January 15, 2023

International Early Lung Cancer Action Program: Screening Protocol

PI: Claudia I. Henschke, PhD, MD
New York, New York

Overview

The development and refinement of the International Early Lung Cancer Action Program (I-ELCAP) screening protocol has been a concern of the I-ELCAP (originally the Early Lung Cancer Action Program) team for the past 25 years (1-11). Its broad research objective has been the advancement of knowledge for screening, early diagnosis and treatment of lung cancer. The protocol has been updated in the framework of the International Conferences (4) organized by this Group. The continued development of the I-ELCAP international consortium on screening for lung cancer has been facilitated by its web-based infrastructure developed in 2001 which has been regularly updated (4, 5). The research program of I-ELCAP is guided by the common protocol (6, 7), pathology protocol (8, 9), continued evaluation of its results (12-15) in smokers and never smokers, its approach to pathology and long-term follow-up (4, 14-19), and comparison with other regimens of screening (13, 20). The references listed above provide further details.

The I-ELCAP regimen of screening predates the American College of Radiology LungRADS 1.0® (21) by more than 20 years as well as the European protocol (22). A comparison of the I-ELCAP with these two published protocols (20) found that the I-ELCAP protocol required fewer additional diagnostic tests and biopsies for each resulting diagnosis of lung cancer than LungRADS® and the European Consortium protocol. It is anticipated that all protocols will continue to develop, as despite the current differences, the three regimens have common elements. All recommend annual screening, define the protocol for different subtypes of nodule consistency (solid, part-solid, and nonsolid nodules), and provide thresholds to recommend workup, separately for the baseline and annual repeat rounds of screening. The size threshold values for the three protocols are different but are all based on either the nodule diameter or volume. The development and updates of the threshold values for the I-ELCAP protocol are detailed in a prior publication (11).

In the framework of the I-ELCAP protocol, there is opportunity to conduct related studies. Various non-CT approaches to screening, including biomarkers in the broadest sense can be deployed in parallel with the low-dose CT to evaluate the sensitivity and specificity and relative merits. The I-ELCAP Investigators look forward to evaluating and integrating innovative tests (e.g., blood, breath, sputum) into the I-ELCAP protocol.

Implementation of screening programs is challenging even among health care organizations that have the motivation, the resources, and more importantly, the goal of providing for life-saving early detection, diagnosis, and treatment of lung cancer. We provided a case study of lung screening implementation in two different healthcare systems to illustrate the commonalities and differences of the implementation in two very different health care systems in very different parts of the United States (23). In that case study, we identified 10 critical components of implementing a screening program. Most important is continual re-evaluation of the screening program based on the ongoing quality assurance program and database of the actual screenings. At minimum, there should be an annual review and updating. As early diagnosis of lung cancer must be followed by optimal treatment to be effective, treatment advances for small, early lung cancers diagnosed as a result of screening also need to be assessed and incorporated into the entire screening and treatment program (24). For this reason, the Initiative for Early Lung Cancer Research on Treatment (IELCART) was started (24).

It is being increasingly recognized that low-dose CT screenings provides for early identification of not only lung cancer but also of cardiovascular diseases and chronic lung diseases which are leading causes of death worldwide (25). The I-ELCAP Investigators, together with clinical experts in the respective clinical disciplines, have researched the key findings on low-dose CT screenings using extensive I-ELCAP database and long-term follow-up to provide workup recommendations when the

findings are identified (25). Recognition that these findings are identified in asymptomatic people at risk of lung cancer is important and must be considered when making recommendations in order to minimize unnecessary tests and invasive procedures. The importance of identifying these additional findings which result from the screening was recognized as an entire session of the 2019 World Lung Cancer Conference in Barcelona Spain was dedicated to this topic (26).

Indications for screening

As screening is for asymptomatic persons, documentation of the symptom profile is needed. Specifically, current presence/absence of potential manifestations of lung cancer which include worsening cough with hoarseness, hemoptysis, and unexplained loss of weight are documented. Symptomatic persons are ineligible for enrollment and should be considered for diagnostic imaging.

Indications for participation may vary among I-ELCAP participating institutions, notably as to age and smoking history, but these must be specified.

Individuals with lung cancer that have been diagnosed as a result of screening or outside of screening are eligible for screening as long as they received curative treatment for the lung cancer. It is important to continue screening after treatment, as individuals, once diagnosed with lung cancer, are at the highest risk of another lung cancer and should be screened for new primary lung cancers once treatment and routine follow-up has been completed.

Frequency of screening

When application of the regimen of screening at baseline does not lead to the diagnosis of malignancy, repeat screening is scheduled for a preset time from the initial, low-dose test at baseline. Whereas the protocol calls for annual repeat screening, each institution is free to choose the timing of the repeat screening. Such variations do not threaten the validity of the results, so long as they arise from compelling circumstantial matters (and thereby are as though randomly assigned) and these variations also provide an opportunity to study the implications of different intervals to repeat screening in the regimen. Of note is that the United States Preventive Services Task Force recommends annual screening, initially in 2014 (27) and updated in 2021 (28). To date, the Centers for Medicare and Medicaid Services mandate it only for the original recommendations (29).

Communication of results

The results and recommendations of the interpretation of the low-dose CT scan are sent simultaneously to the referring physician and to the participant together with a lay summary. It is important to document the actual work-up in the web-based management system even if the participant or his/her physician chooses not to follow the recommendations.

Components of the Regimen of Screening

In this protocol, ‘screening’ refers to the entire process of the pursuit of early, rule-in diagnosis of lung cancer. It begins with the initial low-dose CT scan at baseline and continues with repeat screenings. A positive result of each screening is followed by follow-up diagnostics which include annual repeat screening, shorter follow-up imaging and, potentially, a biopsy.

It is understood that there may need to be occasional exceptions to the protocol. Each site is fully responsible for performance of the CT scans, their interpretation, and workup recommendations.

When the protocol recommendations are not followed, it is very important to document the reasons for this and to record all results of the alternative workup. While the regimen has been continuously updated based on the analysis of accrued results of actual screenings and diagnoses of lung cancer, the basic structure of the protocol has remained unchanged.

1. *Smoking cessation*

Smoking cessation needs to be incorporated into the program, not only for current smokers but also for former smokers to prevent relapse. CT screening provides "a teachable moment" for smoking cessation advice and has been shown not to cause former smokers to restart smoking. Additionally, personalized counseling or referral to Quit Smoking Help Lines and other support groups is useful. Additional reports on the quit rates in I-ELCAP in the context of screening are provided (30-32).

2. *Image production*

In this regimen, the low-dose CT imaging is the same in baseline and repeat screenings. As there are a large variety of CT manufacturers and models which have markedly improved resolution and other capabilities over time, the following are general guidelines for the image production. Scans should be acquired on multi-detector-row scanners with 16 or more rows. Scans should be acquired so that images can be reconstructed at 1.25mm or less, ideally at the thinnest slice thickness (e.g., 0.5mm or 0.625mm). For optimal assessment of change, initial and follow-up CT scans should be obtained using the same or equivalent acquisition parameters.

There is no specific definition of "low-dose," although historically most screening protocols have used scan parameters of 120-140 kVp and 30-100 mAs. Using the principle "*as low as reasonably achievable"*, w**e suggest that scans be obtained at 120 kVp or lower and 40 mAs (effective) or lower.** An alternative is to use dose-modulation which should be established to correspond to approximately the same dose without modulation. Collimation and pitch also affect dose, and these should be set to allow for the lowest dose, while maintaining acceptable image quality. Image reconstruction should be performed using a standard, non-edge enhancing kernel to minimize effects of noise. However, additional reconstructions may also be obtained, including maximum intensity projection (MIP) images. Scan parameters should also be adjusted to allow for different size patients. Dose modulation techniques which adjust for body size are available on most modern scanners. These should be established based either on weight or body mass index. In addition, new dose reduction techniques are being made available by scan manufacturers, and their use is encouraged, providing that acceptable image quality is maintained. Guidance on scan parameters specific to manufacturers make and model can be found on the website of the American Association of Physicists in Medicine (http://www.aapm.org/pubs/CTProtocols/?tab=5#CTabbedPanels).

Images should be acquired in a single breath-hold from the lung apices through the lung bases. Standards should be established to ensure consistent breath holding. **Contrast material is not used.**

Just prior to acquiring the low-dose CT scan, the participant is asked to cough vigorously several times to clear the trachea and major bronchi of possible mucus secretions and avoid additional imaging that might be required to distinguish such secretions from endobronchial lesions.

Follow-up imaging of abnormalities identified as a result of screening should typically be performed using the same low dose parameters used for the baseline and repeat screenings.

3. *Quality assessment of imaging*

Assessment of CT image quality is critical for identification of small nodules and for growth assessment. The I-ELCAP Investigators recognized the considerable variability of CT scanners for growth assessment (10, 11, 33-35) when they started volumetric assessment in the mid 1990's (36-40) and have continued to be refined since that time (41-47). The variability is due to many factors: the scanner itself, both inherent as well as adjustable CT acquisition parameters as well as characteristics of the person being scanned and the nodule itself, both morphologic features and location (35). Unfortunately, the inherent variability of CT scanner acquisition protocols is not widely recognized. Illustrations of the variability and its impact on growth assessment have been detailed (10, 11) using analysis of perfect spheres (35) as shown in Figure 1. Considerable variability can be found in images taken just seconds apart which can lead to a mistaken conclusion that significant volumetric growth or volumetric regression has occurred.

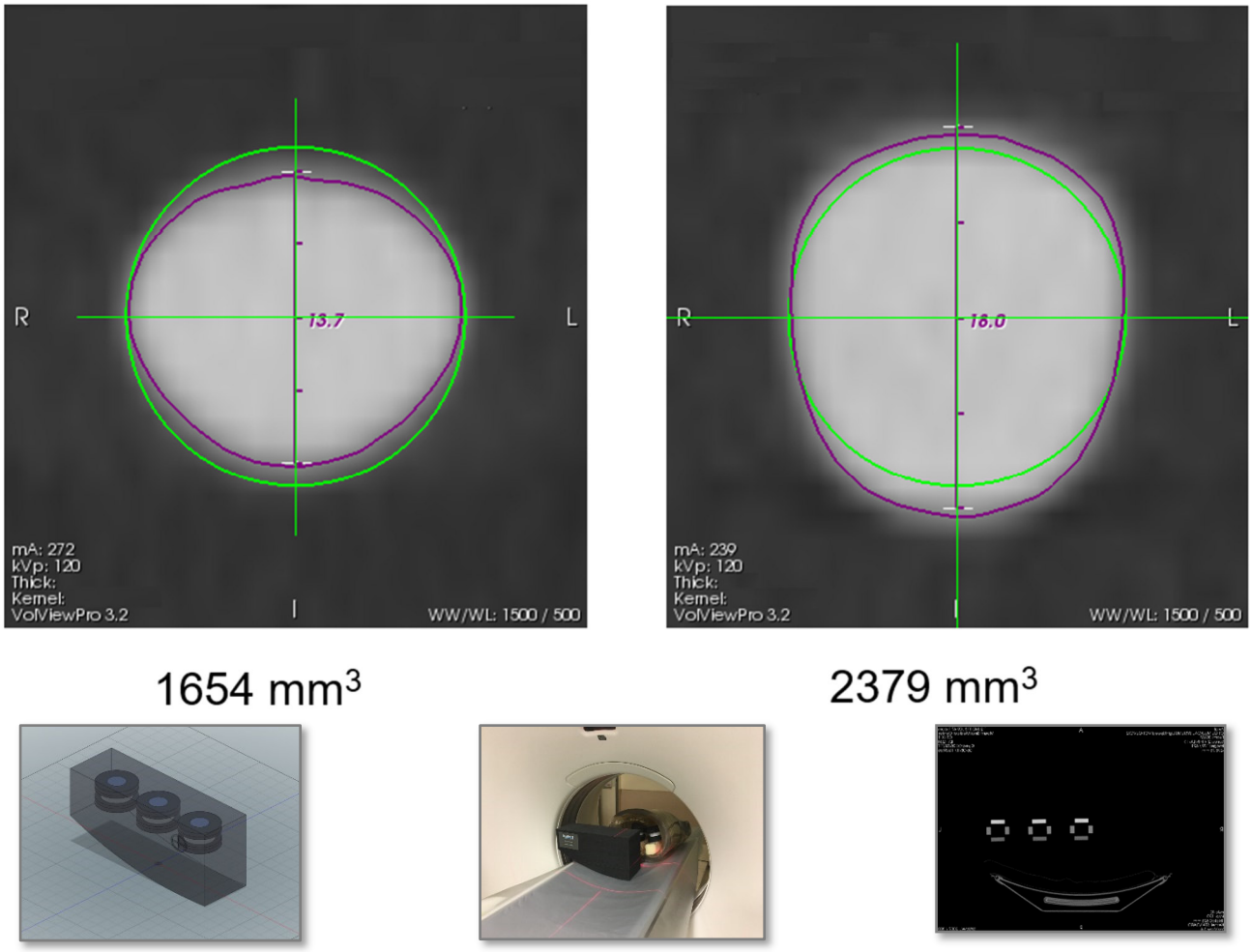


Figure 1. Two scans of a marble that was scanned minutes apart. The volume of the marble is shown and there is a 44% change which is entirely due to the scanner acquisition (35)

4. *Reading of images*

The images are read by a radiologist at the site. The reader is aware from which round of screening (baseline or repeat) that the images derive, as the work-up protocol depends on the round. The reader views the images as they are displayed in a high-resolution monitor at their typical window and level

settings -- scrolling through the images one at a time, documenting nodules, enlarged lymph nodes, mediastinal masses, effusions, and other abnormalities. For clinically significant abnormalities, other than nodules, recommendations specific to screening studies or standard radiologic guidelines are provided. For the purposes of assessing the size of a nodule or that of a mediastinal abnormality, the following settings are used: lung window width 1500 HU and lung window level-650 HU, and mediastinal window width 350 HU and mediastinal window level 25 HU.

In both baseline and repeat screening, the reader's first concern with the images from the first, low-dose test is to *identify all non-calcified nodules* (NCNs) visible in the images.

For repeat screenings, the reader's special concerns are to *identify all new NCNs;* and those that produced a semi-positive result on the CT baseline and that showed growth--either in the overall size of a solid nodule, in the solid component of a part-solid nodule, or in the development of a solid component within a previously nonsolid nodule. To determine whether growth has occurred, the reader compares the current images with the corresponding previous ones, displayed side-by-side.

For each of these nodules in the lung parenchyma or bronchi, the reader documents the location, size, consistency (solid, part-solid or nonsolid), calcifications, and nodule edge characteristics (including spiculations). The definitions of nodules, their consistency and size are given below followed by the assessment of nodule growth.

CT-detected Nodules

1. *Nodule definition*

A nodule is a focal non-linear opacity with a generally spherical shape surrounded by lung parenchyma.

A nodule is classified as a **non-calcified nodule (NCN)** if it fails to meet the usual criteria for benign, calcified nodules (33, 48). Thus, a nodule less than 6.0 mm in diameter is non-calcified if all of it appears less dense than the ribs (on bone and lung windows); a nodule 6.0-20.0 mm in diameter is non-calcified if most of it is non-calcified (by that criterion) and/or the calcification does not correspond to a classical benign pattern (complete, central, lamellated, popcorn) and/or the edge is spiculated to any extent; and a nodule over 20.0 mm in diameter is non-calcified if any part of it is non-calcified judged by the criteria above (33). Focal pleural thickening or pleural plaques are not considered nodules.

A nodule 30.0 mm or more in diameter is designated as a mass.

2. *Nodule consistency*

A nodule is classified as solid unless it has specific characteristics to be classified as subsolid (49-56). **A solid nodule may have external or internal cystic airspace or internal cavitation** (7, 56). **Subsolid nodules may be either nonsolid or part-solid** (50-55). **A part-solid nodule is one that has some internal components that completely obscure the lung parenchyma while other components do not obscure the lung parenchyma (51, 53, 55) . A nonsolid nodule is one where none of the lung parenchyma is completely obscured, except for internal blood vessels (50, 52, 54).**

In making the distinction between part-solid and nonsolid nodule, blood vessels within the nodule, despite their appearance as solid components, are not regarded as solid components. Part-solid nodules are nodules which may start as nonsolid nodules and subsequently develop a solid component within the previously nonsolid nodule. When determining the distinction between part-solid and solid is difficult, the nodule should be classified as solid. When the progression of a part-solid from a nonsolid cannot be confirmed (such as when prior images are not available) and the diameter of the solid component relative to the diameter of the entire nodule is 80% or more, the nodule should be classified as solid (51).

Further workup of subsolid nodules as recommended in baseline and annual repeat rounds should be based on the size of the largest solid component of the part-solid nodule (7, 50, 51). These recommendations are based on a review of the I-ELCAP databases (50, 51) , the National Lung Screening Trial database (52, 53), and the world literature (54, 55) as well as pathology databases (57, 58).

It has been increasingly recognized that some of the lung cancers identified in subsolid nodules can represent very slow-growing lung cancers that can safely be followed until a solid component with the NCN emerges or there is an increase in size of the solid component (50-55, 59, 60).

3. Peri-fissural and costal pleural, mediastinal pleural and diaphragmatic pleural nodules

Four specific subtypes NCNs, perifissural pleural, costal pleural, mediastinal pleural and diaphragmatic pleural nodules, have specific recommendations for follow-up**.**

Peri-fissural nodules are defined as solid, homogenous nodules attached to a fissure or within a specified distance of a fissure. In I-ELCAP, a **peri-fissural nodule** must be attached to a fissure (0 mm from the fissure). Other guidelines allow for some distance from the fissure (61-64)
.
When a peri-fissural nodule has a smooth margin, lentiform, oval, semi-circular, or triangular shape, and is less than 10 mm in diameter, follow-up on annual repeat screening is recommended rather than more immediate workup (61-64).

Costal pleural nodules are defined as solid nodules attached to the costal pleura (0 mm from the costal pleura).

Mediastinal and diaphragmatic pleural nodules are defined as solid nodules attached to the mediastinal or diaphragmatic pleura (0 mm from the mediastinal or diaphragmatic pleura) (65, 66).

When a costal-, mediastinal-, or diaphragmatic-pleural nodule has a smooth margin, triangular, lentiform, oval, or semi-circular shape, and is less than 10 mm in diameter, follow-up on annual repeat screening is recommended (61, 67-69).

These recommendations apply to peri-fissural or costal pleural, mediastinal-pleural and diaphragmatic-pleural nodules found either on baseline or annual repeat screenings.

4. Nodule size

Nodule size is reported according to its average diameter, which is the average of its length and width. Length and width are measured on a single axial CT image which shows the maximum size of the nodule. Length is the longest dimension of the nodule. Width, defined as the longest

perpendicular to the length, is measured on the same CT image. The diameter of the solid component of part-solid nodules is measured in the same way.

These diameter measures should be supplemented by computer-based assessments of volume, though these measures need to be interpreted cautiously in light of CT measurement errors (35, 41-44, 70). **When accuracy of volume measurements reaches acceptable standards, volume measures should replace manual diameter measurements.**

As length and width of each NCN can be measured to the nearest decimal point, the average diameter should also be rounded to the nearest decimal point (71). As shown in the referenced article (71), it should not rounded to the nearest whole number.

5. *Growth assessment on follow-up CT scans*

Growth of a nodule is defined as: 1) enlargement of the overall nodule size, regardless of consistency, 2) growth of the solid component of a part-solid nodule, 3) development of a solid component within a nonsolid nodule.

The current I-ELCAP protocol specifies the necessary change in the nodule diameter to determine "real" growth for tumors with a VDT of 180 days, separately for the baseline (Table 1) and annual repeat rounds (Table 2). These tables are based on the assumption that 64-detector-row or higher CT scanners are used, that acquisition is at sub-millimeter slice thickness, slice spacing is equal or less than slice thickness, reconstruction field of view is less than 30 cm, and that identical acquisition parameters were used to acquire both scans, so that excellent CT images are obtained for accurate growth assessment.

In Tables 1 and 2, the first column gives the change in the nodule diameter (average of length and width) for VDTs of 180 days when there is no measurement error. The second column gives the diameter which must be exceeded when accounting for measurement error. Linear interpolation should be used for values between the table values provided below.

Table 1. Baseline Round: Change needed in nodule diameter to identify growth at a malignant rate for volume doubling times of 180 days or faster

BASELINE ROUND		
Original diameter (mm)	Diameter (mm) in 3 months without measurement error VDT: 180 days	Diameter (mm) in 3 months with measurement error VDT: 180 days
6.0	6.7	7.1
7.0	7.9	8.3
8.0	9.0	9.4
9.0	10.1	10.5
10.0	11.2	11.6
11.0	12.3	12.7
12.0	13.5	13.9
13.0	14.6	15.0
14.0	15.7	16.1

I-ELCAP guidelines for assessment of growth of solid nodules are given in Tables 1 and 2. These guidelines assume that modern scan protocols are used and that the software allow for sub-pixel resolution. It assumes that the solid nodule has little or no attachment to surrounding structures. The diameter change for a cancer with a VDT of 180 days is given in Table 1 and 2 assuming: 1) sub-millimeter CT slice thickness, 2) slice spacing equal or less than slice thickness, 3) 64-detector-row or higher CT scanners. 4) reconstruction field of view is less than 30 cm, and identical parameters on both scans.

The I-ELCAP protocol recommends continued observation for nonsolid nodules as they can grow either in overall size based on a review of the I-ELCAP databases (50, 51), National Lung Screening Trial database (52, 53), and the world literature (54, 55). Thus, nonsolid nodules should continue to be monitored as long as they do not develop an internal solid component. When an internal solid component is identified and for solid nodules, measurement should focus on the solid component of the nodule which is measured either by diameter or computer-assisted volume measurements.

Table 2. Repeat Rounds: Change needed in nodule diameter to identify growth at a malignant rate for volume doubling times of 180 days or faster.

ANNUAL REPEAT ROUNDS		
Original diameter (mm)	Diameter (mm) in 6 months without measurement error VDT: 180 days	Diameter (mm) in 6 months with measurement error VDT: 180 days
3.0	3.8	4.2
4.0	5.0	5.4
5.0	6.3	6.7
Original diameter (mm)	Diameter (mm) in 1 month without measurement error VDT: 180 days	Diameter (mm) in 1 month with measurement error VDT: 180 days
6.0	6.2	7.0
7.0	7.3	8.1
8.0	8.3	9.1
9.0	9.4	10.2
10.0	10.4	11.2
11.0	11.4	12.2
12.0	12.5	13.3
13.0	13.5	14.3
14.0	14.5	15.3

The accuracy of growth assessment depends on nodule size. This size dependence is recognized in the I-ELCAP protocol (Tables 1 and 2) and the QIBA small nodule profile recommendations (72). The I-ELCAP protocol is different than the LungRADs (21, 61) and other guidelines (22) which use a fixed value (i.e. 1.5 mm) to indicate growth. Use of a fixed value means that recognition of growth in smaller tumors with fast growth rates will be delayed (20).

When using any computer-assisted software for size or growth assessment, **there are important lessons that have been learned.** The radiologist must be satisfied with the CT image quality and the computer segmentation results in deciding whether growth has occurred. The computer scans and the segmentation need to be reviewed for image quality (e.g. motion artifacts) and for the quality of the segmentation. The radiologist should visually inspect both nodule image sets side-by-side to verify the quality of the computer segmentation for each image that contains a portion of the nodule. The segmentations should also be examined for errors; for example, a small blood vessel may be included as part of a nodule in one segmentation but not in another segmentation. Scan slice thickness and slice spacing for the purpose of volumetric analysis should not exceed 1.25 mm but preferably as low as possible and at least less than 1 mm. The shorter the time between the CT scans, (e.g., 1-month interval after the annual screening) the greater the measurement error.

Figure 1 illustrates the possible measurement error of CT scanners, even when the acquisition parameters are identical with only seconds between the two scans. In the two scans, minutes apart, a marble showed a 44% change, a volume doubling time of 172 days. If this were an actual nodule, it would be considered to be a moderately fast growing lung cancer. Thus, understanding of the inherent error of quantitative CT measurements is critical for valid management decisions.

To further address accurate CT measurements, the Radiological Society of North American (RSNA) created the QIBA (72, 73). I-ELCAP Investigators have worked to develop the phantom for conformance testing of different scanners and software products. It is far more rigorous for lung nodule measurement assessment than the usual ACR CT accreditation phantom. QIBA is in the final stages of releasing the QIBA CT Small Lung Nodule Profile, which will provide recommendations on assessing growth of small lung nodules (https://qibawiki.rsna.org/index.php/CT_Small_Lung_Nodule_Biomarker_Ctte). While these estimates are meant only as boundaries to be confident that nodule change has actually occurred, they do not address the accuracy of volumetric assessment of growth rates themselves (i.e., volume doubling times (VDTs) which remains a topic of research.

Our overall understanding of growth assessment is rapidly evolving and the following should be considered: Nodule volume doubling times (VDTs) are useful (40-44, 70). VDTs of less than 30 days are more suggestive of an infection than malignancy. Lung cancer VDTs are more than 30 days, typically between 30 and 400 days. VDTs are based on the change in the nodule length, width, and height. However, determination of these measurements on CT are complex and influenced by multiple factors including the intrinsic properties of the nodule, the CT scanner and its adjustable scanner parameters, and the software used to make the measurement. And these factors interact in complex ways (35, 74-76) which has been illustrated by Figures 6 and 7 in the 2020 article in the Journal of Thoracic Imaging (11).

Several groups have developed approaches to incorporate measurement errors into the determination of growth (72-76). The RSNA's Quantitative Imaging Biomarkers Alliance (QIBA) is in the final stages of releasing their recommendations and have made a web-based calculator available at http://accumetra.com/solutions/qiba-lung-nodule-calculator (73).

There is considerable variation among the different hardware and software that is currently available (76). The I-ELCAP guidelines have been developed as a result of the evaluation of our in-house software. It applies only where modern scanners and high-resolution protocols are used. With the careful technical and clinical quality review outlined below, the results of computer analysis are useful in guiding the work-up. The screening sites have access to analysis using the I-ELCAP web-based research tools. When using any computer-assisted software, the radiologist must be satisfied

with the CT image quality and the computer segmentation results -- as, ultimately, the decision is based on clinical judgment as to whether growth has occurred.
While the estimates given in Tables 1 and 2 are meant as boundaries to be confident that nodule change has occurred, they do not prove accurate in determining rate of growth. At this point, decisions regarding confidence intervals for determining malignant growth rates within specified time intervals remains a topic of research. Currently, any estimates of growth rates (or VDTs) should be interpreted with caution and the change in parameters described above only be used as guidelines. The guidelines are intended to provide readers with increased confidence in measuring nodule change and differentiating it from measurement error.

6. Workup of nodules

NCN size thresholds for further workup are continually reevaluated and have changed since the start of ELCAP due to CT acquisition and imaging display advances and increased knowledge (11). Initially, there was no size cutoff for positive results (3, 48). However due to advancing technology and accumulated knowledge and evidence, thresholds were introduced and subsequently updated multiple times (11). **In the current protocol, the nodule diameter threshold for positive result is 6.0 mm on baseline and 3.0 mm on annual repeat screening, but future updates are anticipated (33).**

It has been shown that both solid and subsolid NCNs identified in the lung parenchyma frequently resolve, particularly new ones identified on repeat screenings (50-55, 77). Thus, if identified, follow-up imaging three [3] months after baseline CT or one [1] month after annual repeat CT is useful as the NCNs may resolve and thus avoid unnecessary further diagnostics, especially invasive ones (77).

7. Biopsy

For the biopsy procedure, CT-guided percutaneous transthoracic fine-needle (or core needle) aspiration is preferred, as this is a 1-hour, minimally invasive, outpatient procedure performed with local anesthesia at the needle puncture site (78-82).

If percutaneous transthoracic fine-needle or core biopsies are not feasible, other minimally invasive procedures such as image-guided bronchoscopic biopsy are options. Video-assisted thoracoscopic (VATS) surgical biopsy can be used; however, use of this procedure requires general anesthesia and a very strong suspicion of malignancy. It is recommended that prior to VATS, growth assessment demonstrating growth of the nodule at a malignant rate, and/or PET scan suggesting malignancy be performed. The images of the cytology and histology specimens as well as the text report of all biopsies are entered into the web-based management system.

The biopsy specimens are described and classified into standard diagnostic categories. In the context of CT screening, the primary role of biopsy is to establish a diagnosis of cancer versus a benign etiology. Therefore, the first priority is to establish whether there is sufficient material present in the biopsy specimen to make that determination. Ideally, sufficient specimens to perform immunohistochemical analysis and molecular profiling are obtained, but they are subordinate if they entail additional risk to the patient in obtaining the sample (83, 84).

Cytology and histology slides are submitted for digitization to the coordinating center. These may be reviewed by independent expert pathologists for quality assurance purposes. The diagnoses of these experts are used as the final diagnosis for study purposes, and these are documented on the study forms in the I-ELCAP database (6, 8, 9).

Classification of diagnosed cancers

1. Baseline screen- and interim-diagnosed lung cancer

A diagnosis (rule-in) of lung cancer is classified as a **baseline screen-diagnosed lung cancer** if the nodule is identified on the initial CT on baseline, regardless of when the diagnosis of lung cancer actually is achieved (11, 13). Also, if a diagnosis of lung cancer is only made more than 12 months later, for example on the first annual repeat CT in 12 months. If the result of the initial CT at baseline is negative and diagnostic work-up is prompted by suspicion-raising symptoms (or an incidental finding) before the scheduled first annual repeat screening, the diagnosed cancer is classified as a **baseline interim-diagnosis**, again regardless of when the diagnosis is achieved.

If a participant who was previously enrolled in the screening program returns three or more years later, then the LDCT screening should be reviewed as if it were a baseline LDCT as the probabilities of malignancy are consistent with the original baseline screening. Thus, the baseline protocol rather than the annual repeat protocol should be used for recommendations of any NCN findings.

2. Annual repeat screen- and interim-diagnosed lung cancer

Analogous attributions are applied in the context of repeat-screening cycles. If lung cancer is diagnosed in a new nodule that was first identified on annual repeat, **it is an annual repeat screen-diagnosed cancer,** even if it is seen on the baseline screening in retrospect but was not identified at that time (11, 13). If work-up is prompted by suspicion-raising symptoms (or an incidental finding) in between annual screenings, the diagnosed cancer is classified as an **annual repeat interim-diagnosis**.

3. Clinical staging

Each diagnosed cancer is characterized according to indicators of how early and otherwise significant the cancer is – all of this bearing on the prognostic issues (85-87). Principal among these descriptors or indicators is the *clinical stage* of the disease at diagnosis. Clinical Stage I according to the current guidelines (85), is defined by the size of the tumor (T status), having no manifestations of lymph node metastases in the hila, mediastinum (N status), and supraclavicular or axillary regions, or distant metastases in adrenals, liver, spleen, bones, or soft tissues visible in the chest CT and no signs of metastases on PET scan, if performed (M status). The presence/absence of lymph-node and distant metastases (N and M status) is assessed on the most recent CT scan prior to treatment, and also from a PET scan, if available.

In case of multiple subsolid NCNs, the person is still classified as being of clinical Stage I as long as these imaging studies do not demonstrate evidence of lymph node or distant metastases (N0M0), or other invasive non-adenocarcinomas, as long as the other adenocarcinomas are all less than 30 mm in diameter (15, 17, 18). This approach has now gained widespread acceptance.

Closely related to the clinical stage of the disease is the *size and nodule consistency* of the tumor, notably within Stage I. Quality assurance in respect to this descriptor of the diagnosed malignancies is an important component in the I-ELCAP database, as the study data from the images are available for central determination. Nodule size is determined by the **diameter**, defined as the average of the nodule's length and width measured in the CT image which contains the largest image of the nodule.

Our most recent publications (86, 87) demonstrated that neither CT and SUVmax measures of mediastinal lymph nodes (N2 and N3) metastases were significant predictors of actual metastases in

Stage IA lung cancers. In addition, no N2 or N3 metastases were identified in part-solid or nonsolid NSCLCs less than 30 mms in maximum diameter, in solid NSCLCs ≤ 10 mm or in typical carcinoids 30 mm or less. **We recommend clinical stage IA for that non-small-cell lung cancers less than 30 mm in maximum diameter should be based on size≤30 mm in maximum diameter on pre-surgical CT and short-axis length of mediastinal lymph nodes≤20 mm in maximum diameter.**

4. Cancer volume and volume doubling rate

The nodule volume may be obtained automatically using commercially available software. Important also is the tumor's *volume doubling time (VDT)*. This rate is critical to the early-diagnostic regimen, particularly for tumors less than 15.0 mm in diameter, and is also presumably quite significant from a prognostic perspective. This doubling rate can also be derived centrally – and on the basis of automated assessment of nodule volume. It is emphasized that when performing volumetric assessment, the relative change of the nodule volume is most critical (41, 88).

5. Cell-type

Eminently important are the pathology data, especially for the distinction between cell types, first among small-cell and non-small-cell types (89), and then within the non-small-cell types, between adenocarcinoma and squamous-cell carcinoma. The new classifications of adenocarcinoma should be used depending on the subtypes identified in the pathology specimen (90, 91). Changes include adenocarcinoma-in-situ (AIS), defined as a lepidic-predominant cancer with stromal invasion (replaced bronchioalveolar carcinoma), minimally invasive adenocarcinoma (MIA), defined as having at least 90% lepidic component and no more than 5 mm of invasion. Other descriptors of prognostic significance may be added in the future, if data-analysis affirms their relevance. The study data for analysis are, again, derived centrally.

It is hoped that prognostic characterization of the diagnosed cancers can also, in the not too distant future, be in part based on 'biomarkers' of the cancer's degree of aggressiveness (83, 88). Pursuit of this goal is one of the research aims of I-ELCAP.

Lung cancer probability by size and consistency

The I-ELCAP thresholds are based on the probability of malignancy as documented in the I-ELCAP database. Figures 2 and 3 provide the probability of malignancy. The frequency of malignancy in a newly seen nodule is different in annual repeat rounds of screening than in the baseline round. However, for each annual repeat rounds, the frequency of malignancy in a newly seen nodule is the same.

For smaller size nodules, the probability of malignancy is higher on annual repeat screening than on baseline screening. Also the probability of malignancy is lower for the larger size nodules on annual repeat screening. The actual number of cancers, especially among those nonsolid nodules cannot be fully addressed as diagnosis has not have been pursued in all cases. Based on review over the I-ELCAP experience past 20 years, there was no diagnosis of malignancy on annual repeat rounds in *new* nonsolid nodules greater than 15.0 mm or in part-solid nodules greater than 30.0 mm (11, 50, 51).

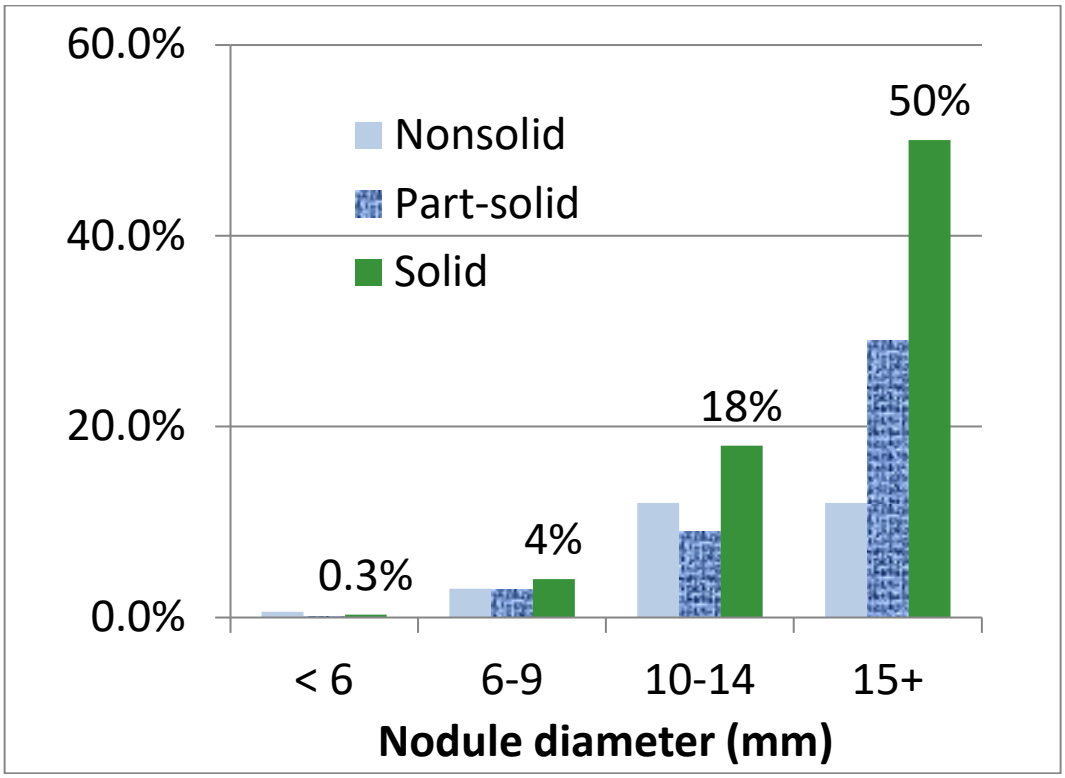


Figure 2. Baseline screening round. The probability of diagnosing lung cancer by nodule consistency and size when it is first identified in the baseline round of screening (12).

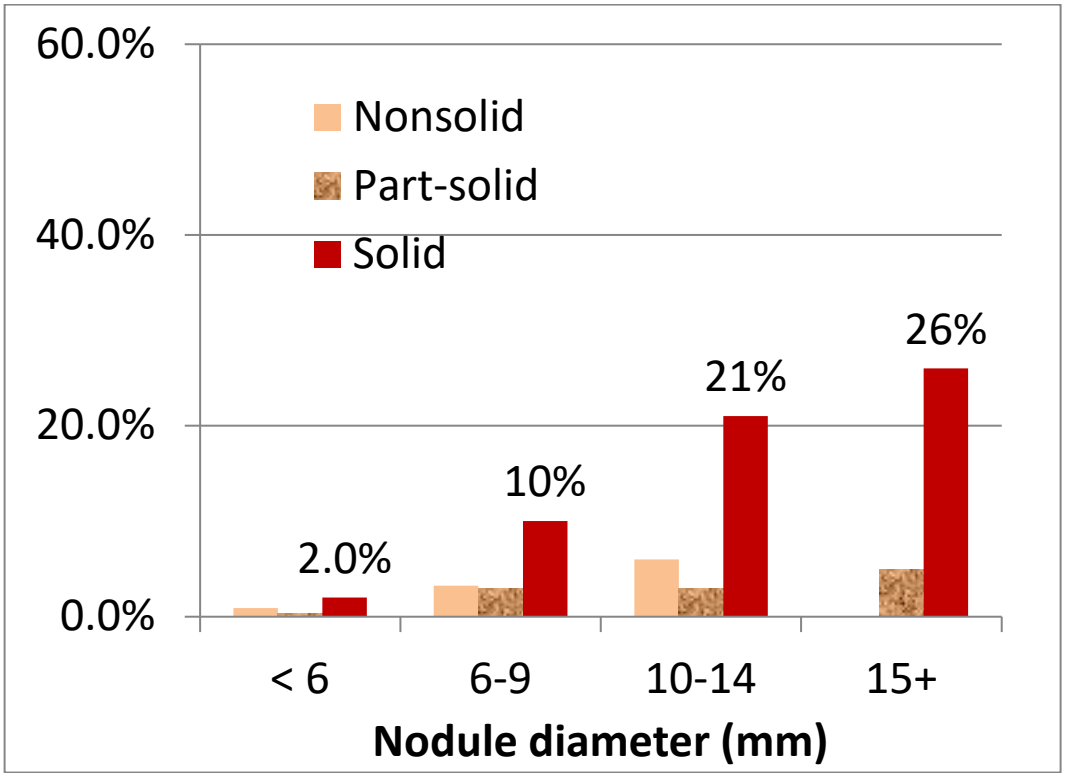


Figure 3. Annual repeat screening round. The probability of diagnosing a lung cancer by nodule consistency and size when it is newly identified in an annual repeat round of screening. (Note that no malignancy were identified in nonsolid nodule 30mm or more in size (12)).

Intervention policy

When lung cancer has been diagnosed by the regimen of early diagnosis, that diagnosis creates a situation not inherently one of medical research but of medical practice. The I-ELCAP protocol does not dictate decisions of practice. However, since the concern in I-ELCAP is to learn from the treatment intervention practices, close documentation of the intervention(s) is required. Also important to carefully document is the occurrence of any complications of the intervention(s), notably surgical death (within 30 days) and other serious complications.

The pathologic stage of the cancer in terms of its size (T status), presence/absence of lymph-node involvement and the respective station (N status), and intrathoracic extension (M status) is based on the surgical findings which are documented. Representative pathology slides are sent to the coordinating center for digitization and potential quality assurance review according to the pathology protocol.

Embedded in the framework of the I-ELCAP, there is opportunity to study the relative merits of *alternative interventions.* With select subtypes of lung cancer diagnoses, some institutions may wish to participate in randomized controlled trials (RCTs) or quasi-experimental or pragmatic studies designed to address the relative merits of different therapeutic interventions. RCTs on prevention options are also possible, for example, chemoprevention of recurrence. Surgery is and will remain the treatment of choice for early lung cancer for the foreseeable future, but trials of primary non-surgical treatment for Stage I lung cancer are increasing and appear promising (92-97). These include small volume targeted radiotherapy, radiofrequency ablation and cryoablation.

Quality of life issues can be addressed using the SF-12 which has been collected as part of the I-ELCAP background and follow-up information since 2000 (98-102).

The increasing numbers of small, early lung cancer diagnoses, mainly by screening, provide unprecedented opportunities to address many research questions about their surgical and non-surgical treatment. I-ELCAP continues to encourage the development of new knowledge through its ongoing screening research and the now coupled treatment research program, such as the pragmatic ongoing Initiative for Early Lung Cancer Research on Treatment (IELCART) (24).

The choice of intervention, including the decision whether to intervene, ideally, is dependent on the prognosis of each individual. To develop new knowledge for such individualization, studies on the role of non-surgical treatment and on the utility of biomarkers are encouraged among I-ELCAP participants.

Outcome determination

Every effort will be made to have 10-year follow-up of all diagnosed cases of lung cancer including documenting whether manifestations of metastases or recurrence have occurred and the cause of death. This starts with documentation of all information that serves to identify the patient over time including the Social Security number in the US (or equivalent internationally). And where the local efforts fail, assistance in locating the person or identifying his/her death will be given (in accordance with local IRB requirements).

Regular reports will be made by the coordinating center, separately for the baseline and annual repeat rounds as to: 1) frequency of positive result, 2) frequency of invasive procedures and results, 3) frequency of complications of invasive procedures, 4) frequency of diagnosis of lung cancer,

5) frequency of diagnosis of other malignancies, 6) frequency of clinical and pathological stages at time of diagnosis, and 7) treatment and vital status (date and cause of death) among lung cancer cases.

The I-ELCAP Management System

Since the earliest days of I-ELCAP, the evolution of the management system has been a critical component (5, 10, 11). It is a web-based interactive system to guide and document the actions and various findings, from the initial contact to schedule the baseline screening to the end of the follow-up of at least 10 years for a diagnosed case of lung cancer. The web-based system is readily accessible by I-ELCAP participating institutions. It presents the context-relevant data form and thereby provides for immediate data entry, at the initial contact and at each subsequent encounter. Not only does it guide the actions in any given encounter, but it also schedules the next one. All of the information is automatically securely transmitted to the institution's data repository. The system monitors protocol conformity as well as completeness and consistency of the data at the time of its entry (10, 11).

The system also provides for secure electronic transmission of CT images (using standard DICOM protocols) and digital pathology 'slides' to the institution's repository. This allows for central reading, including the automatic assessment of nodule volumes and rate of growth. At the same time, each participating institution has secure high-speed computer access to its own data.

The system assures confidentiality and reliability. In the transmission, secure scripts are used. Unique passwords are required for access to particular segments of the central database. Accessing the data from each institution involves built-in encryption to maintain security over the Internet (ssh2 and SSL for web access). Identification of the subject is available only to the participating institution, as only the system-assigned code-identifier is available in the I-ELCAP database.

Quality assurance

In I-ELCAP, quality assurance is a central concern. It begins with application of the criteria for data-contributing institutions' admissibility for collaboration (above), and it is served by the built-in management system described above. Additional elements of image quality are being made an integral part of the I-ELCAP database.

A team of professionals consisting of radiologists, pulmonologists, thoracic surgeons, oncologists, pathologists, study coordinators, computer engineers and information technology specialists working together and meeting regularly has proven to be the most important contribution to assurance of quality in implementing the protocol with efficiency and safety. In I-ELCAP, all are encouraged to participate in the International Conferences on Screening for Lung Cancer.

Coordinators and navigators are critical to the success of the screening program and should become familiar with the requirements of screening enrollment, smoking cessation advice, and follow-up procedures (23).

Radiologists should meet the minimum requirements which requires board-certification and, if possible, sub-specialization in chest imaging. In I-ELCAP, all radiologists were asked to participate in at least 100 dual readings of screening studies with the Coordinating Center radiologists. The

report on these dual readings illustrates its impact on quality improvement (103). Radiologists should have continual access to the electronic teaching files embedded in the management system and are encouraged to visit the I-ELCAP database center and interact with its chest radiologists who are highly experienced in the use of CT in the various phases and situations involved in early diagnosis of lung cancer, including this protocol and relevant publications. The American College of Radiology has also provided guidelines for radiologists interpreting screening studies.

In I-ELCAP, the pathologists in the participating centers were provided information regarding the preparation and interpretation of cytology and histology specimens by the pathology protocol (8, 9). In addition, slides may be sent to the coordinating center for digitization to be reviewed by expert pathologist(s) for quality assurance purposes. Qualifications of the site pathologist consist of board-certification in pathology and, if possible, sub-specialization in lung pathology.

Baseline Screening Protocol, results and workup recommendations

Negative: No nodules, **RETURN FOR ANNUAL REPEAT** **IELCAP = 1**

Semi-Positive: RETURN FOR ANNUAL REPEAT **IELCAP = 2**

a. Only nonsolid nodules, regardless of size, or
b. Largest solid, part-solid (solid component) < 6.0 mm,
c. Peri-fissural nodules< 10.0 mm in diameter with smooth margin and lentiform, oval, or triangular shape;
d. Costal-, mediastinal- and diaphragmatic-pleural nodules<10.0 mm in diameter with smooth margin and lenticular, oval, semi-circular, triangular shape.
e. **Indeterminate:** **IELCAP = 3**
Largest solid, part-solid (solid component) 6.0-14.9 mm. **RETURN FOR FOLLOW-UP LDCT 3 MONTHS** *after baseline, and if nodule shows a) decrease, b) no growth, or c) growth at a nonmalignant rate,* then **RETURN IN 9 MONTHS FOR FIRST ANNUAL REPEAT SCREENING.** **IELCAP = 2**

Positive: **IELCAP = 4**

a. Largest solid, part-solid (solid component) 6.0-14.9 mm *after a follow-up CT scan in 3 months shows growth at a malignant rate;*
b. Largest solid or part-solid nodule 15.0 mm or larger;
c. Solid endobronchial nodule.

WORKUP OPTIONS FOR POSITIVE RESULTS:

A. If the nodule appearance is highly suggestive of lung cancer, immediate biopsy is recommended.

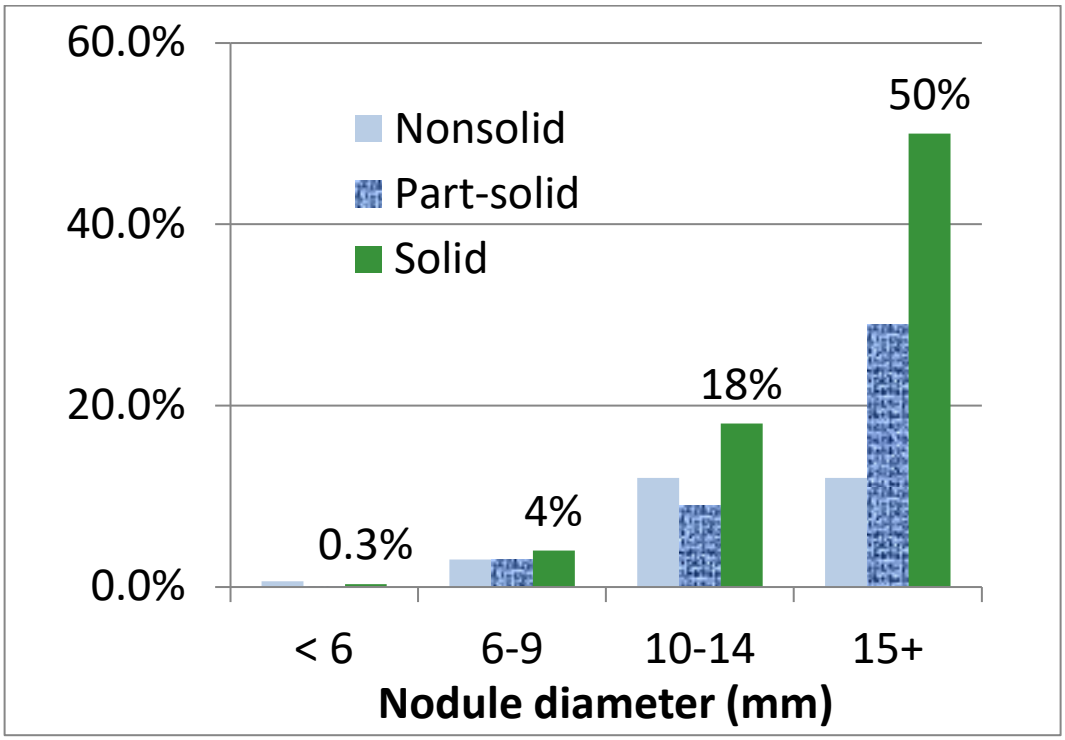
B. Another option for nodules>10mm is to perform PET scan. If the PET result is positive, biopsy is recommended, but, if negative or indeterminate, a low-dose CT 3 months later is performed. If, growth is documented on that CT, biopsy is recommended. If there is partial or complete resolution on CT, further workup stops and return for first annual repeat screening. **IELCAP=2.**

C. When multiple nodules are present and occult infection or inflammation is a possibility, an added option is a course of a broad spectrum antibiotic with anaerobic coverage followed by low-dose CT 1-3 months later (77). If there is further growth, biopsy is recommended. If there is partial or complete resolution on CT, return for first annual repeat screening. **IELCAP=2.**

D. If an endobronchial nodule is identified at the time of the initial CT, the participant is asked to cough vigorously several times and the region of interest is reimaged at that time. If the endobronchial nodule is not recognized at the time of the baseline CT scan, the participant is recalled for a follow-up low-dose CT within one month. At the time of the follow-up CT scan, the participant is asked to cough vigorously several times. If the nodule is still present, the participant is referred for pulmonary consultation, and if necessary, bronchoscopy. If classic features of retained secretions are identified such as low attenuation, air bubbles, stranding and multiplicity, call back is not necessary [also see NCCN Guidelines 2016 (97)].

NOTE: All participants in whom diagnostic work-up was stopped or the biopsy, if adequate, did not lead to a diagnosis of lung cancer, REPEAT CT 12 months is to be performed.

Baseline Round. Probability of malignancy based on nodule size and consistency



Baseline Round: Change needed in nodule diameter to identify growth at a malignant rate for volume doubling times of 180 days or faster

BASELINE ROUND		
Original diameter (mm)	Diameter (mm) in 3 months without measurement error VDT: 180 days	Diameter (mm) in 3 months with measurement error VDT: 180 days
6.0	6.7	7.1
7.0	7.9	8.3
8.0	9.0	9.4
9.0	10.1	10.5
10.0	11.2	11.6
11.0	12.3	12.7
12.0	13.5	13.9
13.0	14.6	15.0
14.0	15.7	16.1

Annual Repeat Screening Protocol, results and workup recommendations

Negative: No new nodules **IELCAP = 1**

Semi-positive: RETURN FOR NEXT ANNUAL REPEAT **IELCAP = 2**

a. Growth of previously seen nodules but still < 3.0 mm;
b. *New* noncalcified nodules < 3.0 mm;
c. New nonsolid nodules, regardless of size.
d. New peri-fissural nodules< 10.0 mm in diameter with smooth margin and lentiform, oval, or triangular shape;
e. New costal-, mediastinal- and diaphragmatic-pleural nodules<10.0 mm in diameter with smooth margin and lenticular, oval, semi-circular, triangular shape.

f. Indeterminate: **IELCAP = 3**

a. Largest solid, part-solid (solid component) 3.0-5.9 mm, return for *follow-up CT scan in 6 months after baseline* and if this follow-up CT shows *a) decrease, b) no change, or c) growth at a nonmalignant rate, then*

IELCAP =2

RETURN IN 6 MONTHS FOR NEXT ANNUAL REPEAT SCREENING.

b. Largest solid, part-solid (solid component) 6.0-14.9 mm, return for 1 month-*follow-up CT, and if this follow-up CT shows decrease, then*

RETURN IN 11 MONTHS FOR NEXT ANNUAL REPEAT. IELCAP = 2

If the 1-montn-follow-up CT shows no growth or growth at a nonmalignant rate, **RETURN FOR ANOTHER LDCT FOLLOW-UP IN 5 MONTHS.** If this LDCT *shows decrease, no growth, or growth at a nonmalignant rate,* **RETURN 6 IN 6 MONTHS FOR NEXT ANNUAL REPEAT SCREENING. IELCAP = 2**

Positive: **IELCAP = 4**

a. Largest *new* or *growing* solid or solid component of part-solid nodule is 3.0-14.9 mm *and follow-up CT scan shows growth at a malignant rate;*
b. Largest new or growing solid or solid component of part-solid nodule ≥15.0 mm;
c. ***New* solid endobronchial nodule.

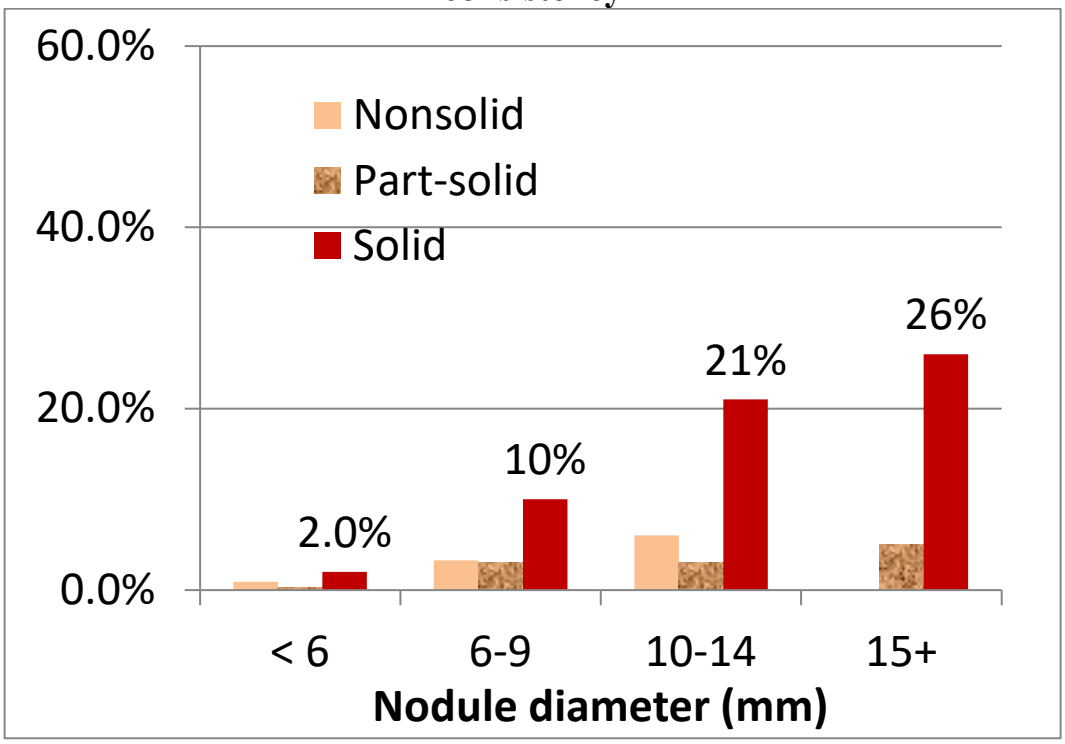
WORKUP OPTIONS FOR POSITIVE RESULTS: For a) and b), options are as follows:

1. Immediate biopsy.
2. An alternative for nodules>10mm is to perform PET scan. If positive, biopsy is recommended; if it is indeterminate or negative, low-dose CT 3 months after the initial CT is performed. If the nodule shows growth, biopsy is recommended, otherwise workup stops.
3, Infections may present as solitary or as multiple nodules (77). Provide an immediate course of a broad-spectrum antibiotic with anaerobic coverage, and 1-month follow-up LDCT.
If the LDCT shows:
a) continued growth, biopsy is recommended;
but if there is b) decrease, return in 11 months for next annual repeat screening. **IELCAP = 2**
c) no growth or growth at a nonmalignant rate, return in 5 months and if LDCT shows decrease, no growth, or growth at a nonmalignant rate, return in 5 months for next annual screening. **IELCAP = 2**

C) If an endobronchial nodule is identified, ideally the participant is asked to cough vigorously several times and the region of interest is reimaged at the same setting. If the endobronchial nodule is not recognized at the time of the screening CT scan, another low-dose CT scan without contrast is performed within 1 month, unless classic features of retained secretions are identified. At the time of the follow-up CT scan, the participant is asked to cough vigorously several times. If the nodule is still present, the participant is referred for pulmonary consultation, and if necessary, bronchoscopy.

NOTE: Whom diagnostic work-up is stopped, REPEAT CT 12 months is to be performed.

Annual Repeat Round. Probability of malignancy based on nodule size and consistency



Annual Repeat Rounds: Change needed in nodule diameter to identify growth at a malignant rate for volume doubling times of 180 days or faster.

ANNUAL REPEAT ROUNDS		
Original diameter (mm)	Diameter (mm) in 6 months without measurement error VDT: 180 days	Diameter (mm) in 6 months with measurement error VDT: 180 days
3.0	3.8	4.2
4.0	5.0	5.4
5.0	6.3	6.7
Original diameter (mm)	Diameter (mm) in 1 month without measurement error VDT: 180 days	Diameter (mm) in 1 month with measurement error VDT: 180 days
6.0	6.2	7.0
7.0	7.3	8.1
8.0	8.3	9.1
9.0	9.4	10.2
10.0	10.4	11.2
11.0	11.4	12.2
12.0	12.5	13.3
13.0	13.5	14.3
14.0	14.5	15.3

Other Findings on Screening CTs and Recommendations

A. Cardiovascular Findings

1. Ordinal coronary artery calcification

Each coronary artery is identified (left main, left anterior descending, circumflex, and right coronary artery). Evidence of calcification in each artery is documented as none, minimal, moderate, or severe, scored as 0, 1, 2, and 3, respectively. Minimal calcification was defined if less than 1/3 of the length of the entire artery, moderate as 1/3-2/3, and severe as more than 2/3 shows calcification. With 4 arteries thus scored, each person receives an Ordinal coronary artery calcium (CAC) Score in the range from 0 to 12 (104-108). With additional effort, the Agatston, volume or mass calcium scores on LDCTs can also be obtained. New rapid scanning techniques minimize cardiac motion and allow for improved Agatston scoring on non-gated examinations.

Ordinal CAC Score	Agatston Score	**RECOMMEND**
0	0	Probability of cardiovascular heart disease (CHD) is low. Reassure and keep healthy lifestyle
1-3	1-100	Probability of CHD is mild to moderately increased; Recommend healthy lifestyle, moderate statin, ASA
4-12	> 100	Probability of CHD is moderate to high. Healthy lifestyle; very intensive statin + second drug as needed; ASA; Consider function testing to r/o obstruction; Aggressive BP lowering; Referral to internist or preventive cardiologist

2. Aortic valve calcification

Using standard mediastinal window setting (width and level of 350 HU and 50 HU with 2.5 mm or 3.0 mm slice thickness) and if needed, multiplanar reconstruction to determine the location of calcifications (109-114). The extent of AVC was classified as:

Mild: single or multiple isolated aortic valve calcifications;
Moderate: multiple larger aortic valve calcifications, but not involving all three aortic leaflets
Severe: multiple larger aortic valve calcifications of all three aortic leaflets.

For moderate and severe AVC, **RECOMMEND** referral to a cardiologist is recommended and possible echocardiography, as there is a high probability of aortic stenosis (AS).

3. Pulmonary artery hypertension

The diameters of the main pulmonary artery (MPA) and ascending aorta (AA) are measured on an axial CT image at the level of the MPA bifurcation at the widest diameter vertical to its long axis and of the adjacent AA diameter (115).
If MPA≥34 mm or MPA:AA≥1.0, **RECOMMEND** a pulmonary consult to determine its etiology and possible echo sonography.

Table B. Pulmonary Findings other than lung cancer

1. Emphysema

The extent of emphysema is identified and classified as none, mild, moderate, or severe. Each subject receives an emphysema score in the range from 0 to 3 (116, 117) .

Mild emphysema (Score 1): no discrete areas of decreased CT attenuation but splaying of blood vessels suggesting parenchymal expansion or having occasional discrete areas of decreased attenuation;

Moderate emphysema (Score 2): discrete areas of decreased attenuation can be identified involving less than half of the lung parenchyma; and,

Severe emphysema (Score 3): discrete areas of decreased attenuation can be identified involving more than half of the lung parenchyma.

If emphysema is present and previously unrecognized, **RECOMMEND** consultation with a pulmonologist.

2. Interstitial findings

Early findings of usual interstitial pneumonitis (UIP) include pre-honeycomb and honeycomb (HC) findings. Other interstitial diseases can also be identified and may differ in location and findings. Pre-honeycomb findings may start with traction bronchiectasis alone and then progress to ground-glass opacification and reticulations, typically at the periphery of the lungs and at the lung bases. The likelihood of disease progression is associated with honeycombing. Early identification is important and consultation with a pulmonologist is recommended (118-121).

If any of these findings are identified, **RECOMMEND** consultation with a pulmonologist.

3. Bronchiectasis

Bronchiectasis is present if: 1) the external diameter of a bronchus is greater than the diameter of its adjacent pulmonary artery, 2) lack of tapering of the bronchial lumen toward the periphery for a length of more than 2.0 cm, or 3) peripheral bronchi can be identified abutting medial pleura or within 1.0 cm of the costal pleura (122-125).

If present**, RECOMMEND** pulmonary consultation for further workup.

4. *Discrete cystic airspaces*

The walls of discrete cystic airspaces should be assessed for progressive wall thickening, both in terms of increasing thickness and increasing circumferential wall involvement, as these may be due to lung cancer (56).

If a nodule emerges, **RECOMMEND** further evaluation or 3-month follow-up CT.

Table C. Breast Findings

1. Breast density

Using mediastinal settings, the CT images of the breast are reviewed and classified according to the Breast Imaging Reporting and Data System (BI-RADS) developed by the American College of Radiology (Sickles EQ, D'Orsi CJ, Basett LW et al. ACR 2013, 4th edition). The BI-RADS classification identifies 4 grades according to the breast density. Calcifications seen in the breast also provide information about coronary artery disease and should be reported (126-129).

The key differentiation is between Grades 1-2 and 3-4 (126, 127).

Grade 1: almost entirely fatty
Grade 2: there are scattered fibroglandular densities
Grade 3: breasts are heterogeneously dense, which may obscure small masses
Grade 4: breasts are extremely dense, which lowers the sensitivity of mammography

For Grade 3 or 4, **RECOMMEND** including this information in the report as it suggests an increased risk for breast cancer and if clinically indicated ultrasound (Mendelson EB, Bohm-Velez M, Berg WA, et al. ACR 2013) or MRI (Morris EA, Cornstock CE, Lee CH, et al. ACR, 2013) of the breast is suggested instead of a mammogram as it might obscure an early cancer or precursor lesion.

2. Breast masses

While a chest CT is never ordered to screening for breast cancer, some breast mass can be seen on chest CT as the images always include breast tissue (130). Breast can be viewed in axial, sagittal, and coronal planes and on MIP images which are routinely obtained for screening. Therefore, detection of breast masses can be done without additional radiation and at no direct cost to the healthcare system.

Multiple studies have reported incidental detection of breast cancers on chest CT but have not reported which projection was optimal for detection of masses (130). In our review by 10 radiologists, we found that MIP images were preferred over axial, coronal, or sagittal images, while sagittal and coronal images were equally preferable to axial images.

When a breast mass is identified, **RECOMMEND** further evaluation by mammography.

Table D. Mediastinal Findings

Mediastinal masses can occur anywhere in the mediastinum, including in the thymus, heart, and esophagus; and masses in the neck, such as the thyroid, may extend into the mediastinum. Such mediastinal and soft tissues masses are documented as to location and size.

Thymic mass (131):

a. ≤ 30 mm in diameter on baseline CT without invasive features (e.g., irregular borders or loss of fat planes), recommend follow-up CT in one year;
b. > 30 mm, **RECOMMEND** further workup according to standard practice is recommended.

Thyroid nodule (132):

a. < 15mm on baseline or annual repeat LDCT with low HU attenuation, **RECOMMEND** annual follow-up;
b. < 15 mm with heterogeneous enlarged appearance, **RECOMMEND** dedicated thyroid ultrasound examination
c. ≥ 15 mm, **RECOMMEND** dedicated thyroid ultrasound examination

Table E. Abdominal Findings

1. Adrenal glands

Adrenal glands are measured on axial CT images (133). If the largest transverse diameter is:

≥ 40mm, **RECOMMEND** further evaluation according to standard of care;
< 40 mm and low attenuation (less than 10 HU), **RECOMMEND** annual low-dose CT scans to assess growth, but if the borders are irregular, heterogeneous, hemorrhagic, central necrosis or calcifications, **RECOMMEND** further evaluation.

2. Liver steatosis

The hepatic portal level is selected to measure liver attenuation (HU) and the liver is divided into four sectors (left lateral, left medial, right anterior, right posterior). In each sector, a standard 1.0 cm^2 region of interest (ROI) is selected, avoiding other lesions and large blood vessel (134-136). HU measurements are made using standard mediastinal window settings (width 350 HU; level 25 HU) and the average attenuation and its standard deviation (SD) are calculated.

If the liver attenuation measurement < 40 HU or liver-spleen ratio <0.8, **RECOMMEND** follow-up with a primary care physician or liver specialist for further evaluation.

Table E. Bone Findings

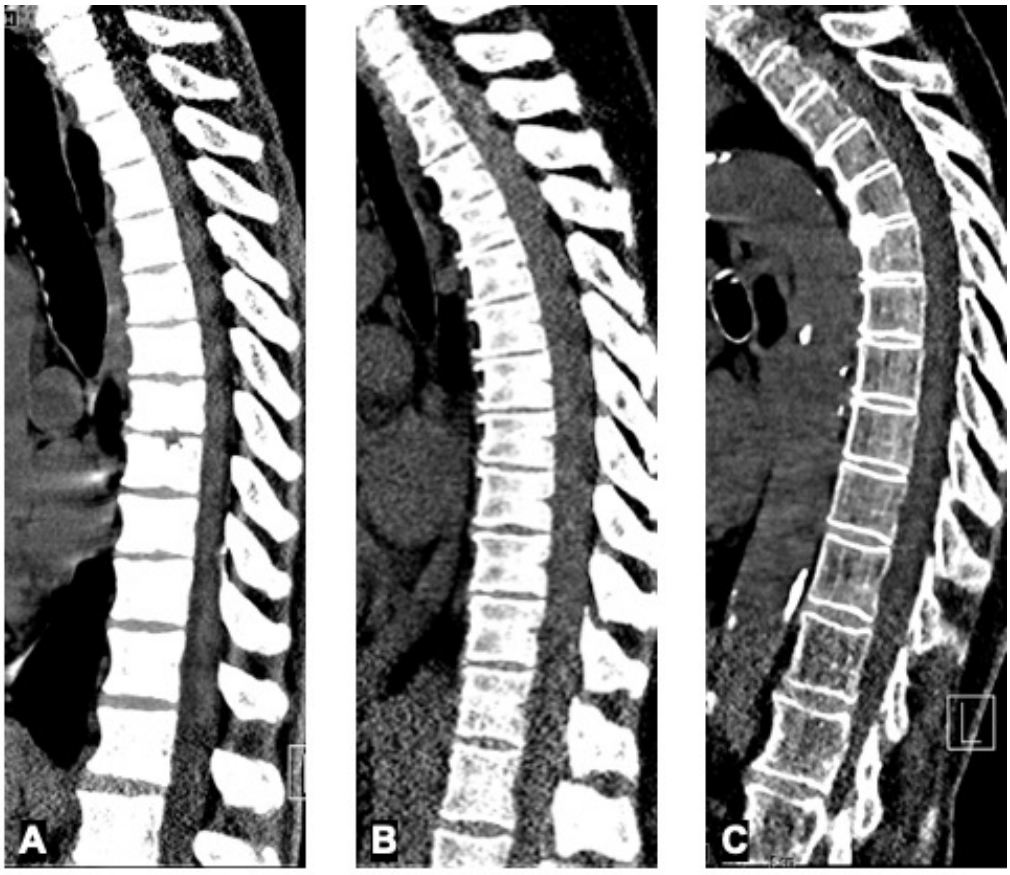
Osteoporosis

Osteoporosis can be identified on low-dose CT by the a) CT attenuation values or by b) comparison to a reference standard. Both are given below (137), (138). (139).

a) The CT attenuation values are measured on the sagittal images of the T12/L1 vertebrae while avoiding the vertebral vein plexus and abnormalities.

If the T12/L1 attenuation < 110 HU, recommend follow-up with a primary care physician or bone specialist for further evaluation (139).

b) Compare the sagittal image of the spine using osteoporosis window settings (width 30 HU; level 80 HU) (137). Visually identify which the most appropriate category (A-C) shown below (138).If visual scoring identifies osteoporosis, recommend follow-up with a primary care physician or bone specialist for further evaluation,



Reference images of each osteoporosis category (window width 350 HU, level 24 HU).
A: normal bone density; B: indeterminate; C; osteoporosis.

References

1. Henschke CI, Miettinen OS, Yankelevitz DF, Libby DM, and Smith JP. Radiographic screening for cancer. Proposed paradigm for requisite research. Clin Imaging 1994; 18:16-20.
2. Henschke C, McCauley D, Yankelevitz D, Naidich D, McGuinness G, Miettinen O, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999; 354:99-105.
3. Henschke C, Naidich D, Yankelevitz D, McGuinness G, McCauley D, Smith J, et al. Early lung cancer action project: initial findings on repeat screenings. Cancer 2001; 92:153-9.
4. International Early Lung Cancer Action Program Investigators. Program and Consensus statements. International Conferences on Screening for Lung Cancer. Available from: http://events.ielcap.org/conferences/past,
5. Reeves A, Kostis W, Yankelevitz D, and Henschke C. A web-based data system for multi-institutional research studies on lung cancer. Radiologic Society of North America Scientific Session.
6. Henschke C, Yankelevitz D, Smith J, Miettinen O, and ELCAP Group. Screening for lung cancer: the early lung cancer action approach. Lung Cancer 2002; 35:143-8.
7. International Early Lung Cancer Action Program Investigators. International Early Lung Cancer Action Program protocol. Available from: www.IELCAP.org/protocols, Jan 3rd, 2018.
8. Vazquez M, Flieder D, Travis W, Carter D, Yankelevitz DF, Miettinen OS, et al. Early lung cancer action project pathology protocol. Lung Cancer 2003; 39:231-2.
9. Vazquez M, Flieder D, Travis W, Carter D, Yankelevitz D, Miettinen O, et al. Early Lung Cancer Action Project Pathology Protocol. Available from: http://www.ielcap.org/sites/default/files/pathology_protocol.pdf,
10. Henschke CI, Yankelevitz DF, Reeves AP, and Yip R. Evolution of Lung Cancer Screening Management. Oncology (Williston Park) 2019; 33
11. 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.
12. Henschke CI, Salvatore M, Cham M, Powell CA, DiFabrizio L, Flores R, et al. Baseline and annual repeat rounds of screening: implications for optimal regimens of screening. Eur Radiol 2018; 28:1085-1094.
13. Yip R, Henschke C, Yankelevitz D, Boffetta P, Smith J, and The International Early Lung Cancer Investigators. The impact of the regimen of screening on lung cancer cure: a comparison of I-ELCAP and NLST. Eur J Cancer Prev 2015; 24:201-8.
14. Henschke CI, Wisnivesky JP, Yankelevitz DF, and Miettinen OS. Small stage I cancers of the lung: genuineness and curability. Lung Cancer 2003; 39:327-30.
15. International Early Lung Cancer Action Program Investigators, Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006; 355:1763-71.
16. NY-ELCAP Investigators. CT Screening for lung cancer: diagnoses resulting from the New York Early Lung Cancer Action Project. Radiology 2007; 243:239-49.
17. Carter D, Vazquez M, Flieder DB, Brambilla E, Gazdar A, Noguchi M, et al. Comparison of pathologic findings of baseline and annual repeat cancers diagnosed on CT screening. Lung Cancer 2007; 56:193-9.
18. Vazquez M, Carter D, Brambilla E, Gazdar A, Noguchi M, Travis WD, et al. Solitary and multiple resected adenocarcinomas after CT screening for lung cancer: histopathologic features and their prognostic implications. Lung Cancer 2009; 64:148-54.

19. Henschke C, Boffetta P, Yankelevitz D, and Altorki N. Computed tomography screening: the international early lung cancer action program experience. Thorac Surg Clin 2015; 25:129-43.
20. Henschke CI, Yip R, Ma T, Aguayo SM, Zulueta J, and Yankelevitz DF. CT screening for lung cancer: comparison of three baseline screening protocols. Eur Radiol 2019; 29:5217-5226.
21. American College of Radiology (ACR). Lung CT screening reporting & data system (Lung-RADS Version 1.0). Available from: https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADS_AssessmentCategories.pdf?la=en, September 11, 2019.
22. Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch H, Heussel CP, et al. European position statement on lung cancer screening. Lancet Oncology 2017; 18:E754-E766.
23. Henschke CI, Yankelevitz DF, Jirapatnakul A, Yip R, Reccoppa V, Benjamin C, et al. Implementation of low-dose CT screening in two different health care systems: Mount Sinai Healthcare System and Phoenix VA Health Care System. Transl Lung Cancer Res 2021; 10:1064-1082.
24. Flores R, Taioli E, Yankelevitz DF, Becker BJ, Jirapatnakul A, Reeves A, et al. Initiative for Early Lung Cancer Research on Treatment: Development of Study Design and Pilot Implementation. J Thorac Oncol 2018; 13:946-957.
25. Yip R, Jirapatnakul A, Hu M, Chen X, Han D, Ma T, et al. Added benefits of early detection of other diseases on low-dose CT screening. Transl Lung Cancer Res 2021; 10:1141-1153.
26. Mini Symposium on "Lung Cancer Screening, Opportunistic Evaluation of Findings". IASLC 2019 WCLC World Conference on Lung Cancer Barcelona, Spain September 9, 2019, 2019.
27. Moyer VA and U. S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014; 160:330-8.
28. Jonas DE, Reuland DS, Reddy SM, Nagle M, Clark SD, Weber RP, et al. Screening for Lung Cancer With Low-Dose Computed Tomography: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2021; 325:971-987.
29. Centers for Medicare and Medicaid Services (CMS). Proposed Decision Memo for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT) (CAG-00439N). http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=274, January 2, 2015.
30. Ostroff J, Buckshee N, Mancuso C, Yankelevitz D, and Henschke C. Smoking cessation following CT screening for early detection of lung cancer. Prev Med 2001; 33:613-21.
31. Anderson C, Yip R, Henschke C, Yankelevitz D, Ostroff J, and Burns D. Smoking cessation and relapse during a lung cancer screening program. Cancer Epidemiol Biomarkers Prev 2009; 18:3476-83.
32. Ostroff J, Henschke C, Yip R, Cervera D, Zulueta J, Roberts H, et al. Patterns and predictors of smoking cessation outcomes among current smokers one year following enrollment in a lung cancer screening program. Cancer Epidemiology, Biomarkers and Prevention 2016. Submitted.;
33. Henschke C, Yip R, Yankelevitz D, and Smith J. Definition of a positive test result in computed tomography screening for lung cancer: a cohort study. Ann Intern Med 2013; 158:246-52.
34. Zhang L, Yankelevitz DF, Henschke CI, Jirapatnakul AC, Reeves AP, and Carter D. Zone of transition: a potential source of error in tumor volume estimation. Radiology 2010; 256:633-9.
35. Henschke C, Yankelevitz D, Yip R, Archer V, Zahlmann G, Krishnan K, et al. Tumor volume measurement error using computed tomography (CT) imaging in a Phase II clinical trial in lung cancer. Journal of Medical Imaging 2016; 3
36. Yankelevitz D, Gupta R, and Henschke C. Is Early Repeat CT Feasible for Evaluation of Pulmonary Nodules: First Order Considerations? Radiological Society of North America (RSNA) 83rd Scientific Assembly and Annual Meeting. Radiology 1997; 205 Suppl:17-749.

37. Reeves A, Zhao B, Yankelevitz D, and Henschke C. Characterization of Three-Dimensional Shape and Size Changes of Pulmonary Nodules Over Time from Helical CT Images. Radiological Society of North America (RSNA) 83rd Scientific Assembly and Annual Meeting. Radiology 1997; 205 Suppl.:17-749.
38. Yankelevitz D, Zhao B, Gupta R, and Henschke C. Early Repeat CT for Assessment of Pulmonary Nodules. American Roentgen Ray Scientific Session April 27, 1998.
39. Yankelevitz D and Henschke C. Determination of malignancy in small pulmonary nodules based on volumetrically determined growth rates. Radiological Society of Noth America (RSNA) 84th Scientific Assembly and Annual Meeting. Radiology 1998; 209 Suppl.:17-872.
40. Yankelevitz DF, Gupta R, Zhao B, and Henschke CI. Small pulmonary nodules: evaluation with repeat CT--preliminary experience. Radiology 1999; 212:561-6.
41. Yankelevitz DF, Reeves AP, Kostis WJ, Zhao B, and Henschke CI. Small pulmonary nodules: volumetrically determined growth rates based on CT evaluation. Radiology 2000; 217:251-6.
42. Kostis W, Reeves A, Yankelevitz D, and Henschke C. Three-dimensional segmentation and growth-rate estimation of small pulmonary nodules in helical CT images. IEEE Trans Med Imaging 2003; 22:1259-74.
43. Kostis W, Yankelevitz D, Reeves A, Fluture S, and Henschke C. Small pulmonary nodules: reproducibility of three-dimensional volumetric measurement and estimation of time to follow-up CT. Radiology 2004; 231:446-52.
44. Reeves A, Chan A, Yankelevitz D, Henschke C, Kressler B, and Kostis W. On measuring the change in size of pulmonary nodules. IEEE Trans Med Imaging 2006; 25:435-50.
45. Reeves AP, Biancardi AM, Apanasovich TV, Meyer CR, MacMahon H, van Beek EJ, et al. The Lung Image Database Consortium (LIDC): a comparison of different size metrics for pulmonary nodule measurements. Acad Radiol 2007; 14:1475-85.
46. Browder WA, Reeves AP, Apananosovich TV, Cham MD, Yankelevitz DF, and Henschke CI. Automated volumetric segmentation method for growth consistency of nonsolid pulmonary nodules in high-resolution CT. SPIE International Symposium on Medidcal Imaging 2007; 6514:65140Y-65140Y-10.
47. Henschke CI, Yankelevitz DF, Yip R, Reeves AP, Farooqi A, Xu DM, et al. Lung Cancers Diagnosed at Annual CT Screening: Volume Doubling Times. Radiology 2012; 263:578-583.
48. Henschke C, Yankelevitz D, Naidich D, McCauley D, McGuinness G, Libby D, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. Radiology 2004; 231:164-8.
49. Henschke C, Yankelevitz D, Mirtcheva R, McGuinness G, McCauley D, and Miettinen O. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 2002; 178:1053-7.
50. Yankelevitz DF, Yip R, Smith JP, Liang M, Liu Y, Xu DM, et al. CT Screening for Lung Cancer: Nonsolid Nodules in Baseline and Annual Repeat Rounds. Radiology 2015; 277:555-64.
51. Henschke CI, Yip R, Smith JP, Wolf AS, Flores RM, Liang M, et al. CT Screening for Lung Cancer: Part-Solid Nodules in Baseline and Annual Repeat Rounds. AJR Am J Roentgenol 2016; 207:1176-1184.
52. Yip R, Yankelevitz DF, Hu M, Li K, Xu DM, Jirapatnakul A, et al. Lung Cancer Deaths in the National Lung Screening Trial Attributed to Nonsolid Nodules. Radiology 2016; 281:589-596.
53. Yip R, Henschke CI, Xu DM, Li K, Jirapatnakul A, and Yankelevitz DF. Lung Cancers Manifesting as Part-Solid Nodules in the National Lung Screening Trial. AJR Am J Roentgenol 2017; 208:1011-1021.

54. Yip R, Wolf A, Tam K, Taioli E, Olkin I, Flores R, et al. Outcomes of lung cancers manifesting as nonsolid nodules. Lung Cancer 2016; 97:35-42.
55. Yip R, Li K, Liu L, Xu D, Tam K, Yankelevitz DF, et al. Controversies on lung cancers manifesting as part-solid nodules. Eur Radiol 2018; 28:747-759.
56. Farooqi A, Cham M, Zhang L, Beasley M, Austin J, Miller A, et al. Lung cancer associated with cystic airspaces. AJR Am J Roentgenol 2012; 199:781-6.
57. Travis W, Brambilla E, Noguchi M, Nicholson A, Geisinger K, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011; 6:244-85.
58. Travis W, Brambilla E, Burke A, Marx A, and Nicholson A. Introduction to the 2015 World Health Organization classification of tumors of the lung, pleura, thymus and heart. Journal of Thoracic Oncology 2015; 10:1240-2.
59. Yankelevitz DF, Chan C, and Henschke CI. Overdiagnosis: "A Malformed Concept". J Thorac Imaging 2019; 34:151-153.
60. Yankelevitz DF and Henschke CI. Overdiagnosis in lung cancer screening. Translational Lung Cancer Research 2021; 10:1136-1140.
61. American College of Radiology (ACR). Lung-RADS v1.1 Assessment Categories. Available from: https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf?la=en, September 11, 2019.
62. Xu DM, van der Zaag-Loonen HJ, Oudkerk M, Wang Y, Vliegenthart R, Scholten ET, et al. Smooth or Attached Solid Indeterminate Nodules Detected at Baseline CT Screening in the NELSON Study: Cancer Risk during 1 Year Follow-up. Radiology 2009; 250:264-272.
63. de Hoop B, van Ginneken B, Gietema H, and Prokop M. Pulmonary perifissural nodules on CT scans: rapid growth is not a predictor of malignancy. Radiology 2012; 265:611-6.
64. Han D, Heuvelmans MA, van der Aalst CM, van Smoorenburg LH, Dorrius MD, Rook M, et al. New Fissure-Attached Nodules in Lung Cancer Screening: A Brief Report From The NELSON Study. J Thorac Oncol 2020; 15:125-129.
65. Zhu Y, Cai Q, Yip R, Sun Q, Li P, Triphuridet N, et al. EP01. 05-011 Radiologic Features of Nodules Attached to the Mediastinal or Diaphragmatic Pleura. Journal of Thoracic Oncology 2022; 17:S186.
66. Zhu Y, Cai Q, Yip R, Zhang J, Sun Q, Li P, et al. Radiologic Features of Nodules Attached to the Mediastinal or Diaphragmatic Pleura. Submitted. 2023;
67. International Early Lung Cancer Action Program Investigators. International Early Lung Cancer Action Program (I-ELCAP) protocol. Available from: https://www.ielcap.org/protocols, January 18, 2021.
68. Zhu Y, Yip R, You N, Henschke CI, and Yankelevitz DF. Management of Nodules Attached to the Costal Pleura at Low-Dose CT Screening for Lung Cancer. Radiology 2020; 297:710-718.
69. Zhu Y, Yip R, You N, Cai Q, Henschke CI, Yankelevitz DF, et al. Characterization of Newly Detected Costal Pleura-attached Noncalcified Nodules at Annual Low-Dose CT Screenings. Radiology 2021:210807.
70. Henschke C, Yankelevitz D, Yip R, Reeves A, Farooqi A, Xu D, et al. Lung cancers diagnosed at annual CT screening: volume doubling times. Radiology 2012; 263:578-83.
71. Li KW, Yip R, Avila R, Henschke CI, and Yankelevitz DF. Size and Growth Assessment of Pulmonary Nodules: Consequences of the Rounding. Journal of Thoracic Oncology 2017; 12:657-662.
72. Quantitative Imaging Biomarkers Alliance (QIBA). QIBA Profile: Small Lung Nodule Volume Assessment and Monitoring in Low Dose CT Screening. Available from:

http://qibawiki.rsna.org/images/a/a8/QIBA_CT_Vol_SmallLungNoduleAssessmentInCTScreening_2018.11.18-clean.pdf, September 4, 2019.
73. Radiological Society of North America Quantitative Imaging Biomarkers Alliance (QIBA) Nodule Profile Calculator. Available from: https://accumetra.com/qiba-nodule-profile-calculator/, September 4, 2019.
74. Avila R, Yankelevitz D, and Archer V. Calibration of computed tomography (CT) volumetric measurements for assessing tumour response to drug therapy in a randomized multicentre oncology study. Insights Imaging 2013; 4:S331.
75. Armato SG, 3rd, McLennan G, McNitt-Gray MF, Meyer CR, Yankelevitz D, Aberle DR, et al. Lung image database consortium: developing a resource for the medical imaging research community. Radiology 2004; 232:739-48.
76. Liang M, Yip R, Tang W, Xu D, Reeves A, Henschke CI, et al. Variation in Screening CT-Detected Nodule Volumetry as a Function of Size. AJR Am J Roentgenol 2017; 209:304-308.
77. Libby DM, Wu N, Lee IJ, Farooqi A, Smith JP, Pasmantier MW, et al. CT screening for lung cancer: the value of short-term CT follow-up. Chest 2006; 129:1039-42.
78. Yankelevitz DF, Henschke CI, Davis SD, Goldberg S, and Williams T. Variability in lesion depth on prone and supine CT scans of the chest: implications for the accuracy of transthoracic needle aspiration biopsy. J Thorac Imaging 1995; 10:117-20.
79. Yankelevitz DF, Davis SD, and Henschke CI. Aspiration of a large pneumothorax resulting from transthoracic needle biopsy. Radiology 1996; 200:695-7.
80. Yankelevitz DF, Vazquez M, and Henschke CI. Special techniques in transthoracic needle biopsy of pulmonary nodules. Radiol Clin North Am 2000; 38:267-79.
81. Linek JA, Henschke CI, Yankelevitz D, F, Flores RM, and Powell CA. Non-Malignant Resection Rate is Lower in Patients Who Undergo Pre-Operative Fine Needle Aspiration (FNA) for Diagnosis of Suspected Early-Stage Lung Cancer. American Journal of Respiratory and Critical Care Medicine 2015; 191:A3561.
82. Cham MD, Henschke CI, and Yankelevitz DF, The radiologist's role in pathologic diagnosis of small lung nodules. Radiographic methods of tissue acquisition., in Current Challenges in Thoracic Surgery. 2020: Boston.
83. Chung JH, Choe G, Jheon S, Sung SW, Kim TJ, Lee KW, et al. Epidermal growth factor receptor mutation and pathologic-radiologic correlation between multiple lung nodules with ground-glass opacity differentiates multicentric origin from intrapulmonary spread. J Thorac Oncol 2009; 4:1490-5.
84. Takamochi K, Oh S, Matsuoka J, and Suzuki K. Clonality status of multifocal lung adenocarcinomas based on the mutation patterns of EGFR and K-ras. Lung Cancer 2012; 75:313-20.
85. Detterbeck FC, Marom EM, Arenberg DA, Franklin WA, Nicholson AG, Travis WD, et al. The IASLC Lung Cancer Staging Project: Background Data and Proposals for the Application of TNM Staging Rules to Lung Cancer Presenting as Multiple Nodules with Ground Glass or Lepidic Features or a Pneumonic Type of Involvement in the Forthcoming Eighth Edition of the TNM Classification. J Thorac Oncol 2016; 11:666-80.
86. Wang Y, Zhu Y, Yip R, Lee D-S, Flores RM, Kaufman A, et al. Pre-surgical assessment of mediastinal lymph node metastases in Stage IA non-small-cell lung cancers. Clinical imaging 2020; 68:61-67.
87. Zhu Y, Cai Q, Wang Y, You N, Yip R, Lee DS, et al. Pre-surgical assessment of mediastinal lymph node metastases in patients having ≥ 30 mm non-small-cell lung cancers. Lung Cancer 2021; 161:189-196.
88. Siddique M, Yip R, Henschke CI, and Yankelevitz DF. The relationship between radiologic indicators of tumor aggressiveness. J Thorac Imaging 2020;

89. Austin JH, Yip R, D'Souza BM, Yankelevitz DF, Henschke CI, and International Early Lung Cancer Action Program I. Small-cell carcinoma of the lung detected by CT screening: stage distribution and curability. Lung Cancer 2012; 76:339-43.
90. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger K, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: international multidisciplinary classification of lung adenocarcinoma: executive summary. Proc Am Thorac Soc 2011; 8:381-5.
91. Travis WD BE, Burke AP, Marx A, Nicholson AG, WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. 2015, Lyon: International Agency for Research on Cancer.
92. Flores R, Bauer T, Aye R, Andaz S, Kohman L, Sheppard B, et al. Balancing curability and unnecessary surgery in the context of computed tomography screening for lung cancer. J Thorac Cardiovasc Surg 2014; 147:1619-26.
93. Altorki N, Yip R, Hanaoka T, Bauer T, Aye R, Kohman L, et al. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. J Thorac Cardiovasc Surg 2014; 147:754-62; Discussion 762-4.
94. Buckstein M, Yip R, Yankelevitz D, Henschke C, Rosenzweig K, and International Early Lung Cancer Action Program Investigators. Radiation therapy for stage I lung cancer detected on computed tomography screening: results from the international early lung cancer action program. Journal of Radiation Oncology 2014; 3:153-7.
95. Flores RM, Nicastri D, Bauer T, Aye R, Andaz S, Kohman L, et al. Computed Tomography Screening for Lung Cancer: Mediastinal Lymph Node Resection in Stage IA Nonsmall Cell Lung Cancer Manifesting as Subsolid and Solid Nodules. Ann Surg 2017; 265:1025-1033.
96. Taioli E, Yip R, Olkin I, Wolf A, Nicastri D, Henschke C, et al. Survival after sublobar resection for early-stage lung cancer: methodological obstacles in comparing the efficacy to lobectomy. J Thorac Oncol 2016; 11:400-6.
97. Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 4.2016. J Natl Compr Canc Netw 2016; 14:255-64.
98. Schwartz RM, Yip R, Olkin I, Sikavi D, Taioli E, Henschke C, et al. Impact of surgery for stage IA non-small-cell lung cancer on patient quality of life. J Community Support Oncol 2016; 14:37-44.
99. Schwartz RM, Yip R, Flores RM, Olkin I, Taioli E, Henschke C, et al. The impact of resection method and patient factors on quality of life among stage IA non-small cell lung cancer surgical patients. J Surg Oncol 2017; 115:173-180.
100. Yip R, Taioli E, Schwartz R, Li K, Becker BJ, Tam K, et al. A Review of Quality of Life Measures used in Surgical Outcomes for Stage I Lung Cancers. Cancer Invest 2018; 36:296-308.
101. Février E, Yip R, Becker BJ, Taioli E, Yankelevitz DF, Flores R, et al. Change in quality of life of stage IA lung cancer patients after sublobar resection and lobectomy. J Thorac Dis 2020; 12:3488-3499.
102. Schwartz RM, Alpert N, Rosenzweig K, Flores R, and Taioli E. Changes in quality of life after surgery or radiotherapy in early-stage lung cancer. Journal of Thoracic Disease 2019; 11:154-161.
103. Xu D, Yip R, Shah P, Taylor J, Peeke J, Widmann M, et al. Dual readings of initial baseline screenings at new sites is useful in decreasing the frequency of positive result and thus of further workup. Radiological Society of North America Scientific Abstract November 28, 2012, 2012.
104. Hecht H, Henschke C, Yankelevitz D, Fuster V, and Narula J. Combined detection of coronary artery disease and lung cancer. Eur Heart J 2014; 35:2792-6.

105. Shemesh J, Henschke CI, Farooqi A, Yip R, Yankelevitz DF, Shaham D, et al. Frequency of coronary artery calcification on low-dose computed tomography screening for lung cancer. Clinical Imaging 2006; 30:181-185.
106. Shemesh J, Henschke C, Shaham D, Yip R, Farooqi A, Cham M, et al. Ordinal scoring of coronary artery calcifications on low-dose CT scans of the chest is predictive of death from cardiovascular disease. Radiology 2010; 257:541-8.
107. Lee C and Forman H. What we can and cannot see coming. Radiology 2010; 257:313-4.
108. Xie Y, Cham MD, Henschke C, Yankelevitz D, and Reeves AP. Automated coronary artery calcification detection on low-dose chest CT images. SPIE International Symposium on Medical Imaging (Vol. 9035, p. 90350F-9). 2014.
109. Zhu Y, Wang Y, Gioia WE, Yip R, Jirapatnakul AC, Chung MS, et al. Visual scoring of aortic valve calcifications on low-dose CT in lung cancer screening. Eur Radiol 2020; 30:2658-2668.
110. Zhu Y, Yip R, Shemesh J, Jirapatnakul AC, Yankelevitz DF, and Henschke CI. Combined aortic valve and coronary artery calcifications in lung cancer screening as predictors of death from cardiovascular disease. Eur Radiol 2020;
111. Koos R, Kühl HP, Mühlenbruch G, Wildberger JE, Günther RW, and Mahnken AH. Prevalence and clinical importance of aortic valve calcification detected incidentally on CT scans: comparison with echocardiography. Radiology 2006; 241:76-82.
112. Cueff C, Serfaty J-M, Cimadevilla C, Laissy J-P, Himbert D, Tubach F, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart 2011; 97:721-726.
113. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. New England Journal of Medicine 2000; 343:611-617.
114. Willmann JrK, Weishaupt D, Lachat M, Kobza R, Roos JE, Seifert B, et al. Electrocardiographically gated multi–detector row CT for assessment of valvular morphology and calcification in aortic stenosis. Radiology 2002; 225:120-128.
115. Steiger D, Han D, Yip R, Li K, Chen X, Liu L, et al. Increased main pulmonary artery diameter and main pulmonary artery to ascending aortic diameter ratio in smokers undergoing lung cancer screening. Clin Imaging 2020; 63:16-23.
116. Zulueta JJ, Wisnivesky JP, Henschke CI, Yip R, Farooqi AO, McCauley DI, et al. Emphysema scores predict death from COPD and lung cancer. Chest 2012; 141:1216-1223.
117. Keller BM, Reeves AP, Henschke CI, Barr RG, and Yankelevitz DF. Variation of quantitative emphysema measurements from CT scans. SPIE International Symposium on Medical Imaging (Vol. 6915, p. 69152I-8). 2008.
118. Salvatore M, Henschke C, Yip R, Jacobi A, Eber C, Padilla M, et al. Evidence of Interstitial Lung Disease on Low-Dose Chest CT Images: Prevalence, Patterns, and Progression. AJR Am J Roentgenol 2016; 206:487-94.
119. Salvatore M, Singh A, Yip R, Fevrier E, Henschke CI, Yankelevitz D, et al. Progression of probable UIP and UIP on HRCT. Clin Imaging 2019; 58:140-144.
120. Whittaker Brown SA, Padilla M, Mhango G, Powell C, Salvatore M, Henschke C, et al. Interstitial Lung Abnormalities and Lung Cancer Risk in the National Lung Screening Trial. Chest 2019; 156:1195-1203.
121. Bertolini A, Capaccione K, Austin JHM, Blum A, Padilla M, B DS, et al. Teleradiology: An opportunity to improve outcomes in pulmonary fibrosis. Clin Imaging 2020; 60:263-264.
122. Kiraly AP, Odry BL, Godoy MC, Geiger B, Novak CL, and Naidich DP. Computer-aided diagnosis of the airways: beyond nodule detection. Journal of thoracic imaging 2008; 23:105-113.

123. Charbonnier J-P, Pompe E, Moore C, Humphries S, van Ginneken B, Make B, et al. Airway wall thickening on CT: relation to smoking status and severity of COPD. Respiratory medicine 2019; 146:36-41.
124. Triphuridet N, Cai Q, You N, Yip R, Yankelevitz DF, and Henschke CI. Clinical findings identified in participants with severe bronchiectasis identified on baseline low-dose CT screening for lung cancer. 2021. Submitted;
125. Cai Q, Triphuridet N, Zhu Y, You N, Yip R, Yankelevitz DF, et al. Bronchiectasis in Low-Dose CT Screening for Lung Cancer. Radiology 2022; 304:437-447.
126. Salvatore M, Margolies L, Kale M, Wisnivesky J, Kotkin S, Henschke C, et al. Breast density: comparison of chest CT with mammography. Radiology 2014; 270:67-73.
127. Margolies L, Salvatore M, Eber C, Jacobi A, Lee I, Liang M, et al. The general radiologist's role in breast cancer risk assessment: breast density measurement on chest CT. Clin Imaging 2015; 39:979-82.
128. Margolies L, Salvatore M, Hecht HS, Kotkin S, Yip R, Baber U, et al. Digital Mammography and Screening for Coronary Artery Disease. JACC Cardiovasc Imaging 2016; 9:350-60.
129. Salvatore M, Margolies L, Bertolini A, Singh A, Yankelevitz D, and Henschke C. The need to be all inclusive: Chest CT scans should include imaged breast parenchyma. Clinical Imaging 2018; 50:243-245.
130. Margolies LR, Salvatore M, Tam K, Yip R, Bertolini A, Henschke CI, et al. Breast mass assessment on chest CT: Axial, sagittal, coronal or maximal intensity projection? Clin Imaging 2020; 63:60-64.
131. Henschke CI, Lee IJ, Wu N, Farooqi A, Khan A, Yankelevitz D, et al. CT screening for lung cancer: Prevalence and incidence of mediastinal masses. Radiology 2006; 239:586-590.
132. Hoang JK, Langer JE, Middleton WD, Wu CC, Hammers LW, Cronan JJ, et al. Managing Incidental Thyroid Nodules Detected on Imaging: White Paper of the ACR Incidental Thyroid Findings Committee. Journal of the American College of Radiology 2015; 12:143-150.
133. Hu MX, Yip R, Yankelevitz DY, and Henschke CI. CT screening for lung cancer: Frequency of enlarged adrenal glands identified in baseline and annual repeat rounds. European Radiology 2016; 26:4475-4481.
134. Chen X, Li K, Yip R, Perumalswami P, Branch AD, Lewis S, et al. Hepatic steatosis in participants in a program of low-dose CT screening for lung cancer. Eur J Radiol 2017; 94:174-179.
135. Chen X, Ma T, Yip R, Perumalswami PV, Branch AD, Lewis S, et al. Elevated prevalence of moderate-to-severe hepatic steatosis in World Trade Center General Responder Cohort in a program of CT lung screening. Clin Imaging 2020; 60:237-243.
136. Jirapatnakul A, Reeves AP, Lewis S, Chen X, Ma T, Yip R, et al. Automated measurement of liver attenuation to identify moderate-to-severe hepatic steatosis from chest CT scans. Eur J Radiol 2020; 122:108723.
137. Pickhardt PJ, Pooler BD, Lauder T, del Rio AM, Bruce RJ, and Binkley N. Opportunistic screening for osteoporosis using abdominal computed tomography scans obtained for other indications. Ann Intern Med 2013; 158:588-95.
138. Zhu Y, Yip R, Jirapatnakul AC, Huang M, Cai Q, Dayan E, et al. Visual Scoring of Osteoporosis in Low-dose CT Screening for Lung Cancer. Submitted. 2023;
139. Zhu Y, Triphuridet N, Yip R, Becker BJ, Wang Y, Yankelevitz DF, et al. Opportunistic CT screening of osteoporosis on thoracic and lumbar spine: a meta-analysis. Clin Imaging 2021; 80:382-390.