QIBA Profile:

CT Tumor Volume Change for Advanced Disease (CTV-AD)

Edition: 2022

Stage: Technically Confirmed

When referencing this document, please use the following format:

QIBA CT Volumetry Biomarker Committee. CT Tumor Volume Change Profile - 2022, Technically Confirmed. Quantitative Imaging Biomarkers Alliance, July 1, 2022. Available at: https://qibawiki.rsna.org/index.php/Profiles

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1. Executive Summary

A QIBA Profile is an implementation guide to generate a biomarker with an effective level of performance, mostly by reducing variability and bias in the measurement.

The expected performance is expressed as **Claims** (Section 1.2). To achieve those claims, **Actors** (Scanners, Technologists, Physicists, Radiologists, Reconstruction Software, and Image Analysis Tools) must meet the Checklist **Requirements** (Section 3) covering Periodic QA, Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA, and Image Analysis.

This Profile is at the Technically Confirmed stage (qibawiki.rsna.org/index.php/QIBA_Profile_Stages) so,

- The requirements have been performed and found to be practical by multiple sites
- The claim is a hypothesis based on committee assessment of literature and QIBA groundwork

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

1.1 Clinical Context

CT Tumor Volume Change is used as a biomarker of disease risk, characterization, progression, and response to treatment.

This involves measuring tumor volumes and assessing longitudinal changes within subjects, based on image processing of CT scans acquired at different timepoints. See Appendix B for a discussion of usage of this biomarker in practice.

1.2 Claims

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

Change Detection Claim: A true change in a lung tumor volume has occurred with 95% confidence if the measured change is larger than 24%, 29%, or 39% respectively when the longest in-plane diameter is initially 50-100mm, 35-49mm, or 10-34mm.

Repeatability Claim: Tumor volume measurement within-tumor coefficient of variation (wCV), is 0.085, 0.103, and 0.141 respectively for lung tumors with diameters of 50-100mm, 35-49mm, or 10-34mm.

The Change Detection Claim is particularly relevant to Clinicians. The Repeatability Claim describes individual measurements and the wCV can be used to compute 95% Confidence Intervals (CI). For example, a tumor measured as 34cm^3 (~40mm diam) then 268 cm^3 (~80mm) yields a 95% CI for the true volume change of [+189 cm^3, +279 cm^3]. See Appendix B for more details.

1.2.1 CURRENT PERFORMANCE

To put the above Claims in perspective, consider a site that is not conforming to the requirements in the QIBA Profile or making similar special image acquisition efforts.

Based on the groundwork studies and literature review carried out by the QIBA CT Volumetry Biomarker Committee, the use of different radiologists and analysis tools at two timepoints for a given tumor, even when the same scanner is used, might be expected to degrade the minimum detectable change in tumor volume for a 10-34mm tumor to the order of 136%. See Table B-1 in Appendix B.

Of course, without ascertaining site practice and without doing a site-specific analysis, the repeatability and change detectability for any given site is essentially unknown. Important benefits from standardizing a site's biomarker process steps include more predictable and reproducible biomarker technical performance, becoming more comparable across scanners and across sites, and ultimately more reliable decision making and improved clinical performance.

1.3 Disclaimers

Standard of Care: The requirements are defined to achieve the Claim and do not supersede proper patient management considerations. Requirements that disqualify an exam or lesion mean the performance in the Claims cannot be presumed, but does not preclude clinical use of the measurement at the discretion of the clinician.

Confirmation of Claims: The claims are informed by groundwork studies, extensive literature review and expert consensus; they have not yet been fully substantiated by studies that strictly conform to the requirements given here. The QIBA Consensus, Claim Confirmation and Clinical Confirmation Stages will collect data on the actual field performance and appropriate revisions will be made to the Claims and/or the details of the Profile. At that point, this caveat may be removed or re-stated. (https://qibawiki.rsna.org/index.php/QIBA_Profile_Stages)

Scope of Claims: The quantitative performance values in the claims were derived from analysis of tumor volumetry consisting solely of lung data. Correspondingly, the claims assert that this performance holds for tumors in the lung. Elsewhere, factors like the degree of visual contrast between the tumor and its background, or injected contrast dynamics may affect volumetry performance in ways that have not yet been fully explored and quantified. Despite this, usage of the methods and requirements in this Profile for segmentation and volumetry of tumors in the kidneys, liver, lymph nodes and elsewhere in the thorax is recommended, however the expected performance has not yet been determined and may differ from that stated in the Claim.

Innovation: Profile requirements are intended to establish a baseline level of performance. Exceeding the requirements and providing higher performance or advanced capabilities is allowed and encouraged. The Profile does not limit the methods institutions and equipment suppliers use to meet the requirements.

2. Conformance

To conform to this Profile, participating Actors (staff and equipment) shall meet each requirement on their checklist in Section 3.

- Some requirements reference a specific **assessment procedure** in Section 4 that shall be used to assess conformance to that requirement. For the rest, any reasonable assessment procedure is acceptable.
- Staff must ensure requirements assigned to them are met; however, for the purpose of conforming to the profile, they may delegate a task rather than physically doing it themselves.
- Staff names represent roles in the profile, not formal job titles or certifications. E.g., Site equipment performance requirements are assigned to the Physicist role. The role may be filled by any appropriate person: a staff physicist, a managed contractor, or a service provided by a vendor.
- If a QIBA Conformance Statement is available for equipment (e.g., published by a scanner vendor), a copy of that statement may be used in lieu of confirming each requirement in that equipment checklist yourself by running the necessary tests.

To make a formal claim of conformance, the organization responsible for equipment or staff shall publish a QIBA Conformance Statement.

QIBA Conformance Statements:

- shall follow the current template: (https://qibawiki.rsna.org/index.php/QIBA_Conformance_Statement_Template)
- shall include an Appendix containing details recorded by the assessor as stated in requirements or assessment procedures (e.g., acquisition parameters)
- shall describe the test data used for conformance testing or alternatively provide access to it

3. Profile Requirement Checklists

The following Checklists are the basis for conforming to this Profile (See Section 2).

Conforms (Y/N) indicates whether conformance to the requirement has been confirmed by the assessor. When responding **N**, it is helpful to include notes explaining why.

Feedback on all aspects of the Profile and associated processes is welcomed. Contact: qiba@rsna.org

3.1 Scanner and Reconstruction Software Checklist

Make/Model/Version: Assessment Date: .

Parameter	Conforms (Y/N)	Requirement
Product Validation (see Section A.1)		
Acquisition & Reconstruction Protocol		Shall prepare a conformant protocol (see "Protocol Design" on Radiologist Checklist).
		Shall validate that the protocol achieves an f50 value that is between 0.3 mm^{-1} and 0.7 mm^{-1} for both air and soft tissue edges. See 4.1. Assessment Procedure: In-plane Spatial Resolution
		Shall validate that the protocol achieves a standard deviation < 60HU. See 4.2. Assessment Procedure: Voxel Noise
Image Header		Shall record in the DICOM header values for tags identified in "Protocol Design" requirements on Radiologist Checklist.

3.2 Image Analysis Tool Checklist

Make/Model/Version: Assessment Date: .

Parameter	Conforms (Y/N)	Requirement
Product Validation (see Section A.1)		
Reading Paradigm		Shall be able to present the reader with both timepoints side-by-side for comparison when processing the second timepoint.
Reading Paradigm		Shall be able to re-process the first timepoint (e.g. if it was processed by a different Image Analysis Tool or Radiologist).
Tumor Volume Computation		Shall be validated to compute volume within 5% of the true volume. See 4.3 Assessment Procedure: Tumor Volume Computation.
Tumor Volume Repeatability		Shall be validated to achieve tumor volume repeatability with: • an overall repeatability coefficient of less than 0.16 • a small subgroup repeatability coefficient of less than 0.21 • a large subgroup repeatability coefficient of less than 0.21 See 4.4. Assessment Procedure: Tumor Volume Repeatability.
Tumor Volume Bias & Linearity		Shall be validated to achieve: • an overall %bias of less than the Allowable Overall %Bias • a shape subgroup %bias for each subgroup (spherical, ovoid, lobulated) of

Parameter	Conforms (Y/N)	Requirement
		less than the Allowable Shape Subgroup %Bias • slope ($\hat{\beta}_1$) between 0.98 and 1.02 • quadratic-term ($\hat{\beta}_2$) between -0.05 and 0.05 The Allowable Overall %Bias and the Allowable Shape Subgroup %Bias are taken from Table 3.2.2-1 based on the overall repeatability coefficient achieved by the Image Analysis Tool using the assessment procedure in Section 4.4. See 4.5 Assessment Procedure: Tumor Volume Bias & Linearity.

Table 3.2.2-1: Allowable Tumor Volume %Bias based on Overall Repeatability Coefficient

Overall Repeatability Coefficient $\widehat{RC}$	Allowable Overall %Bias (RMSE Target: 7.1%)	Allowable Shape Subgroup %Bias (RMSE Target: 7.8%)
0.05	6.60%	7.32%
0.06	6.37%	7.11%
0.07	6.09%	6.86%
0.08	5.75%	6.56%
0.09	5.35%	6.20%
0.10	4.88%	5.79%
0.11	4.30%	5.31%
0.12	3.59%	4.75%
0.13	2.63%	4.06%
0.14	0.84%	3.17%
0.15	0.00%	1.84%
0.155	0.00%	0.00%
0.16	n/a (failed repeatability)	n/a (failed repeatability)

3.3 Physicist Checklist

Note: The role of "Physicist" may be played by an in-house medical physicist, a physics consultant or other staff (such as vendor service or specialists) qualified to perform the validations described.

Physicist Name: Assessment Date: .

Parameter	Conforms (Y/N)	Requirement
Protocol Design (see Section A.4)		
In-plane Spatial Resolution		Shall validate that the protocol achieves an f50 value between 0.3 mm^{-1} and 0.7 mm^{-1} for both air and soft tissue edges. See 4.1. Assessment Procedure: In-plane Spatial Resolution
Voxel Noise		Shall validate that the protocol achieves a standard deviation < 60HU. See 4.2. Assessment Procedure: Voxel Noise

3.4 Technologist Checklist

Technologist Name: Assessment Date: .

Parameter	Conforms (Y/N)	Specification
Subject Handling (see Section A.5)		
Artifact Sources		Shall remove or position potential artifact sources (specifically including breast shields, metal-containing clothing, and EKG leads) such that they will not degrade reconstructed CT volumes.
Table Height		Shall adjust the table height for the mid-axillary plane to pass through the isocenter.
Image Data Acquisition (see Section A.6)		
Acquisition Protocol		Shall select a protocol that has been previously prepared and validated for this purpose.
Localizer		Shall confirm on the localizer image the absence of artifact sources that could affect the volume acquisitions or the attenuation of lung nodules.
Scan Duration for Thorax		Shall set parameter values to cover an axial field of view of 35cm in 10 seconds or less.
Image Data Reconstruction (see Section A.7)		
Reconstruction Protocol		Shall select a protocol that has been previously prepared and validated for this purpose.
Reconstructed Image Thickness		Shall set to between 0.5mm and 2.5mm (inclusive) if not set in the protocol.
Reconstructed Image Interval		Shall set to less than or equal to the Reconstructed Image Thickness (i.e. no gap, may have overlap) and consistent with baseline.
Reconstruction Field of View		Shall ensure the Field of View spans at least the full extent of the thoracic and abdominal cavity, but not substantially greater than that. [Reconstruction Field of View (0018,9317)]

3.5 Radiologist Checklist

Radiologist Name: Assessment Date: .

Parameter	Conforms (Y/N)	Specification
Staff Qualification (see Section A.2)		
Tumor Volume Computation Repeatability		Shall, if operator interaction is required by the Image Analysis Tool to perform measurements, be validated to achieve tumor volume change repeatability with: • an overall repeatability coefficient of less than 0.16 • a small subgroup repeatability coefficient of less than 0.21 • a large subgroup repeatability coefficient of less than 0.21 See 4.4. Assessment Procedure: Tumor Volume Change Repeatability.
Acquisition Protocol		Shall ensure technologists have been trained on the requirements of this Profile.
Protocol Design (see Section A.4)		
Acquisition Protocol		Shall prepare a protocol to meet the specifications in this table.
Total Collimation Width		Shall set to Greater than or equal to 16mm. [Total Collimation Width (0018,9307)]

Parameter	Conforms (Y/N)	Specification
Nominal Tomographic Section Thickness (T)		Shall set to Less than or equal to 1.5mm. [Single Collimation Width (0018,9306)]
Scan Duration for Thorax		Shall set parameter values to cover an axial field of view of 35cm in 10 seconds or less.
IEC Pitch		Shall set to Less than 1.5. [Spiral Pitch Factor (0018,9311)]
Reconstructed Image Thickness		Shall set to between 0.5mm and 2.5mm (inclusive). [Slice Thickness (0018,0050)]
Reconstructed Image Interval		Shall set to less than or equal to the Reconstructed Image Thickness (i.e. no gap, may have overlap). [Spacing Between Slices (0018,0088)]
Subject Handling (see Section A.5)		
Contrast Protocol		Shall prescribe a contrast protocol (which may be No Contrast) expected to achieve enhancement consistent with baseline.
Image QA (see Section A.8)		
Tumor Measurability		Shall disqualify any tumor they feel might reasonably degrade the consistency and accuracy of the measurement. Conversely, if artifacts or attachments are present but the radiologist is confident and prepared to edit the contour to eliminate the impact, then the tumor need not be judged non-conformant to the Profile.
Patient Motion Artifacts		Shall confirm the images containing the tumor are free from artifact due to patient motion.
Dense Object Artifacts		Shall confirm the images containing the tumor are free from artifact due to dense objects, materials or anatomic positioning.
Clinical Conditions		Shall confirm no clinical conditions are affecting the measurability of the tumor.
Tumor Margin Conspicuity		Shall confirm the tumor margins are sufficiently conspicuous and unattached to other structures of equal density to distinguish the volume of the tumor.
Contrast Enhancement		Shall confirm the phase of enhancement, if any, and degree of enhancement are consistent with baseline.
Patient Positioning Consistency		Shall confirm any tumor deformation due to patient positioning is consistent with baseline.
Breath Hold Consistency		Shall confirm breath hold state and degree of inspiration is consistent with baseline.
Reconstructed Image Thickness		Shall confirm the reconstructed image thickness is between 0.5mm and 2.5mm, and consistent (e.g. within 0.5mm) with baseline.
Field of View		Shall confirm the image field of view (FOV) is consistent with baseline.
Tumor Size		Shall confirm (now or during measurement) each tumor longest in-plane diameter is between 10 mm and 100 mm. (For a spherical tumor, this roughly corresponds to a volume between 0.5 cm^3 and 524 cm^3.)
Image Analysis (see Section A.9)		
Reading Paradigm		Shall re-process the first timepoint if it was processed by a different Image Analysis Tool or Radiologist.
Result Verification		Shall review & approve the margin contours produced by the tool.

Note: The Radiologist is responsible for the protocol parameters. They may choose to use a protocol provided by the

scanner vendor. Working collaboratively with a physicist is recommended as some parameters are system dependent and may require special attention.

4. Assessment Procedures

Although most requirements in Section 3 can be assessed for conformance by direct observation and checked off, some requirements (e.g., performance metrics) cannot, in which case the requirement references an Assessment Procedure here in Section 4.

4.1. Assessment Procedure: In-plane Spatial Resolution

This procedure can be used by a manufacturer or an imaging site to assess the In-plane Spatial Resolution of reconstructed images. It is applicable to linear methods (such as conventional filtered back-projection (FBP) and nonlinear methods (such as iterative and deep-learning). Resolution is assessed in terms of the f50 value (in mm^{-1}) of the modulation transfer function (MTF).

Loosely speaking, the MTF represents the blur of an infinitely small feature of interest, f50 represents the spatial frequency at which the contrast of the feature has decreased by 50%, and the inverse of the f50 value represents the size of a feature that would be degraded 50%. Thus, for an f50 value of 0.4 mm^{-1}, features that are 2.5mm would have their contrast degraded by 50% (and smaller features would be degraded more).

The assessor shall:

1. Warm up the scanner's x-ray tube and perform calibration scans (often called air-calibration scans) according to scanner manufacturer recommendations.
2. Select and record acquisition and reconstruction parameters that conform to the Profile (See Protocol Design in the Radiologist Checklist 3.5). Use the same parameters for 4.1 & 4.2, i.e., the noise level during resolution assessment should be that measured during noise assessment.
3. Scan a spatial resolution phantom that has a series of HU-value cylindrical inserts including one with soft-tissue equivalence. E.g., the ACR CT Accreditation Program (CTAP) Phantom module 1 or the AAPM TG233 phantom.
4. Position the phantom with the center of the phantom at isocenter and properly aligned along the z-axis. For details, refer to Section C, Step 3 of the CT Accreditation Testing Instructions: https://www.acraccreditation.org/~/media/ACRAccreditation/Documents/CT/CT-Accreditation-Testing-Instructions.pdf
5. Generate an MTF curve, measured as an average of the MTF in the x-y plane along the edge of a target soft-tissue-equivalent insert using AAPM TG233 or equivalent methodology as implemented in manufacturer analysis software, AAPM TG233 software or equivalent.

   Note: The AAPM TG233 software provides axial resolution (MTF in the z-direction) in addition to the x-y plane MTF.
6. Determine and record the f50 value, defined as the spatial frequency (in mm^{-1} units) corresponding to 0.5 MTF on the MTF curve.
7. Generate another MTF curve and determine and record the f50 value using the edge of the "air insert" (i.e. an empty cutout in the phantom). If the phantom does not have a cutout that provides an internal air edge to assess, it is permitted to use the outer edge of the phantom.

The above procedure is provided as a reference method. This reference method, and the method used by the scanner manufacturer for FDA submission of MTF values, are accepted methods for this assessment procedure. The manufacturer may have specific test methods for non-linear reconstruction algorithms.

Proposed alternative methods may be submitted to QIBA with evidence that the results produced are equivalent to this reference method or to the manufacturer method. Upon review by QIBA, the proposed method may be approved as an accepted assessment procedure in this Profile.

4.2. Assessment Procedure: Voxel Noise

This procedure can be used by a manufacturer or an imaging site to assess the voxel noise of reconstructed images. It is applicable to linear methods (such as conventional filtered back-projection (FBP) and nonlinear methods (such as iterative and deep-learning). Voxel noise is assessed in terms of the standard deviation of pixel values when imaging a material with uniform density.

> Note: This simple assessment is intended to set a reasonable noise limit that is sufficient to avoid degrading segmentation performance. When characterizing reconstruction methods, voxel noise is a limited representation of image noise when noise texture is varied.

The assessor shall:

1. Warm up the scanner's x-ray tube and perform calibration scans (often called air-calibration scans) according to scanner manufacturer recommendations.
2. Select and record acquisition and reconstruction parameters that conform to the Profile (See Protocol Design in the Radiologist Checklist 3.5). Use the same parameters as used for section 4.1.
3. Place at the isocenter of the scanner a phantom of uniform density that includes a 20 cm diameter cylinder of water equivalent material. E.g. ACR CT Accreditation Program (CTAP) Phantom module 3
4. Scan the phantom and select a single representative slice, likely close to the center, from the uniformity portion of the phantom.
5. Place a region of interest (ROI) of at least 400 mm^2 near the center of the slice and record the values reported for the ROI mean and standard deviation.

The assessor is encouraged, but not required, to record and retain the images and associated measurement details. Such details support assessment when the voxel noise is close to the acceptable limit.

Note that noise is assessed here in a standard-sized object. In cases of protocols adaptive to the patient body habitus (such as those using Automatic Exposure Control), the qualification of CT scanner noise should include noise as a function of body habitus (using a phantom such as that provisioned in AAPM TG233) if there is any concern that the noise performance may be outside compliance for different body habitus.

The above procedure is provided as a reference method. This reference method and the method used by the scanner manufacturer for FDA submissions are accepted methods for this assessment procedure.

Proposed alternative methods (such as using the water phantom portion of a manufacturer's QA phantom) may be submitted to QIBA with evidence that the results produced are equivalent to this reference method or to the manufacturer method. Upon review by QIBA, the proposed method may be approved as an accepted assessment procedure in this Profile.

4.3. Assessment Procedure: Tumor Volume Computation Accuracy

This procedure can be used by a manufacturer or an imaging site to assess whether an Image Analysis Tool computes the volume of a single tumor accurately. Accuracy is assessed in terms of the percentage error when segmenting and calculating the volume of a tumor with known truth.

The test files include 11 DICOM sequential images representing a digital reference object (a "virtual phantom") with z-axis resolution of 1.5mm. A spherical "tumor" and a box-shaped "tumor", both with -10 HU radio-density, exist in a flat -1000 HU region of the phantom to make the segmentation intentionally easy since the test is not intended to stress the segmentation tool but to instead evaluate any bias in the volume computation after the tumor is segmented.

The assessor shall:

1. Download the test files from the Quantitative Imaging Data Warehouse (QIDW)
    a. Go to https://qidw.rsna.org/, Select CT Modality Datasets (under Data Inventory)
    Note: The assessor will not be permitted to access the QIDW Data Inventory until they have registered for a (free) user account and logged in.
    b. Select CT Volumetry, then CT Volumetry Profile Conformance
    c. Download the LungMan DRO zip file
2. Use the Image Analysis Tool to segment both the spherical tumor and the box-shaped tumor present in the test images
3. Calculate the volume of each tumor
4. Record the percentage difference between the reported volume and the true value.

The downloaded zip file contains an Excel spreadsheet named "QIBA Volumetry CT - 4.3 Assessment Procedure Tumor Volume Computation" with the coordinates of the centroid of each tumor, the true value for its volume, and statistical tools to support recording the results and assessing the performance.

4.4. Assessment Procedure: Tumor Volume Repeatability

This procedure can be used by a manufacturer or an imaging site to assess the repeatability with which the volume of a single tumor is measured. Repeatability is assessed in terms of the repeatability coefficient when segmenting and calculating the volume of a tumor with known truth at two timepoints. The procedure assesses an Image Analysis Tool and a Radiologist operating the tool as a paired system.

Note: tumor detection is not evaluated by this procedure; the locations of the target lesions are provided.

The assessment procedure has the following stages:

- Obtain a designated test image set (see Section 4.4.1).
- Determine the volume for designated tumors at two timepoints (see Section 4.4.2).
- Calculate statistical metrics of performance (see Section 4.4.3).

4.4.1 OBTAIN TEST IMAGE SET

The test image set consists of multiple target tumors in the lung in multiple subjects, which is representative of the stated scope of the Profile.

The assessor shall:

1. Download the test files from the Quantitative Imaging Data Warehouse (QIDW)
    a. Go to https://qidw.rsna.org/, Select CT Modality Datasets (under Data Inventory)

b. Select CT Volumetry, then CT Volumetry Profile Conformance
c. Select RIDER Lung CT Data
d. Download the RIDER Lung CT Data zip file (roughly 4GB).

The files represent 31 test cases, with two timepoints per case, each with one target tumor to segment. Each timepoint of each case is represented by a set of DICOM files. For some cases, the two timepoints are in different series in the same study and for others the two timepoints are in different studies. The scans have multiple nodules of varying sizes. The target tumor is identified in terms of its x/y/z coordinates. The list of target tumors and coordinates are provided in a .csv file associated with each study in the download package. The RIDER Lung CT Data download package also contains an Excel spreadsheet named "QIBA CTVol TumorVolumeChange Assessment4.4-Repeatability" that summarizes all the tumor locations and will also help the assessor perform the record keeping and calculations later in this assessment procedure.

Note: Eleven of the 31 cases in the test files do not meet the Image QA criteria (e.g. attached/indistinct margins) specified by the Profile (See A.8.2). These cases are marked as "excluded" on the Results page of the QIBA spreadsheet and are not included in the calculation of performance metrics. Assessors may skip measuring those cases.

The test image set has been acquired according to the requirements of this Profile (e.g. patient handling, acquisition protocol, reconstruction).

The target tumors have been selected to be measurable (as defined in the Profile) and have a range of volumes, shapes and types to be representative of the scope of this Profile.

Future assessments may address more body parts (e.g., metastases in the mediastinum, liver, neck, adrenal glands, retroperitoneum, pelvis, etc.) by including such tumors in the test data, and may test boundary condition performance by including test data that is marginally conformant (e.g. maximum permitted slice thickness, maximum permitted noise, etc.) to confirm conformant performance is still achieved.

4.4.2 DETERMINE VOLUMES

The provided spreadsheet may be used to record the volume measurements and will compute the volume change values and the statistical metrics that follow. Recording the amount of time spent on each case and any comments or concerns is not required for the assessment but is welcome feedback to QIBA.

The assessor shall:

1. If evaluating an Image Analysis Tool, use a single reader for this entire assessment procedure.
2. If evaluating a reader (Radiologist), use a single tool for this entire assessment procedure.
3. Import the DICOM files for each case into the analysis software.
4. Have each target tumor segmented at each timepoint as described in the Image Analysis Activity (See Section A.9). The seed point or segmentation may be edited if that is part of the normal operation of the tool.
5. If segmentation edits are performed (e.g. to ensure the volumetric assessment incorporates the whole nodule and excludes any adjacent tissues), report results both with and without editing.
6. Report if any of these test cases were used in development of the tool. It is undesirable to test using training data, but until more datasets are available it may be unavoidable.

7. Record the volume (Y) of each target tumor at timepoint 1 (denoted Y_{i1}) and at timepoint 2 (Y_{i2}) where *i* denotes the *i*-th target tumor.
8. Calculate the resulting % volume change (d) for each target tumor as $d_i = \ln(Y_{i2}) - \ln(Y_{i1})$.

4.4.3 CALCULATE STATISTICAL METRICS OF PERFORMANCE

The assessor shall:

1. Calculate the within-subject Coefficient of Variation (wCV), where N=20 and $wCV = \sqrt{\sum_{i=1}^{N} d_i^2 \,/N}$
2. Estimate the Repeatability Coefficient (RC) as $\widehat{RC} = 2.77 \times wCV$
3. Divide the target tumors into a small subgroup (containing the 14 target tumors with the smallest measured volumes; tagged in the spreadsheet) and a large subgroup (containing the 6 tumors with the largest measured volumes; tagged in the spreadsheet).
4. Repeat the above calculations on both subgroups to estimate a small subgroup repeatability coefficient and a large subgroup repeatability coefficient.

Computing Bland-Altman plots of the volume estimates as part of the assessment record is recommended.

4.5. Assessment Procedure: Tumor Volume Bias and Linearity

This procedure can be used by a manufacturer or an imaging site to assess the bias and linearity with which the volume of a single tumor is measured. Bias is assessed in terms of the percentage bias of the overall and subgroup populations when segmenting and calculating the volume of a number of tumors with known truth. Linearity is assessed in terms of the slope ($\hat{\beta}_1$) of an ordinary least squares (OLS) regression fit to the volume data and the estimated quadratic term ($\hat{\beta}_2$) of a quadratic model fit to the volume data. The procedure assesses an Image Analysis Tool and a Radiologist operating the tool as a paired system.

4.5.1 OBTAIN TEST IMAGE SET

The test image set consists of scans from two different scanners of an anthropomorphic ("Lungman") phantom with multiple synthetic target tumors of different shapes and sizes in the lung.

The assessor shall:

1. Download the test files by going to the Quantitative Imaging Data Warehouse (QIDW)
    a. Go to https://qidw.rsna.org/, select CT Modality Datasets (under Data Inventory)
    b. Select CT Volumetry, then CT Volumetry Profile Conformance
    c. Download the QIBA Lung Collection zip file (roughly 1GB).

The test image set consists of scans of the FDA Lungman N1 phantom using two different scanners from different vendors. Several phantom configurations, using a set of 7 synthetic tumors, each with a different combination of size, shape and diameter (see Table 4.5.1-1), were scanned. The scan of a configuration is repeated 3 times, each resulting in a set of DICOM files. The list of target tumors and centroid coordinates for each scan are provided in an Excel spreadsheet named "QIBA Volumetry CT - 4.5 Tumor volume bias and linearity" in the QIBA Lung Collection download package. The spreadsheet also helps the assessor perform the record keeping and calculations later in this assessment procedure.

The images contain additional tumors that are not identified in the .csv files. Do NOT include measurements of those additional tumors in the results or calculations described in Sections 4.5.2 & 4.5.3.

Table 4.5.1-1: Phantom Target Tumor Characteristics

Shape	Nominal Diameter	Nominal Density
Spherical	10 mm 20 mm 40 mm	+100 HU
Ovoid	10 mm 20 mm	+100 HU
Lobulated	10 mm 20 mm	+100 HU

The target tumors were placed to be measurable (as defined in the Profile) and have a range of volumes and shapes representative of the scope of the Profile.

The test image set has been acquired according to the requirements of this Profile. See Table 4.5.1-2.

Table 4.5.1-2: Test Image Set Acquisition and Reconstruction Parameters

Scanner	Key Parameters	
Philips 16 (Mx8000 IDT)	KVp: Pitch: Collimation: Exposure: Slice Thickness: Increment: Filter: Repeat Scans:	120 1.2 16x1.5 100 mAs 2 mm 1 mm Medium 3
Siemens 64	KVp: Pitch: Collimation: Exposure: Slice Thickness: Increment: Filter: Repeat Scans:	120 1.2 64x0.6 100 mAs 1.5 mm 1.5 mm Medium 3

4.5.2 DETERMINE VOLUME

The provided spreadsheet may be used to record the volume measurements and will compute the statistical metrics that follow. Recording the amount of time spent on each case and any comments or concerns is not required but is welcome feedback to QIBA.

The assessor shall:

1. Use a single reader for this entire assessment procedure.
2. Import the DICOM files for each scan into their analysis software.
3. Segment the tumors identified in the spreadsheet, totaling 39 target tumor segmentations (3 scans each for 7 tumors on 1 scanner and 6 tumors on the other scanner) The seed point or segmentation may be edited if that is part of the normal operation of the tool.
4. If segmentation edits are performed (e.g. to ensure the volumetric assessment incorporates the whole nodule and excludes any adjacent tissues), report results both with and without editing.
5. Record the volume (Y) of each target tumor (denoted Y_i) where *i* denotes the *i*-th target tumor.

4.5.3 CALCULATE STATISTICAL METRICS OF PERFORMANCE

The natural log of the true volumes (X_i) of each target tumor are known and are provided in the dataset.

The assessor shall:

1. Calculate the individual percentage bias (b_i) of the measurement of each target tumor as $b_i = lnY_i - ln\ X_i$
2. Estimate the population bias over the N target tumors as $\widehat{D} = \sum_{i=1}^{N} b_i\ /N$
3. Convert to a percentage bias estimate as $\%\widehat{bias}$ = $\left(\exp\left(\widehat{D}\right) - 1\right) \times 100$.
4. Estimate 95% confidence intervals for the population bias as $CI_{\widehat{D}} = \widehat{D} \pm t_{[\alpha=0.025, df=N-1]} \times SE\left(\widehat{D}\right)$ and $CI_{\%bias} = (\exp(CI_{\widehat{D}}) - 1) \times 100$
5. Derive $Overall\ \%\widehat{bias} = \max(|CI_{\%bias}|)$ to compare to the bias specifications
6. Divide the target tumors into three subgroups (containing the spherical, ovoid and lobulated target tumors respectively).
7. Repeat the population bias, percentage bias, confidence interval, and overall %bias calculations to get a shape subgroup %bias for the spherical, ovoid, and lobulated subgroups, respectively.
8. Fit a quadratic model to the volume data $\log Y_i$ on $[\ln X_i\ , (\ln X_i)^2]$ and estimate quadratic term ($\hat{\beta}_2$)
9. Fit an ordinary least squares (OLS) regression of the $\ln Y_i$ on $\ln X_i$ and estimate the slope ($\hat{\beta}_1$)

The assessor is recommended to also plot the volume estimate ($\ln Y_i$ versus $\ln X_i$) and the OLS regression curve of the volume estimates as part of the assessment record.

Appendix A: Activity Requirements

This Appendix organizes Profile requirements according to the sequence of activities involved in generating the biomarker. The requirements here are the same as those in the requirement checklists in Section 3. The step-by-step activity organization can be more conducive to ferreting out sources of variance by the Biomarker Committee and may be helpful for users of the Profile to understand the big picture. The requirement checklists in Section 3 are more convenient for the individuals, systems, and organizations checking their conformance to the Profile.

A.1. Product Validation

This activity evaluates equipment (Scanner, Reconstruction Software, and Image Analysis Tool) prior to their use in the Profile (e.g. at the factory). Product validation includes validations and performance assessments necessary to reliably meet the Profile Claim.

A.1.1 DISCUSSION

Tumor Volume Computation is assessed to confirm that the software is computing the volume correctly and confirm there is a reasonable lack of bias at individual timepoints.

Tumor Volume Change Repeatability is assessed to confirm that the software produces sufficiently consistent results over a set of test data. *Repeatability* considers multiple measurements taken under the same conditions (same equipment, parameters, reader, algorithm, etc.) but different subjects, while *reproducibility* considers multiple measurements taken where one or more conditions have changed. So while the Profile Claims address reproducibility, this particular requirement is limited to repeatability. Target repeatability values were chosen based on groundwork [1][2][3][4][5].

Segmentation may be performed automatically by software, manually by a human, or semi-automatically with human guidance/intervention, for example to identify a starting seed point, or region, or to edit boundaries. If a human participates in the segmentation, it is suggested that consistent settings be used for conversion of density into display levels (window and level) either by fixing them during the segmentation process or documenting them. When a human operator in involved, product performance assessments should be based on a typical operator (i.e. with standard training and experience).

It is up to products that do not use contours to propose a method for verification by the radiologist.

Reading Paradigms, such as the "sequential locked" paradigm here, can reduce variability from inconsistent judgments (such as where to separate an attached tumor) but may also introduce subconscious biases. The Image Analysis Tool is not prohibited from displaying the volume value from the previous timepoint, but if that is determined to be the source of problems, it might be prohibited in future Profile editions.

Confidence Interval of Result provides a range of plausible values for the change in tumor volume. Presenting the radiologist with the confidence interval (e.g. [2.5 cm^3, 4.9 cm^3]) in addition to, or perhaps instead of, the measured volume (e.g. 3.7 cm^3), potentially provides a better decision-making sense of the result by focusing on the range, not a single value.

The Image Analysis tool is encouraged to calculate and make available to the operator the 95% confidence interval for tumor volume change based on the equation:

$$(Y_2 - Y_1) \pm 1.96 \times \sqrt{(Y_1 \times wCV_1)^2 + (Y_2 \times wCV_2)^2}$$

Where

Y_1 and Y_2 is the volume measured at timepoint 1 and 2,

wCV_1 and wCV_2 is the within-nodule coefficient of variation for Y_1 and Y_2 taken from the following table,

D_1 and D_2 is the longest in-plane diameter of the volume at timepoint 1 and 2:

D_1, D_2	10-34mm	35-49mm	50-100mm
wCV_1, wCV_2	0.141	0.103	0.085

The 95% confidence interval (CI) can be interpreted as follows: If the change in a tumor's volume over two timepoints is measured repeatedly and the CI range is constructed for each measurement, then 95% of those CI ranges would contain the true volume of the tumor.

A reference implementation of a calculator that uses the specified equation is available at: https://www.accumetra.com/NoduleCalculator.html

> Note: While displaying the 95% CI based on an operator configured wCV would be more convenient for the radiologist than transcribing measured values into a web tool, it is currently unclear whether providing such a calculator constitutes a product claim requiring detailed evidence for the FDA. For this reason, Confidence Interval of Result is a suggestion, not a requirement for conformance to the Profile.

Assumptions: The following details were considered safe to reasonably assume, rather than increase the Profile conformance effort by including them as formal requirements. If these assumptions are not met, the staff or equipment are not conformant to the Profile.

- The Image Analysis Tool allows multiple tumors to be measured.
- The Image Analysis Tool correlates each measured tumor across timepoints (manually or automatically). Correlation can be an independent step from segmentation/measurement.

A.1.2 SPECIFICATION

Parameter	Actor	Requirement
Acquisition & Reconstruction Protocol	Scanner	Shall prepare a protocol conformant with section A.4.2 "Protocol Design Specification".
	Scanner	Shall validate that the protocol achieves an f50 value that is between 0.3 mm^{-1} and 0.7 mm^{-1} for both air and soft tissue edges. See 4.1. Assessment Procedure: In-plane Spatial Resolution
	Scanner	Shall validate that the protocol achieves a standard deviation < 60HU. See 4.2. Assessment Procedure: Voxel Noise
Image Header	Reconstruction Software	Shall record in the DICOM header values for tags identified in requirements in A.4.2 "Protocol Design Specification".
Reading Paradigm	Image Analysis Tool	Shall be able to present the reader with both timepoints side-by-side for comparison when processing the second timepoint.
Reading Paradigm	Image Analysis Tool	Shall be able to re-process the first timepoint (e.g. if it was processed by a different Image Analysis Tool or Radiologist).
Tumor Volume Computation	Image Analysis Tool	Shall be validated to compute volume within 5% of the true volume. See 4.3 Assessment Procedure: Tumor Volume Computation.
Tumor Volume Repeatability	Image Analysis Tool	Shall be validated to achieve tumor volume repeatability with: • an overall repeatability coefficient of less than 0.16 • a small subgroup repeatability coefficient of less than 0.21 • a large subgroup repeatability coefficient of less than 0.21 See 4.4. Assessment Procedure: Tumor Volume Repeatability.
Tumor Volume Bias & Linearity	Image Analysis Tool	Shall be validated to achieve: • an overall %bias of less than the Allowable Overall %Bias • a shape subgroup %bias for each subgroup (spherical, ovoid, lobulated) of less than the Allowable Shape Subgroup %Bias • slope ($\hat{\beta}_1$) between 0.98 and 1.02 • quadratic-term ($\hat{\beta}_2$) between -0.05 and 0.05 The Allowable Overall %Bias and the Allowable Shape Subgroup %Bias are taken from Table A.1.2-1 based on the overall repeatability coefficient achieved by the Image Analysis Tool using the assessment procedure in Section 4.4. See 4.5 Assessment Procedure: Tumor Volume Bias and Linearity.

Table A.1.2-1: Allowable Tumor Volume %Bias based on Overall Repeatability Coefficient

Overall Repeatability Coefficient $\widehat{RC}$	Allowable Overall %Bias (RMSE Target: 7.1%)	Allowable Shape Subgroup %Bias (RMSE Target: 7.8%)
0.05	6.60%	7.32%
0.06	6.37%	7.11%
0.07	6.09%	6.86%
0.08	5.75%	6.56%
0.09	5.35%	6.20%
0.10	4.88%	5.79%
0.11	4.30%	5.31%
0.12	3.59%	4.75%

0.13	2.63%	4.06%
0.14	0.84%	3.17%
0.15	0.00%	1.84%
0.155	0.00%	0.00%
0.16	n/a (failed repeatability)	n/a (failed repeatability)

A.2. Staff Qualification

This activity evaluates staff (Radiologist, Physicist, and Technologist) prior to participation in the Profile. Staff Qualification includes training, qualification, or performance assessments necessary to reliably meet the Profile Claim.

A.2.1 DISCUSSION

If measurement contours are prepared by an Image Analyst but reviewed and edited by a Radiologist, validate the repeatability of the Radiologist. If contours are completely delegated to an Image Analyst, validate the repeatability of the Image Analyst.

It is expected that the effect of radiologist volume bias will largely cancel out due to the requirement that the radiologist process both timepoints (see A.9.2), so no Tumor Volume Bias & Linearity validation requirement is placed on the Radiologist.

A.2.2 SPECIFICATION

Parameter	Actor	Specification
Tumor Volume Change Repeatability	Radiologist	Shall, if operator interaction is required by the Image Analysis Tool to perform measurements, be validated to achieve tumor volume change repeatability with: • an overall repeatability coefficient of less than 0.16 • a small subgroup repeatability coefficient of less than 0.21 • a large subgroup repeatability coefficient of less than 0.21 See 4.4. Assessment Procedure: Tumor Volume Repeatability.
Acquisition Protocol	Radiologist	Shall ensure technologists have been trained on the requirements of this Profile.

A.3. Periodic QA

This activity involves quality assurance of the scanners that is periodic, not directly associated with a specific subject. Periodic QA includes calibrations, phantom imaging, performance assessments or validations to ensure the scanner is aligned, calibrated, and functioning as needed to reliably meet the Profile Claim. Performance measurements of specific protocols are addressed in Section A.5, not here.

Assumptions: The following details were considered safe to reasonably assume, rather than increase the Profile conformance effort by including them as formal requirements. If these assumptions are not met, the staff or equipment are not conformant to the Profile.

- The Physicist performs relevant quality control procedures as recommended by the manufacturer and records the date/time of QC procedures for auditing.

A.4. Protocol Design

This activity involves designing and validating image acquisition protocols. Protocol design includes constraints on acquisition and reconstruction parameters necessary to reliably meet the Profile Claim.

A.4.1 DISCUSSION

Protocol Design is considered to take place at the imaging site; however, sites may choose to make use of protocols developed elsewhere. It is not intended that design and validation be repeated for each subject.

These specifications focus as much as possible on the characteristics of the resulting dataset, rather than a particular technique for achieving those characteristics. This is intended to achieve Profile performance targets while allowing patient-specific adjustments (such as increasing acquisition mAs and reconstruction DFOV for larger patients), and flexibility for product innovation. Technique parameter sets in the QIBA Conformance Statements for Scanners and Reconstruction Software may be helpful for those looking for more guidance. The acquisition parameter constraints here have been selected with scans of the chest, abdomen and pelvis in mind.

Specific constraints are not placed on most acquisition and reconstruction protocol parameters. It is presumed that significant changes to those parameters would result in non-conformant changes in Noise and Resolution. Changes that do not affect the Noise and Resolution are considered insignificant for the purposes of the Profile.

It is not expected that Noise and Resolution be assessed for each subject scan, but rather the Scanner and Reconstruction Software be qualified for the expected acquisition and reconstruction parameters.

Total Collimation Width is defined as the total nominal beam width, NxT, where N is the number of detector rows and T is the nominal tomographic section thickness, for example 64x1.25mm. Wider collimation widths can increase coverage and shorten acquisition, but can introduce cone beam artifacts which may degrade image quality. Imaging protocols will seek to strike a balance. This parameter might not be directly visible in all scanner interfaces.

Nominal Tomographic Section Thickness (T), the term preferred by the IEC, is sometimes also called the Single Collimation Width. Thinner slices improve spatial resolution along the subject z-axis and reduce partial volume effects but can increase image noise.

Scan Duration is constrained to facilitate acquisition in a single breath-hold, thereby preventing respiratory motion artifacts or anatomic gaps between breath-holds. This requirement is applicable to scanning of the chest and upper abdomen, and is not required for imaging of the head, neck, pelvis, spine, or extremities.

IEC Pitch is chosen to ensure sufficient acquisition data sampling for adequate image quality.

Reconstruction Characteristics influence the texture and the appearance of tumors in the reconstructed images, which may influence measurements. A softer kernel can reduce noise at the expense of spatial resolution. An enhancing kernel can improve resolving power at the expense of increased noise. Kernel characteristics also interact with acquisition parameters and reconstruction algorithm types; a sharper kernel in a low-dose scan might make a greater difference with an FBP Algorithm than with an Iterative Algorithm. The characteristics of different tissues (e.g. lung) may call for the use of different kernels, and implementers are encouraged to use kernels suitable for the anatomic region and tissue imaged. The use of multiple kernels in a single study is not prohibited by the specification below, but any given tumor must be measured on images reconstructed using consistent kernels at each timepoint.

Reconstructed Image Thickness is the nominal width of the reconstructed image along the z-axis, since the thickness is not technically the same at the middle and at the edges.

Reconstructed Image Interval is the distance between the center of two consecutive reconstructed images. A wider interval that results in noncontiguous data is unacceptable as it may "truncate" the spatial extent of the tumor and degrade the identification of tumor boundaries. A narrower interval can result in **overlap,** increase the number of images, and may slow down throughput, increase reading time and increase storage requirements. For multi-detector row CT (MDCT) scanners, creating overlapping image data sets has NO effect on radiation exposure because multiple reconstructions (e.g. with different intervals) can be reconstructed from the same acquisition data and therefore no additional radiation exposure is needed.

Decisions about overlap (having an interval that is less than the nominal reconstructed slice thickness) need to consider the technical requirements of the clinical trial, including effects on measurement, throughput, image analysis time, and storage requirements. Some studies have shown a benefit in accuracy and precision of overlapping reconstruction with the magnitude of the benefit increasing for smaller nodules.

Spatial Resolution quantifies the ability to resolve spatial details and scales the impact of partial volume effects. Lower resolution can make it difficult to accurately determine the borders of tumors, and thus decreases the accuracy and precision of volume measurements. Higher spatial resolution typically comes with higher noise (see below). If spatial resolution differs significantly between two timepoints, it can affect repeatability. Both balance and consistency is desirable. Maximum spatial resolution is mostly determined by the scanner geometry (which is not usually under user control) and the reconstruction algorithm/kernel (over which the user has some choice).

Resolution is assessed (See section 4.1) in terms of the f50 value of the modulation transfer function (MTF) measured in a scan of a resolution phantom (such as module 1 of the CT Accreditation Program (CTAP) phantom from the American College of Radiology). In the ACR phantom, the resolution is assessed at only one distance from the isocenter. Although spatial resolution may vary with distance from the isocenter and tumors can be expected at various distances from the isocenter, it is considered fair to assume resolution does not degrade drastically relative to the acceptable range of the specification here. Since this Profile addresses tumors both in the lung and elsewhere in the torso, the f50 is evaluated for both air and soft tissue edges.

Voxel Noise metrics quantify the magnitude of the random variation in reconstructed CT numbers. Higher noise can make it difficult for humans and automated to identify the boundary of tumors. If available algorithms are found to be uniformly more "noise tolerant", the threshold here may be raised. Lower image noise may not be beneficial if achieved through undesirable image manipulation (e.g. extreme amounts of image smoothing), or scanning technique (e.g. increases in radiation dose or decreases in reconstructed slice thickness). The Profile does not currently define a minimum noise threshold, although it could be introduced as a means of forcing a balance between the goal of noise reduction, and other priorities.

The preferred metric for voxel noise is the standard deviation of reconstructed CT numbers over a uniform region in a phantom. The use of standard deviation has limitations since it can vary with different reconstruction kernels, which also impact the spatial resolution. While the Noise-Power Spectrum would be a more comprehensive metric, it is not practical to calculate (and interpret) at this time.

Most modern CT scanners are equipped with Automatic Exposure Control that adjusts scanner radiation output to achieve pre-determined target noise levels in the images as a function of patient body habitus.

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.

A.4.2 SPECIFICATION

Note: The Radiologist is responsible for the protocol parameters and for ensuring that the protocol has been validated, which may be done by an in-house medical physicist, a physics consultant or other staff (such as vendor service or specialists) qualified to perform the validations described. Protocol design should be done collaboratively between the physicist and the radiologist with the ultimate responsibility to the radiologist. Some parameters are system dependent and may require special attention from a physicist. They may choose to use a protocol provided by the vendor of the scanner.

Parameter	Actor	Specification
Acquisition Protocol	Radiologist	Shall prepare a protocol to meet the specifications in this table.
Total Collimation Width	Radiologist	Shall set to Greater than or equal to 16mm. [Total Collimation Width (0018,9307)]
Nominal Tomographic Section Thickness (T)	Radiologist	Shall set to Less than or equal to 1.5mm. [Single Collimation Width (0018,9306)]
Scan Duration for Thorax	Radiologist	Shall set parameter values to cover an axial field of view of 35cm in 10 seconds or less.
IEC Pitch	Radiologist	Shall set to Less than 1.5. [Spiral Pitch Factor (0018,9311)]
Reconstructed Image Thickness	Radiologist	Shall set to between 0.5mm and 2.5mm (inclusive). [Slice Thickness (0018,0050)]
Reconstructed Image Interval	Radiologist	Shall set to less than or equal to the Reconstructed Image Thickness (i.e. no gap, may have overlap). [Spacing Between Slices (0018,0088)]
In-plane Spatial Resolution	Physicist	Shall validate that the protocol achieves an f50 value between 0.3 mm^{-1} and 0.7 mm^{-1} for both air and soft tissue edges. See 4.1. Assessment Procedure: In-plane Spatial Resolution
Voxel Noise	Physicist	Shall validate that the protocol achieves a standard deviation < 60HU. See 4.2. Assessment Procedure: Voxel Noise

A.5. Subject Handling

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

A.5.1 DISCUSSION

This Profile refers primarily to “subjects”, keeping in mind that the requirements and recommendations apply to patients in general, and subjects are often patients too.

When the Profile is being used in the context of a clinical trial, refer to relevant clinical trial protocol for further guidance or requirements on **timing relative to index intervention activity**.

This Profile does not presume any **timing relative to other (confounding) activities**. Fasting prior to contemporaneous FDG PET scans or the administration of oral contrast for abdominal CT is not expected to have any adverse impact on this Profile.

Contrast preparation and administration influences the appearance, conspicuity, and quantification of

tumor volumes. Most studies on which this Profile was based were conducted without contrast. But non-contrast CT might not permit an accurate characterization of some malignant visceral/nodal/soft-tissue tumors and assessment of their tumor boundaries.

Contrast Protocols should achieve a consistent phase and degree of enhancement. When intravenous contrast is used, record the type of contrast, actual total volume administered, concentration, injection rate, delay, whether a saline flush was used, and be consistent between scans. Ideally, this should be recorded in the image header by the Scanner. When oral contrast is used, record the total volume and type of contrast used and be consistent for all abdominal imaging timepoints (although the tolerances for oral timing are larger than for intravenous).

Bolus tracking is a good tool if available, but is not required. When using bolus tracking, be consistent between scans with where the triggering ROI is placed and what threshold is used to trigger the scan.

Contrast (intravenous or oral) may not be clinically indicated or may be contra-indicated for some subjects. Radiologists and supervising physicians determine what contrast, if any, is appropriate for the subject. They may omit intravenous contrast or vary administration parameters when required by the best interest of patients or research subjects. If enhancement consistent with baseline is not achieved, they may still choose to measure tumors, but the measurements will not be subject to the Profile claims. Non-contrast at both timepoints is considered to be consistent enhancement at the two timepoints.

Positioning the subject always Supine/Arms Up/Feet First promotes consistency (if it's always the same, then it's always consistent with baseline), and reduces cases where intravenous lines go through the gantry, which could introduce artifacts. Consistent positioning avoids unnecessary differences in gravity-induced shape and fluid distribution, anatomical shape due to posture/contortion, attenuation, and dose modulation algorithm behavior.

Significant positioning details include arm position, anterior-to-posterior spine curvature as determined by pillows under backs or knees, and lateral spine straightness. Prone positioning is not recommended. Positioning wedges under the knees and head are recommended so the lumbar lordosis is straightened and the scapulae are both in contact with the table. The exact size, shape, etc. of the pillows is not expected to significantly impact the Profile Claim. Clinical trials and local clinics may establish preferred positioning. Approaches that promote scan-to-scan consistency are essential. Image header information about patient orientation and table position can be helpful for auditing and repeating baseline characteristics.

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 from the effect of dose modulation algorithms. Making the subject comfortable reduces the potential for motion artifacts and facilitates compliance with breath holding instructions.

Scan Plane may differ between subjects due to the need to position for physical deformities or external hardware. A vertical scan plane (no tilt) is expected for all imaging except some head and neck exams where it is not unusual to use gantry tilt or positioning aids to adjust the slice orientation. Again, for each individual subject, reasonable consistency over timepoints is important.

All that said, there are no direct conformance requirements on patient positioning; rather the radiologist is required to disqualify measurements when the positioning at the two timepoints is different (See A.8.2).

Breast shields are not recommended for this Profile, based on the American Association of Physicists in Medicine recommendation to use other dose reduction methods, such as dose modulation techniques, instead. If used, position breast shields so they do not degrade the reconstructed images.

Artifact sources, in particular metal and other high-density materials, can degrade reconstructed volume data such that it is difficult to determine the true boundary of a tumor. Artifacts can be induced some distance from the artifact source, depending on scan geometry. If feasible, removing artifact sources completely from the patient during the scan is the best solution. Artifacts from residual oral contrast in the esophagus can affect the measurement of nearby small tumors.

Breath holding reduces motion that might degrade the image and full inspiration inflates the lungs, which separates structures and makes tumors more conspicuous. Since motion may occur in the first few seconds after full inspiration due to diaphragmatic relaxation, allowing 5 seconds before initiating the acquisition is recommended. A practice round of the breathing instructions is also recommended. This familiarizes the subject with the procedure, allows any difficulties with the instructions to be addressed, and familiarizes the technologist with the subject's breathing rate.

A single breath-hold acquisition is likely to be more repeatable and avoids problems of tumors on scan boundaries. If two or more breath-holds are needed to fully cover an anatomic region, different tumors may be acquired on different breath-holds. It is still necessary that each tumor be fully included in images acquired within a single breath-hold to avoid discontinuities or gaps that would affect the measurement.

Assumptions: The following details were considered safe to reasonably assume, rather than increase the Profile conformance effort by including them as formal requirements. If these assumptions are not met, the staff or equipment are not conformant to the Profile.

- The Technologist positions the subject such that the "sagittal laser line" lies along the sternum (e.g. from the suprasternal notch to the xiphoid process).
- The Technologist instructs the subject in proper breath-hold, and starts image acquisition shortly after full inspiration and visible movement has ceased, accounting for lag time between full inspiration and diaphragmatic relaxation.

A.5.2 SPECIFICATION

Parameter	Actor	Specification
Contrast Protocol	Radiologist	Shall prescribe a contrast protocol (which may be No Contrast) that achieves enhancement consistent with baseline.
Use of intravenous contrast	Radiologist	Shall determine whether the selected contrast protocol, if any, will achieve sufficient tumor conspicuity.
	Technologist	Shall use the prescribed intravenous contrast parameters.
Use of oral contrast	Radiologist	Shall determine whether the selected contrast protocol, if any, will achieve sufficient tumor conspicuity.
	Technologist	Shall use the prescribed oral contrast parameters.
Artifact Sources	Technologist	Shall remove or position potential artifact sources (specifically including breast shields, metal-containing clothing, and EKG leads) such that they will not degrade reconstructed CT volumes.
Table Height	Technologist	Shall adjust the table height for the mid-axillary plane to pass through the isocenter.

A.6. Image Data Acquisition

This activity involves acquisition of image data for a subject. It includes details necessary to reliably meet the Profile Claim. This activity applies to every subject. Protocol Design (Section A.4) touches on similar parameters, but addresses details that are not done for each subject, such as designing standard protocols and validating protocol performance with phantoms.

A.6.1 DISCUSSION

CT scans for tumor volumetric analysis can be performed on any equipment that complies with this Profile. However, it is strongly encouraged to perform all scans for a given subject using the same manufacturer, model and version, which is expected to further reduce variation (See Table B-2).

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

Acquisition Protocols are often selected by the Technologist at scan time based on the procedure request in the modality worklist. For measurements to be conformant, the technologist must use a validated protocol (see Section A.4.2). The site could communicate which protocols have been validated using tags in the protocol name, a paper list for the technologist, or a special pick-list on the modality console. Or a site might validate ALL protocols for a given procedure so any selected protocol will have been validated.

There is no requirement to scan phantoms before every subject, or for the technologist to validate the protocol themselves.

Image Header recordings of parameter values facilitates confirming conformance.

The **Localizer** provides on opportunity for the technologist to observe and mitigate artifact sources.

A.6.2 SPECIFICATION

Parameter	Actor	Specification
Acquisition Protocol	Technologist	Shall select a protocol that has been previously prepared and validated for this purpose. (See A.4.2 "Protocol Design Specification")
Localizer	Technologist	Shall confirm on the localizer (scout) image the absence of artifact sources that could affect the planned volume acquisitions or alter the attenuation of lung nodules.
Scan Duration for Thorax	Technologist	Shall set parameter values to cover an axial field of view of 35cm in 10 seconds or less.

A.7. Image Data Reconstruction

This activity involves the reconstruction of image data for a subject. It includes criteria and procedures related to producing images from the acquired data that are necessary to reliably meet the Profile Claim. This activity applies to every subject. Protocol Design (Section A.4) touches on similar parameters, but addresses details that are not done for each subject, such as designing standard protocols and validating protocol performance with phantoms.

A.7.1 DISCUSSION

Reconstruction Protocols affect the image pixel characteristics. Protocols that have been validated (See A.4.2) to achieve the required image characteristics are considered essentially interchangeable. As described in A.6.1, the technologist needs to select validated protocols. Making information about the

protocol selected and any significant modifications available to the radiologist will support the Image QA Activity (See A.8).

Reconstruction Field of View is typically selected at the time of each scan and affects reconstructed pixel size because the image matrix size of most reconstruction algorithms is fixed (e.g. 512x512). If the field of view needs to be expanded to encompass more anatomy, the resulting pixels will be larger and the reduced resolution may be insufficient to achieve the claim. Pixel Size directly affects voxel size along the subject x-axis and y-axis. Smaller voxels are preferable to reduce partial volume effects and increase measurement precision. A reconstruction with a smaller field of view specifically for measurements may be necessary, but must still be consistent with baseline.

Pixel size in each dimension is not the same as spatial resolution in each dimension. The spatial resolution of the reconstructed image depends on a number of additional factors including a strong dependence on the reconstruction kernel, however since the kernel is configured in the protocol, it's effect on the spatial resolution will have been evaluated by the f50 requirement in the Protocol Design activity (See A.4.2).

A.7.2 SPECIFICATION

Parameter	Actor	Specification
Reconstruction Protocol	Technologist	Shall select a protocol that has been previously prepared and validated for this purpose. (See A.4.2 "Protocol Design Specification").
Reconstructed Image Thickness	Technologist	Shall set to between 0.5mm and 2.5mm (inclusive) if not set in the protocol.
Reconstructed Image 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.
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. [Reconstruction Field of View (0018,9317)]

A.8. Image QA

This activity involves evaluating the reconstructed images prior to image analysis. It includes image criteria that are necessary to reliably meet the Profile Claim. This activity applies to every subject. Prior activities, such as Subject Handling (Section A.5), include requirements that attempt to avoid issues mentioned here, but it is still necessary to confirm during this QA step whether or not those prior activities were successful.

A.8.1 DISCUSSION

This QA is performed between image generation and analysis. Image content characteristics are checked for conformance with the Profile. It's expected sites perform other QA as part of good imaging practices.

The Radiologist is identified here as ultimately responsible for this activity; however, sites may find it beneficial for technologists to review these details at the time of imaging and identify cases which might require a repeat acquisition and/or reconstruction to address issues with patient motion or artifacts.

Similarly, some or all of these checks may be performed by the radiologist at reporting time to detect whether the technologist was unsuccessful in avoiding them at acquisition time and as a result some or all of the tumor measurements may then be identified as not within the performance target of the Profile.

Patient positioning variation refers to differences in patient orientation (prone, supine, decubitus, etc.) and the use of positioning wedges. If the subject is supine at one time and prone at another, some tumors may deform differently in a cavity, be compressed differently by other structures, or be affected by deformation of the organ in which they are sited.

Scan Plane variation refers to differences in gantry tilt or differences in head/neck positioning. Several factors that affect volumetry are not isotropic, so changing the orientation of the tumor relative to the scan plane from one timepoint to another can increase variability.

Patient motion artifacts can manifest in a variety of ways, such as a perceptible tram tracking appearance of the bronchioles or blurring of the lung architectural contours with lung windows.

Dense object artifacts (both internal and external to the patient) can variably degrade the ability to assess tumor boundaries as discussed in section A.5, resulting in poor change measures and repeatability.

Clinical conditions can degrade the ability to assess tumor boundaries, or influence the structure of the tumor itself. For example, atelectasis, pleural effusion, pneumonia and/or pneumothorax can result in architectural changes to the lung surrounding a nodule. Necrosis may complicate tumor extent decisions.

Tumor Margin Conspicuity refers to the clarity with which the boundary of the tumor can be discerned from the surroundings which can directly impact the ability to segment the tumor. Conspicuity problems can derive from poor contrast enhancement, from the inherent texture, homogeneity or structure of the tumor, or from attachment of the tumor to other structures.

Contrast Enhancement is required to be consistent between the two timepoints. A non-contrast scan at both timepoints satisfies that requirement.

Tumor Measurability is a general evaluation left to the judgement of the radiologist. They oversee segmentation and disqualify tumors with poor measurability or inconsistent segmentation between the two timepoints. If the tumor has varying margin conspicuity on different slices, or is conspicuous but has complex geometry, or the segmentation software is visibly failing, or the background didn't respond to contrast the same way in the two timepoints, the radiologist should disqualify the tumor. Conversely, if the tumor is attached to another structure but the radiologist is confident they can get consistent segmentation over the two timepoints, they may allow a tumor that would be otherwise disqualified.

Tumor Shape is not addressed with an explicit requirement. No specific tumor shapes are considered a priori unsuitable for measurement. Although groundwork has shown that consistent measurements are more readily achieved with simple shapes than with complex shapes (such as spiculated tumors), the tumor size, margin conspicuity, and measurability constraints are typically sufficient. Moreover, complex shapes are even more difficult to assess accurately using simple linear measurements, increasing the relative added value of volumetry.

Tumor Size can affect the accuracy of measurements. Theoretical assessment and the groundwork projects done by QIBA both indicate that for tumors that are small, errors in measurement represent a greater percentage of the measured size. For tumors that are smaller than the range required here, refer to the QIBA Small Lung Nodule Profile. For tumors that are larger than the range required here, the limitations on measurement are driven more by anatomy than imaging physics. Such tumors are likely to cross anatomical boundaries and abut structures that make consistent segmentation difficult.

This Profile is "**lesion-oriented**". If one tumor in a study is excluded from the Profile Claim because the tumor does not conform with the specifications in this section, that does not affect other tumors in the

same study which do conform with these specifications at both timepoints. If a future study results in the excluded tumor being conformant at two timepoints, then the claim holds for those two timepoints.

While the radiologist is responsible for confirming case and tumor conformance with the specifications in A.8.2, individual sites may determine the best approach in their work environment for capturing this audit data. Possible approaches include the use of a QIBA worksheet to capture this information, or dictating parameters into the clinical report (e.g. the scan is free of motion or dense object artifacts, contrast enhancement is consistent with baseline, the tumor margins are sufficiently conspicuous").

A.8.2 SPECIFICATION

The Radiologist shall ensure the following has been evaluated for each tumor being measured.

Parameter	Actor	Specification
Tumor Measurability	Radiologist	Shall disqualify any tumor they feel might reasonably degrade the consistency and accuracy of the measurement. Conversely, if artifacts or attachments are present but the radiologist is confident and prepared to edit the contour to eliminate the impact, then the tumor need not be judged non-conformant to the Profile.
Patient Motion Artifacts	Radiologist	Shall confirm the images containing the tumor are free from artifact due to patient motion.
Dense Object Artifacts	Radiologist	Shall confirm the images containing the tumor are free from artifact due to dense objects, materials or anatomic positioning.
Clinical Conditions	Radiologist	Shall confirm no clinical conditions are affecting the measurability of the tumor.
Tumor Margin Conspicuity	Radiologist	Shall confirm the tumor margins are sufficiently conspicuous and unattached to other structures of equal density to distinguish the volume of the tumor.
Contrast Enhancement	Radiologist	Shall confirm the phase of enhancement, if any, and degree of enhancement are consistent with baseline.
Patient Positioning Consistency	Radiologist	Shall confirm any tumor deformation due to patient positioning is consistent with baseline.
Breath Hold Consistency	Radiologist	Shall confirm the breath hold state and degree of inspiration is consistent with baseline.
Reconstructed Image Thickness	Radiologist	Shall confirm the reconstructed image thickness is between 0.5mm and 2.5mm, and consistent (e.g. within 0.5mm) with baseline.
Field of View	Radiologist	Shall confirm the image field of view (FOV) is consistent with baseline.
Tumor Size	Radiologist	Shall confirm (now or during measurement) each tumor longest in-plane diameter is between 10 mm and 100 mm. (For a spherical tumor, this roughly corresponds to a volume between 0.5 cm^3 and 524 cm^3.)

A.9. 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.

A.9.1 DISCUSSION

This Profile characterizes each designated tumor by its volume change relative to prior image sets.

Typically, the boundary of the tumor is determined ("segmentation"), the volume of the segmented tumor computed and the difference of the tumor volume in the current scan from the baseline scan calculated.

The Profile requires that the same Image Analysis Tool and the same Radiologist measure both timepoints of a given tumor. This requirement is due to the variability introduced when a different Image Analysis Tool and/or Radiologist is used between the two timepoints. (See Table 2-1 and the related Discussion)

The Analysis Tool is recommended (See section A.1) to present to the Radiologist for each volume change the Confidence Interval of Result, which indicates a range of plausible values.

Determination of which tumors should be measured is out of scope for this Profile. Such determination may be specified within a protocol, formal response criteria standards, or local clinical requirements.

A.9.2 SPECIFICATION

Parameter	Actor	Specification
Reading Paradigm	Radiologist	Shall re-process the first timepoint if it was processed by a different Image Analysis Tool or Radiologist.
Result Verification	Radiologist	Shall review & approve margin contours produced by the tool.

Appendix B: Biomarker Usage

This Appendix discusses concepts and considerations related to the meaning of the Claims and the application of this Biomarker in clinical contexts.

Change Confidence Intervals:

95% Confidence Intervals (CI) help to understand measurement uncertainty. It can be instructive to look at both ends of the 95% CI and consider if a clinical decision would be the same for both values. If so, then the measurement behind that CI may be a good basis for that decision. The 95% confidence interval (CI) for a true change in volume is computed as $(Y_2 - Y_1) \pm 1.96 \times \sqrt{(Y_1 \times wCV_1)^2 + (Y_2 \times wCV_2)^2}$, where Y_1 and Y_2 are the volume measurements at baseline and the subsequent timepoint, and wCV_1 and wCV_2 are the wCV estimates corresponding to these measurements. Consider the following example tumors:

Change Example (Diameter)	Baseline Volume	Subsequent Volume	Volume Change Confidence Interval Calculation	95% CI of True Volume Change
100mm -> 50mm	**524 cm³** (100mm)	**65 cm³** (50mm)	**-459 cm³ ± 88 cm³**	**[-547 cm³, -371 cm³]**
40mm -> 80mm	**34 cm³** (40mm)	**268 cm³** (80mm)	**234 cm³ ± 45 cm³**	**[189 cm³, 279 cm³]**
10mm -> 20mm	**0.5 cm³** (10mm)	**4.2 cm³** (20mm)	**3.7 cm³ ± 1.2 cm³**	**[2.5 cm³, 4.9 cm³]**

Note: The 95% CI in the first example includes a volume reduction of 547 cm³ for a tumor initially measured as 524 cm³ because it accounts for variability in the initial measurement (i.e. the tumor may have initially been larger).

Change Detection Confidence Thresholds:

The 95% confidence thresholds (**±**24%, **±**29%, **±**39%) in the Change Detection Claim can be thought of as "error bars" or "noise" around the measurement of volume change. If a change is measured to be within this range, it cannot be ascertained that a change has actually occurred. However, if a tumor changes size beyond these limits, it can be ascertained with 95% statistical confidence that 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.

Clinical Interpretation of Change (progression/response):

The existence of a true change is described in the Change Detection Claim in terms of the minimum measured change required to be 95% confident a change has occurred. So, to be 95% confident there has been a true increase or decrease in tumor volume, the measured change should be at least 24% for a tumor that had a longest in-plane diameter of between 50mm and 100mm at baseline (and at least 29% or 39% for the next two size categories respectively).

Clinical Interpretation of Change Magnitude:
The confidence interval for the magnitude of the true change is described in terms of the 95% Confidence Interval of the measured volume change value. (See the formula in the Section 1.2). If volume was measured as 34 cm^3 at baseline and 268 cm^3 at follow-up (corresponding to a diameter change from 40mm to 80mm), then the 95% CI for the true change would be an increase in volume of 234 $cm^3 \pm 45$. A confidence interval that contains zero indicates one should not conclude a true change has occurred.

Whether a change in tumor volume constitutes *clinically meaningful* disease progression or response is a distinct decision that requires a clinician's judgment. There are currently no validated response criteria based on volume. The most commonly used response criteria in solid tumors, RECIST 1.1, uses unidimensional measurements. For comparison, RECIST 1.1 specifies that progression has occurred when there has been a 20% increase in tumor diameter from baseline (which corresponds to a 73% increase in volume for a spherical tumor) and favorable treatment response has occurred when there has been a 30% decrease in diameter (which corresponds to a 66% decrease in volume).

The Profile lower bound of 10mm on the tumor longest in-plane diameter is set to limit the variability introduced when approaching the resolution of the dataset, e.g. partial volume. The upper bound of 100mm is set to limit the variability introduced by more complex tumor morphology and organ involvement, and also to keep performance assessment procedures manageable.

The performance values in the Repeatability Claim and the Change Detection Claim reflect the likely impact of variations permitted by this Profile. The Profile requires that for a given tumor the same conformant radiologist and image analysis tool must make the measurement at both timepoints. If a different radiologist and/or image analysis tool was used at the baseline, this means the current radiologist and image analysis tool must repeat the baseline measurement for the result to be conformant with this Profile. The Profile permits the other Actors (scanner, technologist, physicist) to differ at the two timepoints, i.e. it is not required that the same scanner be used for both exams of a patient. If one or more of the Actors that are permitted to differ are the same, such as the same scanner for both exams, the implementation is still conformant with this Profile and it is expected that the measurement performance will be improved. To give a sense of the possible improvement, Table B-1 presents expected precision for alternate scenarios; however, except for the bolded column, these precision values are **not** Claims of this Profile. If the radiologist or image analysis tool differ (or any other requirement of the Profile is not met), the measurement might still be clinically useful, but the measurement is no longer conformant with the Profile and the measurement Claims should not be presumed.

Table B-1: Minimum Detectable Change in Tumor Volume (Informative)

	Different Scanner	Same Scanner

Tumor Diameter	Different Radiologist		**Same Radiologist**		Different Radiologist		Same Radiologist	
	Different Analysis Tool	Same Analysis Tool	Different Analysis Tool	**Same Analysis Tool**	Different Analysis Tool	Same Analysis Tool	Different Analysis Tool	Same Analysis Tool
>50mm	43%	24%	43%	**24%**	37%	10%	37%	8%
35-49mm	67%	33%	65%	**29%**	62%	22%	60%	14%
10-34mm	139%	120%	80%	**39%**	136%	117%	75%	28%

Notes:
1. Different Scanner means different models (from the same or different vendors) were used at the two timepoints. Two scanners with different serial numbers but of the same model are considered to be the Same Scanner.
2. Precision is expressed here as the repeatability or reproducibility coefficient, depending on the column.
3. A measured change in tumor volume that exceeds the relevant precision value in the table indicates 95% confidence in the presence of a true change.
4. Minimum detectable differences can be calculated from the following formula: $1.96 \times \sqrt{(2 \times wCV^2)}$, where wCV is estimated from the square root of the sum of the variances from the applicable sources of uncertainty (assuming that the variance components are additive; an assumption that has not yet been tested).
5. The estimates of the sources of variation were derived from several groundwork studies, some on phantoms and some on human subjects.

Appendix C: Acknowledgements and Attributions

This document is proffered by the Radiological Society of North America (RSNA) Quantitative Imaging Biomarker Alliance (QIBA) Volumetric Computed Tomography (CTVol) Biomarker Committee. The committee is composed of representatives from academia, professional societies, scanner manufacturers, image analysis software developers, image analysis laboratories, biopharmaceutical industry, government research organizations and regulatory agencies, among others. All work is considered pre-competitive.

For a description of the committee and its work, see: https://qibawiki.rsna.org/index.php/Committees.

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Bibliography / References

[1] Athelogou M, Kim HJ, Dima A, et al., Algorithm Variability in the Estimation of Lung Nodule Volume From Phantom CT Scans: Results of the QIBA 3A Public Challenge. Acad Radiol 2016.
[2] Buckler AJ, Danagoulian J, Johnson K, et al., Inter-Method Performance Study of Tumor Volumetry Assessment on Computed Tomography Test-Retest Data. Acad Radiol 2015; 22:1–16.
[3] Fenimore C, Lu ZQ, McNitt-Gray MF, et al., Clinician sizing of synthetic nodules to evaluate CT interscanner effects. RSNA 2012.
[4] McNitt-Gray MF, Kim GH, Zhao B, et al., Determining the Variability of Lesion Size Measurements from CT Patient Datasets Acquired Under "No Change" Conditions. Transl Oncol 2015 Feb; 8(1):55-64.
[5] Petrick NP, Kim HJ, Clunie DA, et al., Comparison of 1D, 2D & 3D Nodule Sizing Methods by Radiologists for Spherical and Complex Nodules on Thoracic CT Phantom Images. AcadRadiol 2014;21:30–40.

Change Log

2018.06.22	Initial Publication of Technically Confirmed Profile (2018)
2022.06.26	Re-Publication of Technically Confirmed Profile (2022) Profile used to pilot streamlining initiative. Language was simplified, particularly the Executive Summary, Clinical Context, Claims, and Disclaimers; checklists were moved forward for easy access to primary users of the profile; several requirements were dropped (per Requirement Vetting Process); assessment procedures adopted numbered steps; anatomical scope clarified in Disclaimer section; Approved Change Proposals incorporated.