QIBA Profile:

Small Lung Nodule Volume Assessment and Monitoring in Low Dose CT Screening

Stage: Publicly Reviewed (draft)

When referencing this document, please use the following format:

CT Volumetry Technical Committee. Lung Nodule Assessment in CT Screening Profile - 2017, Quantitative Imaging Biomarkers Alliance. Publicly Reviewed Draft. QIBA.

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Change Log

This table is a best-effort of the authors to summarize significant changes to the Profile.

Date	Sections Affected	Summary of Change
2017.08.24	Section 4	Modifications made to indicate that compliance with the profile can be performed with any QIBA-approved phantom or analysis methods.
2015.08.24	Change Log	A “Change Log” section was added to the document immediately before the Executive Summary which includes an “Open Issues” area and a “Closed Issues” area.

Open Issues:

The following issues are provided here to capture associated discussion, to focus the attention of reviewers on topics needing feedback, and to track them so they are ultimately resolved. In particular, comments on these issues are highly encouraged during the Public Comment stage.

Q. PSF is one approach to expressing resolution in a CT image, but there are other approaches that are also used in the CT medical physics community (e.g. MTF50). Can this Profile support both representations?

A. The current version of the profile mainly provides resolution values in PSF units. However, two equations and a reference are also provided for converting between a PSF representation and an MTF50 representation. Future versions of this profile can provide specifications in both a PSF representation and an MTF50 representation in more places within the profile.

Q. The use of four materials (Air, Acrylic, Delrin, and Teflon) to measure HU bias and noise appears to be more than necessary to determine the performance of a scanner and protocol for supporting CT lung nodule measurements. Can this Profile safely eliminate some of these additional material measurements?

A. It is agreed that less than four phantom materials are needed to understand the impact of HU bias on volumetric solid lung nodule performance. The main two materials are Air and Acrylic. This is because the measurement of a solid lung nodule is primarily determined by a nodule surface intensity gradient that transitions from background lung parenchyma (consisting mainly of Air) to nodule tissue (approximately water HU which is close to Acrylic HU attenuation). Thus, a large HU bias in these two materials has the potential to impact volumetric lung nodule measurement performance. The Profile has been modified to place limits on HU bias only in Air and Acrylic materials and further modified to place noise limits only measured in an Acrylic material. However, it should be noted that the measurement of large amounts of bias and noise within additional materials has the potential to identify image acquisition and reconstruction artifacts that can impact lung nodule volume measurements. The issue of the optimal set of materials to measure HU bias and noise will be revisited in future Profile versions after the collection of more data using the currently proposed phantom, and other QIBA-approved phantoms.

Q. The performance of this Profile for different scanners, reconstruction algorithms, and lesion shapes needs further supporting data and study. Can this Profile perform additional studies to verify that the proposed methods will perform within specifications under varying conditions?

A. Yes. Additional data collection and studies will be performed with the proposed phantom, and other QIBA-approved phantoms, that will provide data with which to make evidence-based adjustments to this Profile.

Q. The Profile places limits on edge enhancement and spatial warping. Are these metrics necessary for establishing solid lung nodule measurement performance?

A. Spatial warping for some scanners that are permitted by this Profile can significantly increase the variance of volumetric change measurements of solid lung nodules, as has been published in Henschke, et al., JMI 2016 (https://www.ncbi.nlm.nih.gov/pubmed/27660808). Edge enhancing recon kernels are known to non-isotropically bias gradient edges making nodule segmentation more challenging for multiple critical components of commonly used segmentation algorithms. In addition, edge enhancement biases the estimation of CT scanner inherent resolution, which strongly impacts solid nodule measurement performance and makes measurement performance orientation dependent. Nevertheless, it is possible that the current requirements are more stringent than necessary. The specifications currently set for these Profile requirements will be further evaluated after additional data has been acquired with the proposed phantom, and other QIBA-approved phantoms. In addition, improved descriptions of measurement methods, including figures, will be added to the Profile.

Closed Issues:

The following issues have been considered closed by the biomarker committee. They are provided here to forestall discussion of issues that have already been raised and resolved, and to provide a record of the rationale behind the resolution.

Q. Is this template open to further revisions?
A. Yes.

This is an iterative process by nature.
Submit issues and new suggestions/ideas to the QIBA Process Cmte.

Q.
A.

1. Executive Summary

The goal of a QIBA Profile is to help achieve a useful level of performance for a given biomarker.

The **Claim** (Section 2) describes the biomarker performance.
The **Profile Activities** (Section 3) contribute to generating the biomarker. Requirements are placed on the **Actors** that participate in those activities as necessary to achieve the Claim.
Assessment Procedures (Section 4) defines the technical methods to be used for evaluating conformance with profile requirements. This includes the steps needed for clinical sites and equipment vendors to be compliant with the profile.

This QIBA Profile (Lung Nodule Volume Assessment and Monitoring in Low Dose CT Screening) addresses the accuracy and precision of quantitative CT volumetry as applied to solid lung nodules of 6-12 mm diameter. It places requirements on Acquisition Devices, Technologists, Radiologists and Image Analysis

Tools involved in activities including Periodic Equipment Quality Assurance, Subject Selection, Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image Quality Assurance, and Image Analysis.

The requirements are focused on achieving sufficient accuracy and avoiding unnecessary variability of the lung nodule volume measurement.

Two sets of claims are provided within this profile. The first claim establishes 95% confidence intervals for volumetric measurement of solid lung nodules that fall within four different diameter and volume size ranges. The second claim provides guidance on the amount of volumetric change percentage needed for an observer to have 95% confidence that the nodule has to exhibited true change. In addition, the second claim also provides guidance on the 95% confidence interval for a volumetric size change measurement, again based on the size of the nodule at two time points.

This document is intended to help clinicians basing decisions on this biomarker, imaging staff generating this biomarker, vendor staff developing related products, purchasers of such products and investigators designing trials with imaging endpoints.

Note that this Profile document only states requirements to achieve the claim, not "requirements on standard of care." Further, meeting the goals of this Profile is secondary to properly caring for the patient.

QIBA Profiles addressing other imaging biomarkers using CT, MRI, PET and Ultrasound can be found at qibawiki.rsna.org.

2. Clinical Context and Claims

Clinical Context

The clinical context of this profile is the quantification of volumes and volume changes over time of solid lung nodules with a longest diameter between 6 mm and 12 mm. Nodules with diameter ≥ 12 mm (volume ≥ 905 mm^3) are the subject of the document "QIBA Profile: CT Tumor Volume Change (CTV-1)".

Conformance with this Profile by all relevant staff and equipment supports the following claims

Claim 1: Nodule Volume

For a measured nodule volume of Y, and a CV as specified in table 1, the 95% confidence interval for the true nodule volume is $Y \pm (1.96 \times Y \times CV)$.

Claim 2: Nodule Volume Change

(a) A measured nodule volume percentage change of X indicates that a true change in nodule volume has occurred if X > (2.77 x CV1 x 100), with 95% confidence.

(b) If Y_1 and Y_2 are the volume measurements at the two time points, and CV1 and CV2 are the corresponding values from Table 1, then the 95% confidence interval for the nodule volume change $Z = (Y_2-Y_1) \pm 1.96 \times \sqrt{[Y_1 \times CV1]^2 + [Y_2 \times CV2]^2}$.

These Claims hold when:

- **the nodule is completely solid**
- **the nodule longest dimension in the transverse (axial) plane is between 6 mm (volume 113 mm3) and 12 mm (volume 905 mm3) at the first time point**
- **the nodule's shortest diameter in any dimension is at least 60% of the nodule's longest diameter in any dimension (i.e., the nodule shape does not deviate excessively from spherical)**
- **the nodule is measurable at both time points (i.e., margins are distinct from surrounding structures of similar attenuation and geometrically simple enough to be segmented using automated software without manual editing)**

Table 1. Coefficients of Variation (CV)

Nodule Diameter (mm)	Nodule Volume (mm^3)	Coefficient of Variation (CV)	True Volume 95% CI Limits (mm^3)
6 mm	113	0.29	± 64
7 mm	154	0.23	± 69
8 mm	268	0.19	± 100
9 mm	382	0.16	± 120
10 mm	524	0.14	± 144
11 mm	697	0.12	± 164
12 mm	905	0.11	± 195

Deleted: 22%

Discussion

Low dose CT provides an effective means of detecting and monitoring pulmonary nodules, and can lead to increased survival (1) and reduced mortality (2) in individuals at high risk for lung cancer. Size quantification on serial imaging is helpful in evaluating whether a pulmonary nodule is benign or malignant. Currently, pulmonary nodule measurements most commonly are obtained as the average of two perpendicular dimensions on axial slices. Investigators have suggested that automated quantification of whole nodule volume could solve some of the limitations of manual diameter measurements (3-9), and many studies have explored the accuracy in phantoms (10-18) and the in vivo precision (19-25) of volumetric CT methods. This document proposes standardized methods for performing repeatable volume measurements on CT images of solid pulmonary nodules obtained using a reduced radiation dose in the setting of lung cancer screening and nodule follow-up in the interval between scans (52).

Lung cancer CT screening presents the challenge of developing a protocol that balances the benefit of detecting and accurately characterizing lung nodules against the potential risk of radiation exposure in this asymptomatic population of persons who may undergo annual screening for more than two decades. Our understanding of the extent to which performing scans at the lowest dose possible with the associated increase in noise affects our ability to accurately measure these small nodules is still evolving. Therefore, any protocol will involve a compromise between these competing needs.

This QIBA Profile makes Claims about the confidence with which lung nodule volume and changes in lung nodule volume can be measured under a set of defined image acquisition, processing, and analysis conditions, and provides specifications that may be adopted by users and equipment developers to meet targeted levels of clinical performance in identified settings. The intended audiences of this document include healthcare professionals and all other stakeholders invested in lung cancer screening, including but not limited to:

- Radiologists, technologists, and physicists designing protocols for CT screening
- Radiologists, technologists, physicists, and administrators at healthcare institutions considering specifications for procuring new CT equipment
- Technical staff of software and device manufacturers who create products for this purpose
- Biopharmaceutical companies
- Clinicians engaged in screening process
- Clinical trialists
- Radiologists and other health care providers making quantitative measurements on CT images
- Oncologists, regulators, professional societies, and others making decisions based on quantitative image measurements
- Radiologists, health care providers, administrators and government officials developing and implementing policies for lung cancer screening

Note that specifications stated as “requirements” in this document are only requirements to achieve the Claim, not “requirements on standard of care.” Specifically, meeting the goals of this Profile is secondary to properly caring for the patient.

This Profile is relevant to asymptomatic persons participating in a CT screening and surveillance program for lung cancer. In theory, the activities covered in this Profile also pertain to patients with known or incidentally-detected solid pulmonary nodules in the 6-12 mm diameter range, though surveillance in this or other settings is not specifically addressed by this Profile.

Clinical Interpretation For Claim 1 (nodule volume)

The true size of a nodule is defined by the measured volume and the 95% confidence intervals. The confidence intervals can be thought of as "error bars" or "uncertainty" or "noise" around the measurement, and the true volume of the nodule is somewhere within the confidence intervals. Application of these Claims to clinical practice is illustrated by the following examples:

Example 1: A nodule is measured as having a volume of 150 mm^3 (6.6 mm diameter). There is a 95% probability that the true volume of the nodule is between 65 mm^3 [150 – (150 x 1.96 x 0.29)] (5.0 mm diameter) and 235 mm^3 [150 + (150 x 1.96 x 0.29)] (7.7 mm diameter).

Example 2: A nodule is measured as having a volume of 500 mm^3 (9.8 mm diameter). There is a 95% probability that the true volume of the nodule is between 343 mm^3 [500 - (500 x 1.96 x 0.16)] (8.7 mm diameter) and 657 mm^3 [500 + (500 x 1.96 x 0.16)] (10.8 mm diameter).

Example 3: A nodule is measured as having a volume of 800 mm^3 (11.5 mm diameter). There is a 95% probability that the true volume of the nodule is between 612 mm^3 [800 - (800 x 1.96 x 0.12)] (10.5 mm diameter) and 988 mm^3 [800 + (800 x 1.96 x 0.12)] (12.4 mm diameter).

If the activities specified in this Profile are followed, the measured volume of nodules in each of the given size ranges can be considered accurate to within the given 95% confidence limits. The different coefficients of variation of the different nodule size ranges in Claim 1 reflect the increasing variability introduced as the resolution limits of the measuring device are approached, and the likely impact of variations permitted by the Specifications of this Profile.

The guidance provided here represents an estimate of minimum measurement error when conforming to the Profile over a wide range of scanner models. However, these estimates can be reduced substantially when using more advanced scanning equipment with improved performance characteristics.

These Claims have been informed by clinical trial data, theoretical analysis, simulations, review of the literature, and expert consensus. They have not yet been fully substantiated by studies that strictly conform to the specifications given here. The expectation is that during implementation in the clinical setting, data on the actual performance will be collected and any appropriate changes made to the Claim or the details of the Profile. At that point, this caveat may be removed or re-stated.

Clinical Interpretation For Claim 2 (nodule volume change)

The precision value in the Claim statement is the change necessary to be 95% certain that there has really been a change. If a tumor changes size beyond these limits, you can be 95% confident there has been a true change in the size of the tumor, and the perceived change is not just measurement variability. Note that this does not address the biological significance of the change, just the likelihood that the measured change is real.

Application of these Claims to clinical practice is illustrated by the following examples:

Example 1: A nodule measuring 524 mm^3 at baseline (10.0 mm diameter) measures 917 mm^3 (12.0 mm diameter) at follow-up, for a measured volume change of +393 mm^3 (or a 75% increase in volume) [i.e. (917-524)/524 x 100 = 75%]. For this 10 mm nodule at baseline, we apply the CV from the fifth row of Table 1: since 75% > 39% [i.e. 75% > 2.77 x 0.14 x 100], we are 95% confident that the measured change represents a real change in nodule volume. To quantify the magnitude of the change, we construct the 95% confidence for the true change. The 95% confidence interval for the true change is (917-524) ± 1.96 x √([0.14 x 524]^2 + [0.11 x 917]^2), which equals 393 ± 244. The 95% CI for the change in volume is thus [149 mm^3 – 637 mm^3]. This means that the nodule at time point 2 is between 149 and 637 mm^3 larger than at baseline.

Example 2: A nodule measuring 180 mm^3 at baseline (7.0 mm diameter) measures 270 mm^3 (8.0 mm diameter) at follow-up, for a measured volume change of 90 mm^3, or +50% [i.e. (270-180)/180 x 100 = 50%]. Since this was a 7 mm nodule at baseline, we apply the CV from the first row of the table: since 50% < 80% [i.e. 50% < 2.77 x 0.23 x 100]; we cannot be confident that this measured change represents a real change in the tumor volume.

If the activities specified in this Profile are followed, the measured change in volume of nodules in each of the given size ranges can be considered accurate to within the given 95% confidence limits. The different coefficients of variation of the different nodule size ranges in Claim 1 reflect the increasing variability introduced as the resolution limits of the measuring device are approached, and the likely impact of variations permitted by the Specifications of this Profile.

These Claims represent the repeatability coefficient ($RC = 1.96 \times \sqrt{2} \times wCV$) for nodules in each size range. The Claims have been informed by clinical trial data, theoretical analysis, simulations, review of the literature, and expert consensus. They have not yet been fully substantiated by studies that strictly conform to the specifications given here. The expectation is that during implementation in the clinical setting, data on the actual performance will be collected and any appropriate changes made to the Claim or the details of the Profile. At that point, this caveat may be removed or re-stated.

Claim 2 assumes the same compliant actors (acquisition device, radiologist, image analysis tool, etc.) at the two time points. If one or more of the actors are different, it is expected that the measurement performance will be reduced.

A web based calculator for computing the equations in the Claims is available at http://www.accumetra.com/NoduleCalculator.html.

3. Profile Activities

The Profile is documented in terms of "Actors" performing "Activities". Equipment, software, staff, or sites may claim conformance to this Profile as one or more of the "Actors" in the following table.

Conformant Actors shall support the listed Activities by demonstrating conformance to all Requirements in the referenced Section.

Table 3-1: Actors and Required Activities

Actor	Activity	Section
Acquisition Device	Product Validation	3.1
Image Analysis Tool	Product Validation	3.1
Technologist	Staff Qualification	3.2
	Subject Handling	3.6
	Image Data Acquisition	3.7
	Image Data Reconstruction	3.8
	Image Quality Assurance	3.9
Radiologist	Staff Qualification	3.2
	Protocol Design	3.4
	Subject Selection	3.5
	Subject Handling	3.6
Physicist	Equipment Quality Assurance	3.3
	Protocol Design	3.4
Referring Clinician	Subject Selection	3.5
Image Analyst	Staff Qualification	3.2
	Image Quality Assurance	3.9
	Image Analysis	3.10

Formal **claims of conformance** by the organization responsible for an Actor shall be in the form of a published **QIBA Conformance Statement**. Manufacturers publishing a QIBA Conformance Statement shall

provide a set of "Model-specific Parameters" describing how their product was configured to achieve conformance.

The Specifications and Assessment Procedures described in Sections 3 & 4 of this Profile reflect those expected in standard clinical CT practice, including the settings in which the data that support the Claims of this Profile were acquired. There is potential to specify more rigorous assessment procedures for both CT equipment and analysis tool software that justify a reduction in the measurement variance found in the current Claims. Through continued investigation of technical sources of variance, and quantitative characterization of the improvements in accuracy and precision that can be achieved by further refining the Specifications of this Profile, it is anticipated that future versions of this Profile will contain both improved Claims and more specific Assessment Procedures relevant to quantitative imaging.

The requirements in this Profile do not codify a Standard of Care; they only provide guidance intended to achieve the stated Claims. Failing to comply with a "shall" in this Profile is a protocol deviation. Although deviations invalidate the Profile Claims, such deviations may be reasonable and unavoidable and the radiologist or supervising physician is expected to do so when required by the best interest of the patient or research subject. How study sponsors and others decide to handle deviations for their own purposes is entirely up to them.

For the Acquisition Device and Image Analysis Tool actors, while it will typically be the manufacturer who claims the actor is conformant, it is certainly possible for a site to run the necessary tests/checks to confirm conformance and make a corresponding claim. This might happen if a manufacturer is no longer promoting an older model device but a site needs a conformance statement to participate in a clinical trial.

The Physicist actor is the preferred person at the site responsible for managing the equipment performance related specifications. At some sites this will be a staff physicist, and at other sites it may be a person who manages a contractor or a service provided by a vendor.

The sequencing of the Activities specified in this Profile is shown in Figure 1:

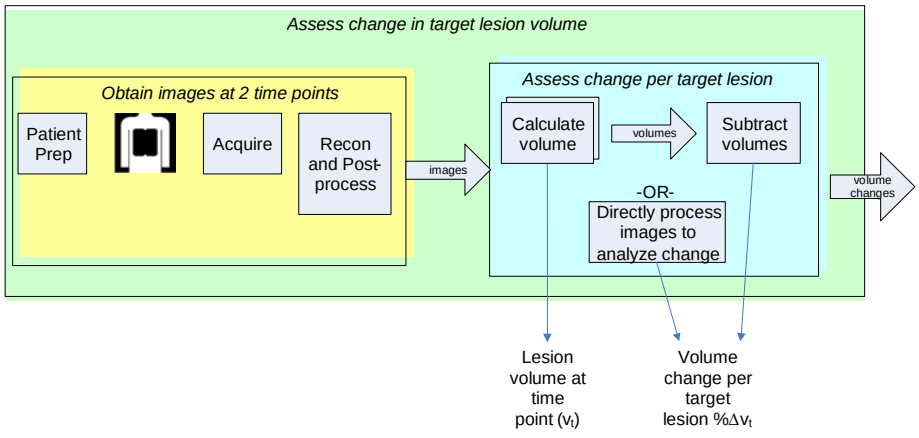

Figure 1: CT Tumor Volumetry - Activity Sequence

The method for measuring change in tumor volume may be described as a multistage process. Subjects are prepared for scanning, raw image data is acquired, images are reconstructed and possibly post-processed. Such images are obtained at one or more time points. Image analysis assesses the degree of change between two time points for each evaluable target nodule by calculating absolute volume at each time point and subtracting. When expressed as a percentage, volume change is the difference in volume between the two time points divided by the volume at time point 1. Although this introduces some asymmetry (volume measurements of 50cm^3 and 100cm^3 represent either a 100% increase or a 50% decrease depending on which was measured first), it is more familiar to clinicians than using the average of the two timepoints as the denominator.

The change may be interpreted according to a variety of different response criteria. These response criteria are beyond the scope of this document. Detection and classification of nodules are also beyond the scope of this document.

The Profile does not intend to discourage innovation, although it strives to ensure that methods permitted by the profile requirements will result in performance that meets the Profile Claim. The above pipeline provides a reference model. Algorithms which achieve the same result as the reference model but use different methods may be permitted, for example by directly measuring the change between two image sets rather than measuring the absolute volumes separately. Developers of such algorithms are encouraged to work with the appropriate QIBA committee to conduct any groundwork and assessment procedure revisions needed to demonstrate the requisite performance.

The requirements included herein are intended to establish a baseline level of capabilities. Providing higher performance or advanced capabilities is both allowed and encouraged. The Profile does not intend to limit how equipment suppliers meet these requirements.

3.1. Product Validation

This activity involves evaluating the product Actors (Acquisition Device and Image Analysis Tool) prior to their use in the Profile (e.g. at the factory). It includes validations and performance assessments that are necessary to reliably meet the Profile Claim.

3.1.1 Discussion

Performance measurements of specific protocols are not addressed here. Those are included in section 3.4.2.

The **Number of Detector Rows** can influence the scan duration, z-axis resolution, and radiation dose. A primary consideration leading to the requirement that CT scanners have a minimum of 16 detector rows is the desire for the **Scan Duration** to be no greater than the time for imaging the entire length of the lungs in a single breath-hold, to minimize motion artifacts, at a pitch that provides adequate z-axis resolution. Scanners with fewer than 16 detectors and pitch high enough to allow the entire lung to be scanned in a single breath hold may result in Z-axis resolution that is inadequate for nodule volumetry in some patients (52). Published investigations have demonstrated the accuracy of CT nodule volumetry meeting the Claims of this Profile using 16-detector scanners.

299 3.1.2 Specification

Parameter	Actor	Requirement
Acquisition Protocol	Acquisition Device	Shall be capable of storing protocols and performing scans with all the parameters set as specified in section 3.4.2 "Protocol Design Specification".
	Acquisition Device	Shall prepare a protocol conformant with section 3.4.2 "Protocol Design Specification" and validate that protocol as described in section 3.4.2.
Acquisition Protocol Variation	Acquisition Device	Shall also validate the protocol under varying conditions from each preferred protocol setting using a Design of Experiments (DOE) approach. See section 4.2 Equipment Vendor Procedures for more information on DOE methods.
Acquisition Consistency	Image Analyst, Physicist and Technologist	Shall use the same compliant scanner and acquisition protocol for acquisition of all time points.
Reading Consistency	Image Analyst	Shall analyze all time points and shall use the same conformant image analysis tool at all analysis time points.
Number of Detector Rows	Acquisition Device	Shall have 16 or more detector rows.
Image Header	Acquisition Device	Shall record in the DICOM image header the actual values for the tags listed in the DICOM Tag column in section 3.4.2 "Protocol Design Specification".
Reading Paradigm	Image Analysis Tool	Shall present Images from both time points side-by-side for comparison.
Change Calculation	Image Analysis Tool	Shall calculate change as the difference in volume between two time points relative to the volume at the earlier time point, expressed in mm^3 units.
Scientific Validation	Image Analysis Tool	Shall have appropriate scientific validation, including the properties of measurement linearity, coefficient of variation, and zero bias.

300

301 ## 3.2. Staff Qualification

302 This activity involves evaluating the human Actors (Radiologist, Physicist, and Technologist) prior to their
303 participation in the Profile. It includes training, qualification or performance assessments that are
304 necessary to reliably meet the Profile Claim.

305 3.2.1 Discussion

306 These requirements, as with any QIBA Profile requirements, are focused on achieving the Profile Claim.
307 Evaluating the medical or professional qualifications of participating actors is beyond the scope of this
308 profile.

309 In clinical practice, it is expected that the **Radiologist** interpreting the examination often will be the **Image**
310 **Analyst**. In some clinical practice situations, and in the clinical research setting, the image analyst may be a
311 non-radiologist professional.

312 **Analyst Training** should be at a level appropriate for the setting and the purpose of the measurements, and
313 may include instruction in topics such as the generation and components of volumetric CT images;

principles of image reconstruction and processing; technical factors influencing quantitative assessment; relevant CT anatomy; definition of a nodule; and image artifacts.

3.2.2 Specification

Parameter	Actor	Specification
ACR Accreditation	Radiologist	Shall fulfill the qualifications required by the American College of Radiology CT Accreditation Program. These include certification by the American Board of Radiology or analogous non-U.S. certifying organization; appropriate licensing; documented oversight, interpretation, and reporting of the required ABR minimum number of CT examinations; and compliance with ABR and licensing board continuing education requirements. See:http://www.acr.org/~/media/ACR/Documents/Accreditation/CT/Requirements
	Technologist	Shall fulfill the qualifications required by the American College of Radiology CT Accreditation Program. These include certification by the American Registry of Radiologic Technologists or analogous non-U.S. certifying organization, appropriate licensing, documented training and experience in performing CT, and compliance with certifying and licensing organization continuing education requirements. See:http://www.acr.org/~/media/ACR/Documents/Accreditation/CT/Requirements
Analyst Training	Image Analyst	Shall undergo documented training in performing CT image volumetric analysis of lung nodules in lung cancer screening by a radiologist having qualifications conforming to the requirements of this profile. Note: if the Image Analyst is a Profile-conformant Radiologist, additional training is not required.

3.3. Equipment Quality Assurance

This activity involves quality assurance of the imaging devices that is not directly associated with a specific subject. It includes calibrations, phantom imaging, performance assessments or validations that are necessary to reliably meet the Profile Claim.

3.3.1 Discussion

This activity is focused on ensuring that the acquisition device is aligned/calibrated/functioning normally. Performance measurements of specific protocols are not addressed here. Those are included in section 3.4.

Conformance with this Profile requires adherence of CT equipment to U.S. federal regulations (21CFR1020.33) or analogous regulations outside of the U.S., CT equipment performance evaluation procedures of the American College of Radiology CT Accreditation Program (http://www.acr.org/~/media/ACR/Documents/Accreditation/CT/Requirements), and quality control

procedures of the scanner manufacturer. These assessment procedures include a technical performance evaluation of the CT scanner by a qualified medical physicist at least annually. Parameters evaluated include those critical for quantitative volumetric assessment of small nodules, such as spatial resolution, section thickness, and table travel accuracy, as well as dosimetry. Daily quality control must include monitoring of water CT number and standard deviation and artifacts. In addition, preventive maintenance at appropriate regular intervals must be conducted and documented by a qualified service engineer.

These specifications reflect the clinical and clinical trial settings which produced the data used to support the Claims of this Profile. Data were obtained from a broad range of CT scanner models having a range of performance capabilities that is reflected in the size of the confidence bounds of the Claims. Ongoing research is identifying the key technical parameters determining performance in the lung cancer screening setting, and establishing metrics that may allow Claims with narrower confidence bounds than are found in this Profile to be met for certain CT scanners through more specific technical specifications and associated assessment procedures. Such metrics and assessment procedures more specific to CT volumetry in lung cancer screening will be addressed in subsequent versions of this Profile.

3.3.2 Specification

Parameter	Actor	Requirement
Quality Control	Physicist	Shall perform quality control procedures consistent with those generally accepted for routine clinical imaging.
Quality Control	Physicist	Shall adhere to installation and periodic quality control procedures specified by the scanner manufacturer and the American College of Radiology CT Accreditation Program. See http://www.acr.org/~/media/ACR/Documents/Accreditation/CT/Requirements
Maintenance	Physicist	Shall ensure that preventive maintenance at appropriate regular intervals are conducted and documented by a qualified service engineer as recommended by the scanner manufacturer.

3.4. Protocol Design

This activity involves designing acquisition and reconstruction protocols for use with the Profile. It includes constraints on protocol acquisition and reconstruction parameters that are necessary to reliably meet the Profile Claim.

3.4.1 Discussion

The Profile considers Protocol Design to take place at the imaging site, however sites may choose to make use of protocols developed elsewhere.

The approach of the specifications here, is to focus as much as possible on the characteristics of the resulting dataset, rather than one particular technique for achieving those characteristics. This is intended to allow as much flexibility as possible for product innovation and reasonable adjustments for patient size (such as increasing acquisition mAs and reconstruction DFOV for larger patients), while reaching the performance targets. Again, the technique parameter sets provided by vendors in their Conformance Statements may be helpful for those looking for more guidance.

Automatic Exposure Control aims to achieve consistent noise levels throughout the lungs by varying the tube current during scan acquisition. Use of automatic exposure control is expected to have little effect on Profile Claims and is considered optional, though as with other acquisition parameters its use should be consistent with baseline. This scanner feature may be a useful tool for reducing unnecessary radiation exposure in certain patients, but it also can increase radiation exposure depending on the target noise level, patient size and anatomy, and the method employed by the vendor. These factors should be kept in mind when deciding whether to use automatic exposure control in an individual patient.

Rotation Time may vary as needed to achieve other settings. Generally, it will be less than or equal to 0.5 seconds.

In CT screening for lung cancer, the choice of scan acquisition parameters is strongly influenced by the desire to minimize radiation dose. The radiation dose delivered by volumetric CT scanning is indicated by the volume CT Dose Index (CTDIvol). The CTDIvol should be chosen to provide the lowest radiation dose that maintains acceptable image quality for detecting pulmonary nodules. Variability in CT nodule volumetry using low dose techniques is comparable to that of standard dose techniques (14, 16-18, 29). As a general guideline, CTDIvol ≤3 mGy should provide sufficient image quality for a person of standard size, defined by the International Commission on Radiation Protection (ICRP) as 5'7"/170 cm and 154 lbs/70 kg. The CTDIvol should be reduced for smaller individuals and may need to be increased for larger individuals, but should be kept constant for the same person at all time points. CTDIvol is determined by the interaction of multiple parameters, including the Tube Potential (kV), Tube Current (mA), tube Rotation Time, and Pitch. Settings for kV, mA, rotation time, and pitch may be varied as needed to achieve the desired CTDIvol. Pitch is chosen so as to allow completion of the scan in a single breath hold with adequate spatial resolution along the subject z-axis.

Nominal Tomographic Section Thickness (T), the term preferred by the International Electrotechnical Commission (IEC), is sometimes also called the Single Collimation Width. Choices depend on the detector geometry inherent in the particular scanner model. The Nominal Tomographic Section Thickness affects the spatial resolution along the subject z-axis and the available options for reconstructed section thickness. Thinner sections that allow reconstruction of smaller voxels are preferable, to reduce partial volume effects and provide higher accuracy due to greater spatial resolution.

Reconstruction Kernel is recommended to be a medium smooth to medium sharp kernel that provides the highest resolution available without edge enhancement.

X-ray CT uses ionizing radiation. Exposure to radiation can pose risks; however as the radiation dose is reduced, image quality can be degraded. It is expected that health care professionals will balance the need for good image quality with the risks of radiation exposure on a case-by-case basis. It is not within the scope of this document to describe how these trade-offs should be resolved.

3.4.2 Specification

Note: The Radiologist is responsible for the protocol parameter requirements, although they may choose to use a protocol provided by the vendor of the acquisition device. The Radiologist is also responsible for ensuring that protocol validation has taken place (e.g. when it is created or modified), although the Physicist actor or the Technologist actor may also perform the validation. The role of the Physicist actor may be played by an in-house medical physicist, a physics consultant or other staff (such as vendor service

399 or specialists) qualified to perform the validations described.
400

Parameter	Actor	Specification	DICOM Tag
Acquisition Protocol	Radiologist	Shall prepare a protocol to meet the specifications in this table. Shall ensure technologists have been trained on the requirements of this profile.	
IEC Pitch	Radiologist	Shall set IEC Pitch to less than or equal to 2.0 for single source scanners, or the equivalent for dual source scanners.	Spiral Pitch Factor (0018,9311)
Nominal Tomographic Section Thickness (T)	Radiologist	Shall set the nominal tomographic section thickness to achieve reconstructed slice thickness less than or equal to 1.25mm.	Single Collimation Width (0018,9306)
Reconstruction Protocol	Radiologist	Shall prepare a protocol to meet the specifications in this table. Shall ensure technologists have been trained on the requirements of this profile.	
Reconstructed Image Thickness	Radiologist	Shall set to less than or equal 1.25mm.	Slice Thickness (0018,0050)
Reconstructed Image Interval	Radiologist	Shall set the reconstructed image interval to less than or equal to the Reconstructed Image Thickness (i.e. no gap, may have overlap).	Spacing Between Slices (0018,0088)
Resolution	Radiologist	Shall validate that the protocol achieves: • A 3D PSF sigma ellipsoid volume of less than or equal to 1.5mm^3, and • A Z PSF sigma less than two times larger than the in-plane PSF sigma.	
Edge Enhancement	Radiologist	Shall validate that the protocol does not result in edge enhancement exceeding 5%.	
HU Deviation	Radiologist	Shall validate that the protocol results in CT HU value deviation of less than 35 HU for Air and Acrylic materials.	
Voxel Noise	Radiologist	Shall validate that the protocol achieves a standard deviation that is <= 50 HU for homogeneous Air and Acrylic materials.	
Spatial Warping	Radiologist	Shall validate that 3D image acquisition results in Spatial warping of less than 0.5mm Root Mean Square Error (RMSE).	

3.5. Subject Selection

This activity describes criteria and procedures related to the selection of appropriate imaging subjects that are necessary to reliably meet the Profile Claim.

3.5.1 Discussion

Pulmonary Symptoms may signify acute or subacute abnormalities in the lungs that could interfere with or alter pulmonary nodule volume measurements, or prevent full cooperation with breath-holding instructions for scanning. Therefore, subjects should be asymptomatic, or at baseline if symptomatic, with respect to cardiac and pulmonary symptoms. If scanning is necessary to avoid an excessive delay in follow-up of a known nodule or to evaluate new symptoms, and these clinical status conditions cannot be met then measurements may not be of sufficient quality to fulfill the Profile Claims. Chronic abnormalities such as pulmonary fibrosis also may invalidate Profile Claims if they affect nodule volume measurement accuracy.

Recent diagnostic or therapeutic **Medical Procedures** may result in parenchymal lung abnormalities that increase lung attenuation around a nodule and invalidate the Claims of this Profile. Examples include bronchoscopy, thoracic surgery, and radiation therapy.

Oral contrast administered for unrelated gastrointestinal imaging studies or abdominal CT that remains in the esophagus, stomach, or bowel may cause artifacts in certain areas of the lungs that interfere with quantitative nodule assessment. If artifacts due to oral contrast are present in the same transverse planes as a quantifiable lung nodule, the Profile Claims may not be valid.

3.5.2 SPECIFICATION

Parameter	Actor	Requirement
Medical Procedures	Referring clinician	Shall schedule scanning prior to or at an appropriate time following procedures that could alter the attenuation of the lung nodule or surrounding lung tissue.
	Radiologist	
Pulmonary Symptoms	Referring clinician	Shall delay scanning for a time period that allows resolution of potential reversible CT abnormalities if pulmonary symptoms are present.
	Radiologist	

3.6. Subject Handling

This activity involves handling each imaging subject at each time point. It includes subject handling details that are necessary to reliably meet the Profile Claim.

3.6.1 DISCUSSION

This Profile will refer primarily to “subjects”, keeping in mind that the requirements and recommendations

apply to patients in general, and subjects are often patients too.

Subject handling guidelines are intended to reduce the likelihood that lung nodules will be obscured by surrounding disease or image artifacts, which could alter quantitative measurements, and to promote consistency of image quality on serial scans.

Intravenous Contrast is not used for CT lung cancer screening (26). Because of the inherently high contrast between lung nodules and the surrounding parenchyma, contrast is unnecessary for nodule detection and quantification. Its use incurs additional cost, the potential for renal toxicity and adverse reactions, and may affect volume quantification (21, 27, 28). If contrast must be used for a specific clinical indication (e.g. for characterization of the nodule, hilar nodes, or another abnormality) the Profile Claims are invalidated.

After obtaining the localizer (scout) image, the technologist should evaluate the image for **Artifact Sources** such as external metallic objects that may produce artifacts that may alter the attenuation of lung nodules, and work with the subject to remove these devices. Internal metallic objects, such as pacemakers and spinal instrumentation, also may produce artifacts.

Bismuth breast shields (used by some to reduce radiation exposure in the diagnostic CT setting) increase image noise. The impact of this imaging artifact on lung nodule volume quantification is unknown, but is likely to be magnified in the lung cancer screening setting due to the lower radiation dose used for screening. The effects of breast shields on image quality may vary depending on the types of shields and their positioning on the chest. The American Association of Physicists in Medicine currently does not endorse the use of breast shields, recommending the use of other dose reduction methods instead (https://www.aapm.org/publicgeneral/BismuthShielding.pdf). Thus, the use of breast shields is not compatible with the Profile Claims and is not recommended for lung cancer screening. However, organ dose modulation techniques that reduce dose in the anterior thorax may be used if implemented on all studies being compared.

Consistent **Subject Positioning** is important, to reduce variation in x-ray beam hardening and scatter and in nodule orientation and position within the gantry. Positioning the chest (excluding the breasts) in the center of the gantry improves the consistency of relative attenuation values in different regions of the lung, and should reduce scan-to-scan variation in the behavior of dose modulation algorithms. The subject should be made comfortable, to reduce the potential for motion artifacts and to facilitate compliance with breath holding instructions.

To achieve these goals, subjects should be positioned supine with arms overhead, in keeping with standard clinical practice. The sternum should be positioned over the midline of the table. The **Table Height and Centering** should be adjusted so that the midaxillary line is at the widest part of the gantry. The use of positioning wedges under the knees and/or head may be needed for patient comfort, or may help to better align the spine and shoulders on the table, and is optional. It is expected that local clinical practice and patient physical capabilities and limitations will influence patient positioning; an approach that promotes scan-to-scan consistency is essential.

Scans should be performed during **Breath Holding** at maximal inspiration, to reduce motion artifacts and improve segmentation. Efforts should be made to obtain consistent, reproducible, maximal inspiratory lung volume on all scans. The use of live breathing instructions given at a pace easily tolerated by the patient is strongly recommended. However, depending on local practice preference and expertise, the use of

prerecorded breathing instructions may provide acceptable results. Compliance with breathing instructions should be monitored by carefully observing the movement of the chest wall and abdomen to insure that the breathing cycle stays in phase with the verbal instructions. The scan should not be initiated until maximal inspiratory volume is reached and all movement has ceased.

To promote patient compliance, performing a practice round of the breathing instructions prior to moving the patient into the scanner also is strongly recommended. This will make the subject familiar with the procedure, make the technologist familiar with the subject's breathing rate, and allow the technologist to address any subject difficulties in following the instructions.

Sample breathing instructions:

1. "Take in a deep breath" (watch anterior chest rise)
2. "Breathe all the way out" (watch anterior chest fall)
3. "Now take a deep breath in…..in……in…..in all the way as far as you can"
4. When chest and abdomen stop rising, say "Now hold your breath".
5. Initiate the scan when the chest and abdomen stop moving, allowing for the moment it takes for the diaphragm to relax after the glottis is closed.
6. When scan is completed, say "You can breathe normally"

3.6.2 SPECIFICATION

Parameter	Actor	Requirement
Intravenous contrast	Analyst	Shall not use images in which intravenous contrast was administered for quantitative nodule volumetry in lung cancer screening or follow-up of screen-detected nodules.
	Radiologist	
Artifact sources	Technologist	Shall remove or position potential sources of artifacts (specifically including breast shields, metal-containing clothing, EKG leads and other metal equipment) such that they will not degrade the reconstructed CT volumes.
Subject Positioning	Technologist	Shall position the subject consistent with baseline.
Table Height & Centering	Technologist	Shall adjust the table height for the mid-axillary plane to pass through the isocenter of the gantry. Shall be consistent with baseline.
Breath holding	Technologist	Shall instruct the subject in proper breath-hold and start image acquisition shortly after full inspiration, taking into account the lag time between full inspiration and diaphragmatic relaxation.

Parameter	Actor	Requirement
		Shall ensure that for each tumor the breath hold state is consistent with baseline

3.7. Image Data Acquisition

This activity involves the acquisition of image data for a subject at either time point. It includes details of data acquisition that are necessary to reliably meet the Profile Claim.

3.7.1 DISCUSSION

CT scans for nodule volumetric analysis can be performed on equipment that complies with the Specifications set out in this Profile. However, performing all CT scans for an individual subject should ideally be done on the same platform (manufacturer, model and version) to reduce variation.

Note that the requirement to "select a protocol that has been prepared and validated for this purpose" is not asking the technologist to scan phantoms before every patient. Sites are required in section 3.4.2 to have validated the protocols that the technologist will be using and conformance with the protocol depends on the tech selecting those protocols.

Many scan parameters can have direct or indirect effects on identifying, segmenting and measuring tumors. To reduce these potential sources of variance, all efforts should be made to have as many of the scan parameters as possible consistent with the baseline.

Consistency with the baseline implies a need for a method to record and communicate the baseline settings and make that information available at the time and place that subsequent scans are performed. Although it is conceivable that the scanner could retrieve prior/baseline images and extract acquisition parameters to encourage consistency, such interoperability mechanisms are not defined or mandated here beyond requiring that certain fields be populated in the image header. Similarly, managing and forwarding the data files when multiple sites are involved may exceed the practical capabilities of the participating sites. Sites should be prepared to use manual methods instead.

Image Header recordings of the key parameter values facilitate meeting and confirming the requirements to be consistent with the baseline scan.

The goal of **parameter consistency** is to achieve consistent performance. Parameter consistency when using the same scanner make/model generally means using the same values. Parameter consistency when the baseline was acquired on a *different* make/model may require some “interpretation” to achieve consistent performance since the same values may produce different behavior on different models. See Section 3.4 "Protocol Design".

Anatomic Coverage For screening purposes a baseline scan should include the entire volume of the lungs (apex through base), minimizing the volume scanned above and below the lungs to avoid unnecessary radiation exposure. For nodule measurement, the scan should include the full nodule and typically 5 to 10 mm of lung region above and below the nodule.

The **localizer (scout) image** should be restricted as closely as possible to the anatomic limits of the thorax, using the minimum kV and mA needed to identify relevant anatomic landmarks. Inspecting the image also provides the opportunity to remove any external objects that may have been missed prior to positioning the subject on the table.

In CT screening for lung cancer, the choice of scan acquisition parameters is strongly influenced by the desire to minimize radiation dose. The radiation dose delivered by volumetric CT scanning is indicated by the volume CT Dose Index (**CTDIvol**). The CTDIvol should be chosen to provide the lowest radiation dose that maintains acceptable image quality for detecting pulmonary nodules. Variability in CT nodule volumetry using low dose techniques is comparable to that of standard dose techniques (14, 16-18, 29). As a general guideline, CTDIvol ≤3 mGy should provide sufficient image quality for a person of standard size, defined by the International Commission on Radiation Protection (ICRP) as 5'7"/170 cm and 154 lbs/70 kg. The CTDIvol should be reduced for smaller individuals and may need to be increased for larger individuals, but should be kept constant for the same person at all time points. CTDIvol is determined by the interaction of multiple parameters, including the **Tube Potential** (kV), **Tube Current** (mA), tube **Rotation Time**, and **Pitch**. Settings for kV, mA, rotation time, and pitch may be varied as needed to achieve the desired CTDIvol. Pitch is chosen so as to allow completion of the scan in a single breath hold with adequate spatial resolution along the subject z-axis. It is recommended that pitch does not exceed 2.0 for CT acquisitions obtained with a single x-ray tube, or the equivalent for acquisitions with dual-source technology.

3.7.2 Specification

The Acquisition Device shall be capable of performing scans with all the parameters set as described in the following table. The Technologist shall set the scan acquisition parameters to achieve the requirements in the following table.

Parameter	Actor	Requirement	DICOM Tag
Acquisition Protocol	Technologist/Radiologist	Shall select a protocol that has been previously prepared and validated for this Profile (See section 3.4.2 "Protocol Design Specification").	
Scan Duration	Technologist	Shall perform the scan in a single breath hold.	
Consistency	Technologist	Shall ensure that follow-up scans use the same CT scanner model and acquisition protocol settings.	

3.8. Image Data Reconstruction

This activity involves the reconstruction of image data for a subject at either time point. It includes criteria and procedures related to producing images from the acquired data that are necessary to reliably meet the Profile Claim.

3.8.1 Discussion

Many reconstruction parameters can have direct or indirect effects on identifying, segmenting, and measuring nodules. To reduce this source of variance, all efforts should be made to have as many of the parameters as possible on follow-up scans consistent with the baseline scan.

Reconstruction Field of View interacts with image matrix size (512x512 for most reconstruction algorithms) to determine the reconstructed pixel size. Pixel size directly affects voxel size in the x-y plane. Smaller voxels are preferable to reduce partial volume effects that can blur the edges of nodules and reduce measurement accuracy and precision. Pixel size in each dimension is not the same as spatial resolution in each dimension, which depends on a number of additional factors including the section thickness and reconstruction kernel. Targeted reconstructions with a small field of view minimize partial volume effects, but have limited effect on the accuracy of nodule volumetry compared to a standard field of view that encompasses all of the lungs (11, 12). A reconstructed field of view set to the widest diameter of the lungs, and consistent with baseline, is sufficient to meet the Claims of this Profile.

The **Reconstructed Slice Thickness** should be small relative to the size of the smallest nodules detected and followed by CT screening (11-13, 31).

The **Reconstruction Interval** should be either contiguous or overlapping (i.e. with an interval that is less than the reconstructed slice thickness). Either method will be consistent with the Profile Claims, though overlap of 50% may provide better accuracy and precision compared to contiguous slice reconstruction (32). Reconstructing datasets with overlap will increase the number of images and may slow down throughput, increase reading time, and increase storage requirements, but has NO effect on radiation exposure. A reconstruction interval that results in gaps between slices is unacceptable as it may “truncate”

the spatial extent of the nodule, degrade the identification of nodule boundaries, and confound the precision of measurement for total nodule volumes.

The **Reconstruction Algorithm Type** most commonly used for CT has been filtered back projection. More recently introduced methods of iterative reconstruction can provide reduced image noise and/or radiation exposure (33). Studies have indicated that iterative methods are at least comparable to filtered back projection for CT volumetry (16-18, 29, 34). Both algorithm types are acceptable for this Profile.

The **Reconstruction Kernel** influences the texture and the appearance of nodules in the reconstructed images, including the sharpness of the nodule edges. In general, a softer, smoother kernel reduces noise at the expense of spatial resolution, while a sharper, higher-frequency kernel gives the appearance of improved resolution at the expense of increased noise. Kernel types may interact differently with different software segmentation algorithms. Theoretically, the ideal kernel choice for any particular scanner is one that provides the highest resolution without edge enhancement, which generally will be a kernel in the medium-smooth to medium-sharp range of those available on clinical scanners. With increasing kernel smoothness, underestimation of nodule volume becomes a potential concern, while with increasing kernel sharpness, image noise and segmentation errors become potential concerns. Use of a reconstruction kernel on follow-up scans consistent with baseline therefore is particularly important for relying on the Profile Claims.

3.8.2 SPECIFICATION

Parameter	Actor	Specification	DICOM Tag
Reconstruction Protocol	Technologist	Shall select a protocol that has been previously prepared and validated for this purpose (See section 3.4.2 "Protocol Design Specification").	
Reconstruction Field of View	Technologist	Shall ensure the Field of View spans at least the full extent of the thoracic and abdominal cavity, but not substantially greater than that, and is consistent with baseline.	Reconstruction Field of View (0018,9317)
Reconstructed Image Thickness	Technologist	Shall set reconstructed image thickness to less than or equal to 1.25 mm and the same as baseline.	Slice Thickness (0018,0050)
Reconstruction Interval	Technologist	Shall set to less than or equal to the Reconstructed Image Thickness (i.e. no gap, may have overlap) and consistent with baseline.	Spacing Between Slices (0018,0088)

Parameter	Actor	Specification	DICOM Tag
Reconstruction Kernel	Technologist	Shall set the reconstruction kernel and parameters consistent with baseline (i.e. the same kernel and parameters if available, otherwise the kernel most closely matching the kernel response of the baseline).	Convolution Kernel (0018,1210), Convolution Kernel Group (0018,9316)

3.9. Image Quality Assurance

This activity involves evaluating the reconstructed images prior to image analysis. It includes image criteria that are necessary to reliably meet the Profile Claim.

3.9.1 Discussion

This Image QA activity represents the portion of QA performed between image generation and analysis where characteristics of the content of the image are checked for conformance with the profile. The Image QA details listed here are the ones QIBA has chosen to highlight in relation to achieving the Profile claim. It is expected that sites will perform many other QA procedures as part of good imaging practices.

Numerous factors can affect image quality and result in erroneous nodule volume measurements. **Motion artifacts** and **Dense Object Artifacts** can alter the apparent size, shape, and borders of nodules. Certain **Thoracic Disease** processes may alter the attenuation of the lung surrounding a nodule and interfere with identification of its true borders. Contact between a nodule and anatomic structures such as pulmonary vessels or the chest wall, mediastinum, or diaphragm also may affect **Nodule Margin Conspicuity** and obscure the true borders. Although screening may still be performed on them, the Claims of this Profile do not apply to nodules affected by image quality deficiencies that impair **Overall Nodule Measurability** and the sensitivity for nodule detection may be reduced.

3.9.2 Specification

Parameter	Actor	Requirement
Motion Artifacts	Technologist	Shall confirm the Images to be analyzed are free from motion artifacts.
	Image Analyst	
Dense Object Artifacts	Technologist	Shall confirm the Images to be analyzed are free from artifacts due to dense objects or anatomic positioning.
	Image Analyst	
Thoracic disease	Image Analyst	Shall confirm the Images to be analyzed are free from disease processes affecting the measurability of the nodule.
Nodule Margin Conspicuity	Image Analyst	Shall confirm the Nodules to be analyzed are sufficiently distinct from and unattached to other structures of similar attenuation.
Nodule Size	Image Analyst	Shall confirm (now or during measurement) that tumor longest in-plane diameter is between 6 mm and 12 mm. (For a spherical tumor this would roughly correspond to a volume between 113 mm^3 and 905 mm^3.)

Parameter	Actor	Requirement
Overall Nodule Measurability	Image Analyst	Shall disqualify any Nodules and images with features that might reasonably be expected to degrade measurement reliability.

3.10. Image Analysis

This activity involves measuring the volume change for subjects over one or more timepoints. It includes criteria and procedures related to producing quantitative measurements from the images that are necessary to reliably meet the Profile Claim.

3.10.1 Discussion

Image analysis should be performed using **Image Analysis Tool** programs that have received appropriate scientific validation. Because different programs use different segmentation algorithms that may result in different volumetric measurements even for ideal nodules, and different versions of the same program or its components may change its performance, a nodule being evaluated for change must be analyzed at both time points with the same software program (manufacturer, model, and version).

The volume of a lung nodule is typically determined by defining the nodule boundary (referred to as segmentation) and computing the volume within the boundary. Segmentation typically is performed by an automated algorithm after the user designates the location of the nodule to be measured with a starting seed point, cursor stroke, or region of interest. A subjective **Segmentation Analysis** should be conducted to closely inspect segmentation volumes in three dimensions for concordance with the visually-assessed nodule margins. Assessment of this concordance can be affected by the **Image Display Settings**, so a window and level appropriate for viewing the lung should be used and kept the same for all time points being compared.

Nodules for which the segmentation tracks the margins most accurately, without manual editing, will most closely meet the Claims of this Profile. If in the radiologist's opinion the segmentation is unacceptable, quantitative volumetry shall not be used and nodule size change should be assessed using standard clinical methods. Nodule location and margin characteristics impact segmentation quality and variance in nodule measurement, which are more favorable for nodules that are isolated, well-separated from adjacent structures, and have smooth borders compared to nodules abutting pulmonary vessels or parietal pleura, and also for smooth nodules compared to spiculated or irregularly shaped nodules (35-40).

When deriving the nodule volume difference between two time points, the **Reading Paradigm** involves direct side-by-side comparison of the current and previous image data at the same time, to reduce interobserver and intraobserver variation. Storing segmentations and measurement results for review at a later date is certainly a useful practice as it can save time and cost. However, segmentation results at both time points should be inspected visually in three dimensions to make sure that they are of sufficient and comparable accuracy in order to meet the Claims of the Profile. If a previous segmentation is unavailable for viewing, or the previous segmentation is not of comparable accuracy to the current segmentation, segmentation at the comparison time point should be repeated.

Methods that calculate volume changes directly without calculating volumes at individual time points are acceptable so long as the results are compliant with the specifications set out by this Profile. Regardless of method, the ability of software to calculate and record volume change relative to baseline for each nodule is recommended.

These Image Analysis specifications are intended to apply to a typical user working in the clinical setting (i.e. without extraordinary training or ability). This should be kept in mind by vendors measuring the performance of their tools and sites validating the performance of their installation. Although the performance of some methods may depend on the judgment and skill of the user, it is beyond this Profile to specify the qualifications or experience of the operator.

3.10.2 SPECIFICATION

Parameter	Actor	Requirement
Image Analysis Tool	Image Analyst	Shall use the same Image Analysis Tool (manufacturer, model, version) for measurements at all time points.
Segmentation Analysis	Image Analyst	Shall disqualify nodules with inadequate automated segmentations or nodules with non-comparable segmentations at both time points.
Image Display Settings	Image Analyst	Shall set the Image display setting (window and level) for the segmentation initiation to the same lung appropriate settings for all time points.
Equipment	Technologist/ Image Analyst	Shall use the same measurement system (scanner model, software, and operator) at the two time points.

4. Conformance

To conform to this Profile, participating staff and equipment ("Actors") shall support each activity assigned to them in Table 3-1. To support an activity, the actor shall conform to the checklist of requirements (indicated by "shall language") listed in the specifications table of that activity subsection in Section 3.

Although some of the requirements described in Section 3 can be assessed for conformance by direct observation, many of the most critical performance-oriented requirements cannot. Thus, the assessment procedures in Section 4 are required.

This section begins with a description of the **Technical Evaluation Methods** (Section 4.1) that will be used to verify the performance requirements of the image acquisition system and the software analysis system. The **Equipment Vendor Assessment Procedure** (Section 4.2) specifies the conformance procedures that equipment vendors must perform for a specific vendor equipment model to comply with the profile. The **Clinical Site Assessment Procedure** (Section 4.3) describes the steps needed by a clinical site to achieve conformance with this profile.

4.1. Technical Evaluation Methods

There are two types of equipment used to perform lung nodule measurements in this Profile. The technical methods to verify the quality of images produced by the CT scanner and acquisition protocol are outlined in Section 4.1.1. The technical methods to verify the quality of measurements produced by the analysis software is outlined in Section 4.1.2. These methods are then used by equipment vendors (Section 4.2) and clinical sites (Section 4.3) to verify conformance with profile requirements.

To date for routine clinical imaging, technical criteria have been typically developed for assessing performance in qualitative imaging applications. With this Profile, we are evaluating the imaging relative to assessing performance in quantitative imaging. To reliably measure small changes in the volume of pulmonary nodules is a very demanding task requiring a rigorous conformance process. One level of testing conformance would be for an Actor to perform the appropriate assessment procedures for relevant Specifications, and if results are within specification then to assert that the Actor is "Conformant". This could be referred to as "self-attestation". A second level would be for a third-party, such as an imaging physicist at a site, or a contractor hired by or for an Actor, to perform the assessment procedures and report the results. A third level would be for a disinterested, neutral, objective third party to perform the assessment procedures and issue a report. This neutral-party conformance process verifies that the level of measurement accuracy embedded in the Profile claim has been met.
Therefore, one way to validate conformance with the Profile, involves acquiring images of a standard reference object and sending the resulting images to a QIBA Conformance evaluation site for review. After automated analysis, a comprehensive report of the scanner performance relative to the conformance requirement of the Profile is sent back to the site (typically within the ensuing hour). The overall goal of this process is to ensure that the CT scanner is performing well enough when set to the specified acquisition parameters such that it can provide accurate and robust imaging information relative to the stated statistical boundaries of the Profile claim.

Note that while use of this conformance process represents one QIBA-accepted method for clinical sites and equipment vendors to demonstrate conformance with this Profile, a site or a vendor may alternatively contact QIBA with a technically equivalent approach for conformance along with supporting data. An

alternative conformance approach that is determined by QIBA to meet the goals of the Profile may also be used for Profile conformance.

4.1.1 CT Image Quality Characteristics

These methods specify the quality characteristics of reconstructed images for a specific CT scanner and acquisition protocol. Image quality is assessed with a collection of five metrics:

- Resolution is assessed in terms of the estimated response of the imaging system to a point source (aka point spread function or PSF). The PSF, in turn, is characterized as a Gaussian with a standard deviation of sigma expressed in mm. The PSF is measured both in-plane and along the Z dimension. Note: decreasing values indicate improving resolution.
- HU Bias is assessed in terms of the HU difference of the mean value from the expected value for a material with uniform density.
- Voxel Noise is assessed in terms of the standard deviation of pixel HU values when imaging a material with uniform density.
- Edge Enhancement is assessed in terms of the maximum percent increase in HU contrast above expected along the outer edge of an ideal cylinder surrounded by air.
- Spatial Warping is assessed in terms of the mean squared error of the outer cylindrical surface compared to an ideal cylindrical reference object surface.

The assessor shall scan a QIBA accepted Quantitative CT reference object using patient-specific settings for an average size patient. **Figure 1** shows the overall design of a QIBA accepted Lung Nodule Phantom which contains three image quality assessment modules placed at different distances from scanner isocenter (approximately 0mm, 102mm, and 204mm) within a 3lb EVA foam housing. Within each module is a hollow cylinder made of Delrin plastic with an inner radius of 17.0 mm +- 0.02mm, an outer radius of 28.0 mm +- 0.02mm and a height of 19.0mm +- 0.02mm. Centered within the inner radius of the hollow cylinder is an Air region with a nominal height of 13 mm. An additional 10 mm radius of Air surrounds the hollow cylinder. 6.0 mm above the hollow cylinder is a homogeneous Teflon cylinder with a height of 10.0mm +- 0.1mm and a diameter of 34mm +- 0.1mm. A homogeneous Acrylic cylinder is also present 6.0 mm below the hollow cylinder with the same dimensions and tolerances as the Teflon cylinder. This phantom also has an iso-centering and alignment target on its outer surfaces.

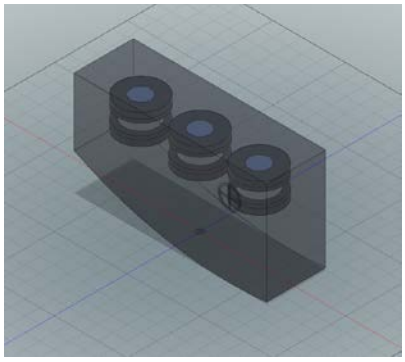

Figure 1: An illustration with translucency showing a QIBA CT Lung Nodule Phantom.

The scan may be performed at any time in the day after the CT scanner has passed its daily ACR CT accreditation and manufacturer calibration checks.

The assessor shall calculate each of the five image quality characteristics at the location of each image quality assessment module.

The assessor shall calculate **Resolution** by scanning a QIBA-accepted reference object and determining the 3D Gaussian PSF sigmas that best fit the partial volume voxels near the surface of the hollow cylinder reference object. The resulting X,Y PSF sigma represents the in-plane resolution and the Z PSF sigma represents the Z resolution, both of which are expressed in mm. The 3D PSF sigma ellipsoid volume ($\mathrm{PSF_v}$) is calculated as the volume of an ellipsoid with semi-axis lengths of X, Y, and Z PSF sigmas, which is expressed as $\mathrm{PSF_v} = \frac{4}{3}\pi\sigma_x\sigma_y\sigma_z$. The 3D PSF sigma volume is expressed in mm^3 where decreasing values indicate improving resolution. A QIBA-accepted reference object is a concentric cylinder placed flat on an X-Z scanner plane and the inner surface of concentric cylinder is used to determine both in-plane resolution and Z resolution. A Modulation Transfer Function at a 50% cutoff frequency (MTF 50) value can be translated to an **In-plane Point Spread Function** sigma using the following equation [53]:

$$\sigma_{xy} = \frac{\sqrt{-2\ln m_0}}{2\pi\mu_0}$$

where m_0 is the MTF frequency and μ_0 is the line pairs per millimeter. Thus, a conversion from PSF to MTF is:

$$m_0 = e^{-(\sigma_{xy}\pi\mu_0)^2}$$

The assessor shall calculate **HU Bias** for a particular material by first measuring the mean of HU density for voxels that are within a QIBA-accepted reference object such that partial volume will NOT impact the measurement. Each measured voxel must be > 2*sigma millimeters from the outer surface of the reference object to avoid bias from partial volume artifact. The expected HU density of the material is then subtracted from the mean HU value to arrive at the HU deviation. The two materials measured for HU Bias are Air and Acrylic and the HU bias is expressed in HU.

The assessor shall calculate **Voxel Noise** for a material by measuring the standard deviation of HU density for voxels that are within a QIBA accepted reference object such that partial volume will NOT impact the measurement. Each measured voxel must be > 2*sigma millimeters from the outer surface of the concentric cylinder to avoid bias from partial volume artifact. The material measured for Voxel Noise is Acrylic.

The assessor shall calculate **Edge Enhancement** using a QIBA accepted method. One method accepted by QIBA is performed by measuring the mean HU density along a series of $\pm$ 10 degree circular arc shaped sampling paths with each path at varying radial distances from a hollow cylinder center, centered on the X axis, and always inside the hollow cylinder reference object placed nominally flat on an X-Z scanning plane. The maximum of the mean HU densities observed minus the measured mean HU for Air represents the maximum observed contrast due to edge enhancement (EEm). The reference level of edge enhancement (EEr) is calculated as the mean HU density for Delrin minus the measured mean HU for Air. Once these are determined the final Edge Enhancement value is then calculated as $\mathrm{EE} = \frac{\mathrm{EE_m}}{\mathrm{EE_r}} - 1.$

The assessor shall calculate **Spatial Warping** by using a QIBA accepted method. One method accepted by QIBA is performed by computing the mean square error (MSE) of the outer cylindrical surface of a hollow Delrin cylinder with respect to the surface of an ideal geometric cylinder at that location. The geometry of a perfect uncapped cylinder is used for the ideal reference object surface and marching cubes with a threshold halfway between the measured mean Delrin HU density and the measured mean Air HU density

is used for the outer cylindrical surface.

4.1.2 Nodule Analysis Software Characteristics

These methods specify the minimum quality characteristics of a nodule measurement software application. Measurement quality is assessed with two metrics:

- Measurement Bias is the deviation of the mean value from its true value for a set of volumetric measurements. This metric is assessed by measuring the volume of repeat scans of geometric objects, each with a manufactured and verified volume, where the objects have varying size and shape.
- Coefficient of Variation (CV) is a measure of variation for repeated volumetric measurements of an object. It is calculated as the ratio of the standard deviation to the mean for a set of measurements. This metric is assessed by measuring the volume of short-time interval repeat scans of nodules, where the nodules have varying size, shape, and attachments as well as by measuring the volume of geometric object scans.

One method for nodule analysis software is described here. The assessor shall obtain two sets of CT scans from the QIBA quality assurance site x.y.org. A "phantom nodule dataset" contains M=10 CT scans of a QIBA provided phantom with numerous geometric objects embedded in foam or another QIBA accepted reference object. A "clinical nodule dataset" contains N=5 repeat CT scans of O=14 different lung nodules of varying shape and size all acquired within a short time interval such that the amount of volumetric change must be close to zero.

Two spreadsheet files are also provided at the x.y.org website. An "object location file" in *.xls format contains the RAS coordinate locations of the geometric objects in the "phantom nodule dataset". A "measurement reporting file" in *.xls format is also provided with a volumetric measurement data entry location for each object to be measured.

The assessor shall load each CT series in the "phantom nodule dataset" and the "clinical nodule dataset" into the nodule measurement software and obtain a volumetric measurement. The assessor shall enter each volumetric measurement into the "measurement reporting file" which will automatically verify that the values reported are conformant. This will specifically verify that the bias for each volumetric measurement of a geometric object is <= 5% of the object's manufactured volume. The spreadsheet will also verify that the coefficient of variation for both geometric objects and repeat lung nodules does not exceed the values in **Table 1**, with 95% confidence. The assessor shall also enter the analysis software name and version number into the "measurement reporting file" and upload the file to the QIBA quality assurance site x.y.org. The specific version of the lung nodule analysis software will be considered compliant when at least two independent clinical sites have successfully performed this procedure. Measurement linearity needs to shown and the slope has to be close to 1.0 (within 5%).

Sites can follow the vendor equipment procedure to verify conformance of software that is not on the list.

4.2. Equipment Vendor Conformance Procedures

Scanner and analysis software vendors will follow the assessment procedures in this section for a specific model of equipment to achieve conformance with this profile. Although vendor assessment procedures will use some of the same methods and tools as clinical sites, the assessment of vendor equipment is designed

to be more rigorous. The combination of thorough testing of equipment by vendors along with numerous field test assessments by clinical sites is intended to help ensure that the claims of this profile will be met.

4.2.1 Scanner Vendor Assessment Procedure

Scanner vendors will first establish a set of preferred protocols (i.e. equipment settings) for clinical sites to use on their equipment. Because slight modifications of a protocol setting (e.g. use of a different mA setting for each patient) is permitted in this profile, scanner vendors are required to verify that the requirements of this profile will still be met even when scanning with common protocol variations. A Design of Experiments (DOE) approach will be used to evaluate the performance of a scanner under varying conditions from each preferred protocol setting.

The scanner vendor will perform the following steps to demonstrate that a specific scanner model is conformant with this profile:

(1) Identify and use a single clinically operating CT scanner for the specific model being evaluated.

(2) Define one or more CT acquisition protocols that will be communicated to clinical sites as a proposed vendor recommended acquisition protocol for this model scanner. Each proposed vendor recommended acquisition protocol must meet the requirements of this profile and obtain a passing automated image quality report according to the steps in section 4.3.1, or may use another QIBA-approved method.

(3) For each vendor recommended acquisition protocol, a 2^4 full factorial DOE will be defined and performed with variation on mAs, field of view, pitch, and iterative recon setting (if appropriate, table height if not). The DOE will also have three repeat acquisitions for the recommended acquisition protocol. For example, a recommended CT acquisition protocol with the following settings:

mAs	40
kVp	100
Rotation Time (s)	0.50
Filed of View (cm)	35.0
Pitch	1.50
Slice Thickness (mm)	1.00
Slice Spacing (mm)	0.75
Reconstruction Kernel	I40-4
Table Height	Centered

Table 2: Acquisition protocol example.

Will have a DOE with the following 19 experiments consisting of 3 repeat CT scans of the recommended CT acquisition protocol (A,B,C) and 16 CT scans that systematically vary mAs, FOV, Pitch, and an iterative reconstruction setting:

Experiment #	mAs	FOV	Pitch	Iterative Recon Setting	Notes
A	40	30.0	1.50	I40-4	Repetition 1

	01	30	30.0	1.25	I40-3	[-, -. -, -]
	02	30	30.0	1.25	I40-5	[-. -, -, +]
	03	30	30.0	1.75	I40-3	[-. -, +, -]
	04	30	30.0	1.75	I40-5	[-, -, +, +]
	05	30	40.0	1.25	I40-3	[-, +, -, -]
	06	30	40.0	1.25	I40-5	[-, +, -, +]
	07	30	40.0	1.75	I40-3	[-, +, +, -]
	08	30	40.0	1.75	I40-5	[-, +, +, +]
	B	40	35.0	1.50	I40-4	Repetition 2
	09	50	30.0	1.25	I40-3	[+, -. -, -]
	10	50	30.0	1.25	I40-5	[+. -, -, +]
	11	50	30.0	1.75	I40-3	[+. -, +, -]
	12	50	30.0	1.75	I40-5	[+, -, +, +]
	13	50	40.0	1.25	I40-3	[+, +, -, -]
	14	50	40.0	1.25	I40-5	[+, +, -, +]
	15	50	40.0	1.75	I40-3	[+, +, +, -]
	16	50	40.0	1.75	I40-5	[+, +, +, +]
	C	40	35.0	1.50	I40-4	Repetition 3

Table 3: Design of experiments example.

(4) For each experiment in the DOE the scanner vendor must meet the requirements of this profile and obtain a passing automated image quality report according to the steps in section 4.3.1, or may use another QIBA-approved method. Vendors will be provided a facility to upload multiple scans for automated analysis.

(5) The scanner model and recommended acquisition protocol will be considered compliant with the profile when all experiments in the full DOE have obtained a passing image quality report, or another QIBA-approved method. The variation tested in the DOE defines an operating envelope that the scanner model has been shown to support. Vendors may wish to repeat DOE experiments to verify conformance with a wider operating envelope and this may include the addition of DOE variables.

Each CT scanner model and recommended vendor acquisition protocol pair that completes these steps will then each be listed by QIBA on x.y.org as a verified conformant CT scanner model and a recommended acquisition protocol.

4.2.2 Analysis Software Vendor Assessment Procedure

Analysis software will be run against a set of testing datasets to assess that the volumetric measurement software performs at a minimum level of performance. Datasets will include phantom scans containing geometric objects of known volumes (i.e. phantom nodule dataset) as well as clinical zero change clinical nodule datasets (i.e. clinical nodule dataset). The phantom nodule dataset and the clinical nodule dataset will be available at x.y.org for download. In addition, a template analysis software measurement spreadsheet for measurement findings will be available at x.y.org that provides the RAS location and data placeholders for software calculated measurements.

Analysis software conformance testing is specific to the name and version number of an analysis software system available to clinical sites for the measurement of CT lung nodules.

Analysis software testing of the phantom nodule dataset will consist of the following steps:

(1) Sequentially load each longitudinal CT series in the phantom nodule dataset into the analysis software and perform automated or semi-automated segmentation of the nodule(s).

(2) Place each calculated volume measurement into the analysis software measurement spreadsheet. As measurements are placed into the spreadsheet the bias and coefficient of variation of each simulated nodule will be automatically calculated by the spreadsheet.

(3) After all measurements have been calculated all bias and coefficient of variation values must be within acceptable limits for this profile. The phantom nodule dataset measurements must produce coefficients of variation no greater than those listed in Table 1. Volume bias may not exceed 5% of the phantom nodule manufactured volume.

Analysis software testing of the clinical nodule dataset will consist of the following steps:

(1) Sequentially load each longitudinal CT series in the clinical nodule dataset into the analysis software and perform automated or semi-automated segmentation of the nodule(s).

(2) Place each calculated volume measurement into the analysis software measurement spreadsheet. As measurements are placed into the spreadsheet the coefficient of variation of each clinical nodule will be automatically calculated by the spreadsheet.

(3) After all measurements have been calculated all coefficient of variation values must be within acceptable limits for this profile. The clinical nodule dataset measurements must produce coefficients of variation no greater than those listed in Table 1.

Analysis software (including version number) that completes these steps will then be listed by QIBA on x.y.org as a verified conformant nodule analysis software.

4.3. Clinical Site Conformance Procedure

One way a clinical site can achieve conformance to this profile is to follow the steps below. Detailed technical information on profile requirements is provided in Section 3.

Technical assessment at a clinical site is performed in two main steps. The **Technical Assessment To Prepare For Lung Nodule Measurement** (**Section 4.3.1**) verifies that the vendor equipment to be used at the clinical site, including the image acquisition protocol, complies with this profile. The **Performing Lung Nodule Measurement** (**Section 4.3.2**) outlines the verification steps needed for lung nodule analysis.

4.3.1 Preparing For Lung Nodule Measurement

(1) CT Scanner and Lung Nodule Analysis Software Verification

For each analysis software application to be used for lung cancer screening nodule measurement:

(a) Verify that the CT scanner manufacturer and model name is on this QIBA verified list at x.y.org.
(b) Verify thatthe software name, including version number, is on this QIBA verified list at x.y.org.

(2) CT QA and Lung Screening Protocol Verification

For each CT scanner to be used for lung cancer screening nodule measurement:

(a) Verify that the CT scanner is consistently following ACR CT accreditation and manufacturer installation and maintenance requirements.

(b) Establish a CT lung cancer screening protocol and save it on the CT scanner. Sites may use their existing lung screening protocol or pick a protocol from a continuously updated list provided by QIBA at x.y.org.

(c) CT scan a QIBA CT reference object with the saved CT lung screening protocol.

(d) Submit the CT reference object scan to x.y.org and obtain a passing automated image quality report. If the site does not receive a passing report, repeat steps 2(b) to 2(d) until a passing report is obtained.

4.3.2 Performing Lung Nodule Measurement

(1) CT Data Acquisition, Lung Nodule, and Segmentation Verification

For each CT lung cancer screening and solid lung nodule follow-up CT scan:

(a) Verify that the patient did not receive IV contrast as part of the CT study.

(b) Visually verify that the nodule is solid, not attached to large vessels or other structures, has a largest diameter between 6mm and 10mm, and that the saved CT lung nodule protocol was used at all nodule scanning time points to be volume measured.

(c) Visually verify that significant artifacts (e.g. motion, streaking) are not present and that image noise is not excessive at the location of the solid nodule to be measured.

(d) Visually verify that the measurement of the solid nodule is free of segmentation issues.

(2) Obtain Volumetric Nodule Measurement Guidance

For each series of CT lung nodule measurements consisting of one or more time points:

Use a QIBA lung nodule profile on-line calculator at x.y.org for guidance on levels of volumetric measurement error for each lung nodule measurement and change measurement.

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Appendices

Appendix A: Acknowledgements and Attributions

This document is proffered by the Radiological Society of North America (RSNA) Lung Nodule Volume Assessment and Monitoring in Low Dose CT Screening Working Group of the Volumetric Computed Tomography (v-CT) Technical Committee. The group is composed of scientists representing academia, the imaging device manufacturers, image analysis tool software developers, image analysis laboratories, biopharmaceutical industry, government research organizations, professional societies, and regulatory agencies, among others. All work is classified as pre-competitive.

A more detailed description of the v-CT committee and its work can be found at the following web link: http://qibawiki.rsna.org/index.php?title=Quantitative-CT.

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Appendix B: Background Information

B.1 Summary of selected references on nodule volumetry accuracy

http://qibawiki.rsna.org/index.php/Work_Product_for_Review

B.2 Summary of selected references on nodule volumetry precision

http://qibawiki.rsna.org/index.php/Work_Product_for_Review

Appendix C: Metrology Methods

Obuchowski NA, Buckler A, Kinahan PE, Chen-Mayer H, Petrick N, Barboriak DP, Bullen J, Barnhart H, Sullivan DC. Statistical Issues in Testing Conformance with the Quantitative Imaging Biomarker Alliance (QIBA) Profile Claims. Academic Radiology in press.

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