Editorial Commentary

Lung cancer screening: tell me more about post-test risk

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Lung cancer screening (LCS) by low-dose computed tomography (LDCT) can save lives because LC is detected in its early asymptomatic stage (1). We have come a long way since the first results of the national lung screening trial (NLST) (2), now confirmed in Europe by volumetric LDCT against control arm by the Nederlands Leuvens Longkanker Screenings Onderzoek (NELSON) (3) and the multicentric Italian lung detection (MILD) (4). The literature shows a substantial variability of LC risk even among screenees selected with strict risk criteria (5-7). Furthermore, the evolving research in LCS provides reinforced evidence on prolonged LCS for continuous and incremental reduction of lung cancer mortality (4,8,9). In such scenario, the relentless development and optimization of LCS practice is about reduction of false positives and radiation exposure, while refining efficiency (10-15).

LCS with longer-than-one-year interval between LDCT rounds looks like an interesting option for such purpose. Longer LCS interval is also known as low intensity approach. Here comes the interesting analysis of Robbins *et al.* who retrospectively interrogated the NLST database with the aim of defining post-test risk of lung cancer by description of LDCT findings (16) (*Table 1*).

Robbins *et al.* classified each screenee according to negative LDCT outcome (NLST criteria: solid nodule <4 mm) and radiological signs of subjective susceptibility to lung damage: emphysema and consolidation. Any LDCT was included in the analysis of post-test risk stratification, either baseline (1 for each screenee) or incidence round (up to 2 for each screenee). As such, the selected descriptors of post-test risk were applied on the top of a validated pre-test risk model, the lung cancer risk assessment tool (LCRAT) (24). The LCRAT is a comprehensive pre-test risk model developed in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and the NLST population, as well as data from the National Health Interview Survey (NHIS). Pre-test risk factors for the development of this model included several covariates: age, gender, ethnicity, education, body mass index, smoking history (pack-years, status, years since quitting, years of smoking, and cigarettes per day), self-reported emphysema, and family history of LC. The LCRAT was selected among the best performers in a model study including nine of the most authoritative pre-test risk models. It was also externally validated with expected–observed ratio 0.97 (in Non-Hispanic white) and area under the curve above 0.75 when applying screening eligibility threshold of 2% LC risk over 5 years (25). In the population selected by Robbins, the next-screen risk of LC by LCRAT was 0.3%. The merging of LCRAT with post-test variables was named LCRAT + CT, intriguingly this composite system returned heterogeneous LC risk stratification among LDCT negative subjects. The post-test implementation could outline three major categories of LC risk among screenees with negative LDCT outcome: 1.6% risk in the 0.6% of screenees with consolidation, 0.5% risk in the 30% of screenees with emphysema, and as low as 0.2% risk in the 70% of screenees with neither. Thereof, both consolidation and emphysema seem to confer higher-than-

Table 1 Retrospective simulation and prospective studies testing lung cancer screening by increased interval

Study	LC screening study	Original LC screening study design	Eligible study population	LC*	Authors' statement
Robbins, 2019 (16)	NLST LDCT arm, 29.722 participants	Three annual LDCT assessment	NLST—at least one negative LDCT	Next-screen risk: 0.2%	A negative CT is insufficient to recommend a longer interval for all-screen negatives. Instead, the decision requires comprehensive risk calculations incorporating pre-screening risk and individual CT findings
			Screen-negatives (NO EMPH-NO CONS)		
			Screen-negatives (WITH EMPH)	Next-screen risk: 0.5%	
			Screen-negatives (WITH CONS)	Next-screen risk: 1.6%	
Tammemägi, 2019 (17)	NLST LDCT arm, 29.722 participants	Three annual LDCT assessment	NLST LDCT participants who had a negative first screen according to Lung-RADS categories (22.167)	264 LC between T3 and T6 (1.2%)	Positive screens seem to increase baseline risk scores and may identify high-risk individuals for continued screening and enrolment into clinical trials
			NLST LDCT participants who had a positive first screen according to Lung-RADS categories (3.156)	109 LC between T3 and T6 (3.5%)	
Schreuder, 2018 (18)	NLST LDCT arm, 29.722 participants	Three annual LDCT assessment	NLST participants who underwent T_0 and T_1 LDCT without those diagnosed with LC before T_1 (24.542)	Polynomial model: correctly select 10.4% of cancer-free participants 1 year after T_0, without delaying a single cancer diagnosis	The number of superfluous 1-year follow-up scans can be reduced by individualising follow-up intervals after the baseline CT scan using patient characteristics and baseline CT scan findings
Patz, 2016 (19)	NLST LDCT arm, 29.722 participants	Three annual LDCT assessment	NLST LDCT arm—Negative T_0 (19.066)	LC incidence: 371.9/100,000 person-years	The incidence of lung cancer in the group of high-risk participants enrolled in the NLST who had a negative low-dose CT prevalence screen was low in the year following this initial screen compared with those with a positive low-dose CT prevalence screen, hence annual screening after a negative screen might be superfluous
				LC-related mortality: 185.8/100,000 person-years	
			NLST LDCT arm—All T_0 (26.231)	LC incidence: 661.2/100,000 person-years	
				LC-related mortality: 277.2/100,000 person-years	
Yousaf-Khan, 2017 (20)	NELSON LDCT arm, 7.900* participants	Increasing screening intervals (baseline, after 1, 3, and 5.5 years since baseline)	NELSON LDCT arm (Round 4–5.5 years) (5.279)	LC probability (Round 3-3 years: NEGATIVE): 0.6%	Individual screening history can be used as a risk stratification tool for their next screening regime
				LC probability (Round 3-3 years: INDETERMINATE): 3.7%	

Table 1 (*continued*)

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Study	LC screening study	Original LC screening study design	Eligible study population	LC*	Authors' statement
Horeweg, 2014 (21)	NELSON LDCT arm, 7.155 Dutch participants (Round 1 and Round 2 combined)	Increasing screening intervals (baseline, after 1, 3, and 5.5 years since baseline)	LDCT: no nodules (7.630)	LC probability within 2 years: 0.4%	Participants whose nodules measured 100–300 mm^3 had a significantly higher 2-year lung cancer risk than did participants without nodules
			LDCT: nodules <100 mm^3 (4.666)	LC probability within 2 years: 0.6%	
			LDCT: nodules 100–300 mm^3 (1.111)	LC probability within 2 years: 2.4%	
			LDCT: nodules >300 mm^3 (617)	LC probability within 2 years: 16.9%	
Horeweg, 2013 (22)	NELSON LDCT arm, 7.900 participants	Increasing screening intervals (baseline, after 1, 3, and 5.5 years since baseline)	Negative round 1 (baseline) (5.986)	5.5 years risk of LC: 1.0%	After the first screening, the individual's lung cancer risk has either decreased by 62% (negative baseline) or increased by 219% (indeterminate baseline), or up to 1,858% (positive baseline)
			Indeterminate round 1(baseline) (1.451)	5.5 years risk of LC: 5.7%	
			Positive round 1 (baseline) (120)	5.5 years risk of LC: 48.3%	
Sverzellati, 2016 (23)	MILD LDCT arms, 2.376 participants	LDCT arm was randomized into two arms with different intervals between LDCT controls	Annual LDCT arm (1.152/1.190, 96.8%)	11 LC (detection rate: 0.96%)	Lung cancer detection rate in LDCT2 increased among participants shifted to annual follow-up, by reduction of recalls (annual recall in only 13% of screenees). This finding suggests that annual follow-up is more appropriate for participants without negative LDCT outcome
				1 year after T_0: 5 LC	
				1-year risk of LC: 0.45%	
		Annual (1.190)	Biennial LDCT arm (1.151/1.186, 97%)	6 LC (0.52%)	
			Participants with an indeterminate or positive LDCT (not classified as LC): shifted to annual LDCT screening interval	152 (13%) subjects shifted to annual follow-up, 1 year after T_0: 2 LC	
		Biennial (1.186)		1-year risk of LC: 1.36%	

*, values not directly available from the literature were derived by calculation, therefore they might reflect a good approximate of the actual value. LC, lung cancer; NLST, National Lung Screening Trial; LDCT, low-dose computed tomography; Lung-RADS, Lung Reporting And Data System; NELSON, Nederlands Leuvens Longkanker Screenings Onderzoek; MILD, multicentric Italian lung detection.

expected risk of LC in 1 year, allegedly as a consequence of subjective susceptibility to tissue damage. Conversely, screenees with negative LDCT and neither emphysema or consolidation showed a lower-than-expected risk of LC in one year. The LCRAT+CT could predict LC at next screen, whilst it was not accurate for interval cancer. By assuming a 0.3% risk threshold for preference sensitive LCS (26), Robbins *et al.* found that LCRAT + CT assigned 58% of screenees below such threshold. Noteworthy, this selection yielded potential reduction of false positives by 50% at the cost of about 24% delayed diagnosis of LC in case of low intensity approach. Intuitively, further reduction of the risk threshold would have reduced the proportion of delayed diagnosis, however also a lower optimization of false positive would have followed, too.

The analysis from Robbins *et al.* comes as a refinement of a previous study by Patz *et al.* who retrospectively stratified LC risk according to lone LDCT outcome by NLST criteria (nodule ≥4 mm) (19). Already, Patz *et al.* could describe a substantial drop of LC risk in subjects with negative baseline screen, selecting about 70% of screenees with 0.34% risk of LC in 1 year and, therefore, addressable to low intensity approach by biennial rounds. It should be underscored that LCRAT could stratify a pre-test risk of 0.3% in negative screenees (this was the expected risk in this selection based on socio-demographic covariates), which was substantially consistent by the post-test risk 0.34% reported by Patz (this was the risk based on the LDCT outcome, without any risk scaling by socio-demographic data). This figure comes as a further confirmation of reliability of LCRAT for selection of screenees. Then, if post-test radiological descriptors (different from nodule, namely emphysema or consolidation) are applied, the composite pre-test and post-test system LCRAT+CT provides even more accurate apportioning of the next-screen risk of LC in 1 year. The integration by Robbins of these two different perspectives on the NLST population suggests that radiological descriptors could master LCS approach by low intensity, either they represent a nodule (potentially a cluster of neoplastic cells) or emphysema and consolidation (representing some increased susceptibility of pulmonary tissue damage). Such evidence unveiled by Robbins *et al.* comes as substantial potential game-changer in the path towards personalized medicine/prevention in the purpose of the most efficient approach to population LCS.

This retrospective exercise by LCRAT + CT offers a valuable opportunity for comparison with previous data. Unlike Robbins, Tammemägi *et al.* showed that a continuously negative LDCT result through the three NLST time-points was still associated with >1.5% risk in subjects that featured a pre-test risk >2.6% by the model called PLCOm2012 (17). The major difference between the two analysis is found in the pre-test risk: very low for Robbins *et al.* and quite high for Tammemägi *et al.* Therefore, the manuscript from Robbins underscores the actual strength of post-test risk stratification, which should be trusted exclusively amongst screenees with relatively low pre-test risk.

Further authors analysed the NLST population with the objective of investigating the feasibility of low intensity LCS. Notably, Schreuder *et al.* proposed and validated a so called *polynomial model*, it was derived from the whole NLST dataset, including screenees with either negative or positive LDCT outcome (for this reason these results cannot be raw-paralleled to the analysis of Robbins) (18). This approach showed interesting evidence about the potential reduction of LDCT and the relevant cost in terms of delayed diagnosis. For instance, the polynomial model retrospectively estimated 68% reduction of LDCT at the cost of 25% delayed diagnosis, whilst zero delayed diagnosis could offer a limited 10% potential reduction of LDCT burden. Such figure tightly overlapped the data from Robbins, further confirming that the LCRAT + CT approach is useful in the large proportion of screenees with negative LDCT, at any time during the personal screening history. Of note, the stratification of the whole population by the polynomial model was granted by further post-test variables than the LCRAT + CT (e.g., presence of subsolid nodule, upper lobe location of the nodule, spiculation, and nodule count), which make the polynomial approach more similar to the Brock model published by McWilliams *et al.* in 2013 (27).

Also, the Brock model was applied to the NLST database for external validation. It resulted in 0.905 area under the curve, but with limited discrimination between benign and malignant cases as analysed by concordance statistic (c-statistic 0.905) (28). Noteworthy, the Brock model appeared to overestimate the probability of cancer in the NLST population. Following this observation, Winter *et al.* could recalibrate the Brock model in the specific NLST population and found significantly improved performance for prediction of malignancy (highest c-statistic 0.914). While the LCRAT + CT addressed subjects with negative LDCT, the polynomial model and NLS-adapted Brock model have a complementary use, namely addressing the risk in all subjects with particular focus on those with

discrete nodules. A side by side comparison of these models would probably show the ideal way to their harmonized contribution for refined post-test risk stratification. Still, their application outside of the NLST dataset would grant further validation and, eventually, recalibration.

Beyond retrospective simulations in the NLST population, prospective trials with low intensity are found in the literature. The low intensity approach was explicitly addressed by the MILD trial, where annual and biennial algorithms were compared (29). Biennial screening in subjects with negative LDCT prospectively granted 86% reduction of first-year LDCT repeats and 38% of all repeats in the biennial arm. Noteworthy, this approach allowed 32% reduction of the total LDCT burden in the biennial arm compared with annual arm, and 37% reduction among subjects with negative baseline LDCT.

The NELSON trial included subsequently lower intensity: 1-, 2-, and 2.5-year intervals. Despite the absence of a control arm with annual screening and the ageing of the population through the progressively lower intensity, also this trial showed that biennial screening is approachable in subjects with negative LDCT outcome (30). Nonetheless, a substantial increase in interval cancers was witnessed in the last six months of the 2.5-year interval screen, hence this extremely low-intensity approach was deemed hazardous.

The most extreme approach to low intensity screening is currently underway at the bioMILD trial, where over 4,000 screenees underwent baseline LDCT and blood sampling: triennial round was assigned in case of negative LDCT and negative blood test (31). Noteworthy, the bioMILD algorithm encompasses biological risk stratification by circulating miRNA (32), which allowed increase of volumetric threshold for definition of negative LDCT and prolonged interval for follow up of indeterminate findings (e.g., 1 year).

Great interest is directed toward optimization of LCS also by reduction of overall radiation burden, here administered to healthy individuals "the screenees". The risk of radiation-induced cancer has been considered not negligible, yet acceptable (33). Nonetheless, obtaining diagnostic images at the lowest radiation exposure is ethical. Recent advances in CT scanners technology allowed to further optimize CT scanning protocols, reaching sub-millisievert levels (34). Several researches tested the impact of the tin-filter technique for dramatic reduction of radiation burden in LCS, both by anthropomorphic phantom experiments (35) and by human patients (36). The use of the tin-filter technique is everything but obvious, especially for application of semi-quantitative software and for the detection of the full range of nodule density. Future studies are fostered testing the possible implementation of ultra-low dose CT in LCS, in particular for investigation of nodule detection as well as characterization of parenchymal abnormalities (i.e., emphysema).

The current technological development in radiology finds a hotspot in LCS (37), where automatic nodule detection and volumetry were developed and applied to help accuracy of the LDCT test (38-43). Volumetry of nodule appears to mismatch diameter (44), whilst volume is deemed a standard of reference (45,46). In 2019, the Lung Reporting And Data System (LungRADS) released the 1.1 version, where a major novelty was represented by inclusion of volumetric thresholds (47). One intrinsic limit of the analysis from Robbins *et al.* comes with the linear (non-volumetric) manual measurement of nodule provided by the NLST database. Any study based on NLST data is obliged to this methodological setting (18,19). Otherwise European studies provide a wealth of information about post-test risk stratification by volumetric LDCT, assisted detection of nodule, and semi-automatic volumetry of nodule (48,49). The volumetric approach is becoming more and more endorsed worldwide, risk models for future application in LCS will have to cope with this method.

Beside volumetry, further nodule-derived post-test metrics potentially could contribute in composite risk models, for instance radiomics. Radiomics is a radiology research field focused on detecting associations between quantitative descriptors from images and clinical parameters (50). A number of studies reported improved diagnostic accuracy by radiomics, notably for discrimination between pulmonary cancer and benign nodules (51). In a NLST-based study, a computer aided diagnosis algorithm was capable of increasing positive predictive values for small pulmonary nodules (52). This is a brand burgeoning frontier of radiology, the reliability of which is still to be confirmed.

A further scientific question arises from the present paper of Robbins: was self-reported emphysema of LCRAT consistent with emphysema detected at CT? This is one of several akin questions that might apply to the context of LCS: radiological verification of self-disclosed variables. One issue from this area of investigation has already been outlined on the MILD data: self-disclosed asbestos exposure was compared with pleural plaques at LDCT (53). The vast majority of screenees with pleural plaques did not report self-disclosed exposure to asbestos and pleural plaques

were associated with higher risk of lung cancer mortality. Is radiological post-test risk stratification again a reference for confirmation of pre-test variables? Should radiologist provide an oversight on the reliability of self-disclosed information?

In conclusion, the way to optimal LCS practice is oriented towards relevant apportioning of LC risk by comprehensive risk models. The analysis by Robbins *et al.* outlines personalized risk profile by relatively simple approach, the so called LCRAT + CT, which confirms the feasibility of low intensity screening in a high-risk population such as NLST. Let us be prepared for optimization of long-term lung cancer screening by LDCT with personalized intensity.

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Footnote

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