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Brief Communication

BRIEF COMMUNICATION

Identification of Candidates for Longer Lung Cancer Screening Intervals Following a Negative Low-Dose Computed Tomography Result

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Abstract

Lengthening the annual low-dose computed tomography (CT) screening interval for individuals at lowest risk of lung cancer could reduce harms and improve efficiency. We analyzed 23 328 participants in the National Lung Screening Trial who had a negative CT screen (no ≥4-mm nodules) to develop an individualized model for lung cancer risk after a negative CT. The Lung Cancer Risk Assessment Tool + CT (LCRAT+CT) updates "prescreening risk" (calculated using traditional risk factors) with selected CT features. At the next annual screen following a negative CT, risk of cancer detection was reduced among the 70% of participants with neither CT-detected emphysema nor consolidation (median risk = 0.2%, interquartile range [IQR] = 0.1%–0.3%). However, risk increased for the 30% with CT emphysema (median risk = 0.5%, IQR = 0.3%–0.8%) and the 0.6% with consolidation (median = 1.6%, IQR = 1.0%–2.5%). As one example, a threshold of next-screen risk lower than 0.3% would lengthen the interval for 57.8% of screen-negatives, thus averting 49.8% of next-screen false-positives among screen-negatives but delaying diagnosis for 23.9% of cancers. Our results support that many, but not all, screen-negatives might reasonably lengthen their CT screening interval.

Although efficacious, low-dose computed tomography (CT) lung cancer screening carries harms including false-positives (1–4) and radiation-induced cancers (2,5). Screening uptake has been low (6) and there is need to improve efficiency (7). Fortunately, multiple studies show that screen-negative individuals have reduced lung-cancer risk over subsequent screens (8–10). This suggests the possibility of lengthening screening intervals after a negative CT (11–14).

However, not all screen-negatives have sufficiently low risk to lengthen intervals (15). It is unclear how to identify appropriate candidates, because existing risk models for screening either combine individuals with negative and abnormal screens (16) or only predict current risk (17). We previously developed the Lung Cancer Risk Assessment Tool (LCRAT) to predict prescreening lung cancer risk. Here, we build on this work to develop a simple model, LCRAT+CT, that predicts short-term lung cancer risk following a negative CT screen. LCRAT+CT accounts for both prescreening risk factors and negative-CT features. We suggest how LCRAT+CT could identify candidates for longer screening intervals.

We analyzed 23 328 CT-arm participants in the U.S. National Lung Screening Trial (NLST) (1) who had at least one negative CT (defined as the absence of any nodules ≥4 mm in longest diameter). Among these participants, most had a negative result at all three screens, and 43 interval cancers and 138 next-screen cancers occurred (Supplementary Table 1, available online). First, we calculated individual one-year baseline "prescreening risk" based on risk factors using the LCRAT (18, 19). Next, we selected features of a negative CT that modify the relationship between prescreening and future lung cancer risk (Supplementary Table 2, available online). Specifically, we fit first-order Markov transition models using log-binomial regression (20, 21).

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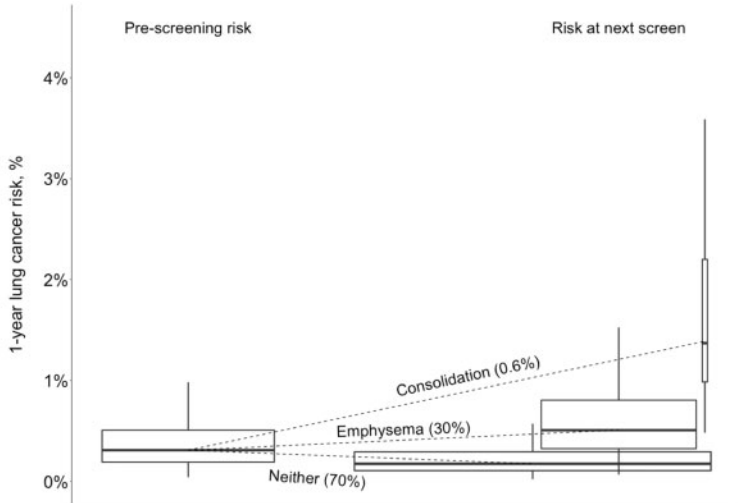


	Pre-screening risk (before negative CT)	Risk at next screen by CT features		
		Neither	Emphysema	Consolidation
Risk calculation	$r_0(x)$	$r_0(x)^{1.08}$	$r_0(x)^{0.96}$	$r_0(x)^{0.77}$
Exponent 95% CI	NA	(1.03, 1.12)	(0.91, 1.00)	(0.60, 0.93)
Median	0.3%	0.2%	0.5%	1.6%
IQR	0.2-0.5%	0.1-0.3%	0.3-0.8%	1.0-2.5%
Median difference	Ref	-0.1%	+0.2%	+1.3%
Median ratio	Ref	0.6	1.6	5.1

Figure 1. Effect of features noted on a negative computed tomography (CT) screen on risk of next-screen lung cancer detection among participants in the National Lung Screening Trial. For illustration, this figure was constructed using data from individuals who had a negative result at the first U.S. National Lung Screening Trial screen (T0) and were subsequently at risk for lung cancer at the second screen (T1) (n = 18 245). Among these individuals, 30% (n = 5484) had emphysema noted on their negative CT, 0.6% (n = 106) had consolidation, and 70% (12 691) had neither (n = 36 when both emphysema and consolidation were included in both risk distributions). Prescreening risk [$r_0(x)$] was calculated using the Lung Cancer Risk Assessment Tool (18). Outliers are not included in the figure but are included in the calculations in the table. Within each group of **boxplots**, **boxplot widths** are scaled by the percentage of the population represented, **boxplot heights** represent the interquartile range (IQR), and the vertical lines (**whiskers**) represent the range of data excluding outliers. CI, confidence interval; Ref, reference.

LCRAT+CT outputs future risk by raising prescreening risk to an exponent determined by negative-CT features. We fit separate models for risk between screens (interval-cancer risk) and at the next annual screen (next-screen risk). The Supplementary Methods (available online) describes methodological details for LCRAT, feature selection, and LCRAT+CT model definition. The NLST was approved by the institutional review board at each study site, and all participants provided informed consent.

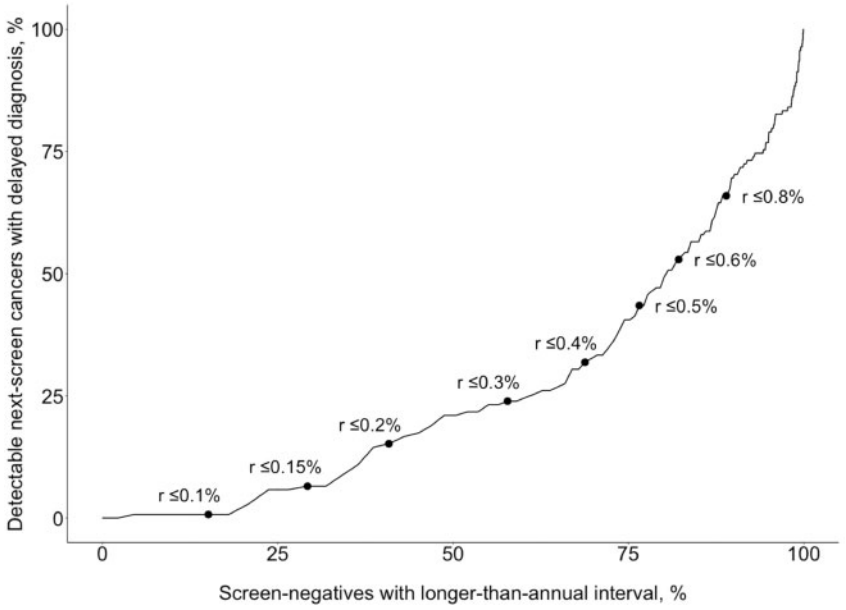
LCRAT+CT accounts for four properties of NLST screening that we observed during model development (Supplementary Methods, available online). First, prescreening risk strongly affected risk during screening. Second, prescreening risk encapsulated the effects of individual risk factors. Third, risk calculations were similar across NLST screens. Fourth, risk calculations were similar among individuals with a recent negative CT, regardless of their prior CT result.

A total of 43 interval cancers arose after 56 921 negative screens, yielding 0.08% mean risk (Supplementary Figure 1, available online). For next-screen cancer, 138 cases were detected following 35 530 negative screens, yielding 0.4% mean risk. The next-screen risk model included terms for CT-detected emphysema and consolidation. It had good cross-validated internal calibration (138 and 138.5 cases observed and predicted, $P = .93$) and reasonable discrimination (optimism-corrected area under the receiver operating characteristic curve = 0.73).

Due to variation in prescreening risk and CT features, next-screen lung cancer risk was heterogeneous (Figure 1). Among the 70% of screen-negatives with neither emphysema nor consolidation on their negative CT, median next-screen risk was reduced from 0.3% prescreening risk to 0.2% (interquartile range [IQR] = 0.1%–0.3%, risk ratio = 0.6). In contrast, for the 30% with CT-detected emphysema, risk increased 1.6-fold (median risk = 0.5%, IQR = 0.3%–0.8%). For the 0.6% with consolidation, risk increased 5-fold (median risk = 1.6%, IQR = 1.0%–2.5%).

We examined potential risk thresholds to identify candidates for longer screening intervals (Figure 2). We considered next-screen risk only, because CT features did not meaningfully stratify interval-cancer risk (Supplementary Methods, available online). First, we considered a threshold of 0.3% risk, below which screening is highly preference sensitive (22). Risk was below this threshold for 20 522, or 57.8%, of screen-negatives, in whom 33 of the 138 next-screen cancers were detected (23.9%) and 1464 of the 2937 next-screen false-positives occurred (49.8%). Therefore, if the screening interval were lengthened for 58% of screen-negatives, then 50% of the false-positives among screen-negatives could have been avoided, but diagnosis would have been delayed for 24% of the cancers. Lower risk thresholds would reduce delayed diagnosis but avert fewer false-positives. For example, at a 0.15% threshold, only 6.5% of cancer diagnoses would be delayed, but only 29.3% would lengthen their interval and only 23.2% of false-positives would be avoided (Figure 2).

Our findings indicate that reassurance from a negative CT is insufficient to recommend a longer interval for all screen-negatives. Instead, the decision requires comprehensive risk calculations incorporating prescreening risk and individual CT findings. In practice, to update a screen-negative's lung cancer



Risk threshold	Screen-negatives with longer interval, N (%)	Cancers with delayed diagnosis, N (%)	False-positives avoided, N (%)
r ≤ 0.1%	5,371 (15.1%)	1 (0.7%)	330 (11.2%)
r ≤ 0.15%	10,395 (29.3%)	9 (6.5%)	681 (23.2%)
r ≤ 0.2%	14,516 (40.9%)	21 (15.2%)	980 (33.4%)
r ≤ 0.3%	20,522 (57.8%)	33 (23.9%)	1,464 (49.8%)
r ≤ 0.4%	24,450 (68.8%)	44 (31.9%)	1,822 (62.0%)
r ≤ 0.5%	27,200 (76.6%)	60 (43.5%)	2,063 (70.2%)
r ≤ 0.6%	29,190 (82.2%)	73 (52.9%)	2,249 (76.6%)
r ≤ 0.8%	31,603 (88.9%)	91 (65.9%)	2,500 (85.1%)
Total	35,530 (100.0%)	138 (100.0%)	2,937 (100.0%)

Figure 2. Potential effect of Lung Cancer Risk Assessment Tool with computed tomography (LCRAT+CT) risk thresholds for longer screening intervals among screen-negative participants in the National Lung Screening Trial. Points and labels indicate potential next-screen risk thresholds for lengthening CT screening intervals beyond one year. For example, if the interval were lengthened for those with a predicted next-screen risk 0.3% or less, then the interval would be lengthened for 57.8% of screen-negatives. Among them, 33 cancers were detected at the next screen and would therefore have their diagnosis delayed (ie, 33 of 138 or 23.9% of all next-screen cancers in screen-negatives). Screen-negatives at both T0 and T1 (and corresponding cancers at T1 and T2) were included in this analysis, such that individuals with a negative result at both screens may be included twice. The denominator for percentages is the total number of screen-negatives, the number of next-screen cancers among screen-negatives, and the number of false-positives at the next screen among screen-negatives, respectively.

risk with LCRAT+CT, one would simply apply the appropriate exponent (corresponding to CT-emphysema and/or consolidation; Figure 1) to the LCRAT prescreening risk. If a risk threshold were established, then a longer interval could be offered to individuals below it, with use of a decision tool.

A risk-based approach to lengthen screening intervals for low-risk participants could substantially improve the efficiency of CT screening. Using a threshold of 0.3% next-screen risk, we found that 57.8% of NLST screen-negatives could lengthen their interval, thereby avoiding 49.8% of next-screen false-positives among screen-negatives. Other benefits that we could not quantify would include reductions in overdiagnosed lung cancers, radiation-induced cancers, and invasive procedures. However, this threshold would have delayed diagnosis for 23.9% of detectable next-screen cancers among screen-negatives. Of these cancers, 55% were stage I, and these in particular might have become incurable if the screening interval had been extended, for example, to two years (diagnosis delayed by one year).

Risk thresholds between 0.10% and 0.40% are well within the range of annual risks for 53-year-old, 30-or-more-pack-year smokers (19), who are currently recommended to begin screening in two years (23). Because such people have a de facto two-year "lengthened interval," their range of one-year risks implicitly identifies potential thresholds for longer intervals that underlie existing guidelines. We note that the proportions in Figure 2 are specific to the NLST and may vary with the population risk distribution and over time (24), though the individual risk-benefit trade-off that they represent might be maintained.

In relation to prescreening risk, next-screen risk after a negative CT is driven by opposing forces: reduced risk from a negative screen countered by increased detection, some of which is screening-induced overdiagnosis. Estimates of overdiagnosis in CT screening vary, but modeling of long follow-up estimates 9% (25). Because we cannot know which cancers are overdiagnosed, LCRAT+CT estimates total next-screen risk.

Our study has limitations. External validation of LCRAT+CT is needed to determine its portability outside the NLST. We did not investigate whether other prescreening risk models can be substituted for LCRAT. We could not determine the specific length that longer intervals should be, because the NLST used

only annual screening. Data from the NELSON and MILD trials support extending to two years but no longer (26–28). Our calculations do not consider that some individuals with deleterious CT features may have reduced life expectancy and thus lower benefit from annual screening. LCRAT+CT only applies to individuals who fit the NLST definition of screen-negative (ie, no ≥4-mm nodules). Finally, we did not estimate the reduction in screening effectiveness from lengthening intervals.

When considering for whom to lengthen screening intervals, guidelines committees might consider the benefit-harm tradeoff we presented within the broader context of feasibility, acceptability to patients, potential reduction in screening effectiveness, and costs. Like the decision to screen, the decision to lengthen intervals may be highly preference-sensitive for many patients (22). Ultimately, the individualized decision-making offered by our approach may provide an important avenue to improve efficiency and reduce harms in CT screening.

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