Concept, status summary, and outlook

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Abridged Version

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Concept

Since the beginning of radiology as a clinical specialty over a hundred years ago, clinical images have predominantly been interpreted qualitatively by a human observer (i.e., radiologist) based on his or her subjective interpretation of the normal or abnormal structures in the image. The inevitable variability associated with the subjective or qualitative interpretation of clinical images is a well-known and well-documented problem in radiologic practice. Many reports published since the 1940s have documented that observer (or "reader") variability is a major problem affecting the reproducibility of results from all imaging modalities and across all diseases studied.

In the past couple of decades, the increased understanding of the molecular bases of health and disease has led to the need for tests in healthcare that can provide information in objective, reproducible form for clinical research and practice. Much of the discrete clinical information used in contemporary medicine is referred to as a biomarker, i.e., a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or responses to therapeutic interventions.

During the same period referred to above, during which molecular medicine made great progress, remarkable advances in medical imaging technology also occurred, making it possible to obtain high resolution anatomic, functional, metabolic, and physiologic information from clinical images, all of which reflect in some way the molecular substrate of the healthy or diseased tissue, organ, or person being imaged. In other words, the output of clinical imaging scans can be characterized as imaging biomarkers. With appropriate calibration, most clinical imaging technologies can provide quantitative information about some properties of the patient's tissue with which the energy has interacted.

Laboratory tests to measure molecular biomarkers in biologic fluids or tissues are called "assays." A system of principles, concepts, methods, and conventions has evolved over the past several decades to standardize the output of assays from one laboratory to another and is widely accepted. It has been a fundamental tenet in QIBA to adapt those assay concepts to quantitative imaging biomarkers. Another important premise in QIBA, and a foundational axiom of measurement science (metrology), is that all measurements have some uncertainty (i.e., lack of precision). Just as it is routine for laboratory test results to be accompanied by an indication of the uncertainty around a particular blood or tissue value, QIBA asserts that quantitative imaging results must be accompanied by an indication of the uncertainty (i.e., precision) of the measurement.

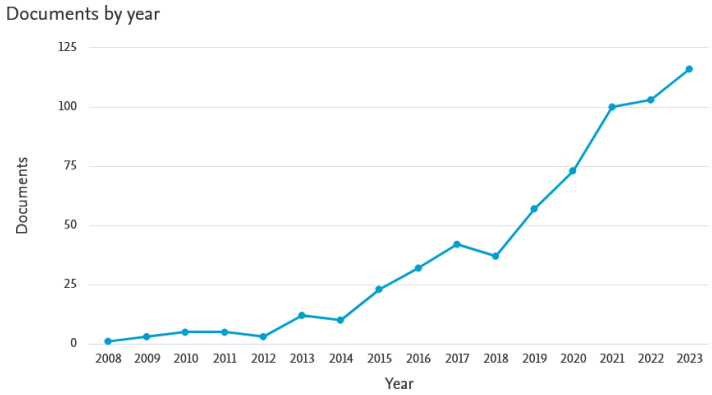
In response to the need for reliable and reproducible quantification of biomedical imaging data, the RSNA in 2007 organized the Quantitative Imaging Biomarkers Alliance (QIBA) to unite researchers, healthcare professionals, and industry stakeholders in the advancement of quantitative imaging and the use of biomarkers in clinical trials and practice. The term "quantitative imaging" was formally defined as "the extraction of quantifiable features from medical images for the assessment of normal or the severity, degree of change, or status of a disease, injury, or chronic condition relative to normal." Quantitative imaging includes the development, standardization, and

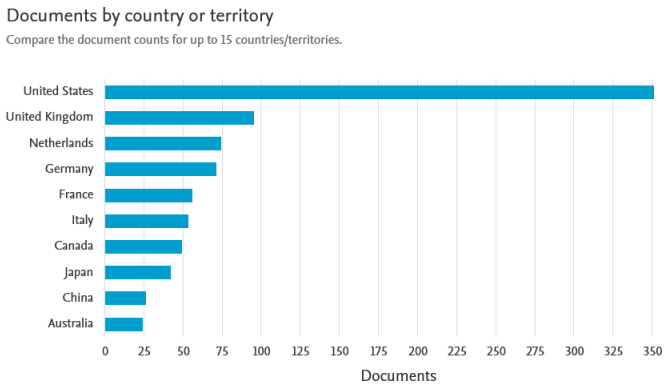
optimization of anatomical, functional, and molecular imaging acquisition protocols, data analyses, display methods, and reporting structures. These features permit the validation of accurately and precisely obtained image-derived metrics with anatomically and physiologically relevant parameters, including treatment response and outcome, and the use of such metrics in research and patient care.

QIBA's mission is to improve the value and practicality of quantitative imaging biomarkers by reducing variability across sites, devices, patients, and time. The QIBA initiative involves: (1) stakeholder collaboration to identify needs, barriers, and solutions to develop and test consistent, reliable, valid, and achievable quantitative imaging results across imaging platforms, clinical sites, and time; and (2) accelerating the development and adoption of hardware and software standards needed to achieve accurate and reproducible quantitative results from imaging methods. More than 150 entities (companies, academic institutions, professional organizations, and other entities in North America, Europe, and Asia) have representatives participating in or monitoring QIBA activities. QIBA participants span a wide range of expertise including (but not limited to) clinical practice, clinical research, physics, statistics, engineering, marketing, senior management, regulatory, pharmaceutical, and computer science.

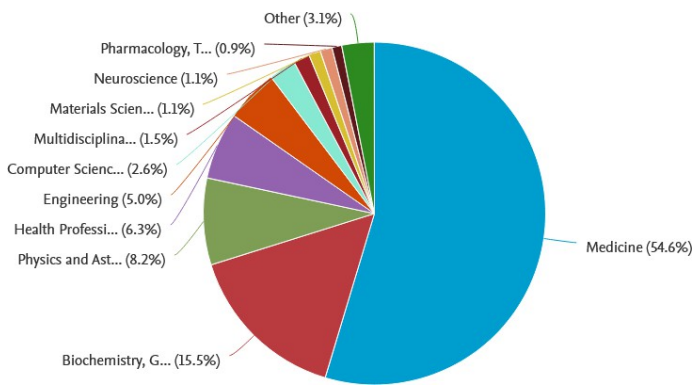
Status

The RSNA organized and sponsored QIBA program has made a great impact on quantitative imaging across many modalities and clinical applications. Hundreds of volunteers and organizations mobilized to give time and resources to advance quantitative imaging. The QIBA process has contributed to the movement of radiology from a qualitative and subjective activity to an increasingly quantitative and objective status.
A search of the Elsevier Scopus database using "QIBA" as an organizational name or acronym as well as the NIBIB contract numbers as a funding source returned a total of 622 documents. Publications appeared in sources from around the world, came from a broad range of disciplines, and were in a wide variety of publication types. To date, at least 10 of these publications were highly cited by Web of Science and/or Overton criteria. QIBA documents were cited by at least 3 clinical guidelines, 2 FDA documents, one think tank document, and one document from a German healthcare agency.

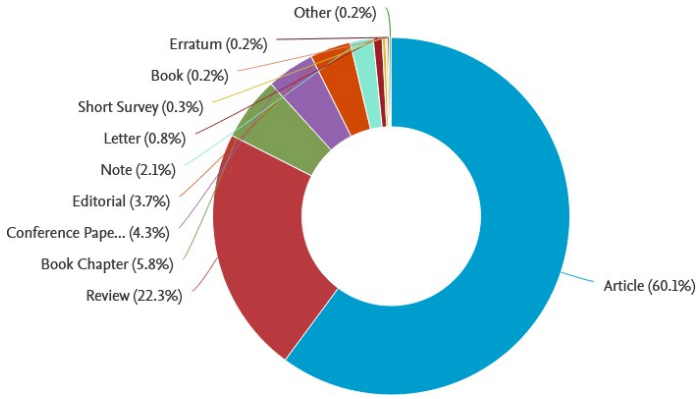




Documents by subject area



Documents by type



Thus, QIBA has had a large impact as measured by traditional academic metrics. Furthermore, high quality quantitative images, informed by QIBA Profiles, are most likely to be the best training sets for AI algorithms which operate at the "man/machine" interface. QIBA qualification has been achieved by industry partners.

From a practical standpoint, quantitative data are increasingly being included in clinical reports and are expected metrics. Examples include the SUV measurements in PET which are among many routinely reported in clinical practice, with most practices following the general guidance of the QIBA profile. Similarly, with the recent approval of amyloid reducing antibody therapies for Alzheimer's Disease, the work in the QIBA amyloid profile has immediate clinical significance. Comparable clinician uptake has been seen in the US shear wave and MRI elastography spaces, among others such as the measurement of Solitary Pulmonary Nodule (SPN).

Other major accomplishments of QIBA include:

- influencing the FDA guidance document for industry (https://www.fda.gov/media/123271/download)
- piloting conformance testing with Invicro, Accumetra, CaliberMRI, EARL, and RadSite
- impact of the QIBA Profile on the advancement of MRE (see below).

QIBA's activities have drawn worldwide attention. To augment and expand on QIBA activities, the Japan Radiological Society formed the Japan Quantitative Imaging Biomarkers Alliance (J-QIBA) in 2015. Similarly, the European Society of Radiology (ESR) combined the ESR Subcommittee on Imaging Biomarkers, the ESR Working Group on Personalised Medicine, and the ESR-European Organisation for Research and Treatment of Cancer (EORTC) Working Group to form the European Imaging Biomarkers Alliance (EIBALL) to similarly advance imaging biomarker standardization. The National Imaging Facility (NIF), Australia's advanced imaging network, similarly seeks to form a QIBA affiliate to parallel and expand on these efforts.

Further, several modality-based professional organizations are actively supporting QIBA activities. The American Institute of Ultrasound in Medicine (AIUM) supports the administration of the Volume Flow and the Pulse-Echo Quantitative Ultrasound biomarker committees. EIBALL administratively supports the arterial spin labeling (ASL) biomarker committee, the International Society of Magnetic Resonance in Medicine (ISMRM) similarly supports the Proton Density Fat Fraction biomarker committee, and the Society of Nuclear Medicine and Molecular Imaging

(SNMMI) has agreed to support a prostate-specific membrane antigen (PSMA) biomarker committee as soon as it is formed. We anticipate identifying similar support for the CT-modality biomarker committees. This buy-in by modality-based professional organizations provides further evidence of the acceptance and impact of QIBA initiatives.

The status of each QIBA Biomarker Committee is described below.

Biomarker Committees

Clinically Feasible Profiles (Stage 3)

Atherosclerosis Biomarkers by Computed Tomography Angiography (CTA)

Biomarker:

Plaque morphology (Maximum wall thickness, lumen area, lumen volume, wall area, plaque volume, plaque burden, Lipid-rich necrotic core, LRNC volume, intra-plaque hemorrhage, IPH area, IPH volume, calcified area, calcified volume

Executive Summary

The clinical application of Computed Tomography Angiography (CTA) is widely available as a technique to optimize the therapeutic approach to treating 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. To establish these biomarkers in clinical practice, techniques are required to standardize quantitative imaging across different manufacturers with cross-calibration. Moreover, the post-processing of atherosclerotic plaque segmentation needs to be optimized and standardized.

The goal of a *Quantitative Imaging Biomarkers Alliance (QIBA)* Profile is to provide an implementation guide to generate a biomarker with an effective level of performance, mostly by reducing variability and bias in the measurement. The performance claims represent expert consensus and will be empirically demonstrated at a subsequent stage. Users of this Profile are encouraged to refer to the following site to understand the document's context: http://qibawiki.rsna.org/index.php/QIBA_Profile_Stages. All statistical performance assessments are stated in carefully considered metrics and according to strict definitions as given in [3-8], which also includes detailed, peer-reviewed rationale on the importance of adhering to such standards.

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

This Profile is at the Clinically Feasible stage (qibawiki.rsna.org/index.php/QIBA_Profile_Stages) which indicate that multiple sites have **performed the Profile and found it to be practical** and expect it to achieve the claimed performance.

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

Claim:

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:

Table 1: Quantitative Claims for individual Plaque Morphology Measurands

Measurement of	Units	Range	Bias	Slope	Inter-reader SD
Lumen Area	mm^2	0.0-30.0	0±1.0	1±0.1	2.5
Wall Area	mm^2	10.0-100.0	0±1.0	1±0.1	4.0
Maximum Wall Thickness (WT)	mm	1.0-5.0	0±1.0	1±0.2	1.0
Plaque Burden (PAV)	unitless ratio	0.4-1.0	0±0.1	1±0.1	0.5
Calcified (CALC) Area	mm^2	0.0-15.0	0±0.5	1±0.1	1.5
Lipid-Rich Necrotic Core (LRNC) Area	mm^2	0.0-15.0	0±1.0	1±0.2	1.5
Intra-plaque Hemorrhage (IPH) Area[1]	mm^2	0.0-15.0	0±2.0	1±0.2	2.0

Table 2: Quantitative Claims for Multi-parametric Plaque Stability Phenotype

Classification of	Units	Agreement with Expert Pathologists
Minimal Disease	% likelihood	AUROC 0.95 [0.9, 1.0] (vs. Stable or Unstable)
Stable Plaque	% likelihood	AUROC 0.9 [0.85, 0.95] (vs. Minimal or Unstable)
Unstable Plaque	% likelihood	AUROC 0.95 [0.9, 1.0] (vs. Minimal or Stable)

The claim tables are built based on de-rating from achievable performance of at least one reference device [22, 23].

BC chairs:

Andrew Buckler, MS, PhD
Luca Saba, MD
Uwe Joseph Schoepf, MD, FAHA, FSCBT-MR, FNASCI, FSCCT

BC Voting members:

See appendix

[1] Limited evidence of prevalence in coronary but included to encourage further studies.

CT Small Lung Nodule Assessment and Monitoring in Low Dose Screening

Biomarker:

Nodule volume, nodule volume change

Executive summary:

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

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

This QIBA Profile (Small Lung Nodule Volume Assessment and Monitoring in Low Dose CT Screening) addresses the accuracy and precision of quantitative CT volumetry as applied to solid lung nodules of 6-10 mm diameter. It places requirements on Acquisition Devices, Technologists, Radiologists and Image Analysis Tools involved in activities including Periodic Equipment Quality Assurance, Subject Selection, Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image Quality Assurance, and Image Analysis.

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

Two sets of claims are provided within this Profile. The first claim establishes 95% confidence intervals for volumetric measurement of solid lung nodules for each different millimeter in diameter from 6-10 mm as this is the size range for baseline measurements.

The second claim provides guidance on the amount of volumetric change percentage needed for an observer to have 95% confidence that the nodule has exhibited true change. In addition, the second claim also provides guidance on the 95% confidence interval for a volumetric size change measurement, again based on the size of the nodule at two time points.

This document is intended to help clinicians reliably measure pulmonary nodule volume as an imaging biomarker, imaging staff generating this biomarker, vendor staff developing related products, purchasers of such products and investigators designing trials with imaging endpoints.

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

This Profile document includes a conformance test that can be performed with a precision engineered phantom designed to test the fundamental imaging performance characteristics of the CT scanner to be used at a clinical site. The steps to perform the conformance test are described in the Profile and can determine if the site scanner is functioning at a level that would be capable of measuring with accuracy sufficient to meet the requirements of the Profile claim.

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

Claims:

Claim 1: Nodule Volume

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

Claim 2: Nodule Volume Change

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

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

These Claims hold when:

- the nodule is completely solid
- the nodule longest dimension in the transverse (axial) plane is between 6 mm (volume 113 mm^3) and 10 mm (volume 905 mm^3) at the first time point
- the nodule's shortest diameter in any dimension is at least 60% of the nodule's longest diameter in any dimension (i.e., the nodule shape does not deviate excessively from spherical)
- the nodule is measurable at both time points (i.e., margins are distinct from surrounding structures of similar attenuation and geometrically simple enough to be segmented using automated software without manual editing)
- Interpolation is used to arrive at CV values between provided table values.

Table 1. Coefficients of Variation (CV)

Nodule Diameter (mm)	Nodule Volume (mm^3)	Coefficient of Variation (CV)	True Volume 95% CI Limits (mm^3)	Minimum Detectable Difference (from Claim 2a)
6 mm	113	0.29	± 64	80.3%
7 mm	154	0.23	± 69	63.7%
8 mm	268	0.19	± 100	52.6%
9 mm	382	0.16	± 120	44.3%
10 mm	524	0.14	± 144	38.8%

11 mm	697	0.12	± 164	33.2%
12 mm	905	0.11	± 195	30.5%

BC chairs:

Artit Jirapatnakul, PhD
James L. Mulshine, MD
Kyle J. Myers, PhD

BC Voting members:

see appendix

CT Tumor Volume Change for Advanced Disease

Biomarker:

Change in lung tumor volume, Volume repeatability

Executive summary:

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

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

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

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

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

Clinical Context: CT Tumor Volume Change is used as a biomarker of disease risk, characterization, progression, and response to treatment. This involves measuring tumor volumes and assessing longitudinal changes within subjects, based on image processing of CT scans acquired at different timepoints. See Appendix B for a discussion of usage of this biomarker in practice.

Claims:

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

Change Detection Claim:

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

Repeatability Claim:

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

relevant to Clinicians. The Repeatability Claim describes individual measurements and the wCV can be used to compute 95% Confidence Intervals (CI). For example, a tumor measured as 34cm3 (~40mm diam) then 268 cm3 (~80mm) yields a 95% CI for the true volume change of [+189 cm3 , +279 cm3]. See Appendix B for more details.

BC chairs:

Ritu Gill, MD, MPH
Rudresh Jarecha, MBBS, DNB, DMRE
Ehsan Samei, PhD

BC Voting members:

see appendix

MR Diffusion-Weighted Imaging (ADC)

Biomarker:

Apparent Diffusion Coefficient

Executive summary:

The goal of a QIBA Profile is to help achieve a useful level of performance for a given biomarker. The Claim (Section 2) describes the biomarker performance and is derived from the body of scientific literature meeting specific requirements, in particular test-retest studies. 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 to ensure acceptable performance.

Diffusion-Weighted Imaging (DWI) and the Apparent Diffusion Coefficient (ADC) are being used clinically as qualitative (DWI) and quantitative (ADC) indicators of disease presence, progression or response to treatment [1-29]. Use of ADC as a robust quantitative biomarker with finite confidence intervals places additional requirements on Sites, Acquisition Devices and Protocols, Field Engineers, Scanner Operators (MR Technologists, Radiologists, Physicists and other Scientists), Image Analysts, Reconstruction Software and Image Analysis Tools [30-37]. Additionally, due to the intrinsic dependence of measured ADC values on biophysical tissue properties, both the Profile Claims and the associated scan protocols (Section 3.6.2) are organ-specific. All of these are considered Actors involved in Activities of Acquisition Device Pre-delivery and Installation, Subject Handling, Image Data Acquisition, Reconstruction, Registration, ADC map generation, Quality Assurance (QA), Distribution, Analysis, and Interpretation. The requirements addressed in this Profile are focused on achieving ADC values with minimal systematic bias and measurement variability [34, 36, 37].

DISCLAIMER: Technical performance of the MRI system can be assessed using a phantom having known diffusion properties, such as the QIBA DWI phantom. The clinical performance target is to achieve a 95% confidence interval for measurement of ADC with a variable precision depending on the organ being imaged and assuming adequate technical performance requirements are met. While in vivo DWI/ADC measurements have been performed throughout the human body, this Profile focused on four organ systems, namely brain, liver, prostate, and breast as having high clinical utilization of ADC with a sufficient level of statistical evidence to support the Profile Claims derived from the current peer reviewed literature. In due time, new DWI technologies with proven greater performance levels, as well as more organ systems will be incorporated in future Profiles.

This document is intended to help a variety of users: clinicians using this biomarker to aid patient management; imaging staff generating this biomarker; MRI system architects developing related products; purchasers of such products; and investigators designing clinical trials utilizing quantitative diffusion-based imaging endpoints.

Note that this document only states requirements specific to DWI to achieve the claim, not requirements that pertain to clinical standard of care. Conforming to this Profile is secondary to proper patient care.

Claims:

Conformance to this Profile by all relevant staff and equipment supports the following claim(s):

Claim 1a: A measured change in the ADC of a brain lesion of 11% or larger indicates that a true change has occurred with 95% confidence.

Claim 1b: A 95% CI for the true change in ADC of a brain lesion is given below, where Y_1 and Y_2 are the ADC measurements at the two time points: $(YY_{22} - YY_{11}) \pm 11.9999 \times \sqrt{(YY_{11} \times 00.000000)^{22} + (YY_{22} \times 00.000000)^{22}}$.

Claim 2a: A measured change in the ADC of a liver lesion of 26% or larger indicates that a true change has occurred with 95% confidence.

Claim 2b: A 95% CI for the true change in ADC of a liver lesion is given below, where Y_1 and Y_2 are the ADC measurements at the two time points: $(YY_{22} - YY_{11}) \pm 11.9999 \times \sqrt{(YY_{11} \times 00.009900)^{22} + (YY_{22} \times 00.009900)^{22}}$.

Claim 3a: A measured change in the ADC of a prostate lesion of 47% or larger indicates that a true change has occurred with 95% confidence.

Claim 3b: A 95% CI for the true change in ADC of a prostate lesion is given below, where Y_1 and Y_2 are the ADC measurements at the two time points: $(YY_{22} - YY_{11}) \pm 11.9999 \times \sqrt{(YY_{11} \times 00.1111)^{22} + (YY_{22} \times 00.1111)^{22}}$.

Claim 4a: A measured change in the ADC of a breast lesion of 13% or larger indicates that a true change has occurred with 95% confidence.

Claim 4b: A 95% CI for the true change in ADC of a breast lesion is given below, where Y_1 and Y_2 are the ADC measurements at the two time points: $(YY_{22} - YY_{11}) \pm 11.9999 \times \sqrt{(YY_{11} \times 00.000000)^{22} + (YY_{22} \times 00.000000)^{22}}$.

BC chairs:

Michael A. Boss, PhD
Dariya Malyarenko, PhD
Daniel J. Margolis, MD

BC Voting members:

see appendix

MR Elastography of the Liver

Biomarker:

Change in hepatic liver stiffness

Executive summary:

The goal of a QIBA Profile is to help achieve a useful level of performance for a given biomarker. The Claim (Section 2) describes the biomarker performance. The 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.

This QIBA Profile (Magnetic Resonance Elastography of the Liver) addresses the application of Magnetic Resonance Elastography (MRE) for the quantification of liver stiffness, which is often used as a biomarker of liver fibrosis. It places requirements on Acquisition Devices, Technologists, Radiologists, Reconstruction Software and Image Analysis Tools involved in Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA and Image Analysis.

The requirements are focused on achieving sufficient accuracy and avoiding unnecessary variability of the measurement of hepatic stiffness. The clinical performance target is to achieve a 95% confidence interval for a true change in stiffness has occurred when there is a measured change in hepatic stiffness of 19% or larger.

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

Note that this document only states requirements to achieve the claim, not “requirements on standard of care.” Conformance to this Profile is secondary to properly caring for the patient. QIBA Profiles addressing other imaging biomarkers using CT, MRI, PET and Ultrasound can be found at qibawiki.rsna.org.

Claims:

Conformance to this Profile by all relevant staff and equipment supports the following claim(s):

A measured change in hepatic stiffness of 19% or larger indicates that a true change in stiffness has occurred with 95% confidence.

BC chairs:

Richard L. Ehman, MD
Patricia Cole, PhD, MD

BC Voting members:

see appendix

PET Amyloid

Biomarker:

SUVR

Executive summary:

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

Profile development is an evolutionary, phased process; this Profile is in the Technical Conformance stage in preparation for being Technically Confirmed. 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.

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.

The **Conformance** section provides **Assessment Procedures** (Section 4) for evaluating specific requirements are defined as needed.

References are provided in section 5.

Appendices (Section 6) are provided that include additional information for performing Activities as well as Checklists that can be completed to evaluate Profile conformance.

In general, QIBA Profiles provide DESCRIPTIVE text sections as background and recommended considerations, and **SPECIFICATIONS** (tables) that include prescriptive (required to meet claim) items in clear boxes and potential or future items in gray boxes.

This QIBA Profile "**18F-labeled PET tracers targeting Amyloid as an Imaging Biomarker"** documents specifications and requirements to provide comparability and consistency for the use of PET imaging using 18F labeled tracers that bind to fibrillar amyloid in the brain. Quantitative measurement of amyloid, a hallmark pathology of Alzheimer's Disease, has become increasingly used in clinical trials for patient inclusion, evaluation of disease progression, and assessment of treatment effects. The current version of the Profile focuses on a longitudinal Claim, where the primary purpose is to assess change in amyloid load due to disease or following an intervention. In this case, precision is most important as long as bias remains constant over time. Characterization of measurement bias will be important for a cross-sectional Claim wherein the amyloid tracer is used primarily to select amyloid positive subjects.

This Profile focuses on the use of Standardized Uptake Value Ratios (SUVRs) to measure amyloid burden, while also describing benefits associated with the Distribution Volume Ratio (DVR) (kinetic modeling) approach. The SUVR is determined using data acquired during a time window following a certain time period after tracer injection that is intended to allow the tracer to reach "pseudo" equilibrium. This approach has practical advantages, particularly for multi-site studies, due to the reduced time required for the patient to be in the scanner (and for older scanners, the lesser amount of data acquired for a single scan).

The document primarily addresses PET/CT imaging; however, a dedicated PET that has transmission capabilities can also be used. PET/MR scanners are not strictly excluded in this version as long as the repeatability of the SUVRs from these scanners is conformant with the assumptions underlying the claims.

The Profile is intended to help clinicians basing decisions on this biomarker, imaging staff generating this biomarker, vendor staff developing related products, purchasers of such products and investigators designing trials with imaging endpoints. The guidance in this Profile can be applied for clinical trial use as well as individual patient management.

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

This Profile, developed through the efforts of the amyloid Profile writing group in the QIBA Nuclear Medicine Technical Subcommittee, shares some content with the QIBA FDG-PET Profile, and includes additional material focused on the devices and processes used to acquire and analyze amyloid tracer PET data. QIBA Profiles addressing other imaging biomarkers using CT, MRI, PET and Ultrasound can be found at qibawiki.rsna.org. This Profile is organized as follows:

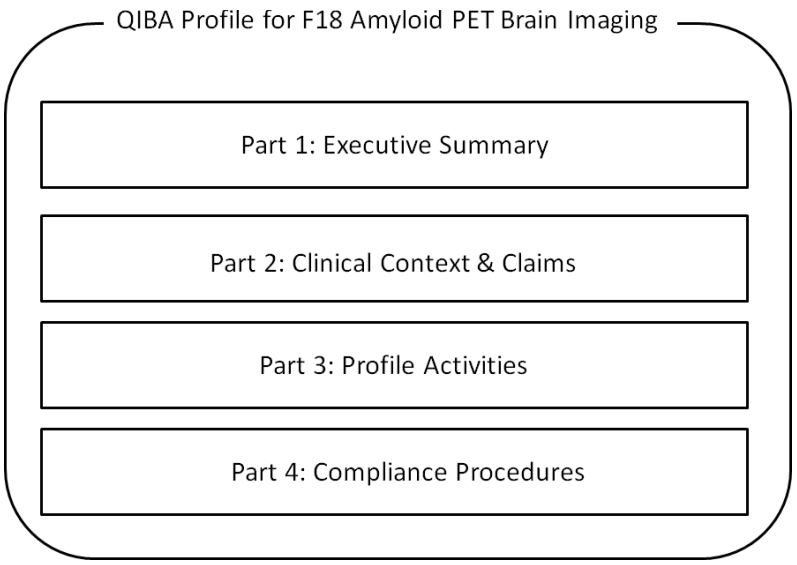


Figure 1: Illustration of the Profile components

The Profile Part 3 is derived from multiple sources, including material contained in the work performed by the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Claims:

If Profile criteria are met, then: Claim 1: Brain amyloid burden as reflected by the SUVR is measurable from 18F amyloid tracer PET with a within-subject coefficient of variation (wCV) of <=1.94%.

BC chairs:

Dawn C. Matthews, MS, MBA
Satoshi Minoshima, MD, PhD
Anne M. Smith, PhD

BC Voting members:

see appendix

PET/CT FDG SUV for Response to Cancer Therapy

Biomarker:

SUVmax CoV, Change of SUVmax

Executive summary:

This QIBA Profile documents specifications and requirements to provide comparability and consistency for quantitative FDG-PET across scanners in oncology. It can be applied to both clinical trial use as well as individual patient management. This document organizes acquisition, reconstruction and post-processing, analysis and interpretation as steps in a pipeline that transforms data to information to knowledge.

The document, developed through the efforts of the QIBA FDG-PET Biomarker Committee, has shared content with the FDG-PET UPICT protocol, as well as additional material focused on the devices used to acquire and analyze the FDG-PET data.

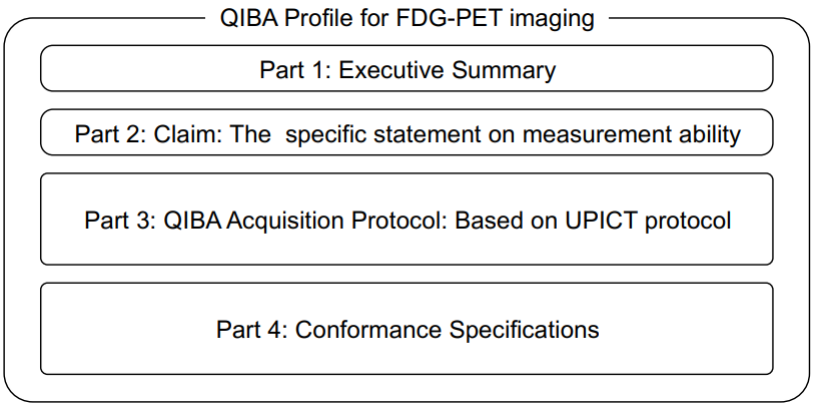


Figure 1: Illustration of the Profile components

The Profile Part 3 is largely derived from the FDG-PET UPICT protocol for FDG-PET imaging in clinical trials. In the UPICT protocol, there is a carefully developed hierarchy with tiered levels of protocol compliance. This reflects the recognition that there are valid reasons to perform trials using different levels of rigor, even for the same disease/intervention combination.

For example, a high level of image measurement precision may be needed in small, early-phase trials whereas a less rigorous level of precision may be acceptable in large, late-phase trials of the same drug in the same disease setting. The three levels of compliance for UPICT protocols are defined as:

ACCEPTABLE: failing to meet this specification will result in data that is likely unacceptable for the intended use of this protocol.

TARGET: meeting this specification is considered to be achievable with reasonable effort and equipment and is expected to provide better results than meeting the ACCEPTABLE specification.

IDEAL: meeting this specification may require unusual effort or equipment but is expected to provide better results than meeting the TARGET.

ACCEPTABLE values are always provided for each parameter in a UPICT Protocol. When there is no reason to expect better results (e.g., in terms of higher image quality, greater consistency, lower radiation dose, etc.), TARGET and IDEAL values are not provided.

This Profile draws on the ACCEPTABLE components of the UPICT Protocol. Later revisions of this Profile are expected to draw on the Target and then Ideal categories of the UPICT Protocol. The Target and Ideal categories are intended to account for advances in the field and the evolving state-of-the-art of FDG-PET/CT imaging. These concepts are illustrated in Figure 2 below.

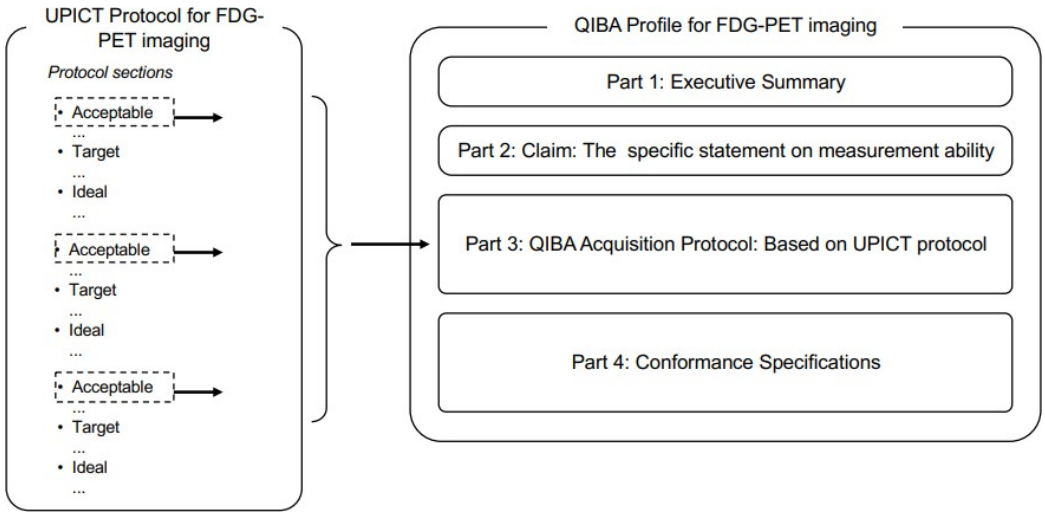


Figure 2. Relationship between the UPICT Protocol and the Profile.

Claims:

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

Claim 1: Tumor glycolytic activity as reflected by the maximum standardized uptake value (SUVmax) is measurable from FDG-PET/CT with a within-subject coefficient of variation of 10-12%.

Claim 2: A measured increase in SUVmax of 39% or more, or a decrease of -28% or more, indicates that a true change has occurred with 95% confidence.

BC chairs:

Nathan C. Hall, MD, PhD
Jeffrey T. Yap, PhD

BC Voting members:

see appendix

US Shear Wave Speed for Liver Fibrosis

Biomarker:

Shear wave speed, change of SWS measurement

Executive summary:

The goal of a QIBA Profile is to help achieve a useful level of performance for a given biomarker. Profile development is an evolutionary, phased process; this Profile is in the consensus stage. 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.

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. **Conformance** (Section 5) regroups Section 3 requirements by Actor to conveniently check Conformance.

This QIBA Profile (Ultrasound Measurement of Shear Wave Speed for Estimation of Liver Fibrosis) addresses estimation of liver fibrosis, which is often used to determine when and how to treat patients with diffuse liver disease, and also monitor progression or response to treatment.

It places requirements on ultrasound scanners (acquisition devices), Scanner Manufacturer/Vendor, Technologists/Sonographers, QA (Quality Assurance) Manager, Radiologists, and Image Analysis Tools involved in pre-delivery steps, scanner installation, periodic QA procedures, subject selection and handling, SWS image acquisition, image QA, and image analysis.

The requirements are focused on achieving sufficient accuracy and avoiding unnecessary variability of the estimation of liver fibrosis. Estimates of liver fibrosis are based on a measurement of shear wave speed (SWS) in the tissue using ultrasound, which in turn is based on the stiffness of the liver tissue.

The clinical performance target is to achieve SWS measurements with a bias of the mean value of ≤ 5% and an overall coefficient of variation (SD/mean) of ≤ 5%. The standard against which to measure bias has not yet been fully defined, so currently there is no bias claim.

At the present time, bias is determined by comparison to the measured SWS and stiffness using a Verasonics ultrasound system in a calibrated QIBA SWS phantom. Currently bias and precision depend on the magnitude of measured SWS (as determined in phantom studies) so bias and variance claims are given for three ranges of measured SWS values. Also, bias and precision depend on the conditions under which the measurements are made.

Bias and precision claims are therefore also given for various measurement conditions. This document is intended to help clinicians basing decisions on this biomarker, imaging staff generating this biomarker, vendor staff developing

related products, purchasers of such products, and investigators designing trials with imaging endpoints. Note that this document only states requirements to achieve the claim, not "requirements on standard of care."

Conformance to this Profile is secondary to properly caring for the patient. QIBA Profiles addressing other imaging biomarkers using CT, MRI, PET and Ultrasound can be found at https://qibawiki.rsna.org/index.php/Main_Page

Claims:

The claims are presented below.

In the claims presented below, the term "imaging system" refers to both the ultrasound scanner (machine) and the operator using the machine to perform SWS measurements. Changing either the operator or ultrasound scanner therefore results in a different imaging system.

Conformance to this Profile by all relevant staff and equipment supports the following claim(s):

Claim 1 (technical performance claim): A shear wave speed measurement has a within-subject coefficient of variation (wCV) depending on the measured SWS and depth of acquisition according to Table 2-1.

Table 2-1 Within-Subject Coefficient of Variation (wCV)

Measured SWS (m/s)	Depth=4.5 cm*	Depth=7.0 cm
0.9 < SWS ≤ 1.2	5%	8%
1.2 < SWS ≤ 2.2	4%	5%
2.2 < SWS ≤ 5.0	10%	12%

***For measurements taken at depths other than the two listed, the SWS Committee has determined that linear interpolation of the Coefficients of Variation (wCV) is appropriate.**

Claim 2 (cross-sectional claim): A 95% confidence interval for the true SWS is $Y \pm (1.96 \times Y \times wCV/100)$, where Y is the measured SWS and wCV is the within-subject coefficient of variation from Table 2-1.

Note: Claims 3a and **3b** hold when the same technologist and same ultrasound scanner are used at the two time points. Claim 3a (longitudinal claim): A true change in SWS measurements (Y1 and Y2) over two time points has occurred with 95% confidence if the measured % change, defined as $\frac{|YY_{22}-YY_{11}|}{(YY_{11}+YY_{22})/22} \times 110000$, is equal to or greater than the repeatability coefficient (RC) given in Table 2-2.

Table 2-2 Repeatability Coefficient (RC)

Measured SWS (m/s)	Depth=4.5 cm*	Depth=7.0 cm
0.9 < SWS ≤ 1.2	14%	22%
1.2 < SWS ≤ 2.2	11%	14%
2.2 < SWS ≤ 5.0	28%	33%

***For measurements taken at depths other than the two listed, the SWS Committee has determined that linear interpolation of the Repeatability Coefficient (RC) is appropriate.**

Claim 3b (longitudinal claim): A 95% confidence interval for the true change over two time points (Y1 and Y2) is:

$(YY_2 - YY_1) \pm 1.96 \times \sqrt{(YY_1 \times wwwwww_1/100)^2 + (YY_2 \times wwwwww_2/100)^2}$, where wCV is based on Table 2-1.

Note: Claims 4a and **4b** hold when a different technologist and/or a different ultrasound scanner is used at the same site at the two time points.

Claim 4a (longitudinal claim): A true change in SWS measurements (Y1 and Y2) over two time points has occurred with 95% confidence if the measured % change, defined as $\frac{|YY_{22}-YY_{11}|}{(YY_{11}+YY_{22})/22} \times \mathbf{110000}$, is equal to or greater than the reproducibility coefficient (RDC) given in Table 2-3.

Table 2-3 Reproducibility Coefficient (RDC) (Same Site)

Measured SWS (m/s)	Depth=4.5 cm	Depth=7.0 cm
0.9 < SWS ≤ 1.2	19%	25%
1.2 < SWS ≤ 2.2	14%	17%
2.2 < SWS ≤ 5.0	33%	39%

***For measurements taken at depths other than the two listed, the SWS Committee has determined that linear interpolation of the Reproducibility Coefficient (RDC) is appropriate.**

Claim 4b (longitudinal claim): A 95% confidence interval for the true change over two time points (Y1 and Y2) is

$(YY_{22} - YY_{11}) \pm 11.9999 \times \sqrt{(YY_{11} \times UU_{11}/110000)^{22} + (YY_{22} \times UU_{22}/110000)^{22}}$, where U is from Table 2-3b.

Table 2-3b Values of U (wCV from different technologist and/or scanner at same site)

Measured SWS (m/s)	Depth=4.5cm	Depth=7.0cm
0.9 < SWS ≤ 1.2	7%	9%
1.2 < SWS ≤ 2.2	5%	6%
2.2 < SWS ≤ 5.0	12%	14%

***For measurements taken at depths other than the two listed, the SWS Committee has determined that linear interpolation of U is appropriate.**

Claims 5a and **5b** hold when a different technologist and/or a different ultrasound scanner is used at different sites at the two time points.

Claim 5a (longitudinal claim): A true change in SWS measurements (Y1 and Y2) over two time points has occurred with 95% confidence if the measured % change, defined as $\frac{|YY_{22}-YY_{11}|}{(YY_{11}+YY_{22})/22} \times 110000$, is equal to or greater than the reproducibility coefficient (RDC) given in Table 2-4.

Table 2-4 Reproducibility Coefficient (RDC) (Different Sites)

Measured SWS (m/s)	Depth=4.5cm	Depth=7.0cm
0.9 < SWS ≤ 1.2	22%	28%
1.2 < SWS ≤ 2.2	17%	19%
2.2 < SWS ≤ 5.0	33%	39%

Claim 5b (longitudinal claim): A 95% confidence interval for the true change (in m/sec) over two time points (Y1 and Y2) is

$(YY_{22} - YY_{11}) \pm 11.9999 \times \sqrt{(YY_{11} \times HH_{11}/110000)^{22} + (YY_{22} \times HH_{22}/110000)^{22}}$, where H is from Table 2-4b.

Table 2-4b Values of H (wCV from different technologist and/or scanner at different sites)

Measured SWS (m/s)	Depth=4.5cm	Depth=7.0cm
0.9 < SWS ≤ 1.2	**8%**	**10%**
1.2 < SWS ≤ 2.2	**6%**	**7%**
2.2 < SWS ≤ 5.0	**12%**	**14%**

The above claims were developed based on phantom studies conducted by the Ultrasound Shear Wave Speed Biomarker Committee and may not accurately reflect performance in patients. The expectation is that during the Claim Confirmation and Clinical Confirmation stages, data on the actual field performance will be collected and changes made to the claims or the details accordingly. At that point, this caveat may be removed or re-stated.

BC chairs:

David Fetzer, MD
Stephen McAleavey, PhD
Stephen Rosenzweig, PhD

BC Voting members:

see appendix

Biomarker Committees

Consensus Profiles (Stage 2)

CT Lung Density

Biomarker:

Lung Volume Adjustment

Executive summary:

The goal of a QIBA Profile is to achieve a repeatable and useful level of performance for measures of lung density from quantitative CT using the RA-950 HU and Perc15 biomarkers of emphysema. Please see Appendix C for more detailed information on the calculation of and rationale for RA-950 HU and Perc15 as the biomarkers of choice.

- The **Claim** (Section 2) describes the performance in terms of bias and precision of RA-950 HU and Perc15 for detecting change in lung density.
- The **Activities** (Section 3) describe how to generate RA-950 HU and Perc15 for longitudinal studies of the change in lung density. Requirements are placed on the **Actors** that participate in those activities as necessary to achieve the Claim in Section 2.
- **Assessment Procedures** (Section 4) for evaluating specific requirements are defined as needed.

This QIBA Profile (CT: Lung Densitometry) addresses RA-950 HU and Perc15 for longitudinal studies which are often used as biomarkers of emphysema progression in chronic obstructive pulmonary disease (COPD) or as a response to cessation of smoking and possible future treatment approaches. It places requirements on Acquisition Devices, Physicists, Technologists, Clinicians, Statisticians, Reconstruction Software and Image Analysis Software involved in Product Qualification, Staff Qualification, Periodic Quality Assurance, Subject Handling, Protocol Design, Image Data Acquisition, Image Data Reconstruction, Image QA, Image Distribution and Image Analysis.

The requirements are focused on achieving negligible bias and avoiding unnecessary variability of the RA-950 HU and Perc15 measurements by compensating for variations in CT number due to inconsistency of lung inflation volume and calibration of the CT scanner, and vendor-specific bias due to CT scanner make and model. To meet the claims, scanner calibration is performed using a well characterized imaging phantom ideally containing lung equivalent density foams as described in Section 4.1.

The clinical performance targets are to achieve bias and repeatability such that a change in RA-950 HU of ≥ 3.7% of the normalized lung volume, or a change in Perc15 of ≥ 11 HU after lung volume adjustment can be accepted as indicative of a true change (with 95% confidence).

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

Note that this document only states requirements to achieve the claim, not "requirements for standard of care." Conformance to this Profile is less important than providing appropriate patient care. The compilation of this document represents the efforts of many individuals over a several years of effort, some but not all of whom are acknowledged in Appendix A. QIBA Profiles addressing other imaging biomarkers using CT, MRI, PET and Ultrasound can be found at qibawiki.rsna.org.

Claims:

Conformance to the requirements of this Profile by all relevant staff and equipment supports the following claims:

Claim 1: With lung volume adjustment (VA), a decrease in Perc15 of at least 11 HU is required for detection of an increase in the extent of emphysema, with 95% confidence.

Claim 2: Without VA, a decrease in Perc15 of at least 18 HU indicates an increase in the extent of emphysema, with 95% confidence.

Claim 3: Without VA, an increase in RA-950* of at least 3.7% indicates an increase in the extent of emphysema, with 95% confidence.

BC chairs:

Charles Hatt, PhD
Miranda Kirby, PhD
Gonzalo Vegas Sánchez-Ferrero, PhD

BC Voting members:

see appendix

MR DCE Quantification

Biomarker:

K^{trans}, $IAUGC_{BN}$

Executive summary:

The RSNA QIBA Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) Technical Committee is composed of scientists representing the imaging device manufacturers, image analysis laboratories, biopharmaceutical industry, academia, government research organizations, and professional societies, among others. All work is classified as pre-competitive. The goal of the DCE-MRI committee is to define basic standards for DCE-MRI measurements and quality control that enable consistent, reliable and fit-for-purpose quantitative transfer constant (K^{trans})[1] and blood normalized initial-area-under-the-gadolinium-concentration-curve ($IAUGC_{BN}$)[2] results across imaging platforms (at 1.5 tesla (1.5 T)), clinical sites, and time.

This effort is motivated by the emergence of DCE-MRI as a method with potential to provide predictive, prognostic and/or pharmacodynamic response biomarkers for cancer [3-11]. Remarkably, the results demonstrating this potential have been obtained despite considerable variation in the methods used for acquisition and analysis of the DCE-MRI data. This suggests there are substantial physiological differences (i.e., benign vs. malignant or non-responsive vs. responsive tumors) underlying these observations. Thus, there appears to be a promising future for use of DCE-MRI for both clinical research and in routine clinical practice. However, in order to fulfill this promise it is essential that common quantitative endpoints are used and that results are independent of imaging platforms, clinical sites, and time.

For the application of DCE-MRI in the development of anti-angiogenic and anti-vascular therapies, there is a consensus [12] on which quantitative endpoints should be employed: K^{trans} and $IAUGC_{BN}$. Hence, the initial focus of the DCE-MRI committee is on these biomarkers. Although there have been general recommendations on how to standardize DCE-MRI methodology[12, 13], there are no guidelines sufficient to ensure consistent, reliable and fit-for-purpose quantitative DCE-MRI results across imaging platforms, clinical sites, and time. Hence, in this profile, basic standards for site and scanner qualification, subject preparation, contrast agent administration, imaging procedure, image post-processing, image analysis, image interpretation, data archival and quality control are defined to provide that guidance.

Summary of Clinical Trial Usage

This technique offers a robust, reproducible measure of microvascular parameters associated with human cancers based on kinetic modeling of dynamic MRI data sets. The rigor and details surrounding these data are described throughout the text of this document in various sub-sections.

Claims:

Quantitative microvascular properties, specifically transfer constant (K^{trans}) and blood normalized initial area under the gadolinium concentration curve ($IAUGC_{BN}$), can be measured from DCE-MRI data obtained at 1.5T using low molecular weight extracellular gadolinium-based contrast agents with a 20% within-subject coefficient of variation for solid tumors at least 2 cm in diameter.*

Profile specified for use with: patients with malignancy, for the following indicated biology: primary or metastatic, and to serve the following purpose: therapeutic response.

* a 20% within-subject coefficient of variation is based on a conservative estimate from the peer-reviewed literature. In general, this suggests that a change of approximately 40% is required in a single subject to be considered significant.

BC chairs:

Hendrik Laue, PhD
James O'Connor, MD, PhD

BC Voting members:

see appendix

MR Dynamic Contrast Susceptibility

Biomarker:

Change in Area Under the Curve – Tissue Normalized

Executive summary:

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

Profile development is an evolutionary, phased process; this Profile is in the Public Comment Resolution Draft stage. 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.

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. Conformance (Section 5) regroups Section 3 requirements by Actor to conveniently check Conformance.

This QIBA Profile, Dynamic-Susceptibility-Contrast Magnetic Resonance Imaging (DSC-MRI), addresses the measurement of an imaging biomarker for relative Cerebral Blood Volume (rCBV) for the evaluation of brain tumor progression or response to therapy. We note here that this profile does not claim to be measuring quantitative rCBV due to lack of existing supporting literature; it does provide claims for a biomarker that is proportional to rCBV, which is the tissue normalized first-pass area under the contrast-agent concentration curve (AUC-TN). The AUC-TN therefore has merit as a potential biomarker for diseases or treatments that impact rCBV. This profile places requirements on Sites, Acquisition Devices, Contrast Injectors, Contrast Media, Radiologists, Physicists, Technologists, Reconstruction Software, Image Analysis Tools and Image Analysts involved in Site Conformance, Staff Qualification, Product Validation, Pre-delivery, Periodic QA, Protocol Design, Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA, Image Distribution, Image Analysis and Image Interpretation.

The requirements are focused on achieving known (ideally negligible) bias and avoiding unnecessary variability of the of the AUC-TN measurements.

The clinical performance is characterized by a 95% confidence interval for the AUC-TN true change (Y_2-Y_1) in enhancing tumor tissue $(YY_2 - YY_1) \pm 1.96 \times \sqrt{(YY_1 \times 0.31)\ 2 + (YY_2 \times 0.31)^2}$ and in normal tissue $(YY_2 - YY_1) \pm 1.96 \times \sqrt{(YY_1 \times 0.40)^2 + (YY_2 \times 0.40)^2}$, where Y_1 is the baseline measurement and Y_2 is the follow-up measurement. These estimates are based on current literature values but may be updated based on future studies (see Section 2.2 for details).

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

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

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

Claims:

Claim 1: For a measured change in Area Under the Curve-Tissue Normalized (AUC-TN) in enhancing tumor tissue of $(YY_{22} - YY_{11})$, the 95% confidence interval for the true change is $(YY_{22} - YY_{11}) \pm 11.9999 \times \sqrt{(YY_{11} \times 00.3311)^{22} + (YY_{22} \times 00.3311)^{22}}$ 174 [14, 15], where Y_2 is the follow-up measurement and Y_1 is the baseline measurement.

Claim 2: For a measured change in Area Under the Curve-Tissue Normalized QIBA (AUC-TN) in normal brain tissue of $(YY_2 - YY_1)$, the 95% confidence interval for the true change is $(YY_{22} - YY_{11}) \pm 11.9999 \times \sqrt{(YY_{11} \times 00.0000)^{22} + (YY_{22} \times 00.0000)^{22}}$, where Y_2 is the follow-up measurement and Y_1 is the baseline measurement.

BC chairs:

Leland S. Hu, MD
Mark S. Shiroishi, MD
Ona Wu, PhD

BC Voting members:

see appendix

MR MSK Cartilage for Joint Disease

Biomarker:

Cartilage matrix T2 relaxation time, Change in T2

Executive summary:

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

The Claim (Section 2) describes the biomarker performance.

The 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.

This QIBA Profile (MR-based cartilage compositional biomarkers (T1ρ, T2)) addresses the application of T1ρ and T2 for the quantification of cartilage composition, which can be used as an imaging biomarker to diagnose, predict and monitor early osteoarthritis. It places requirements on Acquisition Devices, Technologists, MRI Physicists, Radiologists, Reconstruction Software and Image Analysis Tools involved in Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image Quality Assurance (QA) and Image Analysis.

The requirements are focused on achieving sufficient reproducibility and accuracy for measuring cartilage composition.

The clinical performance target is to achieve a reproducibility of 4-5% for measurements of global cartilage composition with T2 and T1ρ relaxation time measurements and a 95% confidence level for a true/critical change in cartilage composition (least significant change) with a precision of 11-14% and 9-12% if only an increase is expected (claim is one-sided). The target applies to 3T MR scanners of one manufacturer with identical scan parameters across different sites. It does not apply to scanners from different manufacturers.

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

Note that this document only states requirements to achieve the claim, not “requirements on standard of care.” Conformance to this Profile is secondary to properly caring for the patient.

Summary for Clinical Trial Use

The MR-based cartilage compositional biomarkers profile defines the behavioral performance levels and quality control specifications for T1ρ, T2 scans used in single- and multi-center clinical trials of osteoarthritis and other trials

assessing cartilage composition longitudinally with a focus on therapies to treat degenerative joint disease. While the emphasis is on clinical trials, this process is also intended to be applied for clinical practice. The specific claims for accuracy are detailed below in the Claims. The specifications that must be met to achieve conformance with this Profile correspond to acceptable levels specified in the T1ρ, T2 Protocols. The aim of the QIBA Profile specifications is to minimize intra- and inter-subject, intra- and inter-platform, and interinstitutional variability of quantitative scan data due to factors other than the intervention under investigation. T1ρ and T2 studies performed according to the technical specifications of this QIBA Profile in clinical trials can provide quantitative data for single timepoint assessments (e.g., disease burden, investigation of predictive and/or prognostic biomarker(s)) and/or for multi-time-point comparative assessments (e.g., response assessment, investigation of predictive and/or prognostic biomarkers of treatment efficacy).

A motivation for the development of this Profile is that while a typical MR T1ρ and T2 measurement may be stable over days or weeks, this stability cannot be expected over the time that it takes to complete a clinical trial. In addition, there are well known differences between scanners and the operation of the same type of scanner at different imaging sites.

The intended audiences of this document include:

- Biopharmaceutical companies, rheumatologists and orthopedic surgeons, and clinical trial scientists designing trials with imaging endpoints.
- Clinical research professionals.
- Radiologists, technologists, physicists and administrators at healthcare institutions considering specifications for procuring new MRI equipment for cartilage measurements.
- Radiologists, technologists, and physicists designing T1ρ and T2 acquisition protocols.
- Radiologists, and other physicians making quantitative measurements from T1ρ and T2 sequence protocols.
- Regulators, rheumatologists, orthopedic surgeons, and others making decisions based on quantitative image measurements.
- Technical staff of software and device manufacturers who create products for this purpose.

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

Claims:

Claim 1A: Cartilage matrix T2 relaxation time values are measurable with MRI at 3T with a within-subject coefficient of variation of 4-5% (test-re-test from the same vendor).

Claim 1B: Cartilage matrix T1ρ relaxation time values are measurable with MRI at 3T with a within-subject coefficient of variation of 4-5% (test-re-test from the same vendor)

Claim 2A: A measured increase/decrease in T2 of 11-14% or more indicates that a true/critical change has occurred with 95% confidence. If only an increase in T2 is expected (progressive cartilage matrix degeneration) the claim is

one-sided and an increase of 9-12% represents a true/critical change. This claim applies to 3T scanners from the same vendor.

Claim 2B: A measured increase/decrease in T1ρ of 11-14% or more indicates that a true/critical change has occurred with 95% confidence. If only an increase in T1ρ is expected (progressive cartilage matrix degeneration) the claim is one-sided and an increase of 9-12% represents a true/critical change. This claim applies to 3T scanners from the same vendor.

BC chairs:

Xiaojuan Li, PhD
Thomas M. Link, MD, PhD

BC Voting members:

see appendix

MRI-based Proton Density fat Fraction (PDFF) of the liver

Biomarker:

Volume fraction of lipid in liver

Executive summary:

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

The expected performance is expressed as Claims (Section 1.2). To achieve those claims, Actors, both human and equipment, (e.g., scanners, data acquisition parameters, data reconstruction software and algorithms, image analysis tools, technologists and radiographers, medical physicists, radiologists) must meet the Checklist Requirements (Section 3) covering Periodic QA, Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA, and Image Analysis.

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

Claim Confirmed: The requirements have been performed and found to be practical by multiple sites; The claim is verified in a multi-site, multi-vendor study; results are expected to be generalizable in similar settings.

Clinically Feasible (formerly Technically Confirmed): The requirements have been performed and found to be practical by multiple sites; The claim is a hypothesis based on committee assessment of literature and QIBA groundwork.

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

Consensus: The requirements are believed to be practical based on consensus of experts within and beyond the committee; The claim is a hypothesis based on committee assessment of literature and QIBA groundwork.

This document is intended to help clinicians and researchers basing decisions on this biomarker, imaging staff generating this biomarker, vendor staff developing related products, purchasers of such products and investigators designing trials with imaging endpoints. Note that this document only states requirements to achieve the claim, not "requirements on standard of care." Conformance to this Profile is secondary to properly caring for the patient.

Claims:

PDFF can be used in the clinical care of patients to quantify hepatic fat content for cross-sectional assessment (diagnosis, severity grading) as well as longitudinal assessment (monitoring, evaluation of response to treatment) on a per-subject basis, in those with suspected or known hepatic steatosis (i.e., fatty liver) of any etiology.

The use of PDFF in patients and research participants may include determination of eligibility in a clinical trial; triaging eligible subjects into cohorts based on severity grade; assessing response to treatment as a primary or secondary endpoint; monitoring for adverse effects such as chemotherapy-induced fatty liver disease; or establishing a database for the development, optimization, and validation of other imaging biomarkers. **Conformance to this Profile by all relevant staff and equipment supports the following claim(s):**

Cross-Sectional Claim:	For a measured PDFF value, the 95% confidence interval for the true PDFF value is within ±5% (absolute difference) of the measured value (PMID: 33464181).
Longitudinal Claim:	A measured absolute change in PDFF value of ± 5% or more indicates that a true change has occurred with ≥ 95% confidence (PMID: 28892458).

These two claims hold when PDFF is measured at each relevant time point in accordance with the conformance requirements outlined in this Profile, including:

- Data acquisition by MRI scanner, data reconstruction, and subsequent PDFF image analysis follow conformance requirements (see flowchart in **Figure 1**).
- Periodic and routine QA scans are implemented to assess performance and maintain Profile conformance.
- No significant image artifacts are identified that may confound determination of liver PDFF values.
- No areas of severe liver iron overload or areas of high R2* values are included in the PDFF regions-of-interest analysis. Mild liver iron overload is acceptable.
- In the liver, ROIs of reasonable size are used on representative acquired slice(s) while avoiding non-tissue structures such as those from the vasculature and biliary system.
- For longitudinal assessment, PDFF measurements are made in the same area of the subject's liver across time points.

The flowchart below (**Figure 1**) summarizes this PDFF Profile as it relates to conformance by MRI manufacturers and vendors, third-party software developers, and end-users. For an MRI manufacturer or third-party developer to be certified as Profile conformant for a given implementation of PDFF (i.e., pulse sequence, data acquisition and reconstruction), evidence satisfying the Claims must be demonstrated using commercial hardware and software products as they would be supplied to a customer (i.e., an end-user site).

An end-user should subsequently be able to further confirm Profile conformance onsite using the same product without modification from the source provider without the need to modify or augment the commercial product implementation. Should an end-user detect that the product PDFF implementation may not be conformant with the Profile requirements, it is recommended that the end-user report the error and provide feedback to the MRI manufacturer or third-party developer as a "Customer Complaint", as for example described in ISO 13485:2016 and 21 CFR Part 820.198.

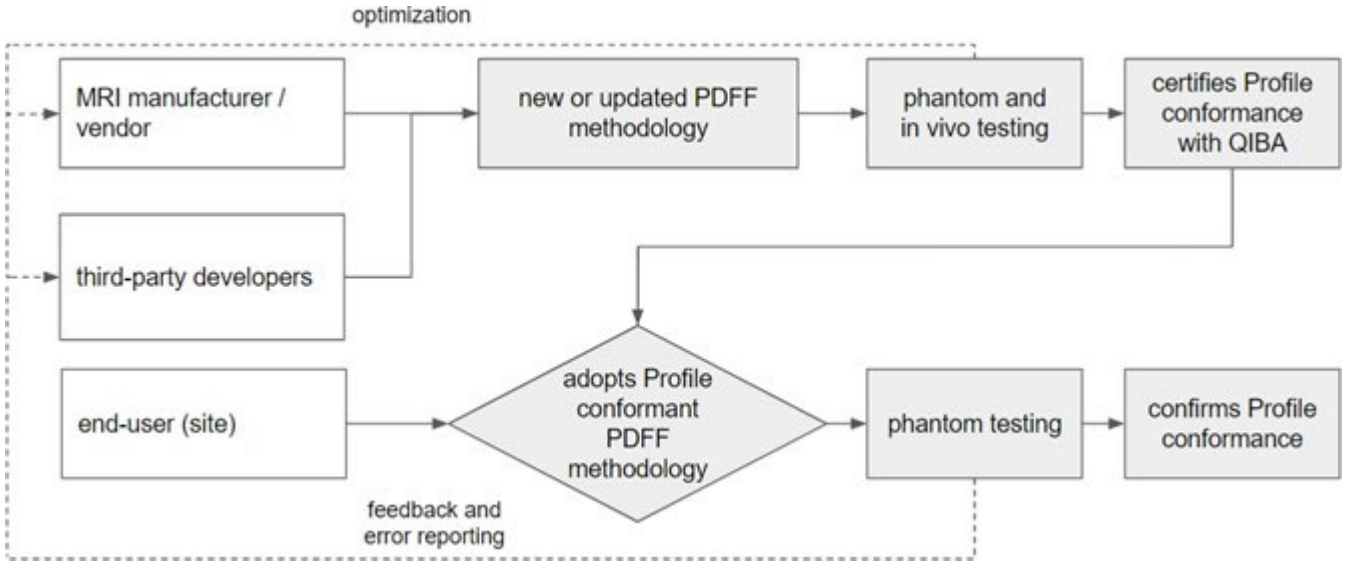


Figure 1. Flowchart for liver PDFF quantification method development and conformance testing.

BC chairs:

Diego Hernando, PhD
Harry H. Hu, PhD

BC Voting members:

see appendix

SPECT Ioflupane for Neurodegenerative Disease

V 2.0

Biomarker:

Specific binding ratios of striata, Caudate: Putamen activity concentration ratio

Executive summary:

Parkinsonism is a major health problem. Distinguishing neurodegenerative causes of parkinsonism from non-degenerative movement disorders that can mimic Parkinson's disease (PD) has important implications for prognosis and clinical management. The goal of this QIBA Profile is to optimize the performance of Iodine-123 (123I) ioflupane single photon emission computed tomography (SPECT) for quantifying the concentration of regional cerebral dopamine transporters (DaT) in patients with movement disorders.

The Claim (Section 2): This profile claims that conformance with its specifications will provide test-retest technical variance of less than 15% COV. In clinical use this might permit the ability to distinguish true biological change from measurement noise in clinical trials of participants who will be studied cross—sectionally, to aid accurate cohort recruitment and longitudinally with 123I-ioflupane. The claim is founded on observations that neurodegenerative disorders, such as idiopathic PD and Diffuse Lewy Body Dementia (DLBD), are associated with dopaminergic neuronal degeneration, which can be particularly pronounced in the substantia nigra. The degeneration of the axonal projections from the substania nigra to the basal ganglia is manifested as a loss of DaT activity. In most clinical imaging contexts where the question is about a neurodegenerative disorder, the loss is first observed in the most posterior aspect of the putamen, and then seems to march anteriorly, with left and right sides showing asymmetric changes. As a result, quantifying DaT can distinguish normal and abnormal states.

The Activities (Section 3) describe what needs to be done to make measurements that reliably distinguish patients from controls with confidence. Requirements are placed on the Actors who participate in those activities as necessary to achieve the Claim.

The Assessment Procedures (Section 4) for evaluating specific requirements are defined as needed. This QIBA Profile, "Quantifying Dopamine Transporters with 123Iodine Labeled Ioflupane in Neurodegenerative Disease", addresses quantitative SPECT imaging, which is often used as a diagnostic, as well as a longitudinal biomarker of disease progression or response to treatment. It places requirements on Acquisition Devices, Technologists, Radiologists, Reconstruction Software and Image Analysis Tools involved in Subject Handling, Image Data Acquisition, Image Data Reconstruction, Image QA and Image Analysis.

The requirements are focused on achieving sufficient accuracy and avoiding technical variability of the DaT measurements to distinguish neurodegenerative causes of parkinsonism from non-degenerative causes.

The clinical performance target is to achieve a 95% confidence interval for the striatal binding ratio with both a reproducibility and a repeatability of +/- 15%.

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

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

This QIBA Profile, and others like it addressing CT, MRI, PET and ultrasound can be found at www.qibawiki.rsna.org.

Claims:

Conformance to this Profile by all relevant staff and equipment supports the following claim:

Claim 1: Technical performance claims

Claim 1a: Measurement of the specific binding ratios (SBR) of striata have a within subject Coefficient of Variation (wCV) of 15%.

*****The wCV was estimated from a phantom experiment where 5 repeat measurements were performed of a striatal phantom on two systems. SBR was determined for L Caudate, L Putamen, R Caudate and R Putamen. The 95% CIs for the wCV varied around [6%, 11%], depending on the degree of corrections performed. The 15% value chosen for the claim reflects recognition of the additional variability in human subjects.

Claim 1b: Measurement of the caudate: putamen activity concentration ratio has a within subject Coefficient of Variation (wCV) of 8%.

***** The wCV was estimated from a phantom experiment where 5 repeat measurements were performed of a striatal phantom on two systems. The estimated wCV from that experiment was 5.6% with 95% CI of [3.8%, 10.7%].

Caveats of Context. These claims hold when:

- Clinical evaluation finds no other cause of parkinsonism, such as recent exposure to known toxins that can present with movement disorders, such as MPTP
- Anatomical imaging, such as magnetic resonance imaging (MRI), has already ruled out other causes of parkinsonism, such as stroke
- The patient has not been taking drugs or nutritional supplements that can transiently influence the measurements, such as dopamine transporter antagonists
- The patient does not have a deformity or condition that prevents proper positioning in the scanner, such as a severe kyphosis
- The patient can tolerate the imaging procedures well enough to prevent motion from confounding the acquisition
- The administration of the radiopharmaceutical is not confounded by infiltration of the dose
- And other such conditions, which, in the opinion of the professional staff, confound the examination.
- Note that a change of 42% is required when considering an individual patient in isolation. Well-powered clinical trials will be able to detect mean changes much smaller than 42%.

BC chairs:

John Dickson, PhD
P. David Mozley, MD
John Seibyl, MD

BC Voting members:

see appendix

SPECT-CT estimating the concentration of ^{99m}Tc based imaging biomarkers in large and small volumes of interest

Biomarker:

Concentration of radioactivity in VoI; Longitudinal change

Executive summary:

The quantification of ^{99m}Tc labeled biomarkers can add unique value in many different settings, ranging from clinical trials of investigation new drugs to the treatment of individual patients with marketed therapeutics. For example, goals of precision medicine include using companion radiopharmaceutical diagnostics as just-in-time, predictive biomarkers for selecting patients to receive targeted treatments, customizing doses of internally administered radiotherapeutics, and assessing responses to treatment.

This Profile describes quantitative outcome measures that represent proxies of target concentration or target mass in topographically specific volumes of interest (VOIs). These outcome measures are usually expressed as the percent injected dose (i.e., radioactivity) per mL of tissue (%ID/mL), a standard uptake value ratio (SUVr), or a target-to-background ratio (TBR). In this profile, targeting is not limited to any single mechanism of action. Targeting can be based on interaction with a cell surface protein, an intracellular complex after diffusion, protein-mediated transport, endocytosis, or mechanical trapping in a capillary bed, as in the case of transarterial administration of embolic microspheres. Regardless, the profile focuses on quantification in well-defined volumes of interest.

Technetium-99m based dopamine transporter imaging agents, such as TRODAT, share similar quantitative analysis as the predecessor profile on ^{123}I-ioflupane for neurodegenerative disorders. (See www.qibawiki.rsna.org) Cancer has often been used as the base case for many of the QIBA profiles, but the intent is to create methods that can be useful in other therapeutic areas where diseases are characterized by spatially-limited anatomical volumes, such as lung segments, or multifocal aggregations of targets, such as white blood cell surface receptors on pulmonary nodules in patients with sarcoidosis. Neoplastic masses that can be measured with x-ray computed tomography (CT) or magnetic resonance imaging (MRI) are the starting point for quantitative assessment of ^{99m}Tc-based radiotracers. However, the intent of this effort is to create a profile that can be extrapolated to diseases in other therapeutic areas that are also associated with focal, or multi-focal pathology, such as pulmonary granulomatous diseases of autoimmune or infectious etiology, non-oncological diseases of organs such as polycystic kidney disease, and the like.

The criteria for measurability are based on the current resolution of most SPECT-CT systems in clinical practice and are independent of criteria for measurability in other contexts. For this SPECT profile, conformance requires that a “small” VOI must be greater than 30 mL to be measurable. It is understood that much smaller VOIs can sometimes exhibit high conspicuity on SPECT, but these use cases are beyond the scope of this profile and will not be tested for

conformance in this version. It is left to individual stakeholders to show the extent to which they can achieve conformance when measuring VOIs less than 30 mL. The detection of smaller changes during clinical trials of large groups can be achieved by referring to the QIBA companion guidance on powering trials.

The Claims (Section 2) asserts that compliance with the specifications described in this Profile will

(1) produce cross sectional estimates of the concentration of radioactivity [kBq/mL] in a volume of interest (VOI) or a target-to-background ratio (TBR) within a defined confidence interval (CI), and

(2) distinguish true biological change from system variance (i.e., measurement error) in individual patients or clinical trials of many patients who will be studied longitudinally with ^{99m}Tc SPECT agents. Both claims are founded on observations that target density varies between patients with the same disease as well as within patients with multi-focal disease.

The Activities (Section 3) describes the requirements that are placed on the **Actors** who need to achieve the Claim. Section 3 specifies what the actors must do in order to estimate the amount of radioactivity in a volume of interest, expressed in kBq/mL (ideal) or as a TBR (acceptable) within a 95% CI surrounding the true value. Measurands such as %ID/mL are targets for nonclinical studies in animal models that use terminal sacrifice to establish ground truth for imaging studies. TBRs can be precarious, as the assumptions that depend on the physiology of the background regions matching the volume of interest can be hard to accept sometimes. It is up to each individual stakeholder to qualify the background regions used in their own use case. This profile qualifies only a few in some very limited contexts as examples.

The Assessment Procedures (Section 4) for evaluating specific requirements are defined as needed. The requirements are focused on achieving sufficient accuracy and avoiding unnecessary variability of the measurements. The clinical performance target is to achieve a 95% confidence interval for concentration in units of kBq/mL (kilobequerels per milliliter) or %ID/mL (percent injected dose per milliliter) or TBR with both a reproducibility and a repeatability of +/- 8% within a single individual under zero-biological-change conditions.

This document is intended to help clinicians base decisions on these biomarkers, imaging staffs generating measurements of these biomarkers, vendors who are developing related products, purchasers of such products, and investigators designing trials to be able to make informed decisions based upon accurate and reproducible SPECT derived biomarkers.

Note that this document only states requirements to achieve the claims, not “requirements on standard of care” nor compliance with any particular protocol for treating participants in clinical trial settings. Conformance to this Profile is secondary to properly caring for patients or adhering to the requirements of a protocol.

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

Claims:

Conformance to this Profile by all relevant staff and equipment supports the following claim(s):

Claim 1: Cross sectional. Calibration.

Claim 1A: Absolute Quantification.

For a target volume > 30 mL with a contrast ratio of more than 2-to-1 in an image with more than 2 million counts, empirical evidence shows the within subject coefficient of variation (wCV) is less than 8% (0.08). When these conditions hold, for a measured concentration of radioactivity of Y in units of kBq/mL or %ID/mL, a 95% confidence interval* for the true activity concentration is $YY \pm 1.96 \times 0.08 \times YY$.

> For example, if the concentration of radioactivity is measured to be 4 kBq/mL after the correction for any known bias as described below, then the 95% CI for the true concentration is (4-0.63)-to-(4+0.63), or [3.37-to-4.63] kBq/mL.
>
> *The CI is constructed from an estimate of the within-subject coefficient of variation, under the assumption of negligible bias.

The assessments described in Section 4 need to be performed to verify that the system meets the total error requirements listed above, such as a wCV ≤ 8%, which includes assessments of actors' measurement bias and precision. The above claim assumes that any known bias has already been corrected and the remaining bias is <5%. For example, if an actor knows that their activity concentration measurements are consistently 20% too low, then they should logically adjust all the activity concentration measurements by increasing the values by 20%. This assumes that operators have applied quantitative calibration as described in Section 4.7. If the bias is volume-dependent (partial volume effects) then a target volume dependent adjustment should be made, for example by using recovery coefficients determined by phantom measurements.

Claim 1B: Target-to-Background Ratio (TBR).

For a target volume > 30 mL, for a measured TBR of Y, a 95% confidence interval for the true uptake ratio is $YY \pm 1.96 \times 0.08 \times YY$. For example, if striated muscle has been qualified as a defensible background region for a tumor imaging agent, and a tumor-to-muscle ratio is 2.5:1, then the 95% CI for the true target tissue-to-muscle ratio is (2.5-0.39) to (2.5+0.39) or [2.11 to 2.89].

> ***The CI is constructed from an estimate of the within-subject coefficient of variation.***

This form of the claim does not require correcting for the bias if, but only if, the percent bias associated with the measurement of the target tissue is adequately similar to the percent bias associated with the background.

Claim 2: Longitudinal Changes Within Subjects

Claim 2A: Longitudinal detection of change.

A measured change in concentration or TBR of Δ% indicates that a true change has occurred with 95% confidence if Δ

is larger than the estimated repeatability coefficient (RC)*. In practice this means that for an activity concentration of Y at timepoint T1, the change at timepoint T2 must exceed 2.77 x wCV x Y, which for a wCV of 0.08 is 0.22 x Y

**The estimated repeatability coefficient (RC) is defined below.*

Claim 2B: Amount of change.

If $\boldsymbol{YY_{11}}$ and $\boldsymbol{YY_{22}}$ are the measurements of concentration or TBR at two time points, a 95% confidence interval for the true change is

$$YY_2 - YY_1 \pm 1.96 \times \sqrt{(YY_1 \times 0.08)^2 + (YY_2 \times 0.08)^2}$$

Note: This claim assumes that the bias at both the time points was the same, and thus cancels out (in other words, that the slope of a regression line of measured versus true values of concentration or TBR is one).

Caveats of Context. These claims hold when:

- Volumes of interest (VOIs) are greater than 30 mL
- The target to background ratio in the VOIs are at least 2-to-1
- Background regions have been qualified by the user as fit-for-purpose, e.g., the cerebellum has been qualified as an adequate background region for dopamine transporter imaging agents, such as ^{99m}Tc-TRODAT. The attributes of an ideal background region include the following, and must be substantiated for each use case by the user:
    - Easily demarcated with a relatively simple verbal description
    - Large (>30 mL, preferably >100 mL)
    - Same biological properties as the target, including blood flow and perfusion, or a known method of compensating for any differences
    - Same tissue density as the target (e.g., it should have nearly the same ADC on MRI or nearly the same HU on CT as the target)
    - The background VOI contains no target tissue
    - The sum of these attributes is such that measurements produce high (>85%) intra- and inter-rater reliability

- Radioactivity represents specific localization in the target tissue of interest, and not a mechanistically unrelated phenomenon, such as excretion into the gallbladder, binding unintended receptors on normal tissues, etc.
- Anatomical imaging, such as x-ray computed tomography (CT) or magnetic resonance imaging (MRI), has already ruled out other causes of radiotracer accumulation, e.g., excretion into a surgically constructed urinary bladder
- The patient has not been taking drugs or nutritional supplements that can transiently influence the measurements, such as multivitamins in the case of folate receptor imaging, or somatostatin in the case of SSR imaging
- The patient does not have a deformity or condition that prevents proper positioning in the scanner, such as a severe kyphosis
- The patient can tolerate the imaging procedures well enough to prevent motion from confounding the acquisition
- The administration of the radiopharmaceutical is not confounded by infiltration of the dose

- The uptake of tracer doses within the region of interest can be considered to be constant over the time of data acquisition, unless saturating doses of the pharmacophore are co-administered
- And other such conditions, which, in the opinion of the professional staff, confound the examination.

BC chairs:

Yuni Dewaraja, PhD
Robert Miyaoka, PhD

BC Voting members:

see appendix

QIBA Profile: Ultrasound Volume Blood Flow (USVBF)

Biomarker:

Ultrasound Volume Blood Flow (USVBF)

Executive summary:

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

The expected performance is expressed as Claims (Section 1.2). To achieve those claims, Actors (Manufacturers/Vendors/Field Service Engineers, Sonographers/Technologists, Physicians, Physicist/Clinical Engineer/QA manager, and Image Analysis Tools) must meet the Checklist Requirements (Section 3) covering Product Validation, Staff Qualification, Pre-delivery, Installation, Periodic QA, Subject Handling, Image Data Acquisition, Image QA, and Image Analysis.

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

- The requirements are believed to be practical by the committee.
- Simplifications will be considered for future versions of the profile.
- The claim is a hypothesis based on committee assessment of literature and QIBA groundwork.

QIBA Profiles for other CT, MRI, PET, and Ultrasound biomarkers can be found at qibawiki.rsna.org.
This QIBA Profile (US Volume Blood Flow) addresses volumetric blood flow (volume of blood passing through a given vessel per unit time), which can be used as a biomarker of normal/abnormal physiologic conditions, disease progression or response to therapy. The requirements are focused on achieving sufficient accuracy and avoiding unnecessary variability of volume blood flow measurements.

In addition, traditional methods for volume flow using 2D imaging and spectral Doppler ultrasound measurements have not been widely used due to high variability, implicit assumptions, and high user interaction requirements.

Claims:

In the claims presented below, the general methodology involves the use of 3D color flow imaging data (velocity and power) in the calculation of volume blood flow. The term “imaging system” refers to both the ultrasound scanner (machine) and the operator using the machine to perform VBF measurements. 150 Changing either the operator or ultrasound scanner therefore results in a different imaging system. The working definition of “pulsatile” for the purposes of this profile is provided in the explanatory text found in Appendix B as footnotes to the claims. Conformance with this Profile by all relevant staff and equipment supports the following claim(s):

• **Claim 1a (cross-sectional, phantom)*:** For a measured constant volume blood flow of Y mL/min, a 95% confidence interval for the true flow is (Y - 0.033Y) +/- 0.069Y * 1.96 mL/min.

• **Claim 1b (cross-sectional, clinical)†:** For a measured constant volume blood flow of Y mL/min, a 95% confidence interval for the true flow is (Y - 0.033Y) +/- 0.2Y * 1.96 mL/min.

• **Claim 1c (cross-sectional, phantom)*:** For a measured pulsatile volume blood flow of Y mL/min, a 95% confidence interval for the true flow is (Y - 0.149Y) +/- 0.143Y * 1.96 mL/min.

• **Claim 1d (cross-sectional, clinical)†:** For a measured pulsatile volume blood flow of Y mL/min, a 165 95% confidence interval for the true flow is (Y - 0.149Y) +/- 0.2Y * 1.96 mL/min.

• **Claim 2a (technical performance claim)** :** For clinical subjects, the volume flow measurement in constant flow has a within-subject coefficient of variation (wCV) < 20%.

• **Claim 2b (technical performance claim)††:** For clinical subjects, the volume flow measurement in pulsatile flow has a within-subject coefficient of variation (wCV) < 20%.

See Appendix B of the profile for associated footnotes.

The above claims were developed based on phantom studies conducted by the QIBA Ultrasound Volume Blood Flow Biomarker Committee and published studies in the peer-reviewed literature except as noted in Appendix B. These claims may not accurately reflect performance in patients under all imaging circumstances. The expectation is that during the Technical Confirmation and Clinical Confirmation phases, data on the actual field performance will be collected and changes made to the claims or the details, accordingly. At that point, this caveat may be removed or re-stated.

BC chairs:

J. Brian Fowlkes, PhD
James Jago, PhD
Oliver Kripfgans, PhD

BC Voting members:

see appendix

Biomarker Committees

Public Comment Profiles (Stage 1)

fMRI for Sensorimotor mapping

Mapping of Sensorimotor Brain Regions using Blood Oxygenation Level Dependent (BOLD) Functional MRI as a Pretreatment Assessment Tool

Biomarker:

Weighted center-of mass of fMRI hand motor activation (wCMA)

Executive summary:

This profile provides guidance for using functional magnetic resonance imaging (fMRI) to map the central brain components of the motor system for use in planning and guiding brain surgery or radiation treatment. The current focus is on using fMRI as a location biomarker for the center-of-mass of brain areas supporting hand movement that may be at risk of damage from invasive treatments. Accordingly, the goal of this QIBA Profile is to help the user to achieve a useful and specified level of performance of the biomarker.

The **Claim** (Section 2) describes the biomarker and its 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 that should help the user in assessing conformance with this profile.

This QIBA Profile (Mapping of Brain Motor Regions using Blood Oxygenation Level Dependent (BOLD) functional MRI as a Pretreatment Assessment Tool) has been developed to provide a systematic approach for optimizing Blood Oxygen Level Dependent (BOLD) fMRI brain mapping for treatment planning prior to surgery or invasive treatment intervention. It places requirements on Acquisition Devices, Technologists, Radiologist, Post-Processing Software and Image Analysis Tools involved in Subject Handling, Image Data Acquisition, Image Data Processing, Image QA and Image Analysis. Note users who plan to bill for imaging services using this profile should also consult the current procedural terminology (CPT) codes which may have additional requirements. Please refer to the ASFNR website for further information (http://www.asfnr.org/cpt-codes/).

Claims:

Conformance to this Profile by all relevant actors and equipment is required to ensure the validity of the following claim:

Claim 1: If X,Y,Z is the measured location of the weighted center-of-mass of a single focus of fMRI hand motor activation (wCMA), then the 95% confidence interval for the X,Y,Z of the true wCMA is +/-5 mm in any direction (Euclidean distance, assuming no systematic bias). (The +/-5 mm precision value represents 1.96 × within-subject standard deviation.)

BC chairs:

Feroze Mohamed, PhD
Jay Pillai, MD
David Soltysik, PhD

BC Voting members:

see appendix

Biomarker Committees

Early Development Profiles (Stage 0)

The following profiles are currently under development by respective QIBA Biomarker Committees

MR	**ASL**	(Arterial Spin Labeling in Neuroimaging Applications) – collaboration with EIBALL
MR	**fMRI**	(BOLD fMRI for Presurgical Language Mapping)
NM	**PET-Myocardial Blood Flow (PET-MBF)**	Positron Emission Tomography measurement of myocardial blood flow
NM	**PET Tau**	Positron Emission Tomography measurement of Tau
US	**CEUS**	(Contrast-Enhanced Ultrasound Quantification of Flow Dynamics)
US	**PEQUS**	Pulse-echo Quantitative US based on Backscatter

Suggestions for the Imaging community going forward:

I. Educate and implement imaging metrology in areas of clinical relevance

   a. Quantitative Imaging Biomarkers can be considered assays

      i. Disease processes such as NASH and Alzheimer's Disease need objective measures of disease progression and response to treatment that might be spatially heterogeneous and quantitative imaging biomarkers can meet that need

   b. ALL measurements – including all assays – have uncertainty

      i. What are the implications in clinical decision-making of that uncertainty?

   c. How does the uncertainty in a particular QIB compare with other commonly used assays?

II. Advocate for imaging experts as leaders in understanding of uncertainty in clinical imaging measurements

III. Educate and implement QIBA concepts, especially measurement uncertainty, into the discussions about AI and its potential in all steps of the imaging value chain (from image generation to image interpretation and decision making)

   a. Emphasize the importance of input data quality for AI algorithms and how that relates to measurement/decision criterion uncertainty

IV. Expand on existing profiles in collaboration with existing and potential new committees

V. Advocate for leveraging the knowledge available in the EIBALL/QIBA Biomarker Inventory for considering QIBs that have solid peer-reviewed literature demonstrating utility but need standardization

VI. Expand beyond radiology-driven efforts to the wants and needs of referring physicians

   a. What would referring physicians like to measure but cannot

VII. Consider patient benefit as priority for the respective disease areas. Help patients to understand uncertainty and the relevance for individual decision making.

VIII. Advocate for multi-parameter QIBs and decision metrics