The RSNA QIBA Profile for Amyloid PET as an Imaging Biomarker for Cerebral Amyloid Quantification

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A standardized approach to acquiring amyloid PET images increases their value as disease and drug response biomarkers. Most ^{18}F PET amyloid brain scans often are assessed only visually (per regulatory labels), with a binary decision indicating the presence or absence of Alzheimer disease amyloid pathology. Minimizing technical variance allows precise, quantitative SUV ratios (SUVRs) for early detection of β-amyloid plaques and allows the effectiveness of antiamyloid treatments to be assessed with serial studies. **Methods:** The Quantitative Imaging Biomarkers Alliance amyloid PET biomarker committee developed and validated a profile to characterize and reduce the variability of SUVRs, increasing statistical power for these assessments. **Results:** On achieving conformance, sites can justify a claim that brain amyloid burden reflected by the SUVR is measurable to a within-subject coefficient of variation of no more than 1.94% when the same radiopharmaceutical, scanner, acquisition, and analysis protocols are used. **Conclusion:** This overview explains the claim, requirements, barriers, and potential future developments of the profile to achieve precision in clinical and research amyloid PET imaging.

Key Words: quantitative imaging biomarkers; amyloid PET; QIBA; guidelines; Alzheimer disease

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The preponderance of evidence indicates that cerebral β-amyloid plaques are a necessary, but insufficient, precursor of synaptic loss and cognitive impairment in Alzheimer disease (AD). Because of the validation of PET imaging in comparison with postmortem examinations, PET imaging has come to play a central role in definitive clinical diagnosis and in pharmaceutical clinical trials. It also has become adopted as the gold standard by which to judge cerebrospinal fluid and plasma amyloid biomarkers. Amyloid PET status is incorporated into National Institute on Aging–Alzheimer Association diagnostic criteria for AD and is a critical component of the amyloid/tau/neurodegeneration classification in the Alzheimer's Association Research Framework (*1,2*).

Before amyloid PET was available, response to antiamyloid treatment could be surmised only occasionally and inconclusively from postmortem studies (*3*). Assessing amyloid load measured as a continuous variable is now used in nearly all antiamyloid therapies in clinical development or in the regulatory pipeline. There are several large, multicenter AD observational studies and prevention trials in which minimizing within-subject and between-site technical variance is a critical concern. With increasing focus on the benefits of early diagnosis and treatment, the potential impact of more precise tissue ratio quantification is now particularly germane. Notably, a first antiamyloid immunotherapy (aducanumab) recently received Food and Drug Administration accelerated approval based in part on significant quantitative reduction of amyloid PET pathology as seen on amyloid PET, and additional antiamyloid agents are progressing in clinical development (e.g., donanemab, lecanemab, and gantenerumab).

Although a visual assessment of amyloid PET images is often used to support patient inclusion or in clinical application, quantification is essential to objectively measure change. The clinical trial of donanemab applied an innovative strategy of using quantitative changes in amyloid PET to decide when individual treatment goals had been achieved and treatment discontinued (*4*). This approach offers an objective method of knowing when an expensive and burdensome therapy can safely be terminated. Quantification also serves a role in both staging disease and predicting the clinical trajectory; for example, data from the Harvard Aging Brain Study indicated that persons with an amyloid burden greater than a quantitative threshold were more likely to progress clinically (*5*). As clinical trials move earlier into the disease process, amyloid levels more

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frequently fall into less visually obvious categories. Quantitative, objective methods can decrease the frequency with which diagnostic assessments are ambiguous or indeterminate.

Many factors influence the reliability and repeatability of quantitative amyloid PET measures. Although detection of major reductions to amyloid burden may be robust to technical variability, the detection of slowed rates of accumulation, or of reductions within a short time frame, require minimized technical variance. In a clinical trial, minimizing technical variance in serial measures of amyloid load can have a substantial impact on the number of patients required to adequately power a study and detect an effect. On an individual basis, reproducibility can influence the amount of change that can be interpreted as technically meaningful. Potential sources of variability are numerous and include scanner characteristics; tracer administration parameters; subject positioning and motion; and image reconstruction, processing, and measurement approaches. As a striking example, selection of the reference tissue region for calculation of SUV ratios (SUVRs) made a difference in requiring 325 versus 8,076 subjects per arm to measure a 25% reduction in the rate of accumulation over 12 mo (*6*), consistent with other studies (*7–9*). Although these and other factors influencing amyloid quantification have been described (*9*), there had not been a standardized procedural guide that is directly tied to expectations for measurement variability. In addition, the quantitative effects of factors such as subject motion on measured amyloid had not been systematically determined. In 2007, the Radiological Society of North America (RSNA) set up the Quantitative Imaging Biomarkers Alliance (QIBA), whose mission is "… to improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, sites, patients and time" (*10,11*). The primary deliverables of the QIBA initiative are standards-based quantitative imaging documents, called profiles, which are derived from a process similar to that of the Integrating the Healthcare Enterprise initiative (*12*). A profile makes a statistically based performance claim about a quantitative imaging biomarker based on clinical context of use when performance requirements and compliance procedures are met. The amyloid PET profile (*11*) describes the measurement precision of ^{18}F-amyloid PET imaging of the brain when meeting defined requirements and quality control specifications. The profile was designed for use both in clinical trials and in the clinic for detecting and monitoring amyloid plaque pathology. It is intended to be a checklist that a site can use to achieve conformance for its ^{18}F PET amyloid biomarker workflow.

Achieving conformance means that the site's quantitative precision will be as specified by the profile claim. Consideration has been given to making their implementation reasonable by community sites as well as advanced research sites. Stage 3, the technically confirmed QIBA profile "^{18}F-Labeled PET Tracers Targeting Amyloid as an Imaging Biomarker" (provided as a supplement to this paper; supplemental materials are available at http://jnm.snmjournals.org) overlaps and builds on imaging protocols already used in observational studies and clinical trials. Although most large, multicenter amyloid imaging studies provide their performance sites with detailed imaging protocol specifications, the QIBA profile includes some potentially important details often not included in study protocols and left to individual sites to implement. The profile proposes a new harmonized reference standard to objectively evaluate acquisition methods and to support regulatory biomarker registration. Although the QIBA profile describes what may be standard operation procedures at many larger, well-equipped imaging centers, these procedures are not universal. The profile will especially benefit sites that have limited physics and instrumentation support and may lack technical expertise to recognize and address sources of variability.

This overview of the QIBA amyloid profile is intended to provide context for the role of quantitative amyloid PET imaging in clinical trials and patient care, describe the profile scope and claim, summarize profile recommendations for actions and parameters to be followed to achieve the claim, provide the rationale for recommendations, describe the work that was performed to address knowledge gaps, explain the relationship between the profile and other initiatives and governing bodies, identify barriers that were overcome to create the profile, and provide a vision for the future.

The profile is available as a supplemental file (*13–57*).

PROFILE STRUCTURE

The overall structure of the profile is shown in Table 1. The context for the profile is described, followed by the claim, which is the central focus of the profile. Examples of clinical applications are provided. The profile then describes and specifies mitigations for the major sources of workflow variability (listed in the profile activities section) in order to achieve the profile claim. The mitigation steps are performed by actors: study sponsor, technologist, acquisition device, reconstruction software, image analysis workstation, image analyst, imaging facility coordinator, nuclear medicine physician, and medical physicist. The mitigation specifications are shown in tables under each heading in the profile, listing the actors

TABLE 1
High-Level Outline of Profile

Item	Details
Executive summary	
Overview	
Summary for clinical trial use	
Intended audiences	
Clinical context and claims	
Claim	
Considerations for claim	
Clinical trial use	
Profile activities	
Subject handling	
Image data acquisition	
Image data reconstruction and postprocessing	
Image analysis	
Image interpretation and reporting	
Quality control	
Conformance procedures	Image acquisition site
	PET acquisition device
	Reconstruction software
	Image analysis workstation
	Software version tracking
References	
Appendices	

TABLE 2
Example from Profile of Mitigating Steps

Parameter	Entity/actor	Specification
PET scanner calibration	Technologist	Must perform daily/weekly/monthly scanner quality assurance and vendor-recommended maintenance procedures (e.g., replace weak transmission sources for dedicated PET scanner); must ensure that output values are acceptable and manually entered on form/electronic database
PET scanner calibration constancy check	Technologist	Must perform constancy phantom (e.g., ^{68}Ge cylinder) scan (preferably NIST-traceable or equivalent to gather information on uniformity as well) at least weekly and after each calibration
Radionuclide calibrator	Physicist	Must be calibrated to ^{18}F using NIST-traceable source or equivalent either by site or by calibrator manufacturer

NIST = National Institute of Standards and Technology.
Only shaded rows are mandatory for profile conformance; white row is recommended and may be mandatory in future profile updates.

and what activities they are expected to perform. When all actors successfully complete their mitigation steps, the site has achieved compliance and can expect to achieve the profile's specified precision. A series of appendices then provides additional detail and information.

The mitigating steps in the profile tables are normative items or requirements that must be performed for the site to claim profile conformance. Surrounding the tables is descriptive text that gives more explanation and examples. Table 2 provides an example from the profile.

PROFILE CLAIM

Claim Description

The claim is the fundamental basis of the profile and describes the precision of the biomarker measurements when conformance is achieved (a technical performance claim). The SUVR was chosen as the biomarker because of its logistic feasibility in multisite trials and its use in large reference studies such as the one supported by the Alzheimer Disease Neuroimaging Initiative (ADNI) (*58*). Because of the fundamental kinetic properties of radiopharmaceuticals, changes in SUVR may not only represent a change in amyloid burden but also include changes in perfusion (*9*) or tissue clearance (*59*). This variability contributes to and is embedded in the precision stated in the claim, "Brain amyloid burden as reflected by the SUVR is measurable using ^{18}F-amyloid PET with a within-subject coefficient of variation (wCV) of $\leq$ 1.94%" (*11*). The claim is equally valid when the measured quantity is centiloids (*60,61*) or distribution volume ratios (DVRs).

The within-subject wCV is a statistical measure of precision. It describes the ability to obtain replicate measurements that agree with one another. It describes not the variability between subjects but the variability within a subject when scanned at time points close enough that no disease progression has occurred (60 d or less (*11*)). Statistically, it is defined as the SD of replicate measurements on a subject, divided by the mean of those measurements. Ideally, wCV should be as close to zero as possible.

The claim is valid only for longitudinal measurements, not for cross-sectional measurements. A cross-sectional measurement claim requires additional estimation of bias, and this information was not available across scanners at the time of profile development. Although the profile focuses on SUVR measurement, the potential benefits of the DVR approach are discussed in detail as a profile appendix.

Claim Application

The wCV stated in the claim can be used to guide the number of subjects included in clinical trials targeting measurement of longitudinal changes in amyloid SUVR. The amount of longitudinal change anticipated or targeted depends on the disease stage of the study population and on the trial objectives. For example, the rates of change expected from an amyloid-removing agent in a prodromal or mild trial with a high amyloid baseline burden may differ from those anticipated in a prevention trial enrolling participants with lower baseline amyloid. Rates of change may also vary between sporadic and familial AD populations.

As a first example, the mean amount of amyloid accumulation in 2 y for a cohort of patients will be estimated. To estimate within $\pm$1% with 95% confidence, assuming mean SUVRs at baseline of 1.0–1.5 (this mean range is highly dependent on the reference region used), no significant changes in perfusion between scans, and a between-subject SD ranging from 0.05 to 0.30, Supplemental Figure 2 from the profile (*11*) shows the number of subjects required for 3 different correlation coefficient (r) values between paired measurements from a subject.

The number of subjects required is reduced as r increases between scan visits. For example, an internal analysis of ^{18}F-florbetapir data, available through ADNI, at baseline and year 2 suggests that the correlation between scans is higher for certain reference regions than others. Using the composite of cerebellum and white matter or only white matter as reference tissue, r was 0.95 or 0.96, respectively, for amyloid-positive subjects (n = 207) and 0.94 for subjects close to the positivity threshold (n = 51). However, using cerebellar cortex or whole cerebellum as reference tissue, r was 0.79 and 0.83, respectively, for amyloid-positive subjects and 0.33 and 0.48, respectively, for subjects close to the positivity threshold.

As a second example, consider a clinical trial comparing the accumulation in amyloid SUVR over time between 2 groups of subjects: those undergoing a new treatment versus a control group. AD patients will be recruited and randomized to either the experimental intervention or the control group. SUVR will be measured in all subjects at baseline and 2 y later. The null hypothesis is that there is no difference in subjects' mean amyloid accumulation between the 2 groups; the alternative hypothesis is that there is a difference

(2-tailed hypothesis). Obuchowski et al. (*62*) reported the sample size needed to detect a 50% reduction in the rate of accumulation over a 2-y period with 80% power based on the assumed wCV of 1.94%. Fewer than 100 subjects were needed per group, assuming a homogeneous patient sample with low between-subject variability. Additionally, reducing the variance in the measured quantity will help when patient-level correlations of amyloid burden reduction to cognitive changes are desired.

Derivation of Technical Performance Claim

The technical performance claim was derived from a metaanalysis of published data of the repeatability of amyloid PET imaging under 2 types of test–retest conditions, coupled with QIBA-sponsored systematic analyses of the quantitative impact of specific sources of variance. The first type of test–retest data consisted of studies in which 2 serial scans were acquired within less than 60 d (*63,64*). The wCV values in the short-duration test–retest studies ranged from 1.15% in healthy controls using a cerebellar cortex reference region to 1.94% in AD patients using a whole-cerebellum reference region (*63,64*). The second set of studies compared baseline values in amyloid-negative cognitively normal participants with those acquired after a 2-y period, a typical clinical trial duration (*6,7*). Since amyloid accumulation is unlikely to occur in most (though not all) amyloid-negative cognitively normal subjects, longitudinal values in this group were examined. These studies provided a practical indicator of longer-term technical variance given a population presumed to be fairly stable with regard to amyloid pathology. In addition, the acquisition and measurement parameters applied in these more recent studies were well characterized and aligned with profile recommendations.

The wCV values derived from studies over a 2-y duration in amyloid-negative cognitively normal controls from the ADNI dataset ranged from 1.25% (white matter reference region) to 1.6% (whole-cerebellum reference region) and in 1 case up to 3.38% (whole-cerebellum reference region, with a different cerebellum boundary definition) (*6,7*). In these published studies, the mean and SD of the longitudinal change were shown in a table, and the ADNI data acquisition protocol (*58*) was used to acquire the data, that in many respects are consistent with the profile (as described in the "Relationship to Other Standards" section). The wCV cited in the claim that 1.95% is the highest of the test–retest studies that occurred within 4 wk from first studies and also satisfies the range of 1.25%–1.6% reported in all but a single 2-y study. Conformance to the claim depends on many factors such as radiopharmaceutical, subject positioning, data acquisition, reconstruction and post-processing. In particular, the choice of the reference region can greatly impact wCV because of the sensitivity of different regions to technical factors. It is important to note that the wCV was less than 1.94% across these 2-y studies only when reference regions incorporating subcortical white matter were used. However, additional QIBA-sponsored studies performed during the development of the profile identified controls to reduce variability when using reference regions such as the cerebellum (*65*). This and related contributors to variance are described in the "Profile Activities and Key Points" section (*6–8,66*).

PROFILE ACTIVITIES AND KEY POINTS

^{18}F PET Amyloid Radiopharmaceuticals and Subject Handling

Although a significant body of work was initially performed with the ^{11}C-amyloid radiopharmaceutical ^{11}C-Pittsburgh compound B (PiB) (*67*), the profile was developed using data from the ^{18}F-amyloid radiopharmaceuticals listed in Table 3, and therefore only these radiopharmaceuticals conform with the profile. That said, there are no technical limitations that prevent the profile from being extended to ^{11}C-PiB, but its clinical use is limited since there is no Food and Drug Administration approval and an on-site cyclotron is required. The site should administer the activity per its local protocol, provided it meets the specifications listed in the profile and the manufacturer's specifications. The subject's head should be positioned at a consistent location within the scanner, with as much axial distance as possible between the edge of the scanner field of view and the subject's head and cerebellum to minimize slice-to-slice variability due to nonuniform scanner axial sensitivity. To prevent head movement, the head should be secured and subjects should be made as comfortable as possible.

Image Data Acquisition

The same scanner, ^{18}F-amyloid radiopharmaceutical, and protocol should be used to acquire serial within-subject images since any bias due to any of these factors will be consistent from scan to scan. The PET acquisition should be broken into a minimum of 5-min dynamic frames, and the dynamic frames should be assessed for significant head movement since this is a known source of quantitative error in PET (*65*). It is ideal for each PET image time frame to be coregistered with the CT image before attenuation and scatter correction are performed. If this is not possible and motion exceeds 4 mm or 4°, removal of selected frames or exclusion of the scan should be considered (*65*). If motion is less, variability

TABLE 3
List of ^{18}F-Amyloid Radiopharmaceuticals and Their Recommended Doses, Uptake Times, and Acquisition Durations

Parameter	Florbetapir*	Flutemetamol†	Florbetaben‡	NAV4694 (*80*)
Administered activity (MBq)	370 (maximum, 50-μg mass dose)	185 (maximum, 20-μg mass dose)	300 (maximum, 30-μg mass dose)	300
Uptake time (postinjection min)	30–50	90	45–130	50–70
Acquisition duration (min)	10	20	15–20	20

*Amyvid (Eli Lilly & Co.) (*77*).
†Vizamyl (GE Healthcare) (*78*).
‡Neuraceq (Piramal Imaging) (*79*).
Data are per U.S. package inserts. There might be some slight variations in package insert information depending on country of approval.

due to patient motion can be reduced through postreconstruction motion correction, in which all emission time frames are aligned with one another before a single averaged image is created. Finally, the dynamic time frames can be averaged or summed to form a single static PET image. An additional control specified by the profile to minimize variability is axial scanner uniformity.

The profile also describes the potential benefits obtained from the use of DVRs calculated from dynamic PET images. Emission scan data are acquired from the time of radiopharmaceutical injection through the late-time-frame period. In full dynamic scanning, a parametric image can be created using physiologic modeling techniques. The image can then be measured using the same analysis as specified by the profile. A benefit is that the contribution of local cerebral blood flow rate to the amyloid value can be separated from that due to amyloid burden. This separation can be important when a therapeutic intervention causes blood flow changes or when the population is one for which blood flow declines significantly during a study.

Image Data Reconstruction and Postprocessing

The reconstruction and postprocessing steps need to conform with the specifications listed in their respective sections in the profile (Table 1). These tasks need to be consistent and not change from scan to scan, including the reconstruction algorithm (*68,69*).

Image Analysis

PET amyloid image analysis packages are complex and highly variable; several exist, both commercially and independently developed. Some approaches use a standard anatomic space and transform the PET amyloid data to this space, often using the subject's MR images to improve the transformation (*70*). Others segment the MR images in native space and apply the boundaries to a coregistered PET image. A widely used analysis is known as the centiloid pipeline (*60,61*), which has already addressed many standardization issues. To mitigate the variability of these packages and evaluate their conformance, a digital-reference-object (DRO) series of synthetic PET data was derived from human anatomy (*71*) and includes T1-weighted MRI. Users should use the DRO series (as per the DRO user's guide in appendix F of the profile) to verify correct implementation of volume-of-interest placement for both target and reference regions, SUVR calculations, PET alignment to standardized atlases (when applicable), system linearity, and system reproducibility. The DRO images can be downloaded at a published link (*72*), and appendix F in the profile explains the rationale behind the DRO and details the conformance process.

Since SUVR is a ratio of target to reference regions, the selection of an appropriate reference region is critical. Reference regions are not prescribed by the profile, but it is imperative that the same region be used across longitudinal studies, and it should be selected to minimize serial or longitudinal variability. For example, the cerebellar cortex can optimize sensitivity because this region typically lacks amyloid, but it can be more vulnerable to subject motion and technical noise given its position near the edge of the axial field of view of the detectors. The cerebellum is positioned in slices of the brain that are more inferior than those of most target amyloid regions. Since scanner sensitivity is not perfectly consistent across the axial field of view, changes in head positioning from one scan to the next, or changes in slice sensitivity, can cause changes in both the numerator (the target region) and the denominator (the reference region) of the amyloid SUVR that do not cancel out and therefore mimic amyloid burden changes. Regions including white matter or superior slices have been shown to reduce variability in radiopharmaceuticals such as ^{18}F-florbetapir (*6–8,66*). Caveats are that the kinetics of white matter can differ from those of the target gray matter, that significant changes in white matter disease or in white matter binding associated with therapeutic intervention may impact longitudinal stability (*73*), and that benefit may depend on the white matter binding characteristics of the radiopharmaceutical (*6–8,66*). Although the standard centiloid pipeline (*60,61*) (which uses the whole cerebellum as a reference region) is compatible with the claim assuming profile conformance is met, Bourgeat et al. (*74*) reported that when a composite reference region that included subcortical white matter was used in the centiloid pipeline analysis for ^{18}F-florbetapir longitudinal studies, higher consistency was achieved.

The target regions should be placed consistently. Larger regions (e.g., cortical average) should reduce variability in studies of large groups but can lose sensitivity if amyloid pathology is regionally restricted early in the disease course or in individuals with atypical presentations. Significant subject brain atrophy over serial scans may require region definition boundaries that minimize impact, aided by serial MRI, for the claim to be valid. Because PET scanners with higher resolution can tolerate more atrophy change, the reading physician will need to decide what level of atrophy can be tolerated on the basis of amyloid radiopharmaceutical reading experience and PET scanner resolution. Partial-volume correction for such issues is discussed in the profile but not specified in this version because of lack of a standardized technique and increased SUVR variability.

Image Interpretation and Reporting

How quantitative response is measured should be specified a priori by the imaging site and should conform with the profile. There is no profile specification for image interpretation, even if based on quantitative SUVRs, since conformance to the profile ensures SUVR precision only across serial PET ^{18}F-amyloid scans.

Image Quality Control

The profile provides a quality control section and appendices for ensuring that the equipment (e.g., dose calibrator), scanner, reconstruction, and postprocessing pass the listed specifications. Various common PET phantoms are used for testing and qualifying the PET scanner, and time schedules for checking scanner and equipment calibrations are also specified.

CONFORMANCE PROCEDURES

Definitions

It is important to define and distinguish the difference between QIBA conformance with a profile and other organizations' similar definitions.

Qualified. Qualified indicates formal approval of the imaging site by an appropriate body (e.g., the American College of Radiology Imaging Network, the Centers for Quantitative Imaging Excellence, the Society of Nuclear Medicine and Molecular Imaging Clinical Trials Network, and EARL [EANM Research GmbH], an imaging laboratory or imaging contract research organization) for a specific clinical research study.

Accredited. Accredited indicates approval by an independent body or group for broad clinical use (requires ongoing quality assurance and quality control); for example, by the American College of Radiology, the Intersocietal Accreditation Commission, and The Joint Commission.

Conformant. Conformant indicates that the imaging site and equipment meet all the requirements described by the profile to meet the QIBA profile claim.

The profile does specify that the site is either qualified or accredited, so it builds on these procedures. The "Conformance Procedures" section in the profile outlines the specifications in the format of performance assessment tables from an actor point of view:

Image Acquisition Site

The image acquisition site specifications cover appropriate imaging equipment calibration and quality control processes, proper training of the various site personnel, and compliant scheduling of subject scans.

PET Acquisition Device

The profile supports PET/CT and PET-only scanners with transmission rods (e.g., ^{68}Ge), both of which must acquire the PET data in 3-dimensional mode (e.g., septa should not be used). PET/MRI scanners are allowed if the repeatability of the SUVR 511-keV μ-maps (used for PET attenuation and scatter corrections) from these scanners is conformant with the assumptions underlying the claims.

Reconstruction Software

The PET data should be reconstructed with full corrections (e.g., for normalization, attenuation, scatter, randoms, decay, and dead time). If available, time of flight can be applied during the reconstruction, but if the point-spread-function filter is available it should not be used.

Image Analysis Workstation

The conformance of the image analysis workstation should be tested, as described in the "Image Analysis" section above.

Software Version Tracking

Software versions, phantom imaging performance data, upgrade versions, and the date that updates occurred should all be tracked at the site and preferably stored in the DICOM image header.

APPENDICES IN PROFILE

The profile contains several appendices:

A: Acknowledgments and attributions: lists the members of the QIBA amyloid PET biomarker committee and their affiliations.
B: Background information for claim: gives details of the meta-analysis that was done to derive the claim.
C: Conventions and definitions: explains the QIBA conventions used in writing profiles, and lists the definitions and abbreviations used in the profile.
D: Model-specific instructions and parameters: lists equipment (e.g., PET/CT scanners) and the type of quality assurance procedures that should be performed to properly maintain the equipment.
E: Data fields to be recorded in common-data-format mechanism: lists the metainformation that is necessary for quantitatively accurate PET SUVRs.
F: Testing of PET display and analysis systems with DRO: is as described in the "Image Analysis" section above.
G: Best practice guidance for Hoffman brain phantom: includes useful tips and tricks for filling the intricate Hoffman brain phantom, written by authors with extensive experience.
H: Detailed example of Hoffman phantom data analysis: explains the standard analysis used for qualifying PET scanners using data from the Hoffman brain phantom.
I: Kinetic modeling and comparison to SUVR: is as described in the "Image Data Acquisition" section above, which discusses the DVR.
J: Site checklist (appendix J): distills the various mitigations required by the profile into a list, organized by actor. This checklist is based on the questionnaire completed by multiple imaging sites during achievement of the technically confirmed stage. The checklist can provide a basis for imaging site qualification, to which other criteria can be added, depending on the study.

RELATIONSHIP TO OTHER STANDARDS

A site that is using the ADNI 2 or 3 protocol (*75*) is close to conforming with the profile (Table 4). The major differences are that the ADNI protocol does not specify accurate SUV or Bq/mL PET image quantification (and therefore lacks related specifications for information entry and equipment); does not specify an acceptable axial uniformity level (should be minimized for accurate serial SUVRs); does not specify how the subject should be positioned in the scanner (head should be centered and serial scans should have subject positioned as identically as possible to the previous scans); does not have a performance assessment for the Image Analysis Workstation; and does not make a claim about SUVR precision for the same subject scanned using the same scanner and protocol.

PROFILE STAGE

QIBA has a process committee that has adopted the stages of profile development as shown in Table 5. This profile has achieved stage 3—technically confirmed. Stages 4 and 5 can be achieved in the future as the profile is implemented and results are reported at more sites.

INFORMATION GAPS ADDRESSED BY GROUNDWORK PROJECTS

During writing of the profile, 3 major previously unknown sources of variability in SUVR were identified, and projects funded by grants from the RSNA in association with this working group were completed to characterize them: the impact of the different Image Analysis Workstation processing algorithms on SUVR (*71*); the impact of patient motion both between the CT and PET acquisitions and during the PET acquisition (*65*); and the impact of the PET reconstruction algorithm (*68,69*).

FUTURE DEVELOPMENTS

The profile can be updated to new versions, and proven technology and advances can be incorporated in the profile specifications. These include PET/MRI scanners (future versions may include specific requirements); partial-volume effect correction (e.g., for atrophy), once accepted and shown not to increase biomarker variability; potentially, body mass index (it is currently unknown how body mass index may affect the claim; studies are needed to determine whether wCV depends on body mass index and, if so, at what value of body mass index the claim is no longer valid); new PET ^{18}F-amyloid radiopharmaceuticals, as they become widely used; and pooling of different amyloid tracers (centiloids (*60,61*) may be able to achieve this goal).

TABLE 4
Differences Between Profile Specifications and ADNI 2 Protocol Specifications

Actor	Profile section for reference	ADNI 2 (*58*)
Site administrator	3.6.1.1: site accreditation/qualification maintenance	Same
Site administrator	3.6.2: imaging facility personnel	Same
Medical physicist	3.6.3: amyloid PET acquisition scanner	Same
Medical physicist	3.6.3.1.1: radionuclide calibrator	Same
Medical physicist	3.6.3.1.2: scales and stadiometers	Not required
Medical physicist	3.6.3.1.4: clocks and timing devices	Not required
Medical physicist	3.6.4.1: uniformity and calibration	Not required
Medical physicist	3.6.4.2: resolution	Same
Medical physicist	3.6.4.3: noise	Same
Medical physicist	3.6.4.4: amyloid PET specific phantom measurements	Same
Medical physicist	4.1: performance assessment: image acquisition site	Same
Technologist	3.1.3.1.2: radiopharmaceutical activity calculation or schedule	Dose structured report not required
Technologist	3.1.3.1.3: radiopharmaceutical administration route	Excludes saline flush and checking for infiltration
Technologist	3.2.1.1: timing of image data acquisition	Same
Technologist	3.2.1.2: subject positioning	Does not cover strict serial scan positioning
Technologist	3.2.1.3: scanning coverage and direction	Same
Technologist	3.2.1.4: scanner acquisition mode parameters: PET acquisition	Same except does not cover if scan is stopped and restarted
Technologist	3.2.1.4: scanner acquisition mode parameters: CT acquisition	Not required
Technologist	3.3.1: imaging data reconstruction	Same except point spread function is allowed
Image Analyst	4.4: performance assessment: image analysis workstation	Not required

A separate profile has been recommended for ^{18}F PET tau radiopharmaceuticals, with the profile serving as a starting base because of a similar workflow, including site qualification, phantoms, and equipment calibration; patient management during scans; sources of technical variability in measurement; image quality control; image processing alignment and spatial registration; and SUVR versus DVR.

The unique aspects of a tau-specific profile include a different set of radiopharmaceuticals and acquisition parameters; implications for clinical use; radiopharmaceutical-specific differences in the tau variants measured and in off-target binding; target regions, reference regions, and optimal measurement methods; radiopharmaceutical-specific differences; considerations in the longitudinal acquisition

TABLE 5
QIBA Profile Development Stages

Profile stages	Description
Public comment	Biomarker committee experts have drafted profile and believe it is practical and expect it to achieve claimed performance
Consensus	Wider community has read profile and judged it to be practical and expect it to achieve claimed performance
Technically confirmed	Several sites have performed profile and found it to be practical and expect it to achieve claimed performance (status of the profile)
Claim confirmed	Some sites have performed profile and found that it achieved claimed performance
Clinically confirmed	Many sites have performed profile and demonstrated claimed performance is widely achievable

time window related to equilibrium; and potentially greater bias in SUVR versus DVR.

PROFILE WRITING AND IMPLEMENTATION BARRIERS

There are several specific challenges in developing and implementing the profile.

First, the supported amyloid radiopharmaceuticals have different pharmacokinetics and vary in their image acquisition parameters, sensitivity, dynamic range, and manufacturer recommendations for measurement approaches (*76*). Including data from all supported amyloid radiopharmaceuticals and diverse members on the biomarker committee overcame this barrier.

Second, QIBA profiles have often used published literature as a basis for establishing the variability in the longitudinal claim. Most early amyloid PET studies used methods and scanners that can increase variability. Focus was placed on recommending methods and scanners that could be reasonably controlled and factored into the claim and on finding which references were applicable.

Another challenge was in deciding between full dynamic (DVR) and late-time-frame (SUVR) image acquisition. Although full dynamic acquisitions enable separation of amyloid measurement from blood flow, these long, labor-intensive protocols are not practical in many clinical settings and clinical trials. Therefore, the focus was late-time-frame SUVR, but an appendix was created to communicate the caveats of late-time-frame measurement and the potential benefits of full dynamic scans.

In addition, because of the lack of wide reimbursement for PET amyloid scans, the commercial availability of amyloid radiopharmaceuticals can be a barrier to clinical use. Antiamyloid treatments will be successful only on patients with biomarker-verified amyloid-positive tests, which may help drive reimbursement.

Finally, achieving profile conformance takes extra effort and training by the sites for routine clinical use. This implementation effort can be justified if PET amyloid imaging is required before and during expensive AD treatments or if extra reimbursement is given for quantitative PET amyloid imaging.

CONCLUSION

The QIBA amyloid profile provides recommendations for image acquisition, processing, and measurement approaches supporting a claim regarding technical variability in longitudinal amyloid measurement. This information can aid in the design of statistically powered clinical trials and in the assessment of longitudinal changes in the clinic. Although it is not QIBA's mission to enforce profile compliance or to govern the requirements of granting agencies, profiles can be used as a guideline for applicants and for reviewer assessments of proposed study designs, with the main objective of minimizing sample size. Given the recent market availability of antiamyloid therapeutics, and the importance of amyloid as an early biomarker in the diagnosis of AD, the profile recommendations can provide an important guide for the consistent, objective monitoring of disease progression and treatment response.

DISCLOSURE

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KEY POINTS

QUESTION: How can a PET amyloid imaging site decrease SUVR variability when performing longitudinal scanning of the same patient?

PERTINENT FINDINGS: Conforming with the QIBA PET amyloid profile can decrease the wCV (e.g., variability) to no more than 1.94%.

IMPLICATIONS FOR PATIENT CARE: As AD treatments improve, visual PET amyloid assessments become more ambiguous, and decreasing the PET SUVR variance may allow for earlier detection of β-amyloid plaques and more effective antiamyloid treatments.

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