QIBA Profile:

Atherosclerosis Biomarkers by (C)CTA - 2019

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Stage: Initial authoring

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1. Executive Summary

Currently, clinical application of (C)CTA and atherosclerosis imaging is widely available as a technique used as a first line investigation of coronary vascular disease and in carotid as a second line for assessment of the plaque structure in order to choose the therapeutic approach (best medical treatment or revascularization). Evaluation of atherosclerotic arterial plaque characteristics is currently based-on qualitative biomarkers. However, the reproducibility of such findings is limited even among experts [1]. While certain imaging biomarkers such as carotid stenosis and coronary calcium scores are well accepted in clinical practice, there are opportunities to add further biomarkers currently only applied in the research arena.

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.

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.

See Appendix D for detailed definitions of the measurands explicitly covered by this profile: Lumen Area, Wall Area, Maximum Wall Thickness, Plaque Burden, Calcified Area, and Lipid-Rich Necrotic Core (LRNC) Area. Image Analysis Tools may also compute other measurands, some derived from these and/or applying to 3D volumes. 3D volumes are covered by this Profile indirectly via requirements placed on how 3D quantities must be calculated (see Section 3).

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

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

2. Clinical Context and Claim(s)

Clinical Context

Atherosclerosis is a major health concern for our aging population. The most significant underlying disease cause of mortality and morbidity in individuals older than 55 years and becoming the leading cause of death worldwide. Given the devastating impact of this widespread disease on individuals and population reflected in spiraling healthcare costs, biomarkers for better risk assessment and diagnosis at early stages, and monitoring of atherosclerosis will have a significant impact on public health. Noninvasive imaging biomarkers that would provide this information will have an impact to transform healthcare delivery and management. There is a critical gap in the biomarker qualification process, which needs to be addressed in order to move these quantitative imaging biomarkers forward.

The presence of atherosclerosis and the amount and type of arterial plaque have strong predictive value for acute events and for future cardiovascular events. Moreover, plaque composition may change dramatically over a few years and cardiovascular risk factors play a major role in these changes – changes that can be tracked with imaging. Further, recent evidences show that atherosclerosis is not only a progressive disease but it is possible to obtain also the plaque regression. Intensive medical (lipid-lowering and anti-inflammatory) therapies may drive plaque regression and conversion to a stable phenotype by strengthening the need to objectively quantify the amount and composition of the atherosclerotic plaque in order to monitor the plaque's response to the therapies. Multiple platforms and approaches exist in plaque assessment. They included both qualitative and quantitative methods. Many of these methods have been associated with outcomes.

CT angiography (CTA) offers the potential to non-invasively detect, quantify and characterize atherosclerotic plaque. Accurate identification and quantification of plaque components using CTA is challenging because of the technical limitations of CTA and requires optimization of image quality, however, CTA may provide valuable information for characterization of plaques. 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 imaging has been widely used to show association with ACS in acute chest pain setting. Data on prognostic value for 2-5 year follow up are also available (e.g., PROMISE [9] and Scot-Heart [10]. Atherosclerosis compositional imaging biomarkers allow earlier diagnosis, better prediction and more sensitive monitoring of vessel wall disease. In particular, compositional atherosclerotic biomarkers (lipid core, calcification, vessel wall area) represent quantitative measures that could reduce the size and duration as well as increase the objectivity of clinical, multi-center trials. The key advantage of these measures is earlier detection before atherosclerotic plaque progression and end organ symptom presentation.

While clearly the scanning protocols and approaches differ widely across different anatomic regions, e.g., chest vs. neck scanning, differences in the analysis of images post reconstruction have sometimes resulted in unnecessary fragmentation in analysis product offerings and inability to leverage histopathologic validation (of course differences in the hardware scanning protocols are appropriate; here we refer to the analysis of reconstructed data). The prevalence of carotid artery disease and CAD are closely related [11]. Furthermore, carotid atherosclerosis has been shown to be an independent predictor for MACE, even in patients without pre-existing CAD [12]. Such findings suggest a common underlying pathogenesis shared in both conditions, which is further supported by the Multi-Ethnic Study of Atherosclerosis (MESA) [13].

Atherosclerosis develops progressively through continuous evolution of arterial wall lesions centered on the accumulation of cholesterol-rich lipids and the accompanying inflammatory response, which changes are closely similar in the coronary arteries, the carotid arteries, and even the aorta [14]. Certain plaque characteristics such as large atheromatous core with lipid-rich content, thin fibrous cap, outward remodeling, infiltration of the plaque with macrophages and lymphocytes and thinning of the media are predisposing to vulnerability and rupture; and are similar in both carotid and coronary artery disease [15].

Plaque composition is similar in coronary and carotid arteries, irrespective of its age, and this will largely determine relative stability [16], suggesting similar presentation at CCTA as at CTA. Minor differences in the extent of the various plaque features may include a thicker fibrous cap and a higher prevalence of intraplaque hemorrhage in the carotid arteries, however, without difference in the nature of plaque components [15]. In addition, the carotid and coronary arteries have many similarities in the physiology of vascular tone regulation that has effect on plaque evolution [17]. 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 [18]. Endothelial shear stress contributes to endothelial health and a favorable vascular wall transcriptomic profile [19]. 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 [20]. Similarly, in the carotid arteries lower wall shear stress is associated with plaque development and localization [21].

It is important to acknowledge that technical challenges are different across arterial beds (e.g. use of gating, vessel size, amount and nature of motion) – but 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).

CLAIMS

When all relevant staff and equipment identified in Table 3-1: Actors and Required Activities conform to the specifications of this Profile as identified in Section 3 and as elaborated where relevant by Section 4, the following statistical performance for measurements taken at a single encounter may reasonably be expected:

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	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
LRNC Area	mm^2	0.0-23.0	±3.0	1.0	1.5

DISCUSSION

- Technical performance claims are indicated as the extreme of the 95% confidence interval, not (only) the point estimate.

- 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, 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).
- Use of vendor components which have only been tested over a smaller range invalidates the claim outside of that range.
- 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 referenced Section.

Table 3-1: Actors and Required Activities

Actor	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 QA
	Image Analysis
Physicist	Image Data Reconstruction
Technologist	Subject Handling
	Image Data Acquisition
	Image Data Reconstruction

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.

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

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

The method for assessing atherosclerosis may be described as a pipeline. Subjects are prepared for scanning, raw image data is acquired, and images are reconstructed and evaluated. Such images may be obtained at (only) one encounter, or multiple longitudinally. When multiple encounters are available, in addition to assessing the disease at each individual encounter (referred to as a "cross sectional" claim) image analysis may further assess the degree of change between the available encounters. When expressed as a percentage, change is the difference for a given measurand between the encounters divided by that at encounter 1. Although this introduces some asymmetry (e.g., measurements of 50mm2 and

100mm2 represent either a 100% increase or a 50% decrease depending on which was measured first), it is more familiar to clinicians than using the average of the two encounters as the denominator.

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

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

3.1. Subject Handling

This activity involves handling each imaging subject at a given encounter.

3.1.1 DISCUSSION COMMON TO ARTERIAL BEDS

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

It is important that the **Contrast Protocol** achieves a consistent phase and degree of enhancement. Bolus tracking is a good tool if available, but is not required. When using bolus tracking, be consistent between encounters with where the ROI used for triggering is placed and the threshold used to trigger the scan. When bolus tracking is not available, be consistent between the encounters with the contrast volume, rate, scan timing after injection, and use (or lack) of a saline flush.

Artifact sources, in particular metal and other high density materials, can degrade the reconstructed data such that it is difficult to determine the true contour of a lesion. Due to the various scan geometries, artifacts can be induced some distance from the artifact source. The simplest way to ensure no degradation of the data is to remove the artifact sources completely from the patient during the scan, if feasible.

Consistent **centering**, as with the use of similar scan settings, during different visits of the patient to overcome potential differences due to different kV settings, for example, of the patient, avoids unnecessary variation in the behavior of dose modulation algorithms during scan.

Nitrate administration timing is intended to allow for optimal artery dilatation.

3.1.2 SPECIFICATION COMMON TO ARTERIAL BEDS

Parameter	Actor	Requirement
Contrast Protocol	Imaging Physician	Shall prescribe a contrast protocol that achieves enhancement consistent with baseline.
Use of intravenous contrast	Imaging Physician	Shall determine whether the selected contrast protocol, if any, will achieve appropriate lumen conspicuity.
	Technologist	Shall use the prescribed intravenous contrast parameters.
Artifact Sources	Technologist	Shall remove or position potential sources of artifacts (specifically including breast

Parameter	Actor	Requirement
		shields, metal-containing clothing, EKG leads, and other metal equipment) such that they will not degrade the reconstructed CT image.
Table Height & Centering	Technologist	Shall adjust the table height for the mid-axillary plane to pass through the isocenter. Shall position the patient such that the "sagittal laser line" lies along the sternum (e.g. from the suprasternal notch to the xiphoid process).
Nitrates	Technologist	Shall administer glyceryl trinitrate (GTN) sublingual tablets by default, within 5 minutes of the start of the acquisition.

3.1.3 DISCUSSION UNIQUE TO CORONARY ARTERIES

Excellent guidelines from the Society of Cardiac Computed Tomography exist, which give a detailed account of CT coronary angiography from referral to reporting [22].

Use of beta blockers is recommended to achieve a target **heart rate** < 65 bpm, and ideally a heart rate < 60 bpm. On average, a higher heart rate results in reduced measurement precision within the coronary arteries. By way of example, here is a sample protocol (provided not as a requirement but as an example):

> 50 mg of oral metoprolol (or similar) is prescribed to be taken 1 hour prior to the CCTA, unless contraindicated. At arrival in the department, heart rate is measured, and a further 50 mg may be given 30 minutes before the CCTA. If insufficient result, IV metoprolol may be administered in increments of 2 mg up to 20 mg.

	Medication	Initial dose	Subsequent doses if pulse >60 bpm and BP >110	Maximum dose
1	Metoprolol	10 mg intravenous over 1 minute	After 5 minutes: 10 mg intravenous metoprolol repeated up to a maximum of 4 times at 3-5 minute intervals	50 mg intravenous metoprolol
2	Verapamil	80 mg oral	After 1 hour: 2.5 mg intravenous verapamil repeated up to a maximum of 2 times at 5 minute intervals	80 mg oral plus 5 mg intravenous verapamil
3	Esmolol	0.25 to 1 mg per kilogram bolus over 30 seconds to one minute	After 5 minutes: 0.25 to 1 mg per kilogram bolus, repeated up to a maximum of 2 times at 5 minute intervals	

Breath holding reduces motion that might degrade the image and can lead to decrease in the heart rate during the scan. Stable breath hold and no motion of the chest or other body parts are critical for optimized image quality. For coronary CT angiography imaging, breath holding commands are typically pre-recorded to allow for standard duration between initiation of the breath holding commands and scan start. This is important as the breath holding commands need to be coordinated with optimal contrast timing. However, care must be taken that the patient is capable of following these demands, and interactive commands may be required. Since a few seconds are needed for inspiration to lower heart rate, it is advised to wait at least 4 seconds between initiation of the breathing instructions and the start of the image acquisition. To promote patient compliance, performing a practice round of the breathing instructions prior to moving the patient into the scanner also is strongly recommended. Sample breathing instructions:

1. To start, say "breathe in, breathe out, breathe in, breathe out and hold your breath"
2. Wait at least four seconds, initiate the scan.
3. When scan is completed, say "You can breathe normally"

With bolus tracking, typically only "breathe in and hold your breath", i.e. one cycle, is possible. To test bolus technique, two cycles of breath in are possible.

Most CT systems now have automated image acquisition start based on a set threshold of contrast

enhancement. By placing a region of interest in the left ventricle for native CCTA and the descending aorta for patients with previous CABG, and setting a threshold of 180 HU, sufficient contrast enhancement in the coronary arteries is usually assured when the monitoring acquisition is started after 13 seconds and 17 seconds, respectively. A low-dose protocol is used for the automated trigger, while the dose for the diagnostic acquisition depends on patient characteristics.

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.
Heart Rate	Technologist	Shall target a heart rate of < 65 BPM
ECG Gating	Technologist	Shall use prospective ECG gating and 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.

3.2. Image Data Acquisition

This activity involves the acquisition of image data for a subject at a given encounter.

3.2.1 DISCUSSION COMMON TO ARTERIAL BEDS

Diagnostic image quality is impacted by both largely uncontrollable patient-centric factors (heart rate, plaque material composition, plaque morphology, etc.) and controllable machine-centric factors (kVp, voxel noise level, spatial resolution, etc.).

A given factor combination and its associated interdependencies will determine the achievable measurement precision and bias for a given measurand (stenosis, lumen area, etc.). The ideal estimator is a mathematical framework, derived from information theory, which provides a quantitative method to ascertain the impact of each factor on overall measurement performance. Utilizing this method, limits were set on all controllable factors to achieve the Profile's performance claims under a range of typical uncontrollable factor conditions or patient populations.

CT scans for quantitative assessment of vessel structure and tissue composition of atherosclerotic plaques can be performed on any equipment that complies with the specifications set out in this Profile. However, we strongly encourage performing all CT scans for an individual subject on the same platform (manufacturer, model and version) using similar scan parameters, which we expect will further reduce variation.

Acquisition Protocols are often selected by the technologist at scan time based on the procedure requested in the modality worklist. For the measurements to be conformant, this Profile requires that the protocol used has been validated (e.g. by a physicist) to meet certain requirements and performance metrics. The site will need to find some way to communicate to the technologist which protocols have been validated. This may be something in the protocol names, or a paper list for the technologist to consult, or a special pick-list on the modality console. Or a site may, for example, validate ALL protocols for a given procedure so that any protocol the technologist selects will have been validated.

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

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

Total Collimation Width (defined as the total nominal beam width, NxT, for example 64x1.25mm) is often not directly visible in the scanner interface. Manufacturer reference materials typically explain how to determine this for a particular scanner make, model and operating mode. Wider collimation widths can increase coverage, shorten acquisition and reduce the need to stitch together multiple sections of imaged anatomy. Imaging protocols will seek to strike a balance to preserve image quality while providing sufficient coverage to keep acquisition times short.

Nominal Tomographic Section Thickness (T), the term preferred by the IEC, is sometimes also called the Single Collimation Width. It affects the spatial resolution along the subject z-axis.

Smaller voxels are preferable to reduce partial volume effects and provide higher accuracy due to higher spatial resolution. Voxel size becomes increasingly important as the size of the object to be analyzed decreases [See Appendix C]. The resolution/voxel size that reaches the analysis software is affected by both acquisition parameters and reconstruction parameters.

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 healthcare 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.

Image reconstruction is modeled as a separate Activity in this QIBA Profile. Although it is closely related to image acquisition, and is usually performed on the Acquisition Device, reconstruction may be performed, or re-performed, separate from the acquisition. Many reconstruction parameters will be influenced or constrained by related acquisition parameters. This specification is the result of discussions to allow a degree of separation in their consideration without suggesting they are totally independent.

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

Spatial Resolution quantifies the ability to resolve spatial details and scales the impact of partial volume effects. Increased spatial resolution typically comes with an increase in noise which may degrade segmentation. If the spatial resolution is significantly different between the two encounters, these impacts will change which can affect repeatability. So 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 filter (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). An implication of using the ACR phantom is that the resolution is assessed at only one distance from the isocenter. Although spatial resolution may vary with distance from the isocenter and atherosclerotic plaques can be expected at various distances from the isocenter, it is considered fair to assume that resolution does not degrade drastically relative to the acceptable range of the resolution specification here. Since this Profile addresses atherosclerotic plaques primarily consisting of either calcified or lipid tissues, 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. Increased levels of noise can make it difficult to identify the boundary of vessel lumen, wall, and atherosclerotic plaque by humans and automated algorithms. If algorithms become uniformly more "noise tolerant", the maximum threshold may be raised. Decreased image noise is not always 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 resolution). The profile does not currently define a minimum threshold, because lower noise is always superior when achieved within acceptable patient dose levels. The preferred metric for voxel noise is the standard deviation of reconstructed CT numbers over a uniform region in a phantom.

It is not expected that the Voxel Noise be measured for each subject scan, but rather the Acquisition Device and Reconstruction Software be qualified for the expected acquisition and reconstruction parameters using the procedure provided in section 4.2, “Assessment Procedure: Voxel Noise”. Operating tube potential (kVp) may need adjustments to accommodate for larger or smaller patients in concert with pre-defined operating constraints or limits on maximum x-ray tube output and optimal patient dose levels. Where possible, a lower tube potential (kVp) can be used to improve lumen and soft-tissue contrast.

Note also that most modern CT scanners are equipped with Automatic Exposure Control that adjusts the scanner radiation output to achieve pre-determined target noise levels in the images as a function of patient size. The qualification of CT scanner noise needs to account for this provision in that the noise is quantified in a standard size phantom object (such as the CT Accreditation Program phantom from the American College of Radiology) and further as a function of size if there is any concern that the noise performance may be outside compliance for larger sizes.

Scan Plane (transaxial is preferred) may differ between subjects due to the need to position for physical deformities or external hardware. For an individual subject, a consistent scan plane will reduce unnecessary differences in the appearance of the lesion. A vertical scan plane (no tilt) is expected for all imaging except some head and neck exams.

3.2.2 SPECIFICATION COMMON TO ARTERIAL BEDS

Parameter	Actor	Requirement	DICOM Tag
Acquisition Protocol	Imaging Physician	Shall prepare a protocol to meet the specifications in this table. Shall ensure technologists have been trained on the requirements of this profile.	
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.	
In-plane Spatial	Acquisition	Shall validate that the protocol achieves an f50 value that is Greater	

Parameter	Actor	Requirement	DICOM Tag
Resolution	Device	than 0.35 mm^{-1} for both air and soft tissue edges. See section 4.1. Assessment Procedure: In-plane Spatial Resolution	
Voxel Noise	Acquisition Device	Shall validate that the protocol achieves a standard deviation that is < 30HU. See 4.2. Assessment Procedure: Voxel Noise	
Acquisition Protocol	Technologist	Shall select a protocol that has been previously prepared and validated for this purpose.	

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 30mm.	Total Collimation Width (0018,9307)
Nominal Tomographic Section Thickness (T)	Imaging Physician	Shall set to Less than or equal to 1.0mm.	Single Collimation Width (0018,9306)
Scan Duration	Imaging Physician	Shall achieve a table speed of at least 4cm per second, if table motion is necessary to cover the required anatomy.	Table Speed (0018,9309)
Revolution Time	Imaging Physician	Shall achieve a revolution time of Less than or equal to 350ms.	Revolution Time (0018,9305)
ECG Gating	Imaging Physician	Shall enable with trigger set for mid diastolic for heart rates less than or equal to 70 bpm, and end systole for heart rates above 70 bpm	

3.2.4 SPECIFICATION UNIQUE TO CAROTID ARTERIES

Parameter	Actor	Requirement	DICOM Tag
Total Collimation Width	Imaging Physician	Shall set to Greater than or equal to 16mm.	Total Collimation Width (0018,9307)
Nominal Tomographic Section Thickness (T)	Imaging Physician	Shall set to Less than or equal to 1.0mm.	Single Collimation Width (0018,9306)
Scan Duration	Imaging Physician	Shall achieve a table speed of at least 4cm per second, if table motion is necessary to cover the required anatomy.	Table Speed (0018,9309)

3.3. Image Data Reconstruction

This activity involves the reconstruction of image data for a given encounter.

3.3.1 DISCUSSION

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

Reconstruction Protocol affects the image pixel characteristics. The selection and reporting requirements imply a need for a method to record and communicate the protocol selected and any significant

modifications and make that information available to the Imaging Physician for the QA Activity. The Profile does not dictate any specific method. Manual methods are acceptable.

Reconstruction Field of View affects reconstructed pixel size because the fixed image matrix size of most reconstruction algorithms is 512x512. If it is necessary to expand the field of view to encompass more anatomy, the resulting larger pixels may be insufficient to achieve the claim. A targeted reconstruction with a smaller field of view may be necessary, but a reconstruction with that field of view would need to be performed for every encounter. Pixel Size directly affects voxel size along the subject x-axis and y-axis. Smaller voxels are preferable to reduce partial volume effects and provide higher measurement precision.

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 filter, however since the filter is configured in the protocol, its effect on the spatial resolution will have been evaluated by the f50 requirement when determining conformance.

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

Reconstructed Image Interval is the distance between two consecutive reconstructed images. An interval that results in discontiguous data is unacceptable as it may degrade the identification of vessel wall and plaque contours, confound the precision of measurement for total plaque burden measurands, etc. 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.

Reconstructing datasets with **overlap** will 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; this is true because multiple reconstructions having different filter, slice thickness and intervals can be reconstructed from the same acquisition (raw projection data) and therefore no additional radiation exposure is needed.

Reconstruction Characteristics influence the texture and the appearance of lesions in the reconstructed images, which may influence measurements. A softer filter can reduce noise at the expense of spatial resolution. An enhancing filter can improve resolving power at the expense of increased noise. Filter characteristics also interact with acquisition parameters and reconstruction algorithm types; a sharper filter 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. calcified vs lipid) may call for the use of different filters, and implementers are encouraged to use filters suitable for the anatomic region and tissue imaged. The use of multiple filters in a single study is not prohibited by the specification below, but any given vessel and atherosclerotic plaque must be measured on images reconstructed using consistent filters at each encounter.

3.3.2 SPECIFICATION

Parameter	Actor	Requirement	DICOM Tag
Reconstruction Protocol	Imaging Physician	Shall prepare a protocol to meet the specifications in this table. Shall ensure technologists have been trained on the requirements of this profile.	

Parameter	Actor	Requirement	DICOM Tag
	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.	
Reconstructed Image Thickness	Imaging Physician	Shall set to between 0.5mm and 1mm (inclusive).	Slice Thickness (0018,0050)
	Technologist	Shall set to between 0.5mm and 1mm (inclusive) if not set in the protocol.	
Reconstructed Image Interval	Imaging Physician	Shall set to less than or equal to the Reconstructed Image Thickness (i.e. no gap, may have overlap).	Spacing Between 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	Imaging Physician	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	
Voxel Noise	Physicist	Shall validate that the protocol achieves a standard deviation that is < 30HU. See section 4.2. Assessment Procedure: Voxel 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 QA

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

3.4.1 DISCUSSION

This Image QA activity represents the portion of QA performed between image generation and analysis where characteristics of the content of the image are checked for conformance with the profile. The Image QA details listed here are the ones QIBA has chosen to highlight in relation to achieving the Profile claim. It

is expected that sites will perform many other QA procedures as part of good imaging practices.

The Imaging Physician 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 repeating acquisition and/or reconstruction to address issues with patient motion or artifacts.

Similarly, some or all of these checks may be performed at reporting time and as a result some or all of the lesion measurements may then be identified as not falling within the performance Claim of the Profile.

Scan Plane variation refers to differences in gantry tilt or differences in head/neck positioning. Since several factors that affect quantitative assessment are not isotropic, changing the orientation of the lesion relative to the scan plane from one encounter to another can increase variability.

Dense object artifacts (both internal and external to the patient) can variably degrade the ability to assess lesion contours as discussed in section 3.5, resulting in poor change measures and repeatability.

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

3.4.2 SPECIFICATION

The Imaging Physician shall ensure that the following specifications have been evaluated for each lesion being measured.

Parameter	Actor	Requirement
Patient Motion Artifacts	Imaging Physician	Shall confirm the images containing the lesion are free from artifact due to patient motion.
Dense Object Artifacts	Imaging Physician	Shall confirm the images containing the lesion are free from artifact due to dense objects, materials, or anatomic positioning.
Contrast Enhancement	Imaging Physician	Shall confirm that the phase of enhancement, if any, and degree of enhancement are consistent with baseline.
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).
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.

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.

3.5.1 DISCUSSION

Segmentation may be performed automatically by a software algorithm, manually by a human reader, or semi-automatically by an algorithm with human guidance/intervention, for example to identify a starting seed point or region, or to edit contours. Values may or may not correspond to the total of all the segmented voxels. The algorithm may consider partial volumes, do surface smoothing, lesion or organ

modeling, or interpolation of user editing. The algorithm may also pre-process the images prior to segmentation. If a human reader participates in the segmentation, either by determining while looking at the images the proper settings for an automated process, or by manually editing contours, the settings for conversion of density into display levels (window and level) should either be fixed during the segmentation process or documented so that readers can apply consistent display settings at future encounters (or a different reader for the same encounter, if multiple readers may read each encounter, as for a clinical trial).

Segmentation Object Storage Storing segmentations and measurement results that can be loaded by Image Analysis Tool analyzing data collected at a later date is certainly a useful practice as it can save time and cost. For this to happen reliably, the stored format must be compatible and the data must be stored and conveyed.

Tool Version Medical devices such as Image Analysis Tool are typically made up of multiple components (the hardware, the operating system, the application software, and various function libraries within those). Changes in any of the components can affect the behavior of the device. In this specification, the "device version" should reflect the total set of components and any changes to components should result in a change in the recorded device version. This device version may thus be different than the product release version that appears in manufacturer documentation.

Determination of which lesions should be measured is out of scope for this Profile. Such determination may be specified within a protocol or specified by formal response criteria standards, or may be determined by clinical requirements. Lesions to be measured may be designated by the Imaging Physician at a clinical site, by a reader at a central reading facility, or they may be designated automatically by the software analysis tool.

Audit Trail and **Provenance** details can be helpful when auditing the performance of the biomarker and the site using it. For example, it is helpful for the system to record the software version, set-up and configuration parameters used, or to be capable of recording intermediate contour objects as a DICOM Segmentation or NRRD file. Systems based on models should be capable of recording the model and parameters.

Multiple Encounters The Image Analysis Tool should be prepared to process multiple encounters and support matching across encounters in order to derive change.

3.5.2 SPECIFICATION

<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 for measurements of Lumen Area, Wall Area, Maximum Wall Thickness, and Plaque Burden. 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</td><td>Image Analysis</td><td>Shall be validated to achieve bias and linearity (expressed as intercept, slope, and</td></tr>
</table>

<table>
<tr><th>Parameter</th><th>Actor</th><th>Requirement</th></tr>
<tr><td>Composition</td><td>Tool</td><td>quadratic term) within the values shown in the following table for measurements of Calcified Area, and LNRC Area. 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 for measurements of Lumen Area, Wall Area, Maximum Wall Thickness, Plaque Burden, Calcified Area, and LRNC Area. 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>
<tr><td>Calcified Area (mm^2)</td><td>Intra-reader wSD: 1.0, Inter-reader wSD: 1.5</td></tr>
<tr><td>LRNC Area (mm^2)</td><td>Intra-reader wSD: 1.0, Inter-reader wSD: 1.5</td></tr>
</table></td></tr>
<tr><td>Basis of cross-sectional area results</td><td>Image Analysis Tool</td><td>Shall base cross-sectional area results on obliquely-resliced orthogonal to centerline at spacing less than or equal to 0.5mm</td></tr>
<tr><td>Basis of volume results</td><td>Image Analysis Tool</td><td>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)</td></tr>
<tr><td>Confidence interval</td><td>Image Analysis Tool</td><td>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.</td></tr>
<tr><td>Provenance records</td><td>Image Analysis Tool</td><td>Shall record the identity, timing, and processing parameter settings for steps taken in the analysis of images and make them available to both visual as well as programmatic query.</td></tr>
<tr><td>Result Verification</td><td>Imaging Physician</td><td>Shall review & approve margin contours produced by the tool.</td></tr>
<tr><td>Multiple Lesions</td><td>Image Analysis Tool</td><td>Shall allow multiple lesions to be measured.
Shall either correlate each measured lesion across encounters or support the Imaging Physician to unambiguously correlate them.</td></tr>
<tr><td rowspan="2">Multiple encounters</td><td>Imaging Physician</td><td>Shall re-process the first encounter if it was processed by a different Image Analysis Tool or Imaging Physician.</td></tr>
<tr><td>Image Analysis Tool</td><td>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).</td></tr>
</table>

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). 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%. So for an f50 value of 0.4 mm^{-1}, features that are 2.5mm (or smaller) would have their contrast degraded by 50% (or more).

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, which has a series of HU-value cylindrical inserts including one with soft-tissue equivalence. The acquisition protocol and reconstruction parameters shall conform to this Profile (See Section 3.2.2, 3.2.3, 3.2.4, and 3.3.2). The same protocol and parameters shall be used when performing the assessments in section 4.1 and 4.2, i.e., the noise level during resolution assessment should correspond to that measured during noise assessment.

The phantom shall be positioned with the center of the phantom at isocenter and properly aligned along the z-axis. For further details, refer to Section C, Step 3 of the CT Accreditation Testing Instructions:

http://www.acraccreditation.org/~/media/ACRAccreditation/Documents/CT/CT-Accreditation-Testing-Instructions.pdf

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.

Sites may submit to QIBA a proposed alternative method and evidence that the results produced by the proposed method are equivalent to this reference method or to the manufacturer method. Upon review and approval by QIBA, the alternative method will also become an accepted assessment procedure in this

Profile.

This assessment procedure is applicable to conventional filtered backprojection and to iterative reconstruction.

Note that in addition to the x-y plane MTF, the AAPM TG233 phantom and software also provides an axial resolution measurement (MTF in the z-direction), which may be used as a confirmation of the axial resolution anticipated from the reconstructed image thickness.

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. Voxel 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 voxel noise when adjusted to accommodate for patient size. By way of example, a chart of general guidelines on how to adjust scan parameters to achieve a constant voxel noise level across patient of all sizes:

BMI	mA	AIDR mA	kVp
18	400	200	100
19	440	220	
20	450	230	
21	500	250	
22	520	260	
23	530	270	
24	540	270	
25	560	280	
26	570	290	
27	510	260	120
28	520	260	
29	520	260	
30	530	270	
31	560	280	
32	570	290	
33	570	290	
34	570	290	
35	580	290	
36	580	290	
37	580	290	
38	580	290	
39	480	240	135
40	490	250	
40+	500	250	

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 then 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. The acquisition protocol and reconstruction parameters shall be conformant with this Profile (See Section 3.2.2, 3.2.3, 3.2.4, and 3.3.2). The same protocol and parameters shall be used when performing the assessments in section 4.1 and 4.2.

When the scan is performed, the assessor shall select a single representative slice 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.

The assessor is encouraged to record and retain the images and associated measurement details but it is not required beyond the two values listed above. Such details can be helpful 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 size (such as those using Automatic Exposure Control), the qualification of CT scanner noise should include noise as a function of size (using phantom such as that provisioned in AAPM TG233) if there is any concern that the noise performance may be outside compliance for different sizes.

The procedure described above is provided as a reference method. Sites may submit to QIBA a proposed alternative method (such as using the water phantom portion of a manufacturer's QA phantom) and evidence that the results produced by the proposed method are equivalent to this reference method or manufacturer methodology. Upon review and approval by QIBA, the alternative method will also become an accepted assessment procedure in this Profile.

This assessment procedure is intended to be a simple phantom measurement that can be used to set a reasonable limit on the noise which is considered sufficient to avoid degrading segmentation performance. The procedure may be used for both conventional filtered backprojection and iterative reconstruction methods. It is noted that when characterizing reconstruction methods, voxel noise is a limited representation of image noise when noise texture is varied.

4.3. Assessment Procedure: Vessel Structure Bias and Linearity

This procedure can be used by a manufacturer or an imaging site 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 1). Data is provided by the registrant for self-attestation (QIBA Registered) and may in future be provided by QIBA for a certification program.

The phantoms must 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 must be filled with contrast media utilized in practice and scanned in a range of at least 4 scanner settings that is representative of current clinical practice but which meet the requirements of this Profile. Statistical measures of bias were estimated from these data.

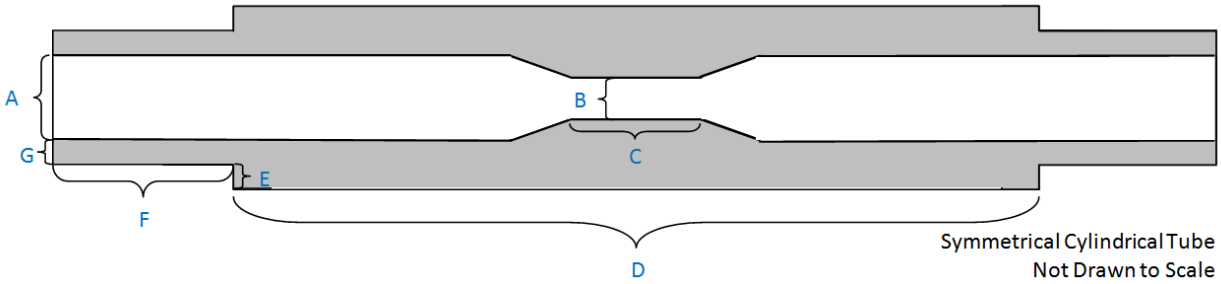

Figure 4-1: Physical Dimensions of Vascular Phantoms

An example material is Noryl, which has a density of 1.06 g/ml. The specifications for the phantoms that must be used are displayed on Table 4-1. If a given manufacturer wishes to support a subset rather than the whole range, then a representation of conformance needs to clearly note the reduced scope.

Table 4-1. 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 at least one 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 must 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. [23].

Suspend the phantoms in a plastic cage submerged in a box of vegetable oil, and scan at the same time. Acquire the test image set according to the requirements of this Profile (e.g. patient handling, acquisition protocol, reconstruction), to minimally include four admissible variations of scan parameters. By using a variance in CT scanning parameters, the performance analysis evaluates a spectrum of images rather than only one.

4.3.2 DETERMINE MEASURANDS

Import the DICOM files into the analysis software and perform the analysis, recording how requirements as described in the Image Analysis Activity have been met.

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 natural log of 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

$$\%\widehat{bias} = \left(\exp\left(\widehat{D}\right) - 1\right) \times 100.$$

The assessor shall fit an ordinary least squares (OLS) regression of the $\ln Y_i$ on $\ln X_i$ and shall estimate the slope ($\hat{\beta}_1$), intercept, and quadratic term.

The assessor shall divide the targets into a small vessel subgroup (vessels <4.5 mm) and a large subgroup (vessels >= 4.5 mm). The assessor shall repeat the percentage population bias calculation on each subgroup to estimate subgroup percentage bias, and then assess the ability to pool the results.

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: Tissue Characteristics Bias and Linearity

This procedure can be used by a manufacturer or an imaging site 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. Data is provided by the registrant for self-attestation (QIBA Registered) and may in future be provided by QIBA for a certification program.

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 must be performed using only raw CT, scrupulously avoiding use of the image analysis tool's computed segmentations to preserve objectivity in the matching.

Subjectivity of 3D placement must 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 2: 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 3: 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, recording how requirements as described in the Image Analysis Activity have been met.

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, a single reader of average capability who has been trained on the tool shall be used for this entire assessment procedure.

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 must be performed in a strictly held-out set of subjects, and cannot be done iteratively. One 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.

Fit a linear model, where the dependent variable is the image analysis tool measurement (Y) and the independent variable is the histopathology value (X). Generalized estimating equations (to account for the fact that subjects have more than one target) may be used to estimate the linear function, as follows: $E(Y|X) = \beta 0 + \beta 1X$. An exchangeable working covariance may be used. Construct a 95% CI for the intercept β_0 from the fitted model. CIs not containing 0 indicate constant bias. Also construct a 95% CI for the slope, intercept, and quadratic term. These calculations allow conclusions to be drawn regarding the linearity of the measurements (32).

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 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: Reader / Image Analysis Tool Variability

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.

4.5.1 OBTAIN TEST IMAGE SET

Data is provided by the registrant for self-attestation (QIBA Registered) and may in future be provided by QIBA for a certification program.

4.5.2 DETERMINE MEASURANDS

For each measurand, first 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 in the conformance statement. 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.

4.5.3 CALCULATE STATISTICAL METRICS OF PERFORMANCE

Then calculate the between-reader within-section SD, estimated from one calculation by two or more different readers. The Reproducibility Coefficient (RDC) was estimated as 2.77 $\times$ 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.

Appendices

Appendix A: Acknowledgements and Attributions

This document is proffered by the Radiological Society of North America (RSNA) QIBA Atherosclerosis Biomarkers Biomarker Committee. The committee is composed of representatives from academia, professional societies, imaging device manufacturers, image analysis image analysis tool developers, image analysis laboratories, biopharmaceutical industry, government research organizations, and regulatory agencies, among others. All work is classified as pre-competitive.

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

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Appendix B: Conventions and Definitions

Acquisition vs. Analysis vs. Interpretation: This document organizes acquisition, reconstruction, post-processing, analysis and interpretation as steps in a pipeline that transforms data to information to knowledge. Acquisition, reconstruction and post-processing are considered to address the collection and structuring of new data from the subject. Analysis is primarily considered to be computational steps that transform the data into information, extracting important values. Interpretation is primarily considered to be judgment that transforms the information into knowledge. (The transformation of knowledge into wisdom is beyond the scope of this document.)

Image Analysis, Image Review, and/or Read: Procedures and processes that culminate in the generation of imaging outcome measures, such lesion response criteria. Reviews can be performed for eligibility, safety or efficacy. The review paradigm may be context specific and dependent on the specific aims of a trial, the imaging technologies in play, and the stage of drug development, among other parameters.

Image Header: that part of the image file (or dataset containing the image) other than the pixel data itself.

Imaging Phantoms: devices used for periodic testing and standardization of image acquisition. This testing must be site specific and equipment specific and conducted prior to the beginning of a trial (baseline), periodically during the trial and at the end of the trial.

Encounter: a discrete period during the course of a clinical trial when groups of imaging exams or clinical exams are scheduled.

Lesion Definition Variability: the clarity of the lesion contour in the images. It originates from the biological characteristics of the lesion, technical characteristics of the imaging process, and perhaps on the perception, expertise and education of the operator.

Technical Variability - originates only from the ability to drawing unequivocal objects. In other words, the perception of lesion definition is supposed absolutely clear and similar for any given operator when attempting to assess “Technical” variability.

Global Variability - partitioned as the variability in the lesion definition plus the “Technical” variability.

Intra-Reader Variability - is the variability in the interpretation of a set of images by the same reader after an adequate period of time inserted to reduce recall bias.

Inter-Reader Variability - is the variability in the interpretation of a set of images by the different readers.

Repeatability – considers multiple measurements taken under the same conditions (same equipment, parameters, reader, algorithm, etc.) but different subjects.

Reproducibility – considers multiple measurements taken where one or more conditions have changed.

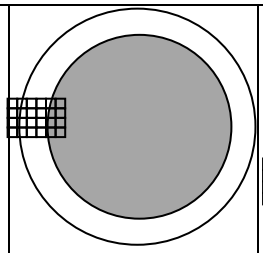
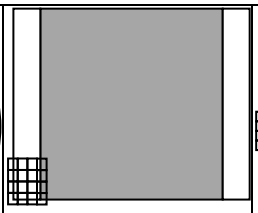
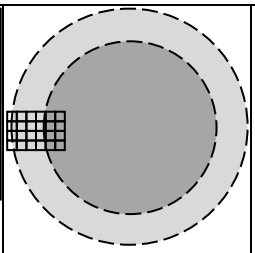
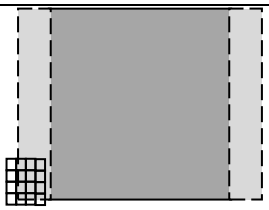
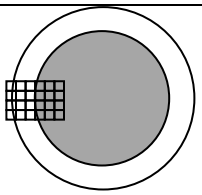
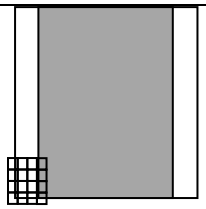
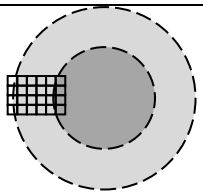
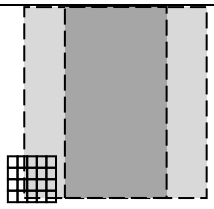
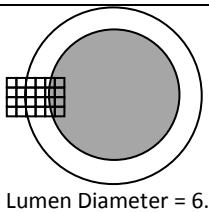
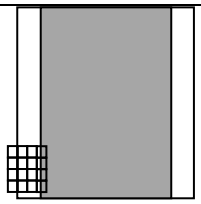
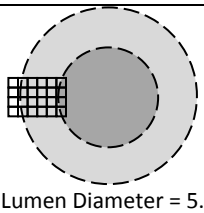
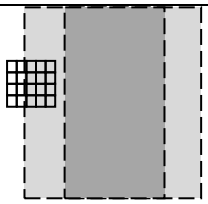
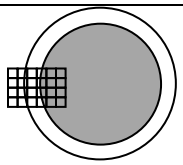
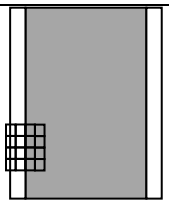
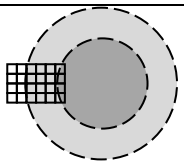
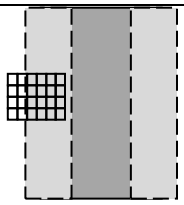
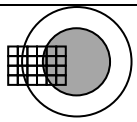
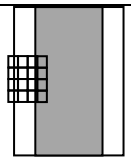
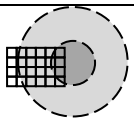
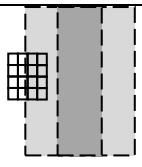
Appendix C: Imaging Resolution Details

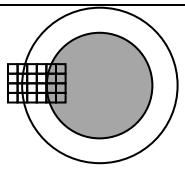
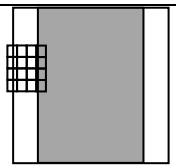
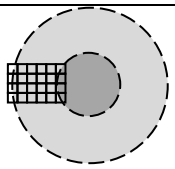
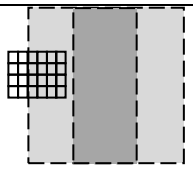
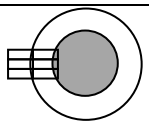
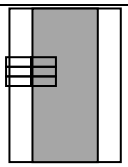
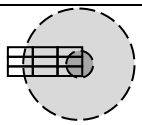
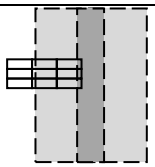
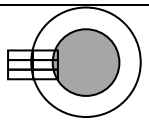
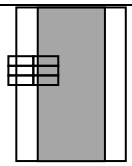
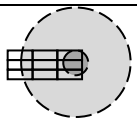
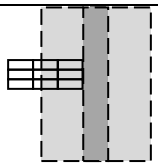
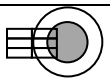
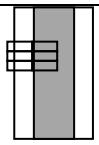
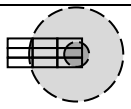
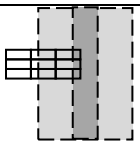
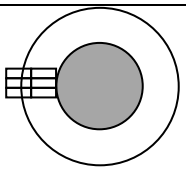
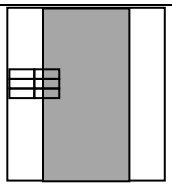
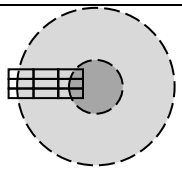
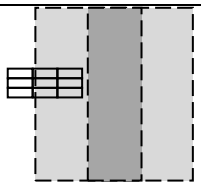
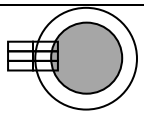
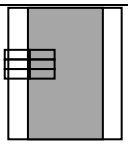
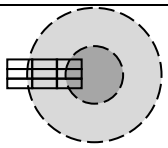
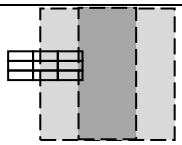
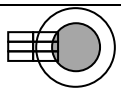
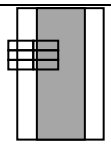
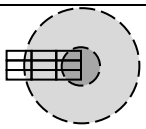
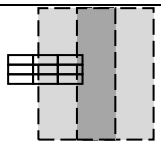
LAD = Left Anterior Descending
LCA = Left Coronary Artery
RCA = Right Coronary Artery

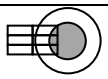
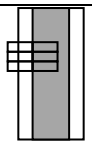
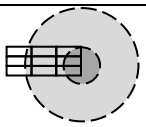
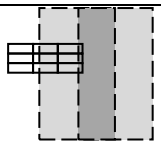
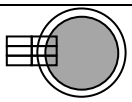
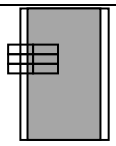
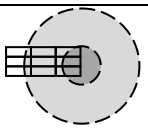
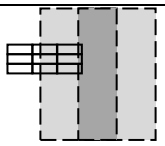
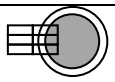
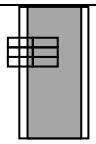
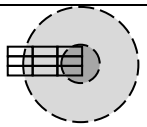
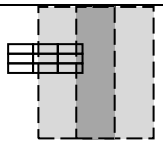
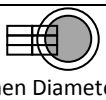
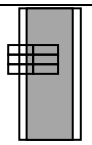
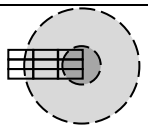
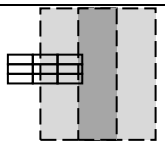
Black = lumen
Gray = plaque
White = wall

*****Resolution column scale: 0.5 inch = 1 mm*****

*****Healthy and Diseased Artery columns scale: 1 inch = 10 mm*****

Vessel	Resolution (mm)	Healthy (Axial)	Healthy (Coronal/Sagittal)	Diseased (Axial)	Disease (Coronal/Sagittal)
CT FEMORAL Axial Orientation Scan					
Common Femoral Artery	0.5 x 0.5 x 0.63 	 Lumen Diameter = 9.5 mm Wall Thickness = 1.42 mm		 Lumen Diameter = 9.02 mm Wall Thickness = 1.66 mm	
Superficial Femoral Artery	0.5 x 0.5 x 0.63 	 Lumen Diameter = 7 mm Wall Thickness = 1.27 mm		 Lumen Diameter = 5.28 mm Wall Thickness = 2.13 mm	
Deep Femoral Artery (profunda)	0.5 x 0.5 x 0.63 	 Lumen Diameter = 6.8 mm Wall Thickness = 1.2 mm		 Lumen Diameter = 5.2 mm Wall Thickness = 2 mm	
CT CAROTID Axial Orientation Scan					
Common Carotid Artery	0.5 x 0.5 x 0.63 	 Lumen Diameter = 6.3 mm Wall Thickness = 0.8 mm		 Lumen Diameter = 3.02 mm Wall Thickness = 2.44 mm	
External Carotid Artery	0.5 x 0.5 x 0.63 	 Lumen Diameter = 3.5 mm		 Lumen Diameter = 2.3 mm	

		Wall Thickness = 1.1 mm		Wall Thickness = 1.7 mm	
Internal Carotid Artery	0.5 x 0.5 x 0.63 	 Lumen Diameter = 5.5 mm Wall Thickness = 1.3 mm		 Lumen Diameter = 3.3 mm Wall Thickness =2.4 mm	
CT CORONARY					
Proximal RCA	0.5 x 0.5 x 1.25 	 Lumen Diameter = 3.4 mm Wall Thickness = 1.2 mm		 Lumen Diameter = 1.4 mm Wall Thickness = 2.2 mm	
Mid RCA	0.5 x 0.5 x 1.25 	 Lumen Diameter = 3.5 mm Wall Thickness = 1.1 mm		 Lumen Diameter = 1.3 mm Wall Thickness = 2.2 mm	
Distal RCA	0.5 x 0.5 x 1.25 	 Lumen Diameter = 2.1 mm Wall Thickness = 1.0 mm		 Lumen Diameter = 1.3 mm Wall Thickness = 1.8 mm	
Left Main Coronary Artery	0.5 x 0.5 x 1.25 	 Lumen Diameter = 4.5 mm Wall Thickness = 1.85 mm		 Lumen Diameter = 2.8 mm Wall Thickness = 2.7 mm	
Proximal LAD Branch of LCA	0.5 x 0.5 x 1.25 	 Lumen Diameter = 3.9 mm Wall Thickness = 1.0 mm		 Lumen Diameter = 3.0 mm Wall Thickness = 2.0 mm	
Mid LAD Branch of LCA	0.5 x 0.5 x 1.25 	 Lumen Diameter = 2.5 mm Wall Thickness = 1.0 mm		 Lumen Diameter = 2.0 mm Wall Thickness = 2.0	

				mm	
Distal LAD Branch of LCA	0.5 x 0.5 x 1.25 	 Lumen Diameter = 1.85 mm Wall Thickness = 0.79 mm		 Lumen Diameter = 1.85 mm Wall Thickness = 2.0 mm	
Proximal Circumflex Branch of LCA	0.5 x 0.5 x 1.25 	 Lumen Diameter = 3.8 mm Wall Thickness = 0.42 mm		 Lumen Diameter = 2.0 mm Wall Thickness = 2.0 mm	
Mid Circumflex Branch of LCA	0.5 x 0.5 x 1.25 	 Lumen Diameter = 2.8 mm Wall Thickness = 0.42 mm		 Lumen Diameter = 2.0 mm Wall Thickness = 2.0 mm	
Distal Circumflex Branch of LCA	0.5 x 0.5 x 1.25 	 Lumen Diameter = 2.4 mm Wall Thickness = 0.42 mm		 Lumen Diameter = 2.0 mm Wall Thickness = 2.0 mm	

[1] Wall thickness measurements taken from [24]
[2] Lumen diameter measurements taken from [25]
[3] Lumen diameter measurements taken from [26]
[4] Wall thickness measurements taken from [27]
[5] Lumen diameter measurements taken from [28]
[6] Lumen diameter measurements taken from [29]
[7] Wall thickness measurements taken from [30-32]
[8] Estimated
[9] Measurements taken from review of typical images

Appendix D: Measurand Definitions and Units

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
Wall Area	The cross-sectional area of a vessel at position along the vessel centerline minus the LumenArea at that position.	mm^2
Plaque Burden	An index calculated as Wall Area / (Wall Area + Lumen Area).	None (expressed as a unitless ratio)
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
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

Appendix E: CT Angiography 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 [33], 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.

Examination of arterial beds using radiological imaging is common among three image modalities: ultrasound, CT, and MRI. A particularly thorough review paper [34] 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: 23 of which investigated ultrasound, 18 CT, 18 MRI, 2 that investigated both CT and ultrasound, and 1 that investigated both MRI and ultrasound. 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 [35]	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 [35]	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 [36]	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 [37]	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 [38]	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 [38]	CT	Intra-observer	535 Human coronaries	Vessel Area (mm2)	-1%	7%
Papadopoulou 2012 [39]	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 [40]	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 [40]	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 [41]) 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. The main advantage of this technology compared with conventional mechanical spiral CT scanner is that it consists of multiple

detector rows, which allow simultaneous acquisition of multiple slices. CT scanners using e.g. 16 and 64 – slice technology offer a very high spatial resolution and can generate very thin slices allowing the acquisition of isotropic voxels. It has been shown, using 16-slice CT, that non-calcified coronary lesions could be detected with a reasonable sensitivity of 78%. 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 [35]) 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 [42]) 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 [43], states:

- (from discussion) This study provides proof of principle that the tissue characteristics of atherosclerotic plaques determined by CTA accurately reflects tissue characteristics of the lesion as defined by histologic examination.
- (from results) 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 (i.e., mean Hounsfield attenuation for each histologic component and the 95% confidence intervals for these densities) are displayed in Table 2. 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.

Table 2 here reproduced for convenience (and with permission):

Table 2: Mean in-vivo CT Hounsfield density, SD, and 95% confidence interval for each histologic component*

Histologic Component	Mean (HU)	SD (HU)	95% Confidence Interval (HU)	
Lipid-rich necrotic core	32.6	20.0	−7.4	72.5
Connective tissue	46.4	19.9	6.6	86.2
Hemorrhage	97.5	22.0	53.5	141.6
Calcifications	256.7	30.2	216.3	297.1

Note:—HU indicates Hounsfield units.
* Determined by comparison of each 2 × 2-mm square electronically drawn on the in vivo CT reformatted images with corresponding histologic and micro-CT squares.

Wintermark's Table 2, de Weert's result regarding cutoff values [35], and also work by Sieren [44] 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 [45]:

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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