**Potential impact of risk-based follow-up for abnormal CT results during lung screening with biennial intervals**

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**Abstract**

**Objective:** Studies support biennial screening intervals for most people with a negative lung cancer screen. However, after an abnormal result deemed not to be cancer, the best approach to screening intervals is unclear. We developed a model for individual risk of cancer detection 1 year after a non-malignant abnormal LDCT. We then examined whether the model could avoid delayed diagnosis in biennial screening by selecting high-risk individuals to return in 1 year.

**Design, setting, and participants:** Analysis of 8,299 LDCT-arm participants in the National Lung Screening Trial (NLST). We extended the Lung Cancer Risk Assessment Tool +CT (LCRAT+CT) model to predict next-screen risk following a non-malignant abnormal LDCT based on individual pre-screening risk and features from the abnormal LDCT image.

**Main outcome measures:** Lung cancer detection at the next annual screen following a non-malignant abnormal LDCT.

**Results:** Lung cancer (n=235) was detected at the next screen following 1.8% of non-malignant abnormal CTs, substantially exceeding the 0.4% risk following a negative CT (RR=4.7, p<0.001). Risk increased with pre-screening risk, maximum nodule diameter, upper-lobe location, mixed attenuation, spiculated or indeterminate margins, and growth. During biennial screening, LCRAT+CT could efficiently identify high-risk individuals who should instead return after 1 year. For example, 68% of detectable next-screen cancers could be identified among the only 25% of individuals with a non-malignant abnormal LDCT and next-screen risk ≥2%.

**Conclusions:** Next-screen lung cancer risk is much higher after a non-malignant abnormal LDCT than after a negative CT. During biennial screening, using a risk model to select high-risk people for a 1-year interval could be an efficient approach.

**Introduction**  
  
Building on the success of two large randomized trials,1,2 screening by low-dose computed tomography (LDCT) is currently recommended for certain heavy smokers in the USA and a targeted national programme is planned by England’s National Health Service.3,4 While annual screening is recommended in the USA, biennial or longer intervals are being considered in other settings, including the draft plan for NHS England.

Biennial screening intervals are likely a safe approach for most individuals with a negative recent LDCT screening result.5–7 However, in the USA National Lung Screening Trial (NLST), 24% of all screens showed at least one nodule with longest diameter 4mm or greater. Using current guidelines, some of these abnormal results are recommended a surveillance LDCT, and the vast majority are ultimately determined to be non-malignant.1,8,9 Since most prior research to support biennial lung screening focused on screen-negative individuals, it is unclear which of these individuals with a non-malignant abnormal LDCT could safely return to biennial screening.

To maximize screening efficiency, one possible approach would be to recommend annual screening, instead of a 2-year interval, for a subset of people with non-malignant abnormal results who have largest predicted future risk. A wealth of information is available to characterize risk from an abnormal LDCT, including features of nodules (size, location, attenuation, margins, and growth) and non-nodule features (emphysema, consolidation, adenopathy, fibrosis, etc.). However, while calculators are available to predict *current* risk of malignancy,10–13 no method is available to calculate *future* risk of cancer detection for individuals whose abnormal result is deemed non-malignant.

Here, we developed a model to predict individual risk of lung cancer detection at the screen 1 year following a non-malignant abnormal LDCT. This model integrates risk predicted by the Lung Cancer Risk Assessment Tool (LCRAT) with features of the non-malignant abnormal LDCT, and constitutes the second component of the “LCRAT+CT” risk model.5 Considering a framework of biennial screening, we examined whether using such a risk model could avoid delayed lung cancer diagnoses by selecting high-risk individuals to remain in annual screening.

**Methods**Data source and analysis cohortThe NLST randomized 53,452 current and former smokers to 3 annual screens (denoted T0, T1, and T2) with either LDCT or radiography.1 Eligibility required age 55-74 years, 30 or more pack-years of smoking, and 15 or fewer quit-years. A positive (“abnormal”) CT was defined by the presence of at least one non-calcified nodule with longest diameter 4mm or greater, or, for a small proportion of LDCTs, the presence of other suspicious abnormalities.1,14 Information was consistently recorded regarding the presence, size, location, attenuation, and margins of nodules; nodule changes measured by comparison with the prior year’s screening LDCT; and non-nodule features such as emphysema. Growth of nodules was recorded by comparing the current and the prior screening LDCT (i.e., over a 1-year interval).

We analyzed risk of lung cancer detection among LDCT-arm participants who completed the baseline questionnaire and had one or more abnormal LDCT results that were not classified as lung cancer (i.e., non-malignant abnormal LDCTs, labeled “false-positives” in the NLST). We defined “next-screen” cancers as those detected due to a positive result at the next annual screen (e.g., T1) after the non-malignant abnormal LDCT (e.g., T0). A “linked-year method” identified next-screen cancers as those occurring within 1 year of a diagnostic follow-up initiated within 1 year after a positive screen.15 We did not consider interval cancers, which by NLST definition occurred after negative screens. Specifically, at the T1 screen, we analyzed cancer detection risk among participants who a) had a non-malignant abnormal LDCT at the T0 screen and b) attended the T1 screen and had a valid result. For the T2 screen, we analogously analyzed detection risk among participants who had a non-malignant abnormal LDCT at the T1 screen.

Statistical analysis  
We constructed LCRAT+CT as a discrete-time Markov risk model16 for the binary indicator of lung-cancer status. LCRAT+CT combines pre-screening risk-factors with characteristics from the current LDCT screen.5 The model first calculates 1-year pre-screening risk using the Lung Cancer Risk Assessment Tool (LCRAT), a model for risk of incident lung cancer in the absence of screening.17,18 The LCRAT includes demographics, smoking, and other lung cancer risk-factors and was successfully validated in 4 cohorts after development in the PLCO community care arm.17,19

We accounted for features on an abnormal LDCT image by fitting log-binomial regression models.20 We previously described this approach in detail.5 Briefly, these models calculate next-screen detection risk by raising LCRAT 1-year pre-screening risk to an exponent, where the exponent is calculated as the sum of the regression coefficients corresponding to features of the abnormal LDCT.

Among 29 features of abnormal LDCTs that were routinely collected in the NLST, we selected a reduced set of features for inclusion in LCRAT+CT. We separately applied a) backwards-stepwise selection to minimize the AIC (Akaike Information Criterion) and b) the lasso (least absolute shrinkage and selection operator)21. We then fit a model including all features selected by either approach, and then excluded those that no longer contributed to the model or had low potential to be consistently identified in clinical practice.

Using the final model, we assessed calibration using 10-fold cross-validation, and discrimination using the optimism-corrected area under curve (AUC) statistic.22 We re-fit the model using generalized estimating equations (GEE) to confirm that residual intra-individual correlation did not affect estimates (data not shown). We used alpha=0.05 for all statistical tests.

**Results**Analysis cohortWe analyzed risk among 8,299 NLST participants who had at least one abnormal CT result (**Table 1**). More than half (56.6%) had an abnormal result at both T0 and T1, and were thus included in risk analyses at both T1 and T2. Baseline lung cancer risk factors varied across participants, leading to wide variation in 1-year pre-screening risks (median 0.35%, interquartile range 0.21%-0.58%, and range (excluding outliers) 0.04%-1.14%).

Overall risk of next-screen lung cancer after a non-malignant abnormal LDCT  
A total of 235 lung cancer cases were detected following 12,993 non-malignant abnormal screens, giving an average risk of 1.8%. This is 4.7 times higher than the 0.4% average risk of next-screen detection after a negative screen5 (p<0.001) and also higher than median 1-year pre-screening risk among people with a non-malignant abnormal LDCT (0.35%, p<0.001). Thus, a non-malignant abnormal CT substantially increases future risk of lung cancer detection at the next annual screen.

Individual risk of next-screen lung cancer after a non-malignant abnormal LDCT

Detailed results of the model building procedure are provided in the **Supplement.** The final model included a term for the longest diameter among all nodules, along with terms for the presence of any nodule(s) in the upper lobe(s), in the lingula or right middle lobe, with mixed attenuation, with spiculated margins, with indeterminate margins, and showing growth between screens (**Supplementary Table 1**). It showed good cross-validated internal calibration (235 cases observed vs. 238.1 predicted, p=0.84) and discrimination (optimism-corrected AUC=0.79).

We used the LCRAT+CT model to predict next-screen lung cancer risk for each individual following a non-malignant abnormal LDCT. **Table 2** outlines the risk calculation. For example, consider an individual at median pre-screening risk by LCRAT (0.35%) whose abnormal LDCT shows a 7-mm solid nodule (initial exponent value of 0.92) in the left upper lobe (contribution of -0.07 to exponent) with only smooth margins (no contribution to exponent). The exponent for pre-screening risk is 0.92 (initial value) – 0.07 (upper lobe) = 0.85. Therefore, the predicted next-screen detection risk is 0.35%0.85 = 0.82% (note that exponents less than 1 increase risk).

Overall, low-risk nodule features were common: 39% of individuals had a 4-5mm nodule (median next-screen risk 0.49%) while another 30% had a 6-7mm nodule (median risk 0.78%) (see **Table 2,** which describes abnormal T1 screens and their risk at T2). The most common high-risk features were upper-lobes nodules (45% of individuals, median next-screen risk 1.4%) and indeterminate margins (28% of individuals, median risk 1.7%). Some less-common features conferred very high risk, such as nodule growth between screens (6% of individuals, median next-screen risk 7.0%), spiculated margins (10% of individuals, median risk 3.9%), and nodules larger than 10mm (6% had a nodule 11-13mm with median risk 4.5%, and 7% had a nodule ≥14mm with median risk 3.9%).

Potential impact of risk-tailored screening intervals for non-malignant abnormal LDCTs

**Figure 1** illustrates the potential impact of LCRAT+CT in the setting of biennial screening, using predictions generated by cross-validation. Compared with an approach that returns all non-malignant abnormal LDCTs to biennial screening, an approach that recommends annual screening to a high-risk subset could identify next-screen cancers with high efficiency. For example, in a higher-resource setting, a 1-year interval could be suggested for all non-malignant abnormal CTs with next-screen risk of 0.5% or higher. In the NLST, this would capture 95% of next-screen cancers by recommending a 1-year return for 70% of abnormal CTs. To reduce use of resources, a higher threshold such as 3% could be used, which would identify 54% of detectable next-screen cancers by recommending an annual interval to only 16% of people with non-malignant abnormal LDCTs. An intermediate threshold of 2% would identify 68% of cancers among only 25% of non-malignant abnormal LDCTs.

A different perspective might consider the setting of annual screening, where longer intervals are considered only for people at very low risk. For this setting, we previously proposed 0.3% next-screen lung cancer detection risk as a potential threshold for identifying individuals with a negative screen result who have sufficiently low risk for a longer-than-annual interval.5 In the current analysis, risk was below 0.3% for only 16% of participants with a non-malignant abnormal LDCT. Importantly, however, only 2% would have initially been eligible for screening if a risk model had been used to determine eligibility (LCRAT, with an eligibility threshold of 1.9% 5-year risk).17 Therefore, in the setting of annual screening with eligibility based on a risk model, it is unlikely that any participants with abnormal LDCTs could be offered a screening interval longer than 1 year.

**Discussion**

Multiple aspects of lung cancer screening are moving toward management based on continual individualized risk assessment, including eligibility for screening, tailoring of screening intervals, and management of abnormal LDCTs. Here, we found that non-malignant abnormal LDCTs – despite having been deemed not to indicate cancer – confer a substantial increase in risk at the next screen (1.8% on average, compared with 0.4% following a negative LDCT5). Using the LCRAT+CT risk model, we predicted individual risk of next-screen cancer by accounting for pre-screening risk and key features of nodules identified on an abnormal LDCT. In the setting of biennial screening, such a risk model could efficiently identify individuals who should instead be screened annually. For example, using a risk threshold of 2% in the NLST, 68% of detectable next-screen cancers would have been identified by assigning an annual interval to only 25% of participants with a non-malignant abnormal result.

In a biennial screening program, a default design might recommend a surveillance LDCT to monitor nodules after 3 or 6 months, but return individuals to biennial screening if the result does not prompt diagnostic follow-up. However, our data illustrate that risk at the next annual screen following a non-malignant abnormal LDCT is high, reaching 1.8% in the NLST compared with 0.4% following a negative result. In the UK, where baseline detection rates may be three-fold higher than NLST (3% vs. 1%),1,23 it is likely that risk following an abnormal LDCT may substantially exceed 1.8%. Our results illustrate that using a prediction model for next-screen risk could efficiently identify individuals with a non-malignant abnormal LDCT who should remain in annual screening. At a threshold of 2%, only one-quarter of such individuals would return 1 year early, but 68% of the detectable next-screen cancers would be identified. In the NLST, the corresponding detection rate at a 2% risk threshold was 4.9%, compared with 3.3% at a 1% threshold, 6.2% at a 3% threshold, and 9.3% at a 5% threshold. These detection rates depend on the underlying population risk distribution, and therefore might vary in other settings.

Considerations differ for a screening program with annual intervals by default. Multiple studies have shown that individuals with a negative LDCT screen (i.e., no nodules or only nodules <4mm) have reduced risk over future screening,7,24,25 and further research supports extending the screening interval to 2 years in a subset of these individuals.6,26,27 In prior work, we found that if a threshold of 0.3% next-screen risk were used to extend screening intervals, then 58% of screen-negatives would extend their interval while delaying diagnosis for 24% of detectable next-screen cancers among screen-negatives.5 Here, after a non-malignant abnormal LDCT, only 16% of individuals fell below this potential 0.3% threshold. Furthermore, almost none of them would have initially entered screening if the LCRAT risk model (instead of categorical NLST criteria) had been used for assessing eligibility. Thus, in the setting of risk-based annual screening, it is unlikely that any individual with a non-malignant abnormal LDCT would be an appropriate candidate for longer-than-annual screening intervals.

After adjusting for selected nodule characteristics, we investigated residual effects of pre-screening information and found that risk remained higher in non-Hispanic blacks (**Supplement**). We did not include this effect in our model, as it was estimated in a very small group (N=272 individuals, 3% of NLST). If we had included the effect, the exponent for pre-screening risk would have decreased by 0.13 among non-Hispanic blacks, but the other coefficients were not affected. Thus, it is possible that lung cancer detection risk after a non-malignant abnormal LDCT is higher in blacks even after accounting for their independently increased pre-screening risk17 and the features of their abnormal LDCT. Important lung cancer disparities in blacks persist, including a younger mean age at diagnosis28 and lower 5-year survival.29 This additional possible disparity – that blacks may have higher risk after a non-malignant abnormal LDCT – warrants further investigation in datasets with larger minority populations to determine whether tailored management might be appropriate.

The nodule features included in LCRAT+CT are largely consistent with prior findings for immediate malignancy risk, such as increased risk with nodules in the upper lobes, with spiculated margins, and with larger diameter.10,12,13 However, we emphasize that our model does not calculate immediate risk and applies only to individuals whose abnormal LDCT has been deemed not to indicate cancer. After adjusting for detailed nodule features, we did not find any difference in risk between new and pre-existing nodules. It is therefore possible that new nodules have increased risk that is largely immediate,30 and does not carry forward to the subsequent screen if the current screen is deemed non-malignant.

When an indeterminate nodule is detected on a screening LDCT, it is commonly followed up with a surveillance low-dose CT performed at 3 or 6 months to assess nodule growth.9 The most important limitation of our analysis is that data from these surveillance scans were not collected in the NLST; therefore, we could not account for information obtained during the process of nodule follow-up. When deciding what action to take after a surveillance scan is obtained, the LCRAT+CT risk score could be taken into consideration along with the change in nodule size and other information from the surveillance scan. In the future, our model should be updated to additionally account for information from surveillance scans.

NLST data do not directly link nodules on LDCT images to subsequent cancer diagnoses, so when cancer was detected one year after an abnormal LDCT, we could not ascertain whether the cancer was “missed” at the prior abnormal CT or had arisen *de novo* in the inter-screen interval. Therefore, the reason for increased risk after a non-malignant abnormal screen is unclear, but we speculate that it comprises both missed cancers at the abnormal LDCT (due to lack of follow-up, false-negative biopsy, etc.) and a “field effect” whereby those with false-positive nodules are more likely to develop cancer in the future. Though our model appears internally valid, it still requires validation in external populations. The NLST did not record volumetric measurements of nodules, which may provide additional risk stratification.

In conclusion, we found that risk of lung cancer detection increases substantially at the screen following a non-malignant abnormal LDCT. Further research is needed to understand why this occurs, and whether additional diagnostic workup could have identified some NLST cancers at an earlier timepoint. In the setting of biennial screening, a risk model such as LCRAT+CT could efficiently identify individuals with high 1-year risk of lung cancer detection who should instead be offered a screen after 1 year.

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**Table 1: National Lung Screening Trial LDCT-arm participants included in analysis of lung cancer risk after a non-malignant abnormal LDCT, by characteristics included in the Lung Cancer Risk Assessment Tool**

|  |  |
| --- | --- |
| **Characteristic (at T0 screen)** | **N (%) or median (IQR)** |
| Total number of unique individuals | 8,299 |
| 1-year pre-screening risk at T0 | 0.35% (0.21%-0.58%) |
| Included in analysis of next-screen cancer risk |  |
| Once (at either T1 or T2) | 3,605 (43.4) |
| Twice (at both T1 and T2) | 4,694 (56.6) |
| Sex |  |
| Male | 4,858 (58.5) |
| Female | 3,441 (41.5) |
| Age |  |
| 55-59 | 3,205 (38.6) |
| 60-64 | 2,566 (30.9) |
| 65-69 | 1,660 (20.0) |
| 70-74 | 868 (10.5) |
| Race/ethnicity |  |
| Non-Hispanic White | 7,628 (91.9) |
| Non-Hispanic Black | 272 (3.3) |
| Hispanic | 127 (1.5) |
| Asian/Other | 272 (3.3) |
| Education |  |
| No high school diploma | 511 (6.2) |
| High school graduate/GED | 2,210 (26.6) |
| Post-high school training other than college | 1,171 (14.1) |
| Associate degree or some college | 1,896 (22.8) |
| Bachelor’s degree | 1,361 (16.4) |
| Graduate school | 1,150 (13.9) |
| Body mass index |  |
| Underweight | 84 (1.0) |
| Normal weight | 2,451 (29.5) |
| Overweight | 3,487 (42.0) |
| Obese | 2,277 (27.4) |
| Family history of lung cancer |  |
| No first-degree relatives | 6,979 (84.1) |
| 1 first-degree relative | 1,233 (14.9) |
| 2 or more first-degree relatives | 87 (1.0) |
| Years since quitting smoking |  |
| Current smoker | 4,381 (52.8) |
| 1 to 5 | 1,465 (17.7) |
| 6 to 10 | 1,205 (14.5) |
| 11 or more | 1,248 (15.0) |
| Total pack-years |  |
| 30-39 | 1,972 (23.8) |
| 40-49 | 2,241 (27.0) |
| 50 or more | 4,086 (49.2) |
| Total years smoked |  |
| <30 | 514 (6.2) |
| 30-39 | 3,090 (37.2) |
| 40-49 | 3,730 (44.9) |
| 50 or more | 965 (11.6) |
| Cigarettes per day |  |
| <20 | 416 (5.0) |
| 20-29 | 3,911 (48.1) |
| 30-39 | 1,956 (23.6) |
| 40 or more | 1,936 (23.3) |
| Self-reported emphysema |  |
| No | 7,544 (90.9) |
| Yes | 755 (9.1) |

Missing values were imputed as previously described.17

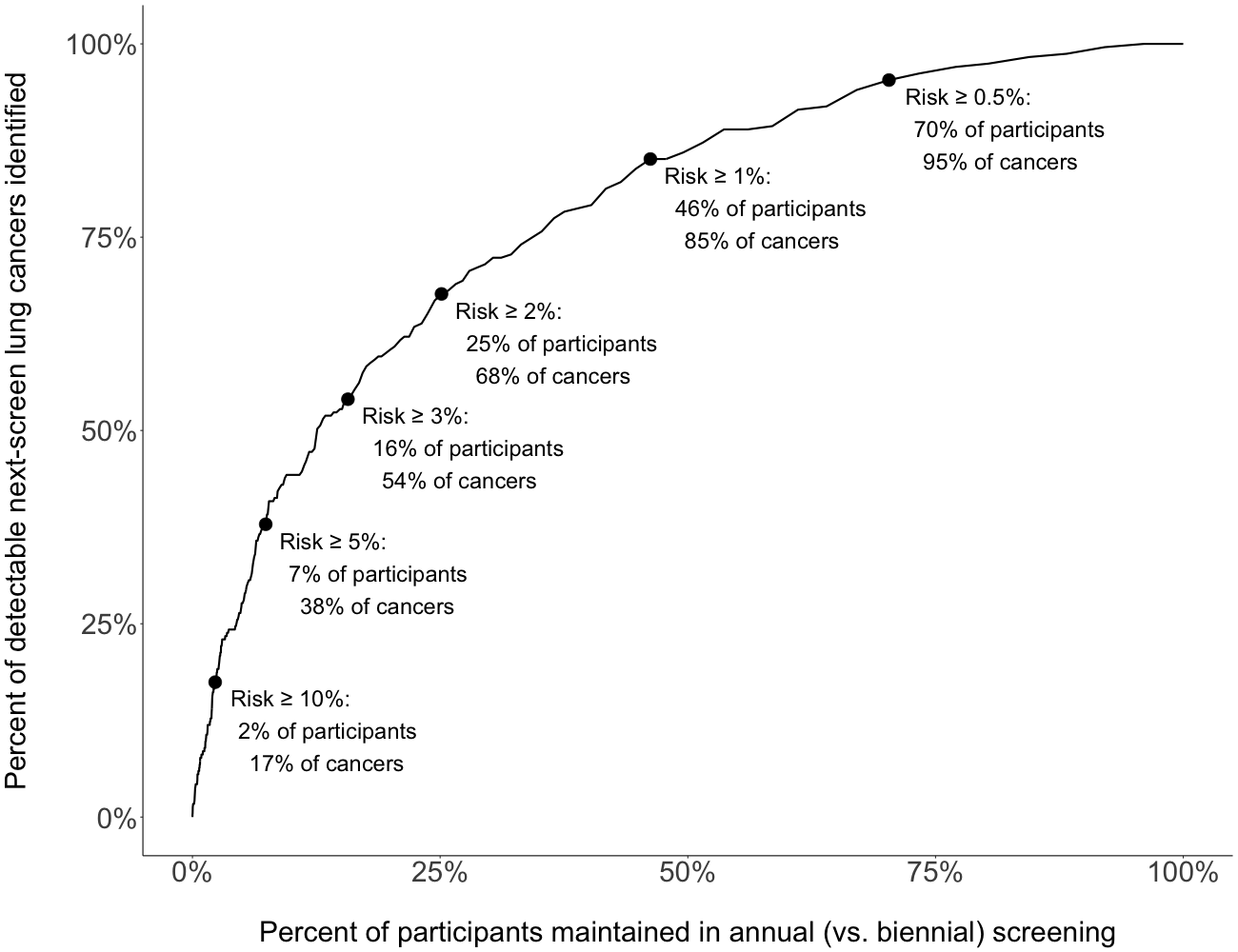
**Table 2: Effect of features noted on a non-malignant abnormal CT screen on risk of next-screen lung cancer among participants in the National Lung Screening Trial**

|  |  |  |  |
| --- | --- | --- | --- |
| Next-screen detection risk = r0(x)y  with exponent y for pre-screening risk calculated as follows: | | Prevalence of feature | Median risk (IQR) |
| What was the longest diameter among all nodules? | This gives the initial value: |  |  |
| N/A\* | 0.78 (0.64-0.97) | 1.9% | 1.4% (0.98-2.3%) |
| 4-5mm | 0.98 (0.91-1.06) | 39.0% | 0.49% (0.27-0.88%) |
| 6-7mm | 0.92 0.85-0.99) | 30.0% | 0.78% (0.42-1.5%) |
| 8-10mm | 0.80 (0.73-0.87) | 16.4% | 1.9% (1.1-3.4%) |
| 11-13mm | 0.71 (0.64-0.79) | 5.7% | 4.5% (2.5-7.5%) |
| 14mm or greater | 0.76 (0.69-0.84) | 7.2% | 3.9% (2.3-7.4%) |
| Was any nodule in the upper lobes? | If yes, subtract 0.07 (0.02-0.12) | 44.9% | 1.4% (0.69-3.1%) |
| Was any nodule in the right middle lobe or lingula? | If yes, add 0.09 (0.02-0.15) | 26.4% | 0.57% (0.26-1.3%) |
| Did any nodule have mixed attenuation? | If yes, subtract 0.07 (0.0-0.14) | 5.3% | 3.2% (1.5-6.1%) |
| Did any nodule have spiculated margins? | If yes, subtract 0.16 (0.10-0.22) | 9.6% | 3.9% (2.1-7.3%) |
| Did any nodule have indeterminate margins? | If yes, subtract 0.09 (0.04-0.14) | 28.1% | 1.7% (0.84-3.6%) |
| If evaluable, did any nodule show interval growth? | If yes, subtract 0.26 (0.20-0.32) | 6.0% | 7.0% (3.1-15.6%) |

The prevalence and risks for nodule features are calculated using data from individuals who screened positive at the second NLST screen (T1) but in whom lung cancer was not immediately detected, and were subsequently at risk for lung-cancer detection at the third screen (T2) (N=6,510). These screens were selected to allow for evaluation of nodule growth from T0 to T1.

\*Screen was positive for a reason (i.e., suspicious abnormalities) other than a nodule ≥4 mm.

**Figure 1: Potential impact, in the context of a biennial screening program, of using the LCRAT+CT risk model to identify individuals with a non-malignant abnormal CT who should be screened annually.**

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LCRAT+CT risks were calculated by 10-fold cross-validation, so that no record contributes to its own prediction.