# QIBA Profile:

# Atherosclerosis Biomarkers by Computed Tomography Angiography (CTA) - 2019

Stage: Consensus

When referencing this document, please use the following format:

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# 1. Executive Summary

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

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

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

This document is intended to help clinicians making decisions based on these biomarkers, imaging staff generating these biomarkers, vendor staff developing related products, purchasers of such products, and investigators designing trials with imaging endpoints. The **Claim** (Section 2) describes the biomarker performance. The **Activities** (Section 3) contribute to generating the biomarker. Requirements are placed on the **Actors** that participate in those activities as necessary to achieve the Claim. **Assessment Procedures** (Section 4) for evaluating specific requirements are defined as needed.

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

# 2. Clinical Context and Claim(s)

## Clinical Context

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

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

**Table 1: Measurands Covered by this Profile**

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

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

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

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

## CLAIMS

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

**Table 2 Quantitative Claims**

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

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

DISCUSSION

- Technical performance claims indicate the extreme of the 95% confidence interval, not (only) the point estimate. Specifically, we say that not only is a point estimate of the performance as claimed, but that we are 95% confident that it is as claimed.
- All statistical performance metrics are stated according to strict definitions as given in [3-8].
- Section 4, Assessment Procedures, identifies the data collection and analysis procedures for the assessment:
    - 95% CI Bias for structural measurands (maximum wall thickness, lumen area, wall area, and plaque burden) are assessed as described in section 4.3. Assessment Procedure: Vessel Structure Bias and Linearity, using phantoms.
    - 95% CI Bias for tissue characteristics (LRNC area, and calcified area) are assessed as described in section 4.4. Assessment Procedure: Tissue Characteristics Bias and Linearity, using ex vivo histology, accounting for both subjectivity due to pathologist annotation as well as 2D-3D spatial alignment as identified in the assessment procedure.
    - 95% CI for reader variability is assessed as within-subject standard deviation (wSD) as described in section 4.5. Assessment Procedure: Reader / Image Analysis Tool Variability, using clinical (not phantom) data sets representing the range of presentations, specifically to include multiple arterial beds (e.g., carotid and coronary).

  Regarding linearity, we make a distinction between (1) the assessment of linearity, or nonlinearity, for a biomarker for developing the profile claims, and (2) testing conformance of an actor or site to the assumptions underlying the claims. For #1, methods described in Tholen DW. Alternative statistical techniques to evaluate linearity. Arch. Pathol Lab Med. 1992; 116(7):746-756 are applicable in doing so. Then, given this, actors with linearity requirements identified in Section 3 of this Profile verify that their results agree with the assumptions made for the claims. For this (i.e. #2), actors (only) need to verify linearity in the range included in the claims (not a full assessment of linear and nonlinear parts) and verify that the slope is in the range assumed in the claims. This simplicity is important for practicality of the Profile's assessment procedures.
- Use of vendor components (specifically, the first three actors from Table 3-1 below) which have only been tested over a smaller range than specified in the claim invalidates the claim outside of that range for the combined system including all actors.
- Maximum wall thickness refers to the largest value for point-wise wall thickness within the lesion or target.

# 3. Profile Requirements

The Profile is documented in terms of "Actors" performing "Activities". Equipment, software, staff or sites may claim conformance to this Profile as one or more of the "Actors" in the following table. Conformant Actors shall support the listed Activities by conforming to all requirements in the section named in the Activity column.

**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 Quality Assurance |
| | Image Analysis |
| Physicist | Image Data Acquisition |
| | Image Data Reconstruction |
| | Image Quality Assurance |
| Technologist | Subject Handling |
| | Image Data Acquisition |
| | Image Data Reconstruction |
| | Image Quality Assurance |
| | Image Analysis |

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

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

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 selects the optimized acquisition and reconstruction protocols, after participating in the equipment selection, installation, acceptance testing and quality assurance program. They are further involved in establishing the best parameters for analysis software and for confirming results against phantoms, when possible.

Technologists are the first line for Image Quality Assurance as they often screen for inadequate images

prior to sending to PACS. They are also often the actor performing the quantitative measurements, sometimes in a dedicated 3D or post-processing lab.

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 that 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, it is important to 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. 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.

### 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 protocol. |
| Artifact Sources | Technologist | Shall remove or position potential sources of artifacts (specifically including breast shields, metal-containing clothing, EKG leads, and other metal equipment) such that they will not degrade the reconstructed CT image. |
| Table Height & Centering | Technologist | Shall adjust the table height for the mid-axillary plane to pass through the isocenter. Shall center the thorax shall be centered in the AP and L/R directions according to the following: table height shall be adjusted for the mid axillary plane to pass through the isocenter and the sagittal laser line shall pass through the sternum from suprasternal notch to xiphoid process. |

| Parameter | Actor | Requirement |
|---|---|---|
| Nitrates | Technologist | Shall administer nitrates as prescribed, 5 minutes prior to 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 [16].

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 CTA, unless contraindicated. At arrival in the department, heart rate is measured, and a further 50 mg may be given 30 minutes before the CTA. 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.

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 bolus tracking. Scan delay times are patient specific and affected by heart rate, patient size, etc. They also depend on the threshold for triggering. A low radiation dose protocol is used for the automated trigger, while the radiation 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 |

## 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, pixel noise level, spatial resolution, etc.).

**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.

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 while reaching the performance targets.

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.

### 3.2.2 SPECIFICATION COMMON TO ARTERIAL BEDS

| Parameter | Actor | Requirement | DICOM Tag |
|---|---|---|---|
| In-plane Spatial Resolution | Acquisition Device | Shall validate that the protocol achieves an f50 value that is greater than 0.35 line pairs per mm for both air and soft tissue edges.<br>See section 4.1. Assessment Procedure: In-plane Spatial Resolution | |
| Pixel noise | Acquisition Device | Shall validate that the protocol achieves a standard deviation that is < 30HU. See 4.2. Assessment Procedure: Pixel noise | |
| Acquisition Protocol | Acquisition Device | Shall be capable of making validated protocols (designed and validated by the manufacturer and/or by the site) available to the technologist at scan time. | |
| | Physicist | Shall prepare a protocol to meet the specifications in this table.<br>Shall ensure technologists have been trained on the requirements of this profile. | |
| | 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 18mm. | Total Collimation Width (0018,9307) |

| Parameter | Actor | Requirement | DICOM Tag |
|---|---|---|---|
| Nominal Tomographic Section Thickness (T) | I Physicist | Shall set to Less than or equal to 0.75mm. | Single Collimation Width (0018,9306) |
| Revolution Time | Physicist | Shall achieve a revolution time of Less than or equal to 350ms. | Revolution Time (0018,9305) |
| ECG Gating | Physicist | Shall enable with trigger set for mid diastole for heart rates less than or equal to 70 bpm, and end systole for heart rates above 70 bpm, or at heart rate appropriate for scanner according to SCCT guidelines. | |

#### 3.2.4 SPECIFICATION UNIQUE TO CAROTID ARTERIES

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

## 3.3. Image Data Reconstruction

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

#### 3.3.1 DISCUSSION

**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 Quality Assurance Activity. The Profile does not dictate any specific method. Manual methods are acceptable.

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.

#### 3.3.2 SPECIFICATION

| Parameter | Actor | Requirement | DICOM Tag |
|---|---|---|---|
| Reconstruction Protocol | Physicist | Shall prepare a protocol to meet the specifications in this table.<br>Shall ensure technologists have been trained on the requirements of this profile. | |
| | Reconstruction Software | Shall be capable of performing reconstructions and producing images with all the parameters set as specified "Protocol Design Specification". | |
| | Technologist | Shall select a protocol that has been previously prepared and validated for this purpose. | |
| ECG Gating | Technologist | Shall use prospective ECG gating and iterative | |

| Parameter | Actor | Requirement | DICOM Tag |
|---|---|---|---|
| | | reconstruction to allow for the lowest possible radiation exposure. If the heart rate is too high, retrospective ECG gating with a target on 70-90% RR interval may be required to obtain optimal motion free images. | |
| Reconstructed Image Thickness | Physicist | Shall 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 | Physicist | 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 | Physicist | Shall set to less than or equal to 0.625mm | (0028,0030) |
| In-plane Spatial Resolution | Physicist | Shall validate that the protocol achieves an f50 value that is Greater than 0.35 $mm^{-1}$ for both air and soft tissue edges. See section 4.1. Assessment Procedure: In-plane Spatial Resolution | |
| Pixel noise | Physicist | Shall validate that the protocol achieves a standard deviation that is < 30HU. See section 4.2. Assessment Procedure: Pixel noise | |
| Image Header | Reconstruction Software | Shall record in the DICOM image header the actual values for the tags listed in the DICOM Tag column "Protocol Design Specification" as well as the model-specific Reconstruction Software parameters utilized to achieve conformance. | |
| Reconstruction Field of View | Technologist | Shall ensure the Field of View spans at least the full extent of the thoracic cavity, but not substantially greater than that. | Reconstruction Field of View (0018,9317) |
| Image Header | Reconstruction Software | Shall record in the DICOM image header the actual values for the tags listed in the DICOM Tag column "Protocol Design Specification" as well as the model-specific Reconstruction Software parameters utilized to achieve conformance. | |

## 3.4. Image Quality Assurance

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

### 3.4.1 DISCUSSION

285 This Image Quality Assurance activity represents the portion of Quality Assurance performed between image generation and analysis where characteristics of the content of the image are checked for conformance with the profile. The Image Quality Assurance 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 Quality Assurance 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 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 |
|---|---|---|
| Motion Artifacts | Imaging Physician | Shall confirm the images containing the lesion are free from artifact due to motion. |
| Artifacts | Imaging Physician | Shall confirm the images containing the lesion are free from artifacts due to dense objects, anatomic positioning (e.g., arms down at sides), or equipment issues (e.g., ring artifacts). |
| Contrast Enhancement | Imaging Physician | Shall confirm that the 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.

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

### 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 at a later date is a useful practice as it can save time and cost. For this to happen reliably, the stored format shall be compatible and the data shall 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 by target, vessel, and lesion 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>
</table>
</td></tr>
</table>

<table>
<tr><th>Parameter</th><th>Actor</th><th>Requirement</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Maximum Wall Thickness (mm)</td><td><u>Bias</u>: ±1, <u>Intercept</u>: ±1, <u>Slope</u>: 1±.1, <u>Quadratic term</u>: ±.1</td></tr>
<tr><td>Plaque Burden (ratio)</td><td><u>Bias</u>: ±0.1, <u>Intercept</u>: ±.1, <u>Slope</u>: 1±.1, <u>Quadratic term</u>: ±.1</td></tr>
</table>
</td></tr>
<tr><td>Tissue Composition</td><td>Image Analysis Tool</td><td>Shall be validated to achieve bias and linearity (expressed as intercept, slope, and quadratic term) within the values shown in the following table 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><u>Bias</u>: ±1.5, <u>Intercept</u>: ±2, <u>Slope</u>: 1±.5, <u>Quadratic term</u>: ±.1</td></tr>
<tr><td>LRNC Area ($mm^2$)</td><td><u>Bias</u>: ±3, <u>Intercept</u>: ±3.5, <u>Slope</u>: 1±.8, <u>Quadratic term</u>: ±.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><u>Intra-reader wSD</u>: 2.5, <u>Inter-reader wSD</u>: 5.0</td></tr>
<tr><td>Wall Area ($mm^2$)</td><td><u>Intra-reader wSD</u>: 2.5, <u>Inter-reader wSD</u>: 5.0</td></tr>
<tr><td>Maximum Wall Thickness (mm)</td><td><u>Intra-reader wSD</u>: 0.75, <u>Inter-reader wSD</u>: 1.0</td></tr>
<tr><td>Plaque Burden (ratio)</td><td><u>Intra-reader wSD</u>: 0.1, <u>Inter-reader wSD</u>: 0.1</td></tr>
<tr><td>Calcified Area ($mm^2$)</td><td><u>Intra-reader wSD</u>: 1.0, <u>Inter-reader wSD</u>: 1.5</td></tr>
<tr><td>LRNC Area ($mm^2$)</td><td><u>Intra-reader wSD</u>: 1.0, <u>Inter-reader wSD</u>: 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>Result Verification</td><td>Imaging Physician</td><td>Shall review & approve segmentations produced by the Image Analysis Tool.</td></tr>
<tr><td>Multiple Lesions</td><td>Image Analysis Tool</td><td>Shall allow multiple lesions to be measured.<br>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.<br>Shall be able to re-process the first encounter (e.g. if it was processed by a different</td></tr>
</table>

| Parameter | Actor | Requirement |
|---|---|---|
| | | Image Analysis Tool or Imaging Physician). |

# 4. Assessment Procedures

To conform to this Profile, participating staff and equipment ("Actors") shall support each activity assigned to them in Table 3-1. Although most of the requirements described in Section 3 can be assessed for conformance by direct observation, some of the performance-oriented requirements cannot, in which case the requirement references an Assessment Procedure subsection here in Section 4.

## 4.1. Assessment Procedure: In-plane Spatial Resolution

This procedure can be used by a manufacturer or an imaging site to assess the In-plane Spatial Resolution of reconstructed images. Resolution is assessed in terms of the f50 value (in $mm^{-1}$) of the modulation transfer function (MTF).

The assessor shall first warm up the scanner's x-ray tube and perform calibration scans (often called air-calibration scans) according to scanner manufacturer recommendations.

The assessor shall scan a spatial resolution phantom, such as the ACR CT Accreditation Program (CTAP) Phantom's module 1 or the AAPM TG233 phantom, 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: Pixel noise

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

Scan parameters, especially current (mA) and tube potential (kVp), strongly influence achieved pixel noise when adjusted to accommodate for patient size. By way of example, a chart of general guidelines on how to adjust acquisition protocol to achieve a constant pixel 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 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 image from the uniformity portion of the phantom.

A region of interest (ROI) of at least 400 $mm^2$ shall be placed near the center of the phantom. The assessor shall record the values reported for the ROI mean and standard deviation.

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 several different sizes 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 Quality Assurance 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, pixel noise is a limited representation of image noise when noise texture is varied.

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

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

### 4.3.1 OBTAIN TEST IMAGE SET

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

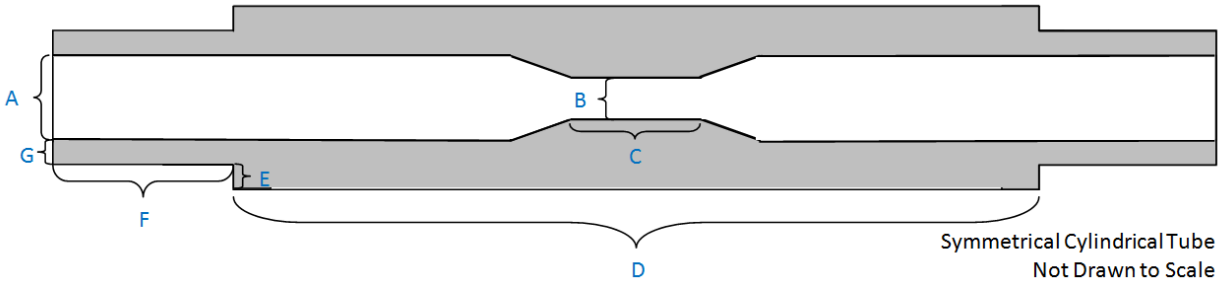


**Figure 4-1: Physical Dimensions of Vascular Phantoms**

An example material is Noryl, which has a density of 1.06 g/ml. The specifications for the phantoms that shall be used are displayed on Table 4-3, or equivalent with scientific justification. If a given Image Analysis Tool vendor wishes to support a subset of the phantoms listed rather than the whole range, then a

representation of conformance needs to clearly note the reduced scope (i.e., only a portion of the range indicated in the Image Analysis specification section).

**Table 4-3. Phantom Specifications**

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

Each tube is a surrogate for one or more blood vessel. Phantom 1, 2, and 3 represent the size range of coronary arteries. Phantom 3 represents coronary and vertebral arteries. Phantom 4, 5, and 6 represent carotid arteries.

For the scans, the phantoms shall be filled with diluted contrast agent (e.g., Omnipaque) between 10-12 mg Iodine /ml to achieve the same contrast between vessel wall and lumen found in patient CTA scans at 100-120 kVp (based on published relationship of iodine concentration vs. HU for 80-120 kVp, ref. [17]).

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 acquisition protocol (that is, meeting requirements of this Profile). 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, and perform steps as required by the Image Analysis Tool to segment lumen and wall consistent with the requirements set in the Image Analysis activity specification.

The assessor is permitted to edit the segmentation or seed point if that is part of the normal operation of the tool. If segmentation edits are performed, results should explicitly indicate whether they were achieved with and without editing.

When evaluating Image Analysis Tool, at least two readers of average capability who have been trained on the tool shall be used for this assessment procedure.

When evaluating an Imaging Physician, it is acceptable to use a single tool for the assessment procedure.

The assessor shall calculate the measurands (Y) of each cross-section (denoted $Y_i$) where Y denotes the measurand, and *i* denotes the *i*-th target.

### 4.3.3 CALCULATE STATISTICAL METRICS OF PERFORMANCE

The true measurements ($X_i$) as assessed by micrometer of each cross-section are known and are provided in the dataset.

The assessor shall calculate the individual percentage bias ($b_i$) of the measurement of each cross-section as

$$b_i = lnY_i - ln\,X_i$$

The assessor shall estimate the population bias over the N cross-sections as

$$\widehat{D} = \sqrt{\sum_{i=1}^{N} b_i\,/N}$$

The assessor shall convert to a percentage bias estimate as

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

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

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

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

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

### 4.4.1 OBTAIN TEST IMAGE SET

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 4.4.2 DETERMINE MEASURANDS

Import the DICOM files into the analysis software and perform the analysis, and perform steps as required by the Image Analysis Tool to determine tissue characteristics consistent with the requirements set in the Image Analysis activity specification.

When evaluating an Imaging Physician, a single tool shall be used for this entire assessment procedure.

The assessor shall calculate the measurands (Y) of each cross-section (denoted $Y_i$) where Y denotes the measurand, and *i* denotes the *i*-th target.

### 4.4.3 CALCULATE STATISTICAL METRICS OF PERFORMANCE

The following shall be performed in a strictly held-out set of subjects, and cannot be done iteratively. Once the hold-out set has been used for evaluation, it may not be used for a later evaluation after the software

changes, accept insofar as regression tests are performed where there is no material algorithm changes. It is highly advisable to anticipate this in advance when data is collected, and to pre-identify cohorts, and with sufficient numbers collected to support potentially many year development programs.

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

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

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

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

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

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

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

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

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

### 4.5.1 OBTAIN TEST IMAGE SET

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

### 4.5.2 DETERMINE MEASURANDS

For each measurand, calculate the within-section Standard Deviation (wSD) estimated from two or more replicate calculations by the same reader. A minimum of 40 cross-sections from 7 or more subjects per arterial bed indicated are required. Pooling of subjects across carotid and coronary arterial beds is only allowable with rigorous statistical justification, and in any case, does not diminish the minimum counts.

### 4.5.3 CALCULATE STATISTICAL METRICS OF PERFORMANCE

For each measurand, calculate between-reader within-section SD estimated from one calculation by two or more different readers. The Reproducibility Coefficient (RDC) shall be estimated as 2.77 $\times$ 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.

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

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 Typical Values

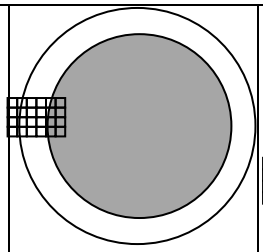
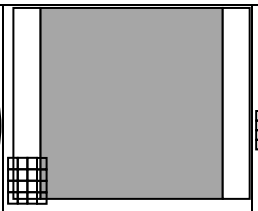
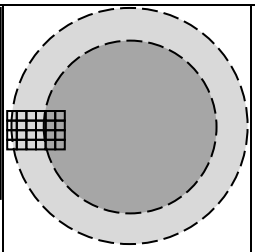
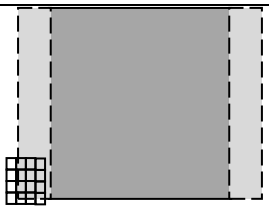
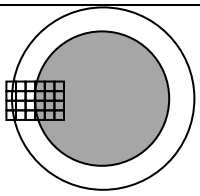
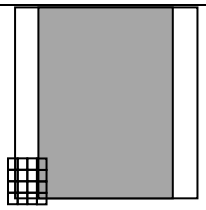
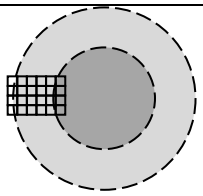
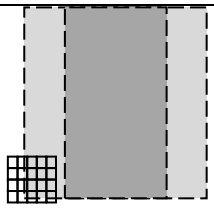
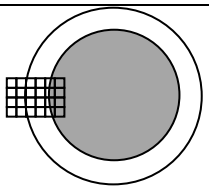
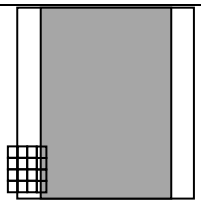
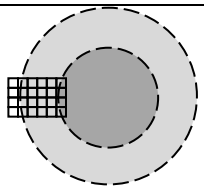
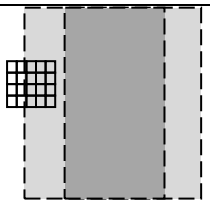
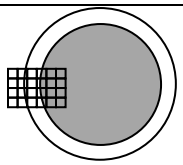
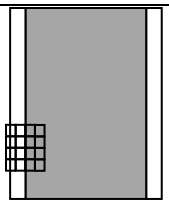
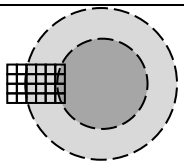
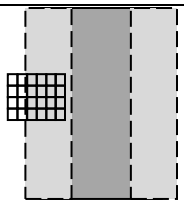
Whereas the specifications and requirements provided in the body of the Profile are considered definitive, the table below provides typical values of imaging resolution across applications of plaque morphology by CTA. Typical values rather than ranges are shown in order to emphasize that these do not comprise requirements but are merely illustrative.

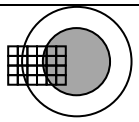
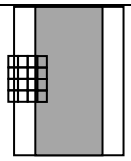
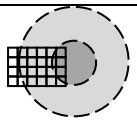
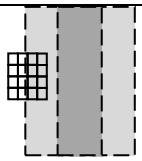
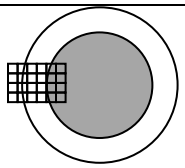
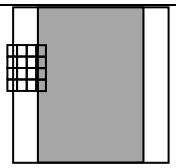
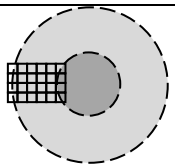
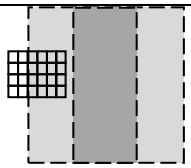
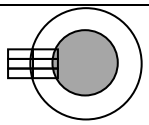
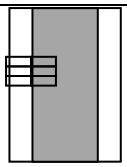
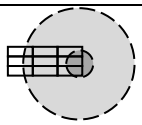
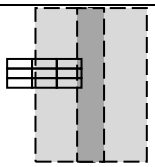
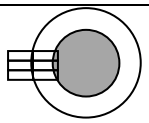
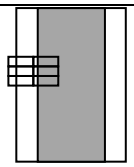
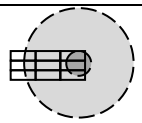
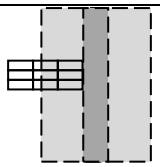
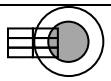
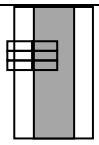
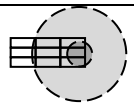
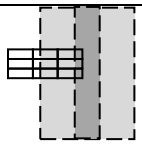
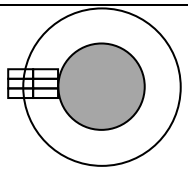
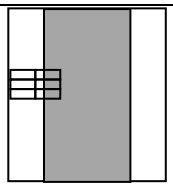
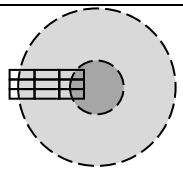
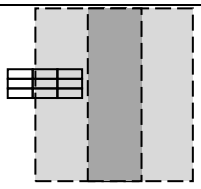
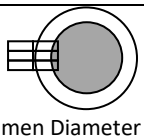
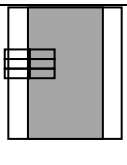
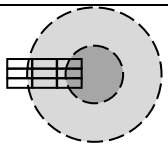
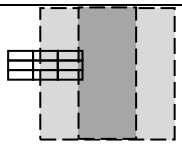
LAD = Left Anterior Descending
LCA = Left Coronary Artery
RCA = Right Coronary Artery

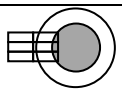
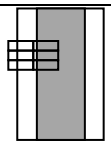
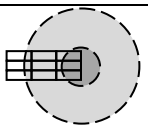
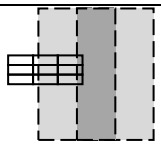
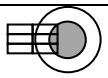
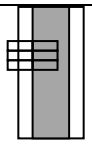
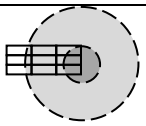
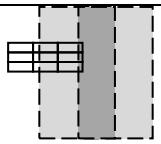
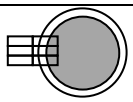
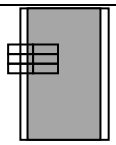
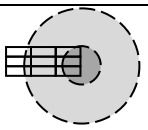
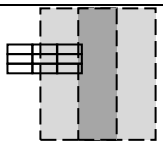
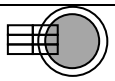
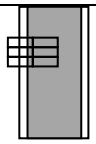
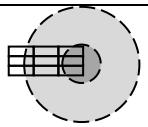
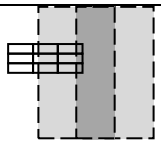
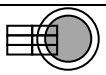
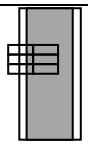
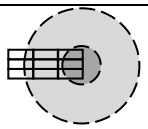
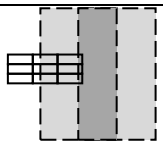
Black = lumen
Gray = plaque
White = wall

*****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 Wall Thickness = 1.1 mm |  |  Lumen Diameter = 2.3 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 [18]
[2] Lumen diameter measurements taken from [19]
[3] Lumen diameter measurements taken from [20]
[4] Wall thickness measurements taken from [21]
[5] Lumen diameter measurements taken from [22]
[6] Lumen diameter measurements taken from [23]
[7] Wall thickness measurements taken from [24-26]
[8] Estimated
[9] Measurements taken from review of typical images

# Appendix D: 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 [27], suggesting less specificity. Ideal image processing would take this factor and partial volume effects into account. The speed and high-resolution of standard CTA scan protocols brings promise of more widespread adoption.

Examination of arterial beds using radiological imaging is common among three image modalities: ultrasound, CT, and MRI. A particularly thorough review paper [28] investigated the use of noninvasive imaging techniques in identifying plaque components and morphologic characteristics associated with atherosclerotic plaque vulnerability in carotid and coronary arteries. The review found 62 studies: 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 [29] | CT | Inter-observer | 7 Human carotid | Plaque Area (mm2) | -5% constant over 74-111 mm2 range; poor below | 8% constant over 74-111 mm2 range; poor below |
| de Weert 2006 [29] | CT | Inter-observer | 13 Human carotid | Lumen Area (mm2) | 0% constant over 22-63 mm2 range; poor below | 1% constant over 22-63 mm2 range; poor below |
| Kwee 2009 [30] | CT Auto | 1.5T MR | 14 Human carotid | Lumen Area | 9% constant over 19-72 mm2 range; poor below | 37% % constant over 19-72 mm2 range; poor below |
| Obaid 2013 [31] | CT | Intra-observer | 22 Human coronaries | Lumen Area (mm2) | -1% constant over 352-468 mm2 range; poor below | 4% constant over 352-468 mm2 range; poor below |
| Papadopoulou 2013 [32] | CT | Intra-observer | 162 Human coronaries | Lumen Area (mm2) | 2% constant over 12.8-23.2 mm2 range; poor below | 10% constant over 12.8-23.2 mm2 range; poor below |
| Papadopoulou 2013 [32] | CT | Intra-observer | 535 Human coronaries | Vessel Area (mm2) | -1% | 7% |
| Papadopoulou 2012 [33] | CT | Intra-observer | 435 Human coronaries | Plaque Area (mm2) | 1% constant over 6.1-16.4 mm2 range; poor above | 14% constant over 6.1-16.4 mm2 range; poor above |
| Rinehart 2011 [34] | CT | Inter-observer | 85 Human coronaries | Minimum Lumen Diameter (mm) | -2% constant over 1.7-4.4 mm range; poor below | 8% constant over 1.7-4.44 mm range; poor below |
| Rinehart 2011 [34] | CT | Inter-observer | 179 Human coronaries | Minimum Lumen Area (mm2) | 0% constant over 1.6-21.2 mm2 range; poor below | 14% constant over 1.6-21.2 mm2 range; poor below |

## TISSUE COMPOSITION

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

- (quoted directly from introduction in [35]) In view of the limitations of [digital subtraction angiography], there is an increasing interest in CTA as a modality for assessing the carotid artery bifurcation. Computed tomography angiography is an imaging modality that can be used to accurately visualize the severity of luminal stenosis in 3D. With CTA it is extremely easy to detect calcifications in the carotid artery. CTA has also become an established method for successful artery calcium scoring in coronary arteries. With the introduction of Multi-detector CT (MDCT) in 1998 fast imaging at high temporal and spatial resolution became possible. 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 [29]) The present study shows that MDCT is capable of characterizing and quantifying plaque burden, calcifications, and fibrous tissue in atherosclerotic carotid plaque in good correlation with histology, and that lipid core can be adequately quantified in mildly calcified plaques. Furthermore the MDCT-based assessment of atherosclerotic plaque component quantities was possible with moderate observer variability.
- (quoted directly from conclusions in [36]) Our study results indicate that [dual-source computed tomography] angiography of the carotid arteries is feasible and the evaluation of carotid tissue characteristics allows non-invasive assessment of different plaque components. Although some limitations remain, [dual-source computed tomography] offers a high potential to non-invasively assess the patients at a higher risk for stroke.

An often cited study supporting the use of CT to characterize plaques, while also documenting the factors which can complicate overly simplistic methods [37], states:

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

More recently [39]:

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

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