QIBA PET Amyloid Biomarker Committee: Overview and Status Update

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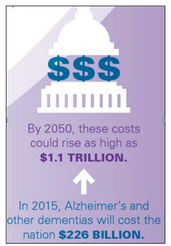
Quantitative Imaging Biomarkers Alliance — RSNA

Alzheimer's Disease

Facts & Societal Impact

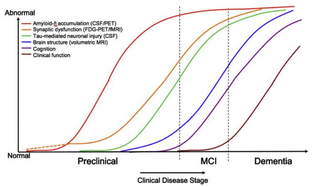


From Alzheimer's Association
www.alz.org

Alzheimer's disease (AD) is a type of dementia which involves progressive cognitive and behavioral problems.
Of the estimated 5.3 million Americans with AD, an estimated 5.1 million are age 65 or older. Almost two-thirds of Americans with AD are women. Barring medical breakthroughs to prevent or cure the disease, the number of people age 65 or older affected with the disease will be 7.1 million Americans by 2025. Alzheimer's is the sixth leading cause of death in the U.S.; it is the only disease among the 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.

Imaging Biomarkers

Further investigations are needed to better understand the relationship between beta amyloid (and tau) deposition in the brain relative to the clinical symptoms of AD. Critical to these investigations is the use of biomarkers to assess the natural history of the disease as well as to assess the effect of therapies to prevent or slow disease incidence and progression.

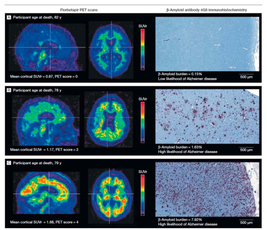


Imaging of Alzheimer's Disease has been directed at changes in brain anatomy (global and regional), glucose metabolism, cerebral perfusion and neurochemistry (neurotransmitters, receptors, and enzymes), as well as deposition of abnormal proteins. There are currently three FDA approved F18 labelled amyloid tracers with additional candidate radiotracers under investigation.

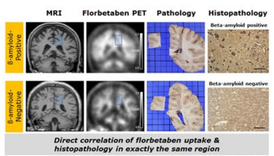
R. Sperling, P. Aisen, L. Beckett et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011 May; 7(3): 280-292

Amyloid Imaging - Histopathology

A: Florbetapir (FBP)



B: Florbetaben (FBB)



Histopathology studies show the relationship between amyloid imaging (shown with FBP (A) and FBB (B)) and β-amyloid pathology, supportive that this imaging technique can reliably detect or exclude amyloid pathology.

RSNA 2015

Profile Status

Amyloid Profile for Quantitative PET

The Profile addresses each of the tasks in the workflow from technical preparedness 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 is an outline of some specific items applicable to the Amyloid Profile.

- **Prep**
  - Equipment Calibration
  - Patient
- **Acquisition**
  - Timing
  - Longitudinal Consistency
- **Reconstruction**
  - Optimized for Image Quality
  - Consistency across scanners
- **Analysis**
  - Assure accuracy and consistency
- **Reporting**
  - Common measurand
  - Statistical significance

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

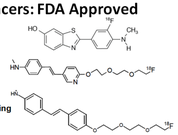
Items under active committee discussion:
- How to address the contribution of intra-subject cross time point cerebral perfusion differences to SUVR changes
- Where to find common requirements for all radiotracers versus where tracer specific requirements should be allowed
- How to define performance requirements and quality assurance methodology to assess head motion

β-Amyloid radiotracers: FDA Approved

Vizamyl™, Flutemetamol, GEHC

Amyvid™, Florbetapir, Eli Lilly

Neuraceq™, Florbetaben, Piramal Imaging

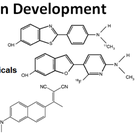


β-Amyloid radiotracers: In Development

C-11 PiB

NAV4694, Flutafuranol, Navidea Biopharmaceuticals

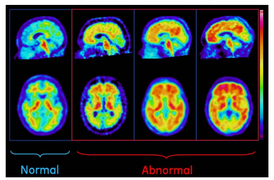
FDDNP, TauMark



Amyloid PET Imaging Interpretation

Radiotracers are currently approved for amyloid clinical imaging to estimate ☒amyloid neuritic plaque density in adults with cognitive impairment being evaluated for AD. Images are interpreted using visual qualitative criteria by physicians certified based on specific training requirements. The QIBA group is defining technical performance requirements to use these radiotracers quantitatively. The current Claim will be used across time points (longitudinal claim) to assess the degree of change necessary to be considered significant.

Images to the right show a spectrum of normal to abnormal uptake using F18-flutemetamol PET imaging (differing degrees of abnormal in different patients) displayed with a color scale referenced to the brainstem.



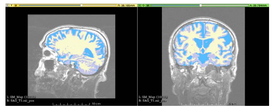
As of April 2015, the Centers for Medicare & Medicaid Services has approved the protocol for a four-year, $100 million study called Imaging Dementia- Evidence for Amyloid Scanning (IDEAS). The study, which will be managed by the American College of Radiology, aims to examine how well amyloid imaging performs in clinical practice. The study will assess whether getting an amyloid PET scan can affect the diagnosis, management and future healthcare of people whose cognitive symptoms cannot be definitively attributed to a cause by clinical diagnosis alone.

Phantom Projects: Physical & DRO

Evaluating bias and precision is a core component of the QIBA PET Amyloid Profile. The Profile is currently using the well-established FDG-PET 3D Hoffman brain phantom for evaluating conformance. However a phantom that is more representative of amyloid uptake in the brain is under development.

PET Amyloid Uptake Digital Reference Object (DRO)

Goal: Design and construct a prototype brain Digital Reference Object (DRO) phantom with properties appropriate for testing software used to characterize PET amyloid uptake patterns in a quantitative fashion

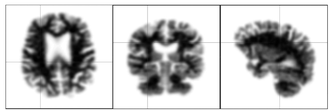


Sections through a T1w MRI patient image after processing

This patient was from the UW database and illustrates anatomical characteristics of Alzheimer's disease (e.g. enlarged sulci)

The processed T1w image was converted to a PET amyloid uptake image by defining uptake values in each region and adding realistic levels of noise and blurring

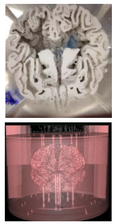
Sections through the first version of the PET amyloid tracer digital reference object (DRO)



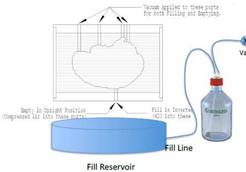
DRO was then used to (1) evaluate software used to characterize PET amyloid uptake patterns, and (2) provide a base for construction of a physical phantom (below)

PET Amyloid Uptake Physical Phantom

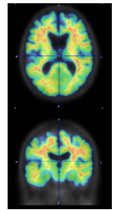
- **More representative of amyloid distribution**
- **Easy to fill (no bubbles, less dose for person filling)**
- **Help qualify and calibrate PET scanners**



Phantom assembly (top) and a rendered CT scan of assembled phantom (bottom).



Phantom fill procedure uses low pressure air to push the radioactive solution into the main brain compartment using 8 fill holes. Vent holes allow for air to escape easily during filling.



Transverse (top) and coronal (bottom) view of the digital representation of the phantom.

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 No. HHSN268201000050C, No. HHSN268201300071C.

Planned Activities 2016

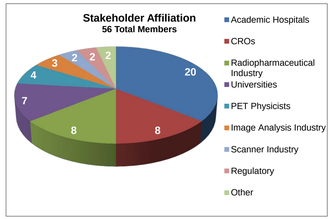
Profile: Writing the Profile has been the Amyloid PET Biomarker Committee's (BC) primary activity to date. The document is undergoing BC review after which it will be released for public comment. Each suggested revision will be addressed by the BC and resolved. The committee's goal is to provide a published Profile by early 2016.

Checklist: Each of the performance requirements in the Profile will be compiled as a checklist. This list will be developed 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
Develop procedure for standardizing PET spatial resolution (co-project with FDG-PET PI: Martin Lodge, PhD	This project will develop an experimental procedure for measuring PET spatial resolution that could potentially be incorporated into future QIBA profiles as a tool to aid quality assurance of scanner performance. The experimental procedure is simple, robust and uses a low-cost cylinder phantom that is already widely employed for other aspects of scanner quality assurance. The resulting measurement reflects the spatial resolution that is achieved with clinical protocols, not the limits of performance that can be obtained under optimized conditions. This procedure, which can be applied across all scanner models and various studies, may help facilitate greater standardization of performance across multiple sites.
Analyses to support amyloid imaging PI: Dawn Matthews, MS,MBA	This project will systematically quantify the effect of three sources of variability upon measured amyloid burden: (1) subject head motion during image acquisition causing misalignment between emission and transmission scans; (2) effect of reference region selection and boundary definition; and (3) effect of target region definition upon measured SUVR. Head motion evaluation will characterize region-specific error in reconstructed scan intensities using a range of pre-defined translation and rotational mismatches between emission and transmission scan.
Amyloid PET test-re-test meta-analysis PI: Rathan Subramaniam, MD, PhD, MPH	This is a systematic review and meta analytical project on test – retest repeatability of ^{18}F Amyloid brain PET radiopharmaceuticals to establish the claim for the Amyloid brain PET profile. This project will estimate the repeatability co-efficient and coefficient of variation for ^{18}F Amyloid brain PET radiopharmaceuticals, based on published literature and grey literature (unpublished work).

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