Quantitative Imaging Biomarkers Alliance RSNA

QIBA Profile:

Atherosclerosis Biomarkers by Computed Tomography Angiography (CTA) - 2019

Stage: Consensus

When referencing this document, please use the following format:

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1. Executive Summary

Clinical application of Computed Tomography Angiography (CTA) is widely available as a technique to optimize therapeutic approach of vascular disease. Evaluation of atherosclerotic arterial plaque characteristics is currently based-on qualitative biomarkers. However, the reproducibility of such findings has historically been limited even among experts [1].

Quantitative imaging biomarkers have been shown to have additive value above traditional qualitative imaging metrics and clinical risk scores regarding patient outcomes [2]. However, many definitions and cut-offs are present in the current literature, therefore standardization of quantitative evaluation of CTA datasets is needed before becoming a valuable tool in daily clinical practice. In order to establish these biomarkers in clinical practice, techniques to standardize quantitative imaging across different manufacturers with cross-calibration is required. Moreover, post-processing of atherosclerotic plaque segmentation needs to be optimized and standardized.

The goal of a Quantitative Imaging Biomarker Alliance (QIBA) Profile is to help achieve a useful level of performance for a given biomarker. Profile development is an evolutionary, phased process. The performance claims represent expert consensus and will be empirically demonstrated at a subsequent stage. Users of this Profile are encouraged to refer to the following site to understand the document's context: http://qibawiki.rsna.org/index.php/QIBA_Profile_Stages. All statistical performance assessments are stated in carefully considered metrics and according to strict definitions as given in [3-8], which also includes detailed, peer-reviewed rationale on the importance of adhering to such standards.

This document is intended to help clinicians making decisions based on these biomarkers, imaging staff generating these biomarkers, vendor staff developing related products, purchasers of such products, and investigators designing trials with imaging endpoints. The **Claim** (Section 2) describes the biomarker performance. The **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) for evaluating specific requirements are defined as needed.

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.

2. Clinical Context and Claim(s)

Clinical Context

Plaque composition is associated with the likelihood for rupture and downstream ischemic events, but is known to be highly variable presently. Standardized protocols and analysis of plaque characteristics can increase early identification of patients at increased risk for adverse events. Plaque composition is similar in coronary and carotid arteries, irrespective of its age, and this will largely determine relative stability [9], suggesting similar presentation at coronary CTA (CCTA) as at CTA elsewhere. Minor differences in the extent of the various plaque features may include a thicker fibrous cap and a higher prevalence of intra-plaque hemorrhage in the carotid arteries, however, without difference in the nature of plaque components [10]. In addition, the carotid and coronary arteries have many similarities in the physiology of vascular tone regulation that has effect on plaque evolution [11]. Myocardial blood perfusion is regulated by the vasodilation of epicardial coronary arteries in response to a variety of stimuli such as NO, causing dynamic changes in coronary arterial tone that can lead to multifold changes in coronary blood flow. In a similar fashion, carotid arteries are more than simple conduits supporting the brain circulation; they demonstrate vasoreactive properties in response to stimuli, including shear stress changes [12]. Endothelial shear stress contributes to endothelial health and a favorable vascular wall transcriptomic profile [13]. Clinical studies have demonstrated that areas of low endothelial shear stress in the coronary tree are associated with atherosclerosis development and high-risk plaque features [14]. Similarly, in the carotid arteries lower wall shear stress is associated with plaque development and localization [15].

All measurements are taken within a prescribed anatomical target comprising one or more vessels, and at perpendicular cross-sections along the centerline of each vessel. Each cross-section thereby presents as a roughly circular lumen area (representing the blood channel) and an annular wall area (presenting the vessel wall, including plaque with its constituent tissues).

Table 1: Measurands Covered by this Profile

Measurand	Definition	Units
Maximum Wall Thickness	The cross-sectional thickness of a vessel wall as measured at the point of greatest wall thickness (given that the wall thickness is not uniform for each cross-section).	mm
Lumen Area	The cross-sectional area of a blood channel at a position along the vessel centerline.	mm^2
Lumen Volume	3D volume of lumen, irrespective of how it is sliced	mm^3
Wall Area	The cross-sectional area of a vessel at position along the vessel centerline minus the Lumen Area at that position.	mm^2
Wall Volume	3D volume of wall, irrespective of how it is sliced	mm^3
Plaque Burden	An index calculated as Wall Area / (Wall Area + Lumen Area).	unitless ratio
Lipid-Rich Necrotic Core (LRNC) Area	The area of the Lipid-Rich Necrotic Core (which is a pathologic retention of lipids, particularly lipoproteins, by intimal/medial cells leading to progressive cell loss, cell death, degeneration, and necrosis. LRNC is a mixture of lipid, cellular debris, blood and water in various concentrations).	mm^2
LRNC Volume	3D volume of LRNC, irrespective of how it is sliced	mm^3
Calcified Area	The area that has been calcified (due to physiologic defensive biological process of attempting to stabilize plaque, which has a mechanism akin to bone formation).	mm^2
Calcified Volume	3D volume of calcified tissue, irrespective of how it is sliced	mm^3

Arterial plaque volume as well as the volume of the specific tissue types are recognized key features and are a focus of this Profile as detailed in Table 1. It is noted, however, that validation of 3D volume measurements is currently difficult, as extraction of volume information from histology specimens for ground truth is technically challenging, and this is exacerbated by the large number of specimens that would be needed to have statistical significance of the bias estimates. As a result, the performance requirements and assessment procedures are currently defined at the cross-section level, which is not to indicate the greater importance of area measurements but which already at this level represent a significant advancement in the field were at least these measurements to be rigorously validated as we indicate here. We reason that volumetry will also benefit from this validation, and provided that image analysis software meet the qualitative requirements of using fully resolved 3D objects rather than simplifying assumptions such as the multiplication of areas by slice thickness to obtain volumes, that this Profile will also make specific contribution to our intended purpose, namely, that both volumes as well as cross-sectional areas are important.

Technical challenges differ across arterial beds (e.g., use of gating, vessel size, amount and nature of motion). In general, these effects are mitigated by scan protocol, which result in approximate in-plane voxel sizes in the 0.5-0.75mm range, and the reconstruction and scan settings often resulting in through-plane resolution of coronary (the smaller vessels) is actually better than, rather than inferior to, that of carotids (with the voxels often being reconstructed to be closer to isotropic in coronary and not so in the neck and larger vessels extremities). Where Profile requirements differ across arterial beds, separate tables are used. Unless explicitly noted, the specifications and requirements are the same across beds.

While accurate measurement of degree stenosis is not indicated in the Profile explicitly, the cross-sectional lumen area is included as more objective. The intention is that it is taken at a reference point and at each cross section. This Profile does not address the question of whether diameter-based vs. area-based stenosis would be of higher utility clinically, or the placement of reference. The specific question of reference has been extensively covered by NASCET and ECST. QIBA's contribution is to add area measurement (rather than being limited to diameter), but leave the topic of reference for these other works.

CLAIMS

When all relevant staff and equipment conform to this Profile, the following statistical performance for measurements taken at a single encounter may reasonably be expected[1]:

Table 2 Quantitative Claims

Measurement of	Units	Range	Bias	Intra-reader Variability	Inter-reader Variability
Lumen Area	mm^2	0.0-30.0	±2.0	2.5	5.0
Wall Area	mm^2	10.0-100.0	±2.0	2.5	5.0
Maximum Wall Thickness	mm	1.0-5.0	±1.0	0.75	1.0
Plaque Burden	unitless ratio	0.4-1.0	±0.1	0.1	0.1
Calcified Area	mm^2	0.0-40.0	±1.5	1.0	1.5
Lipid-Rich Necrotic Core (LRNC) Area	mm^2	0.0-23.0	±3.0	1.0	1.5

DISCUSSION

- Technical performance claims indicate the extreme of the 95% confidence interval, not (only) the point estimate. Specifically, we say that not only is a point estimate of the performance as claimed, but that we are 95% confident that it is as claimed.
- All statistical performance metrics are stated according to strict definitions as given in [3-8].
- Section 4, Assessment Procedures, identifies the data collection and analysis procedures for the assessment:
    - 95% CI Bias for structural measurands (maximum wall thickness, lumen area, wall area, and plaque burden) are assessed as described in section 4.3. Assessment Procedure: Vessel Structure Bias and Linearity, using phantoms.
    - 95% CI Bias for tissue characteristics (LRNC area, and calcified area) are assessed as described in section 4.4. Assessment Procedure: Tissue Characteristics Bias and Linearity,

[1] QIBA Profile Claims are developed successively through the stages of Profile development (defined at https://qibawiki.rsna.org/index.php/QIBA_Profile_Stages). The current status of this Profile is "Consensus", with the authorship believing it to be practical and expect it to achieve the claimed performance. Specifically, the performance figures on which these claims are currently based are derived from Appendix D, and will be more fully tested in later stages of Profile development.

using ex vivo histology, accounting for both subjectivity due to pathologist annotation as well as 2D-3D spatial alignment as identified in the assessment procedure.

- 95% CI for reader variability is assessed as within-subject standard deviation (wSD) as described in section 4.5. Assessment Procedure: Reader / Image Analysis Tool Variability, using clinical (not phantom) data sets representing the range of presentations, specifically to include multiple arterial beds (e.g., carotid and coronary).

Regarding linearity, we make a distinction between (1) the assessment of linearity, or nonlinearity, for a biomarker for developing the profile claims, and (2) testing conformance of an actor or site to the assumptions underlying the claims. For #1, methods described in Tholen DW. Alternative statistical techniques to evaluate linearity. Arch. Pathol Lab Med. 1992; 116(7):746-756 are applicable in doing so. Then, given this, actors with linearity requirements identified in Section 3 of this Profile verify that their results agree with the assumptions made for the claims. For this (i.e. #2), actors (only) need to verify linearity in the range included in the claims (not a full assessment of linear and nonlinear parts) and verify that the slope is in the range assumed in the claims. This simplicity is important for practicality of the Profile's assessment procedures.

- Use of vendor components (specifically, the first three actors from Table 3-1 below) which have only been tested over a smaller range than specified in the claim invalidates the claim outside of that range for the combined system including all actors.
- Maximum wall thickness refers to the largest value for point-wise wall thickness within the lesion or target.

3. Profile Requirements

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 conforming to all requirements in the section for that activity.

Acquisition Device: Image Data Acquisition.

Reconstruction Software: Image Data Reconstruction.

Image Analysis Tool: Image Analysis.

Imaging Physician: Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image Quality Assurance, and Image Analysis.

Physicist: Image Data Acquisition, Image Data Reconstruction, and Image Quality Assurance.

Technologist: Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image Quality Assurance, and Image Analysis.

Formal claims of conformance by the organization responsible for an Actor shall be in the form of a published QIBA Conformance Statement. QIBA Conformance Statements for Acquisition Devices, Reconstruction Software and Image Analysis Tools shall describe configuration settings or "Model-specific Parameters" (e.g., protocols) used to achieve conformance.

The requirements in this Profile do not codify a Standard of Care; they only provide guidance intended to achieve the stated Claim. Failing to conform to a "shall" in this Profile is a protocol deviation. Although deviations invalidate the Profile Claim, such deviations may be reasonable and unavoidable and the Imaging

Physician 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.

3.1. Subject Handling

3.1.2 SPECIFICATION COMMON TO ARTERIAL BEDS

Parameter	Actor	Requirement
Use of intravenous contrast	Imaging Physician	Shall prescribe a contrast protocol to achieve appropriate lumen conspicuity relative to wall tissues.
	Technologist	Shall use the prescribed intravenous contrast protocol.
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 image.

3.1.4 SPECIFICATION UNIQUE TO CORONARY ARTERIES

Parameter	Actor	Requirement
Breath hold	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.
Table Height & Centering	Technologist	Shall adjust the table height for the mid-axillary plane to pass through the isocenter. Shall center the thorax shall be centered in the AP and L/R directions according to the following: table height shall be adjusted for the mid axillary plane to pass through the isocenter and the sagittal laser line shall pass through the sternum from suprasternal notch to xiphoid process.
Nitrates	Technologist	Shall administer nitrates as prescribed, 5-7 minutes after nitro is administered.

3.2. Image Data Acquisition

3.2.2 SPECIFICATION COMMON TO ARTERIAL BEDS

Parameter	Actor	Requirement	DICOM Tag
In-plane Spatial Resolution	Acquisition Device	Shall validate that the protocol achieves an f50 value that is greater than 0.35 line pairs per mm for both air and soft tissue edges. See section 4.1. Assessment Procedure: In-plane Spatial Resolution	
Pixel noise	Acquisition Device	Shall validate that the protocol achieves a standard deviation that is < 30HU. See 4.2. Assessment Procedure: Pixel noise	
Acquisition Protocol	Acquisition Device	Shall be capable of making validated protocols (designed and validated by the manufacturer and/or by the site) available to the technologist at scan time.	
	Physicist	Shall prepare a protocol to meet the specifications in this table. Shall ensure technologists have been trained on the requirements of this profile.	
	Technologist	Shall select a protocol that has been previously prepared and validated	

Parameter	Actor	Requirement	DICOM Tag
		for this purpose.	

187 3.2.3 SPECIFICATION UNIQUE TO CORONARY ARTERIES

Parameter	Actor	Requirement	DICOM Tag
Total Collimation Width	Imaging Physician	Shall set to Greater than or equal to 18mm.	Total Collimation Width (0018,9307)
Nominal Tomographic Section Thickness (T)	Physicist	Shall set to Less than or equal to 0.75mm.	Single Collimation Width (0018,9306)
Temporal Resolution	Acquisition Device	Shall achieve an effective rotation time of less than or equal to 350ms.	
Artery motion during scan	Technician	Shall achieve a heart rate such that the temporal resolution effectively freezes that motion to less than .01 mm.	

188 3.2.4 SPECIFICATION UNIQUE TO CAROTID ARTERIES

Parameter	Actor	Requirement	DICOM Tag
Total Collimation Width	Physicist	Shall set to Greater than or equal to 16mm.	Total Collimation Width (0018,9307)
Nominal Tomographic Section Thickness (T)	Physicist	Shall set to Less than or equal to 1.0mm.	Single Collimation Width (0018,9306)

189 3.3. Image Data Reconstruction

Parameter	Actor	Requirement	DICOM Tag
Reconstruction Protocol	Physicist	Shall prepare a protocol to meet the specifications in this table. Shall ensure technologists have been trained on the requirements of this profile.	
	Reconstruction Software	Shall be capable of performing reconstructions and producing images with all the parameters set as specified "Protocol Design Specification".	
	Technologist	Shall select a protocol that has been previously prepared and validated for this purpose.	
ECG Gating	Technologist	Shall use prospective ECG gating and consider iterative reconstruction to allow for the lowest possible radiation exposure. If the heart rate is too high, retrospective ECG gating with a target on 70-90% RR interval may be required to obtain optimal motion free images.	
Reconstructed Image Thickness	Physicist	Shall be less than 1mm.	Slice Thickness (0018,0050)
	Technologist	Shall be less than 1mm if not set in the protocol.	
Reconstructed	Physicist	Shall set to less than or equal to the Reconstructed Image	Spacing Between

Parameter	**Actor**	**Requirement**	**DICOM Tag**
Image Interval		Thickness (i.e. no gap, may have overlap).	Slices (0018,0088)
	Technologist	Shall set to less than or equal to the Reconstructed Image Thickness (i.e. no gap, may have overlap) and consistent with baseline.	
Reconstructed In-plane Voxel Size	Physicist	Shall set to less than or equal to 0.625mm	(0028,0030)
In-plane Spatial Resolution	Physicist	Shall validate that the protocol achieves an f50 value that is Greater than 0.35 mm^{-1} for both air and soft tissue edges. See section 4.1. Assessment Procedure: In-plane Spatial Resolution	
Pixel noise	Physicist	Shall validate that the protocol achieves a standard deviation that is < 30HU. See section 4.2. Assessment Procedure: Pixel noise	
Image Header	Reconstruction Software	Shall record in the DICOM image header the actual values for the tags listed in the DICOM Tag column "Protocol Design Specification" as well as the model-specific Reconstruction Software parameters utilized to achieve conformance.	
Reconstruction Field of View	Technologist	Shall ensure the Field of View spans at least the full extent of the thoracic cavity, but not substantially greater than that.	Reconstruction Field of View (0018,9317)
Image Header	Reconstruction Software	Shall record in the DICOM image header the actual values for the tags listed in the DICOM Tag column "Protocol Design Specification" as well as the model-specific Reconstruction Software parameters utilized to achieve conformance.	

3.4. Image Quality Assurance

This activity involves evaluating the quality of reconstructed images prior to image analysis.

Parameter	Actor	Requirement
Patient Motion Artifacts	Imaging Physician	Shall confirm the images containing the lesion are free from artifact due to motion.
Physiological motion artifact (particularly cardiac)	Imaging Physician	Shall confirm the images containing the lesion are free from artifact due to motion based on visual review for blurred anatomic features.
Artifacts	Imaging Physician	Shall confirm the images containing the lesion are free from artifacts due to dense objects, anatomic positioning (e.g., arms down at sides), or equipment issues (e.g., ring artifacts).
Contrast Enhancement	Imaging Physician	Shall confirm that the intravascular level of contrast enhancement, if any, is appropriate for evaluating the lesion.
Patient Positioning Consistency	Imaging Physician	Shall confirm that any lesion deformation due to patient positioning is consistent with baseline (e.g. lesions may deform differently if the patient is supine in one scan and prone in another).

Parameter	Actor	Requirement
Scan Plane Consistency	Imaging Physician	Shall confirm that the anatomical slice orientation (due to gantry tilt or patient head/neck repositioning) is consistent with baseline.
Field of View	Imaging Physician	Shall confirm that the image field of view (FOV) resulting from acquisition and reconstruction settings appears consistent with baseline.
Pacemaker leads, stents	Imaging Physician	Shall confirm that anatomy assessed does not contain metal artifacts.

3.5. Image Analysis

This activity involves quantitative assessment of vessel structure and tissue composition of plaque morphology within a target vessel, lesion, or vessel subtree.

It is not expected that the technical performance specifications be assessed for each site, but rather the Image Analysis Tool be qualified by the vendor using the procedure provided in section 4.3, 4.4, and 4.5 for each major software version.

<table>
<tr><th>Parameter</th><th>Actor</th><th>Requirement</th></tr>
<tr><td>Vessel structure</td><td>Image Analysis Tool</td><td>Shall be validated to achieve bias and linearity (expressed as intercept, slope, and quadratic term) within the values shown in the following table. See 4.3. Assessment Procedure: Vessel Structure Bias and Linearity, noting that the full 95% confidence intervals (not only the point estimates) shall meet or exceed the indicated specifications when tested over range as given in Claims section:
<table>
<tr><td>Lumen Area (mm^2)</td><td>Bias: ±2, Intercept: ±1.0, Slope: 1±.1, Quadratic term: ±.1</td></tr>
<tr><td>Wall Area (mm^2)</td><td>Bias: 2, Intercept: ±10, Slope: 1±.1, Quadratic term: ±.1</td></tr>
<tr><td>Maximum Wall Thickness (mm)</td><td>Bias: ±1, Intercept: ±1, Slope: 1±.1, Quadratic term: ±.1</td></tr>
<tr><td>Plaque Burden (ratio)</td><td>Bias: ±0.1, Intercept: ±.1, Slope: 1±.1, Quadratic term: ±.1</td></tr>
</table></td></tr>
<tr><td>Tissue Composition</td><td>Image Analysis Tool</td><td>Shall be validated to achieve bias and linearity (expressed as intercept, slope, and quadratic term) within the values shown in the following table. See 4.4. Assessment Procedure: Tissue Characteristics Bias and Linearity, noting that the full 95% confidence intervals (not only the point estimates) shall meet or exceed the indicated specifications when tested over range as given in Claims section:
<table>
<tr><td>Calcified Area (mm^2)</td><td>Bias: ±1.5, Intercept: ±2, Slope: 1±.5, Quadratic term: ±.1</td></tr>
<tr><td>LRNC Area (mm^2)</td><td>Bias: ±3, Intercept: ±3.5, Slope: 1±.8, Quadratic term: ±.3</td></tr>
</table></td></tr>
<tr><td>Reader variability</td><td>Image Analysis Tool</td><td>Shall be validated to achieve Intra-reader wSD and Inter-reader wSD less than the values shown in the following table. See 4.5. Assessment Procedure: Reader / Image Analysis Tool Variability, noting that the full 95% confidence intervals (not only the point estimates) shall meet or exceed the indicated specifications when tested over range as given in Claims section.
<table>
<tr><td>Lumen Area (mm^2)</td><td>Intra-reader wSD: 2.5, Inter-reader wSD: 5.0</td></tr>
<tr><td>Wall Area (mm^2)</td><td>Intra-reader wSD: 2.5, Inter-reader wSD: 5.0</td></tr>
<tr><td>Maximum Wall Thickness (mm)</td><td>Intra-reader wSD: 0.75, Inter-reader wSD: 1.0</td></tr>
<tr><td>Plaque Burden (ratio)</td><td>Intra-reader wSD: 0.1, Inter-reader wSD: 0.1</td></tr>
</table></td></tr>
</table>

Parameter	Actor	Requirement
		Calcified Area (mm^2) — *Intra-reader wSD*: 1.0, *Inter-reader wSD*: 1.5 **LRNC Area** (mm^2) — *Intra-reader wSD*: 1.0, *Inter-reader wSD*: 1.5
Basis of cross-sectional area results	Image Analysis Tool	Shall base cross-sectional area results on obliquely-resliced orthogonal to centerline at spacing less than or equal to 0.5mm
Basis of volume results	Image Analysis Tool	Shall base volume results on three-dimensional object definitions (specifically excluding methods such as determining cross-sectional areas and multiplying by the slice thickness, or other approximations)
Confidence interval	Image Analysis Tool	Shall be able to display to the Imaging Physician, for each measurand, the range of plausible values for the given measurement stated in terms of the completed validation for the tool as a 95% interval.
Result Verification	Imaging Physician	Shall review & approve segmentations produced by the Image Analysis Tool.
Multiple Lesions	Image Analysis Tool	Shall allow multiple lesions to be measured. Shall either correlate each measured lesion across encounters or support the Imaging Physician to unambiguously correlate them.
Multiple encounters	Imaging Physician	Shall re-process the first encounter if it was processed by a different Image Analysis Tool or Imaging Physician.
	Image Analysis Tool	Shall be able to present the reader with both encounters side-by-side for comparison when processing the second encounter. Shall be able to re-process the first encounter (e.g. if it was processed by a different Image Analysis Tool or Imaging Physician).

4. Assessment Procedures

To conform to this Profile, participating staff and equipment ("Actors") shall support each activity assigned to them in Table 3-1. Although most of the requirements described in Section 3 can be assessed for conformance by direct observation, some of the performance-oriented requirements cannot, in which case the requirement references an Assessment Procedure subsection 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. Resolution is assessed in terms of the f50 value (in mm^{-1}) of the modulation transfer function (MTF).

The assessor shall first warm up the scanner's x-ray tube and perform calibration scans (often called air-calibration scans) according to scanner manufacturer recommendations. The assessor shall scan a spatial resolution phantom, such as the ACR CT Accreditation Program (CTAP) Phantom's module 1 or the AAPM TG233 phantom. The phantom shall be positioned with the center of the phantom at isocenter and properly aligned along the z-axis. When the scan is performed, the assessor shall 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. The assessor shall then determine and record the f50 value, defined as the spatial frequency (in mm^{-1} units) corresponding to 0.5 MTF on the MTF curve.

The assessor shall also generate the MTF curve and determine 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 air edge to assess, it is permitted to use the edge of the phantom.

The procedure described above 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. Note that for iterative reconstruction, the manufacturer may have specific test methodologies appropriate for the given algorithm.

4.2. Assessment Procedure: Pixel noise

This procedure can be used by a manufacturer or an imaging site to assess the pixel noise of reconstructed images. Pixel noise is assessed in terms of the standard deviation of pixel values when imaging a material with uniform density.

Scan parameters, especially current (mA) and tube potential (kVp), strongly influence achieved pixel noise when adjusted to accommodate for patient size. The assessor shall scan a phantom of uniform density, such as the ACR CT Accreditation Program (CTAP) Phantom's module 3, which is a 20 cm diameter cylinder of water equivalent material. The phantom shall be placed at the isocenter of the scanner. When the scan is performed, the assessor shall select a single representative image from the uniformity portion of the phantom. A region of interest (ROI) of at least 400 mm^2 shall be placed near the center of the phantom. The assessor shall record the values reported for the ROI mean and standard deviation.

4.3. Assessment Procedure: Bias and Linearity when Measuring Vessel Structure

This procedure is intended to be done by the Image Analysis Tool vendor to assess the bias and linearity of vessel structure measurements (lumen area, wall area, maximum wall thickness and plaque burden). The bias and linearity of vessel structure measurements is estimated using a set of phantoms where ground truth measurements assessed by micrometer are known.

4.3.1 OBTAIN TEST IMAGE SET

The test image set consists of scanned physical phantoms (Figure 4-1). The phantoms shall be fabricated according to specifications that mimic appropriate CT characteristics and in sizes that represented a range of vessel sizes and presentations of interest. The phantoms shall be filled with contrast media utilized in practice and scanned in a range of at least three different scanner settings which meet the requirements of this Profile (so as to account for acquisition protocol variations). Statistical measures of bias were estimated from these data.

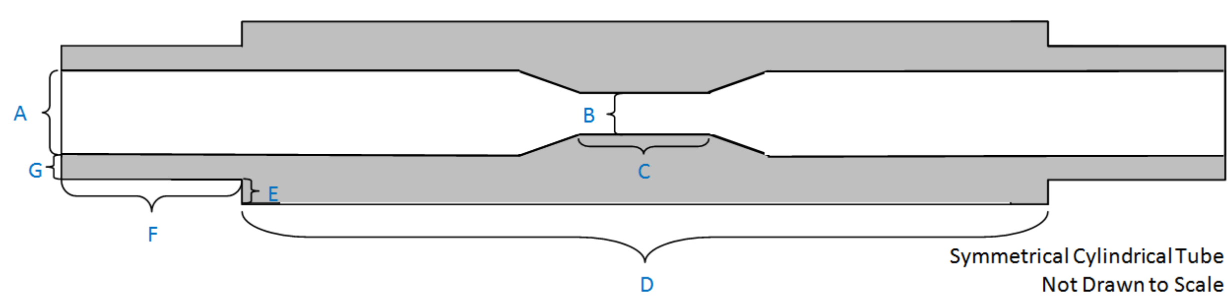

Figure 4-1: Physical Dimensions of Vascular Phantoms

An example material is Noryl, which has a density of 1.06 g/ml. The specifications for the phantoms that shall be used are displayed on Table 4-3, or equivalent with scientific justification. If a given Image Analysis Tool vendor wishes to support a subset of the phantoms listed rather than the whole range, then a representation of conformance needs to clearly note the reduced scope (i.e., only a portion of the range indicated in the Image Analysis specification section).

Table 4-3. Phantom Specifications

		A		B		C			D	E	F	G
Phantom number	**Surrogate artery**	**Reference diameter (mm)**	**Reference area (mm^2)**	**Stenosis diameter (mm)**	**Stenosis area (mm^2)**	**Stenosis length (mm)**	**Diameter stenosis (%)**	**Area stenosis (%)**	**Tube length1 (mm)**	**Tube thick1 (mm)**	**Tube length2 (mm)**	**Tube thick2 (mm)**
1	coronary	2.0	3.1	0.7	0.4	10.0	65.0	87.8	40.0	1.0	80.0	1.0
2	coronary	4.0	12.6	1.3	1.3	10.0	67.5	89.4	40.0	1.0	80.0	1.0
3	coronary	4.0	12.6	2.7	5.7	10.0	32.5	54.4	40.0	1.0	80.0	1.0
4	carotid	6.0	28.3	2.0	3.1	10.0	66.7	88.9	40.0	1.0	80.0	1.0
5	carotid	6.0	28.3	3.0	7.1	20.0	50.0	75.0	80.0	1.0	60.0	1.0
6	carotid	6.0	28.3	4.0	12.6	20.0	33.3	55.6	80.0	1.0	60.0	1.0

Each tube is a surrogate for one or more blood vessel. Phantom 1, 2, and 3 represent the size range of coronary arteries. Phantom 3 represents coronary and vertebral arteries. Phantom 4, 5, and 6 represent carotid arteries. For the scans, the phantoms shall be filled with diluted contrast agent (e.g., Omnipaque) between 10-12 mg Iodine /ml to achieve the same contrast between vessel wall and lumen found in patient CTA scans at 100-120 kVp (based on published relationship of iodine concentration vs. HU for 80-120 kVp, ref. [17]).

4.3.2 DETERMINE MEASURANDS

Import the DICOM files into the analysis software and perform the analysis, and perform steps as required by the Image Analysis Tool to segment lumen and wall consistent with the requirements set in the Image Analysis activity specification. The assessor is permitted to edit the segmentation or seed point if that is part of the normal operation of the tool. If segmentation edits are performed, results should explicitly indicate whether they were achieved with and without editing. When evaluating Image Analysis Tool, at least two readers of average capability who have been trained on the tool shall be used for this assessment procedure. When evaluating an Imaging Physician, it is acceptable to use a single tool for the assessment procedure. The assessor shall calculate the measurands (Y) of each cross-section (denoted Y_i) where Y denotes the measurand, and *i* denotes the *i*-th target.

4.3.3 CALCULATE STATISTICAL METRICS OF PERFORMANCE

The true measurements (X_i) as assessed by micrometer of each cross-section are known and are provided in the dataset. The assessor shall calculate the individual percentage bias (b_i) of the measurement of each cross-section as $b_i = lnY_i - ln\, X_i$

The assessor shall estimate the population bias over the N cross-sections as $\widehat{D} = \sqrt{\sum_{i=1}^{N} b_i \,/N}$

The assessor shall convert to a percentage bias estimate as $\%\widehat{bias}$ = $\left(\exp\left(\widehat{D}\right) - 1\right) \times 100.$

To assess linearity, the assessor shall use the NCCLS approach, EP06-A "Evaluation of the linearity of quantitative measurement procedures: A statistical approach; Approved Guideline (2003), of fitting first, second, and third order polynomials and testing that the nonlinear coefficients are near zero. Then estimating the linear slope and provide a 95% CI. The assessor is recommended to also plot the measurand estimate ($\ln Y_i$ versus $\ln X_i$) and the OLS regression curve of the estimates as part of the assessment record.

4.4. Assessment Procedure: Bias and Linearity when Measuring Tissue Characteristics

This procedure is intended to be done by the Image Analysis Tool vendor to assess the bias and linearity with which tissue characteristics are measured. Histopathology is used as ground truth.

4.4.1 OBTAIN TEST IMAGE SET

Perform histology processing and assessment only at accredited centers and to ensure that ground truth processing be blinded to all other study data. Ground truth is defined as 2-dimensional annotations for each tissue type on at least 90 sections from excised tissue samples from at least 18 subjects by board-certified pathologists, which are then positioned within the 3-dimensional CTA volume blinded to any results of the Image Analysis Tool. With reference to the sample size considerations provided below, a given tool may require a larger number of sections and/or specimens to properly characterize the performance. Results from this assessment procedure may be applied across arterial beds, provided that the source of tissue samples is explicitly indicated in the conformance statement.

Process sections at 2.0 mm throughout the length of the tissue specimen. It is acceptable to exclude sections (within reason and in no event cherry picking desirable sections) when the sample is too distorted, if it is missing significant portions due to specimen processing, if there is not enough visible tissue characteristics or distinct morphology to orient the *ex vivo* histology image to the *in vivo* radiology imaging, or if the pathologist marked tissue as a mixture of tissue types.

Correlate histology cross-sections with locations in the CT image volume. In one acceptable method:

- tissue portions of histopathologic images are converted into a mesh to facilitate returning its shape to its *in vivo* original using a finite element method (FEM) that factors in the tissue material type to simulate the stretching/compression of the relatively elastic material, and then
- allow a positioner to rotate, tilt, and move the histology cross-section in 3D to provide a plausible alignment between the histopathology and radiology presentation.

It is important to note that the matching shall be performed using only primary CT images, scrupulously avoiding use of the image analysis tool's computed segmentations to preserve objectivity in the matching.

Subjectivity of 3D placement shall be systematically mitigated with consideration due to the sources of potential misalignment: (a) longitudinal displacement up or down the length of the vessel, (b) the angular tilt of the plane away from perpendicular to the vessel, and (c) the angular spin about the vessel.

Sample Size Considerations: Determination of the number of specimens and sections depends on the performance of the image analysis tool. In the example below, the width of 95% confidence intervals for the bias and the between-subject variance as a function of sample size according to the following assumptions were made:

1) the cross-sectional area calculations are normally distributed;
2) targets from the same subject are moderately correlated (r=0.25);
3) results from different arteries can be pooled;
4) the precision of the image analysis tool calculations is 25-75% of the cross-sectional area calculation.

If the SD was 75% of the mean cross-sectional area, then we expect to be able to construct a 95% CI for the bias of half-width of 20% with n=20. Similarly, from Table 8, if the SD was 75% of the mean cross-sectional area, then with n=20 we expect to be able to construct a 95% CI for the precision of total length 29%.

Table 4: Width of 95% CIs for Bias Based on Total Sample Size (n)*

	n=10	n=20	n=30
SD=6.25 (25%)	±2.42	±1.67	±1.36
SD=12.5 (50%)	±4.84	±3.35	±2.71
SD=18.75 (75%)	±7.26	±5.02	±4.07

*The effective sample size, m, is calculated as m=n×s / [1+(s-1)×0.5]), where s is the number of sections per specimen (=7 in this example). Then the half-width of the 95% CI for bias is $t_{(m-1),\frac{\alpha}{2}}\ (SD/\sqrt{m})$.

Table 5: Estimated 95% CIs for SD Based on Total Sample Size (n)*

	n=10	n=20	n=30
SD=6.25	[4.94,8.51]	[5.27,7.68]	[5.43,7.37]
SD=12.5	[9.88,17.0]	[10.5,15.4]	[10.8,14.7]
SD=18.75	[14.8,25.5]	[15.8,23.0]	[16.3,22.1]

*The effective sample size, m, is calculated as m=n×s / [1+(s-1)×0.5]), where s=7. Then the 95% CI for the SD is $\left[\sqrt{\frac{(m-1)s^2}{\chi^2_{\frac{\alpha}{2},(m-1)}}},\ \sqrt{\frac{(m-1)s^2}{\chi^2_{\left(1-\frac{\alpha}{2}\right),(m-1)}}}\right]$.

4.4.2 DETERMINE MEASURANDS

Import the DICOM files into the analysis software and perform the analysis, and perform steps as required by the Image Analysis Tool to determine tissue characteristics consistent with the requirements set in the Image Analysis activity specification. When evaluating an Imaging Physician, a single tool shall be used for this entire assessment procedure. The assessor shall calculate the measurands (Y) of each cross-section (denoted Y_i) where Y denotes the measurand, and *i* denotes the *i*-th target.

4.4.3 CALCULATE STATISTICAL METRICS OF PERFORMANCE

The following shall be performed in a strictly held-out set of subjects, and cannot be done iteratively. Once the hold-out set has been used for evaluation, it may not be used for a later evaluation after the software changes, accept insofar as regression tests are performed where there is no material algorithm changes. It is highly advisable to anticipate this in advance when data is collected, and to pre-identify cohorts, and with sufficient numbers collected to support potentially many year development programs.

In order to properly account for sources of subjectivity, a minimum of three independent pathologist annotations, and four positioned-radiologist reader combinations (that is, two independent positionings crossed with two independent radiology readings at each respective position), shall be collected and included in the analysis.

To assess bias, plot the value calculated by histopathologic examination versus the value calculated by image analysis tool. Inspect the resulting plot for associations between the magnitude of the histopathologic measurement and bias, associations between the magnitude of the histopathologic measurements and heteroscedasticity in the image analysis tool measurements, and limits of quantitation of image analysis tool measurements.

To assess linearity, the assessor shall use the NCCLS approach, EP06-A “Evaluation of the linearity of quantitative measurement procedures: A statistical approach; Approved Guideline (2003), of fitting first, second, and third order polynomials and testing that the nonlinear coefficients are near zero. Then estimating the linear slope and provide a 95% CI.

Estimate the precision of the image analysis tool measurements by the standard deviation:

$\sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(Y_i - X_i - \bar{d})^2}$, where $\bar{d}$ is the sample mean of the differences, $\bar{d} = \frac{1}{n}\sum_{i=1}^{n}(Y_i - X_i)$.

Construct a 95% CI for the standard deviation using bootstrap methods.

Present the bias profile (bias of measurements for various ranges of histopathology values versus the histopathology value) and precision profile (standard deviation of image analysis tool measurements from subjects with similar histopathologic values versus the histopathologic value) as summaries of image analysis tool measurement performance for the bias and precision components, respectively. Report the coverage probability at 80% coverage. The coverage probability is the probability that the absolute difference between the value calculated by image analysis tool measurements and the value calculated by histology is less than d0, i.e., $\pi = \Pr(|Y - X| < d0)$. Plot the coverage probability for a range of values for d0.

4.5. Assessment Procedure: Variability of Readers using the Image Analysis Tool

This procedure can be used by a manufacturer or an imaging site to assess the variability with which Lumen Area, Wall Area, Maximum Wall Thickness, Plaque Burden, Calcified Area, and LRNC Area are measured. Variability is assessed in terms of the within-section Standard Deviation (wSD) estimated from two or more replicate calculations by the same reader. The procedure assesses an Image Analysis Tool and an Imaging Physician operating the tool as a paired system.

Data is provided by the registrant for self-attestation (QIBA Registered) and may in the future be provided by QIBA for a certification program. For each measurand, calculate the within-section Standard Deviation (wSD) estimated from two or more replicate calculations by the same reader. A minimum of 40 cross-sections from 7 or more subjects per arterial bed indicated are required. Pooling of subjects across carotid and coronary arterial beds is only allowable with rigorous statistical justification, and in any case, does not diminish the minimum counts. For each measurand, calculate between-reader within-section SD estimated from one calculation by two or more different readers. The Reproducibility Coefficient (RDC) shall be estimated as 2.77 × inter-reader wSD. A 95% CI using a chi square statistic should be used as the pivotal statistic was constructed for the RDC. Minimum counts are as described above for intra-reader variability.

Appendix: CTA Signal Applicability and Published Performance

The ability of standard CTA to reliably identify atherosclerotic plaque tissue characteristics and correlate them with cardiovascular events relative to the more widely reported use of MRI has not previously been well established in the literature. In principle, the Hounsfield Unit scale used by CT has the potential to be more quantitative than MRI due to the objective basis on which the voxel values are based, but terms like "soft plaque" instead of more specific terms like lipid-rich necrotic core are sometimes used in literature [27], suggesting less specificity. Ideal image processing would take this factor and partial volume effects into account. The speed and high-resolution of standard CTA scan protocols brings promise of more widespread adoption. A particularly thorough review paper [28] investigated the use of noninvasive imaging techniques in identifying plaque components and morphologic characteristics associated with atherosclerotic plaque vulnerability in carotid and coronary arteries. The review found 62 studies. The 50 studies on the carotid arteries used histology as reference method, while the 12 studies on the coronary arteries used IVUS (but this would not be considered definitive as IVUS is itself not validated by histology).

VESSEL STRUCTURE

Source	*Imaging Method*	*Reference*	*object*	*Structure measurement*	*Offset*	*Variability*
de Weert 2006 [29]	CT	Inter-observer	7 Human carotid	Plaque Area (mm2)	-5% constant over 74-111 mm2 range; poor below	8% constant over 74-111 mm2 range; poor below
de Weert 2006 [29]	CT	Inter-observer	13 Human carotid	Lumen Area (mm2)	0% constant over 22-63 mm2 range; poor below	1% constant over 22-63 mm2 range; poor below
Kwee 2009 [30]	CT Auto	1.5T MR	14 Human carotid	Lumen Area	9% constant over 19-72 mm2 range; poor below	37% % constant over 19-72 mm2 range; poor below
Obaid 2013 [31]	CT	Intra-observer	22 Human coronaries	Lumen Area (mm2)	-1% constant over 352-468 mm2 range; poor below	4% constant over 352-468 mm2 range; poor below
Papadopoulou 2013 [32]	CT	Intra-observer	162 Human coronaries	Lumen Area (mm2)	2% constant over 12.8-23.2 mm2 range; poor below	10% constant over 12.8-23.2 mm2 range; poor below
Papadopoulou 2013 [32]	CT	Intra-observer	535 Human coronaries	Vessel Area (mm2)	-1%	7%
Papadopoulou 2012 [33]	CT	Intra-observer	435 Human coronaries	Plaque Area (mm2)	1% constant over 6.1-16.4 mm2 range; poor above	14% constant over 6.1-16.4 mm2 range; poor above
Rinehart 2011 [34]	CT	Inter-observer	85 Human coronaries	Minimum Lumen Diameter (mm)	-2% constant over 1.7-4.4 mm range; poor below	8% constant over 1.7-4.44 mm range; poor below
Rinehart 2011 [34]	CT	Inter-observer	179 Human coronaries	Minimum Lumen Area (mm2)	0% constant over 1.6-21.2 mm2 range; poor below	14% constant over 1.6-21.2 mm2 range; poor below

TISSUE COMPOSITION

With a specific focus on CT, we quote a small illustrative sampling here to indicating the nature and utility of CT for characterizing atherosclerotic plaque:

- (quoted directly from introduction in [35]) In view of the limitations of [digital subtraction angiography], there is an increasing interest in CTA as a modality for assessing the carotid artery bifurcation. Computed tomography angiography is an imaging modality that can be used to accurately visualize the severity of luminal stenosis in 3D. With CTA it is extremely easy to detect calcifications in the carotid artery. CTA has also become an established method for successful artery calcium scoring in coronary arteries. With the introduction of Multi-detector CT (MDCT) in 1998 fast imaging at high temporal and spatial resolution became possible. … It has been also shown, with comparison to histology, that assessment of carotid atherosclerotic plaque components is feasible with MDCT using different plaque components Hounsfield units (HU) densities in vitro [20] and in vivo [21]. In Figure 1.3 an illustration from of atherosclerotic plaques in MDCT cross-sectional slices and corresponding histology samples are shown.
- (quoted directly from conclusions in [29]) The present study shows that MDCT is capable of characterizing and quantifying plaque burden, calcifications, and fibrous tissue in atherosclerotic

carotid plaque in good correlation with histology, and that lipid core can be adequately quantified in mildly calcified plaques. Furthermore the MDCT-based assessment of atherosclerotic plaque component quantities was possible with moderate observer variability.

- (quoted directly from conclusions in [36]) Our study results indicate that [dual-source computed tomography] angiography of the carotid arteries is feasible and the evaluation of carotid tissue characteristics allows non-invasive assessment of different plaque components. Although some limitations remain, [dual-source computed tomography] offers a high potential to non-invasively assess the patients at a higher risk for stroke.

An often cited study supporting the use of CT to characterize plaques, while also documenting the factors which can complicate overly simplistic methods [37], states: “The mean CT Hounsfield attenuation was measured for each of the 2x2-mm squares that were electronically drawn on the CT reformatted images and considered in the linear regression model with respect to the percentages of connective tissue, lipid-rich necrotic core, hemorrhage, and calcifications in the corresponding histologic and micro-CT squares. The results of the linear mixed model. There was significant overlap in CT Hounsfield densities between lipid-rich necrotic core and connective tissue. There was also some overlap between connective tissue and hemorrhage. Cutoff densities between lipid-rich necrotic core and connective tissue, connective tissue and hemorrhage, and hemorrhage and calcifications were determined as the halfway Hounsfield attenuation between the average densities for each of the components: 39.5 Hounsfield units (HU) between lipid-rich necrotic core and connective tissue, 72.0 HU between connective tissue and hemorrhage, and 177.1 HU between hemorrhage and calcifications.”

Wintermark’s Table 2, de Weert’s result regarding cutoff values [29], and also work by Sieren [38] in lung tissues considered for purposes of establishing the basic relationships between tissue types and their HU values generally provide points of comparison with our work. These reference works highlight both what is good about using HUs for characterization of lesion characteristics but at the same that which makes it challenging. The principal challenge to QIBA-conformant image analysis tool is to mitigate limitations gleaned from the various studies.

More recently [39]:

1. Tissue characteristics implicated in high risk atherosclerotic plaque may be quantitatively measured from routinely available CTA in high correlation with histopathology (with Pearson correlation coefficients for measurements greater than 5mm^2 of 0.973, 0.856, and 0.885 for Calcification, LRNC, and Matrix respectively) and low reader variability (with Repeatability Coefficients ≤ 1.8 mm^2 and Reproducibility Coefficients ≤ 4.4 mm^2), assessed on 2D cross-sections within calculated 3D volumes.
2. Overestimation of calcification on CTA may be successfully mitigated as evidenced by bias in measurements of calcified area being -0.096 mm^2 and demonstrating the property of linearity as confirmed by histopathology when evaluated on held-out test data.
3. Underestimation of lipid-rich necrotic core (LRNC) on CTA may be successfully mitigated as evidenced by bias in measurements of LRNC area being 1.26 mm^2 and demonstrating the property of linearity as confirmed by histopathology when evaluated on held-out test data.
4. Bias in measurements of tissue matrix area on CTA was -2.44 mm^2 and demonstrating the property of linearity as confirmed by histopathology when evaluated on held-out test data.

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