LDCT lung cancer screening in populations at different risk for lung cancer

Gustavo Borges da Silva Teles [1], Ana Carolina Sandoval Macedo,[1] Rodrigo Caruso Chate,[1] Viviane Arevalo Tabone Valente,[2] Marcelo Buarque de Gusmao Funari,[1] Gilberto Szarf[1]

[1]Department of Radiology, Hospital Israelita Albert Einstein, São Paulo, Brazil
[2]Preventive Health Center, Hospital Israelita Albert Einstein, São Paulo, Brazil

Correspondence to
Dr Gustavo Borges da Silva Teles;
gustavo.teles@einstein.br

ABSTRACT

Introduction The improvement of low-dose CT (LDCT) lung cancer screening selection criteria could help to include more individuals who have lung cancer, or in whom lung cancer will develop, while avoiding significant cost increase. We evaluated baseline results of LDCT lung cancer screening in a population with a heterogeneous risk profile for lung cancer.

Methods LDCT lung cancer screening was implemented alongside a preventive health programme in a private hospital in Brazil. Individuals older than 45 years, smokers and former smokers, regardless of tobacco exposure, were included. Patients were classified according to the National Lung Screening Trial (NLST) eligibility criteria and to $PLCO_{m2012}$ 6-year lung cancer risk. Patient characteristics, CT positivity rate, detection rate of lung cancer and false-positive rate were assessed.

Results LDCT scans of 472 patients were evaluated and three lung adenocarcinomas were diagnosed. CT positivity rate (Lung-RADS 3/4) was significantly higher (p=0.019) in the NLST group (10.1% (95% CI, 5.9% to 16.9%)) than in the non-NLST group (3.6% (95% CI, 2.62% to 4.83%)) and in the $PLCO_{m2012}$ high-risk group (14.3% (95% CI, 6.8% to 27.7%)) than in the $PLCO_{m2012}$ low-risk group (3.7% (95% CI, 2.9% to 4.8%)) (p=0.016). Detection rate of lung cancer was also significantly higher (p=0.018) among $PLCO_{m2012}$ high-risk patients (5.7% (95% CI, 2.5% to 12.6%)) than in the $PLCO_{m2012}$ low-risk individuals (0.2% (95% CI, 0.1% to 1.1%)). The false-positive rate for NLST criteria (16.4% (95% CI, 13.2% to 20.1%)) was higher (p<0.001) than for $PLCO_{m2012}$ criteria (7.6 (95% CI, 5.3% to 10.5%)).

Discussion Our study indicates a lower performance when screening low-risk individuals in comparison to screening patients meeting NLST criteria and $PLCO_{m2012}$ high-risk patients. Also, incorporating $PLCO_{m2012}$ 6-year lung cancer risk ≥0.0151 as an eligibility criterion seems to increase lung cancer screening effectiveness.

Key messages

► How the CT positivity, lung cancer detection rate and false-positive rate in low-dose CT lung cancer screening varies in a population with a heterogeneous risk profile for lung cancer, according to National Lung Screening Trial (NLST) and $PLCO_{m2012}$ eligibility criteria?

► Screening low-risk individuals had lower CT positivity and lower lung cancer detection rate in comparison with screening patients meeting NLST criteria and $PLCO_{m2012}$ high-risk individuals. Also, the false-positive rate for $PLCO_{m2012}$ criteria was lower than for NLST criteria.

► Even though lung cancer can be found in low-risk individuals, screening high-risk patients (using NLST criteria and $PLCO_{m2012}$ 6-year lung cancer risk) rendered higher diagnostic yield in our sample.

26.7% of all individuals currently being diagnosed with lung cancer in the USA meet the strict NLST eligibility criteria.[2] Accordingly, there is a need to improve screening selection criteria in order to select more individuals who have lung cancer, or in whom lung cancer will develop, while avoiding significant cost increase.

Some risk assessment models that incorporate additional risk factors have been developed and demonstrated to improve lung cancer screening efficiency in North America and the UK, including $PLCO_{m2012}$ and Liverpool Lung Project Model.[3 4] The performance of these models has been evaluated in several studies in the USA, UK, Canada, Germany and Australia, but have not been validated in South America.[3–10]

Also, LDCT positivity has been recently demonstrated as an independent risk factor for future lung cancer in high-risk individuals. Having at least one positive screen is associated with increased $PLCO_{m2012}$ risk and improved lung cancer risk prediction.[11]

INTRODUCTION

The National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality for screening with low-dose CT (LDCT) versus chest radiography using age and smoking exposure as selection criteria for lung cancer screening.[1] However, only

We compared baseline results of LDCT lung cancer screening in a population with a heterogeneous risk profile for lung cancer in Brazil, according to NLST criteria and to $PLCO_{m2012}$ 6-year lung cancer risk.

METHODS

LDCT lung cancer screening was implemented alongside a preventive health programme in a private hospital in Brazil, where cardiovascular risk and respiratory symptoms were assessed. After discussing harms and benefits, individuals older than 45 years, smokers and former smokers, regardless of tobacco exposure, were offered participation in the screening.

Baseline LDCT scans performed from May 2015 to April 2016 were reviewed. CT scans were reported by board-certified thoracic radiologists and examinations were interpreted using Lung-RADS 1.0 classification. Patients with CT positive results (Lung-RADS 3 and 4) were referred to a pulmonologist. Patients with other potentially clinically significant findings (Lung-RADS S category) were referred to their clinicians. Lung cancer data were acquired from direct contact with patients,

Table 1 Characteristics of individuals who attended the screening, stratified by NLST criteria

Variable	NLST criteria	non-NLST criteria	All	P value
No. of attendees (%)	79 (16.7)	393 (83.3)	472 (100.0)	–
Mean age (±SD), y	60.6 (5.2)	48.7 (8.7)	50.6 (9.3)	**<0.001**
Sex (%)				0.728*
Female	19 (24.1)	94 (23.9)	113 (23.9)	
Male	60 (75.9)	299 (76.1)	359 (76.1)	
Body mass index (mean±SD)	28.3 (5.1)	27.9 (4.1)	28.1 (4.3)	0.364
Smoking status (%)				0.22*
Former	36 (45.6)	153 (38.9)	189 (40.0)	
Current	43 (54.4)	240 (61.1)	283 (60.0)	
Pack-years (median; quartile)	40 (31; 60)	15 (7.5; 25)	20 (9; 30)	**<0.001†**
Personal cancer				**0.004‡**
Negative	70 (88.6)	383 (97.4)	453 (96.0)	
Positive	9 (11.4)	10 (2.6)	19 (4.0)	
COPD, emphysema, bronchitis				**<0.001‡**
Negative	41 (51.9)	347 (88.2)	388 (82.2)	
Positive	38 (48.1)	46 (11.8)	84 (17.8)	
Family history of lung cancer				>0.999‡
Negative	78 (98.7)	387 (98.5)	465 (98.7)	
Positive	1 (1.3)	6 (1.5)	7 (1.5)	
Education (n=438)				**<0.001§**
Less than high school	7 (9.9)	2 (0.5)	10 (2.1)	
High school	16 (22.5)	35 (9.5)	57 (12.1)	
College	29 (40.8)	129 (35.1)	169 (35.8)	
Postgraduate	21 (26.8)	201 (54.8)	236 (50.0)	
Race				0.700§
White	70 (88.6)	361 (91.9)	431 (91.3)	
Black	5 (6.3)	12 (3.1)	17 (3.6)	
Hispanic	0 (0.0)	4 (1.0)	4 (0.8)	
Asian	4 (5.1)	16 (4.1)	20 (4.2)	

T-test.
Bold values indicate statistical significance.
*χ^2 test.
†Mann-Whitney U test.
‡Fisher's exact test.
§Likelihood ratio test.
COPD, chronic obstructive pulmonary disease; NLST, National Lung Screening Trial.

Table 2 Characteristics of individuals, stratified by PLCO$_{m2012}$ 6-year lung cancer risk

Variable	PLCO high risk	PLCO low risk	All	P value
Number of attendees (%)	35 (8.0)	403 (92.0)	438 (100.0)	–
Mean age (±SD), y	64.4 (6.1)	49.4 (8.5)	50.6 (9.3)	<0.001
Sex (%)				0.339*
Female	6 (17.1)	98 (24.3)	104 (23.7)	
Male	29 (82.9)	305 (75.7)	334 (76.3)	
Body mass index (mean±SD)	27.3 (5.6)	28.1 (4.2)	28.1 (4.3)	0.286
Smoking status (%)				0.031*
Former	8 (22.9)	167 (41.4)	175 (40.0)	
Current	27 (77.1)	236 (58.6)	263 (60.0)	
Pack-years (median; quartile)	47 (34; 60)	17.5 (8; 30)	21 (9; 30)	<0.001†
Personal cancer				0.009‡
Negative	29 (85.3)	391 (96.8)	420 (95.9)	
Positive	5 (14.7)	13 (3.2)	18 (4.1)	
COPD, emphysema, bronchitis				<0.001‡
Negative	15 (44.1)	345 (85.4)	360 (82.2)	
Positive	19 (55.9)	59 (14.6)	78 (17.8)	
Family history of lung cancer				0.444‡
Negative	34 (97.1)	397 (98.5)	431 (98.4)	
Positive	1 (2.9)	6 (1.5)	7 (1.6)	
Education (n=438)				<0.001§
Less than high school	5 (14.3)	4 (1.0)	9 (2.1)	
High school	15 (42.9)	36 (8.9)	51 (11.6)	
College	11 (31.4)	147 (36.5)	158 (36.1)	
Postgraduate	4 (11.4)	216 (53.6)	220 (50.2)	
Race				0.838§
White	33 (94.3)	371 (92.1)	404 (92.2)	
Black	1 (2.9)	11 (2.7)	12 (2.7)	
Hispanic	0 (0.0)	4 (1.0)	4 (0.9)	
Asian	1 (2.9)	17 (4.2)	18 (4.1)	

T-test.
*χ^2 test.
†Mann-Whitney U test.
‡Fisher's exact test.
§Likelihood ratio test.
COPD, chronic obstructive pulmonary disease; NLST, National Lung Screening Trial.

their families and physicians. The ongoing review was approved by the institutional review board.

Initially, patients were divided into two groups according to NLST eligibility criteria: NLST group (55–74 years of age, ≥30 pack-years of smoking and <16 years since quitting)[1] and non-NLST group. PLCO$_{m2012}$ 6-year lung cancer risk was calculated and patients with cancer risk ≥0.0151 were considered PLCO$_{m2012}$ high risk.[3] The PLCO$_{m2012}$ low-risk group included patients with 6-year lung cancer risk <0.0151. Patient characteristics, CT positivity rate, detection rate of lung cancer and false-positive rate were also assessed.

Patient and public involvement

Patients or other external influences had no involvement in the design and conduct of this study, in the writing of the manuscript and in decision-making regarding publishing the article.

RESULTS

The preventive health programme included 4911 patients, 1165 (23.7%) of which were offered participation in the lung cancer screening programme; 472 patients (40.5%) underwent LDCT scans. Baseline characteristics according to NLST criteria are detailed in

Table 3 Risk profile of individuals according to NLST criteria and PLCO$_{m2012}$ 6-year lung cancer risk

Variable	PLCO high risk	PLCO low risk	All	P value
NLST				<0.001
NLST criteria	29 (82.9)	42 (10.4)	71 (16.2)	
Non-NLST criteria	6 (17.1)	361 (89.6)	367 (83.8)	
Total	35 (100.0)	403 (100.0)	438 (100.0)	

McNemar's test (McNemar's test is used to compare paired proportions).
NLST, National Lung Screening Trial.

Table 5 Lung-RADS classification of LDCT, according to PLCO$_{m2012}$ 6-year lung cancer risk

Variable	PLCO high risk	PLCO low risk	All	P value
Lung-RADS				0.016
Positive	5 (14.3)	15 (3.7)	20 (4.6)	
Negative	30 (85.7)	388 (96.3)	418 (95.4)	
Total	35 (100.0)	403 (100.0)	438 (100.0)	

Lung-RADS positive (categories 3 and 4), negative (categories 1 and 2).
Fisher's exact test.
LDCT, low-dose CT.

table 1. Seventy-nine patients (16.7%) met NLST criteria (mean age: 60.6 years (±5.2); median tobacco exposure: 40 pack-years (IQR 31–60) and 393 patients (83.3%) were included in the non-NLST group (mean age: 48.7 years (±8.7); median tobacco exposure: 15 pack-years (IQR 7.5–25)).

There were no statistically significant differences between the groups regarding sex, race, smoking status and body mass index. Educational information was obtained from 438 patients (92.8%). The NLST group had a significantly lower educational level compared with the non-NLST group.

Thirty-five patients (8.0%) were included in the PLCO$_{m2012}$ high-risk group and 403 patients (92.0%) were considered PLCO$_{m2012}$ low-risk individuals. Baseline characteristics stratified by PLCO$_{m2012}$ 6-year lung cancer risk are detailed in table 2. The correlation between groups according to NLST criteria and PLCO$_{m2012}$ 6-year lung cancer risk is described in table 3.

The CT positivity rate was 10.1% (95% CI: 5.9% to 16.9%) in the NLST group, significantly higher (p=0.019) than in the non-NLST group (3.6% (95% CI: 2.62% to 4.83%)) (table 4).

CT positivity rate was 14.3% (95% CI: 6.8% to 27.7%) in patients with PLCO$_{m2012}$ high risk, also significantly higher (p=0.016) than in patients with PLCO$_{m2012}$ low risk (3.7% (95% CI: 2.9% to 4.8%)) (table 5).

Three lung adenocarcinomas were diagnosed after baseline LDCT results (figure 1). The detection rate of lung cancer among NLST patients (2.5% (95% CI: 1.1% to 5.6%)) was higher than in non-NLST patients (0.3% (95% CI: 0.1% to 1.3%)), but not statistically significant (p=0.070) (table 6).

Table 4 Lung-RADS classification of LDCT, according to NLST criteria

Variable	NLST criteria	non NLST criteria	All	P value
Lung-RADS				0.019
Positive	8 (10.1)	14 (3.6)	22 (4.7)	
Negative	71 (89.9)	379 (96.4)	450 (95.3)	
Total	79 (100.0)	393 (100.0)	472 (100.0)	

Lung-RADS positive (categories 3 and 4), negative (categories 1 and 2).
Fisher's exact test.
LDCT, low-dose CT; NLST, National Lung Screening Trial.

Detection rate of lung cancer in PLCO$_{m2012}$ high-risk patients (5.7% (95% CI: 2.5% to 12.6%)) was significantly higher (p=0.018) than in the PLCO$_{m2012}$ low-risk group (0.2% (95% CI: 0.1% to 1.1%)) (table 7).

The false-positive rate for NLST criteria was 16.4% (95% CI: 13.2% to 20.1%), significantly higher (p<0.001) than for PLCO$_{m2012}$ criteria (7.6% (95% CI: 5.3% to 10.5%)).

DISCUSSION

Our study compared LDCT screening in populations at different lung cancer risk and found low baseline detection rates of lung cancer in low-risk populations (0.3% in non-NLST individuals and 0.2% in the PLCO$_{m2012}$ low-risk group). Only a few studies evaluated LDCT screening in populations at low risk for lung cancer, almost exclusively in Asia. A screening study in China that included never smokers (most of them women) found lung cancer detection rate among never smokers (0.34%) to be higher compared with the group of smokers (including second-hand smokers and low-intensity smokers).[12] The authors explain this because there are far more non-smokers female lung adenocarcinomas patients in East Asia than in Europe and the USA, often associated with *EGFR* gene mutations.

The baseline detection rate of lung cancer among individuals meeting NLST criteria in our study (2.5%) was higher than other studies, such as NLST (1.0%),[1] NELSON (0.9%)[13] and BRELT1 (1.3%),[14] the latter being the only CT screening study conducted in Brazil, which included patients meeting NLST criteria. One possible explanation for that may be related to the small number of patients at high risk in our study.

Our Lung-RADS CT positivity rate was 10.1% in the NLST group and 3.6% in the non-NLST population, 14.3% in PLCO$_{m2012}$ high-risk group and 3.7% in the PLCO$_{m2012}$ low-risk group. Pinsky *et al* found a similar positivity rate in high-risk individuals applying Lung-RADS to the NLST population (13.6%).[15] To our knowledge, no other study has evaluated CT screening positivity rate in low-risk individuals using the Lung-RADS classification.

The use of PLCO$_{m2012}$ 6-year lung cancer risk as an eligibility criterion demonstrated to improve lung cancer screening efficiency compared with NLST criteria in North America.[3] Crosbie *et al* also used PLCO$_{m2012}$ 6-year
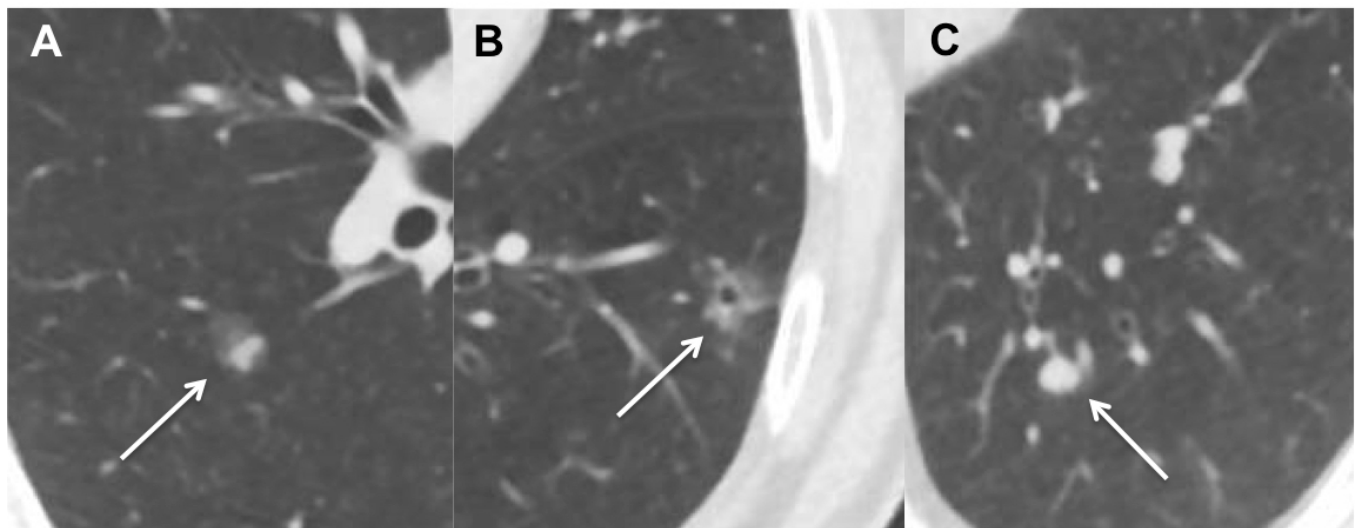
Figure 1 Baseline LDCT scans show nodules (arrows) diagnosed as lung cancers in the screening. (A) 57-year-old man, non-NLST criteria, subsolid nodule measuring 1.3 cm (solid component 0.8 cm)—Lung-RADS 4B; (B) 68-year-old man, NLST criteria, subsolid nodule measuring 1.3 cm (solid component <6 mm)—Lung-RADS 3; (C) 55-year-old man, NLST criteria, solid nodule measuring 0.8 cm—Lung-RADS 4A. LDCT, low-dose CT; NLST, NationalLung Screening Trial.

lung cancer risk ≥0.0151 to target high-risk individuals in deprived areas of Manchester and found a high prevalence of lung cancer (3%).[10] In our study, the use of $PLCO_{m2012}$ 6-year lung cancer risk for defining the high-risk group has shown to increase CT positivity and lung cancer detection rate. Furthermore, the false-positive rate for $PLCO_{m2012}$ criteria was lower than for NLST criteria, indicating an improvement of screening efficiency, even in a country with a high incidence of granulomatous disease as Brazil.

This study has limitations. First, it included a relatively small screening population. Second, it included only baseline LDCT examinations. Therefore, it was not possible to evaluate interval lung cancer incidence or accurately assess false-negative results.

A number of factors need to be taken into consideration in making decisions about implementing LDCT lung cancer screening in communities, including eligibility criteria, CT positivity and false-positive results, which may have a great impact on the cost-effectiveness of the programme.[16] Previous studies have shown that patients at higher risk for lung cancer achieve the greatest benefit of screening related to lung cancer mortality.[3]

Our study indicates that the screening yield of low-risk individuals is lower in comparison with high-risk patients, as CT positivity and lung cancer detection rate were significantly lower in the low risk groups. As a result, screening low-risk patients could lead to a higher number of CT scans, due to its lower diagnostic yield, resulting in increased costs compared with screening a high-risk population. On the other side, incorporating $PLCO_{m2012}$ 6-year lung cancer risk ≥0.0151 as an eligibility criterion seems to increase lung cancer screening effectiveness.

Table 6 Lung cancers stratified by NLST criteria

Variable	Lung cancer	No lung cancer	All	P value
NLST				0.070
NLST criteria	2 (66.7)	77 (16.4)	79 (16.7)	
Non-NLST criteria	1 (33.3)	392 (83.6)	393 (83.3)	
Total	3 (100.0)	469 (100.0)	472 (100.0)	

Fisher's exact test.
NLST, National Lung Screening Trial.

Table 7 Lung cancers stratified by $PLCO_{m2012}$ 6-year lung cancer risk

Variable	Lung cancer	No lung cancer	All	P value
$PLCO_{m2012}$				0.018
PLCO high risk	2 (66.7)	33 (7.6)	35 (8.0)	
PLCO low risk	1 (33.3)	402 (92.4)	403 (92.0)	
Total	3 (100.0)	435 (100.0)	438 (100.0)	

Fisher's exact test.

ORCID iD
Gustavo Borges da Silva Teles http://orcid.org/0000-0002-5405-5029

REFERENCES

1 Aberle DR, Adams AM, Berg CD, *et al*. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
2 Pinsky PF, Berg CD. Applying the National lung screening trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? *J Med Screen* 2012;19:154–6.
3 Tammemägi MC, Katki HA, Hocking WG, *et al*. Selection criteria for lung-cancer screening. *N Engl J Med* 2013;368:728–36.
4 Field JK, Duffy SW, Baldwin DR, *et al*. UK lung cancer RCT pilot screening trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax* 2016;71:161–70.
5 Ten Haaf K, Jeon J, Tammemägi MC, *et al*. Risk prediction models for selection of lung cancer screening candidates: a retrospective validation study. *PLoS Med* 2017;14:e1002277.
6 Katki HA, Kovalchik SA, Petito LC, *et al*. Implications of nine risk prediction models for selecting ever-smokers for computed tomography lung cancer screening. *Ann Intern Med* 2018;169:10–19.
7 Li K, Hüsing A, Sookthai D, *et al*. Selecting high-risk individuals for lung cancer screening: a prospective evaluation of existing risk models and eligibility criteria in the German EPIC cohort. *Cancer Prev Res* 2015;8:777–85.
8 Weber M, Yap S, Goldsbury D, *et al*. Identifying high risk individuals for targeted lung cancer screening: Independent validation of the PLCOm2012 risk prediction tool. *Int J Cancer* 2017;141:242–53.
9 Tammemagi MC, Schmidt H, Martel S, *et al*. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single-arm, prospective study. *Lancet Oncol* 2017;18:1523–31.
10 Crosbie PA, Balata H, Evison M, *et al*. Implementing lung cancer screening: baseline results from a community-based 'Lung Health Check' pilot in deprived areas of Manchester. *Thorax* 2019;74:405–9.
11 Tammemägi MC, Ten Haaf K, Toumazis I, *et al*. Development and validation of a multivariable lung cancer risk prediction model that includes low-dose computed tomography screening results: a secondary analysis of data from the National lung screening trial. *JAMA Netw Open* 2019;2:e190204.
12 Luo X, Zheng S, Liu Q, *et al*. Should nonsmokers be excluded from early lung cancer screening with low-dose spiral computed tomography? community-based practice in Shanghai. *Transl Oncol* 2017;10:485–90.
13 Yousaf-Khan U, van der Aalst C, de Jong PA, *et al*. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. *Thorax* 2017;72:48–56.
14 dos Santos RS, Franceschini JP, Chate RC, *et al*. Do current lung cancer screening guidelines apply for populations with high prevalence of granulomatous disease? results from the first Brazilian lung cancer screening trial (BRELT1). *Ann Thorac Surg* 2016;101:481–8.
15 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;162:485–91.
16 Kumar V, Cohen JT, van Klaveren D, Kent DM, *et al*. Risk-Targeted lung cancer screening: a cost-effectiveness analysis. *Ann Intern Med* 2018;168:161–9.