BJR

https://doi.org/10.1259/bjr.20170401

Received: 30 May 2017 | Revised: 04 August 2017 | Accepted: 15 August 2017

Cite this article as:
Rydzak CE, Armato SG, Avila RS, Mulshine JL, Yankelevitz DF, Gierada DS. Quality assurance and quantitative imaging biomarkers in low-dose CT lung cancer screening. *Br J Radiol* 2018; **91**: 20170401.

THE ROLE OF IMAGING IN SCREENING SPECIAL FEATURE: REVIEW ARTICLE

Quality assurance and quantitative imaging biomarkers in low-dose CT lung cancer screening

[1]CHARA E RYDZAK, MD, PhD, [2]SAMUEL G ARMATO, PhD, [3]RICARDO S AVILA, MS, [4]JAMES L MULSHINE, MD, [5]DAVID F YANKELEVITZ, MD and [1]DAVID S GIERADA, MD

[1]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO, USA
[2]Department of Radiology, University of Chicago, Chicago, IL, USA
[3]Accumetra, LLC, Clifton Park, NY, USA
[4]Department of Internal Medicine, Rush University, Chicago, IL, USA
[5]Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Address correspondence to: Dr David S Gierada
E-mail: *gieradad@wustl.edu*

ABSTRACT

After years of assessment through controlled clinical trials, low-dose CT screening for lung cancer is becoming part of clinical practice. As with any cancer screening test, those undergoing lung cancer screening are not being evaluated for concerning signs or symptoms, but are generally in good health and proactively trying to prevent premature death. Given the resultant obligation to achieve the screening aim of early diagnosis while also minimizing the potential for morbidity from workup of indeterminate but ultimately benign screening abnormalities, careful implementation of screening with conformance to currently recognized best practices and a focus on quality assurance is essential. In this review, we address the importance of each component of the screening process to optimize the effectiveness of CT screening, discussing options for quality assurance at each step. We also discuss the potential added advantages, quality assurance requirements and current status of quantitative imaging biomarkers related to lung cancer screening. Finally, we highlight suggestions for improvements and needs for further evidence in evaluating the performance of CT screening as it transitions from the research trial setting into daily clinical practice.

INTRODUCTION

Low-dose CT screening detects lung cancer with high sensitivity, usually at an early stage with excellent chance for cure.[1,2] Thus, the major potential benefit of CT lung cancer screening (CTLCS) is reduced mortality.[3,4] Unfortunately, several inherent limitations of CTLCS may counteract its effectiveness, such as the high frequency of indeterminate lung nodules, workup of benign and incidental abnormalities, and increased radiation exposure.[5] Most persons who undergo CTLCS will not develop lung cancer, so will not benefit from screening, yet will be subject to these potential risks as well as expenses they would not otherwise have incurred. Therefore, it is incumbent upon CTLCS providers to optimize the quality of this service and stay abreast of international research and evidence-based recommendations to achieve the most favourable balance of benefits and risks.

One of the most important improvements for CTLCS is an emphasis on incorporating quality assurance procedures into each step of the screening process, including assessment of eligibility/lung cancer risk, performing and interpreting the low-dose screening CT examination, reporting the results and monitoring compliance with the recommendations for evaluating CT abnormalities. Procedures designed to optimize efficacy and ensure quality in CTLCS have been codified in guidelines developed by numerous professional societies and regulatory agencies (Tables 1 and 2);[5–19] the considerations and recommendations in this review reflect our own experience in the US health care system and with US-based organizations that have issued guidelines. Quantitative imaging biomarkers that help to objectively characterize indeterminate lung nodules are on the horizon and may further improve the quality of CTLCS, although come with additional quality assurance recommendations.

ELIGIBILITY

The overall efficacy and efficiency of any cancer screening process are influenced by the disease prevalence.[20] It follows

Table 1.Regulatory Agency and Professional Society Guidelines & Recommendations for CTLCS[5–18]

Recommendations	ACCP	ACS	AATS	CMS	CTFPHC	ESR/ERS	ESTS	IASLC	NCCN	STS	USPSTF	Multisociety[a]
Multidisciplinary screening program	X	X	X	X	X	X	X	X	X	X	X	X
Use of eligibility criteria	X	X	X	X	X	X	X	X	X	X	X	X
CT quality controls	X	X	X	X	–	X	X	X	X	X	X	X
Standardized scan interpretation process	X	X	–	X	X	X	X	X	–	X	X	X
Standardized intervention and management algorithm	X	X	X	X	X	X	X	X	X	X	X	X
Ongoing use of quality metrics	X	–	–	X	X	X	X	X	–	X	X	X
Participation in registry and data collection	X	–	X	X	X	X	X	X	–	X	X	X
Research participation	X	–	X	–	–	–	–	X	–	X	X	X
Patient education, counselling, shared decision-making	X	X	–	X	X	X	–	–	X	X	X	X
Smoking cessation	X	X	X	X	X	X	X	X	X	X	X	X

AATS, American Association of Thoracic Surgery; ACCP, American College of Chest Physicians; ACS, American Cancer Society; ASCO, American Society of Clinical Oncologists; ATS, American Thoracic Society; CMS, Center for Medicare & Medicaid Services; CTFPHC, Canadian Task Force on Preventive Health Care; ESR/ERS, European Society of Radiology and the European Respiratory Society; ESTS, European Society of Thoracic Surgeons; IASLC, International Association for the Study of Lung Cancer; LC III, Lung Cancer Guidelines (3rd ed); NCCN, National Comprehensive Cancer Network; STS, Society of Thoracic Surgeons; USPSTF, United States Preventive Services Task Force.

[a]ACCP, ASCO and ATS.

Table 2.Summary of radiology imaging facilities requirements for CMS reimbursement and designation as an ACR Lung Cancer Screening Center

CMS criteria[14]	ACR designation requirements & recommendations[19]
Imaging facility eligibility criteria:	
Written order for LDCT lung cancer screening from a qualified physician or non-physician practitioner that includes: • Patient's date of birth • Pack-year smoking history (number) • Current smoking status; if former smoker, the number of years since quitting • Statement that the patient is asymptomatic • National Provider Identifier (NPI) of the ordering practitioner	
Documentation of lung cancer screening counselling & shared decision making for initial screen that includes: • Determination of eligibility based on established eligibility criteria (Table 3) • Discussion of benefits and harms of screening; use of one or more decision aids • Discussion of the importance of adherence to annual CTLCS, implications of comorbidities and ability or willingness to undergo diagnosis and treatment • Smoking cessation counselling for current smokers, discussion of the importance of maintaining abstinence if a former smoker; provide information on tobacco cessation intervention	
$CTDI_{vol}$ for LCDT ≤ 3.0 mGy for a standard sized patient of 5′ 7″ and 155 pounds (BMI of ~ 24)	$CTDI_{vol}$ ≤ 3.0 mGy for a standard-sized patient
Dose adjustment based on BMI	Dose adjustment based on BMI
Quality assurance plan	• Majority of patients meet standard eligibility guidelines • Compliance with the quality control program in the ACR CT Quality Control Manual • Use of multidetector helical CT scanners for CTLCS • Radiographers and medical physicists must meet CT accreditation program requirements of the ACR
Participation in CMS approved registry	Dose monitoring, data collection and research participation • Participation in the ACR Dose Index Registry
Lung nodule identification, classification & reporting system	Follow the ACR Practice Parameter for Communication of Diagnostic Imaging Findings • Use a structured reporting system that includes management recommendations, such as Lung-RADS • Use of standardized procedures for referring patients with abnormal results to a qualified health care provider or specialist for management and treatment
Availability of smoking cessation interventions	Mechanism for providing or referring for smoking cessation counselling or materials

ABR, American Board of Radiology; ACR, American College of Radiology; BMI, body mass index; CME, continuing medical education; CMS, Centers for Medicare and Medicaid Services; $CTDI_{vol}$, CT dose index; LDCT, low-dose CT; Lung-RADS, Lung CT screening reporting and data system; NPI, National Provider Identifier.

that optimizing quality in CTLCS begins with limiting screening to an appropriate target population. Since the first reports of CTLCS were published,[21,22] the main lung cancer risk factors of age and smoking history have defined the population for lung cancer screening. The National Lung Screening Trial (NLST), which enrolled a high-risk population with an estimated 2–20% chance of developing lung cancer within 10 years,[10,23] found a 4.0% rate of lung cancer and a 20% reduction in lung cancer-specific mortality among those undergoing three annual rounds of low-dose CT screening and then followed for a median of 6.5 years.[4] As the only fully powered randomized screening study to demonstrate a mortality benefit of CTLCS, the NLST is the basis for current screening eligibility criteria and other guidelines, with some modifications as expected in the shift to public health application.

Target population

The CTLCS eligibility guidelines of the U.S. Preventive Services Task Force (USPSTF)[5] and the Centers for Medicare and Medicaid Services (CMS)[14] (Table 3), which must be followed in the USA for private and government insurance reimbursement, are based on the main NLST entry criteria of (1) age 55–74 years, (2) smoking history 30 pack years or more and (3) less than 15 years since quitting if no longer smoking.[5] Modelling studies using NLST and other epidemiologic data[24] informed the USPSTF recommendation to perform screening at annual

Table 3.Summary of standard and extended eligibility criteria for annual CTLCS

Standard eligibility criteria (USPSTF and CMS)[a5,14]	Extended eligibility criteria[b]
55–80 years (CMS: 55–77 years)	50 years or older
≥30 pack-year smoking history	≥20 pack-year smoking history
Either current smoker or quit smoking within the last 15 years	One additional risk factor[c] including: • Previous smoking-related cancer • Family history of lung cancer • Lung disease history—including pulmonary fibrosis and COPD • Radon exposure • Occupational exposure—including asbestos, arsenic, beryllium, cadmium, chromium VI, diesel fumes, nickel and silica
Must be asymptomatic	Must be asymptomatic

CMS, Centers for Medicare and Medicaid Services; COPD, chronic obstructive pulmonary diesease; USPSTF, US preventive services task force.

[a]Recommendations of USPTF and requirement of CMS. The USPSTF recommends discontinuing screening after a person has not smoked for >15 years, if they develop a health problem that significantly limits life-expectancy, or are no longer able or willing to undergo curative lung cancer treatment.

[b]Recommended by National Comprehensive Cancer Network and American Association for Thoracic Surgery.

[c]Secondhand smoke exposure is not considered an additional risk factor.

intervals until age 80 years, while CMS provides reimbursement up to age 77, the age at which the oldest NLST participants had their final screening examination. Some guidelines also recommend lowering the minimum age and smoking history for persons who have another recognized risk factor in addition to smoking (Table 3).[16,25]

Analyses of NLST[26,27] and other trial data[28,29] have found that lung cancer risk varies substantially among all persons who fall within the current age and smoking history-based eligibility guidelines. For example, using a prediction model for lung cancer death based on an increased number of risk factors, it was found that the 60% of patients at highest risk of lung cancer mortality made up 88% of prevented lung cancer deaths in the NLST, while the 20% of patients at lowest risk represented only 1% of prevented lung cancer deaths.[26] In another study,[27] use of an individual risk model for CTLCS eligibility was estimated to prevent a greater number of lung cancer deaths over a 5-year timeframe when compared with a model based on USPSTF recommendations. Refinement of risk-based targeting is a promising means to improve screening efficiency and effectiveness, and could be incorporated into future guidelines.

Shared decision-making

Ethical considerations dictate that patients be made aware of the potential limitations and harms as well as the benefits of CTLCS. Unfortunately, nearly 30% of screen-detected lung cancers in the NLST were of advanced Stage (III or IV) with low survival rates,[4] so many screen-detected cancers will not be curable. In addition, undergoing CTLCS entails a small chance of being subjected to the risks of additional imaging and invasive procedures to evaluate ultimately benign findings for no benefit.[4,6] Multiple professional groups recommend, and Medicare insurance reimbursement requires, an individualized shared decision-making encounter between patients and their health care provider (Tables 1 and 2).

Shared decision-making should review the pros and cons of screening, including expected outcomes and their likelihood, and treatment options, as each patient has unique preferences and risk tolerance. Counselling should also address patient-specific risk relative to comorbidities and curative therapy, and provide accurate information about the risks of cancer associated with specific findings. Some organizations provide written materials that describe and illustrate the information that patients should know about CTLCS, and shared decision-making tools have been made publicly available on websites.[30–32] In addition, several prediction models that estimate the percent chance of developing lung cancer based on multiple individual risk factors have been published or made publicly available as web-based calculators.[28,30,33,34] Research to determine the impact of these tools on the quality and outcome of the shared decision-making process is a current need.

Verifying patient eligibility for screening

Limiting CTLCS to eligible individuals is important for providing optimal care as well as maintaining compliance with insurance regulations. Many screening programs use a dedicated CTLCS nurse navigator or program coordinator[35,36] to verify the appropriate documentation of eligibility criteria and shared decision-making. The nurse navigator also serves as a liaison between patients, referring physicians, administrative support staff, technicians performing the scans and radiologists.[35,36]

Nurse navigators are ideally positioned to encourage smoking cessation and provide educational materials and referrals for counselling. These activities are encouraged by most professional organizations, required by CMS and supported by findings that smoking cessation interventions in the lung cancer screening setting increase smoking cessation rates,[37] as does an abnormal screening CT examination result.[38] The value of a nurse navigator, for eligibility verification, smoking cessation efforts and as a central part of overall lung cancer screening program management, cannot be overemphasized. The success of lung cancer screening on a wider scale will rest in large part on the ability to replicate the quality and processes of patient selection, screening, and monitoring in the same thorough, systematic way achieved by the NLST and other screening trials.

THE CT SCREENING EXAMINATION

Quality issues associated with the CT screening examination relate to the physical act of scanning patients and generating images, and to image interpretation. Implementing quality control measures for these processes helps to maximize the

Table 4.Recommended technical parameters for LDCT in lung cancer screening

Technical parameters for LDCT	For visual review[a39]	For quantitative volumetry[b]
Peak kilovoltage	100–140, adjusted for patient size	Same
Tube current-time product (mAs)	Adjust with kVp to achieve $CTDI_{vol}$ ≤ 3.0 mGy in average-size patient: • Small patient (50–70 kg) = $CTDI_{vol}$ 0.25–2.8 mGy • Average patient (70–90 kg) = $CTDI_{vol}$ 0.5–4.3 mGy • Large patient (90–120 kg) = $CTDI_{vol}$ 1.0–5.6 mGy	Same
Pitch	0.83–1.43 (scanner specific)	Same
Nominal section thickness (mm)	≤2.5 mm, ≤1.0 mm preferred	≤1.25 mm
Section interval	≤section thickness	Same
Reconstruction filter	Manufacturer-specific; coronal & sagittal and maximum intensity projection reformations recommended	Highest resolution without edge enhancement
Multidetector CT scanner	Typically 16 detector rows or greater	Minimum 16 detector rows; 64 or greater preferred

LDCT, low-dose CT.
[a]From the American Association of Physicists in Medicine; see ref. 39 for parameters specific to numerous scanner models.
[b]Scanner model and technical parameters should be the same for baseline and follow-up scans.

potential benefit of CTLCS. Emerging quantitative CT imaging biomarkers for use in CTLCS require additional quality considerations and are discussed separately.

CT imaging for visual review

Technical specifications for CT scanning for visual interpretation (Table 4) are guided by the primary screening tasks of detecting and characterizing lung nodules using a low radiation dose.[39] Meeting these requirements typically requires scanners with 16 or more detector rows. Intravenous contrast is not used, as the air attenuation of the lungs provides inherently sufficient contrast for nodule detection, and including contrast would reduce the overall safety and cost effectiveness. The entirety of the lungs should be scanned in a single breath-hold to avoid motion artefacts, with pitch ideally under 1.5 to limit *z*-axis blurring. To depict the small nodules relevant to CTLCS, sections should be contiguous or overlapping with thickness no greater than 2.5 mm, and preferably 1.25 mm or less. Adding overlapping maximum intensity projection reconstructions can increase nodule detection sensitivity, and multiplanar reconstructions may help distinguish nodules from scars, atelectasis, or other abnormalities.

Even though the risks of radiation exposure from low-dose CTLCS are exceedingly small compared to the risk of lung cancer in the screening population, minimizing radiation dose while maintaining satisfactory image quality is an important goal and quality metric in CTLCS. Regulatory and professional society guidelines stipulate that CT should be performed with $CTDI_{vol}$ ≤3.0 mGy for a standard size patient of 5′ 7″ and 155 pounds.[14,39] Dose adjustment for patient body mass index is important not only for achieving satisfactory image quality in larger patients, but also for radiation dose reduction in smaller patients. If automatic exposure control is used, patient centring in the gantry is critical for proper functioning of the system.[39] However, caution with AEC is advised, because systems designed to maintain a specific level of image noise may actually increase overall dose in some patients. Breast shields are not recommended, as they have a variable effect on image quality depending on the type and positioning, may increase dose in some circumstances, and waste image-forming photons.[40]

Programming the low-dose CT protocol into the scanner helps ensure that the correct parameters are applied by different radiographers. Radiation dose monitoring software is another tool for radiation quality control, and has been shown to increase CT operator awareness and reduce the number of dose notifications associated with human error.[41] It is worth noting here that the tradeoffs between dose and image quality have not been rigorously defined and vary between scan manufacturers, so this is an area open for improvement.

A prospective quality assurance program during the NLST was associated with infrequent CT imaging errors (0–5% for different parameters) which were minor[42] and should be largely preventable (Table 5). However, population-based screening may be associated with higher rates of suboptimal quality, as was found in a screening program implemented at multiple Veterans Health Administration hospitals.[43] The extent to which imaging quality will be an issue in the more heterogeneous clinical practice setting still needs to be determined.

CT imaging for quantitative biomarkers

One of the simplest and most straightforward nodule biomarkers is size, which is the primary determinant of malignant potential and pulmonary nodule management in CTLCS.[16,44] In the current clinical setting, nodule size is most commonly ascertained as the average of bidimensional linear measurements made manually with electronic calipers using a computer mouse. Although very effective in managing lung nodules, there is substantial variability among radiologists in making these measurements[45,46] and in determining whether a nodule is growing.[47,48] In addition, two perpendicular measurements in the transverse plane may not fully reflect the size of non-spherical nodules. Ideally, nodule size assessment should be accurate, unbiased and reproducible, regardless of the particular CT machine and radiologist.

Table 5.Common scanning pitfalls effecting subjective image quality[42]

Common pitfalls[a]	Recommendations for error correction & quality assurance
FOV error	• Radiographer training in defining appropriate FOV • Periodic review of FOV guidelines
Motion	• Radiographer training in appropriate patient coaching, observation, & image review
Incomplete inspiration	• Radiographer training in appropriate patient coaching & observation • Rehearsal of inspiration and monitoring of full inspiration for breath-holding
Scan length error • Over-scanning > 3 cm below the lungs • Incomplete coverage of the lungs	• Radiographer training on minimizing abdominal scanning including use of maximum inspiration for topogram and spiral images and use of lateral topogram • Complete preliminary review of all images to ensure full coverage before patient leaves the scanner as part of examination completion checklist • Periodic review of scan length guidelines
Artefacts obscuring anatomy • Streak • Ring • Beam-hardening • Excessive noise	• Review scanner technology limitations and adjust acquisition parameters and/or conduct dedicated troubleshooting and maintenance procedures • For patients with metal implants, such as orthopedic shoulder joint replacements, careful positioning is of benefit to minimize artefact

FOV, field of view.

[a]For CTLCS, FOV should be <3 cm beyond outer rib margins. No degradation of the study due to respiratory or trunk motion, and pulsation artefact should be minimized. Sufficient inspiration resulting in no more than minimal dependent atelectasis. A complete CTLCS examination includes the entire cephalocaudal length of lungs with no missing images, lung anatomy or gaps between sections. The number of CT sections below the most caudal lung containing image should be minimized. Anatomic feature should not be obscured by image artefacts (*e.g.* streak, ring or beam-hardening artefact).

Computer-aided quantitative measurement of lung nodule volume, or CT volumetry, is well suited for achieving these goals. In this technique, a software algorithm objectively identifies the nodule boundaries and voxels contained within and calculates the nodule volume. Although the process can be totally automated, measurement variability also exists with quantitative nodule volumetry, due to technical variables that affect depiction of nodule borders. Scanning and reconstruction parameters recommended for CT volumetry (Table 4) are within the ranges of those recommended for visual interpretation, but are more specific and require attention to important details to optimize accuracy (how closely the measurement corresponds to the true volume) and precision (variability of repeated measurements). While a full discussion of image analysis software is beyond the scope of this review, it should be noted that different algorithms for measuring lung nodule volume may produce different results.[49,50] Thus, the same nodule volume analysis program should be used when making comparisons, or if different programs are used, equivalency of the results produced should be verified.

To ensure satisfactory scanner performance, the appropriate governmental regulatory and manufacturer guidelines regarding scanner setup, routine testing and maintenance should be followed. Participation in a voluntary scanner accreditation program, such as that offered by the ACR,[51] verifies individual scanner performance and facilitates correction of deficiencies. Performing follow-up scans on the same scanner model reduces measurement variance related to scanner hardware and software differences. Prior to scanning, metallic objects that may produce image artefacts should be removed. Patients should be consistently positioned within the centre of the CT gantry, because resolution may vary at different distances from isocentre.[52] In addition, patients should be rehearsed and monitored to reach full inspiration for breath-holding during the scan, as lung volume variation affects lung nodule volume measurements.[53,54] In a busy clinical setting with multiple scanner models and rotating radiographers, extra effort may be necessary to maintain quality standards related to scanner selection, patient preparation and handling, such as radiographer and radiologist education, use of a checklist and operator recertification.

Scanning parameters to keep constant (Table 4) include tube voltage and current, which affect image noise levels and can impact nodule segmentation;[55,56] pitch, which affects z-axis resolution; and detector collimation, to allow sufficiently thin reconstructions. Volumetric measurements are influenced by the reconstruction field-of-view,[57] which determines in-plane voxel dimensions, and although constrained by patient size should be held constant on serial follow-up scans in individual patients. The reconstructed slice thickness is a critical determinant of volume measurement accuracy for nodules in the 5–10 mm range,[55,57–59] and should be 1.25 mm or less, contiguous or overlapping. The highest-resolution reconstruction kernel with no edge enhancement is preferred.[60] Nodule volume measurements with iterative reconstruction kernels are similar to those using filtered back-projection.[56,61,62]

As understanding of the CT technical factors and fundamental image properties affecting small nodule volumetry increases, there is potential to implement more advanced image quality metrics specific to the depiction of small nodules. Parameters such as resolution, HU accuracy, voxel noise, edge enhancement and spatial warping may be assessed to determine the nodule detection and measurement capabilities of specific scanners and parameter settings.[63] Such assessments are beyond the scope of most radiology practices, but could be facilitated through an accrediting system established by a professional society, with electronic transfer of test images for technical analysis.

Computer-aided analysis also can extract numerous other quantitative CT features as potential biomarkers, such as shape, edge contours, attenuation and spatial variation of attenuation within the nodule (texture). Often referred to as radiomics,[64] such features have been used to estimate the likelihood that a nodule is malignant,[65–68] or to predict the clinical behaviour/

aggressiveness of lung cancers.[69,70] As with CT volumetry, an advantage of this approach lies in its objectivity and potential reproducibility across users. The impact of technical variables on these biomarkers has yet to be addressed, but the same image quality considerations as in nodule volumetry likely apply.

Visual image interpretation

Accurate image interpretation is central to CTLCS; however, variability is inherent among radiologists in nodule detection, size measurement and follow-up recommendations.[43,45–47] Nodule detection sensitivity and the nodule size threshold for defining a positive study influence false-positive screening rates, sensitivity and positive and negative predictive values.[71–73] Radiologist sensitivity for nodule detection can be increased with the use of maximum-intensity projection images or computer-aided nodule detection software,[74,75] to a similar degree in one study.[76] Use of a standardized reporting system also has been advocated to improve the uniformity of image interpretation and management of abnormalities as part of quality assurance in CTLCS.

The Lung CT Screening Reporting and Data System (Lung-RADS)[44] of the ACR is a model reporting system for visual interpretation using manual nodule measurements. Lung-RADS criteria were developed using data from the NLST, International Early Lung Cancer Action Program, and the European Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial. The scheme (Table 6) defines five results and management categories based on the cancer risks associated with lung nodules of different size and attenuation.

The Lung-RADS system does not actually use the terms "positive" or "negative" to classify screens, reinforcing the concept of CTLCS as a process of ongoing surveillance. However, it has been estimated that use of Lung-RADS criteria would have decreased the NLST rate of false positives requiring further workup before the next annual screen from 27 to 13%, and increased the positive predictive value from 3.8 to 6.9%, at the expense of a decrease in sensitivity;[77] similar projections were found at a single community screening program.[78] Standardized reporting systems will facilitate evaluation of reader variability and discrepancies in diagnosis and management recommendations, providing a mechanism for quality control and improved patient care.

Quantitative imaging biomarker interpretation

Even with strict attention to high-quality imaging technique, unavoidable variation in factors such as patient positioning, lung volume, X-ray beam quality, and detector response prevent lung nodules from being depicted identically at the quantitative voxel level on different CT scans. Awareness of the specific amount of variability in CT nodule volumetry is therefore essential for using the measurements in clinical practice. As recognized by

Table 6.Summary of Lung-RADS scheme for results and management categories[44]

Result category[a]	Finding	Risk	Management
0—Incomplete	Not all parts of the lung can be evaluated or prior imaging being obtained for comparison	N/A	Incomplete study requiring additional imaging or comparison
1—Negative	No pulmonary nodules or only nodules with benign calcification pattern	<1%	Continued annual low-dose CTLCS
2—Benign appearance or behaviour Likely benign nodules with very low likelihood of malignancy	Solid nodule(s) <6 mm or new <4 mm Part solid nodule(s) <6 mm (baseline) Non-solid nodules(s) [ground glass nodules] <20 mm or ≥ 20 mm and unchanged or slow growing	<1%	Continued annual low-dose CTLCS
3—probably benign Probably benign nodules but short term follow-up is recommended	Solid nodule(s) ≥6 to <8 mm or new 4 to < 6 mm Part solid nodule(s) ≥6 mm with solid component < 6 mm or new < 6 mm Non-solid nodule(s) ≥20 mm on baseline CT or new	1–2%	6-month LDCT
4A—Suspicious Additional diagnostic testing and/or tissue sampling is recommended	Solid nodule(s) ≥8 to <15 mm at baseline or growing <8 mm or new 6 to <8 mm Part solid nodule(s) ≥6 mm with solid component ≥6 mm to <8 mm or with a new or growing <4 mm solid component Endobronchial nodule	5–15%	3-month LDCT; alternatively, if the solid component of the nodule is ≥ 8 mm, PET/CT may be used
4B—Suspicious Additional diagnostic testing and/or tissue sampling is recommended	Solid nodule(s) ≥15 mm or new or growing and ≥ 8 mm Part solid nodule(s) with a solid component ≥ 8 mm OR a new or growing ≥ 4 mm solid component	>15%	Chest CT with or without contrast, PET/CT and/or tissue sampling depending on patient comorbidities and probability of malignancy. For nodules with solid components ≥ 8 mm, PET/CT may be used.
4X—Suspicious Additional diagnostic testing and/or tissue sampling is recommended	Nodules in category 3 or 4 with other imaging features or findings that increases the concern for malignancy	>15%	Same as 4B

CTLCS, CT lung cancer screening; LDCT, low-dose CT; Lung-RADS, Lung CT screening reporting and data system; PET, positron emission tomography.

[a]Additional result modifiers for all categories: "S"—other clinically significant findings; "C"—prior lung cancer.

the Quantitative Imaging Biomarker Alliance of the Radiological Society of North America, quantifying variability requires a level of rigour comparable to calibrating laboratory assays or physiologic tests, by deriving information from phantom studies, clinical images, and theoretical modelling, and applying statistically valid metrology methods.[79–82]

Clinical investigations have shown that *in vivo* CT volume measurements of nodules ranging from 2 to 10 mm in diameter change by up to ±30% (95% confidence limits), when rescanned using the same scanner and settings after a short interval within which change could not have occurred.[83–86] A full assessment of variability must account for the geometric reality that the relative proportion of nodule voxels on the surface and subject to partial volume averaging increases rapidly as a nodule becomes progressively smaller, so that small variations in nodule depiction and edge detection lead to exponentially increasing variation in volume measurement. In one model-based estimate derived from theory and phantom, clinical, and simulation data, the expected 95% confidence limits for a single low-dose CT lung nodule volume measurement increase from ±27% to ±37 to ±57% for nodule diameters of 10, 8 and 6 mm, respectively.[87] Furthermore, because there is uncertainty with each measurement, the uncertainty in the volume change over two time points is greater than the uncertainty at a single time point. Based on statistical metrology concepts and the measurement variation at a single time point, nodules of 10, 8 and 6 mm diameter would have to increase by 39%, 53, and 80%, respectively, in order to be 95% certain that a true increase in size has occurred.[87]

It must be emphasized that these specific confidence limits for volume and change apply to defined measurement conditions: solid nodules, adequately segmented without manual editing, scanned using the same scanner model and technical parameters when evaluating for change. Automated processing methods for subsolid nodules are promising,[88,89] but measurement variability may be greater for nodules attached to structures such as blood vessels, the chest wall, or mediastinum[90] or those that require manual editing, or if the scanner model or technical parameters differ at the two time points. Measurement variation also may be greater for nonspherical or spiculated nodules compared with spherical or smooth nodules.[85,90,91] The data used to determine these reference values encompass a broad range of scanner models and configurations from 16 to 320 detector rows, and the performance of the more advanced scanners is generally superior to that of less advanced models.

An excellent example of how quantitative volumetry could be applied in clinical practice was demonstrated in the NELSON trial,[92] a randomized controlled trial designed to determine the mortality benefit of CT screening and not yet completed. In this trial, automated volume measurements were obtained for solid nodules not attached to the pleura, and for the solid component of part-solid nodules (other nodules were measured manually). Using a defined algorithm based on nodule volume thresholds to determine which nodules to reassess for growth by follow-up CT and which nodules to refer to a pulmonologist for workup and diagnosis, sensitivity and specificity for lung cancer ranged from 95 to 99%, depending on the screening round.[93] Another possible benefit of automated volumetry for nodule surveillance is a shorter time to diagnosis of malignant nodules.[94]

Thus far, no quantitative CT biomarkers in the realm of radiomics have been completely reliable for making a malignant or benign diagnosis. However, the prediction models using radiomic features provide an objective, reproducible percentage probability that a nodule is malignant, which can improve radiologist performance in classifying nodules[95,96] and could be very useful in lung nodule management. Newer machine learning methods that use CT images of benign and malignant nodules to train a computer algorithm to discriminate them may outperform these traditional multiparametric models.[97–99] Certain radiomic signatures also may reflect the histologic grade and aggressiveness of known lung cancers,[69,70] so may be of value in treatment planning. Clinical studies will need to determine whether the use of CT volumetry or radiomics improves patient care or efficiency compared with current methods.

COMMUNICATING SCREENING RESULTS

Without effective and efficient communication and continuity of care, the benefits of screening will diminish. Nurse navigators are extremely valuable for sustaining continuity of care and managing the administrative components necessary for a successful CTLCS program,[35,36] providing a line of communication between patients and the multidisciplinary team of providers. Mailing result letters to patients and providers and direct phone communication help to ensure receipt of results and facilitate timely follow-up of patients with abnormal findings. Documentation of communication also serves as a quality assurance measure. A dedicated computer database or electronic medical record system capable of tracking patients through the various stages of the screening process is virtually mandatory, and can assist with automated notification of results, prevent patients from being lost to follow-up, and provide reminders for annual screening.

Development of a standardized algorithm for results communication and management should take into consideration the unique characteristics of the individual institution. Depending on local capabilities and preferences, scheduling patient follow-up for abnormalities may be handled directly by the lung cancer screening program via the nurse navigator, who may make direct referrals to pulmonology or thoracic surgery clinics and assist providers with scheduling of interval follow-up scans. Other sites or individual referring providers may prefer that the referring health care provider directly handle any follow-up that may require referral for specialized care.

MONITORING SCREENING OUTCOMES

Monitoring patient characteristics, screening results, long-term compliance and outcomes will be an important part of screening quality assurance over time. Systematic collection of screening patient data and/or participation in a data registry will be essential for assessing and improving CTLCS. The dedicated CTLCS computer databases now commercially available allow collection and analysis of data elements specific to these needs.

As the use of CTLCS grows, standardized screening results can be compared across radiologists and sites to analyse reasons for any outliers. Patient and provider compliance with management recommendations, and frequency of specific diagnostic tests and complication rates, can be monitored to better understand the trade-offs of risks and benefits of screening outside of the clinical trial setting. Perhaps most importantly, quality improvement and the need for any modifications of current best practices will require analysis of lung cancer rates, stage distribution and survival in the screening population and specific subgroups. Registry data may be particularly valuable in this regard, as it may facilitate comparisons of the performance of different standardized interpretation and management algorithms. Finally, diagnostic evaluation rates for incidentally detected abnormalities provide the opportunity to assess their frequency and positive or negative impact on the screened population.[100]

SUMMARY

Quality assurance for CTLCS must include a number of key elements designed to maintain patient management and imaging quality across different radiologists, within the larger multidisciplinary team, and at different sites. Continual collection and analysis of screening metrics such as patient characteristics, the CT technical specifications applied in practice, screening results, diagnostic workups, and lung cancer rates, stage and survival will be critical to monitor and improve patient outcomes in the real-world outside of the clinical trial setting. Understanding the interplay of these multiple factors will be necessary to effectively guide and improve lung cancer screening programs in the future. Use of quantitative imaging biomarkers with computer-aided analysis offer additional potential for quality improvement, and will also require assessment of the impact on outcomes.

ACKNOWLEDGMENTS

Samuel G. Armato is a consultant for Aduro Biotech, Inc. and receives royalties and licensing fees for computer-aided diagnosis technology through The University of Chicago. Ricardo S. Avila is CEO and co-owner of Accumetra, LLC, an imaging technology company, and owner of Paraxial, LLC, an information technology consulting company. David F. Yankelevitz is a named inventor on a number of patents and patent applications relating to the evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation are non-exclusively licensed to General Electric. As an inventor of these patents, Dr. Yankelevitz is entitled to a share of any compensation which CRF may receive from its commercialization of these patents. He is also on the medical advisory board for GRAIL and owns stock in Accumetra.

REFERENCES

1. National Lung Screening Trial Research Team. Church TR, Black WC, Aberle DR, Berg CD, Clingan KL, , et al. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med* 2013; **368**: 1980–91. doi: https://doi.org/10.1056/NEJMoa1209120
2. Aberle DR, DeMello S, Berg CD, Black WC, Brewer B, Church TR, et al. Results of the two incidence screenings in the National Lung Screening Trial. *N Engl J Med* 2013; **369**: 920–31. doi: https://doi.org/10.1056/NEJMoa1208962
3. Henschke CI, Boffetta P, Gorlova O, Yip R, Delancey JO, Foy M. Assessment of lung-cancer mortality reduction from CT Screening. *Lung Cancer* 2011; **71**: 328–32. doi: https://doi.org/10.1016/j.lungcan.2010.10.025
4. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; **365**: 395–409. doi: https://doi.org/10.1056/NEJMoa1102873
5. Moyer VA, US Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014; **160**: 330-338–8. doi: https://doi.org/10.7326/M13-2771
6. Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA* 2012; **307**: 2418–29. doi: https://doi.org/10.1001/jama.2012.5521
7. Lung Cancer Screening Committee. *Providing guidance on lung cancer screening to patients and physicians*. Washington, DC: American Lung Association; 2012.
8. Field JK, Smith RA, Aberle DR, Oudkerk M, Baldwin DR, Yankelevitz D, et al. International Association for the Study of Lung Cancer Computed Tomography Screening Workshop 2011 report. *J Thorac Oncol* 2012; **7**: 10–19. doi: https://doi.org/10.1097/JTO.0b013e31823c58ab
9. Jacobson FL, Austin JH, Field JK, Jett JR, Keshavjee S, MacMahon H, et al. Development of The American Association for Thoracic Surgery guidelines for low-dose computed tomography scans to screen for lung cancer in North America: recommendations of The American Association for Thoracic Surgery Task Force for Lung Cancer Screening and Surveillance. *J Thorac Cardiovasc Surg* 2012; **144**: 25–32. doi: https://doi.org/10.1016/j.jtcvs.2012.05.059
10. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; **143**(5 Suppl): e78S–92. doi: https://doi.org/10.1378/chest.12-2350
11. Rocco G, Allen MS, Altorki NK, Asamura H, Blum MG, Detterbeck FC, et al. Clinical statement on the role of the surgeon and surgical issues relating to computed tomography screening programs for lung cancer. *Ann Thorac Surg* 2013; **96**: 357–60. doi: https://doi.org/10.1016/j.athoracsur.2013.05.067
12. Wender R, Fontham ETH, Barrera E, Colditz GA, Church TR, Ettinger DS, et al. American Cancer Society lung cancer screening guidelines. *CA: A Cancer Journal for Clinicians* 2013; **63**: 106–17. doi: https://doi.org/10.3322/caac.21172
13. ACR-STR. *ACR-STR practice parameter for the performance and reporting of lung cancer screening thoracic computed tomography (CT)*. 2014; Available from: https://www.acr.org/~/media/ACR/Documents/PGTS/

guidelines/LungScreening.pdf [Accessed April 26, 2017]
14. CMS.gov. Decision memo for screening for lung cancer with low dose computed tomography (LDCT) (CAG-00439N). 2015; Available from: https://www.cms.gov/medicare-coverage-database/details/ncadecision-memo.aspx?NCAId=274 [Accessed 26 April 2017]
15. Kauczor HU, Bonomo L, Gaga M, Nackaerts K, Peled N, Prokop M, et al. ESR/ERS white paper on lung cancer screening. *Eur Radiol* 2015; **25**: 2519–31. doi: https://doi.org/10.1007/s00330-015-3697-0
16. National Comprehensive Cancer Network. Lung Cancer Screening Version 1. 2017; Available from: https://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf [Accessed 26 April 2017].
17. Pedersen JH, Rzyman W, Veronesi G, D'Amico TA, Van Schil P, Molins L, et al. Recommendations from the European Society of Thoracic Surgeons (ESTS) regarding computed tomography screening for lung cancer in Europe. *Eur J Cardiothorac Surg* 2017; **51**: ezw418–20. doi: https://doi.org/10.1093/ejcts/ezw418
18. Lewin G, Morissette K, Dickinson J, Bell N, Bacchus M, Singh H, et al. Recommendations on screening for lung cancer. *CMAJ* 2016; **188**: 425–32. doi: https://doi.org/10.1503/cmaj.151421
19. American College of Radiology. ACR designated lung cancer screening center. 2017; Available from: http://www.acraccreditation.org/lung-cancer-screening-center [Accessed 28 April 2017].
20. Obuchowski NA, Graham RJ, Baker ME, Powell KA. Ten criteria for effective screening: their application to multislice CT screening for pulmonary and colorectal cancers. *AJR Am J Roentgenol* 2001; **176**: 1357–62. doi: https://doi.org/10.2214/ajr.176.6.1761357
21. Kaneko M, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology* 1996; **201**: 798–802. doi: https://doi.org/10.1148/radiology.201.3.8939234
22. Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999; **354**: 99–105. doi: https://doi.org/10.1016/S0140-6736(99)06093-6
23. Bach PB, Kattan MW, Thornquist MD, Kris MG, Tate RC, Barnett MJ, et al. Variations in lung cancer risk among smokers. *J Natl Cancer Inst* 2003; **95**: 470–8. doi: https://doi.org/10.1093/jnci/95.6.470
24. de Koning HJ, Meza R, Plevritis SK, ten Haaf K, Munshi VN, Jeon J, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. *Ann Intern Med* 2014; **160**: 311–20. doi: https://doi.org/10.7326/M13-2316
25. Jaklitsch MT, Jacobson FL, Austin JH, Field JK, Jett JR, Keshavjee S, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. *J Thorac Cardiovasc Surg* 2012; **144**: 33–8. doi: https://doi.org/10.1016/j.jtcvs.2012.05.060
26. Kovalchik SA, Tammemagi M, Berg CD, Caporaso NE, Riley TL, Korch M, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med* 2013; **369**: 245–54. doi: https://doi.org/10.1056/NEJMoa1301851
27. Katki HA, Kovalchik SA, Berg CD, Cheung LC, Chaturvedi AK. Development and Validation of Risk Models to Select Ever-Smokers for CT Lung Cancer Screening. *JAMA* 2016; **315**: 2300–11. doi: https://doi.org/10.1001/jama.2016.6255
28. Tammemägi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, et al. Selection criteria for lung-cancer screening. *N Engl J Med* 2013; **368**: 728–36. doi: https://doi.org/10.1056/NEJMoa1211776
29. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med* 2013; **369**: 910–9. doi: https://doi.org/10.1056/NEJMoa1214726
30. Memorial Sloan-Kettering Cancer Center website. http://www.mskcc.org/mskcc/html/12463.cfm. 2003; [Accessed May 9, 2017].
31. Siteman Cancer Center. Your Disease Risk - The Source on Prevention. 2013; Available from: http://www.yourdiseaserisk.wustl.edu/YDRDefault.aspx?ScreenControl=YDRGeneral&ScreenName=YDRCancer_Index. [Accessed May 9, 2017].
32. AHRQ. AHRQ Lung Cancer Screening Tools - Is Lung Cancer Screening Right for Me? 2016; Available from: https://effectivehealthcare.ahrq.gov/tools-and-resources/patient-decision-aids/lung-cancerscreening/patient/. [Accessed May 9, 2017].
33. Marcus MW, Chen Y, Raji OY, Duffy SW, Field JK. LLPi: Liverpool Lung Project Risk Prediction Model for Lung Cancer Incidence. *Cancer Prev Res* 2015; **8**: 570–5. doi: https://doi.org/10.1158/1940-6207.CAPR-14-0438
34. Ten Haaf K, Jeon J, Tammemägi MC, Han SS, Kong CY, Plevritis SK, et al. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. *PLoS Med* 2017; **14**: e1002277. doi: https://doi.org/10.1371/journal.pmed.1002277
35. Fischel RJ, Dillman RO. Developing an effective lung cancer program in a community hospital setting. *Clin Lung Cancer* 2009; **10**: 239–43. doi: https://doi.org/10.3816/CLC.2009.n.032
36. Miller DL, Mayfield WR, Luu TD, Helms GA, Muster AR, Beckler VJ, et al. Community-Based Multidisciplinary Computed Tomography Screening Program Improves Lung Cancer Survival. *Ann Thorac Surg* 2016; **101**: 1864–9. doi: https://doi.org/10.1016/j.athoracsur.2015.11.001
37. Park ER, Gareen IF, Japuntich S, Lennes I, Hyland K, DeMello S, et al. Primary Care Provider-Delivered Smoking Cessation Interventions and Smoking Cessation Among Participants in the National Lung Screening Trial. *JAMA Intern Med* 2015; **175**: 1509–16. doi: https://doi.org/10.1001/jamainternmed.2015.2391
38. Tammemägi MC, Berg CD, Riley TL, Cunningham CR, Taylor KL. Impact of lung cancer screening results on smoking cessation. *J Natl Cancer Inst* 2014; **106**: dju084: dju084: . doi: https://doi.org/10.1093/jnci/dju084
39. American Association of Physicists in Medicine. Lung Cancer Screening Protocols Version 4.0. 2016. Available from:http://www.aapm.org/pubs/CTProtocols/documents/LungCancerScreeningCT.pdf [Accessed 11 May 2017].
40. American Association of Physicists in Medicine. AAPM Position Statement of the Use of Bismuth Shielding for the Purpose of Dose Reduction in CT scanning. 2012; Available from: https://www.aapm.org/publicgeneral/BismuthShielding.pdf [Accessed 5 November 2017].
41. Heilmaier C, Zuber N, Bruijns B, Weishaupt D. Does real-time monitoring of patient dose with dose management software increase CT technologists' radiation awareness? *AJR Am J Roentgenol* 2016; **206**: 1049–55. doi: https://doi.org/10.2214/AJR.15.15466
42. Gierada DS, Garg K, Nath H, Strollo DC, Fagerstrom RM, Ford MB. CT quality assurance in the lung screening study component of the National Lung Screening Trial: implications for multicenter imaging

trials. *AJR Am J Roentgenol* 2009; **193**: 419–24. doi: https://doi.org/10.2214/AJR.08.1995
43. Kinsinger LS, Anderson C, Kim J, Larson M, Chan SH, King HA, et al. Implementation of Lung Cancer Screening in the Veterans Health Administration. *JAMA Intern Med* 2017; **177**: 399–406. doi: https://doi.org/10.1001/jamainternmed.2016.9022
44. American College of Radiology. Lung CT Screening Reporting and Data System (Lung-RADS). 2014. Available from: http://www.acr.org/Quality-Safety/Resources/LungRADS [Accessed 26 April 2017]
45. Gierada DS, Pilgram TK, Ford M, Fagerstrom RM, Church TR, Nath H, et al. Lung cancer: interobserver agreement on interpretation of pulmonary findings at low-dose CT screening. *Radiology* 2008; **246**: 265–72. doi: https://doi.org/10.1148/radiol.2461062097
46. Pinsky PF, Gierada DS, Nath PH, Kazerooni E, Amorosa J. National lung screening trial: variability in nodule detection rates in chest CT studies. *Radiology* 2013; **268**: 865–73. doi: https://doi.org/10.1148/radiol.13121530
47. Singh S, Pinsky P, Fineberg NS, Gierada DS, Garg K, Sun Y, et al. Evaluation of reader variability in the interpretation of follow-up CT scans at lung cancer screening. *Radiology* 2011; **259**: 263–70. doi: https://doi.org/10.1148/radiol.10101254
48. Li K, Yip R, Avila R, Henschke CI, Yankelevitz DF. Size and Growth Assessment of Pulmonary Nodules: Consequences of the Rounding. *J Thorac Oncol* 2017; **12**: 657–62. doi: https://doi.org/10.1016/j.jtho.2016.12.010
49. de Hoop B, Gietema H, van Ginneken B, Zanen P, Groenewegen G, Prokop M. A comparison of six software packages for evaluation of solid lung nodules using semi-automated volumetry: what is the minimum increase in size to detect growth in repeated CT examinations. *Eur Radiol* 2009; **19**: 800–8. doi: https://doi.org/10.1007/s00330-008-1229-x
50. Ashraf H, de Hoop B, Shaker SB, Dirksen A, Bach KS, Hansen H, et al. Lung nodule volumetry: segmentation algorithms within the same software package cannot be used interchangeably. *Eur Radiol* 2010; **20**: 1878–85. doi: https://doi.org/10.1007/s00330-010-1749-z
51. American College of Radiology. Accreditation: CT. 2017. Available from: https://www.acr.org/Quality-Safety/Accreditation [Accessed 28 April 2017].
52. Toth T, Ge Z, Daly MP. The influence of patient centering on CT dose and image noise. *Med Phys* 2007; **34**: 3093–101. doi: https://doi.org/10.1118/1.2748113
53. Goo JM, Kim KG, Gierada DS, Castro M, Bae KT. Volumetric measurements of lung nodules with multi-detector row CT: effect of changes in lung volume. *Korean J Radiol* 2006; **7**: 243–8. doi: https://doi.org/10.3348/kjr.2006.7.4.243
54. Petkovska I, Brown MS, Goldin JG, Kim HJ, McNitt-Gray MF, Abtin FG, et al. The effect of lung volume on nodule size on CT. *Acad Radiol* 2007; **14**: 476–85. doi: https://doi.org/10.1016/j.acra.2007.01.008
55. Larici AR, Storto ML, Torge M, Mereu M, Molinari F, Maggi F, et al. Automated volumetry of pulmonary nodules on multidetector CT: influence of slice thickness, reconstruction algorithm and tube current. Preliminary results. *Radiol Med* 2008; **113**: 29–42. doi: https://doi.org/10.1007/s11547-008-0231-3
56. Wielpütz MO, Lederlin M, Wroblewski J, Dinkel J, Eichinger M, Biederer J, et al. CT volumetry of artificial pulmonary nodules using an ex vivo lung phantom: influence of exposure parameters and iterative reconstruction on reproducibility. *Eur J Radiol* 2013; **82**: 1577–83. doi: https://doi.org/10.1016/j.ejrad.2013.04.035
57. Ravenel JG, Leue WM, Nietert PJ, Miller JV, Taylor KK, Silvestri GA. Pulmonary nodule volume: effects of reconstruction parameters on automated measurements--a phantom study. *Radiology* 2008; **247**: 400–8. doi: https://doi.org/10.1148/radiol.2472070868
58. Goo JM, Tongdee T, Tongdee R, Yeo K, Hildebolt CF, Bae KT. Volumetric measurement of synthetic lung nodules with multi-detector row CT: effect of various image reconstruction parameters and segmentation thresholds on measurement accuracy. *Radiology* 2005; **235**: 850–6. doi: https://doi.org/10.1148/radiol.2353040737
59. Nietert PJ, Ravenel JG, Leue WM, Miller JV, Taylor KK, Garrett-Mayer ES, et al. Imprecision in automated volume measurements of pulmonary nodules and its effect on the level of uncertainty in volume doubling time estimation. *Chest* 2009; **135**: 1580–7. doi: https://doi.org/10.1378/chest.08-2040
60. Ohkubo M, Narita A, Wada S, Murao K, Matsumoto T. Technical Note: Image filtering to make computer-aided detection robust to image reconstruction kernel choice in lung cancer CT screening. *Med Phys* 2016; **43**: 4098–. doi: https://doi.org/10.1118/1.4953247
61. Chen B, Barnhart H, Richard S, Robins M, Colsher J, Samei E. Volumetric quantification of lung nodules in CT with iterative reconstruction (ASiR and MBIR. *Med Phys* 2013; **40**: 111902. doi: https://doi.org/10.1118/1.4823463
62. Willemink MJ, Borstlap J, Takx RA, Schilham AM, Leiner T, Budde RP, et al. The effects of computed tomography with iterative reconstruction on solid pulmonary nodule volume quantification. *PLoS One* 2013; **8**: e58053. doi: https://doi.org/10.1371/journal.pone.0058053
63. Henschke CI, Yankelevitz DF, Yip R, Archer V, Zahlmann G, Krishnan K, et al. Tumor volume measurement error using computed tomography imaging in a phase II clinical trial in lung cancer. *J Med Imaging* 2016; **3**: 035505. doi: https://doi.org/10.1117/1.JMI.3.3.035505
64. Lambin P, Rios-Velazquez E, Leijenaar R, Carvalho S, van Stiphout RG, Granton P, et al. Radiomics: extracting more information from medical images using advanced feature analysis. *Eur J Cancer* 2012; **48**: 441–6. doi: https://doi.org/10.1016/j.ejca.2011.11.036
65. Aoyama M, Li Q, Katsuragawa S, Li F, Sone S, Doi K. Computerized scheme for determination of the likelihood measure of malignancy for pulmonary nodules on low-dose CT images. *Med Phys* 2003; **30**: 387–94. doi: https://doi.org/10.1118/1.1543575
66. Gierada DS, Politte DG, Zheng J, Schechtman KB, Whiting BR, Smith KE, et al. Quantitative Computed Tomography Classification of Lung Nodules: Initial Comparison of 2- and 3-Dimensional Analysis. *J Comput Assist Tomogr* 2016; **40**: 589–95. doi: https://doi.org/10.1097/RCT.0000000000000394
67. McNitt-Gray MF, Hart EM, Wyckoff N, Sayre JW, Goldin JG, Aberle DR. A pattern classification approach to characterizing solitary pulmonary nodules imaged on high resolution CT: preliminary results. *Med Phys* 1999; **26**: 880–8. doi: https://doi.org/10.1118/1.598603
68. Way TW, Sahiner B, Chan HP, Hadjiiski L, Cascade PN, Chughtai A, et al. Computer-aided diagnosis of pulmonary nodules on CT scans: improvement of classification performance with nodule surface features. *Med Phys* 2009; **36**: 3086–98. doi: https://doi.org/10.1118/1.3140589
69. Kawata Y, Niki N, Ohmatsu H, Kusumoto M, Tsuchida T, Eguchi K, et al. Quantitative classification based on CT histogram analysis of non-small cell lung cancer: correlation with histopathological characteristics and recurrence-free survival. *Med Phys* 2012; **39**: 988–1000. doi: https://doi.org/10.1118/1.3679017

70. Raghunath S, Maldonado F, Rajagopalan S, Karwoski RA, DePew ZS, Bartholmai BJ, et al. Noninvasive risk stratification of lung adenocarcinoma using quantitative computed tomography. *J Thorac Oncol* 2014; **9**: 1698–703. doi: https://doi.org/10.1097/JTO.0000000000000319
71. Gierada DS, Pinsky P, Nath H, Chiles C, Duan F, Aberle DR. Projected outcomes using different nodule sizes to define a positive CT lung cancer screening examination. *J Natl Cancer Inst* 2014; **106**. doi: https://doi.org/10.1093/jnci/dju284
72. Lee H, Um SW, Sw U. Probability of lung cancer based on the size threshold and volume-doubling time for lung nodules detected in low-dose CT screening. *Ann Transl Med* 2015; **3**: 21. doi: https://doi.org/10.3978/j.issn.2305-5839.2015.01.04
73. Yip R, Henschke CI, Yankelevitz DF, Smith JP. CT screening for lung cancer: alternative definitions of positive test result based on the national lung screening trial and international early lung cancer action program databases. *Radiology* 2014; **273**: 591–6. doi: https://doi.org/10.1148/radiol.14132950
74. Rubin GD, Lyo JK, Paik DS, Sherbondy AJ, Chow LC, Leung AN, et al. Pulmonary nodules on multi-detector row CT scans: performance comparison of radiologists and computer-aided detection. *Radiology* 2005; **234**: 274–83. doi: https://doi.org/10.1148/radiol.2341040589
75. Das M, Mühlenbruch G, Mahnken AH, Flohr TG, Gündel L, Stanzel S, et al. Small pulmonary nodules: effect of two computer-aided detection systems on radiologist performance. *Radiology* 2006; **241**: 564–71. doi: https://doi.org/10.1148/radiol.2412051139
76. Park EA, Goo JM, Lee JW, Kang CH, Lee HJ, Lee CH, et al. Efficacy of computer-aided detection system and thin-slab maximum intensity projection technique in the detection of pulmonary nodules in patients with resected metastases. *Invest Radiol* 2009; **44**: 105–13. doi: https://doi.org/10.1097/RLI.0b013e318190fcfc
77. Pinsky PF, Gierada DS, Black W, Munden R, Nath H, Aberle D, et al. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. *Ann Intern Med* 2015; **162**: 485–91. doi: https://doi.org/10.7326/M14-2086
78. McKee BJ, Regis SM, McKee AB, Flacke S, Wald C. Performance of ACR Lung-RADS in a clinical CT lung screening program. *J Am Coll Radiol* 2015; **12**: 273–6. doi: https://doi.org/10.1016/j.jacr.2014.08.004
79. Sullivan DC, Obuchowski NA, Kessler LG, Raunig DL, Gatsonis C, Huang EP, et al.Metrology standards for quantitative imaging biomarkers. *Radiology* 2015; **277**: 813–25. doi: https://doi.org/10.1148/radiol.2015142202
80. Mulshine JL, Gierada DS, Armato SG, Avila RS, Yankelevitz DF, Kazerooni EA, et al. Role of the Quantitative Imaging Biomarker Alliance in optimizing CT for the evaluation of lung cancer screen-detected nodules. *J Am Coll Radiol* 2015; **12**: 390–5. doi: https://doi.org/10.1016/j.jacr.2014.12.003
81. Radiological Society of North America. Quantitative imaging biomarkers alliance (QIBA). 2017; Available from: http://qibawiki.rsna.org/index.php/Main_Page [Accessed 5 March 2017].
82. Obuchowski NA, Barnhart HX, Buckler AJ, Pennello G, Wang XF, Kalpathy-Cramer J, et al. Statistical issues in the comparison of quantitative imaging biomarker algorithms using pulmonary nodule volume as an example. *Stat Methods Med Res* 2015; **24**: 107–40. doi: https://doi.org/10.1177/0962280214537392
83. Wormanns D, Kohl G, Klotz E, Marheine A, Beyer F, Heindel W, et al. Volumetric measurements of pulmonary nodules at multi-row detector CT: in vivo reproducibility. *Eur Radiol* 2004; **14**: 86–92. doi: https://doi.org/10.1007/s00330-003-2132-0
84. Goodman LR, Gulsun M, Washington L, Nagy PG, Piacsek KL. Inherent variability of CT lung nodule measurements in vivo using semiautomated volumetric measurements. *AJR Am J Roentgenol* 2006; **186**: 989–94. doi: https://doi.org/10.2214/AJR.04.1821
85. Gietema HA, Schaefer-Prokop CM, Mali WP, Groenewegen G, Prokop M. Pulmonary nodules: interscan variability of semiautomated volume measurements with multisection CT-- influence of inspiration level, nodule size, and segmentation performance. *Radiology* 2007; **245**: 888–94. doi: https://doi.org/10.1148/radiol.2452061054
86. Marchianò A, Calabrò E, Civelli E, Di Tolla G, Frigerio LF, Morosi C, et al. Pulmonary nodules: volume repeatability at multidetector CT lung cancer screening. *Radiology* 2009; **251**: 919–25. doi: https://doi.org/10.1148/radiol.2513081313
87. Radiological Society of North America. QIBA Profile: Lung nodule assessment in CT screening-2017. 2017. Available from: http://qibawiki.rsna.org/index.php/Small_Lung_Nodule_TF [April 26, 2017]
88. Scholten ET, Jacobs C, van Ginneken B, van Riel S, Vliegenthart R, Oudkerk M, et al. Detection and quantification of the solid component in pulmonary subsolid nodules by semiautomatic segmentation. *Eur Radiol* 2015; **25**: 488–96. doi: https://doi.org/10.1007/s00330-014-3427-z
89. Cohen JG, Goo JM, Yoo RE, Park CM, Lee CH, van Ginneken B, et al. Software performance in segmenting ground-glass and solid components of subsolid nodules in pulmonary adenocarcinomas. *Eur Radiol* 2016; **26**: 4465–74. doi: https://doi.org/10.1007/s00330-016-4317-3
90. Wang Y, van Klaveren RJ, van der Zaag-Loonen HJ, de Bock GH, Gietema HA, Xu DM, et al. Effect of nodule characteristics on variability of semiautomated volume measurements in pulmonary nodules detected in a lung cancer screening program. *Radiology* 2008; **248**: 625–31. doi: https://doi.org/10.1148/radiol.2482070957
91. Petrou M, Quint LE, Nan B, Baker LH. Pulmonary nodule volumetric measurement variability as a function of CT slice thickness and nodule morphology. *AJR Am J Roentgenol* 2007; **188**: 306–12. doi: https://doi.org/10.2214/AJR.05.1063
92. Xu DM, Gietema H, de Koning H, Vernhout R, Nackaerts K, Prokop M, et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. *Lung Cancer* 2006; **54**: 177–84. doi: https://doi.org/10.1016/j.lungcan.2006.08.006
93. van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R, et al. Management of lung nodules detected by volume CT scanning. *N Engl J Med* 2009; **361**: 2221–9. doi: https://doi.org/10.1056/NEJMoa0906085
94. Ko JP, Berman EJ, Kaur M, Babb JS, Bomsztyk E, Greenberg AK, et al. Pulmonary nodules: growth rate assessment in patients by using serial CT and three-dimensional volumetry. *Radiology* 2012; **262**: 662–71. doi: https://doi.org/10.1148/radiol.11100878
95. Li F, Aoyama M, Shiraishi J, Abe H, Li Q, Suzuki K, et al. Radiologists' performance for differentiating benign from malignant lung nodules on high-resolution CT using computer-estimated likelihood of malignancy. *AJR Am J Roentgenol* 2004; **183**: 1209–15. doi: https://doi.org/10.2214/ajr.183.5.1831209
96. Way T, Chan HP, Hadjiiski L, Sahiner B, Chughtai A, Song TK, et al. Computer-aided

diagnosis of lung nodules on CT scans: ROC study of its effect on radiologists' performance. *Acad Radiol* 2010; **17**: 323–32. doi: https://doi.org/10.1016/j.acra.2009.10.016

97. Cheng JZ, Ni D, Chou YH, Qin J, Tiu CM, Chang YC, et al. Computer-aided diagnosis with deep learning architecture: applications to breast lesions in US images and pulmonary nodules in CT scans. *Sci Rep* 2016; **6**: 24454. doi: https://doi.org/10.1038/srep24454
98. Li W, Cao P, Zhao D, Wang J. Pulmonary nodule classification with deep convolutional neural networks on computed tomography images. *Comput Math Methods Med* 2016; **2016**: 1–7. doi: https://doi.org/10.1155/2016/6215085
99. Erickson BJ, Korfiatis P, Akkus Z, Kline TL. Machine learning for medical imaging. *Radiographics* 2017; **37**: 505–15. doi: https://doi.org/10.1148/rg.2017160130
100. Morgan L, Choi H, Reid M, Khawaja A, Mazzone PJ. Frequency of incidental findings and subsequent cvaluation in low-dose CT scans for lung cancer screening. *Ann Am Thorac Soc* 2017; **14**: 1450–6. doi: https://doi.org/10.1513/AnnalsATS.201612-1023OC