DOES CT-SCREENING HAVE ANY ROLE IN NSCLC ?

YES

Harry J. de Koning, MD, PhD
Professor of Public Health & Screening evaluation
Erasmus MC

PI NELSON-trial

Rotterdam, The Netherlands

NELSON
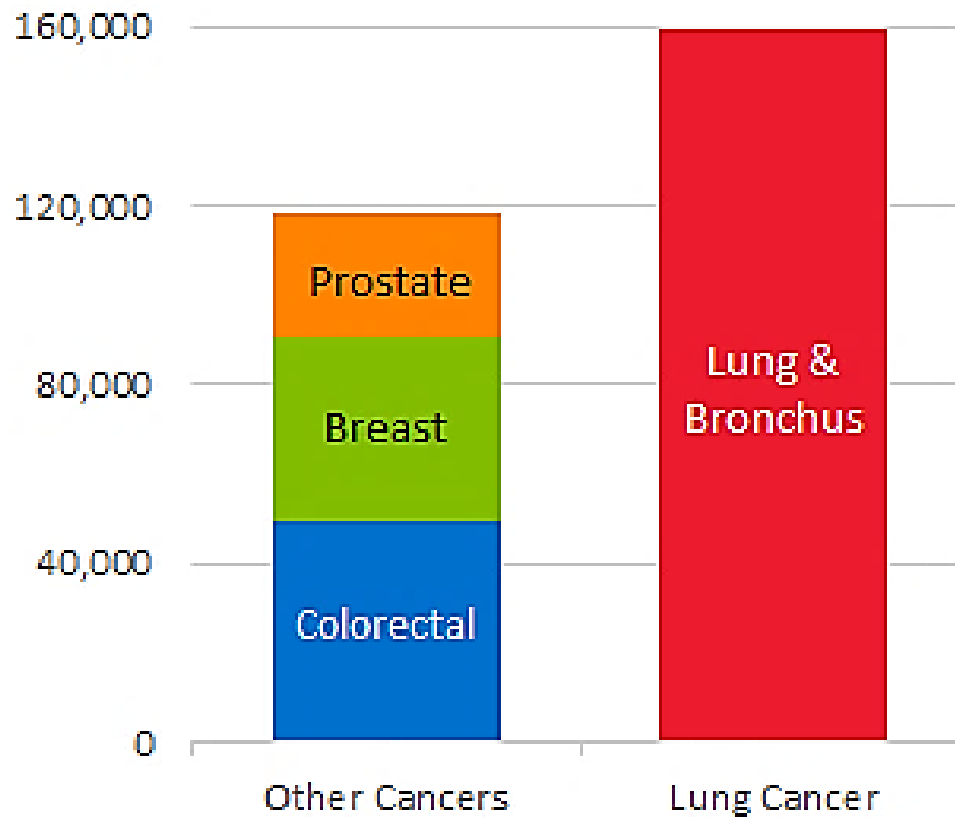
elcc2016.org

The NELSON trial is supported by:

Siemens Germany provided workstations for uniform reading
Roche Diagnostics provided funds for a side-study on proteomics

Department receives research funds from NIH/NCI, and EU regarding LC

Cancer epidemiology

Estimated Cancer Deaths by Site, 2015[2]

National Lung Screening Trial (NLST): USA

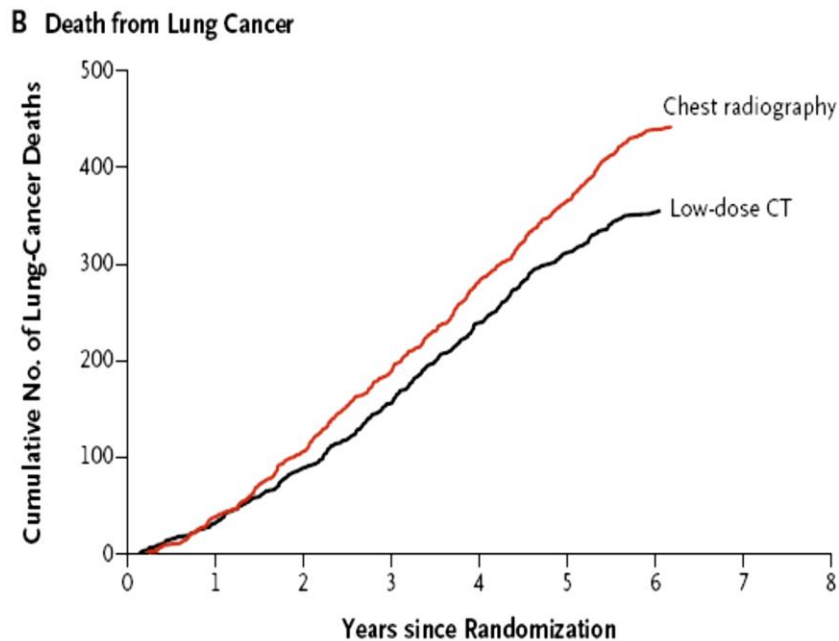**B   Death from Lung Cancer**

Figure 1. Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer.

The number of lung cancers (Panel A) includes lung cancers that were diagnosed from the date of randomization through December 31, 2009. The number of deaths from lung cancer (Panel B) includes deaths that occurred from the date of randomization through January 15, 2009.

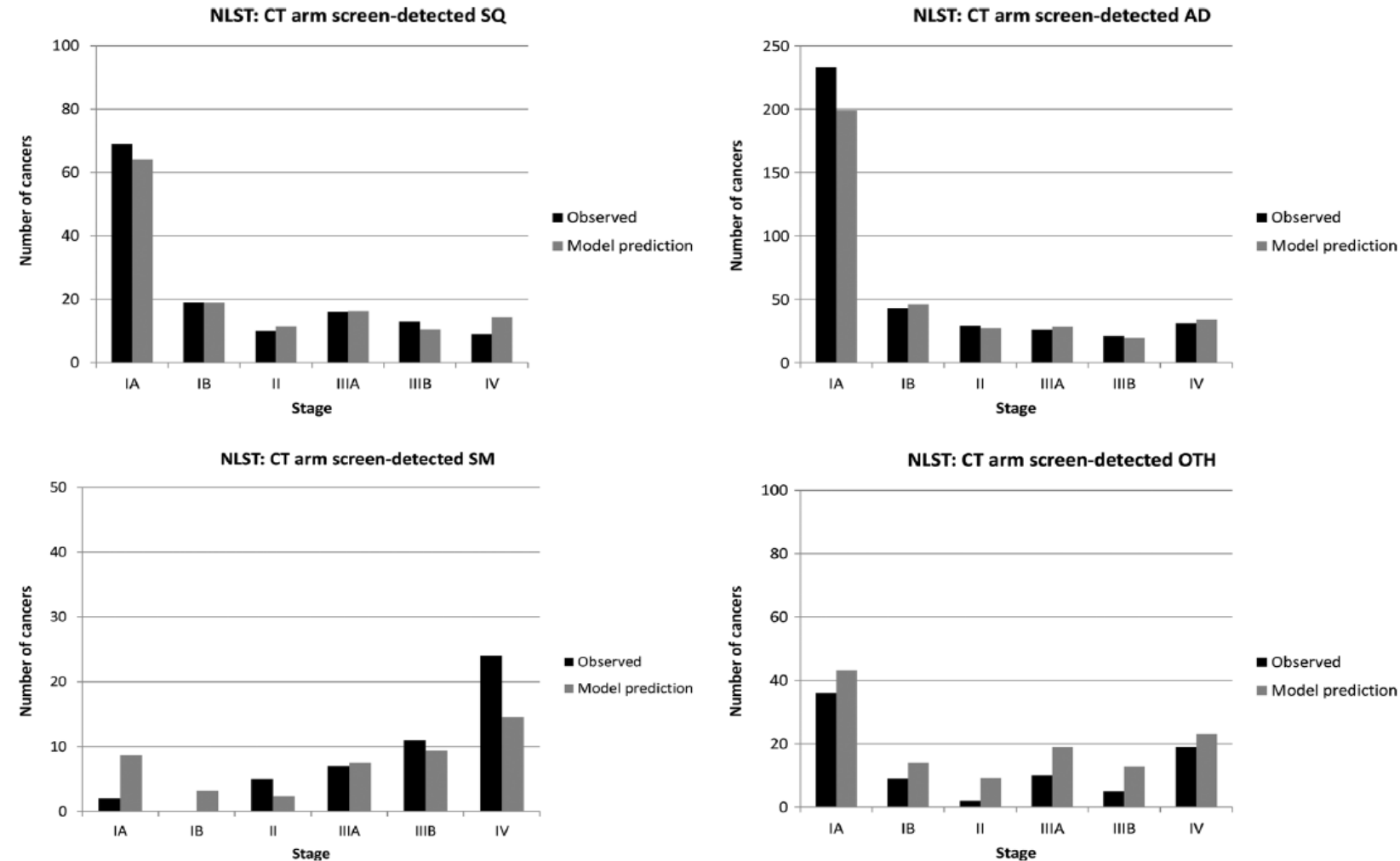# NLST CT arm screen-detected lung cancers by histology and stage

NLST: CT arm screen-detected SQ

NLST: CT arm screen-detected AD

NLST: CT arm screen-detected SM

NLST: CT arm screen-detected OTH

Figure 1.
NLST CT arm screen-detected lung cancers by histology and stage. Abbreviations: AD, adenocarcinoma; OTH, other non–small cell carcinoma; SM, small cell carcinoma; SQ, squamous cell carcinoma.

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]

Sensitivity estimates by histology/ stage/method (ten Haaf et al., CEBP 2015)

	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%

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

Preclinical duration of lung cancer by gender, histology and stage

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 adeno-carcinoma 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.

Benefits and Harms of Computed Tomography Lung Cancer Screening Strategies: A Comparative Modeling Study for the U.S. Preventive Services Task Force

Harry J. de Koning, MD; Rafael Meza, PhD; Sylvia K. Plevritis, PhD; Kevin ten Haaf, MSc; Vidit N. Munshi, MS; Jihyoun Jeon, PhD; Saadet Ayca Erdogan, PhD; Chung Yin Kong, PhD; Summer S. Han, PhD; Joost van Rosmalen, PhD; Sung Eun Choi, SM; Paul F. Pinsky, PhD; Amy Berrington de Gonzalez, PhD; Christine D. Berg, MD; William C. Black, MD; Martin C. Tammemägi, PhD; William D. Hazelton, PhD; Eric J. Feuer, PhD*; and Pamela M. McMahon, PhD*

LC MORTALITY REDUCTION RESULTS FOR 9 DIFFERENT ANNUAL SCENARIOS (55/60 ENDING THROUGH AGE 80) – USPSTF -
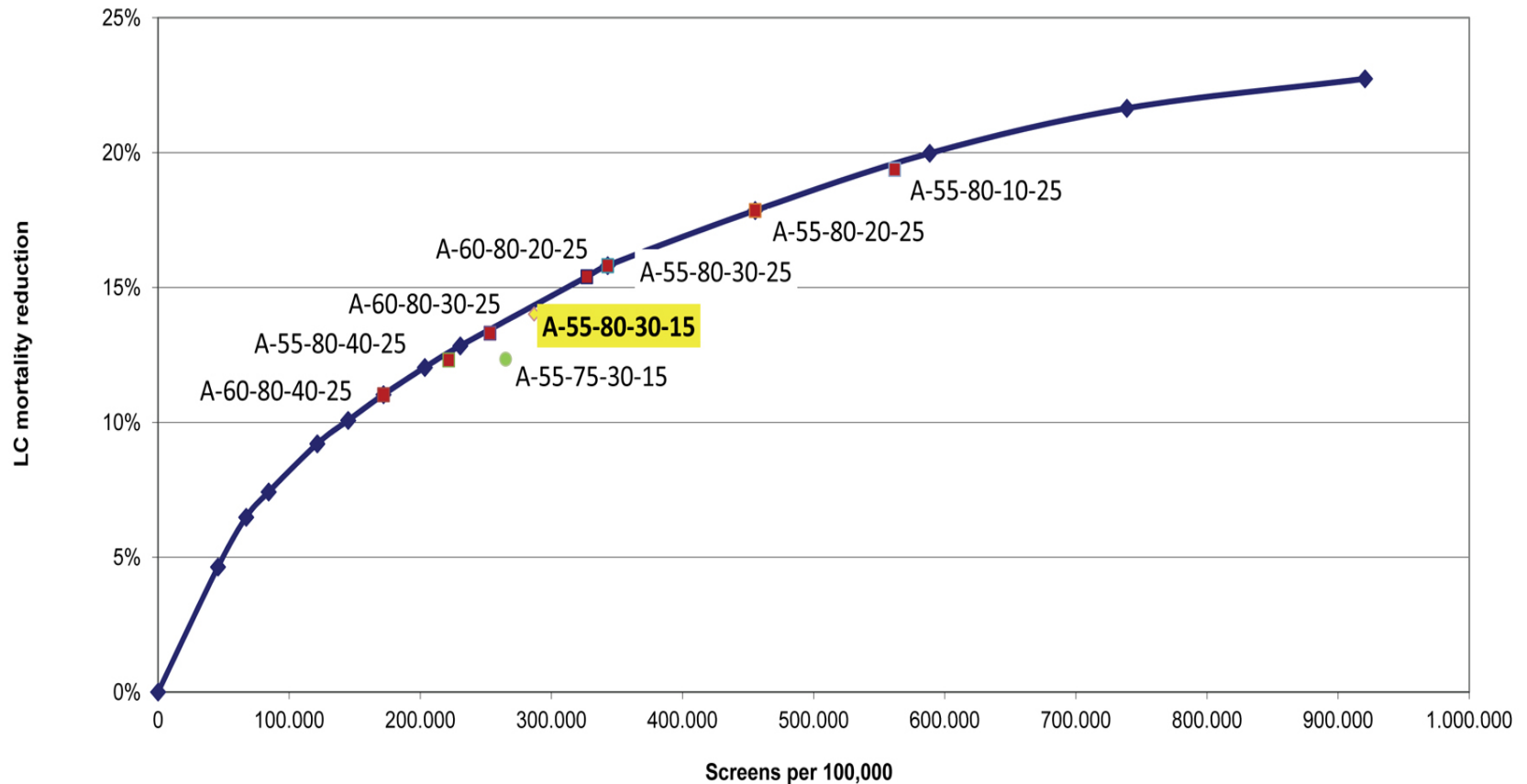
All model averages: Scenarios up to age 80
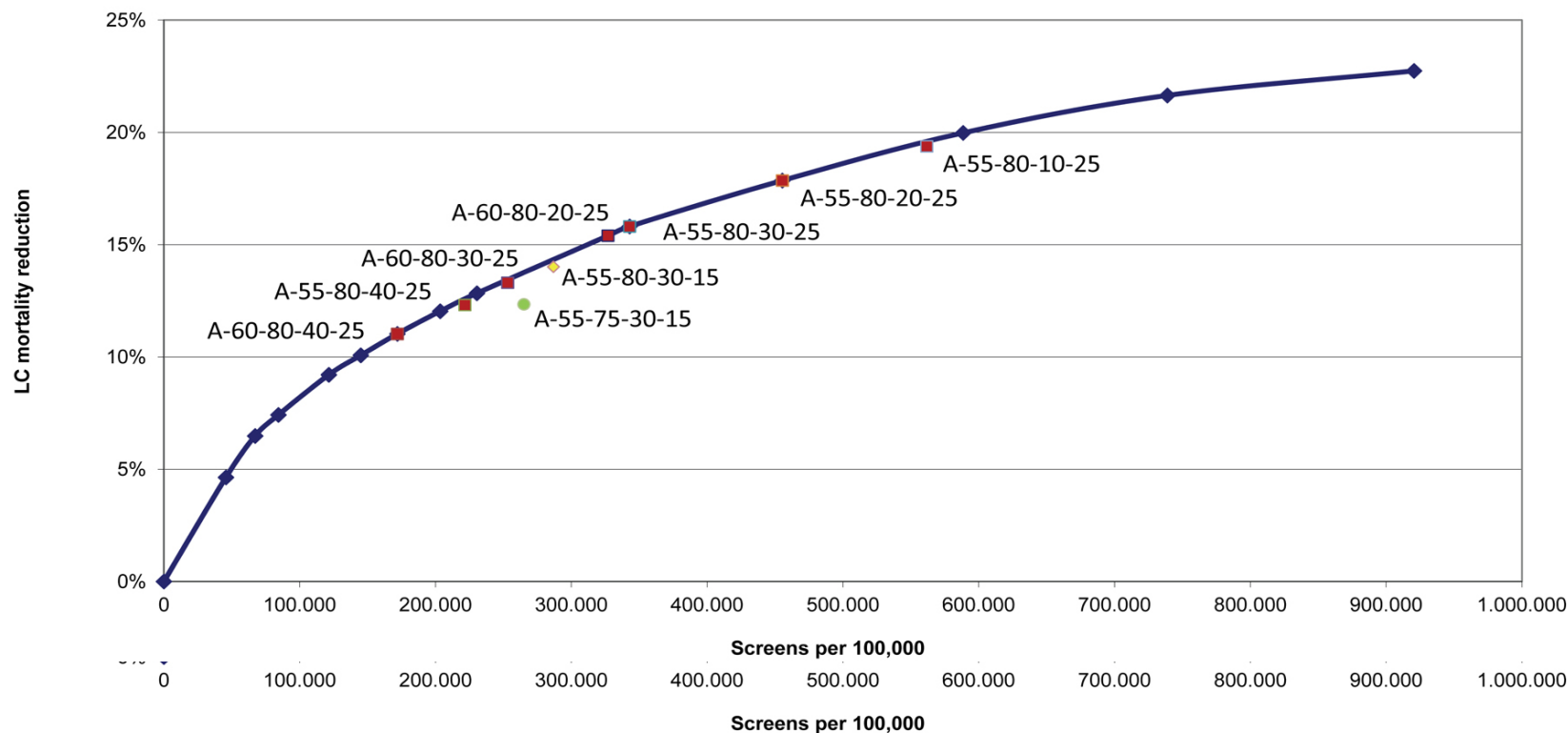
H.J. de Koning et al., Annals of Internal Medicine 2014

Advantageous scenario (USPSTF)

All model averages: Scenarios up to age 80

Benefits

- Lung cancer mortality reduction
- Reduction advanced disease
- Life years gained

Harms

- False-positives
- Over diagnosis
- Over treatment
- Radiation exposure
- Costs
- Quality of life

Conclusions

- Triennial and biennial screens reduce LC mortality by only 5-10%

- Expanding the original NLST criteria by 5 more years (**A 55-80-30-15**) and/or to start 5 years later (at age 60), but extending the risk group (up to 25 years since quit smoking) are more effective and more efficient

- Extending eligibility to fewer pack-years lead to higher benefits, but more additional harms

- **Advantageous scenario: Annual CT-screening 55 through 80 (30-15)** (minimum 30 pack-years; maximum quit smoking 15 years: 19% eligible)
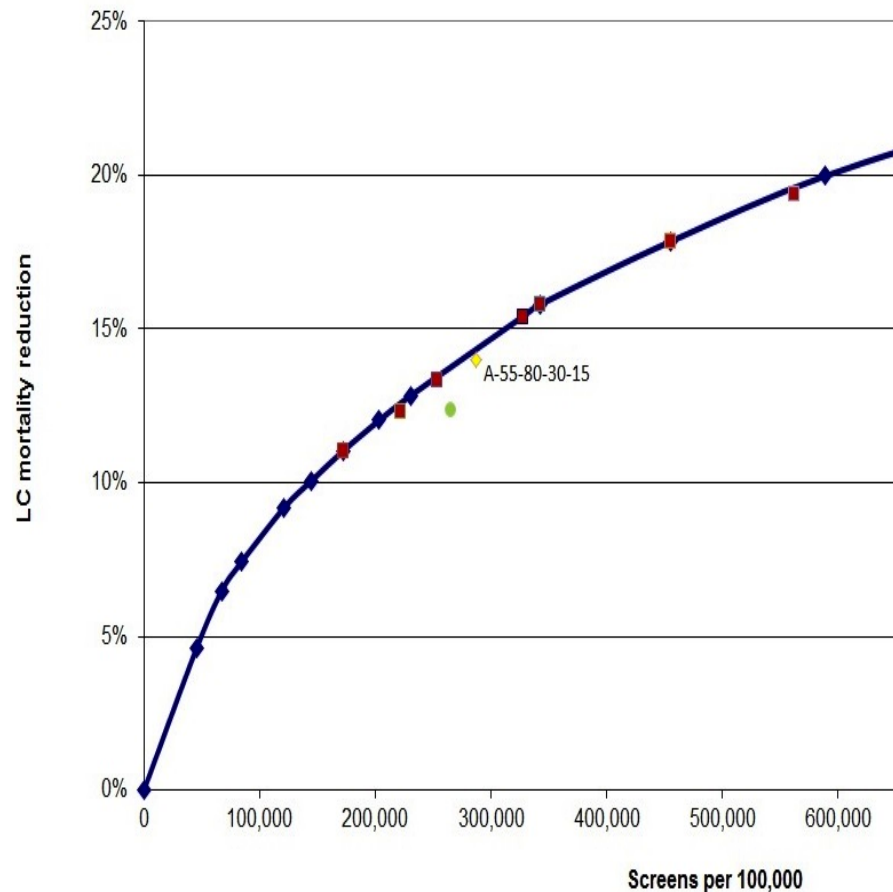
  287,000 screens - 500 LC deaths prevented (ratio 1:575)

  5,250 life-years gained

  190 overdiagnosed cases (10% of screen-detected cases)

NLST-criteria (stop 75) not efficient

All model averages: Scenarios up to age 80

A-55-80-30-15

LC mortality reduction

Screens per 100,000

LC mortality reduction results for 9 different annual scenarios (100,000 US-1950 cohort followed 45-90)

All model averages: Scenarios up to age 80
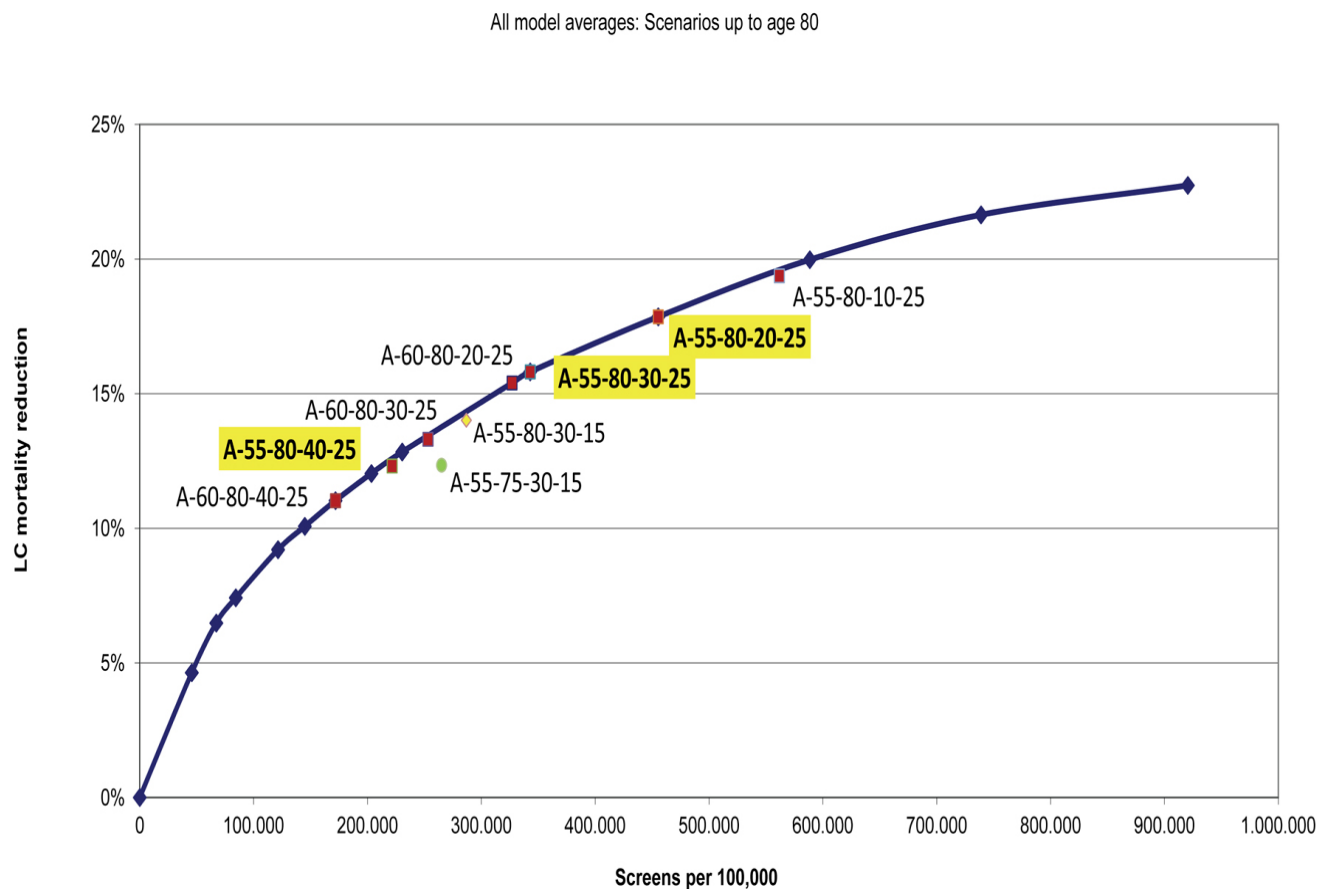
Should Never-Smokers at Increased Risk for Lung Cancer Be Screened?

Kevin ten Haaf, MSc, and Harry J. de Koning, MD, PhD

Characteristics of RCT on LDCT screening for lung cancer

Table 2. Characteristics of randomised controlled trials on LDCT screening for lung cancer

Trial	Participants	Initiation	Design	Screenings	Characteristics participants			
	N	Year		N	Sex	Age*	Smoking	Cessation
NLST[97,138]	53,439	2002	LDCT vs. CXR	3	M/F	55-74	≥30 py	<15 yrs
NELSON[108,139]	15,822	2004	LDCT vs. no screening	4	M/F	50-75	≥15/day for 25 yrs or ≥10/day for 30 yrs	≤10 yrs
DLST[99]	4,104	2004	LDCT vs. no screening	5	M/F	50-70	≥20 py	<10 yrs
MILD[100]	4,099	2005	LDCT vs. no screening	5/10	M/F	≥49	≥20 py	<10 yrs
LUSI[101]	4,052	2007	LDCT vs. no screening	4	M/F	50-70	≥15/day for 25 yrs or ≥10/day for 30 yrs	≤10 yrs
UKLS[102,140]	4,000	2011	LDCT vs. no screening	1	M/F	50-75	≥5% risk of lung cancer in 5 yrs	
ITALUNG[103]	3,206	2004	LDCT vs. no screening	4	M/F	55-70	≥20 py	<10 yrs
DANTE[104]	2,472	2001	Initial CXR, followed by LDCT vs. no screening	4	M	60-75	≥20 py	<10 yrs

Definition of abbreviations: LDCT = low-dose computed tomography; CXR = chest x-ray; M = male; F = female; py = pack-years; yrs = years.
* Age range up to, but not including upper limit.

From: Screening for Lung Cancer With Low-Dose Computed Tomography: A Systematic Review to Update the U.S. Preventive Services Task Force Recommendation

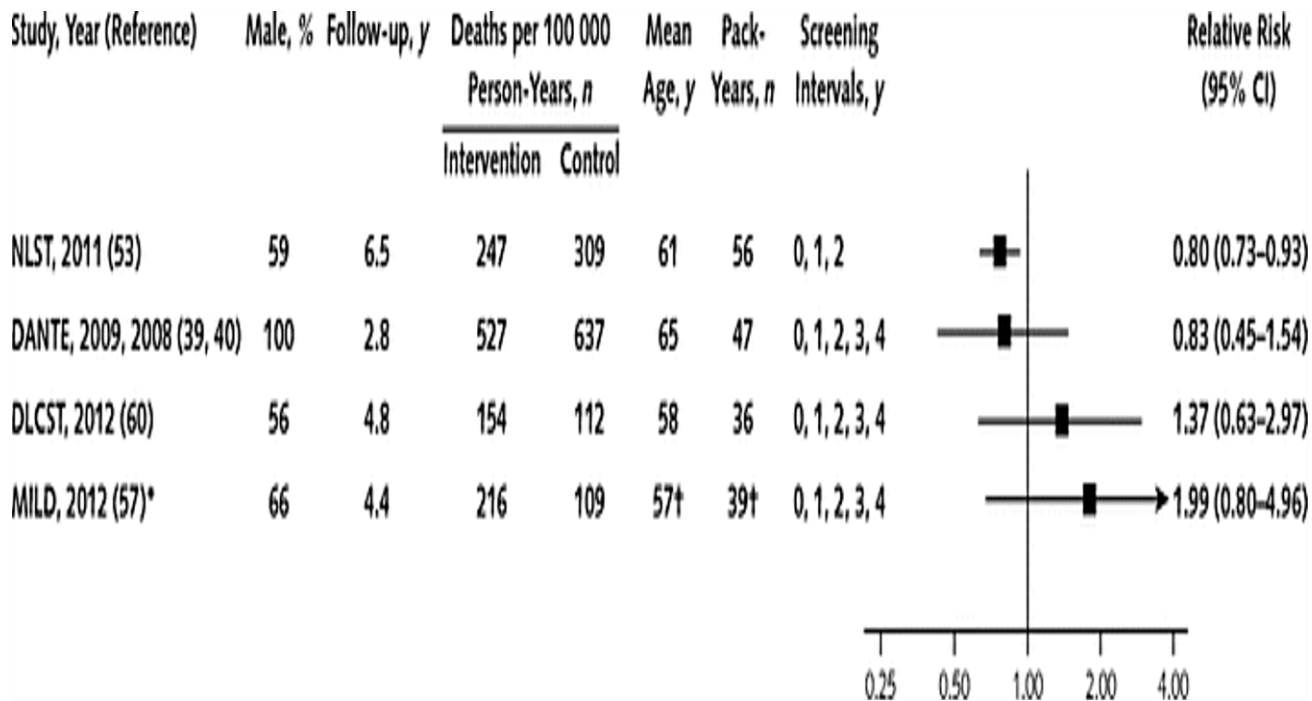| Study, Year (Reference)	Male, %	Follow-up, y	Deaths per 100 000 Person-Years, n		Mean Age, y	Pack-Years, n	Screening Intervals, y		Relative Risk (95% CI)
			Intervention	Control					
NLST, 2011 (53)	59	6.5	247	309	61	56	0, 1, 2		0.80 (0.73–0.93)
DANTE, 2009, 2008 (39, 40)	100	2.8	527	637	65	47	0, 1, 2, 3, 4		0.83 (0.45–1.54)
DLCST, 2012 (60)	56	4.8	154	112	58	36	0, 1, 2, 3, 4		1.37 (0.63–2.97)
MILD, 2012 (57)*	66	4.4	216	109	57†	39†	0, 1, 2, 3, 4		1.99 (0.80–4.96)

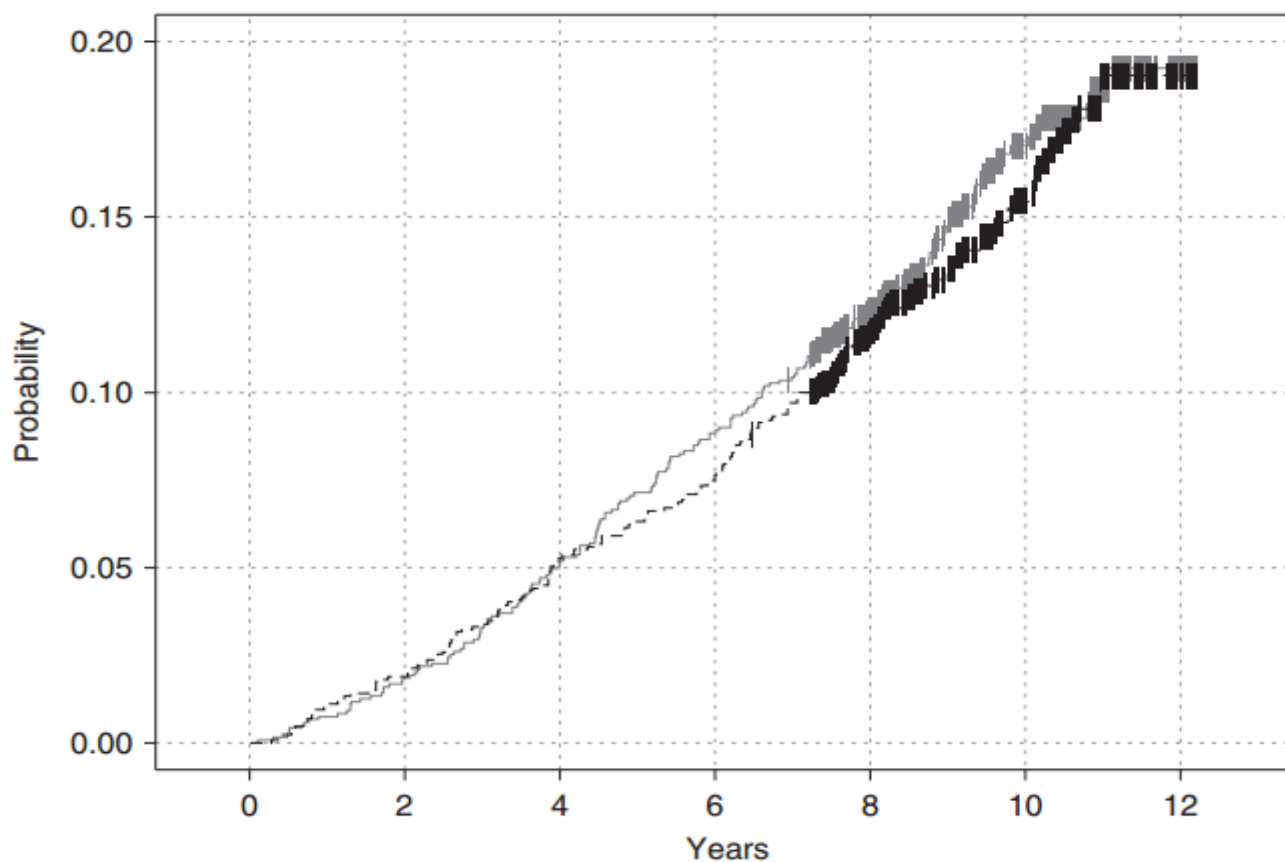**Figure Legend: Trial results for lung cancer mortality.**
DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST = Danish Lung Cancer Screening Trial; MILD = Multicentric Italian Lung Detection; NLST = National Lung Screening Trial.
* Annual screening group compared only with control group; biennial screening group not shown.
† Median.

Long-term follow-up results of the DANTE trial: a randomized study of lung cancer screening with spiral computed tomography
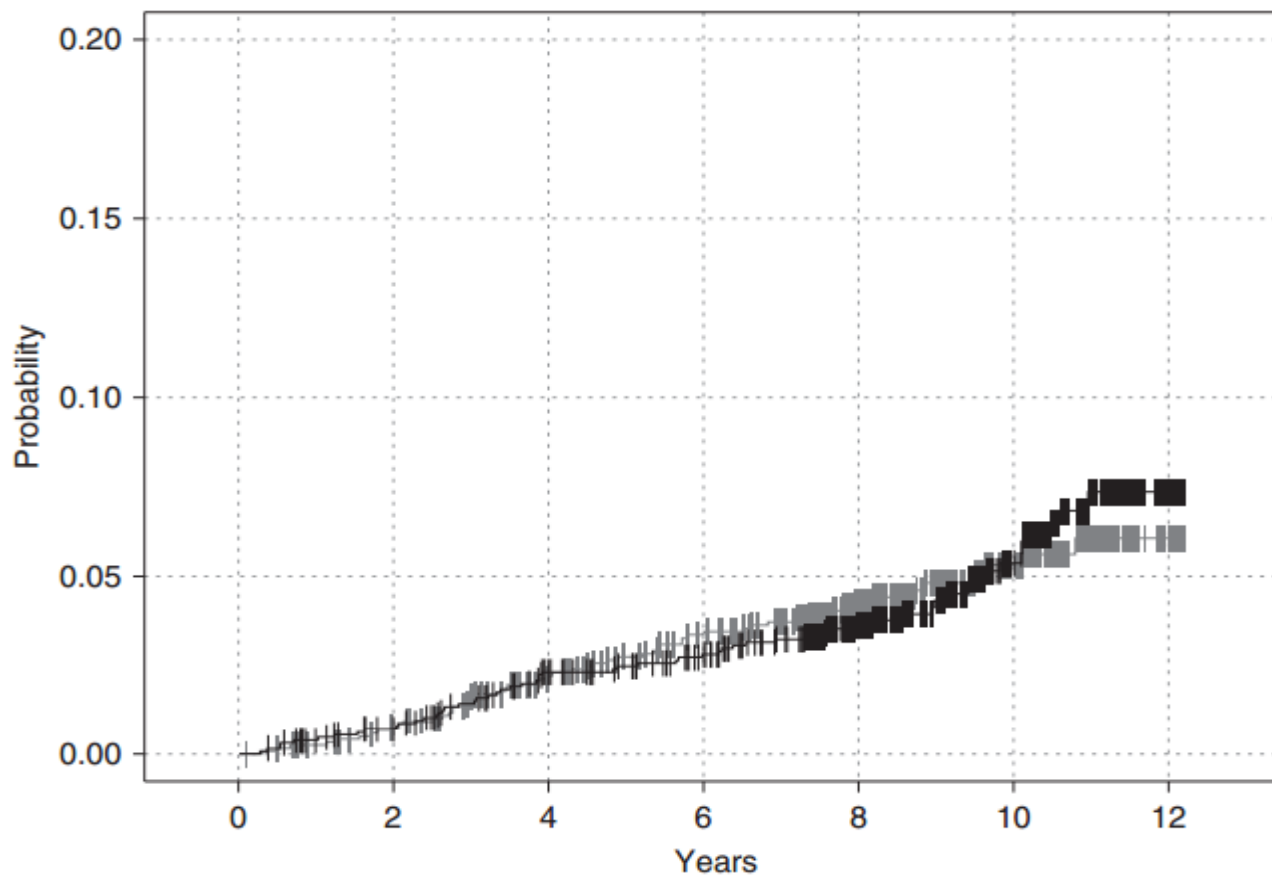
Infante M, Cavuto S, Lutman ER, et al (2015)

Figure 3. Cumulative probability of death from all causes. Hazard ratio = 0.947 (95% confidence interval, 0.769–1.165). LDCT = low-dose spiral computed tomography.

At risk							
Control	1184	1162	1122	1078	748	335	20
LDCT	1264	1239	1197	1167	807	373	15

Figure 2. Cumulative probability of death from lung cancer. Hazard ratio = 0.993 (95% confidence interval, 0.688–1.433). LDCT = low-dose spiral computed tomography.

Table 4. Lung Cancer–Specific and All-Cause Mortality Rates (per 100,000 Person-Years)

	LDCT	Control	All
Study subjects, n (%)	1,264 (51.59)	1,186 (49.41)	2,450 (100)
FU, person-years	10,875	10,104	20,979
Cause of death, n (%)			
Cancer of the lung	59 (4.66)	55 (4.64)	114 (4.65)
Cancer of other organs	54	59	
Nonneoplastic disease	65	62	
Unknown*	2	—	
Total deaths	180 (14.24)	176 (14.84)	356 (14.53)
Lung cancer mortality (95% CI)	543 (413–700)	544 (410–709)	543 (448–653)
All-cause mortality (95% CI)	1,655 (1,422–1,916)	1,742 (1,494–2,019)	1,697 (1,525–1,883)

Definition of abbreviations: CI = confidence interval; FU = follow-up; LDCT = low-dose spiral computed tomography.
*One patient died of disseminated cancer of unknown origin, and one patient died of unknown causes in a foreign country.

Table 4. Causes of death in DLCST				
Cause of death		**All** N= 328	**Screening group** N= 165	**Control group** N= 163
Cancer	Lung	77 (23)	39 (24)	38 (23)
	Pancreatic	22 (6.7)	9 (5.5)	13 (8.0)
	Cerebral	9 (2.7)	5 (3.0)	4 (2.5)
	Liver or biliary	7 (2.1)	3 (1.8)	4 (2.5)
	Esophagus	7 (2.1)	4 (2.4)	3 (1.8)
	Colon or rectal	7 (2.1)	5 (3.0)	2 (1.2)
	Bladder	7 (2.1)	2 (1.2)	5 (3.1)
	Prostate	6 (1.8)	3 (1.8)	3 (1.8)
	Gastric	5 (1.5)	4 (2.4)	1 (0.6)
	Other types*	34 (10)	18 (11)	16 (9.8)
Ischemic heart disease		22 (6.7)	12 (7.3)	10 (6.1)
Stroke		16 (4.9)	5 (3.0)	11 (6.7)
COPD		15 (4.6)	7 (2.4)	8 (4.9)
Alcohol addiction		12 (3.7)	3 (1.8)	9 (5.5)
Alcoholic liver cirrhosis		9 (2.7)	5 (3.0)	4 (2.5)
Aortic aneurism		8 (2.4)	4 (2.4)	4 (2.5)
Sepsis		5 (1.5)	3 (1.8)	2 (1.2)
Other†		50 (15)	26 (16)	24 (15)
Unknown		10 (3.0)	8 (4.8)	2 (1.2)

Data presented as N (%).

*Other types of cancer involve less than 5 participants and include: Breast cancer, sarcomas, malignant melanoma, leukaemia, lymphoma, carcinoid cancer, tonsil cancer, oral cancer, and others.

†Other causes of death involve less than 5 participants and include: Amyotrophic lateral sclerosis, heart failure, suicide, diabetes mellitus with complications, HIV, gastro-intestinal haemorrhage, necrotic fasciitis, and others.

DLCST – in conclusion

- No differences in LC mortality and all-cause mortality between groups
- Twice as many LC in screen group
- Mainly early-stage adenocarcinomas
- No difference in number of high-stage LC (III+IV) between groups

- Study is underpowered on its own
- (annual incidence of lung cancer in the control group was 0.27% instead of 0.50% expected)

- Somewhat astonishing death results:
  77 LC, 22 pancreatic, 21 alcohol, 22 ischaemic, 34 other cancers,
  50 other

-

Table 3 Lung cancer incidence and mortality, and all-cause mortality per 100 000 person-years in the Multicentric Italian Lung Detection study at 5-year follow-up, by study arm

| | Group | | | | | |
| | Control | | Biennial CT | | Annual CT | |
	N	Rate	N	Rate	N	Rate
Person-years (incidence)	6432.9		5470.9		5481.9	
Person-years (mortality)	6449.5		5516.8		5556.7	
Lung cancer incidence	20	310.9	25	457.0	34	620.2
Lung cancer deaths	7	108.5	6	108.8	12	216.0
Total deaths	20	310.1	20	362.5	31	557.9

CT, computed tomography.

NELSON vs. NLST

	NELSON	NLST
Positive test results	< 3%	24%
PPV	40.4%	3.8%
Sens*	92.5%	93.8%
Spec*	98.3%	73.4%
Stage I	62%	59%
Stage IIIB/IV	18%	23%

*First (annual) screening round

N Horeweg et al., Lancet Oncology 2014

Design NELSON trial

- Randomized controlled trial
- Population-based recruitment
- Screening vs. no screening

Does LDCT screening of high-risk subjects* for developing lung cancer, lead to lung cancer mortality with 25% or more at 10 years after randomization?

*High risk subjects:
- Age 50 to 75 years
- Smoking history: 15+ cigarettes/day for 25 years or 10+ cigarettes/day for 30 years
- Current or former smokers (cessation ≤10yrs)
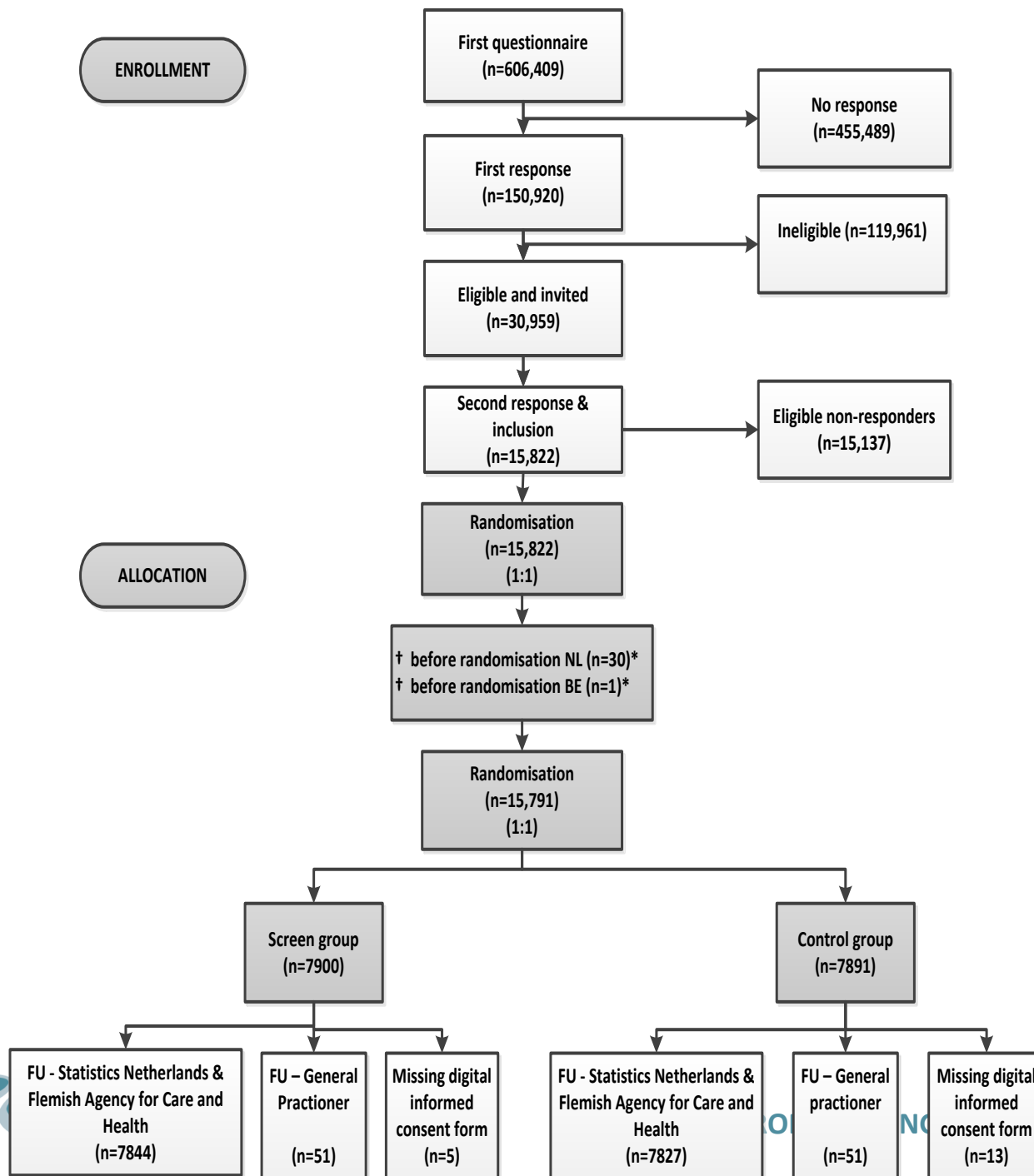
Baseline Characteristics and Mortality Outcomes of Control Group Participants and Eligible Non-Responders in the NELSON Lung Cancer Screening Study

Uraujh Yousaf-Khan, MD, Nanda Horeweg, PhD, MD,* Carlijn van der Aalst, PhD,**
Kevin ten Haaf, MSc, Mathijs Oudkerk, PhD, MD,† and Harry de Koning, PhD, MD**
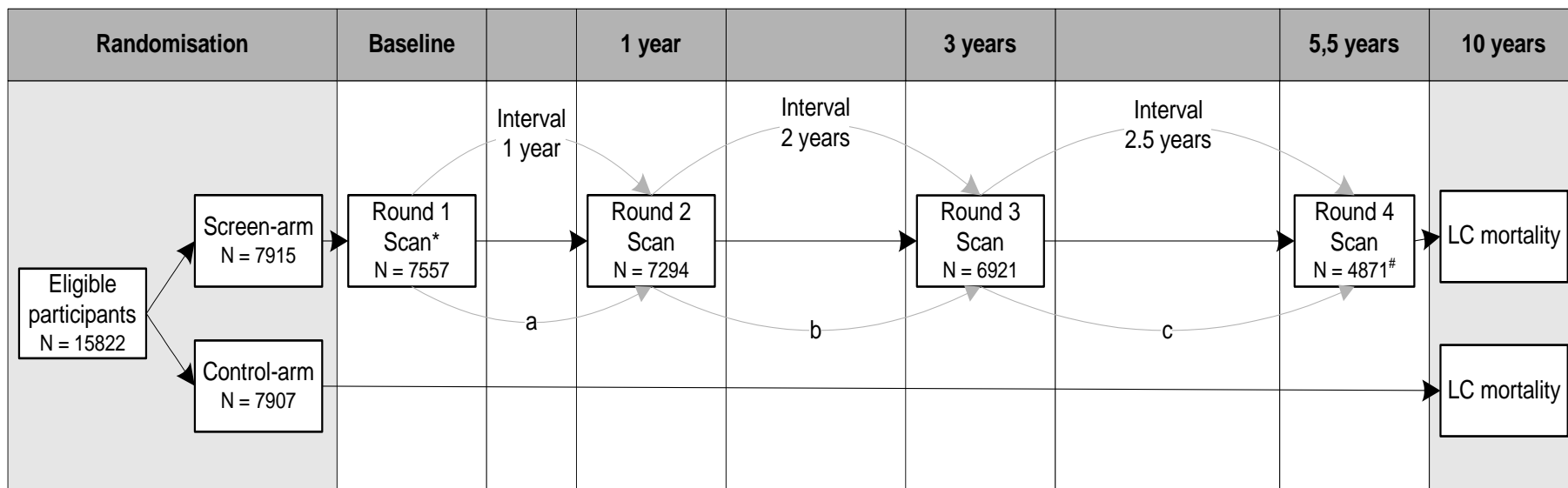
Generalisability NELSON trial

- Control group participants vs. Eligible non-responders
- Small healthy participant effect:
    - Younger age
    - More physically active
    - Higher educated
    - More often former smokers
- No differences: history of lung cancer, pack-yrs
- Mortality rate lower among participants
- However, differences are modest

- **Results are inferable for the general high-risk population**

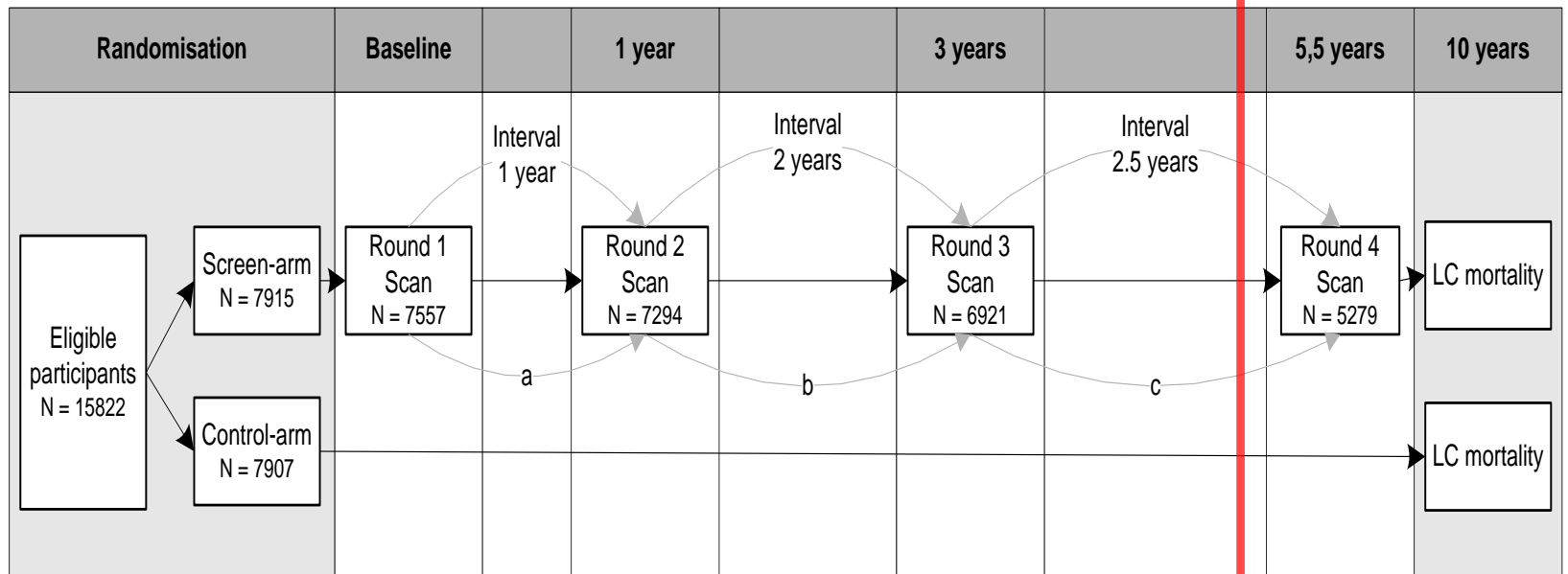(A.U. Yousaf et al., JTO 2015)

Design NELSON trial

Randomisation	Baseline	1 year	3 years	5,5 years	10 years

Eligible participants N = 15822

Screen-arm N = 7915

Control-arm N = 7907

Round 1 Scan* N = 7557

Interval 1 year

Round 2 Scan N = 7294

Interval 2 years

Round 3 Scan N = 6921

Interval 2.5 years

Round 4 Scan N = 4871[#]

a

b

c

LC mortality

LC mortality

5.5 yr risk calculations

First screening result

- Negative

- Indeterminate

- Positive

Risk screen detected lung cancer

- 1.0%

- 5.7%

- 48.3%

N. Horeweg et al., ERJ 2013

Design NELSON trial

- 4 rounds of low-dose multi-slice computer tomography scanning
- Only trial with increasing length of the screening interval:
  1 yr, 2 yr and 2.5 yr

Randomisation	Baseline	1 year	3 years	5,5 years	10 years

Interval 1 year
Interval 2 years
Interval 2.5 years

Eligible participants
N = 15822

Screen-arm
N = 7915

Control-arm
N = 7907

Round 1 Scan
N = 7557

Round 2 Scan
N = 7294

Round 3 Scan
N = 6921

Round 4 Scan
N = 5279

LC mortality

LC mortality

a

b

c

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*

Results: combined effect of size and growth rate on lung cancer probability
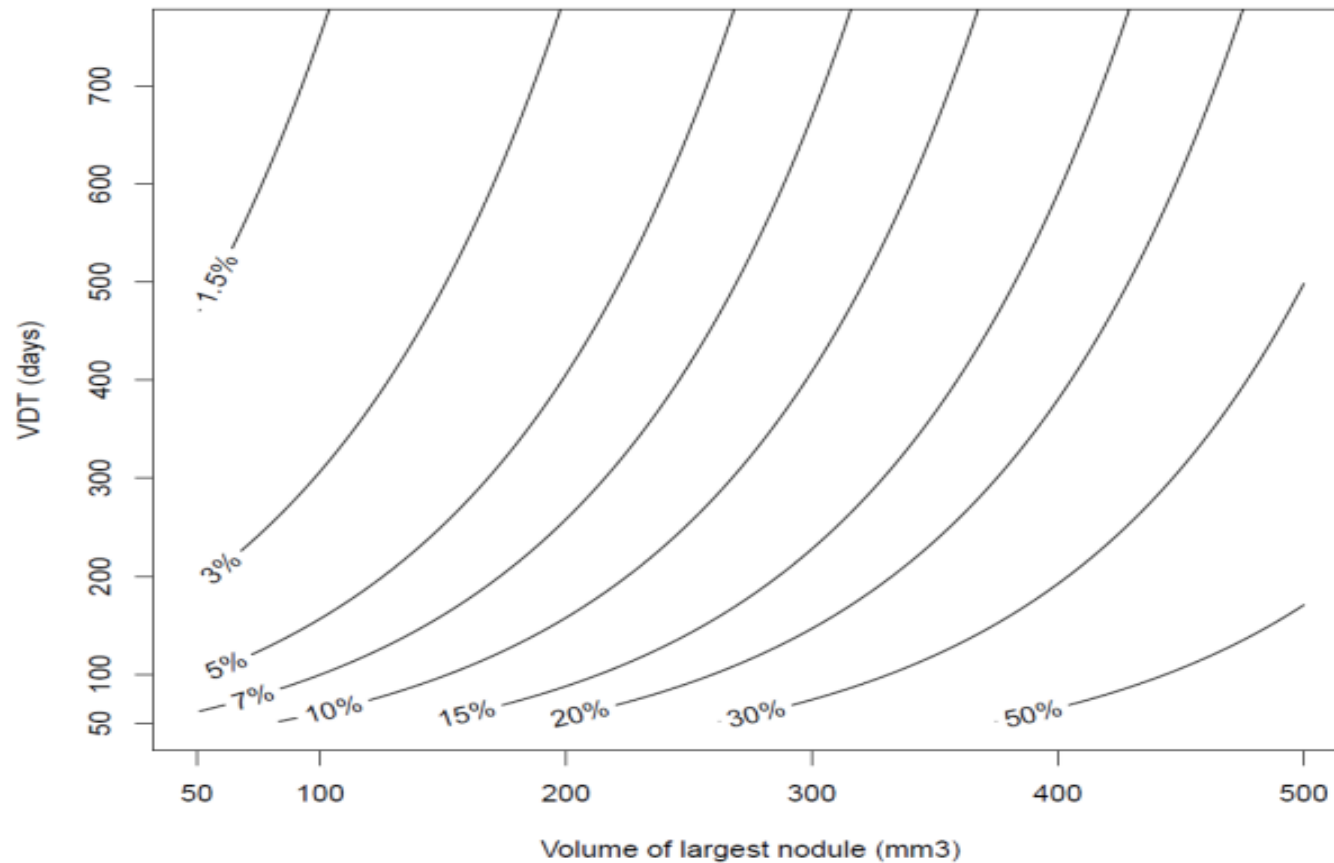
Results: nodule volume algorithm based on LC probability

Screening result	Nodule volume
negative	< 100 mm³
indeterminate*	≥ 100 to 300 mm³
positive	≥ 300 mm³

*Follow-up CT for VDT assessment:
- final screening result negative for VDT ≥ 600 days
- final screening result positive for VDT < 600 days

Results: performance nodule volume algorithm

Screen test parameters	Performance percentage (95%CI)
Diagnostic work-up	5.9%
Follow-up CT scan	7.8%
Sensitivity	90.9 (81.2-96.1)
Specificity	94.9 (94.4-95.4)
Positive predictive value	14.4 (11.3-18.1)
Negative predictive value	99.9 (99.8-100.0)

Results: nodule diameter algorithms

Screening result	Algorithm based on nodule diameter percentage (95%CI)	Algorithm based on Fleischner criteria percentage (95%CI)
negative	< 5 mm	< 4 mm
indeterminate	≥ 5 to 10 mm*	≥ 4 to 8 mm†
positive	≥ 10 mm	≥ 8 mm

* follow-up CT for VDT assessment:

final result negative for VDT ≥ 600 days
final result positive for VDT < 600 days

† follow-up CT for VDT assessment:

final result negative for VDT ≥ 400 days
final result positive for VDT < 400 days

Results: performance compared to current guideline

Screen test parameters	Algorithm based on nodule diameter percentage (95%CI)	Algorithm based on Fleischner criteria percentage (95%CI)
Diagnostic work-up	9.1%	11.6%
Follow-up CT scan	22.2%	29.8%
Sensitivity	93.9 (85.0-98.1)	92.4 (83.1-97.1)
Specificity	91.8 (91.1-92.4)	89.2 (88.4-89.9)
Positive predictive value	9.6 (7.6-12.2)	7.4 (5.8-9.4)
Negative predictive value	99.9 (99.8-100.0)	99.9 (99.8-100.0)

Results: R1-R3 vs. R4

Participation rate by round

Informed consent original protocol			Additional Consent (screened)	
R1	R2	R3	R4	
95.5 %	92.2 %	87.5 %	80.5%	(97.1%)

Screen results

	R1-R3	R4
Negative	87.2%	96.0%
Indeterminate	10.8%	2.0%
Positive	2.0%	2.0%

elcc

Results: R1-R3 vs. R4

Screen-detected LC	R1-R3	R4
Participants (n)	200	43
LC (n)	209	46

LC detection rate	R1	R2	R3	R4
	0.9%	0.8%	1.1%	0.8%

Cumulative LC detection rate	R1-R3	R4
	2.6%	3.4%

NNS to detect 1 LC	R1-R3	R4
	85-122	123

Test characteristics NELSON nodule management strategy

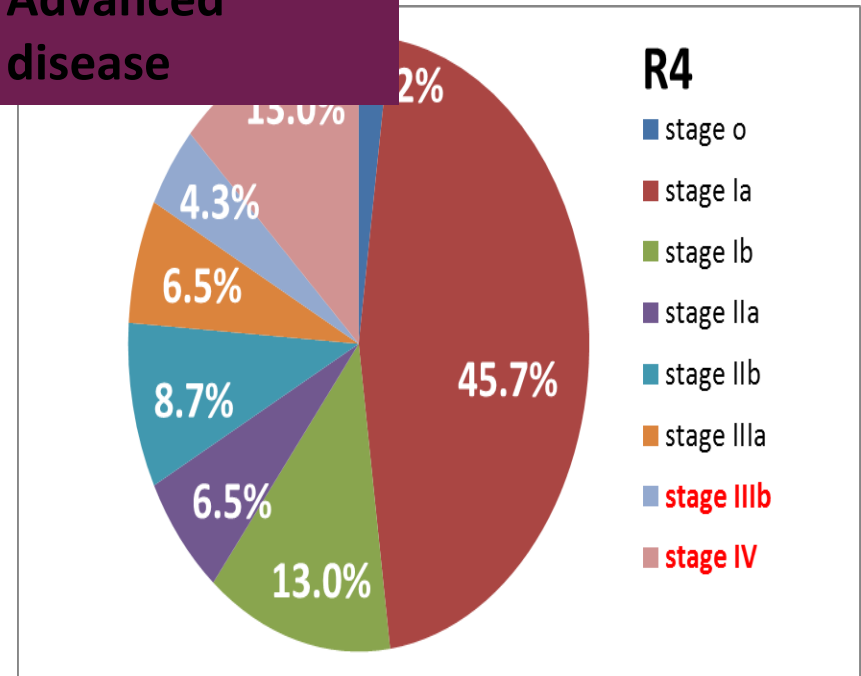| R1-R3 (combined)		R4	
◆ Sensitivity:	84.6%	◆ Sensitivity*:	-
◆ Specificity:	98.6%	◆ Specificity*:	-
◆ FP rate:	59.4%	◆ FP rate:	59.0%
◆ Overall FP rate:	1.2%	◆ Overall FP rate:	1.2%
◆ PPV:	40.4%	◆ PPV:	41.0%
◆ NPV:	99.8%	◆ NPV*:	-

*: data about FN were not available yet
N. Horeweg et al., ERJ 2013, N. Horeweg et al., Lancet Oncology 2014
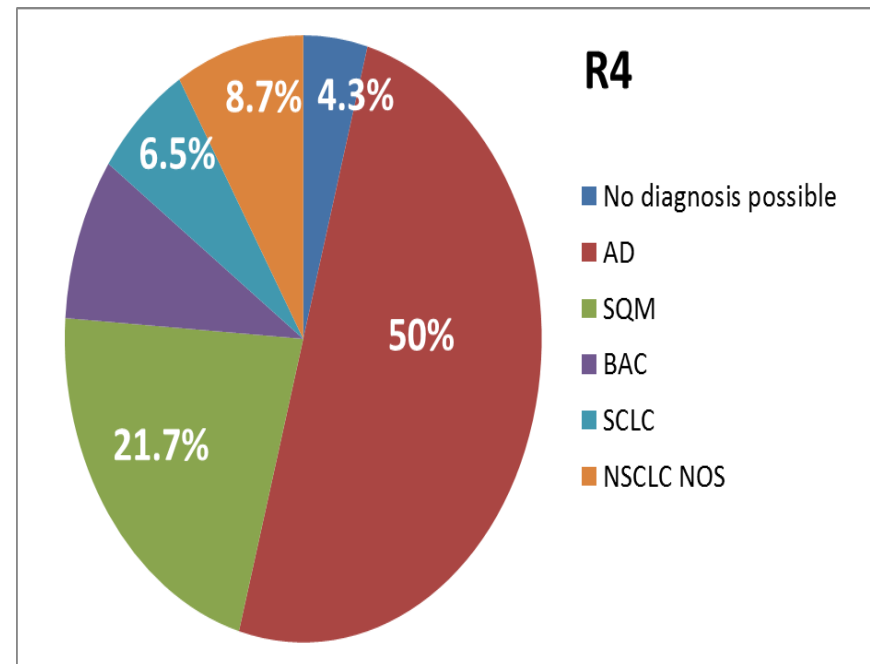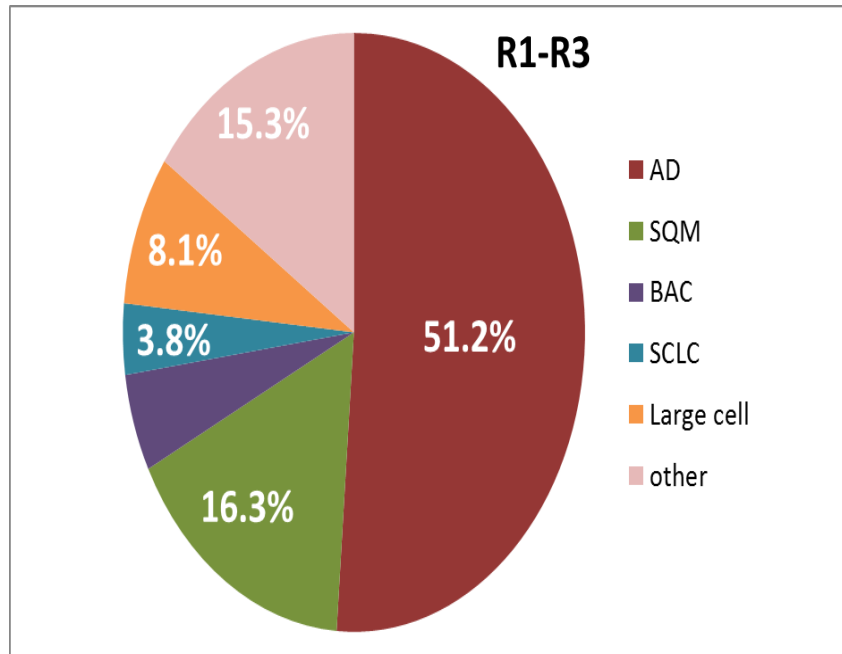
Stage distribution screen-detected lung cancers

R1-3

- stage o
- stage Ia
- stage Ib
- stage IIa
- stage IIb
- stage IIIa
- **stage IIIb**
- **stage IV**

4.8%
3.3%
14.4%
6.7%
5.3%
65.6%

Advanced disease

P < 0.001

R4

- stage o
- stage Ia
- stage Ib
- stage IIa
- stage IIb
- stage IIIa
- **stage IIIb**
- **stage IV**

13.0%
4.3%
6.5%
8.7%
6.5%
13.0%
45.7%

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N. Horeweg et al., Am J Respir Crit Care Med 2013
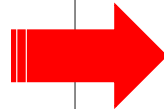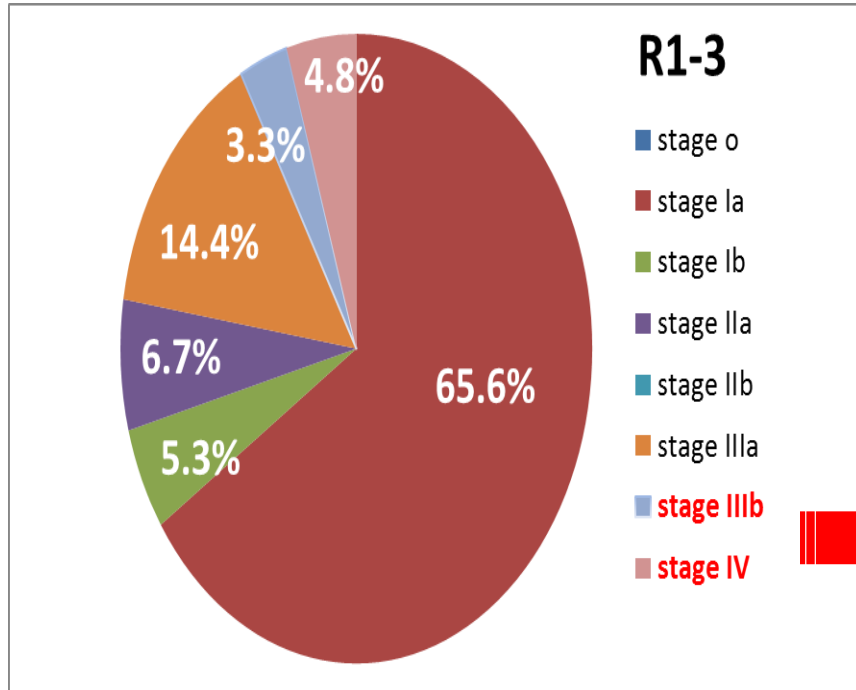
Screening Round	Stage I	Stage II	Stage III	Stage IV	
First	64.9%	9.5%	18.9%	6.8%	**Interval 1 year**
Second	75.8%	6.9%	13.7%	3.4%	**Interval 2 years**
Third	72.7%	3.9%	19.5%	3.9%	**Interval 2.5 years**
Fourth	62.2%	13.3%	11.1%	13.3%	

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RENCE 2016

Histology screen-detected lung cancers

R1-R3

- AD — 51.2%
- SQM — 16.3%
- BAC — 3.8%
- SCLC
- Large cell — 8.1%
- other — 15.3%

R4

- No diagnosis possible — 4.3%
- AD — 50%
- SQM — 21.7%
- BAC — 6.5%
- SCLC
- NSCLC NOS — 8.7%

P =0.055

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N. Horeweg et al., Am J Respir Crit Care Med 2013

UK Lung Cancer RCT Pilot Screening Trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening
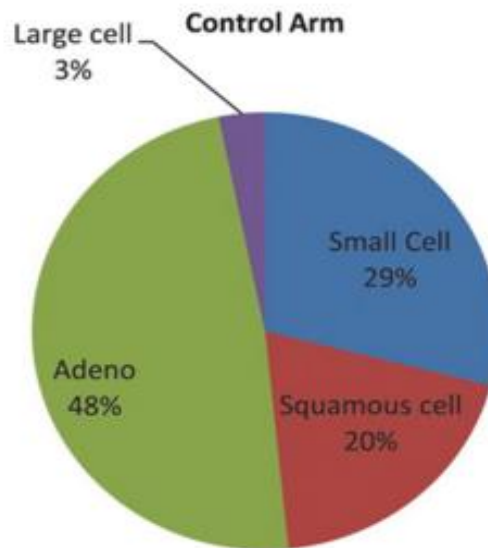
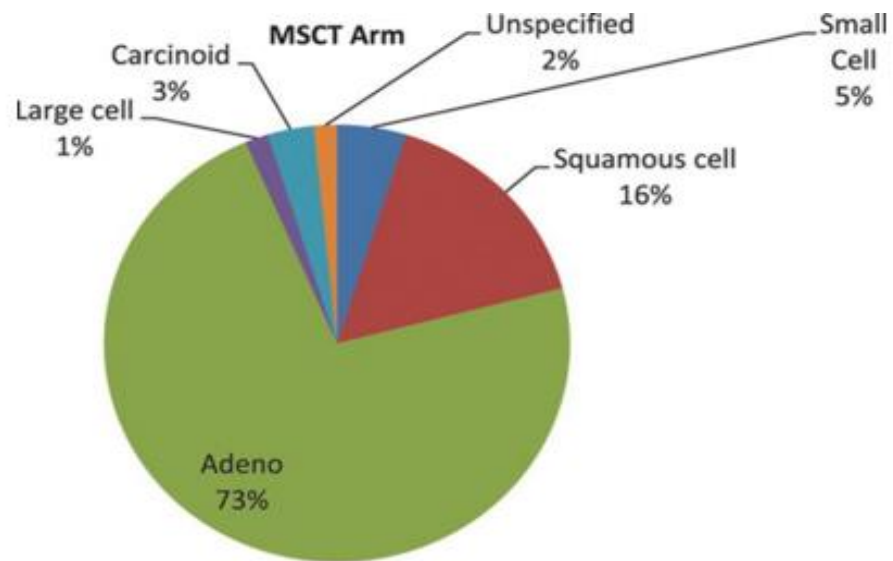J K Field, S W Duffy, D R Baldwin et al (2015)

UKLS – lung cancer pathology

- N = 42
  - Adenocarcinoma, n = 25
  - SCLC, n = 3
  - Typical carcinoid, n = 1
  - BAC, n = 1
- Total stage I/II, 86%:
  - stage I, n = 42 (67%); stage II, n = 8/42 (19%)
- Treatment:
  - 92% of stage I/II LC patients had surgery
  - 2 had radical radiotherapy
  - 7 did not undergo resection

Randomized Study on Early Detection of Lung Cancer with MSCT in Germany

Results of the First 3 Years of Follow-up After Randomization

N Becker, E. Motsch, M.L. Gross et al (2015)

MSCT Arm

- Unspecified 2%
- Small Cell 5%
- Squamous cell 16%
- Carcinoid 3%
- Large cell 1%
- Adeno 73%

Control Arm

- Large cell 3%
- Small Cell 29%
- Squamous cell 20%
- Adeno 48%

Risk-based selection from the general population in a screening trial: Selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON)

Carola A. van Iersel[1,2]*, Harry J. de Koning[1], Gerrit Draisma[1], Willem P.T.M. Mali[3], Ernst Th. Scholten[4], Kristiaan Nackaerts[5], Mathias Prokop[3], J.Dik.F. Habbema[1], Mathijs Oudkerk[6] and Rob J. van Klaveren[2]

[1]*Department of Public Health, Erasmus MC, Rotterdam, The Netherlands*
[2]*Department of Pulmonology, Erasmus MC, Rotterdam, The Netherlands*
[3]*Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands*
[4]*Department of Radiology, Kennemer Gasthuis Haarlem, The Netherlands*
[5]*Department of Pulmonology, University Hospital Gasthuisberg, Leuven, Belgium*
[6]*Department of Radiology, University Medical Center Groningen, Groningen, The Netherlands*

NELSON projected power overview (Belgian participants included)

Projected power for NELSON trial (*updated*)

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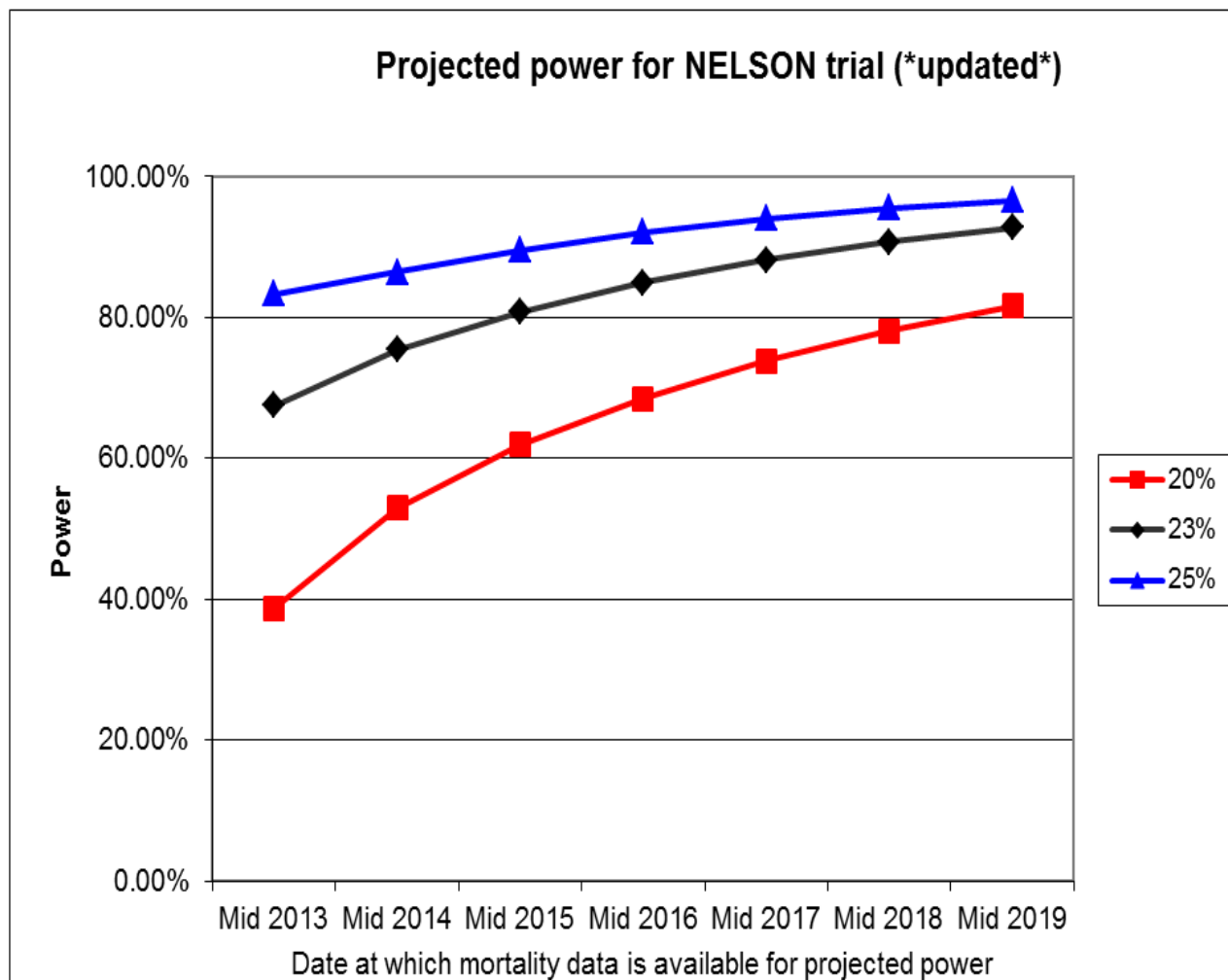
Future plans

Causes of death reviews NELSON (70% complete)

◆ Lung cancer mortality analyses

- interim analysis NELSON

- establish criteria for possible pooling for subgroup analyses
(Italung, UKLS, German; 11,000, …)

◆ Risk-based algorithms

◆ Microsimulation of screening scenarios & cost-effectiveness
based on NELSON

◆ Validation study lung nodules (also in clinical care)

Conclusions

◆ One large CT-trial has shown statistically significant results on LC mortality reduction

◆ USPSTF formulated, based on quantifications from CISNET-models, an advantageous scenario -- possibly cost-effective

◆ 2.5 year interval is too long

◆ Important drawbacks in the original US-scenario

◆ NELSON trial much better screening algorithm

◆ So far, encouraging results in NELSON

◆ Still some patience