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

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RSNA QIBA Profile for Amyloid PET

ABSTRACT

A standardized approach to acquiring amyloid PET images increases their value as disease and drug response biomarkers. The majority of ^{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's disease amyloid pathology. Minimizing technical variance allows precise, quantitative, standardized uptake value ratios (SUVRs) for early detection of aβ amyloid plaques and the effectiveness of anti-amyloid treatments to be assessed with serial studies. **Methods:** The Quantitative Imaging Biomarkers Alliance (QIBA) Amyloid PET Biomarker Committee developed and validated a Profile to characterize and reduce the variability of SUVRs, increasing statistical power for these assessments. **Results:** Upon achieving conformance, sites can justify a claim that brain amyloid burden reflected by the SUVR is measurable to a within-subject coefficient of variation (wCV) of ≤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's disease

INTRODUCTION

The preponderance of evidence indicates that cerebral aβ amyloid plaques are a necessary, but insufficient precursor of synaptic loss and cognitive impairment in Alzheimer's disease (AD). Because of its validation in comparison with postmortem examinations, PET imaging has come to play central role in definitive clinical diagnosis and in pharmaceutical clinical trials. It also has become adopted as the gold standard by which to judge CSF and plasma amyloid biomarkers. Amyloid PET status is incorporated into National Institute on Aging-Alzheimer's Association diagnostic criteria for AD and a critical component of the A/T/N classification in the Alzheimer's Disease Research Framework (*1,2*). Before amyloid PET was available, response to anti-amyloid treatment could only be surmised occasionally and inconclusively from postmortem studies (*3*). Assessing amyloid load measured as a continuous variable is now employed in nearly all anti-amyloid therapies in clinical development or the regulatory pipeline. There are several large multicenter AD observational studies and prevention trials where 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 measurement of tissue ratio quantification is now particularly germane. Notably, a first anti-amyloid immunotherapy (aducanumab) recently received Food and Drug Administration (FDA) accelerated approval based in part upon significant quantitative reduction amyloid PET pathology using amyloid PET, and additional anti-amyloid agents are progressing in clinical development (e.g. donanemab, lecanemab, and gantenerumab).

While 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 donanamab 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 be safely terminated.

Quantification also serves a role in both staging disease and predicting 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 and earlier in the disease process, amyloid levels more frequently fall into less visually obvious categories. Quantitative, objective methods can decrease the frequency that diagnostic assessments are ambiguous or indeterminate.

Many factors influence the reliability and repeatability of quantitative amyloid PET measures. While 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 timeframe, require minimized technical variance. In a clinical trial, minimizing technical variance in serial measures of amyloid load can have 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 standardized uptake value ratios (SUVR) made a difference in requiring 325 vs. 8,076 subjects per arm to measure a 25% reduction in the rate of accumulation over 12 months (*6*), consistent with other studies (*7-9*). While 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 upon 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, 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 similar process as the Integrating the Healthcare Enterprise (IHE) 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 requirement and quality control specifications. The Profile was designed for use both in clinical trials and 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 their ^{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 these reasonably implemented by community sites as well as advanced research sites. The Stage 3, Technically Confirmed QIBA Profile "18F-labeled PET tracers targeting Amyloid as an Imaging Biomarker" (provided as a supplement to this paper) overlaps and builds upon imaging protocols already used in observational studies and clinical trials. While 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 for objectively evaluating 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 with limited physics and instrumentation support and where technical expertise to recognize and address sources of variability may be lacking.

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, and 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 a vision for the future.

The Profile is available as an online supplemental file (*13-57*).

PROFILE STRUCTURE

The overall structure of the Profile is shown in Table 1. Context for the Profile is described, followed by the Claim that is the central focus of the Profile. Examples of clinical application 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 (IAW), Image Analyst, Imaging Facility Coordinator, Nuclear Medicine Physician and Medical Physicist. The mitigation specifications are listed in tables under each heading in the Profile, listing the actors 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 – these must be performed for the site to claim Profile conformance. Surrounding the tables is descriptive text that gives more explanation and examples. Some of the table entries are shaded in gray – these are not mandatory requirements but are suggested current and future requirements. See Table 2 for an example from the Profile.

THE 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 due to its logistical feasibility in multi-site trials, and its use in large reference studies such as the one supported by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (*58*). Due to 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*) and/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 ≤ 1.94%.**

The claim is equally valid when the measurand is centiloids (*60,61*) or distribution volume ratios (DVRs).

The within-subject coefficient of variation (wCV) is a statistical measure of precision. It describes the ability to obtain replicate measurements that agree with one another. It does not describe variability between subjects, but rather the variability within a subject when scanned at time points close enough such that no disease progression occurred. Statistically, it is defined as the standard deviation of replicate measurements on a subject, divided by the mean of those measurements. Ideally, wCV should be very small, i.e., as close to zero as possible.

The claim is only valid for longitudinal measurements and 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. While the Profile focuses on the SUVR measurement, the potential benefits of the DVR approach are discussed in detail as a Profile Appendix.

Application of the Claim

The wCV stated in the claim can be used to guide the number of subjects included in clinical trials targeting measurement of longitudinal change in amyloid SUVR. The amount of longitudinal change anticipated or targeted depends upon the study population disease stage as well as trial objectives. For example, the rates of change expected from an amyloid removing agent in a prodromal/mild trial with a high amyloid baseline burden may differ from a 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 a two-year period for a cohort of patients will be estimated. In order to estimate the mean accumulation within ±1% with 95% confidence, assuming mean SUVR values at baseline from 1.0-1.5 (note that this mean range is highly dependent on reference region used), no significant changes in perfusion between scans, and between-subject standard deviation (SD_B) ranging from 0.05 to 0.30, Supplemental Figure 2 from the Profile (*11*) shows the number of subjects required for three different correlation coefficient values r between paired measurements from a subject.

Note that the number of subjects required is reduced as r increases between scan-visits. For example, an internal analysis of florbetapir data, available through ADNI, at baseline and year two 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 values were 0.79 and 0.83, respectively, for amyloid positive subjects and 0.33 and 0.48, respectively, for subjects close to positivity threshold.

As a second example, consider a clinical trial comparing the accumulation in amyloid SUVR over time between two groups of subjects: those undergoing a new treatment vs. a control group. Alzheimer's 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 two years later. The null hypothesis is that there is no difference in subjects' mean amyloid accumulation between the two groups; the alternative hypothesis is that there is a difference (two-tailed hypothesis). Obuchowski et al (*62*) reported the sample size needed to detect a 50% reduction in the rate of accumulation over a 2-year period with 80% power based on the assumed wCV of 1.94%. Fewer than 100 subjects were needed per groups, assuming a homogenous patient sample with low between-subject variability. Additionally, reducing the measurand variance will help when patient-level correlations of amyloid burden reduction to cognitive changes are desired.

Derivation of the Technical Performance Claim

The technical performance claim was derived from a meta-analysis of published data of the repeatability of amyloid PET imaging under two 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 two serial scans were acquired within periods of less than 60 days (*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 to those acquired after a two-year period, a typical clinical trial duration (*6,7*). Since amyloid accumulation is unlikely to occur in a majority (though not all) of 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 two-year duration in amyloid negative normal controls from the ADNI data set ranged from 1.25% (white matter reference region) to 1.6% (whole cerebellum reference region) and in one case up to 3.38% (whole cerebellum reference region, with a different cerebellum boundary definition) (*6,7*). In these published studies, the mean and standard deviation of the longitudinal change were shown in a table and the ADNI data acquisition protocol (*58*) was used to acquire the data, which in many respects, is consistent with this Profile (see Relationship to Other Standards Section below). The wCV cited in the claim of 1.95% is the highest of the test-retest studies that occurred within a four-week period from first studies and also satisfies the range of 1.25% to 1.6% reported in all but one two-year study. Conformance to the claim depends upon many factors as listed below and in the Profile. In particular, the choice of the reference region can greatly impact wCV due to the sensitivity of different regions to technical factors. It is important to note that the wCV was less than 1.94% across these two-year studies only when reference regions incorporating subcortical white matter were used. However, additional QIBA-sponsored studies performed during the development of this Profile identified controls to reduce variability when using reference regions such as the cerebellum (*65*). This and related contributors to variance are described further below (*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 PiB (*67*), the Profile was developed using data from the ^{18}F amyloid radiopharmaceuticals listed in Table 3, and therefore only these radiopharmaceuticals conform to the Profile. That said, there are no technical limitations that prevent the Profile to be extended to ^{11}C PiB,

but its clinical use is limited since there is no FDA approval and it requires an on-site cyclotron. 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 FOV and the subject's head and cerebellum to minimize the slice-to-slice variability due to non-uniform 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 images within-subject 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 time frames assessed for head movement since significant head motion is a known source of quantitative error in PET (*65*). It is ideal for each PET image time frame to be co-registered with the CT image prior to performing attenuation and scatter correction. If this is not possible, removal of selected frames or exclusion of the scan should be considered if motion exceeds 4 mm or 4 degrees (*65*). If the patient movement is less, then post-reconstruction motion correction where all emission time frames are aligned to one another prior to creating a single averaged image can reduce variability due to patient motion. 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 for 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 physiological modeling techniques. The parametric 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 can be important in cases where a therapeutic intervention causes blood flow changes, or for populations that decline significantly in blood flow over the duration of a study.

Image Data Reconstruction and Post-processing

The reconstruction and post-processing steps need to be conformant to the specifications listed in their respective sections in the Profile (see 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, and several exist both commercially and independently developed. Some approaches use a standard anatomical space and transform the PET amyloid data to this space, often using the subject's MRI to improve the transformation (*70*). Others segment the MRI in native space and apply the boundaries to a co-registered 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 based on human anatomy (*71*) and includes a 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 VOI 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 the link in reference (*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 appropriate reference region is critical (as noted above). Reference regions are not prescribed by the Profile but it is imperative that the same region is used across longitudinal studies, and should be selected to minimize serial or

longitudinal variability. For example, cerebellar cortex can optimize sensitivity as it is typically absent of amyloid, but it can be more vulnerable to subject motion and technical noise given its position near the edge of the axial FOV 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 denominator (the reference region) of the amyloid SUVR that do not cancel out, and therefore mimic amyloid burden changes. Regions including white matter and/or superior slices have been shown to reduce variability in radiopharmaceuticals such as florbetapir (*6-8,66*). Caveats are that the kinetics of white matter can differ from those of the target gray matter, significant changes in white matter disease or in white matter binding associated with therapeutic intervention may impact longitudinal stability (*73*), and benefit may depend upon white matter binding characteristics of the radiopharmaceutical (*6-8,66*). While 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 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 very 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. PET scanners with higher resolution can tolerate more atrophy change, so the reading physician will need to decide what level of atrophy can be tolerated based on amyloid radiopharmaceutical reading experience and PET scanner resolution. Note that partial

volume correction for such issues is discussed in the Profile but not specified in this version due to 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 to the Profile. There is no Profile specification for image interpretation, even if based on quantitative SUVRs, since conformance to the Profile only ensures SUVR precision 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 post-processing pass the listed specifications. Various commonly used 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

It is important to define and distinguish the difference between QIBA conformance to a Profile and other organization's similar definitions:

- Qualified: the imaging site is formally approved by an appropriate body (e.g., American College of Radiology Imaging Network, Centers for Quantitative Imaging Excellence, Society of Nuclear Medicine and Molecular Imaging-Clinical Trials Network, European Association of Nuclear Medicine - Research GmbH, an imaging laboratory or imaging contract research organization) for a specific clinical research study
- Accredited: approval by an independent body or group for broad clinical usage (requires ongoing quality assurance/control) e.g., American College of Radiology, Intersocietal Accreditation Commission, and The Joint Commission

- Conformant: the imaging site and equipment meet all the requirements described by the Profile, which are necessary to meet the QIBA Profile claim

Please note that 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

This Profile supports PET/CT and PET only scanners with transmission rods (e.g., ^{68}Ge), both of which must acquire the PET data in 3D mode (e.g. septa should not be used). PET-MR scanners are allowed if the repeatability of the SUVRs 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 (i.e., normalization, attenuation, scatter, randoms, decay, dead-time, etc.) If available, time of flight (TOF) can be applied during the reconstruction, but the point spread function (PSF) filter should not be used if available.

Image Analysis Workstation

The conformance of the image analysis workstation should be tested, please see Image Analysis Section above.

Software Version Tracking

Software versions, phantom imaging performance data, upgrade versions and date they 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: Acknowledgements 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

- Series of Tables that lists equipment (e.g., PET/CT scanners) and the type of Quality Assurance procedures that should be performed in order to properly maintain the equipment

E: Data fields to be recorded in Common Data Format Mechanism

- Lists the meta-information that is necessary for quantitatively accurate PET SUVRs.

F: Testing PET display and analysis systems with Digital Reference Object (DRO)

- See Image Analysis Section above

G: Best Practice Guidance for Hoffman Brain Phantom

- Very 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

- See Image Data Acquisition Section above that discusses the DVR

J: Site Checklist

- The Checklist provided as Appendix J distills the various mitigations required by the Profile into a list, organized by actor. It is based upon the Questionnaire that was completed by multiple imaging sites in the process of achieving the Technically Confirmed stage. The checklist can provide a basis for imaging site qualification, to which other criteria can be added depending upon the study.

RELATIONSHIP TO OTHER STANDARDS

A site that is using the ADNI 2 or 3 protocol (*75*) is very close to conforming to this Profile (see Table 4). The major differences are that the ADNI protocol:

- does not specify accurate SUV or Bq/mL PET image quantification; therefore, related specifications for information entry and equipment are not present
- does not specify an acceptable axial uniformity level (should be minimized for accurate serial SUVRs)
- does not specify how subject should be positioned in scanner (head should be centered and serial scans should have subject positioned as identical as possible to the previous scans)
- does not have a performance assessment for the IAW

- 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 could be achieved in the future as the Profile is implemented and results are reported at more sites.

INFORMATION GAPS ADDRESSED BY GROUND-WORK PROJECTS

During the writing the Profile, three major unknown sources of variability on the SUVR were identified and projects funded by grants from the RSNA in association with this working group were completed to characterize them:

1. The impact of the different IAW processing algorithms on the SUVR (*71*).
2. The impact of patient motion both between the CT acquisition and during the PET acquisition (*65*).
3. 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-MR scanners: future versions may include specific requirements.
- Partial volume effects correction (e.g., for atrophy): once accepted and shown not to increase biomarker variability.
- It is currently unknown how body mass (BMI) may affect the claim. Studies should be undertaken to determine if there is a dependence of wCV on BMI, and if so, at what value of BMI is the claim no longer valid.

- New PET ^{18}F amyloid radiopharmaceuticals: as they become widely used.
- Extend claim to pooling of different amyloid tracers: centiloids (*60,61*) may be able to achieve this goal.

A separate Profile has been recommended for ^{18}F PET tau radiopharmaceuticals with this Profile serving as a starting base due to similar workflow, including:

- Site qualification, phantoms, and equipment calibration
- Patient management during scan
- Sources of technical variability in measurement
- Image quality control
- Image processing alignment and spatial registration
- SUVR vs. DVR

The unique aspects for a Tau-specific Profile are:

- 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 longitudinal acquisition time window related to equilibrium
- Bias in SUVR vs. DVR may be larger

PROFILE WRITING AND IMPLEMENTATION BARRIERS

Specific challenges in developing and implementing the Profile were/are:

1. The supported amyloid radiopharmaceuticals have different pharmacokinetics, and vary in their image acquisition parameters, sensitivity, dynamic range, and differences in

manufacturer recommendations for measurement approaches (*76*). Including data from all supported amyloid radiopharmaceuticals and diverse members on the biomarker committee overcame this barrier.

2. QIBA Profiles have often used published literature as a basis for establishing the variability in the longitudinal claim. The majority of 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 which references were applicable.
3. Deciding between full dynamic (DVR) versus late time frame (SUVR) image acquisition. Although full dynamic acquisitions enable the 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.
4. Due to lack of wide reimbursement for PET amyloid scans, the commercial availability of amyloid radiopharmaceuticals can be a barrier to clinical use. Anti-amyloid treatments will only be successful on patients with biomarker-verified amyloid positive tests, which may help drive reimbursement.
5. 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 extra reimbursement is given for quantitative PET amyloid imaging.

CONCLUSIONS

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 be used to aid in the design of statistically powered clinical trials and in the assessment of longitudinal change in the clinic. While it is not QIBA's mission to enforce Profile compliance or to govern the requirements of granting agencies, Profiles could 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 anti-amyloid therapeutics, and the importance of amyloid as an early biomarker in the diagnosis of Alzheimer's disease, the Profile recommendations can provide an important guide for the consistent, objective monitoring of disease progression and treatment response.

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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 to the QIBA PET Amyloid Profile can decrease the within-subject coefficient of variation (e.g. variability) to ≤ 1.94%.

IMPLICATIONS FOR PATIENT CARE:

As Alzheimer's treatments improve, visual PET amyloid assessments become more ambiguous and decreasing the PET SUVR variance may allow for earlier detection of aβ amyloid plaques and more effective anti-amyloid treatments.

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TABLES

TABLE 1. High level outline of the Profile.

Executive Summary
Overview
Summary for clinical trial use
Intended audiences
Clinical Context and Claims
Claim
Considerations for claim
Clinical trial utilization
Profile Activities
Subject handling
Image data acquisition
Image data reconstruction and post-processing
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. Only the white rows are mandatory for Profile conformance, while the gray row is recommended and may be mandatory in future Profile updates.

Parameter	Entity/Actor	Specification
PET Scanner Calibration	Technologist	Shall perform daily/weekly/monthly scanner QA and vendor recommended maintenance procedures (e.g., replace weak transmission sources for dedicated PET scanner); ensure that output values are acceptable and manually enter on form/electronic database
PET Scanner Calibration Constancy Check	Technologist	Shall perform constancy phantom (e.g., Ge-68 cylinder) scan (preferably NIST traceable or equivalent to gather information regarding uniformity as well) at least weekly and after each calibration.
Radionuclide Calibrator	Physicist	Calibrated to ^{18}F using NIST traceable source or equivalent either by site or calibrator manufacturer.

TABLE 3. List of ^{18}F amyloid radiopharmaceuticals and their recommended dose, uptake time and acquisition duration as per their respective US package insert. *(Note that there might be some slight variations in package insert depending on the country of approval.)*

Parameter	Florbetapir (Amyvid®) (*77*)	Flutemetamol (Vizamyl®) (*78*)	Florbetaben (Neuraceq®) (*79*)	NAV4694 (*80*)
Admin Activity	370 MBq Max 50 μg mass dose	185 MBq Max 20 μg mass dose	300 MBq Max 30 μg mass dose	300 MBq
Uptake Time (mpi = mins post inj)	30 – 50 mpi	90 - mpi	45 - 130 mpi	50 – 70 mpi
Acquisition Duration	10 min	20 min	15 – 20 min	20 min

TABLE 4. The differences between the Profile specifications and the ADNI 2 protocol specifications.

Actor	Profile Section for Reference	ADNI 2 (58)
Site Admin	3.6.1.1 Site Accreditation/Qualification Maintenance	Same
Site Admin	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 and/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 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 (PSF) is allowed
Image Analyst	4.4 Performance Assessment: Image Analysis Workstation	Not required

TABLE 5. QIBA Profile development stages.

Profile Stages	Description
1 Public Comment	The Biomarker Committee experts have **drafted the Profile** and believe it is practical and expect it to achieve the claimed performance.
2 Consensus	The wider community has read the Profile and **judged it to be practical** and expect it to achieve the claimed performance
3 Technically Confirmed	Several sites have **performed the Profile and found it to be practical** and expect it to achieve the claimed performance (status of this Profile).
4 Claim Confirmed	Some sites have performed the Profile and **found it achieved the claimed performance**
5 Clinically Confirmed	Many sites have performed the Profile and demonstrated the **claimed performance is widely achievable**.