

***International Early Lung Cancer Action Program:
Screening Protocol***

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Overview	2
Indications for screening	2
Frequency of screening	2
Communication of results	2
Regimen of screening.....	3
Smoking cessation.....	3
Image production.....	3
Reading of images	4
Definitions of nodules	4
Definitions of nodule consistency	4
Definition of nodule size	5
Probability of lung cancer by nodule size and consistency	5
Assessment of growth	7
Baseline screening.....	10
Repeat screening	11
Other findings to be reported.....	12
Discrete cystic airspaces.....	12
Emphysema	12
Interstitial findings	12
Mediastinal and thymic masses.....	12
Coronary arteries	13
Breast density	13
Adrenal enlargement	14
Biopsy.....	14
Classification and characterization of diagnosed cancers.....	14
Intervention policy	15
Outcome determination	16
I-ELCAP Management System.....	16
Quality assurance	17
References	18

Flow charts are available

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 [1-9]. Its broad research objective has been the advancement of knowledge for 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], and its approach to long-term follow-up [10-15]. Further details are given in these cited publications.

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 test for their validation, relative merits, and value as add-ons.

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.

If Stage I, II, or IIIA lung cancer has been diagnosed as a result of screening or outside of screening and curative treatment is provided, screening for new primary lung cancers may be provided once treatment is 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. The United States Preventive Services Task Force recommends annual screening [16] and the Centers for Medicare and Medicaid Services mandate it [17].

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 (with a lay summary). If the participant or his/her physician chooses not to follow the recommended regimen, the actual work-up must be carefully documented using the web-based management system.

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. In those cases for which protocol recommendations are not followed, it is necessary 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.

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 [18-20].

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.

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. **We 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 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.

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. For the purposes of assessing the size of a nodule or that of a mediastinal abnormality, however, 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.

Definitions of nodules

A nodule is a focal non-linear opacity with a generally spherical shape surrounded by lung parenchyma. It is classified as **non-calcified** if it fails to meet the usual criteria for benign, calcified nodules. Thus, a nodule less than 6 mm in diameter is non-calcified if all of it appears less dense than the ribs (on bone and lung windows); a nodule 6-20 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 mm in diameter is non-calcified if any part of it is non-calcified judged by the criteria above. Focal pleural thickening or pleural plaques are not considered nodules. **Opacities of 30 mm or more are considered masses.**

Definitions of nodule consistency

A nodule is classified solid unless it has specific characteristics to be classified as subsolid [21].

Solid nodules may have external or internal cystic airspace or internal cavitation [7, 22].

Subsolid nodules may be either nonsolid or part-solid [23-27].

A part-solid nodule is one that has internal components that completely obscure the lung parenchyma; and considered nonsolid if none of the lung parenchyma is completely obscured.

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. And 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 [24].

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, 23, 24]. This recommendation is based on the radiologic findings as well as the pathology findings [28, 29].

Definition of nodule size

Nodule size is reported according to its diameter, which is the average of its length and width.

Length and width are measured on a single CT image (axial, sagittal, or coronal) 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. And the diameter of the solid component of part-solid nodules is documented in the same way.

These diameter measures should be supplemented by computer-based assessments of volume, though these measures need to be interpreted cautiously as these still are considered experimental [30-35]. When there is sufficient evidence of their validity, volume measures should replace manual diameter measurements.

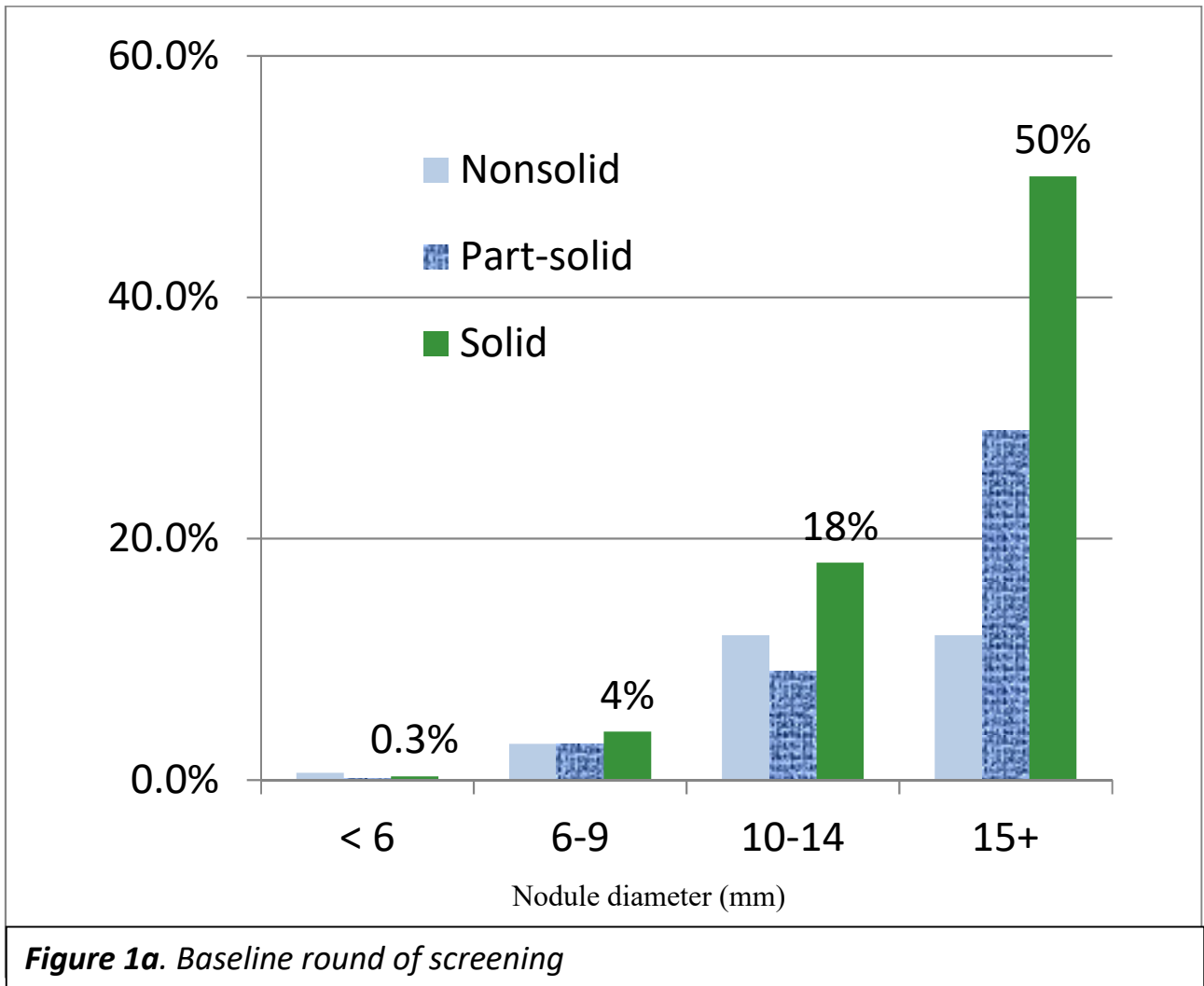
Probability of lung cancer by nodule size and consistency

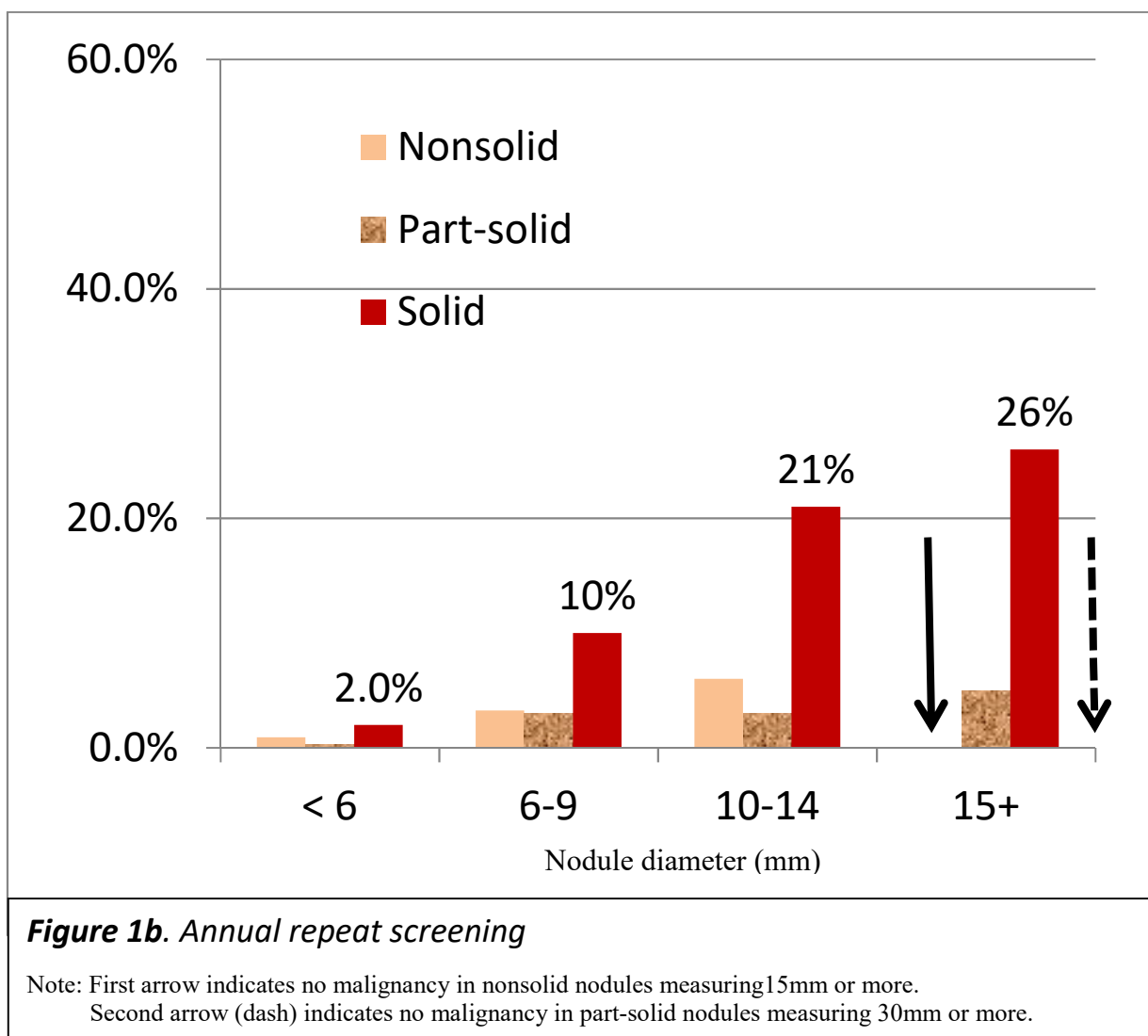
The nodule size thresholds for definition of positive result definitions continually are reevaluated and have changed since the start of ELCAP. Initially, there was no size cutoff for positive results [3, 36]. However new thresholds have been introduced and updated multiple times since then due to advancing technology and accumulating evidence [12, 21, 36-40]. **In the current protocol, the nodule diameter threshold for positive result is 6 mm on baseline and 3 mm on annual repeat screening [7, 39], but future updates are anticipated.**

It has been shown that some solid and many subsolid nodules that are identified in the lung parenchyma resolve, particularly new ones identified on repeat screenings [23-26, 41-43]. Thus, follow-up imaging three (3) months after baseline or one (1) month after annual repeat screening is useful to avoid unnecessary further diagnostics, especially invasive ones.

Figure 1 shows the probability of diagnosing lung cancer by nodule size and consistency [44]. The frequency of malignancy by nodule size is different in the baseline round than in annual repeat rounds. 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 mm or in part-solid nodules greater than 31+ mm [23, 24, 45].





Assessment of growth

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 and 4) increased attenuation of nonsolid components of a nonsolid nodule.

The I-ELCAP protocol recommends continued observation for nonsolid nodules as they can grow either in overall size [30-35], or internally as manifested by increasing attenuation [46]. Nevertheless, it is important to monitor these changes. For solid nodules, changes in the nodule diameter or computer-assisted volume measurements can be used.

Our overall understanding of growth assessment is rapidly evolving and the following should be considered: Nodule volume doubling times (VDTs) are useful [30-35]. VDTs of less than 30 days are more suggestive of an infection than malignancy [41]. 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 [47-50].

Several groups have developed approaches to incorporate measurement errors into the determination of growth. 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>. The American College of Radiology (ACR) specifies growth for a nodule of any size requires "an increase of 1.5 mm or more" [51, 52]. Both the QIBA and ACR approaches allow for large degrees of measurement error to cover a wide range of CT scanners and the protocols.

I-ELCAP guidelines are given in two tables below assume that modern scan protocols and software allow for sub-pixel resolution.

For solid nodules with little or no attachment to surrounding structures or for the solid component of part-solid nodules, the diameter change for a cancer with a VDT of 180 days is given in Table 1 and 2 assuming:

- sub-millimeter CT slice thickness
- slice spacing equal or less than slice thickness
- 64-detector-row or higher CT scanners
- reconstruction field of view is less than 30 cm, and
- identical parameters on both scans.

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 for growth at a malignant rate (VDT 180 days or faster)

BASELINE ROUND		
Original diameter (mm)	Diameter in 3 months without measurement error VDT: 180 days	Diameter 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

The shorter the time between CT scans, (e.g., 1 month interval after the annual screening) the greater the impact of the measurement error, so that the measurement error itself is greater.

Table 2. Repeat Rounds: Change needed in nodule diameter for growth at a malignant rate (VDT 180 days or faster)

ANNUAL REPEAT ROUNDS		
Original diameter (mm)	Diameter in 6 months without measurement error (mm)	Diameter in 6 months with measurement error (mm)
3.0	3.8	4.2
4.0	5.0	5.4
5.0	6.3	6.7
Original diameter (mm)	Diameter in 1 month VDT: 180 days	Diameter in 1 month 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

Computer-assisted evaluation of growth rates and volume doubling times still is a topic of research; and there is variation among the different hardware and software that is currently available. 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.

The computer scans and the segmentation should be inspected 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 such as when a vessel is segmented as part of a nodule in one scan but not in the other. Scan slice thickness for the purpose of volumetric analysis should not exceed 1.25 mm.

While these estimates are meant only as boundaries to be confident that nodule change has occurred, they do not prove accurate regarding 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.

Baseline screening

The results of the baseline CT scans are classified as:

Negative result: No nodules

Semi-Positive result:

- a. Nonsolid nodules, regardless of size, or
- b. Largest solid, part-solid (solid component) less than 6.0 mm, or
- c. Largest solid, part-solid (solid component) 6.0-14.9 mm if follow-up CT scan in 3 months after baseline shows growth at a nonmalignant rate (see Table 1).

Follow-up: The participant is scheduled for the first annual screening, twelve months after baseline.

Positive result:

- a. Largest solid, part-solid (solid component) 6.0-14.9 mm in size after a follow-up CT scan in 3 months shows growth at a malignant rate (Table 1), or
- b. Largest solid or part-solid nodule 15.0 mm or larger, or
- c. Solid endobronchial nodule.

Follow-up options for positive results:

- A). If the nodule appearance is highly suggestive of lung cancer, immediate biopsy is recommended.
- B) Another option is to perform PET scan, particularly if the solid component of the nodule is 10 or more mm in diameter. If the PET result is positive, biopsy is recommended, but if negative or indeterminate a low-dose CT 1-3 months later is performed. If there is growth, biopsy is recommended, but if there is partial or complete resolution on CT, the workup stops.
- 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 [41]. The result is acted on as specified in option B.
- 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 (1) 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 2016 [53]).

For all participants in whom the diagnostic work-up was stopped or the biopsy (considered to be adequate) did not lead to a diagnosis of lung cancer, repeat CT 12 months after the initial baseline CT is to be performed.

Repeat screening

The result of the repeat CT scan is classified as:

Negative result: No new nodules

Semi-positive result:

- a. Growth of previously seen nodules but still < 3.0 mm, or
- b. *New* noncalcified nodules < 3.0 mm, or
- c. Nonsolid nodules, regardless of size.

Follow-up: The participant is scheduled for the next annual screening, twelve months later.

Positive result:

- a. Largest *new* or *growing* solid or part-solid nodule (solid component) is 3.0 mm or larger, or
- b. *New* solid endobronchial nodule.

Follow-up options:

- A) If all the solid component of any newly identified NCN is more than 3.0 mm but less than 6.0 mm in diameter then low-dose non contrast CT is performed at six (6) months after the screening. Any nodule showing further growth at a malignant rate (Table 2) is recommended for biopsy; otherwise the work-up stops.
- B) If at least one of the newly identified NCNs that has a solid component that is 6.0 mm in diameter or larger then options 1-3 can be used:
 1. Perform low-dose CT one month after the screening. If the NCN shows growth at a malignant rate, biopsy is recommended. If there is partial or complete resolution, the workup stops. If the nodule is unchanged, particularly if the nodule is 10 mm or larger, Option 2 can be used, otherwise three-month follow-up CT is performed; if growth at a malignant rate, biopsy is recommended, otherwise the work-up stops.
 2. For solid or part-solid nodules, particularly if the solid components is 10 mm or larger, an immediate PET scan can be performed. If it is positive, biopsy is recommended while 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 [41]. This option is to provide an immediate course of a broad-spectrum antibiotic with anaerobic coverage, and perform a follow-up low-dose CT 1 month later. If the NCN shows growth at a malignant rate, biopsy is recommended, if nodule(s) are unchanged, option 2 or 3-month follow-up CT is recommended, while if there is partial or complete resolution, the workup stops. If MAC or other chronic infection is suspected, pulmonary consultation is recommended.
- 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.

For all individuals in whom the work-up was stopped or the biopsy did not lead to a diagnosis of lung cancer, repeat CT 12 months after the prior screening is to be performed.

Other findings to be documented on the low-dose CT scan

The reader is also responsible for documenting other findings in the lungs and chest, including those visualized in the mediastinum, heart, breast, soft tissues, abdomen, and bones.

Discrete cystic airspaces

The walls of discrete cystic airspaces should be assessed for progressive wall thickening, both in increasing thickness and increasing circumferential wall involvement, as these may due to lung cancer [22].

Emphysema

The extent of emphysema is identified and classified as none, mild, moderate, or severe, each being scored 0 to 3, respectively. Mild emphysema is defined by having 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 if discrete areas of decreased attenuation can be identified involving less than half of the lung parenchyma; and, severe emphysema if discrete areas of decreased attenuation can be identified involving more than half of the lung parenchyma. Each subject receives an emphysema score in the range from 0 to 3 [54].

If emphysema is present and previously unrecognized, consultation with a pulmonologist are recommended [55].

The I-ELCAP management system can provide, for the purposes of research, automated lung analysis [54-60] which include: lung volume assessment (separately for right and left), standard emphysema scoring (using -910 and -950 HU values), of the lung (top, middle, and lower) and measurements of airway wall thickness.

Interstitial findings

Early findings of usual interstitial pneumonitis (UIP) have been classified as pre-honeycomb and honeycomb (HC) findings [61, 62]. Other interstitial diseases can also be identified and may differ in location and findings [62]. 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.

Mediastinal and thymic masses

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.

Based on the frequency and natural course of *thymic masses* identified in baseline and annual repeat screenings for lung cancer [63], the following work-up recommendations are made: If the mass is 3.0 cm or less in diameter on baseline CT without invasive features (e.g., irregular borders or loss of fat planes), follow-up CT one year later is recommended. If the thymic mass is greater than 3.0 cm or shows growth on the follow-up CT, then further workup according to standard practice is recommended.

Coronary arteries

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 subject received an Ordinal coronary artery calcium (CAC) Score in the range from 0 to 12 and the corresponding recommendations are given in the section on the workup of ancillary findings [64, 65]. Currently, it is also possible to obtain the Agatston, volume or mass calcium scores on low-dose CT scans and then the standard Agatston recommendations can be used. New rapid scanning techniques minimize cardiac motion and allow for improved Agatston scoring on non-gated examinations. However, the equivalence of these scores to standard dose gated scanning is still being established [66, 67]. In the future, the process may become automated [67-70].

The recommendations for Ordinal Score are based on prior analyses of screening data [64-67]. Additional analysis showed there is excellent agreement in the ordinal CAC Score for the categories of the Agatston Scores. Latest recommendations are detailed in SCCT/STR guidelines [71].

Ordinal CAC Score	Agatston Score	Recommendation
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; 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

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, Bassett LW et al. ACR 2013, 4th edition). The BI-RADS classification identifies 4 grades according to the breast density.

- 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

The key differentiation is between Grades 1-2 and 3-4 [72, 73]. If the percentage of breast tissue is, Grade 3 or Grade 4, then this should be noted 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 as the mammogram might obscure an early cancer or precursor lesion. Automation of the breast density on CT scans is being developed [74]. Calcifications seen in the breast also provide information about coronary artery disease and should be reported [70, 75]

Adrenal enlargement

When either adrenal gland measures 40 mm or more in the largest transverse diameter, further evaluation is recommended [76].

Adrenal enlargement of less than 40 mm in transverse diameter and low attention (less than 10 H.U.) and can be followed by annual low-dose CT scans until growth is identified [76].

Liver steatosis

If liver attenuation is below 40 HU and/or the liver-spleen ratio below 0.9, then we recommend follow-up with a primary care physician or liver specialist for further evaluation of possible hepatic steatosis detected incidentally on CT imaging [77].

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]. If this is 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.

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.

Classification and characterization of diagnosed cancers

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 actually is achieved [7, 45]. Also, it would be classified in this way if the result was semi-positive and an annual repeat CT in 12 months would be recommended. 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 [7, 45].

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 [7, 45]. If work-up is prompted by suspicion-raising symptoms (or an incidental finding) in between annual screening, the diagnosed cancer is classified as an annual interim-diagnosis.

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 [7]. Principal among these descriptors/indicators is the *clinical stage* of the disease at diagnosis. Clinical Stage I, for purposes of further research, is defined by the size of the tumor (T status), 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. The person is 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, even when there is more than 1 adenocarcinoma, all less than 30 mm in diameter [6, 11, 13, 14]. This approach in considering the individual subsolid lesions as representing separate primaries has now gained widespread acceptance [79-81].

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 internal to the I-ELCAP database, as the study data from the images are available for central determination. Two measurements of nodule size can be used. One of these is the ‘diameter’ used in the present regimen of early diagnosis. The ‘diameter’ is the average of the nodule’s length and width. In addition, the nodule volume may be obtained automatically using commercially available software.

Important also is the tumor’s *volume doubling rate*. This rate is critical to the early-diagnostic regimen, particularly for tumors less than 15 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.

Eminently important are the pathology data, especially for the distinction between cell types, most first among small-cell and non-small-cell types [82] and 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 [83, 84]. 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. Pursuit of this goal is one of the research aims of I-ELCAP.

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 the Program 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 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 [82, 85-89]. 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 information since 2000 [90].

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.

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, 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

The I-ELCAP Management System

For the purposes of I-ELCAP, there 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 system is web-based and thus 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.

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.

Qualifications of the radiologists in the participating institutions are board-certification and, if possible sub-specialization in chest imaging. They have continual access to the electronic teaching files embedded in the management system and are encouraged to visit the I-ELCAP database center for training sessions provided by 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 (cf. Regimen of Early Diagnosis, above). As for the pathologists in the participating centers, information regarding the preparation and interpretation of cytology and histology specimens is provided 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. Pathologists are encouraged to participate in the International Conferences on Screening for Lung Cancer.

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