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# Incidental Findings in Lung Cancer Screening: Which Ones are Relevant?

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## Introduction

Recently, there has been an increasing interest in the potential benefits of lung cancer screening related to the diagnosis and earlier treatment of unsuspected diseases in screening participants. In this regard, besides there being a significant (20%) reduction in the lung specific mortality rate in the National Lung Screening Trial (NLST), there was a 6.7% reduction in all-cause mortality (ACM) in participants screened with annual low-dose computed tomography (LDCT) compared to screening with chest radiograph.[1] The decrease in ACM may be at least partly attributable to the detection and treatment of incidental findings (IFs) such as coronary artery calcification (CAC), chronic obstructive pulmonary disease (COPD), and interstitial lung disease as well as extrapulmonary neoplasms. In fact, LDCT-detected IFs are not uncommon and are reported in up to 79% of screening participants, although most do not require further investigation.[2-5] However, the relevance of some of these IFs is high. The mortality rate from cardiovascular disease (24.8%) in the NLST was higher than the mortality rate from lung cancer (24.1%). Extrapulmonary neoplasms (22.3%) and respiratory illness (10.4%) were also a significant cause of death.[1] The earlier diagnosis and treatment of these entities potentially provides an opportunity to decrease morbidity and mortality in screening participants.

In a systematic review of 4 lung cancer screening studies by Jacobs et al,[6] 14.2% of participants had at least 1 clinically significant IF that required further investigation whereas in the NELSON trial 7% of participants had IFs requiring additional investigation.[5,6] There are implications related to the workup of these IFs, including additional radiation exposure and the risk of iatrogenic injury associated with diagnostic procedures, such as biopsies. Furthermore, the detection of IFs has the potential to undermine the cost-effectiveness of lung screening. The average cost per IF has been estimated to be $103-$106 in screening trials performed in Italy and Canada, which corresponds to approximately $12 when distributed over the total number of screening participants.[2,3,7]

Importantly, there are no established guidelines to determine which IFs should be considered relevant. In this regard, the American College of Radiology Lung-RADS classification (used to standardize LDCT screening interpretation, reporting, and recommendations for management of identified lesions) leaves the relevance of detected IFs to the discretion of the reader and simply provides a category S modifier for screening participants who have a clinically significant or potentially clinically significant non–lung cancer finding. In some lung cancer screening trials IFs have been defined as relevant if they require additional investigation. However, other findings such as CAC and COPD can be considered relevant even if they require no additional investigation, as they can be predictors of acute events and thus provide an opportunity for clinical intervention. In this article we review the most common clinically significant or potentially clinically significant IFs in lung cancer screening.

## Cardiovascular Disease

Lung screening participants are at higher risk for cardiovascular disease due to their advanced age and smoking history. LDCT allows quantification of CAC and extracoronary calcifications (ECC) which is useful for cardiovascular risk stratification. The resultant use of primary and secondary preventive efforts including smoke cessation, dietary changes, exercise, aspirin therapy and lipid-lowering intervention can potentially improve patient outcomes.

The Agatston scoring method has been traditionally used for CAC quantification on electrocardiogram-gated computed tomography (CT) or electron-beam CT. However, recent studies have demonstrated that calcium scoring can be performed in non–electrocardiogram-gated LDCT, despite increased image noise and motion.[8] Additionally, there is a

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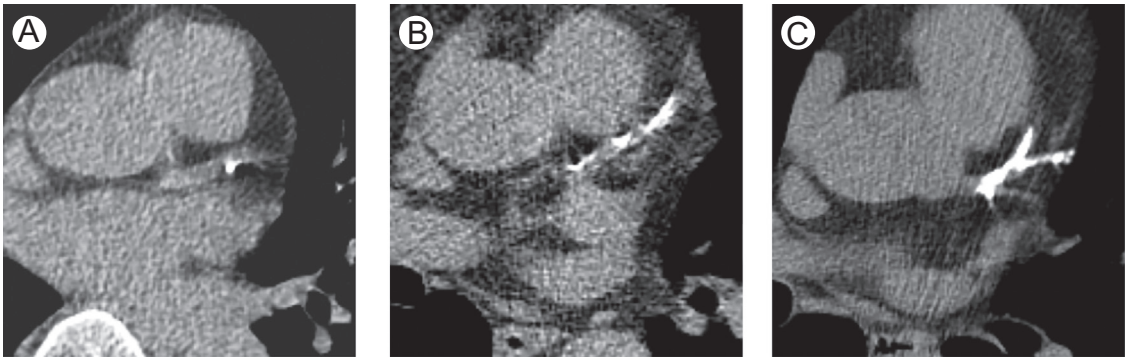


**Figure 1** Coronary artery calcification. Examples of mild (A), moderate (B), and heavy (C) CAC. CAC is classified as mild if there is only isolated flecks of CAC within a segment, as heavy if there is continuous CAC within a segment, and as moderate if there is more CAC than could be considered mild, but less than the description of heavy CAC.

good correlation between the more practical visual analysis of CAC (Fig. 1) and the Agatston scoring method.[9,10] In a study by Chiles et al,[9] 5 cardiothoracic radiologists evaluated 1575 LDCTs from a subset of the NLST participants. Three different CAC scoring methods to assess risk of coronary heart disease (CHD) death and ACM across levels of CAC scores were used. Scoring methods included overall visual assessment (qualitative scoring), segmented vessel-specific scoring (qualitative scoring), and Agatston scoring (quantitative scoring). In multivariate analysis of time to CHD death, participants with moderate and heavy CAC are at highest risk. Agatston scores of 1-100, 101-1000, and greater than 1000 were associated with hazard ratios of 1.27 (95% CI: 0.69-2.53), 3.57 (95% CI: 2.14-7.48), and 6.63 (95% CI: 3.57-14.97), respectively; hazard ratios for segmented vessel-specific scores of 1-5, 6-11, and 12-30 were 1.72 (95% CI: 1.05-3.34), 5.11 (95% CI: 2.92-10.94), and 6.10 (95% CI: 3.19-14.05), respectively; and hazard ratios for overall visual assessment of mild, moderate, or heavy CAC were 2.09 (95% CI: 1.30-4.16), 3.86 (95% CI: 2.02-8.20), and 6.95 (95% CI: 3.73-15.67), respectively.[9] The interreader agreement was good (between 0.8 and 0.9) or high ($\geq$0.9) for all 3 scoring methods.[9] Because overall visual analysis has similar predictive ability, is reproducible and is simpler and faster than segmented vessel-specific or Agatston scoring, the use of this method has been proposed for CAC quantification in LDCT screening.

Over the past decade, evidence has accumulated that ECC (thoracic aorta, aortic valve, and mitral valve or annulus) correlates with coronary calcified plaque burden, CHD, cardiovascular and ACM.[10] In the "CT-Risk" Trial, Dirrichs et al[10] evaluated the presence and degree of ECC (aortic, the aortic valve, and the mitral valve) and CAC in LDCT obtained for lung cancer screening in 501 men that had been exposed to asbestos or carbon dust, or both. The study confirmed that both ECC and CAC scores can be accurately determined by visual analysis and that these scores correlate with the Agatston score. A good correlation was seen between ECC and CAC (2-sided Spearman = 0.515; $P < 0.001$).[10] Additionally, there was a strong correlation between ECC scores and risk prediction models for cardiovascular events such as Framingham risk score and the prospective cardiovascular münster study (PROCAM). Interestingly, CAC scores were associated only with the presence of hypercholesterolemia, providing further evidence that ECC scoring may complement CAC scoring for broader risk assessment, including prediction of extracoronary vascular events, such as cerebrovascular disease, aortic disease, and peripheral arterial disease. Additionally, Mets et al[11] have reported that quantification of coronary and aortic calcium volumes in LDCT images can be used to predict cardiovascular risk, especially when associated with demographic data. They evaluated LDCTs from 3648 participants of the NELSON trial. Age, smoking status, smoking history, and cardiovascular history, together with automatically quantified coronary and aortic calcium volume from the screening CT, were included as independent predictors in a prediction model. When high risk was defined as a 3-year risk of 6% and higher, 589 of 1725 males were regarded as high risk and 72 of 118 of all events were correctly predicted by the model.[11] The use of CAC and ECC has the potential to reduce cardiovascular morbidity and mortality and may enhance the cost-effectiveness of CT-based screening in heavy smokers.[11]

## Chronic Obstructive Pulmonary Disease

COPD, the fourth leading cause of death in the United States and an independent risk factor for the development of lung cancer, is unfortunately substantially underdiagnosed.[12-14] However, COPD is a common IF on LDCT screening and the potential for earlier detection may improve clinical management. LDCT screening may be useful to assess disease severity and predict risk for exacerbations.[15,16]

Based on CT findings, 2 phenotypes of COPD have been described: emphysema-predominant and airway-predominant (Fig. 2), which can be evaluated either visually or by software quantitative analysis.[16] The Global Obstructive Lung Disease (GOLD) system has been widely used to identify and classify the severity of postbronchodilator airflow limitation in COPD. Individuals with identical GOLD stages can have different morphologic appearances at CT, which may reflect significant differences in the underlying pathophysiology and genomic profile of COPD.[17] In this scenario, CT phenotyping may improve diagnostic accuracy and help optimize COPD

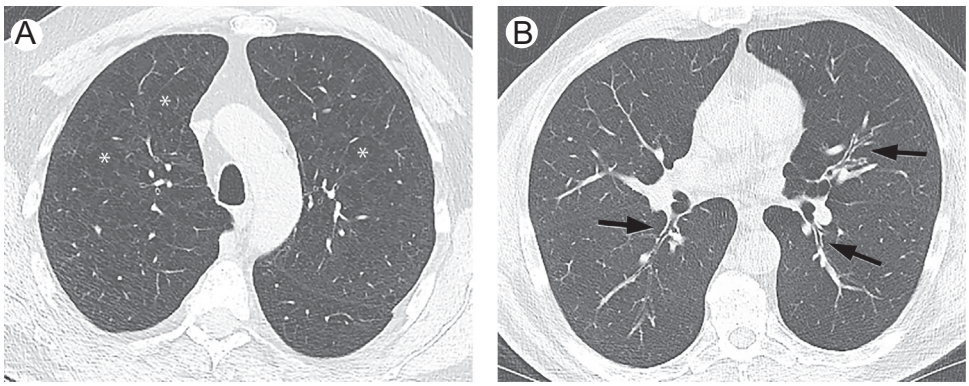


**Figure 2** COPD phenotyping. (A) Emphysema-predominant. Note moderate centrilobular emphysema with lung destruction manifesting as multifocal parenchymal lucencies without an identifiable wall (asterisks). (B) Airway-predominant emphysema. Note the diffuse bronchial wall thinking (arrows). Overlap between the 2 types of COPD is frequent.

treatment (Fig. 3).[16] Therefore, LDCT lung cancer screening reports should include the presence, type, and severity of emphysema and airway disease to alert both the patient and the health care provider to a diagnosis of COPD.

Mets et al[13] evaluated the diagnostic accuracy of LDCT for automated detection of COPD using pulmonary function tests as the reference standard in a subset of patients from the Dutch and Belgian Lung Cancer Screening Trial. The authors used the standard threshold of −950 HU and a 15th percentile of the attenuation distribution curve in inspiratory CT to identify emphysema, and the ratio of lung attenuation in inspiratory and expiratory CT to assess air trapping. COPD was diagnosed in 274 of 437 (63%) patients with proven COPD by spirometry. Importantly, in most participants the diagnosis of COPD was new.[13] In a subsequent analysis of their trial participants, Mets et al,[18] used automated quantification of bronchial wall thickening as a third imaging biomarker for COPD, additional to age, body mass index, smoking history, and smoking status. The diagnostic model that included all 3 CT biomarkers (CT emphysema, CT air trapping, and CT bronchial wall thickness) had a sensitivity and specificity of 73.2% and 88%, respectively. The positive and negative predictive values were 80.2% and 84.2%, respectively.[18] The added value of the expiratory CT data was limited, showing inspiratory CT biomarkers alone are probably sufficient to identify patients with COPD in the lung cancer screening setting.[18]

## Interstitial Lung Disease

Heavy smokers have an increased risk for developing interstitial lung abnormalities (ILA), including usual interstitial pneumonia, nonspecific interstitial pneumonia, respiratory bronchiolitis (RB), RB-interstitial lung disease, and

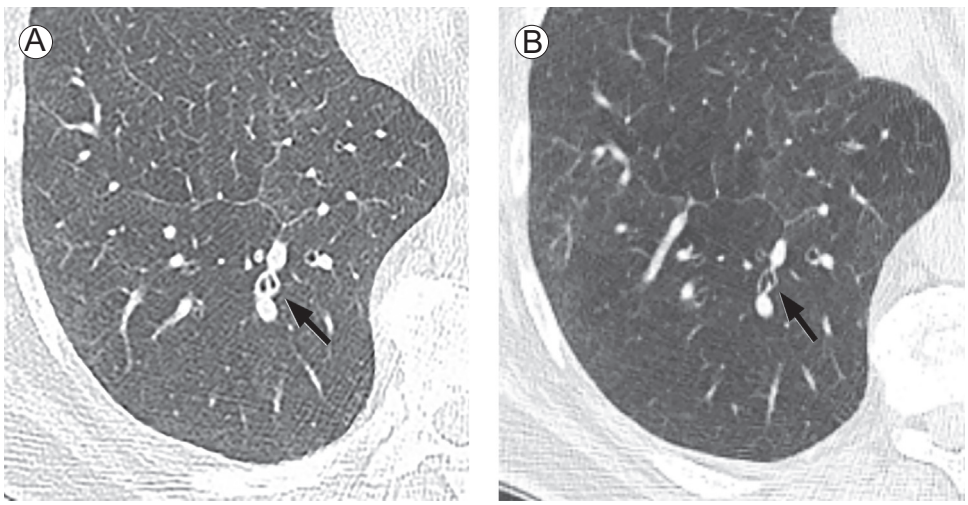


**Figure 3** Airway-predominant COPD. (A) LDCT image shows diffuse bronchial wall thickening in the right lower lobe on baseline screening (arrow), consistent with chronic bronchitis. Patient underwent treatment for smoking cessation. (B) Improvement of bronchial wall thickening on annual LDCT screening follow-up (arrow). Increased thickness of airway walls is associated with the presence of COPD, with reversibility of airway obstruction, and with symptoms of chronic bronchitis. In patients with COPD, bronchial wall thickening is an important independent predictor of FEV1 and of the risk of acute exacerbation. FEV1, forced expiratory volume in 1 s.

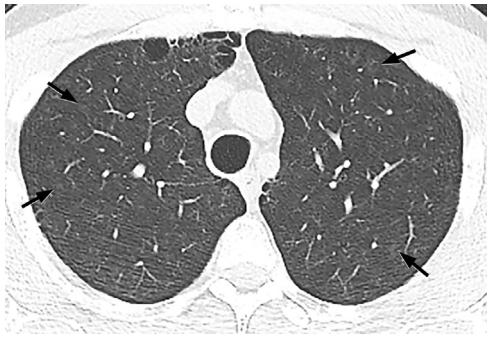

**Figure 4** Respiratory bronchiolitis-interstitial lung disease (RB-ILD). LDCT image shows multiple poorly marginated small centrilobular ground-glass nodules (arrows) in a heavy smoker. Patient presented with chronic dyspnea. Respiratory bronchiolitis interstitial lung disease (RB-ILD) is a smoking-related interstitial lung disease closely related to respiratory bronchiolitis, but presenting more severe histological, imaging, and clinical findings.

desquamative interstitial pneumonia.[16,19,20] A recent study revealed a prevalence of 9.7% of ILA in patients undergoing LDCT for lung cancer screening (86 of 884 patients). The pattern was nonfibrotic in 5.9%, fibrotic in 2.1%, and mixed fibrotic on 1.7%.[19] The percentage of current smokers and mean number of cigarette pack-years were significantly higher in those with ILA than those without ($P = 0.001$). At 2-year follow-up of those with ILA, findings of nonfibrotic ILA improved in 49% of cases and progressed in 11%. Fibrotic ILA improved in 0% and progressed in 37% of cases.[19]

RB is the most common smoke-related interstitial abnormality, histologically present in virtually all smokers, but usually asymptomatic.[20] When extensive, it may be identified at CT as centrilobular ground-glass nodular opacities and can result in clinical symptoms, then considered RB-interstitial lung disease (Fig. 4).[19,20]

## Extrapulmonary Neoplasms

In terms of the potential to decrease morbidity and mortality, extrapulmonary malignancies are one of the most important of the IFs. In this regard, in the CT arm of the NLST trial, 22.3% of the certified deaths (416 of 1865) were due to extrapulmonary malignancy, compared with 22.9% of deaths from lung cancer (427 of 1865).[1] The prevalence of extrapulmonary malignancy in LDCT lung cancer screening participants published in the literature varies from 0%-1.6%. This range is most likely due to differences in the number of participants in the screening studies, as well as the variations in scanning range, duration of surveillance and inclusion of additional imaging modalities, particularly positron emission tomography-computed tomography (PET/CT), in LDCT screening protocols being used nationally and internationally.[1-5,7,21,22]

In the study by Rampinelli et al,[22] 27 extrapulmonary neoplasms were detected in the 5201 participants undergoing a LDCT. Renal cell carcinoma (7) and lymphoma (5) were the most commonly diagnosed malignancies.[22] Others tumors types included thyroid cancer (3), thymoma (2), pancreatic neoplasm (2), schwannoma (1), hepatocellular carcinoma (1), gastrointestinal stromal tumor (1), prostate cancer (1), breast cancer (1), adrenal gland neoplasm (1) and ovarian cancer (1). In 5 participants the extrapulmonary neoplasms were overlooked by the initial readers, but could be retrospectively detected.[22]

To date, there are no specific recommendations for the management of extrapulmonary lesions detected in LDCT lung cancer screening although future editions of Lung-RADS may address this issue. Although IFs should be evaluated on a case-by-case basis, there are general guidelines available for the management of extrapulmonary lesions in the thyroid gland, liver, kidney, pancreas, and adrenal gland. A white paper on the management of IFs in the thyroid gland recommends evaluation with sonography and possibly fine needle aspiration in participants with nodules $>1.5$ cm or nodules with findings suspicious for malignancy including microcalcifications, mixed solid and cystic attenuation, local invasion as well as associated lymphadenopathy or nodules that are (18)F-fluorodeoxyglucose (FDG)-avid fludeoxyglucose on PET/CT imaging.[23] Management of abdominal IFs should follow American College of Radiology recommendations.[24] Liver and renal lesions that are sharply marginated with

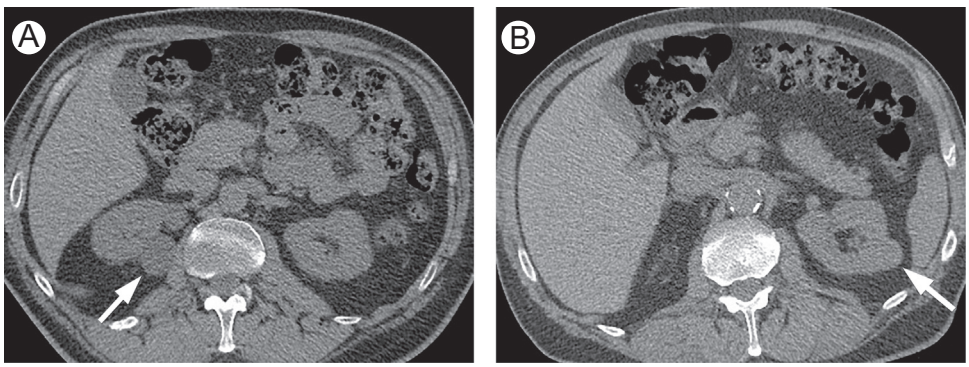


**Figure 5** Incidental findings: renal lesions. (A). Exophytic lesion in the medial aspect of the right kidney measuring 15 HU in attenuation (arrow), consistent with a cyst. No additional workup needed. (B) Exophytic lesion in the lateral aspect of the left kidney measuring 35 HU in attenuation (arrow). A solid renal nodule was confirmed by ultrasonography. This lesion subsequently increased in size on follow-up CT imaging, suspicious for renal cell carcinoma.

homogeneous low attenuation (0-20 HU) require no further evaluation. Renal lesions with >20 HU attenuation or those with wall thickening, nodularity, calcification or septa, should be further evaluated with sonography, CT, or MRI (Fig. 5). Adrenal gland lesions that are stable in size for 12 months when compared with available prior images, or are <4 cm with homogeneous attenuation and smooth margins or have attenuation ≤10 HU require no further evaluation. Adrenal gland lesions >4 cm should be evaluated with sonography, CT, MRI, or PET/CT. Pancreatic lesions <2 cm require no immediate further evaluation and are assessed for stability at subsequent annual screening. Pancreatic lesions 2-3 cm should be further evaluated, preferably with MR/MRCP, lesions ≥3 cm should be aspirated and those >4 cm, considered for resection.

## Conclusion

In summary, IFs are common in LDCT lung cancer screening participants although most do not require further evaluation. The impact of detecting IFs such as CAC, ECC, diffuse pulmonary disease, and extrapulmonary neoplasms is still to be determined, but has the potential to decrease mortality and morbidity in screening participants. Further analysis of the available data and new trials are warranted to determine the importance of IFs and the effect of intervention on patient outcome. This will allow refinement of management recommendations for screen-detected IFs. Additionally, the development of standardized guidelines for reporting and management of IFs will avoid excessive workup and cost.

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