

Review Article

The Pivotal Role of Baseline LDCT for Lung Cancer Screening in the Era of Artificial Intelligence

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ABSTRACT

In this narrative review, we address the ongoing challenges of lung cancer (LC) screening using chest low-dose computerized tomography (LDCT) and explore the contributions of artificial intelligence (AI), in overcoming them. We focus on evaluating the initial (baseline) LDCT examination, which provides a wealth of information relevant to the screening participant's health. This includes the detection of large-size prevalent LC and small-size malignant nodules that are typically diagnosed as LCs upon growth in subsequent annual LDCT scans. Additionally, the baseline LDCT examination provides valuable information about smoking-related comorbidities, including cardiovascular disease, chronic obstructive pulmonary disease, and interstitial lung disease (ILD), by identifying relevant markers. Notably, these comorbidities, despite the slow progression of their markers, collectively exceed LC as ultimate causes of death at follow-up in LC screening participants. Computer-assisted diagnosis tools currently improve the reproducibility of radiologic readings and reduce the false negative rate of LDCT. Deep learning (DL) tools that analyze the radiomic features of lung nodules are being developed to distinguish between benign and malignant nodules. Furthermore, AI tools can predict the risk of LC in the years following a baseline LDCT. AI tools that analyze baseline LDCT examinations can also compute the risk of cardiovascular disease or death, paving the way for personalized screening interventions. Additionally, DL tools are available for assessing osteoporosis and ILD, which helps refine the individual's current and future health profile. The primary obstacles to AI integration into the LDCT screening pathway are the generalizability of performance and the explainability.

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Lung Cancer Screening

Lung cancer (LC) is the leading cause of cancer-related deaths worldwide.¹ While smoking and age are the primary risk factors for LC, making smoking cessation the main preventive measure, two randomized clinical trials – the National Lung Screening Trial (NLST)² in the US and the NELSON³ in Europe – have demonstrated that annual screening with low-dose computed tomography (LDCT) significantly reduces mortality from LC compared to annual chest X-rays or no screening. Consequently, LC screening with annual LDCT is recommended for smokers or former smokers aged 50–80 years.^{4,5} However, the reduction in LC mortality associated with LDCT screening is modest. A meta-analysis of nine trials reported an

average relative risk of 0.84 for LC mortality (95% CI: 0.76–0.92) in LDCT-screened subjects compared to non-screened subjects.⁶ This justifies efforts to enhance LC screening with LDCT by addressing its persistent challenges^{7,8} in selecting subjects for screening,^{9–13} improving the LDCT screening examination,^{3,10–18} and incorporating other biomarkers from plasma, serum, sputum, or exhaled breath (Table 1).^{11–17}

This article aims to review the established achievements and ongoing efforts in addressing some challenges of LC screening through artificial intelligence (AI) applications. Specifically, we focus on AI tools that evaluate the baseline LDCT, which is the most crucial examination in the LC screening regimen from an individual health perspective.

The Pivotal Role of Baseline LDCT for LC Screening

Participants in LC screening programs typically undergo annual LDCT examinations and, if abnormalities are found, further tests

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Table 1
Challenges of LC Screening With LDCT.

Main Challenge	Sub-challenges	Options
Selection of subjects to be screened	LC risk stratification Recruitment method Smoking-related comorbidities	General practitioner or pneumonologist – driven Self-referral via internet or phone Chronic obstructive pulmonary disease Cardiovascular disease
LDCT screening examination	Frequency Logistic organization Decrease of false negative and false positive tests Validation of ultralow (<1 mSv) dose acquisitions	Annual Biennial Centralized Distributed Hospital-centered Mobile CT units
Roles of other biomarkers in plasma, serum, sputum or exhaled breath	Selection of higher risk subjects before LDCT Differentiation of benign and malignant nodules after LDCT	

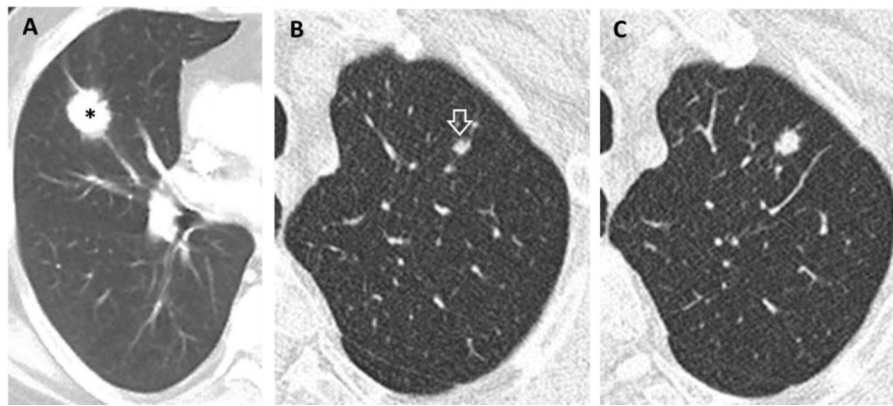


Fig. 1. (A–C). Prevalent and pseudo-incident screen-detected LC at baseline LDCT. Stage IA adenocarcinoma in a 60-year-old man from ITALUNG (A) appearing at baseline LDCT as a large (26 mm in mean diameter) solid nodule in the right upper lobe (*). Pseudo-incident stage IA squamous cell carcinoma in a 67-year-old man from ITALUNG (B and C) appearing at baseline LDCT (B) as an infra-threshold (5.2 mm in mean diameter) solid nodule in the left anterior lobe (white empty arrowhead) and showing growth (10 mm in mean diameter) at the first annual repeat (C).

to diagnose or exclude LC. The baseline (first) LDCT is crucial for several reasons. First, most LCs diagnosed during the initial 2–4 annual screening rounds are already present in the baseline LDCT. In particular, screen-detected LCs diagnosed within the first year following the initial LDCT screening test, defined as prevalent LCs (Fig. 1), are typically more numerous (range 55.4–84%) than those diagnosed after the subsequent annual repeat LDCT screening, defined as incident LCs.^{2,3,18–22} Moreover, most (77–80%) incident LCs are already present in baseline (or prior) LDCT scans^{20,23} (Fig. 1). However, these “pseudo-incident” LCs require time to grow and reach a size threshold that qualifies them as suspicious or actionable nodules, and can ultimately be diagnosed as LCs only years after their appearance. The combination of prevalent and “pseudo-incident” LCs allows the retrospective identification of malignant lesions in the baseline LDCT in up to 92% of subjects with screen-detected LCs within the first three-four years of screening.^{13,20,24} Awareness of the distribution of screen-detected LCs is essential given the expected new start and adoption of LC screening as a population-based intervention in Europe⁴ and elsewhere. Second, baseline LDCT allows the extraction of markers of smoking-related comorbidities, such as coronary artery calcifications (CAC) for cardiovascular disease (CVD) and pulmonary emphysema for chronic obstructive pulmonary disease (COPD). In particular, pulmonary emphysema can be assessed using visual semi-quantitative scales^{25,26} (Figs. 2 and 3) or quantitatively with the extraction of several indices using automatic software, including deep learning (DL) algorithms^{27–30} (see “CVD, Respi-

ratory and Overall Mortality Prediction” section). Emphysema is associated with an increased LC incidence,^{31–33} but, more importantly, in the perspective of LC screening programs, both CAC and emphysema indices predict long-term overall, CVD and respiratory mortality^{25,34–37} (Figs. 2 and 3). For this reason, in principle, LDCT assessment of CAC and emphysema allows for screening regimen personalization⁹ and early initiation of therapies that can delay comorbidities progression. A compelling argument underscoring the pivotal role of LDCT is that the assessment of smoking-related disease markers, such as CAC and emphysema indices, in the baseline LDCT provides sufficient prognostic information at the individual level. In fact, longitudinal studies have shown that only about 15% of subjects with emphysema, who participated in LC screening, experienced a mild progression of emphysema itself.³⁸ Also the progression of CAC is relatively slow, with only one out of five subjects without CAC developing some within 4–5 years.³⁹ Third, changes consistent with interstitial lung abnormalities (ILA) or disease (ILD) are observed in 3–10% of subjects undergoing baseline LDCT⁴⁰ (Fig. 5). These changes imply a greater risk of LC and are associated with an increased rate of complications from LC treatments.⁴¹ Detection of these abnormalities, especially when they extend to at least 5% of the lung parenchyma, justifies referral to a multidisciplinary team to prevent and manage their progression^{40,42} (Fig. 5). Fourth, the baseline LDCT can reveal several additional incidental findings, the most important and frequent being bronchiectasis, consolidations, aortic valve disease, mediastinal masses, enlarged mediastinal or hilar lymph nodes,

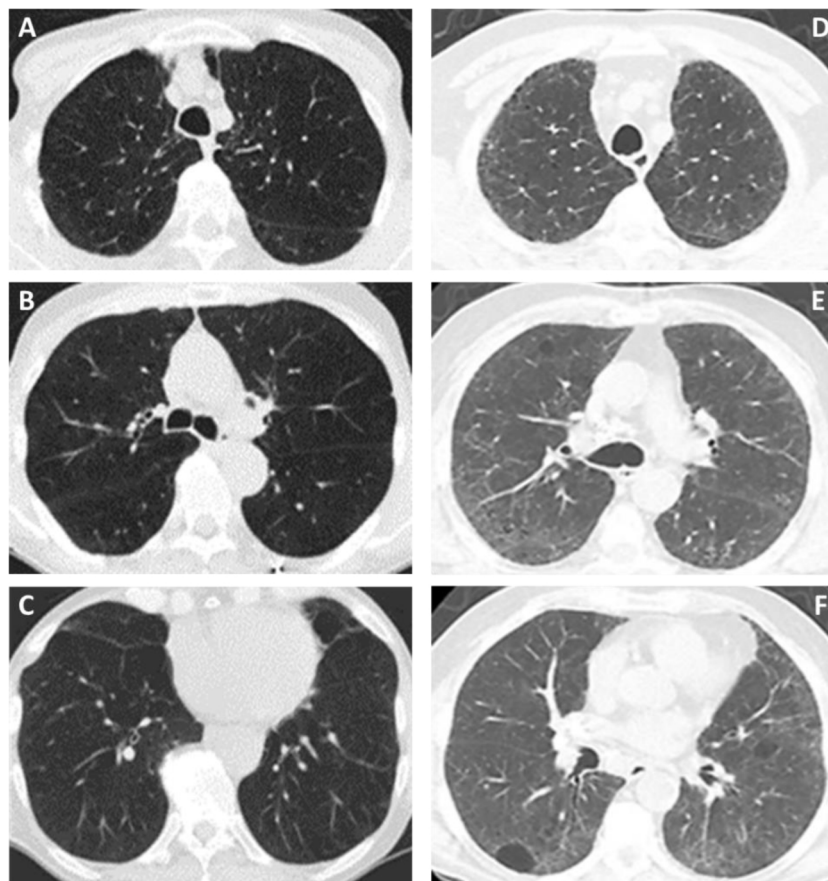


Fig. 2. (A–F) Diffuse lung disease at baseline LDCT. Advanced destructive pulmonary emphysema (A–C) in a 65-year-old man from NLST who died of respiratory disease (ICD code J449) 835 days after randomization. Interstitial lung disease (D–F) in a 73-year-old man from NLST who died of respiratory disease (ICD code J849 – interstitial pulmonary disease unspecified) 2462 days after randomization.

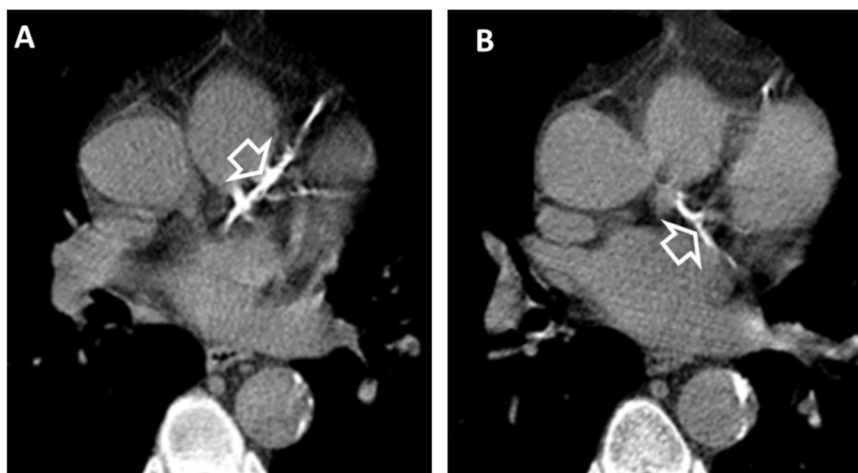


Fig. 3. (A and B). Coronary artery calcifications at baseline LDCT. Severe coronary artery calcifications in the anterior interventricular artery (white empty arrowhead A) and left circumflex artery (white empty arrowhead B) at baseline LDCT in a 69-year-old man from NLST who died of atherosclerotic heart disease (ICD code I251) 226 days after randomization.

and thyroid abnormalities.⁴⁰ Fifth, eligible subjects often undergo baseline LDCT only and then quit the screening program. In fact, in the US, adherence to the recommended screening intervals can be as low as 57%, especially among subjects with negative tests or benign nodules.⁴³ Finally, in the UK LC Screening trial, which offered just one LDCT to eligible subjects of the intervention arm,⁴⁴ a decrease in mortality from LC was observed in the screened subjects compared to controls (no screening).⁶ This benefit might be valuable for deprived world areas where limited

economic resources do not allow serial annual LDCT examinations.

Application of AI to Baseline LDCT for Problem-Solving in LC Screening

In the usual screening workflow, each LDCT examination undergoes a double reading by radiologists, who meticulously examine them for early signs of cancer,⁴⁵ focusing on the characteristics of

the pulmonary nodules, including size, morphology, location, and change over time. The LDCT examination also allows the opportunistic assessment of smoking-related comorbidities, especially emphysema and CVD.⁴⁶ This makes medical image interpretation the cornerstone of LC screening activities, requiring significant time and expertise.⁴⁷ With the new USPSTF guidelines expanding the cohort of eligible individuals for LC screening in the US,⁴⁸ the already high radiologists workload⁴⁹ is expected to increase further, making fully manual reporting of LDCT examinations impractical.

In recent years, the integration of AI into healthcare has brought significant changes in LC screening practice. By leveraging machine learning (ML) and DL algorithms (see Yu et al.⁵⁰ for a review), researchers and clinicians can efficiently harness the vast amounts of data generated by LDCT to address critical challenges in LC screening. This section explores diverse applications of AI in baseline LDCT imaging for problem-solving in LC screening.

CAD for Lung Nodules

Detecting lung nodules in LDCT images is central to LC screening workflows, as it guides participant management. However, the repetitive nature of this task and the overwhelming volume of images contribute to high intra- and inter-observer variability and a high false positive rate.^{51,52} Computer-aided diagnosis (CAD) systems assist radiologists by automatically identifying subtle findings, thereby mitigating human limitations like memory, distraction, and fatigue and offering objective data interpretation.⁵³ Computer-aided detection (CADe) systems are used for detection, while computer-aided diagnosis (CADx) systems are used for diagnosis.^{51,53} CADe systems have been shown to reduce the rate of false-negative baseline LDCT examinations.^{3,54–61} Additionally, they can help detect infra-threshold nodules that do not qualify as positive according to Lung-RADS,⁶² but need to be monitored in subsequent LDCT examinations.²⁹ However, only a small fraction (below 1%) of micronodules (<4 mm) evolves into LC,⁶³ indicating that the specificity of a micronodule at baseline LDCT is extremely low.

Using CADe for the computation of lung nodule volume rather than diameters has improved classification of nodules and decreased the number of indeterminate or false positive LDCT examinations.⁶⁴ However, the clinical integration of CADe remains limited due to persistent concerns over high false positive rates.^{65,66} Researchers are addressing this issue through several strategies. CADe tools may be used as pre-screening instruments to rule out negative LDCT examinations, allowing radiologists to concentrate on more challenging and suspicious cases.^{67,68} Another strategy involves integrating more data into the models. For example, a ‘collaborative CAD’ system incorporating radiologists’ gaze patterns into a 3D multi-task convolutional neural network (CNN), a particular DL architecture,⁶⁹ achieved a 97% classification accuracy in identifying nodules.⁷⁰

In LC screening, it is crucial to distinguish between benign lung nodules, which constitute the vast majority observed in low-dose CT scans of screened subjects according to Lung-RADS v2022,⁶² and malignant lung nodules. This differentiation often leads to additional examinations, such as follow-up LDCTs at intervals of 1–3–6 months, FDG-PET,⁷¹ and invasive procedures, significantly increasing both the costs and potential harms associated with screening.⁷ Notably, malignant nodules demonstrate an increase in size, density, or both over subsequent 3 or 6-month follow-up LDCT scans, as outlined in Lung-RADS v2022.⁶² The calculation of volume doubling time (VDT) serves as a practical and effective method to assess nodule growth characteristics and malignancy risk.⁶⁴ The Lung-RADS guidelines recommend specific management strategies for baseline LDCT-detected nodules, particularly

solid non-calcified nodules ≥ 6 mm in diameter or ≥ 113 mm³ in volume, which helps streamline further investigations aimed at confirming malignancy and minimizing unnecessary procedures.⁷² Furthermore, this differentiation can be enhanced by integrating LDCT features such as nodule size and density, the number of nodules, and presence of emphysema, with pertinent subject history, as incorporated in the PanCan/Brock model,^{73,74} or with biomarker results such as plasma DNA methylation⁷⁵ or plasma total cfDNA.¹³ However, the PanCan/Brock model has been developed, tested, and calibrated specifically for prevalent solid nodules ≥ 6 mm in diameter.^{73,74,76} It may not be well-suited for newly appearing nodules detected at next LDCT screening rounds.⁷⁶ Additionally, this model may not effectively identify malignant micronodules, potentially leading to the delayed (“pseudo-incident”) LC diagnosis. Therefore, DL algorithms predicting LC based on baseline LDCT and radiomics^{77–80} may improve the characterization of these small nodules. For example, an ML approach combining epidemiological, clinical and radiomic features, extracted from the nodules present at baseline LDCT, was able to predict the nodule’s malignancy risk score with an area under receiving operator curve (AUROC) of 0.93, outperforming the PanCan/Brock model and with optimal performance for both solid and sub-solid nodules.⁸¹ Still, a generative approach to enhance the characterization of indeterminate nodules from the baseline LDCT scan⁸⁰ exploited a growth model based on the Wasserstein generative adversarial network framework (GP-WGAN) to predict the nodule growth patterns in the 1-year follow-up LDCT scans. By leveraging the ability of GANs to generate data similar to the original, they can simulate follow-up LDCT examinations requiring only the baseline LDCT as input. The results demonstrated that the generated follow-up nodule images, when used as input to a model for LC malignancy prediction, achieved performance comparable to using real follow-up nodule images (AUROC of 0.82 ± 0.02 for generated nodules, compared to 0.86 ± 0.02 for real nodules).⁸⁰

LC Risk Stratification

For LC screening to be effective and minimize related harms, it is crucial to carefully select the at-risk population.⁴⁹ Once selected, LDCT examination information allows for valuable risk stratification, enabling a tailored screening schedule.⁸² Several models for estimating LC risk have incorporated baseline LDCT findings.^{83–85} Their implementation is hindered by limited external validation and the need for manual input of LDCT findings into the model to calculate the score. Unlike traditional models, AI-based algorithms autonomously analyze the entire LDCT volume, identify lung nodules and incidental findings, and combine this information with demographic data to generate a comprehensive, automated risk score.

The Google DL model evaluates LDCT examinations to predict LC incidence. It extracts local and global features from the current, and optionally prior, LDCT examinations and estimates the likelihood of a LC diagnosis within a year.⁸⁶ Despite achieving a high AUROC of 0.959 on single LDCT examination and outperforming radiologists, the model was criticized for its ‘black-box’ nature, lack of source code availability, and small validation set.⁸⁷

DeepScreener is a DL algorithm designed to predict a patient’s cancer status from CT scans through three tasks: nodule segmentation, nodule-level classification and patient-level classification.^{88,89} For each nodule, the nodule-level classifier extracts morphological, textural and other features and combines them with the nodule location to calculate a risk score. Subsequently, the patient-level classifier aggregates the risk scores of all detected nodules to generate an overall risk score for the patient and determine the label (“cancer” or “no cancer”). The model achieved an AUROC of 0.89

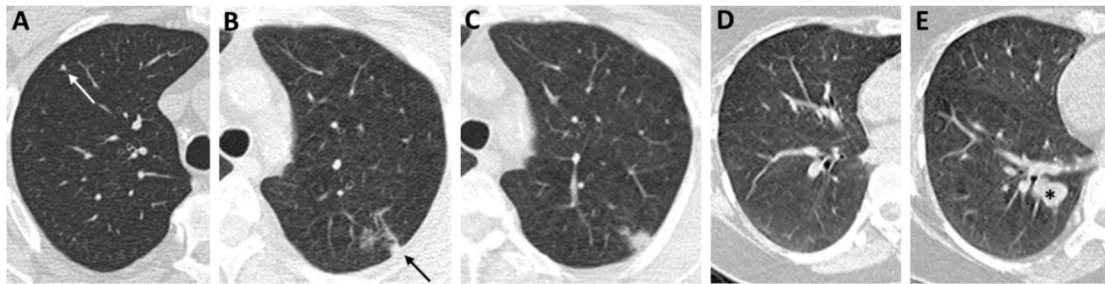


Fig. 4. (A–E) Assessment of risk of LC in the next 1–6 years based on the analysis of baseline LDCT with the Sybil deep learning algorithm.⁹⁰ (A) Prediction of a very low probability of LC after 1 year (risk score = 0.0109) and 6 years (risk score = 0.0831) since baseline LDCT in a 59-year-old man from NLST with a small infra-threshold (1.8 mm in mean diameter) solid benign nodule in the right upper lobe (white arrow) at baseline LDCT who was alive 11 years after randomization. (B and C) Prediction of a moderate probability of LC after 1 year (risk score = 0.3057) and 6 years (risk score = 0.5998) since baseline LDCT in a 56-year-old woman from NLST with a small infra-threshold (3.8 mm in mean diameter) (black arrow) solid nodule in the left upper lobe at baseline LDCT (B) which showed growth (9 mm in mean diameter) at the annual LDCT performed two years later (C) consistent with a pseudo-incident LC and who received a diagnosis of stage IA adenocarcinoma and was alive 11 years after randomization. (D and E) Prediction of a very low risk of LC after 1 (risk score = 0.0017) and 6 years (risk score = 0.0329) since baseline LDCT in a 57-year-old woman from NLST with a negative baseline LDCT (D) who showed a large (18 mm in mean diameter) solid lesion (*) at the next annual LDCT (E) consistent with an incident LC who received a diagnosis of small cell carcinoma and died of LC (ICD code C349) 1559 days after randomization.

and a sensitivity of only 42.4%, indicating that further refinement and validation are needed.⁸⁹

Sybil, a DL model designed to predict using a 0–1 score the LC risk from a single LDCT examination up to the next six years, without the need for radiologist annotations or additional data, represents a recent advancement.⁹⁰ It achieved AUROC for LC prediction at one year of 0.86–0.94 in three different datasets. Interestingly, when Sybil predicts high LC risk, the used signal localizes to specific at-risk regions rather than being equally spread over the entire thorax.⁹⁰

DL algorithms such as Sybil could be used to stratify the risk of LC after a baseline LDCT and could be particularly valuable in providing the LC risk in a screened subject showing infra-threshold nodules, that correspond to benign or pseudo-incident LC, or, after a negative baseline LDCT, anticipating interval or incident LC. Examples of application of the Sybil algorithm are shown in Fig. 4.

CVD, Respiratory and Overall Mortality Prediction

Tobacco smoking is a well-established risk factor for CVD, COPD, and LC. In LC screening cohorts, which primarily include current and former smokers, these conditions are the leading causes of death,^{2,3,91,92} and are often referred as the ‘Big 3 killers’. Using AI to extract comorbidity-related biomarkers from baseline LDCT images offers a valuable opportunity to enhance LC screening. AI can help optimize screening schedules – such as determining when to start, how frequently to screen, and when to stop – by refining individual risk profiles.⁹ Although radiologists’ visual scoring of comorbidities provides adequate predictive values^{25,35} (Figs. 2 and 3), AI-derived biomarkers offer greater robustness and objectivity, all without increasing the clinician’s workload.⁹³ One significant proof of this concept is a DL algorithm for the automatic quantification of coronary calcium.⁹⁴ The resulting calcium scoring showed a high correlation with readings from expert radiologists and demonstrated robust test-retest accuracy.⁹⁴ Beyond using AI-derived CAC as a predictor of CV events in LC screening cohorts,^{94–97} researchers are exploring additional approaches. For instance, a model was developed that based on the extraction of the coronary calcium and juxta-cardiac fat uses a single LDCT examination and provides a 0–1 score to estimate the probability of CVD risk.⁹⁸ The model’s ability to predict the risk of CVD and CV mortality equalized or surpassed that of radiologists and surpassed that of other state-of-the-art DL tools.^{94,98,99} Examples of its application to predict CV death in subjects with no or mild CAC are shown in Fig. 5. Other DL-derived indices include the prediction of adverse

events based on the left atrial volume¹⁰⁰ and of CV risk based on epicardial adipose tissue amount alone.¹⁰¹

COPD is typically diagnosed and evaluated through symptom assessment, spirometric testing, and tracking respiratory exacerbations.¹⁰² While lung densitometry is more reproducible than visual assessment of emphysema¹⁰³ and is increasingly used for COPD assessment,^{29,31,104} it is notably sensitive to variations in CT scanners and acquisition/reconstruction parameters, such as slice thickness, radiation dose, and reconstruction kernel.¹⁰⁵ A two-step DL model was developed to normalize the kernel effect for emphysema quantification in LDCT Images.^{105,106} This tool allows accurate emphysema quantification even when images are reconstructed using different kernels, thus improving consistency across large screening trials.¹⁰⁵

Combining quantitative and semi-quantitative biomarkers for CVD and COPD in risk stratification after LDCT examinations is gaining attention. A logistic regression model that integrates participant demographics with LDCT measures of LC, CVD and COPD was developed to predict the 5-year risk of competing death. This approach helps identify individuals who may benefit more from preventive care for other conditions than from LC screening.¹⁰⁷ The results suggest that a model based exclusively on quantitative LDCT measures, even when automatically derived, is suitable for calculating risk scores in a LC screening cohort and informing the post-LDCT screening process. Similarly, the predictive value of CAC visual score and of densitometry assessment of emphysema (relative area of the lung with density below –950 Hounsfield Units – RA950) in baseline LDCT along with age, gender, smoking status and pack-years were evaluated to predict the overall, LC, and CVD mortality in a screening cohort.³⁶ Using an ML paradigm based on decision trees¹⁰⁸ and the SHAP framework¹⁰⁹ to assess the importance of each feature, the model interpretation revealed that RA950 was the first ranking feature for predicting overall and CVD mortality, with AUROC values of 0.70 and 0.73, respectively. The most important features for predicting LC mortality were pack-years and RA950, with an AUROC of 0.61.

Osteoporosis Assessment

COPD is frequently associated with other extra-pulmonary systemic manifestations, including osteoporosis,¹¹⁰ that leads to an increased risk of fractures.¹¹¹ Since bone attenuation measured on routine chest CT has shown strong correlation with bone mass density (BMD) assessed by dual-energy X-ray absorptiometry (DXA) in patients with COPD,¹¹² opportunistic DL-aided assessment of osteoporosis in LDCT scans in LC screening cohorts has emerged.

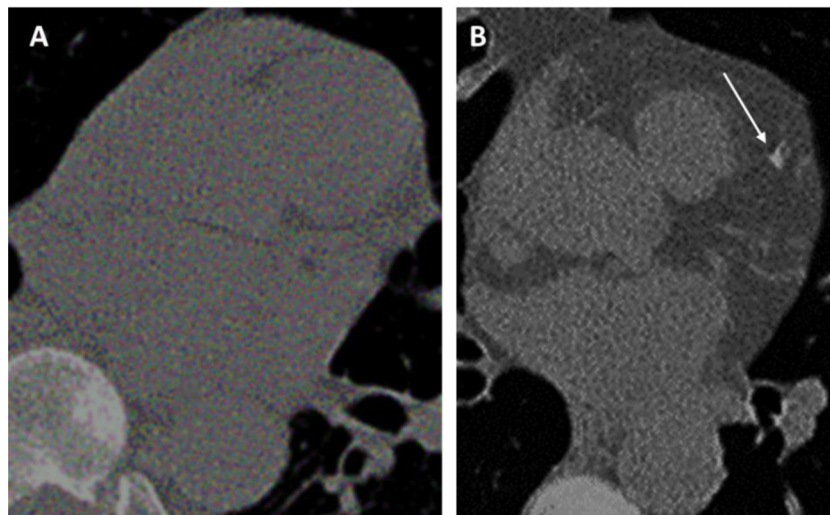


Fig. 5. (A and B) Assessment of risk of CV disease based on the analysis of baseline LDCT with Chao et al. deep learning algorithm.⁹⁸ The algorithm attributes a moderate (score = 0.351) CV risk in a 55-year-old man from NLST who did not show any coronary artery calcification at baseline LDCT (A) and who died of ischemic heart disease (ICD code I250) 2004 days after randomization. The algorithm attributes a high (score = 0.700) CV risk in a 70-year-old woman from NLST with mild coronary artery calcifications (white arrow) at baseline LDCT (C) and who died of acute myocardial infarct (ICD code I219) 511 days after randomization.

Different approaches have been proposed. A DL model was combined with geometric operations to automatically measure BMD from LDCT scans achieving a good agreement with quantitative CT.¹¹³ AI-RAD Companion was evaluated as an end-to-end solution to derive a LDCT biomarker for osteoporosis in LC screening whose score moderately correlated with WHO *T*-scores allowing to stratify participants into normal, osteopenia, and osteoporosis categories.¹¹⁴ Additionally, the combination of ML with radiomics texture analysis of automatically detected vertebral body achieved an AUROC of 0.90 and 0.72 on internal and external validation cohorts, respectively,¹¹⁵ establishing that osteoporosis can be part of the evaluation of LDCT for LC screening with impacts on morbidity, mortality, and the overall efficacy of LC screening.

Classification and Prediction of ILD Evolution

Recently, several studies have demonstrated the capability of DL algorithms to help classify the ILD detected in full dose thin-section CT^{116–119} and, more importantly, to predict the progression of the disease and the mortality due to this condition.^{120–122} Validation of these algorithms in the LDCT examinations performed for LC screening is still required.

Conclusions

While numerous AI models have been developed for LC screening, significant challenges remain that hinder their effective integration into clinical practice. Key issues include the generalizability of AI models across different populations – complicated by the limited availability of open-access datasets –, the explainability of AI decisions,^{47,52,65,123,124} and the assessment of AI tools deployment. These concerns have been extensively discussed in recent literature,^{125–129} highlighting the urgent need for ongoing research and collaboration in this rapidly evolving field.

Conflict of interests

The authors state that they have no conflict of interests.

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References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71:209–49, <http://dx.doi.org/10.3322/caac.21660>.
- The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011;365:395–409, <http://dx.doi.org/10.1056/NEJMoa1102873>.
- de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med.* 2020;382:503–13, <http://dx.doi.org/10.1056/NEJMoa1911793>.
- Kauczor H-U, Baird A-M, Blum TG, Bonomo L, Bostantzoglou C, Burghuber O, et al. ESR/ERS statement paper on lung cancer screening. *Eur Radiol.* 2020;30:3277–94, <http://dx.doi.org/10.1007/s00330-020-06727-7>.
- US Preventive Services Task Force. Screening for lung cancer: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2021;325:962–70, <http://dx.doi.org/10.1001/jama.2021.1117>.
- Field JK, Vulkan D, Davies MPA, Baldwin DR, Brain KE, Devaraj A, et al. Lung cancer mortality reduction by LDCT screening: UKLS randomised trial results and international meta-analysis. *Lancet Reg Health Eur.* 2021;10:100179, <http://dx.doi.org/10.1016/j.lanepe.2021.100179>.
- Mascalchi M, Picozzi G, Puliti D, Diciotti S, Deliperi A, Romei C, et al. Lung cancer screening with low-dose CT: what we have learned in two decades of ITALUNG and what is yet to be addressed. *Diagnostics (Basel).* 2023;13:2197, <http://dx.doi.org/10.3390/diagnostics13132197>.
- Henschke CI, Yip R, Shaham D, Zulueta JJ, Aguayo SM, Reeves AP, et al. The regimen of computed tomography screening for lung cancer: lessons learned over 25 years from the International Early Lung Cancer Action Program. *J Thorac Imaging.* 2021;36:6–23, <http://dx.doi.org/10.1097/RTI.0000000000000538>.
- ten Haaf K, van der Aalst CM, de Koning HJ, Kaaks R, Tammemägi MC. Personalising lung cancer screening: an overview of risk-

- stratification opportunities and challenges. *Int J Cancer*. 2021;149:250–63, <http://dx.doi.org/10.1002/ijc.33578>.
10. Pastorino U, Rossi M, Rosato V, Marchianò A, Sverzellati N, Morosi C, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev*. 2012;21:308–15, <http://dx.doi.org/10.1097/CEJ.0b013e328351e1b6>.
 11. Boutsikou E, Hardavella G, Fili E, Bakiri A, Gaitanakis S, Kote A, et al. The role of biomarkers in lung cancer screening. *Cancers*. 2024;16:1980, <http://dx.doi.org/10.3390/cancers16111980>.
 12. Seijo LM, Peled N, Ajona D, Boeri M, Field JK, Sozzi G, et al. Biomarkers in lung cancer screening: achievements, promises and challenges. *J Thorac Oncol*. 2019;14:343–57, <http://dx.doi.org/10.1016/j.jtho.2018.11.023>.
 13. Bisanzi S, Puliti D, Picozzi G, Romei C, Pistelli F, Deliperi A, et al. Baseline cell-free DNA can predict malignancy of nodules observed in the ITALUNG Screening Trial. *Cancers*. 2024;16:2276, <http://dx.doi.org/10.3390/cancers16122276>.
 14. Carozzi FM, Bisanzi S, Carrozzi L, Falaschi F, Lopes Pegna A, Mascalchi M, et al. Multimodal lung cancer screening using the ITALUNG biomarker panel and low dose computed tomography. Results of the ITALUNG biomarker study. *Int J Cancer*. 2017;141:94–101, <http://dx.doi.org/10.1002/ijc.30727>.
 15. Pastorino U, Boeri M, Sestini S, Sabia F, Milanese G, Silva M, et al. Baseline computed tomography screening and blood microRNA predict lung cancer risk and define adequate intervals in the BioMILD trial. *Ann Oncol*. 2022;33:395–405, <http://dx.doi.org/10.1016/jannonc.2022.01.008>.
 16. Weiss G, Schlegel A, Kottwitz D, König T, Tetzner R. Validation of the SHOX2/PTGER4 DNA methylation marker panel for plasma-based discrimination between patients with malignant and nonmalignant lung disease. *J Thorac Oncol*. 2017;12:77–84, <http://dx.doi.org/10.1016/j.jtho.2016.08.123>.
 17. Cortés-Ibáñez FO, Johnson T, Mascalchi M, Katzke V, Delorme S, Kaaks R. Serum-based biomarkers associated with lung cancer risk and cause-specific mortality in the German randomized Lung Cancer Screening Intervention (LUSI) trial. *Transl Lung Cancer Res*. 2023;12, <http://dx.doi.org/10.21037/tlcr-23-548>.
 18. Saghir Z, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax*. 2012;67:296–301, <http://dx.doi.org/10.1136/thoraxjnl-2011-200736>.
 19. Horeweg N, Scholten ET, de Jong PA, van der Aalst CM, Weenink C, Lammers JWJ, et al. Detection of lung cancer through low-dose CT screening (NELSON): a pre-specified analysis of screening test performance and interval cancers. *Lancet Oncol*. 2014;15:1342–50, [http://dx.doi.org/10.1016/S1470-2045\(14\)70387-0](http://dx.doi.org/10.1016/S1470-2045(14)70387-0).
 20. Mascalchi M, Picozzi G, Falchini M, Vella A, Diciotti S, Carrozzi L, et al. Initial LDCT appearance of incident lung cancers in the ITALUNG trial. *Eur J Radiol*. 2014;83:2080–6, <http://dx.doi.org/10.1016/j.ejrad.2014.07.019>.
 21. Scholten ET, Horeweg N, de Koning HJ, Vliethehart R, Oudkerk M, Mali WPTM, et al. Computed tomographic characteristics of interval and post screen carcinomas in lung cancer screening. *Eur Radiol*. 2015;25:81–8, <http://dx.doi.org/10.1007/s00330-014-3394-4>.
 22. Becker N, Motsch E, Gross M-L, Eigentopf A, Heussel CP, Dienemann H, et al. Randomized study on early detection of lung cancer with MSCT in Germany: results of the first 3 years of follow-up after randomization. *J Thorac Oncol*. 2015;10:890–6, <http://dx.doi.org/10.1097/JTO.0000000000000530>.
 23. Xu DM, Yip R, Smith JP, Yankelevitz DF, Henschke CI, I-ELCAP Investigators. Retrospective review of lung cancers diagnosed in annual rounds of CT screening. *AJR Am J Roentgenol*. 2014;203:965–72, <http://dx.doi.org/10.2214/AJR.13.12115>.
 24. Lopes Pegna A, Picozzi G, Falaschi F, Carrozzi L, Falchini M, Carozzi FM, et al. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. *J Thorac Oncol*. 2013;8:866–75, <http://dx.doi.org/10.1097/JTO.0b013e3182868d6>.
 25. Chiles C, Duan F, Gladish GW, Ravenel JG, Baginski SG, Snyder BS, et al. Association of coronary artery calcification and mortality in the National Lung Screening Trial: a comparison of three scoring methods. *Radiology*. 2015;276:82–90, <http://dx.doi.org/10.1148/radiol.15142062>.
 26. Lynch DA, Austin JHM, Hogg JC, Grenier PA, Kauczor H-U, Bankier AA, et al. CT-definable subtypes of chronic obstructive pulmonary disease: a statement of the Fleischner Society. *Radiology*. 2015;277:192–205, <http://dx.doi.org/10.1148/radiol.2015141579>.
 27. Cano-Espinosa C, González G, Washko GR, Cazorla M, Estépar RSJ. Automated Agatston score computation in non-ECG gated CT scans using deep learning. *Proc SPIE Int Soc Opt Eng*. 2018;10574, <http://dx.doi.org/10.1117/12.2293681>, 105742K.
 28. Lessmann N, Van Ginneken B, Zreik M, De Jong PA, De Vos BD, Viergever MA, et al. Automatic calcium scoring in low-dose chest CT using deep neural networks with dilated convolutions. *IEEE Trans Med Imaging*. 2018;37:615–25, <http://dx.doi.org/10.1109/TMI.2017.2769839>.
 29. Mascalchi M, Camiciottoli G, Diciotti S. Lung densitometry: why, how and when. *J Thorac Dis*. 2017;9:3319–45, <http://dx.doi.org/10.21037/jtd.2017.08.17>.
 30. Murawski M, Walter J, Schwarzkopf L. Assessing the lung cancer comorbidity: an analysis of German claims data. *Lung Cancer*. 2019;127:122–9, <http://dx.doi.org/10.1016/j.lungcan.2018.11.030>.
 31. Labaki WW, Xia M, Murray S, Hatt CR, Al-Abcha A, Ferrera MC, et al. Quantitative emphysema on low-dose CT imaging of the chest and risk of lung cancer and airflow obstruction. *Chest*. 2021;159:1812–20, <http://dx.doi.org/10.1016/j.chest.2020.12.004>.
 32. Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman CR, Fisher SN, et al. Association of radiographic emphysema and airflow obstruction with lung cancer. *Am J Respir Crit Care Med*. 2008;178:738–44, <http://dx.doi.org/10.1164/rccm.200803-4350C>.
 33. de Torres JP, Bastarrika G, Wisnivesky JP, Alcaide AB, Campo A, Seijo LM, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. *Chest*. 2007;132:1932–8, <http://dx.doi.org/10.1378/chest.07-1490>.
 34. Almatrafi A, Thomas O, Callister M, Gabe R, Beeken RJ, Neal R. The prevalence of comorbidity in the lung cancer screening population: a systematic review and meta-analysis. *J Med Screen*. 2023;30:3–13, <http://dx.doi.org/10.1177/09691413221117685>.
 35. Mascalchi M, Puliti D, Romei C, Picozzi G, De Liperi A, Diciotti S, et al. Moderate-severe coronary calcification predicts long-term cardiovascular death in CT lung cancer screening: the ITALUNG trial. *Eur J Radiol*. 2021;145:110040, <http://dx.doi.org/10.1016/j.ejrad.2021.110040>.
 36. Mascalchi M, Romei C, Marzi C, Diciotti S, Picozzi G, Pistelli F, et al. Pulmonary emphysema and coronary artery calcifications at baseline LDCT and long-term mortality in smokers and former smokers of the ITALUNG screening trial. *Eur Radiol*. 2023;33:3115–23, <http://dx.doi.org/10.1007/s00330-023-09504-4>.
 37. Pinsky PF, Lynch DA, Gierada DS. Incidental findings on low-dose CT scan lung cancer screenings and deaths from respiratory diseases. *Chest*. 2022;161:1092–100, <http://dx.doi.org/10.1016/j.chest.2021.11.015>.
 38. Mascalchi M, Sverzellati N, Falchini M, Favilli G, Lombardo S, Macconi L, et al. Changes in volume-corrected whole-lung density in smokers and former smokers during the ITALUNG screening trial. *J Thorac Imaging*. 2012;27:255–62, <http://dx.doi.org/10.1097/RTI.0b013e3182541165>.
 39. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2007;115:2722–30, <http://dx.doi.org/10.1161/CIRCULATIONAHA.106.674143>.
 40. O'Dowd EL, Tietzova I, Bartlett E, Devaraj A, Biederer J, Brambilla M, et al. ERS/ESTS/ESTRO/ESR/ESTI/EFOMP statement on management of incidental findings from low dose CT screening for lung cancer. *Eur J Cardiothorac Surg*. 2012;42, <http://dx.doi.org/10.1093/ejcts/ezad302>, ezad302.
 41. Frank AJ, Dagogo-Jack I, Dobre IA, Tait S, Schumacher L, Fintelmann FJ, et al. Management of lung cancer in the patient with interstitial lung disease. *Oncologist*. 2023;28:12–22, <http://dx.doi.org/10.1093/oncolo/oyac226>.
 42. Silva M, Picozzi G, Sverzellati N, Anglesio S, Bartolucci M, Cavigli E, et al. Low-dose CT for lung cancer screening: position paper from the Italian college of thoracic radiology. *Radiol Med*. 2022;127:543–59, <http://dx.doi.org/10.1007/s11547-022-01471-y>.
 43. Lin Y, Fu M, Ding R, Inoue K, Jeon CY, Hsu W, et al. Patient adherence to lung CT screening reporting & data system—recommended screening intervals in the United States: a systematic review and meta-analysis. *J Thorac Oncol*. 2022;17:38–55, <http://dx.doi.org/10.1016/j.jtho.2021.09.013>.
 44. Field JK, Duffy SW, Baldwin DR, Whynes DK, Devaraj A, Brain KE, 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, <http://dx.doi.org/10.1136/thoraxjnl-2015-207140>.
 45. Snoeckx A, Franck C, Silva M, Prokop M, Schaefer-Prokop C, Revel M-P. The radiologist's role in lung cancer screening. *Transl Lung Cancer Res*. 2021;10:2356–67, <http://dx.doi.org/10.21037/tlcr-20-924>.
 46. Adams SJ, Stone E, Baldwin DR, Vliethehart R, Lee P, Fintelmann FJ. Lung cancer screening. *Lancet*. 2023;401:390–408, [http://dx.doi.org/10.1016/S0140-6736\(22\)01694-4](http://dx.doi.org/10.1016/S0140-6736(22)01694-4).
 47. Rajpurkar P, Chen E, Banerjee O, Topol EJ. AI in health and medicine. *Nat Med*. 2022;28:31–8, <http://dx.doi.org/10.1038/s41591-021-01614-0>.
 48. Maki KG, Talluri R, Toumazis I, Shete S, Volk RJ. Impact of U.S. Preventive Services Task Force lung cancer screening update on drivers of disparities in screening eligibility. *Cancer Med*. 2023;12:4647–54, <http://dx.doi.org/10.1002/cam4.5066>.
 49. Lancaster HL, Heuvelmans MA, Oudkerk M. Low-dose computed tomography lung cancer screening: clinical evidence and implementation research. *J Intern Med*. 2022;292:68–80, <http://dx.doi.org/10.1111/joim.13480>.
 50. Yu K-H, Beam AL, Kohane IS. Artificial intelligence in healthcare. *Nat Biomed*. 2018;2:719–31, <http://dx.doi.org/10.1038/s41551-018-0305-z>.
 51. De Margerie-Mellon C, Chassagnon G. Artificial intelligence: a critical review of applications for lung nodule and lung cancer. *Diagn Interv Imaging*. 2023;104, <http://dx.doi.org/10.1016/j.diii.2022.11.007>.
 52. Grenier PA, Brun AL, Mellot F. The potential role of artificial intelligence in lung cancer screening using low-dose computed tomography. *Diagnostics*. 2022;12:2435, <http://dx.doi.org/10.3390/diagnostics12102435>.
 53. Eadie LH, Taylor P, Gibson AP. A systematic review of computer-assisted diagnosis in diagnostic cancer imaging. *Eur J Radiol*. 2012;81:e70–6, <http://dx.doi.org/10.1016/j.ejrad.2011.01.098>.
 54. Fraioli F, Bertolotti L, Napoli A, Pediconi F, Calabrese FA, Masciangelo R, et al. Computer-aided detection (CAD) in lung cancer screening at chest MDCT: ROC analysis of CAD versus radiologist performance. *J Thorac Imaging*. 2007;22:241–6, <http://dx.doi.org/10.1097/RTI.0b013e318033aae8>.
 55. van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R, et al. Management of lung nodules detected by volume CT scanning. *N Engl J Med*. 2009;361:2221–9, <http://dx.doi.org/10.1056/NEJMoa0906085>.

56. Brown MS, Lo P, Goldin JG, Barnoy E, Kim GHJ, McNitt-Gray MF, et al. Toward clinically usable CAD for lung cancer screening with computed tomography. *Eur Radiol.* 2014;24:2719–28, <http://dx.doi.org/10.1007/s00330-014-3329-0>.
57. Huang P, Park S, Yan R, Lee J, Chu LC, Lin CT, et al. Added value of computer-aided CT image features for early lung cancer diagnosis with small pulmonary nodules: a matched case-control study. *Radiology.* 2018;286:286–95, <http://dx.doi.org/10.1148/radiol.2017162725>.
58. Cai J, Xu D, Liu S, Cham MD. The added value of computer-aided detection of small pulmonary nodules and missed lung cancers. *J Thorac Imaging.* 2018;33:390–5, <http://dx.doi.org/10.1097/RTI.0000000000000362>.
59. Kozuka T, Matsukubo Y, Kadoba T, Oda T, Suzuki A, Hyodo T, et al. Efficiency of a computer-aided diagnosis (CAD) system with deep learning in detection of pulmonary nodules on 1-mm-thick images of computed tomography. *Jpn J Radiol.* 2020;38:1052–61, <http://dx.doi.org/10.1007/s11604-020-01009-0>.
60. Peters AA, Christe A, von Stackelberg O, Pohl M, Kauczor H-U, Heußel CP, et al. Will I change nodule management recommendations if I change my CAD system? Impact of volumetric deviation between different CAD systems on lesion management. *Eur Radiol.* 2023;33:5568–77, <http://dx.doi.org/10.1007/s00330-023-09525-z>.
61. Gao S, Xu Z, Kang W, Lv X, Chu N, Xu S, et al. Artificial intelligence-driven computer aided diagnosis system provides similar diagnosis value compared with doctors' evaluation in lung cancer screening. *BMC Med Imaging.* 2024;24:141, <http://dx.doi.org/10.1186/s12880-024-01288-3>.
62. Christensen J, Prosper AE, Wu CC, Chung J, Lee E, Elicker B, et al. ACR Lung-RADS v2022: assessment categories and management recommendations. *J Am Coll Radiol.* 2024;21:473–88, <http://dx.doi.org/10.1016/j.jacr.2023.09.009>.
63. Munden RF, Chiles C, Boiselle PM, Sicks JD, Aberle DR, Gatsonis CA. Micronodules detected on computed tomography during the national lung screening trial: prevalence and relation to positive studies and lung cancer. *J Thorac Oncol.* 2019;14:1538–46, <http://dx.doi.org/10.1016/j.jtho.2019.05.045>.
64. Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch H, Heussel CP, et al. European position statement on lung cancer screening. *Lancet Oncol.* 2017;18:e754–66, [http://dx.doi.org/10.1016/S1470-2045\(17\)30861-6](http://dx.doi.org/10.1016/S1470-2045(17)30861-6).
65. Quanyang W, Yao H, Sicong W, Linlin Q, Zewei Z, Donghui H, et al. Artificial intelligence in lung cancer screening: detection, classification, prediction, and prognosis. *Cancer Med.* 2024;13:e7140, <http://dx.doi.org/10.1002/cam4.7140>.
66. Schreuder A, Scholten ET, Van Ginneken B, Jacobs C. Artificial intelligence for detection and characterization of pulmonary nodules in lung cancer CT screening: ready for practice? *Transl Lung Cancer Res.* 2021;10:2378–88, <http://dx.doi.org/10.21037/tlcr-2020-lcs-06>.
67. Lancaster HL, Zheng S, Aleshina OO, Yu D, Yu Chernina V, Heuvelmans MA, et al. Outstanding negative prediction performance of solid pulmonary nodule volume AI for ultra-LDCT baseline lung cancer screening risk stratification. *Lung Cancer.* 2022;165:133–40, <http://dx.doi.org/10.1016/j.lungcan.2022.01.002>.
68. Obuchowski NA, Bullen JA. Statistical considerations for testing an AI algorithm used for prescreening lung CT images. *Contemp Clin Trials Commun.* 2019;16:100434, <http://dx.doi.org/10.1016/j.conctc.2019.100434>.
69. Caruana R. Multitask learning. In: Thrun S, Pratt L, editors. *Learning to learn*. Boston, MA: Springer US; 1998. p. 95–133.
70. Khosravan N, Celik H, Turkbey B, Jones EC, Wood B, Bagci U. A collaborative computer aided diagnosis (C-CAD) system with eye-tracking, sparse attentional model, and deep learning. *Med Image Anal.* 2019;51:101–15, <http://dx.doi.org/10.1016/j.media.2018.10.010>.
71. Garcia-Velloso MJ, Bastarrrika G, de-Torres JP, Lozano MD, Sanchez-Salcedo P, Sancho L, et al. Assessment of indeterminate pulmonary nodules detected in lung cancer screening: diagnostic accuracy of FDG PET/CT. *Lung Cancer.* 2016;97:81–6, <http://dx.doi.org/10.1016/j.lungcan.2016.04.025>.
72. McKee BJ, Regis SM, McKee AB, Flacke S, Wald C. Performance of ACR Lung-RADS in a clinical CT lung screening program. *J Am Coll Radiol.* 2015;12:273–6, <http://dx.doi.org/10.1016/j.jacr.2014.08.004>.
73. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med.* 2013;369:910–9, <http://dx.doi.org/10.1056/NEJMoa1214726>.
74. Tammemagi M, Ritchie AJ, Atkar-Khattra S, Dougherty B, Sanghera C, Mayo JR, et al. Predicting malignancy risk of screen-detected lung nodules-mean diameter or volume. *J Thorac Oncol.* 2019;14:203–11, <http://dx.doi.org/10.1016/j.jtho.2018.10.006>.
75. Xing W, Sun H, Yan C, Zhao C, Wang D, Li M, et al. A prediction model based on DNA methylation biomarkers and radiological characteristics for identifying malignant from benign pulmonary nodules. *BMC Cancer.* 2021;21:263, <http://dx.doi.org/10.1186/s12885-021-08002-4>.
76. González Maldonado S, Delorme S, Hüsing A, Motsch E, Kauczor H-U, Heussel C-P, et al. Evaluation of prediction models for identifying malignancy in pulmonary nodules detected via low-dose computed tomography. *JAMA Netw Open.* 2020;3:e1921221, <http://dx.doi.org/10.1001/jamanetworkopen.2019.21221>.
77. Tao G, Zhu L, Chen Q, Yin L, Li Y, Yang J, et al. Prediction of future imagery of lung nodule as growth modeling with follow-up computed tomography scans using deep learning: a retrospective cohort study. *Transl Lung Cancer Res.* 2022;11:250–62, <http://dx.doi.org/10.21037/tlcr-22-59>.
78. Li M. Prediction of pulmonary nodule growth: current status and perspectives. *J Clin Images Med Case Rep.* 2023;4, <http://dx.doi.org/10.52768/2766-7820/2393>.
79. Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures. They are data. *Radiology.* 2016;278:563–77, <http://dx.doi.org/10.1148/radiol.2015151169>.
80. Wang Y, Zhou C, Ying L, Chan H-P, Lee E, Chughtai A, et al. Enhancing early lung cancer diagnosis: predicting lung nodule progression in follow-up low-dose CT scan with deep generative model. *Cancers.* 2024;16:2229, <http://dx.doi.org/10.3390/cancers16122229>.
81. Warkentin MT, Al-Sawaihey H, Lam S, Liu G, Diergaarde B, Yuan J-M, et al. Radiomics analysis to predict pulmonary nodule malignancy using machine learning approaches. *Thorax.* 2024;79:307–15, <http://dx.doi.org/10.1136/thorax-2023-220226>.
82. Haaf K, Aalst CM, Koning HJ, Kaaks R, Tammemagi MC. Personalising lung cancer screening: an overview of risk-stratification opportunities and challenges. *Int J Cancer.* 2021;149:250–63, <http://dx.doi.org/10.1002/ijc.33578>.
83. Robbins HA, Berg CD, Cheung LC, Chaturvedi AK, Katki HA. Identification of candidates for longer lung cancer screening intervals following a negative low-dose computed tomography result. *J Natl Cancer Inst.* 2019;111:996–9, <http://dx.doi.org/10.1093/jnci/djz041>.
84. Schreuder A, Schaefer-Prokop CM, Scholten ET, Jacobs C, Prokop M, van Ginneken B. Lung cancer risk to personalise annual and biennial follow-up computed tomography screening. *Thorax.* 2018;73:626–33, <http://dx.doi.org/10.1136/thoraxjnl-2017-211107>.
85. Tammemagi MC, ten Haaf K, Toumazis I, Kong CY, Han SS, Jeon J, 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, <http://dx.doi.org/10.1001/jamanetworkopen.2019.0204>.
86. Ardila D, Kiraly AP, Bharadwaj S, Choi B, Reicher JJ, Peng L, et al. End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. *Nat Med.* 2019;25, <http://dx.doi.org/10.1038/s41591-019-0447-x>.
87. Jacobs C, van Ginneken B. Google's lung cancer AI: a promising tool that needs further validation. *Nat Rev Clin Oncol.* 2019;16:532–3, <http://dx.doi.org/10.1038/s41571-019-0248-7>.
88. Lazebnik S, Schmid C, Ponce J. Beyond bags of features: spatial pyramid pooling for recognizing natural scene categories. 2006 IEEE Computer Society Conference on Computer Vision and Pattern Recognition – Volume 2 (CVPR'06), vol. 2. New York, NY, USA: IEEE; 2006. p. 2169–78.
89. Causey JL, Li K, Chen X, Dong W, Walker K, Qualls JA, et al. Spatial pyramid pooling with 3D convolution improves lung cancer detection. *IEEE/ACM Trans Comput Biol Bioinform.* 2022;19:1165–72, <http://dx.doi.org/10.1109/TCBB.2020.3027744>.
90. Mikhael PG, Wohlwend J, Yala A, Karstens L, Xiang J, Takigami AK, et al. Sybil: a validated deep learning model to predict future lung cancer risk from a single low-dose chest computed tomography. *J Clin Oncol.* 2023;41:2191–200, <http://dx.doi.org/10.1200/JCO.22.01345>.
91. Becker N, Motsch E, Trotter A, Heussel CP, Dienemann H, Schnabel PA, et al. Lung cancer mortality reduction by LDCT screening – results from the randomized German LUSI trial. *Int J Cancer.* 2020;146:1503–13, <http://dx.doi.org/10.1002/ijc.32486>.
92. Paci E, Puliti D, Lopes Pegna A, Carrozzi L, Picozzi G, Falaschi F, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. *Thorax.* 2017;72:825–31, <http://dx.doi.org/10.1136/thoraxjnl-2016-209825>.
93. Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts HJWL. Artificial intelligence in radiology. *Nat Rev Cancer.* 2018;18:500–10, <http://dx.doi.org/10.1038/s41568-018-0016-5>.
94. Zeleznik R, Foldyna B, Eslami P, Weiss J, Alexander I, Taron J, et al. Deep convolutional neural networks to predict cardiovascular risk from computed tomography. *Nat Commun.* 2021;12:715, <http://dx.doi.org/10.1038/s41467-021-20966-2>.
95. Chamberlin J, Kocher MR, Waltz J, Snoddy M, Stringer NFC, Stephenson J, et al. Automated detection of lung nodules and coronary artery calcium using artificial intelligence on low-dose CT scans for lung cancer screening: accuracy and prognostic value. *BMC Med.* 2021;19:55, <http://dx.doi.org/10.1186/s12916-021-01928-3>.
96. Sabia F, Balbi M, Ledda RE, Milanese G, Ruggirello M, Valsecchi C, et al. Fully automated calcium scoring predicts all-cause mortality at 12 years in the MILD lung cancer screening trial. *PLoS One.* 2023;18, <http://dx.doi.org/10.1371/journal.pone.0285593>, e0285593.
97. Ruggirello M, Valsecchi C, Ledda RE, Sabia F, Vigorito R, Sozzi G, et al. Long-term outcomes of lung cancer screening in males and females. *Lung Cancer.* 2023;185, <http://dx.doi.org/10.1016/j.lungcan.2023.107387>.
98. Chao H, Shan H, Homayounieh F, Singh R, Khera RD, Guo H, et al. Deep learning predicts cardiovascular disease risks from lung cancer screening low dose computed tomography. *Nat Commun.* 2021;12:2963, <http://dx.doi.org/10.1038/s41467-021-23235-4>.
99. van Velzen SGM, Zreik M, Lessmann N, Viergever MA, de Jong PA, Verkooijen HM, et al. Direct prediction of cardiovascular mortality from low-dose chest CT using deep learning; 2018.
100. Aquino GJ, Chamberlin J, Mercer M, Kocher M, Kabakus I, Akkaya S, et al. Deep learning model to quantify left atrium volume on routine non-contrast chest CT and predict adverse outcomes. *J Cardiovasc Comput Tomogr.* 2022;16:245–53, <http://dx.doi.org/10.1016/j.jcct.2021.12.005>.
101. Foldyna B, Hadzic I, Zeleznik R, Langenbach MC, Raghu VK, Mayrhofer T, et al. Deep learning analysis of epicardial adipose tissue to predict cardiovascular risk in heavy smokers. *Commun Med.* 2024;4:1–9, <http://dx.doi.org/10.1038/s43856-024-00475-1>.

102. Labaki WW, Martinez CH, Martinez FJ, Galbán CJ, Ross BD, Washko GR, et al. The role of chest computed tomography in the evaluation and management of the patient with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;196:1372–9, <http://dx.doi.org/10.1164/rccm.201703-0451PP>.
103. Cavigli E, Camiciottoli G, Diciotti S, Orlandi I, Spinelli C, Meoni E, et al. Whole-lung densitometry versus visual assessment of emphysema. *Eur Radiol*. 2009;19:1686–92, <http://dx.doi.org/10.1007/s00330-009-1320-y>.
104. Mets OM, Buckens CFM, Zanen P, Isgum I, Van Ginneken B, Prokop M, et al. Identification of chronic obstructive pulmonary disease in lung cancer screening computed tomographic scans. *JAMA*. 2011;306:1775–81, <http://dx.doi.org/10.1001/jama.2011.1531>.
105. Jin H, Heo C, Kim JH. Deep learning-enabled accurate normalization of reconstruction kernel effects on emphysema quantification in low-dose CT. *Phys Med Biol*. 2019;64:135010, <http://dx.doi.org/10.1088/1361-6560/ab28a1>.
106. Boedeker KL, McNitt-Gray MF, Rogers SR, Truong DA, Brown MS, Gjertson DW, et al. Emphysema: effect of reconstruction algorithm on CT imaging measures. *Radiology*. 2004;232:295–301, <http://dx.doi.org/10.1148/radiol.2321030383>.
107. Schreuder A, Jacobs C, Lessmann N, Broeders MJM, Silva M, Išgum I, et al. Scan-based competing death risk model for re-evaluating lung cancer computed tomography screening eligibility. *Eur Respir J*. 2022;59:2101613, <http://dx.doi.org/10.1183/13993003.01613-2021>.
108. Chen T, Guestrin C. XGBoost: a scalable tree boosting system. In: *Proceedings of the 22nd ACM SIGKDD international conference on knowledge discovery and data mining*. 2016. p. 785–94.
109. Lundberg SM, Lee S-I. A unified approach to interpreting model predictions n.d.:10.
110. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J*. 2009;33:1165–85, <http://dx.doi.org/10.1183/09031936.00128008>.
111. Weltgesundheitsorganisation. Prevention and management of osteoporosis: report of a WHO scientific group. In: *WHO scientific group meeting on prevention and management of osteoporosis*. Geneva, 7–10 April. Geneva: World Health Organization; 2003.
112. Romme EA, Murchison JT, Phang KF, Jansen FH, Rutten EP, Wouters EF, et al. Bone attenuation on routine chest CT correlates with bone mineral density on DXA in patients with COPD. *J Bone Miner Res*. 2012;27:2338–43, <http://dx.doi.org/10.1002/jbmr.1678>.
113. Pan Y, Shi D, Wang H, Chen T, Cui D, Cheng X, et al. Automatic opportunistic osteoporosis screening using low-dose chest computed tomography scans obtained for lung cancer screening. *Eur Radiol*. 2020;30:4107–16, <http://dx.doi.org/10.1007/s00330-020-06679-y>.
114. Yang J, Liao M, Wang Y, Chen L, He L, Ji Y, et al. Opportunistic osteoporosis screening using chest CT with artificial intelligence. *Osteoporos Int*. 2022;33:2547–61, <http://dx.doi.org/10.1007/s00198-022-06491-y>.
115. Chen Y-C, Li Y-T, Kuo P-C, Cheng S-J, Chung Y-H, Kuo D-P, et al. Automatic segmentation and radiomic texture analysis for osteoporosis screening using chest low-dose computed tomography. *Eur Radiol*. 2023;33:5097–106, <http://dx.doi.org/10.1007/s00330-023-09421-6>.
116. Ahmad Y, Mooney J, Allen IE, Seaman J, Kalra A, Muelly M, et al. A machine learning system to indicate diagnosis of idiopathic pulmonary fibrosis non-invasively in challenging cases. *Diagnostics*. 2024;14:830, <http://dx.doi.org/10.3390/diagnostics14080830>.
117. Chang M, Reicher JJ, Kalra A, Muelly M, Ahmad Y. Analysis of validation performance of a machine learning classifier in interstitial lung disease cases without definite or probable usual interstitial pneumonia pattern on CT using clinical and pathology-supported diagnostic labels. *J Imaging Inform Med*. 2024;37:297–307, <http://dx.doi.org/10.1007/s10278-023-00914-w>.
118. Bradley J, Huang J, Kalra A, Reicher J. External validation of Fibre-solve, a machine-learning algorithm, to non-invasively diagnose idiopathic pulmonary fibrosis. *Am J Med Sci*. 2024;367:195–200, <http://dx.doi.org/10.1016/j.amjms.2023.12.009>.
119. Chung JH, Chelala L, Pugashetti JV, Wang JM, Adegunsoye A, Matyga AW, et al. A deep learning-based radiomic classifier for usual interstitial pneumonia. *Chest*. 2024;165:371–80, <http://dx.doi.org/10.1016/j.chest.2023.10.012>.
120. Walsh SLF, Mackintosh JA, Calandriello L, Silva M, Sverzellati N, Larici AR, et al. Deep learning-based outcome prediction in progressive fibrotic lung disease using high-resolution computed tomography. *Am J Respir Crit Care Med*. 2022;206:883–91, <http://dx.doi.org/10.1164/rccm.202112-2684oc>.
121. Moran-Mendoza O, Singla A, Kalra A, Muelly M, Reicher JJ. Computed tomography machine learning classifier correlates with mortality in interstitial lung disease. *Respir Investig*. 2024;62:670–6, <http://dx.doi.org/10.1016/j.resinv.2024.05.010>.
122. Selvan KC, Reicher J, Muelly M, Kalra A, Adegunsoye A. Machine learning classifier is associated with mortality in interstitial lung disease: a retrospective validation study leveraging registry data. *BMC Pulm Med*. 2024;24:254, <http://dx.doi.org/10.1186/s12890-024-03021-w>.
123. Koh D-M, Papanikolaou N, Bick U, Illing R, Kahn CE, Kalpathi-Cramer J, et al. Artificial intelligence and machine learning in cancer imaging. *Commun Med*. 2022;2:133, <http://dx.doi.org/10.1038/s43856-022-00199-0>.
124. Thong LT, Chou HS, Chew HSJ, Lau Y. Diagnostic test accuracy of artificial intelligence-based imaging for lung cancer screening: a systematic review and meta-analysis. *Lung Cancer*. 2023;176:4–13, <http://dx.doi.org/10.1016/j.lungcan.2022.12.002>.
125. El Naqa I, Karolak A, Luo Y, Folio L, Tarhini AA, Rollison D, et al. Translation of AI into oncology clinical practice. *Oncogene*. 2023;42:3089–97, <http://dx.doi.org/10.1038/s41388-023-02826-z>.
126. He J, Baxter SL, Xu J, Xu J, Zhou X, Zhang K. The practical implementation of artificial intelligence technologies in medicine. *Nat Med*. 2019;25:30–6, <http://dx.doi.org/10.1038/s41591-018-0307-0>.
127. Widner K, Virmani S, Krause J, Nayar J, Tiwari R, Pedersen ER, et al. Lessons learned from translating AI from development to deployment in healthcare. *Nat Med*. 2023;29:1304–6, <http://dx.doi.org/10.1038/s41591-023-02293-9>.
128. Vokinger KN, Feuerriegel S, Kesselheim AS. Mitigating bias in machine learning for medicine. *Commun Med*. 2021;1:25, <http://dx.doi.org/10.1038/s43856-021-00028-w>.
129. Lenharo M. The testing of AI in medicine is a mess. Here's how it should be done. *Nature*. 2024;632:722–4, <http://dx.doi.org/10.1038/d41586-024-02675-0>.