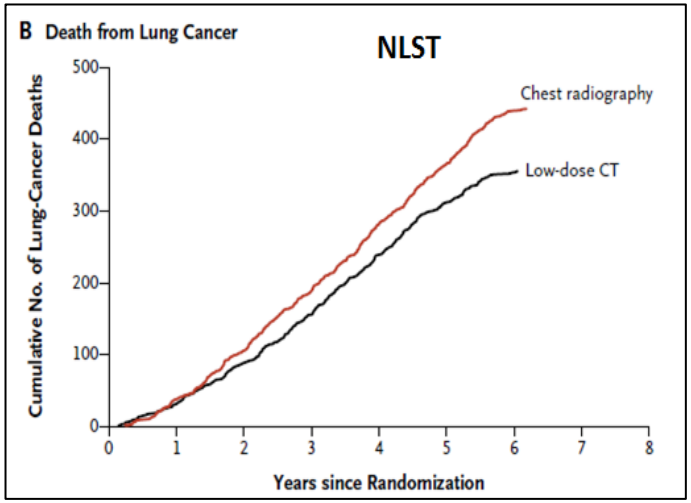
Erasmus MC

Test characteristics low-dose CT (AHRQ 2020)

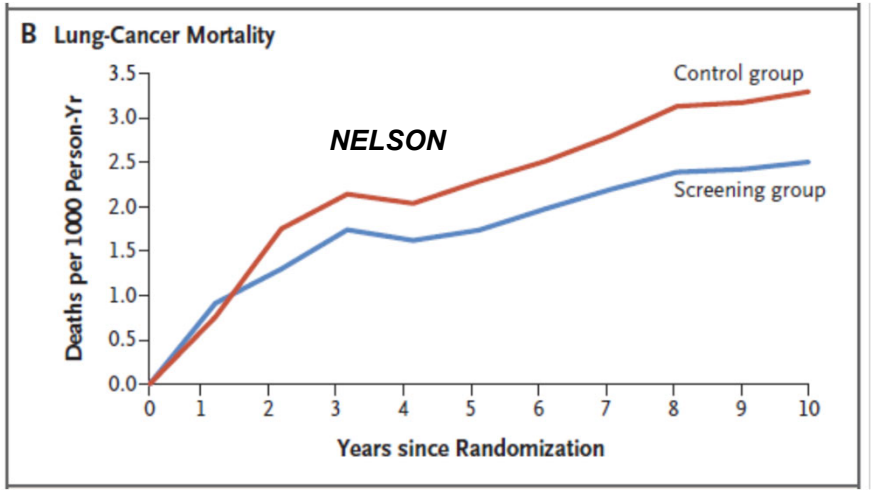
Trial	Sensitivity	Specificity	PPV
DANTE	79.5	75.5	19
ITALUNG	95	26.4	4
LUSI	93.5	62.0	7
MILD	71	99.2	41
NELSON	**59**	**95.8**	**44**
NLST	**93**	**76.5**	**3**
median	80	76.4	21
range	(59-95)	(26.4-99.2)	(3-44)

Both (!) RCT's have confirmed substantial reductions in lung cancer mortality with low-dose computed tomography (LDCT) screening in high-risk populations

The National Lung Screening Trial (NLST; n=53,454) and Dutch-Belgian Lung Cancer Screening trial (NELSON; n=15,792): 8-24% (men) and 26-61% (women)



NLST team. NEJM. 2011



De Koning et al. NEJM. 2020

Erasmus MC

Test characteristics low-dose CT (AHRQ 2020)

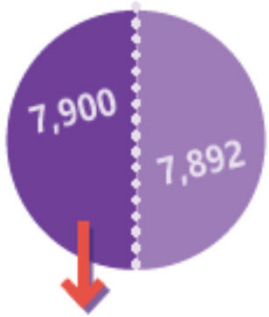
Trial	Sensitivity	Specificity	PPV
DANTE	79.5	75.5	19
ITALUNG	95	26.4	4
LUSI	93.5	62.0	7
MILD	71	99.2	41
NELSON	**59**	95.8	44
NLST	93	76.5	3
median	80	76.4	21
range	(59-95)	(26.4-99.2)	(3-44)

Erasmus MC

NELSON males (AHRQ report 2020)

	Lung cancer in FU	No lung cancer in FU	Total	PV (%)
Test positive	**203**	264	467	44
Test negative	141	**5,975**	6,116	98
Total	**344**	6,239	6,583	
sensitivity	**59%**			
specificity		95.8%		

NELSON trial



15,792 people voluntarily participated in the study. 85% of these participants are male.

The study was designed to include mainly male volunteers because of the difference in smoking behaviour in the past, but there is also relevance for women. The results that we present here are only about men. Those of the women follow in more detail.

The participants were randomly assigned to one of the study groups:

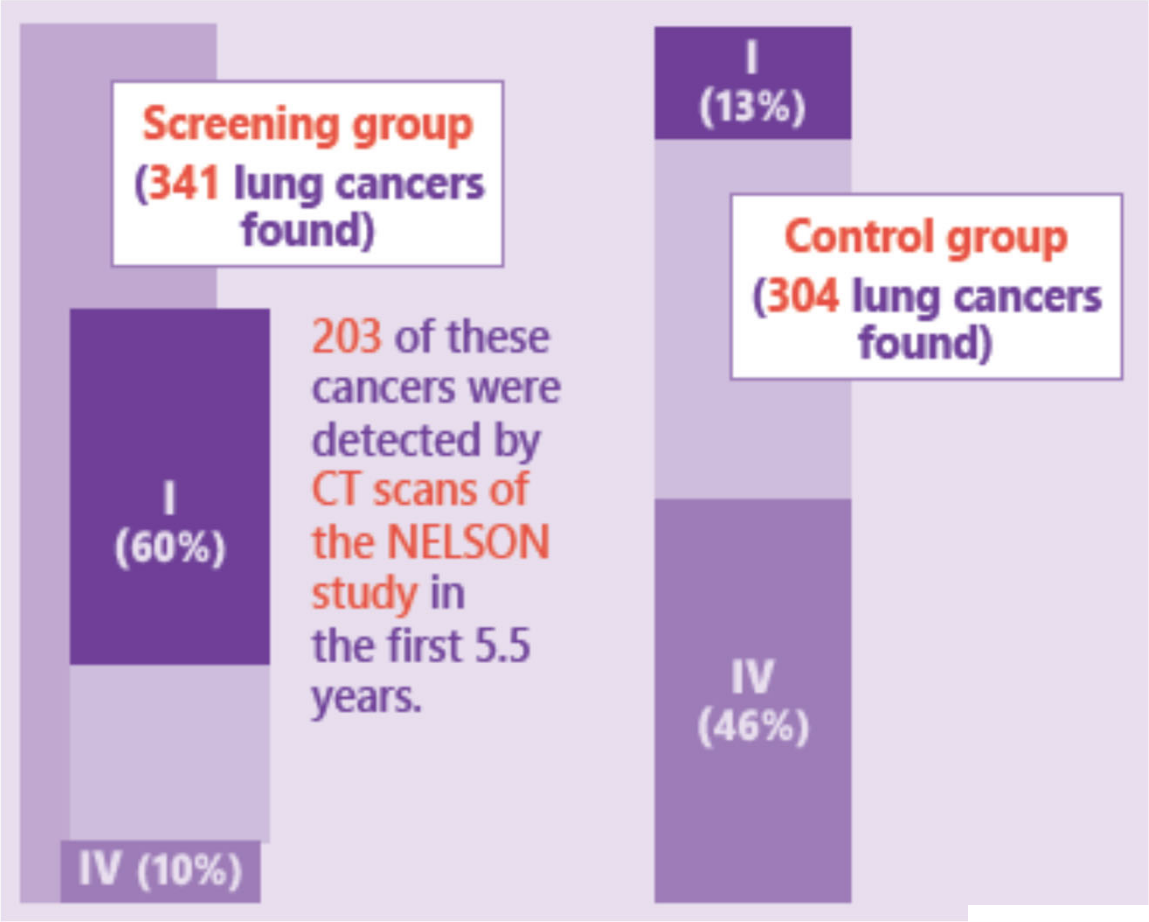
- Screening group: 7,900 participants receive a series of CT scans
- Control group: 7,892 participants do not receive a CT scan (usual care)

Lung cancer screening

Participants in the screening group received four CT scans, with increasing intervals.

De Koning et al., NEJM 2020

Stage Shift NELSON males



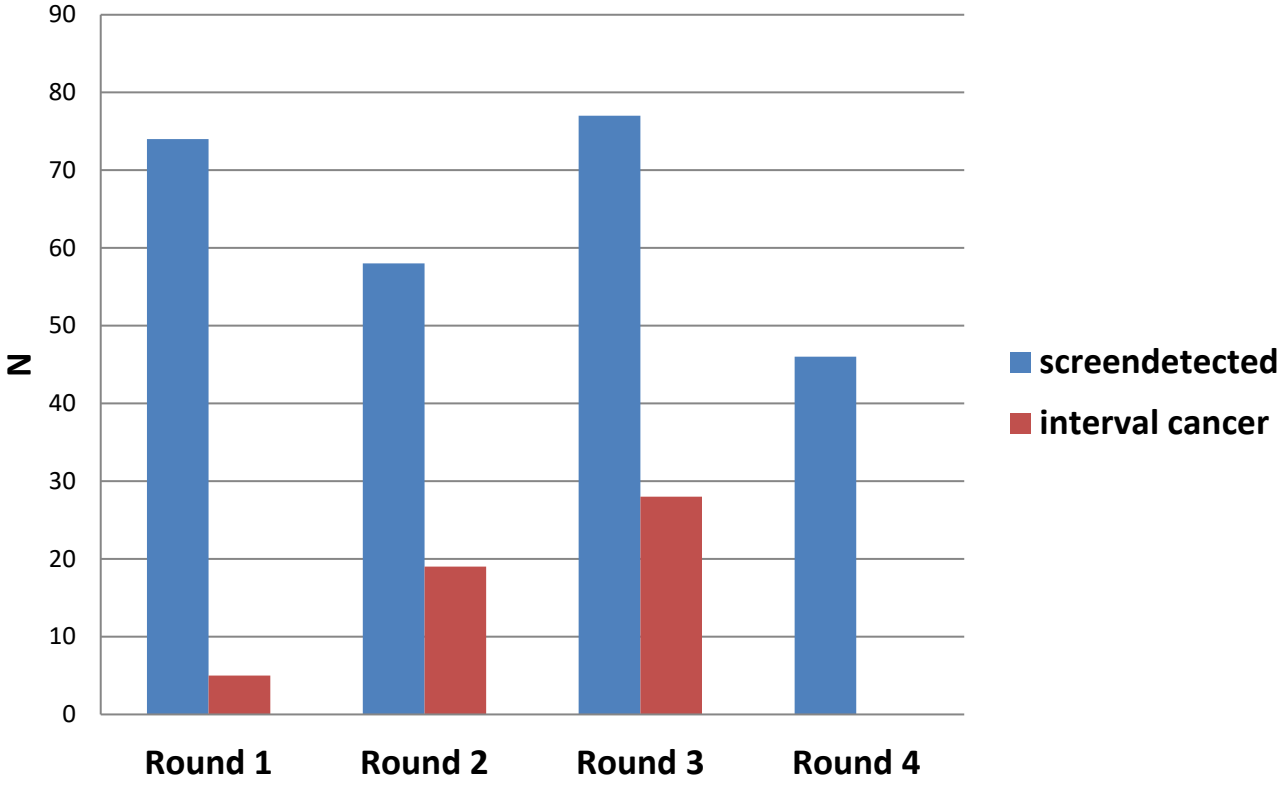
De Koning et al. NEJM. 2020

Erasmus MC

“Programme sensitivity”

- NELSON: 59% (203/ 203+44**+97**); 10-year FU
- NLST: 61% (649/ 649+44**+367**); 7-year FU

Test sensitivity
(Screen-detected versus interval cancers)



Horeweg et al., Blue Journal 2013, Horeweg *et al.*, Lancet Oncol 2014, Yousaf-Khan *et al,* Thorax 2015

Sensitivity of CT-LC Screening by histology and stage NLST

Erasmus MC

	AD	SQ	SM	OTH
CXR				
IA	16.91%	9.72%	2.51%	6.27%
IB	27.13%	28.90%	4.25%	7.57%
II	27.26%	30.02%	6.64%	7.57%
IIIA	48.11%	46.31%	14.74%	29.78%
IIIB	49.29%	47.96%	53.18%	34.40%
IV	96.31%	78.62%	97.31%	36.94%
CT				
IA	56.63%	30.95%	8.83%	20.78%
IB	64.12%	38.05%	10.28%	24.75%
II	64.48%	39.19%	11.19%	24.78%
IIIA	75.93%	69.67%	41.58%	60.40%
IIIB	80.21%	79.39%	87.06%	68.27%
IV	98.88%	97.66%	99.35%	95.67%

CXR sensitivity: 2.51% - 97.31%

CT sensitivity: 8.83% - 99.35%

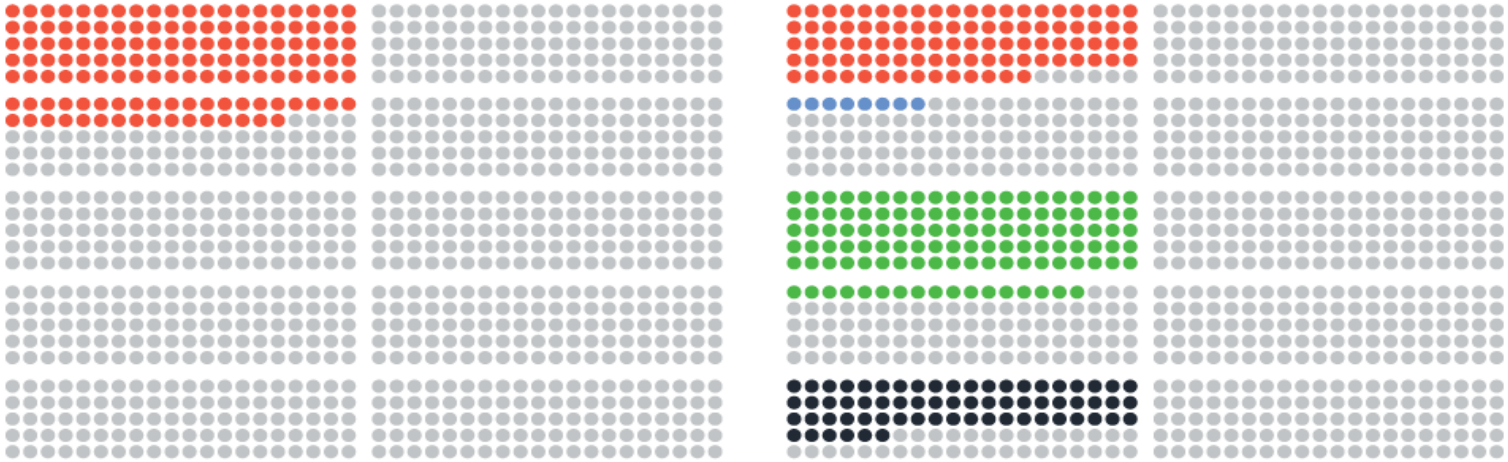
CT: > 3-fold higher sensitivity for detecting lung cancer stage I

ten Haaf et al., CEBP 2015

Benefits and harms of lung cancer screening

This graphic represents 1000 persons that would be eligible for lung cancer screening at any point in their life. The left panel shows how many of these 1000 persons are expected to die of lung cancer when they are not screened. The right panel shows the lifetime benefits and harms when these 1000 individuals would undergo lung cancer screening using annual low-dose computed tomography scans.

1000 ever-eligible persons without screening | **1000 ever-eligible persons with screening**



	Without screening	With screening
Persons dying of lung cancer	136	94
Persons with lung cancer that would never cause symptoms *	-	8
False positive scan results (per 1000 scans) **	-	117
Persons undergoing surgery or biopsy for benign lesion ***	Unknown	66
Other persons	864	715

Test characteristics low-dose CT (AHRQ 2020)

Trial	Sensitivity	Specificity	PPV
DANTE	79.5	75.5	19
ITALUNG	95	26.4	4
LUSI	93.5	62.0	7
MILD	71	**99.2**	**41**
NELSON	59	**95.8**	**44**
NLST	93	76.5	3
median	80	76.4	21
range	(59-95)	(26.4-99.2)	(3-44)

Erasmus MC

- At present, the high referral rates seen in the US do not seem feasible in Europe, and mortality results are therefore needed from the European trials with lower referral rates

In: European Guide on Quality Improvement in Comprehensive Cancer Control (2017) by Tit Albreht, R. Kiasuwa & M. van den Bulcke

Erasmus MC

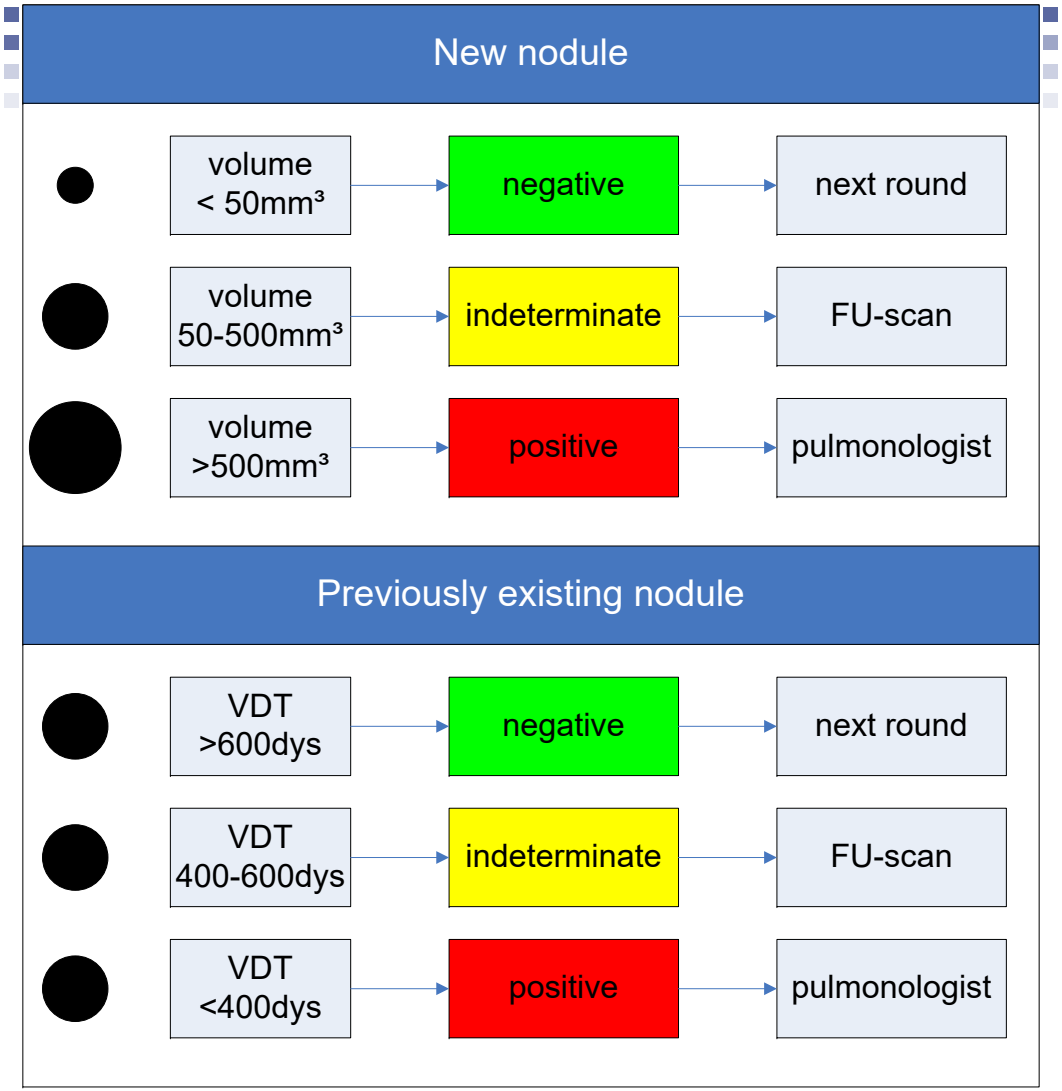
Screening Test Results in Male Participants

Table 2. Screening-Test Results in Each Screening Round for Male Participants in the Screening Group.

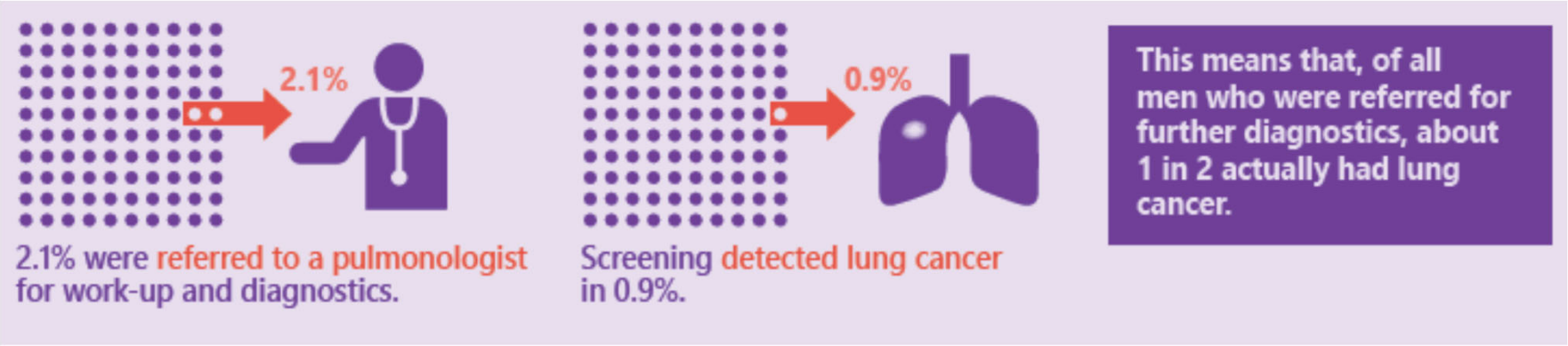
Screening	Screening Uptake		Indeterminate Test	Positive Test	Detection of Lung Cancer	Positive Predictive Value
	Men Eligible for Screening	Men Undergoing Randomization				
	number/total number (percent)					*percent*
Round 1	6309/6583 (95.8)	6309/6583 (95.8)	1241/6309 (19.7)	147/6309 (2.3)	56/6309 (0.9)	38.1
Round 2	6086/6459 (94.2)	6086/6583 (92.5)	357/6086 (5.9)	95/6086 (1.6)	45/6086 (0.7)	47.4
Round 3	5768/6285 (91.8)	5768/6583 (87.6)	385/5768 (6.7)	136/5768 (2.4)	65/5758 (1.1)	47.8
Round 4	4437/5771 (76.9)	4437/6583 (67.4)	86/4437 (1.9)	89/4437 (2.0)	37/4437 (0.8)	41.6
Total	22,600/25,098 (90.0)	22,600/26,332 (85.8)	2069/22,600 (9.2)	467/22,600 (2.1)	203/22,600 (0.9)	43.5

De Koning et al. NEJM. 2020

NELSON Nodule Management Protocol



NELSON trial (males)

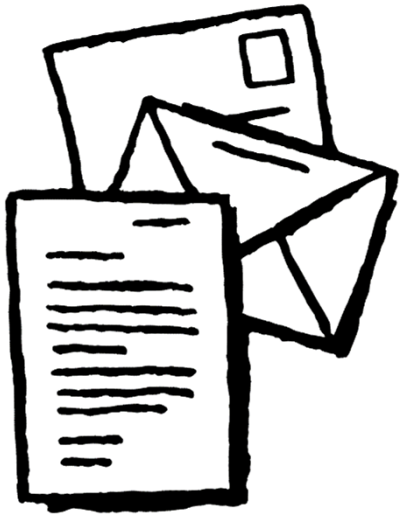


De Koning et al. NEJM. 2020

Erasmus MC

Message indeterminate screening test result

"We have observed a very small abnormality in your lung (5–10 mm long). Such a small abnormality is often detected in many persons and it usually represents a small scar or a minor inflammation. Therefore, at this moment there is no need for any further investigations. However, in order to see whether there has been any change in this abnormality, a new CT scan of the lungs will be made after 3 to 4 months."



Lancet Oncol 2014; 15: 1332–41

Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening

Nanda Horeweg*, Joost van Rosmalen*, Marjolein A Heuvelmans, Carlijn M van der Aalst, Rozemarijn Vliegenthart, Ernst Th Scholten, Kevin ten Haaf, Kristiaan Nackaerts, Jan-Willem J Lammers, Carla Weenink, Harry J Groen, Peter van Ooijen, Pim A de Jong, Geertruida H de Bock, Willem Mali, Harry J de Koning*, Matthijs Oudkerk*

Lancet Oncol 2016; 17: 907–16

Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial

Joan E Walter, Marjolein A Heuvelmans, Pim A de Jong, Rozemarijn Vliegenthart, Peter M A van Ooijen, Robin B Peters, Kevin ten Haaf, Uraujh Yousaf-Khan, Carlijn M van der Aalst, Geertruida H de Bock, Willem Mali, Harry J M Groen, Harry J de Koning, Matthijs Oudkerk

Complications after lung surgery

April 2004 – December 2008

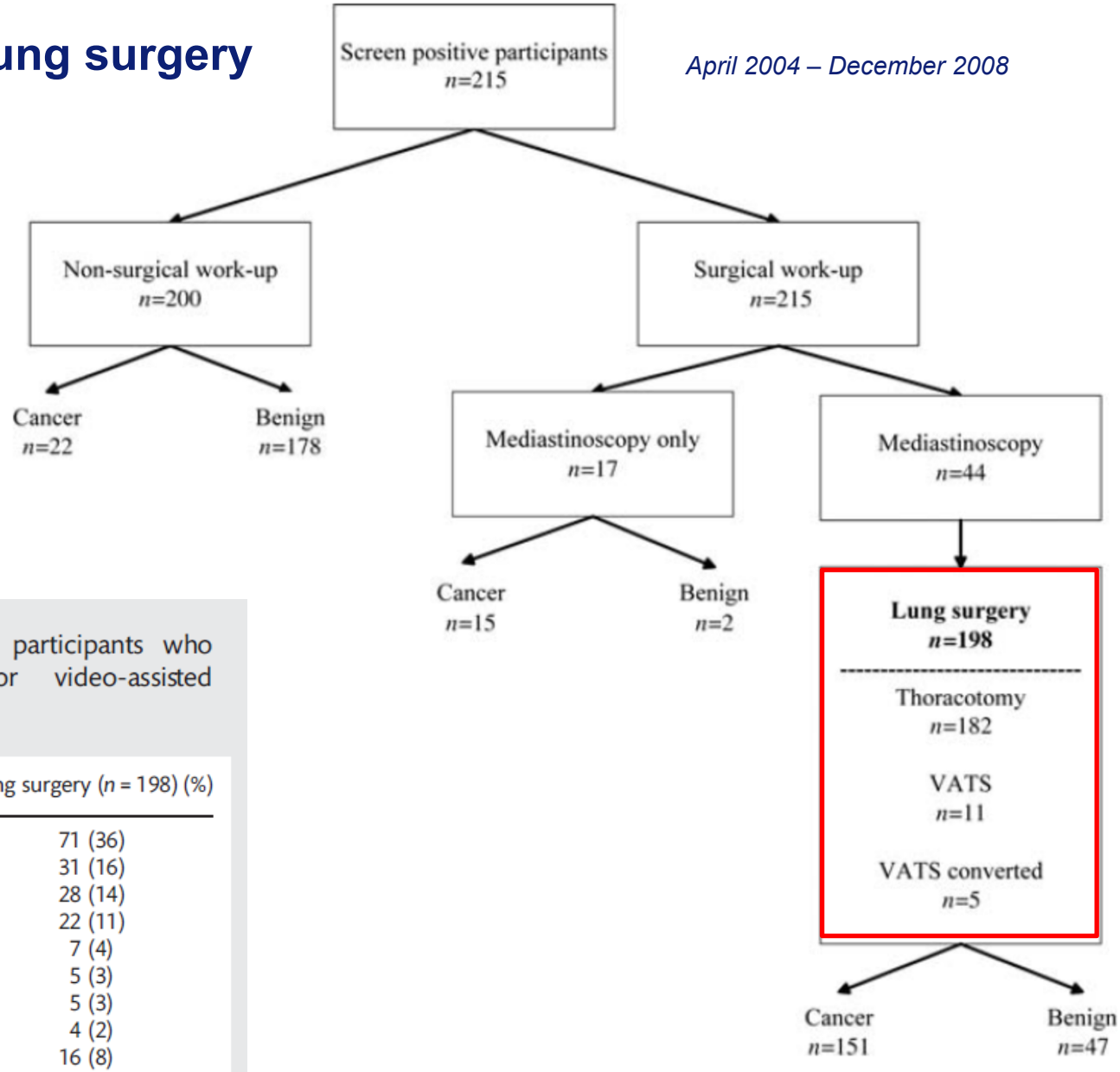


Table 2: Co-morbidity in NELSON participants who underwent a thoracotomy and/or video-assisted thoracoscopic surgery (VATS)

Co-morbidity	Lung surgery (n = 198) (%)
Chronic obstructive pulmonary disease	71 (36)
Coronary artery disease	31 (16)
Diabetes mellitus	28 (14)
Peripheral vascular disease	22 (11)
Peptic ulcer disease	7 (4)
Cerebrovascular disease	5 (3)
Congestive heart failure	5 (3)
Connective tissue disease	4 (2)
Any prior tumour	16 (8)
Chronic kidney disease	2 (1)

Van 't Westeinde SC, et al. European Journal of Cardio-Thoracic Surgery 42 (2012) 420–429

NLST Results

Table 2. **Positive and False-Positive Screening Results and Diagnostic Follow-up, by Age**

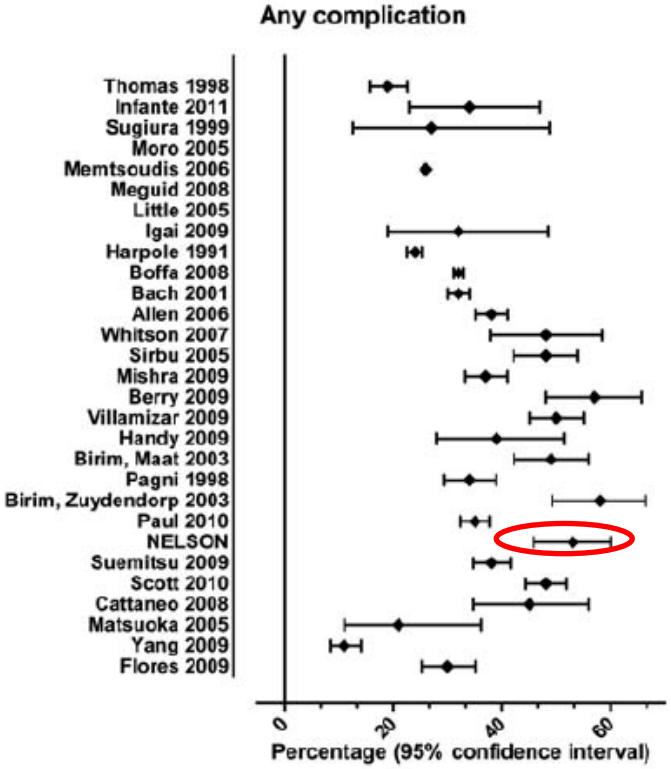
Variable	Under-65 Cohort				65+ Cohort			
	Year 0	Year 1	Year 2	Total	Year 0	Year 1	Year 2	Total
Screened, *n*	19 306	18 184	17 798	55 288	7003	6531	6304	19 838
Participants screened, *n* (%)								
Positive result	4947 (25.6)	4773 (26.3)	2726 (15.3)	12 446 (22.5)	2244 (32.0)	2131 (32.6)	1320 (20.9)	5695 (28.7)
Cancer not present at screening*	19 147 (99.2)	18 081 (99.4)	17 664 (99.3)	54 892 (99.3)	6874 (98.2)	6456 (98.9)	6211 (98.5)	19 541 (98.5)
False-positive results among participants with cancer not present at screening, *n* (%)	4796 (25.1)	4678 (25.9)	2603 (14.7)	12 077 (22.0)	2125 (30.9)	2058 (31.9)	1232 (19.8)	5415 (27.7)
Procedures among participants with false-positive results, *n* (%)								
Surgical procedure	60 (1.3)	34 (0.7)	25 (1.0)	119 (1.0)	29 (1.4)	17 (0.8)	18 (1.5)	64 (1.2)
Invasive procedure	168 (3.5)	84 (1.8)	73 (2.8)	325 (2.7)	86 (4.1)	44 (2.1)	47 (3.8)	177 (3.3)
Complications among participants with invasive procedures, *n* (%)								
Complications	10 (5.9)	14 (16.7)	8 (11.0)	32 (9.8)	8 (9.3)	2 (4.5)	5 (11.6)	15 (8.5)
Major complications	1 (0.6)	2 (2.4)	3 (4.1)	6 (1.9)	2 (2.3)	2 (4.6)	2 (4.3)	6 (3.4)

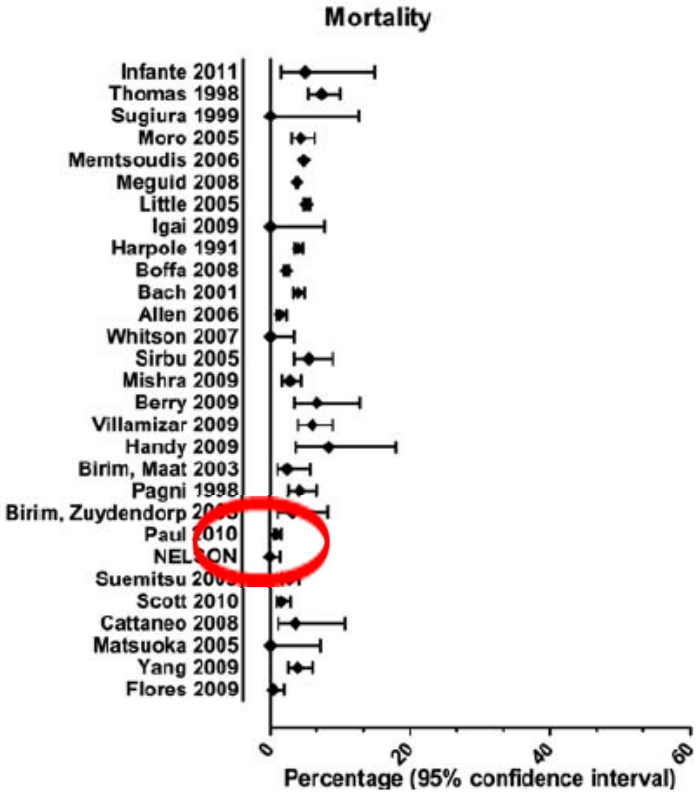
* Includes tests with positive results and incomplete information on diagnostic follow-up (n = 102 [year 0], 113 [year 1], and 103 [year 2] in the under-65 cohort; n = 37 [year 0], 49 [year 1], and 34 [year 2] in the 65+ cohort).

Pinsky et al. Ann Intern Med. 2014;161:627-633.

NELSON vs non-screening series

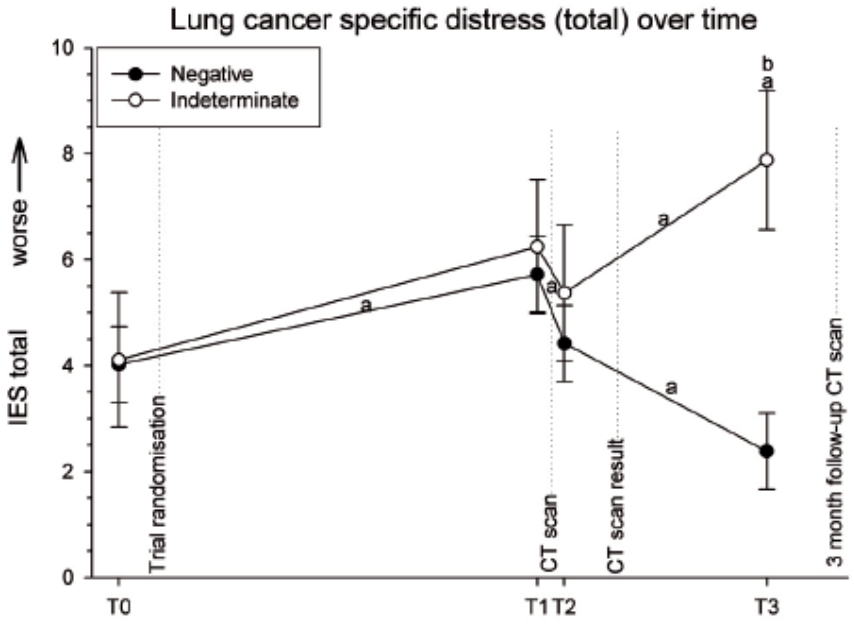
Complication and mortality rates after thoracotomy in the NELSON lung cancer screening trial in comparison with non-screening series from the literature.

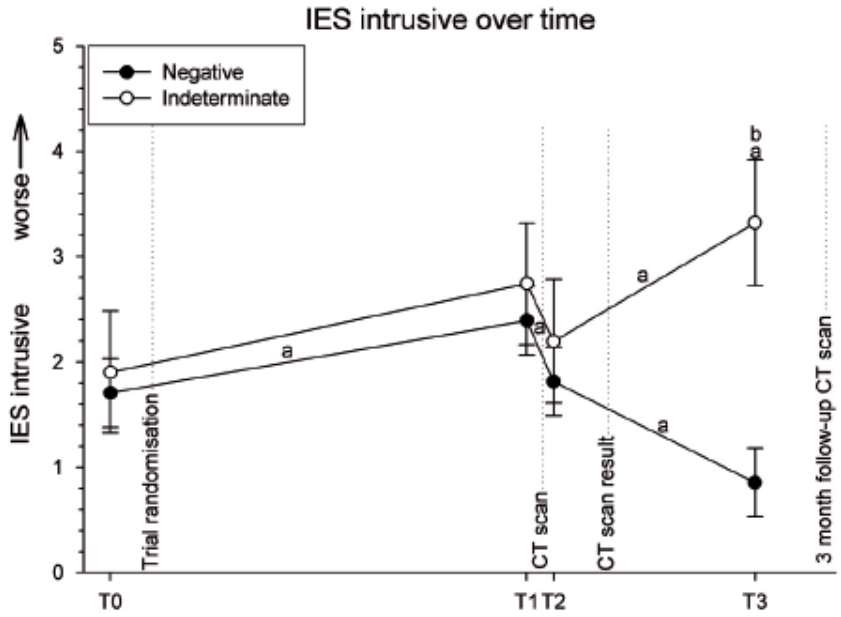




Van 't Westeinde SC, et al. European Journal of Cardio-Thoracic Surgery 42 (2012) 420–429

Long-term effects CT lung cancer screening on HRQoL





Van den Bergh K et al. Eur Respir J. 2011 Jul;38(1):154-61

Short-term effects CT lung cancer screening on HRQoL

- This longitudinal study among participants of the NELSON lung cancer-screening program showed that in the short-term recipients of an indeterminate result experienced increased lung cancer-specific distress, whereas the HRQoL changes after a negative baseline screening result may be interpreted as a relief.
  - T0 = 1 day prior screening, T1= 1 day post-screening, T2= 6 months post-screening
  - SF-12, EQ-5D, STAI-6 (anxiety), IES (Lung cancer distress)
- Results
  - 87-99% experienced no discomfort related to the CT scan
  - 46-51% experienced discomfort related to waiting for the results

Van den Bergh K. et al. Br J Cancer 2010;102(1):27-34

Long-term effects CT lung cancer screening on HRQoL

Lung cancer CT screening had no negative effects on HRQoL.

At 2-years follow-up the HRQoL of screened subjects was similar to that of control subjects, the unfavorable short-term effects of an indeterminate baseline screening result had resolved, and an indeterminate result at the second screening round requiring a one-year follow-up CT had no impact on HRQoL 6 months later.

Van den Bergh K et al. Eur Respir J. 2011 Jul;38(1):154-61

Erasmus MC

Interrelationship with sojourn times

Table 2. MPST estimates (in years) of preclinical stages by gender[a]

	AD	SQ	SM	OTH
Men				
IA	1.82	2.16	1.25	1.96
IB	0.64	0.76	0.44	0.69
II	0.46	0.55	0.32	0.50
IIIA	0.46	0.55	0.32	0.50
IIIB	0.36	0.42	0.25	0.39
IV	0.74	0.88	0.51	0.80
Total mean preclinical duration[b]	4.48	5.32	3.09	4.84
Women				
IA	2.44	2.15	1.36	2.31
IB	0.86	0.76	0.48	0.81
II	0.62	0.55	0.34	0.59
IIIA	0.62	0.55	0.35	0.59
IIIB	0.48	0.42	0.27	0.45
IV	0.99	0.88	0.55	0.94
Total mean preclinical duration[b]	6.01	5.31	3.35	5.69

Abbreviations: AD, adenocarcinoma; OTH, other non–small cell carcinoma; SM, small cell carcinoma; SQ, squamous cell carcinoma.

[a]The MPST estimates should be interpreted as follows: the time for an adenocarcinoma cancer to progress from preclinical stage IA to preclinical stage II (or be clinically detected in stage IB) in a male is on average 2.46 (1.82 + 0.64) years, of which 1.82 years are spent in the preclinical state of stage IA and 0.64 years are spent in the preclinical state of stage IB.

[b]If discovered clinically in stage IV.

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Lung Cancer Detectability by Test, Histology, Stage, and Gender: Estimates from the NLST and the PLCO Trials

Kevin ten Haaf[1], Joost van Rosmalen[2], and Harry J. de Koning[1]

Erasmus MC

Lung cancer mortality rate ratio (95% CI)	Year 7	Year 8	Year 9	Year 10
MALES		**0.76** (0.60-0.97)	**0.76** (0.61-0.96)	**0.76** (0.61-0.94)
FEMALES	**0.46** (0.21-0.96)	**0.41** (0.19-0.84)	**0.52** (0.28-0.94)	**0.67** (0.38-1.14)

Rand: 23-12-2003 – 06-07-2006

FU: 23-12-2003 – 31-12-2015

De Koning et al. NEJM. 2020

Erasmus MC

Lung cancer mortality rate ratio (95% CI)	Year 8 NELSON	Year 8 NLST	Year 8 NLST-eligible in NELSON
MALES	0.76	0.92	0.78 (0.59-1.04)
FEMALES	0.41	0.73	0.37 (0.14-0.87)

Rand: 23-12-2003 – 06-07-2006

FU: 23-12-2003 – 31-12-2015

De Koning et al. NEJM. 2020

Pinsky et al. Cancer 2013

Erasmus MC

Discussion & conclusion CT lung scanning

- We did not discuss possible systematic false-positives / false-negatives at consecutive screens (eg in CRC FIT)
- We did not discuss ways to improve performance (eg double read, AI)
- We did not discuss additional findings on CT scan (CAC, COPD)

- CT test sensitivity can be around 90%, and has resulted in substantial clinical utility (difficult task for a biomarker)
- CT specificity can and should be improved (safely) substantially, by volume CT scanning, using indeterminate test results, and/or increasing cut-off for referral