QIBA PET Amyloid Biomarker Committee: Overview and 2016 Update

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Quantitative Imaging Biomarkers Alliance — RSNA

Alzheimer's Disease

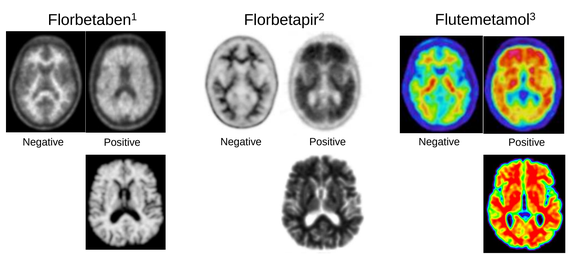
Overview & Facts

- Alzheimer's disease (AD) is a type of dementia which manifests as progressive cognitive and behavioral problems.
- Of the estimated 5.3 million Americans with AD, most patients are 65 or older.
- Barring breakthroughs to prevent or cure the disease, 7.1 million Americans aged 65 or older will be affected by 2025.
- AD is the sixth leading cause of death in the U.S.; it is the only one of top 10 causes of death that cannot be prevented, cured or even slowed at this time.
- There have been significant advances in the scientific understanding of the pathophysiology of the disease, but there is yet much to learn.
- Pathologic hallmarks of the disease include extracellular beta-amyloid (AB) plaque formation and neurofibrillary tangles associated with hyperphosphorylated tau protein.

Amyloid-PET Tracers

Image Display

Three ^{18}F-radiotracers are currently approved for amyloid clinical imaging to estimate β–amyloid neuritic plaque density in adults with cognitive impairment being evaluated for AD. In clinical practice, images are interpreted using visual qualitative criteria by physicians certified based on specific training requirements. There is a specified image display unique to each of the approved radiotracers as shown in the top row below; images are taken from the specific tracer's label.



The lower row of images shows a representative slice from version 1.0 of the Amyloid Digital Reference Object with image display using the color scheme for each of the radiotracers above it.

1. Piramal Imaging SA (2014). Neuraceq (Florbetaben F 18 Injection): Prescribing Information. Matran, Switzerland
2. Eli Lilly (2012). Amyvid (Florbetapir F 18 Injection): Prescribing Information. Indianapolis, IN
3. Vizamyl (Flutemetamol F 18 Injection): Prescribing Information. Manufactured for GE Healthcare by Medi-Physics, Inc. Arlington Heights, IL

Profile Status

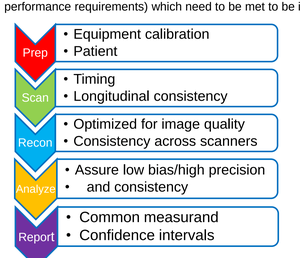
For the amyloid-PET Profile, the current longitudinal claims address assessment of the change in beta amyloid deposition in the brain.

Claim 1: A measured change in SUVR of Δ % indicates that a true change has occurred if Δ > 8 %, with 95% confidence.
Claim 2: If Y1 and Y2 are the SUVR measurements at two time points, then the 95% confidence interval for the true change is (Y2-Y1) ± 1.96 × √([Y1 ×0.043]^2+[Y2 ×0.043]^2).

The clinical utility for this fit-for-purpose is to assess the efficacy of a therapeutic intervention as distinct from biologic age-relevant change. Consequently, the goal is to confidently define a threshold measure of change (primarily reduction) which indicates therapeutic efficacy. A future goal is to describe a cross-sectional discriminatory claim to support a surrogate quantitative imaging biomarker distinguishing subpopulations of patients with a disease associated with abnormal beta amyloid deposition (particularly Alzheimer's disease) from patients without evidence of such deposition with greater confidence and reproducibility than achieved with qualitative assessment. This requires further work on defining and assessing bias.

Workflow & Technical Requirements

The Profile addresses each of the tasks in the workflow from technical requirements of the PET scanner and the process at the imaging facility to preparing for and performing the amyloid PET exam to the analysis and interpretation component. Below and to the left is a time sequenced presentation (top to bottom) of the workflow tasks to which technical specification thresholds are set by the Profile. To the right are some example activities (for which there are specific performance requirements) which need to be met to be in conformance with the Profile.



- ✓ **Quality control diligence**
- ✓ **Correct subject positioning**
- ✓ **Head stabilization to minimize motion**
- ✓ **Apply all quantitative corrections during image recon**
- ✓ **Use standardized reference objects to assess workstation conformance**
- ✓ **Evaluate image registration; re-align or exclude data as necessary**
- ✓ **Ensure correct ROI placement to target and reference regions**

Amyloid Profile Overview & Issues

Decisions made for first version of the Profile:
- Same scanner, same analysis tool and same radiotracer across time points as requirement
- Includes use of PET/CT and in line PET; not PET/MR
- Measurand is change in SUVR
- Phantom scanning requirement includes use of anthropomorphic phantom (e.g., Hoffman) to assess gray/white matter distinction
- No partial volume correction to be used
- Across radiotracer requirements defined generally, with radiotracer specific requirements where needed

New Committee decisions & updates (2016):
- Changes in intra-subject cerebral perfusion: Developed informative text to raise awareness of this concern; currently no technical requirement or conformance methodology to assess quantitatively
- Assessing & addressing head motion: Incorporated findings based on 2016 groundwork project

Open Items under active discussion and for Public Comment:
- Developing Conformance methodology for image analysis workstations using 'in development' enhanced series of Digital Reference Objects (DROs)

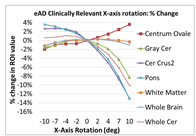
2016 Groundwork Projects

Analyses to Support Profile Development

Objectives:
- Quantify the impact of misalignment between emission (Em) and transmission (Tx) scans upon measured cortical average SUVR
- Quantify the effect of reference region and target region definition upon measured SUVR

Key Findings:
- Misalignment between Em and Tx scans during attenuation correction (AC) can have a significant impact upon measured amyloid values, varying with direction and worsened with combined translation and rotation.
- The effects of misalignment were in most cases relatively modest until 4 mm translation or 4 degrees rotation, but increased rapidly as misalignment increased.

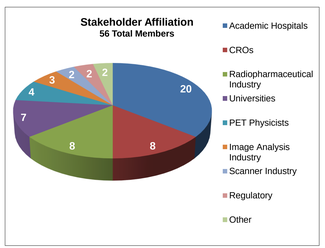
- Certain target ROIs were more vulnerable to error, including superior frontal cortex, frontal pole, orbitofrontal gyrus and rostral anterior cingulate.
- Certain reference regions were more vulnerable to error; cerebellum and pons were more error-prone than white matter.



- The majority of error in the "Clinically Relevant" case is due to embedded attenuation correction error, not realignment.
- The error introduced by misregistration of image to template (alignment to ROI) can be substantial, even without Em-Tx alignment error; particularly beyond 2 mm or 2 degrees of misregistration.

Consideration for Longitudinal Profile Claim:
If using a single threshold for all forms of misalignment and all regions, image frames with misalignment of Em and Tx exceeding 4 mm or 4 degrees should be excluded. Alternatively, realignment on a frame-by-frame basis of Em and Tx scan prior to AC is advised.

Amyloid PET Biomarker Committee



The Amyloid PET Biomarker Committee is composed of volunteers who work together in a pre-competitive, international forum. The current composition of the of the group is indicated by stakeholder category in the accompanying graphic. Membership is open to qualified and interested individuals. Questions or comments about QIBA or regarding material on this poster should be addressed to qiba@rsna.org

Planned Activities 2017

Profile: Writing the Profile has been the Amyloid PET Biomarker Committee's (BC) primary activity to date. The document is undergoing final BC review after which it will be released for public comment. Each suggested revision will be addressed by the BC and resolved. The committee's goal is to provide a published Profile by 4Q2016 with a Public Consensus version by 1Q2017.

Checklist: Each of the performance requirements in the Profile is being compiled as a checklist. This list will serve as a tool whereby an imaging site can be evaluated for conformance with the Profile.

Feasibility Testing: The checklist can also be used as a quality control tool to assess the ability (or practicality/willingness) of a site to perform each of the Profile's performance specifications. The results of this feasibility test will then be used to streamline and tighten the Profile performance requirements. Subsequently, it is envisioned that an organizational effort will support this qualification process built around checklists in turn based on the Profile.

Project Title Primary Investigator	Project Summary
Quantification of reconstruction method impact on measured amyloid load **PI: Dawn Matthews, MS, MBA** **ADM Diagnostics LLC**	This project will quantify the impact of reconstruction on brain amyloid measurement and develop recommendations for reconstruction method and ROI definition based upon amyloid quantification objectives. The project will use a comprehensive set of scans that can be systematically reconstructed using numerous algorithms and parameters. In addition to ROI analysis, the team will employ an advanced multivariate machine learning platform to characterize differences between reconstruction methods.
Development of digital phantom for software and validation **PI: Paul Kinahan, PhD** **University of Washington**	This project will create a series of digital reference objects (DROs) or digital amyloid phantoms to support efforts to better characterize the quantitative measurement of amyloid imaging agents for PET. This is the second phase of a project; prototype digital and physical phantoms were constructed in the first phase. Many suggestions for improvements were listed in the final report for the first project. In this second phase, lessons learned from the first project will be extended to result in the implementation of a series of amyloid DROs simulating an range of anatomical variants, with an array of amyloid distributions.

QIBA in context of other activities

Efforts by the QIBA Amyloid PET BC complement the work of other consortia and collaborative efforts, including:

· The Alzheimer's Disease Neuroimaging Initiative (ADNI): A longitudinal multi-site study of imaging and other biomarkers as related to Alzheimer's disease and its progression from preclinical through dementia phases. The data and analyses from ADNI have helped to provide an understanding of amyloid accumulation rates and factors influencing reliable amyloid measurement

· The Coalition Against Major Diseases (CAMD): A program of the Critical Path Institute, which is a public-private partnership that works with regulatory agencies (FDA, EMA) to achieve qualification of imaging and other biomarkers for use in clinical trials. CAMD is aimed at creating new tools and methods that can be applied to increase the efficiency of the development process of new treatments for Alzheimer's disease and related neurodegenerative disorders

· The Centiloid Project: An initiative to create a common measurement scale for different amyloid tracers and measurement methods that otherwise would produce different numeric measures of amyloid burden

· The IDEAS trial (Imaging Dementia—Evidence for Amyloid Scanning). A $100 million multi-site study for more than 18,000 patients with mild cognitive impairment or dementia of uncertain origin that is being funded by the Centers for Medicare and Medicaid Services (CMS) to assess the impact of diagnostic amyloid imaging upon patient outcomes, to support possible reimbursement by Medicare and other third party payors

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