For the last several decades lung cancer has been the most commonly diagnosed cancer worldwide with an estimated 2.1 million new lung cancer diagnoses in 2018 and accounting for 12% of the global cancer burden (1). Lung cancer is the leading cause of cancer-related death in the United States and the five-year survival rate for non-small cell lung cancer and small cell lung cancer combined is a dismal 19% (2). The high mortality rates and poor survival outcomes of this disease are primarily attributed to the majority of patients diagnosed with late stage disease, when the prospects for cure are limited. However, local therapy for lung cancers diagnosed at early stage is associated with significantly improved overall survival which highlights a critical need for identifying early-stage lung cancers. In 2011, results of the U.S. National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality for individuals screened by low-dose helical computed tomography (LDCT) compared to standard chest radiography among high-risk current and former smokers (3). Following the publication of the NLST results, recommendations for annual CT screens for eligible high-risk individuals were issued by the U.S. Preventive Services Task Force (4) and Centers for Medicare and Medicaid Services (CMS) (5).

Despite the conclusive benefits shown by the NLST, there are noted limitations and concerns associated with lung cancer screening by LDCT including high rates of false-positives and indeterminate pulmonary nodules of which only a fraction actually develop into cancer. Another unanswered question is the optimal frequency of LDCT screening, especially among screen-negative individuals since studies have reported a significant reduction in lung cancer incidence among NLST participants with a baseline negative screen compared to those with a baseline positive screen (6,7). Increasing the time between screening intervals among individuals at lowest risk of lung cancer could mitigate potential harms associated with lung cancer screening including false-positives and radiation-induced cancers. As such, Robbins et al. (8) analyzed 23,328 participants in the NLST who had a negative LDCT screen, defined as the absence of any nodules \( \geq 4 \) mm in longest diameter, to develop an individualized model for lung cancer risk after a negative-screen. They sought to build on their previously developed Lung Cancer Risk Assessment Tool (LCRAT) (9) to develop a new model that predicts short-term lung cancer risk following a negative CT screen. Using conventional lung cancer risk factors and the LCRAT, the authors calculated individual one-year baseline “prescreening risk” and then included the most informative radiological CT findings (LCRAT + CT) that influence the relationship between prescreening risk and future lung cancer risk. The CT features included eleven radiological (“semantic”) features that are included in the NLST dataset (e.g., CT-detected emphysema, consolidation, and pleural thickening or effusion). Using their newly developed LCRAT + CT model, the authors report that among the ~70% of screen-negatives that did not
have emphysema nor consolidation, their lung cancer risk at
the next screening interval was reduced from 0.3% median
risk (prescreening risk) to 0.2% median risk (risk at next
screen). Among the ~30% screen-negatives that had CT-
detected emphysema, lung cancer risk increased ~1.6-fold
(0.3% median prescreening risk to 0.5% median risk at
next screen); among the 0.6% of screen-negatives with
consolidation, lung cancer risk increased ~5-fold (0.3%
median prescreening risk to 1.6% median risk at next
screen). The authors also examined potential risk thresholds
to identify participants for longer screening intervals. In a
scenario using a threshold of 0.3% next-screen lung cancer
risk, 57.8% of screen-negatives (N=20,522) were below this
threshold of which 33 of the 138 next-screen lung cancers
were detected (23.9%) and 1,464 of the 2,937 next-screen
false-positives occurred (49.8%). This finding suggests that
if the screening interval were increased for these 57.8%
screen-negatives, diagnosis would have been delayed for
about 24% of the lung cancers but ~50% false-positives
could have been avoided among the screen-negatives.

Certainly, the authors do acknowledge some limitations
including lack of external validation, lack of comparisons
with other prescreening risk models, they could not provide
specific length for longer intervals since the NLST used
annual screening intervals, and the absence of an estimated
reduction of screening effectiveness from lengthening
intervals. There are other potential limitations, not noted
by the authors, including use of the radiological features in
the NLST dataset of which their validity are indeterminate.
It's not evident if the radiologists in the NLST were trained
to report these abnormalities and nonspecific findings in
a uniform and standardized way. As such, the variability,
accuracy, and completeness of these specific data elements
are unknown because a systematic review of these CT
images with standardized reporting would be necessary.
However, a nested case-control study (10) of the NLST
utilized radiologists to extract semantic radiologic features
from negative screens with small pulmonary nodules and
identified a model with 5 features that yielded a receiver
operating characteristic curve of 0.932 to predict cancer
risk. Of particular note, results from the nested case-control
study (10) found that one of the most informative features
was emphysema which was also found in the LCRAT+CT
model. Clearly, the utility of image-based features for
biomarkers to predict lung cancer risk is certainly of
merit (11). Another potential limitation are the significant
differences in overall and progression-free survival among
screen-detected (incident) lung cancers depending upon
whether the antecedent screens were negative or positive
prior to the screen of the cancer diagnosis (7). Specifically,
although there were fewer screen-detected lung cancers with
negative screens at earlier time points, these individuals had
significantly lower survival outcomes than those with positive
antecedent screens. These results imply that screen-detected
lung cancers following previous negative screens are a more
aggressive phenotype despite having a lower cancer risk and
lower incidence of lung cancer. Further studies that balance
cancer risk and survival outcomes will likely be necessary
to determine optimal screening intervals and frequency.
Additionally, risk-benefit analyses should be conducted prior
to this, or any, decision tool is implemented clinically.

Overall, the LCRAT + CT model demonstrates the potential
utility in reducing harm associated with frequent
CT screening (i.e., false-positives, increased cancer risk)
while maintaining efficacy of early detection by LDCT. As
it is imperative that other datasets be utilized to validate
these results, recent lung cancer screening randomized
trials having been published: the Multicentric Italian Lung
Detection (MILD) trial (12) and the German Lung Cancer
Screening Intervention (LUSI) trial (13). Additionally, since
the publication of the NLST results (3), the implementation
and evolution of lung cancer screening guidelines (14,15)
have improved nodule management in the lung cancer
screening setting. Thus, post hoc analyses conducted in the
NLST may not necessarily reflect what is occurring in more
recent clinical trials and in the “real world setting”. In fact,
the MILD trial reduced unnecessary surgery through active
surveillance of subsolid lesions and selective use of PET
imaging which improved differential diagnosis, especially
when compared to the NLST [4.5% surgical resection
rate for benign histology versus 24.4% in the NLST (3)].
Thus, with the emergence of the MILD (12) and LUSI
trials (13), and anticipated publication of the results of
the NELSON trial (16), risk models and decision tools
that were based solely on data from the NLST will likely
need to be reassessed in these newer clinical trials. The
thoughtful approach presented by Robbins et al. (8) provide
the framework for future post hoc analyses to determine
optimal screening frequencies especially among patients
with initially negative screens.

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**Footnote**

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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