QIBA PET Amyloid Biomarker Committee: Overview and 2018 Update

Dawn C. Matthews[1], Satoshi Minoshima[2], Anne M. Smith[3], Eric S. Perlman[4], Kevin O'Donnell[5], Rachid Fahmi[3], Tammie Benzinger[6], Ronald Boellaard[7], Christopher Buckley[8], Santi Bullich[9], Susan M. DeSanti[9], John M. Hoffman[2], Paul E. Kinahan[10], Greg Klein[11], Adriaan Lammertsma[12], Martin A. Lodge[13], Nancy Obuchowski[14], Rathan Subramaniam[15], John J. Sunderland[16], Jean-Luc Vanderheyden[17], Richard Wahl[6]

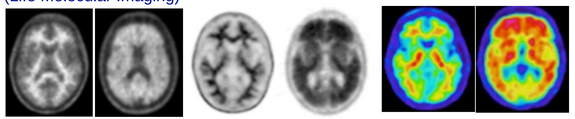
[1]ADM Diagnostics, [2]University of Utah, [3]Siemens Medical Solutions USA, Inc., [4]Perlman Advisory Group, [5]Canon Medical Research USA, [6]Washington University Mallinckrodt Institute of Radiology, [7]University of Groningën, [8]GE Healthcare, [9]Life Molecular Imaging, [10]University of Washington,[11]Roche, [12]VU Medical Center, [13]Johns Hopkins School of Medicine, [14]Cleveland Clinic Foundation, [15]UT Southwestern, [16]University of Iowa, [17]JLVMI Consulting

Quantitative Imaging Biomarkers Alliance — RSNA

Amyloid Imaging Importance in clinical trials and patient care

Beta amyloid plaques are a hallmark of Alzheimer's disease, accumulating years prior to symptom onset. Fibrillar amyloid can be measured using PET and there are now three FDA approved ^{18}F tracers, while ^{11}C-PIB is still used for research in some centers. A negative amyloid scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition. A positive amyloid scan is consistent with the presence of amyloid pathology.

Florbetaben (Life Molecular Imaging) — Florbetapir (Lilly/Avid) — Flutemetamol (GE)



Negative Positive Negative Positive Negative Positive

Amyloid imaging is a critical part of many clinical trials as:

- An inclusion criterion, confirming presence of AD pathology
- An endpoint, particularly for anti-amyloid therapeutics

In patient care, the IDEAS study (www.ideas-study.org) has demonstrated in 3,979 participants that amyloid imaging changed medical management in 67.8% of MCI patients and 65.9% of dementia patients.

The impact of quantitative methods

With accumulation rates averaging 1 to 3% per year, changes in amyloid burden over the duration of a clinical trial can only be measured using quantitative methods. However, measurement is influenced by many technical factors beyond amyloid, as illustrated below.

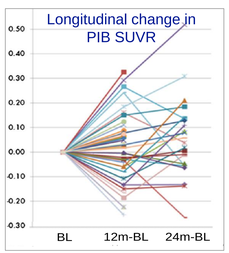


Table: The impact of reference region on the number of Aβ+ MCI subjects required to detect a 25% reduction in (i) amyloid accumulation rate over 12 months or (ii) amyloid burden (from Chen K et al, 2015)

Reference region	(i) Number required	(ii) Number required
White matter	325	13
Pons	2,718	109
Cerebellum	8,076	324

Figure: Erratic changes in PIB SUVR from baseline at 12 and 24 months in ADNI MCI subjects, often due to technical factors (from Schmidt M et al, 2012)

Amyloid PET Profile Scope

- Focus on late timeframe period when the tracer has come to "pseudo-equilibrium", during which a **Standardized Uptake Value Ratio** (SUVR: target region mean value / reference region mean value) is calculated
- Limitations of SUVR and potential benefits of **full dynamic modeling** are also described.

Profile Claim and Clinical Context

Technical Performance Claim: Brain amyloid burden as reflected by the SUVR is measurable from ^{18}F amyloid tracer PET with a within-subject coefficient of variation (wCV) of <=1.94%.

Claim is to be interpreted in the context of considerations stated in the profile, including reference region selection. Contextual examples are provided to illustrate the practical application of the profile, as in determining number of subjects required for a trial.

Profile Activities and Guidelines

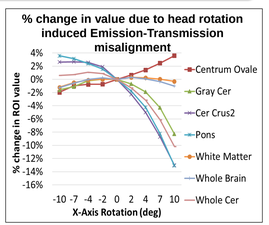
The profile identifies critical factors and recommendations impacting test-retest variability at each stage in image acquisition, processing and analysis, with highlights summarized here.

SUBJECT HANDLING

- **Tracer preparation, amount injected, and injection time window** should be consistent and according to manufacturer label
- **Subject positioning** should ensure complete brain coverage, distanced from edge of scanner field of view, with subject comfortable and firmly secured to prevent head motion.

IMAGE ACQUISITION

- **Same** scanner should be used to acquire serial images within-subject.
- **Time window:** Same post-injection time window should be used for all scans.
- **Subject motion: Major contributor to error,** must minimize motion within and between emission and transmission scans.
- **Frames:** Multiple timeframes should be used (<= 5 min. each) to enable realignment if subject motion occurs.



Misalignment between emission and transmission scan can cause error of a few to many percent

IMAGE RECONSTRUCTION AND POST PROCESSING

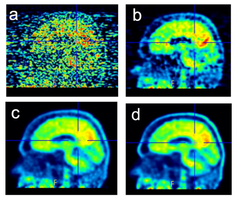
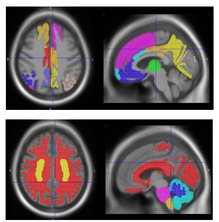


Image reconstructed using (a) FBP 0mm smooth; (b) FBP 5mm; (c) OSEM 4i24s 5mm; (d) OSEM+PSF 4i24s 5mm.

- **Same reconstruction method and parameters** should be used, as based on a QIBA groundwork project, within-subject regional changes can exceed 10%, lower when cortical average is used
- **Emission – Transmission scan alignment** is critical as differences can introduce several percent error as quantified in a QIBA groundwork project
- **Intra-scan inter-frame motion correction** is important to avoid variability due to motion induced tissue misalignment

IMAGE ANALYSIS

- **Co-registration and warping** must be consistent with goodness of fit verified; serial PET to PET co-registration can provide greater alignment, reducing variability
- **Reference region should be selected to minimize longitudinal variability**. Cerebellar cortex can optimize sensitivity but can be vulnerable to scanner noise and subject motion, and its low z-axis location relative to target regions can create longitudinal error from scanner axial variability. Regions including white matter and/or superior slices can reduce variability (florbetapir studies).
- **Target regions** must be placed consistently. Use of a cortical average can reduce variability. Atrophy rate may influence measurement.



Example regions of interest (top) and reference regions (bottom).

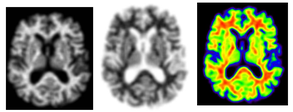
QUALITY CONTROL

The Quality Control section and Appendices provide guidelines on procedures such as phantom imaging to ensure equipment and site quality, and examples of results.

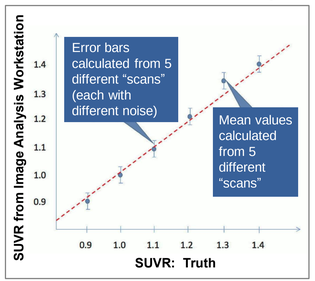
Conformance Testing

The Conformance Testing section of the Profile specifies performance criteria and evaluation methods to ensure that an imaging site, equipment, and analysis workstation/software meet the requirements described in the Profile as necessary to meet the QIBA Profile claim.

A Digital Reference Object (DRO) has been developed through a QIBA Groundwork Project to enable testing of image workstation software linearity and repeatability, and in the future can be used to test accuracy.



Representative slice from Amyloid DRO displayed with color schemes for florbetaben, florbetapir, and flutemetamol. Right: DRO enables testing of a given image analysis software at 6 intensity levels, each with 5 simulated noise levels.



Amyloid PET Profile Development Status

Profile Drafted → Public Comment → Consensus Stage → Technically Confirmed → Claim Confirmed

Public review and incorporation of comments into the profile have been completed, achieving Consensus Stage. The profile is now in the Technical Confirmation process.

Next steps

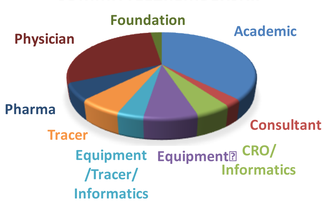
- Survey sites for implementation feasibility
- Incorporate site feedback

Potential Version 2 Expansion

- Accuracy (cross-sectional) claim
- Expanded guidelines: Centiloid, partial volume correction

Amyloid Biomarker Committee

COMMITTEE MEMBERSHIP



How to be involved

- Monthly calls
- Annual meeting at RSNA
- Profile review and input
- Profile testing
- Profile implementation

For more information, visit http://qibawiki.rsna.org

Various QIBA projects and activities have been funded in whole or in part with Federal funds from the National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, Department of Health and Human Service, under Contracts Nos. HHSN268201000050C, HHSN268201300071C and HHSN268201500021C.