

QIBA PET Amyloid Biomarker Committee: Overview and 2017 Update

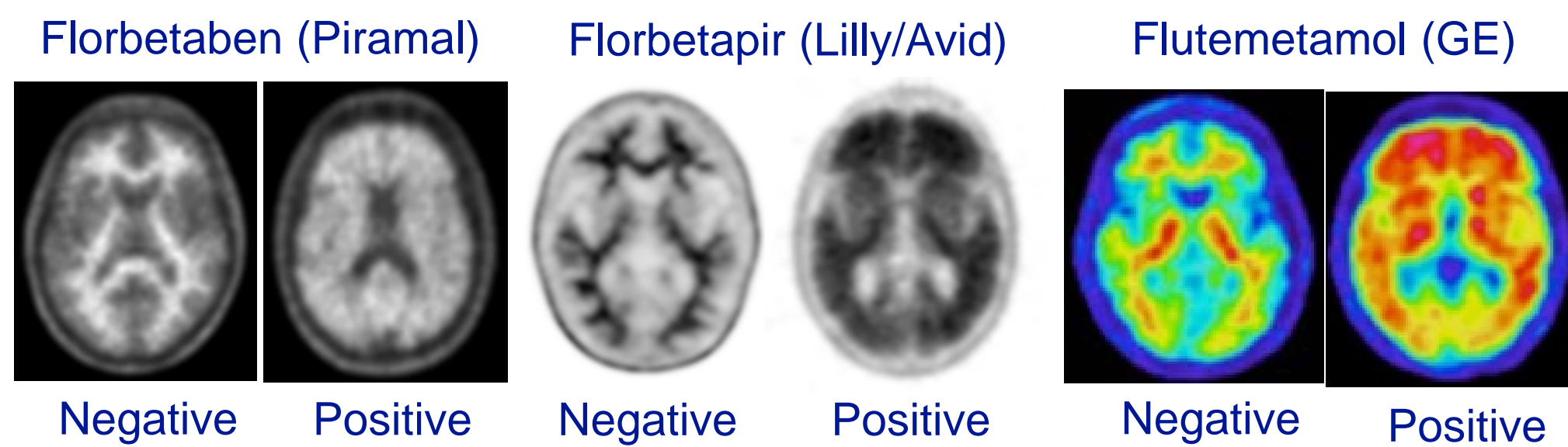
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Amyloid Imaging Importance in clinical trials and patient care

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 F-18 tracers, while 11C-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.



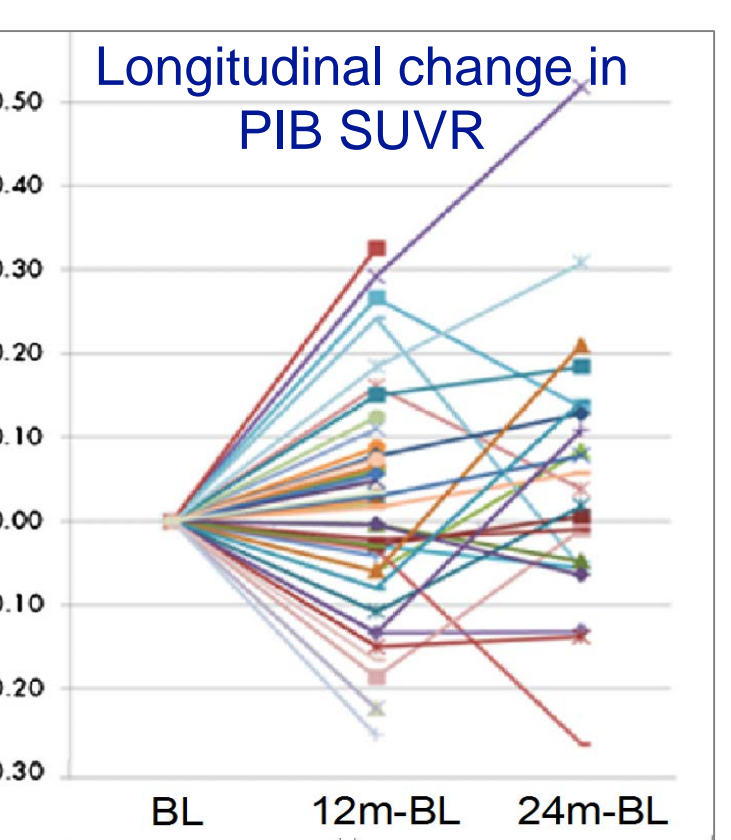
Amyloid imaging is a critical part of many clinical trials as:

- 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. Measurement of amyloid removal also requires quantitation. However, measurement is influenced by many technical factors beyond amyloid. The graph and table below respectively illustrate (a) the erratic changes in PIB SUVR from baseline at 12 and 24 months in ADNI MCI subjects that are often associated with technical factors, and (b) the impact of reference region on the number of Am+ MCI subjects required to detect a 25% reduction in amyloid accumulation rate over 12 months (left) or amyloid burden (right).



the impact of reference region on the number of Am+ MCI subjects required to detect a 25% reduction in amyloid accumulation rate over 12 months (left) or amyloid burden (right).

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

From: Chen K et al, JNM, 2015

Amyloid PET Profile Scope

- Initial focus on late timeframe period in which the tracer has come to "pseudo-equilibrium", during which a **Standardized Uptake Value Ratio** (SUVR: Target region value / reference region value) is calculated
- Focus chosen due to the number of imaging sites able to implement, and the data that has been / is being acquired using this approach.
- Potential benefits of full dynamic modeling are also described.

Profile Claims

Claims describe the performance achievable when profile guidelines are followed. Initial claims focus on **test-retest variability** and implications for:

- Confidence interval for a single scan in an individual
- Information to calculate number of subjects required to detect a particular longitudinal change or reduction of change rate

An accuracy (cross sectional magnitude) claim is anticipated for version 2.

Profile Activities and Guidelines

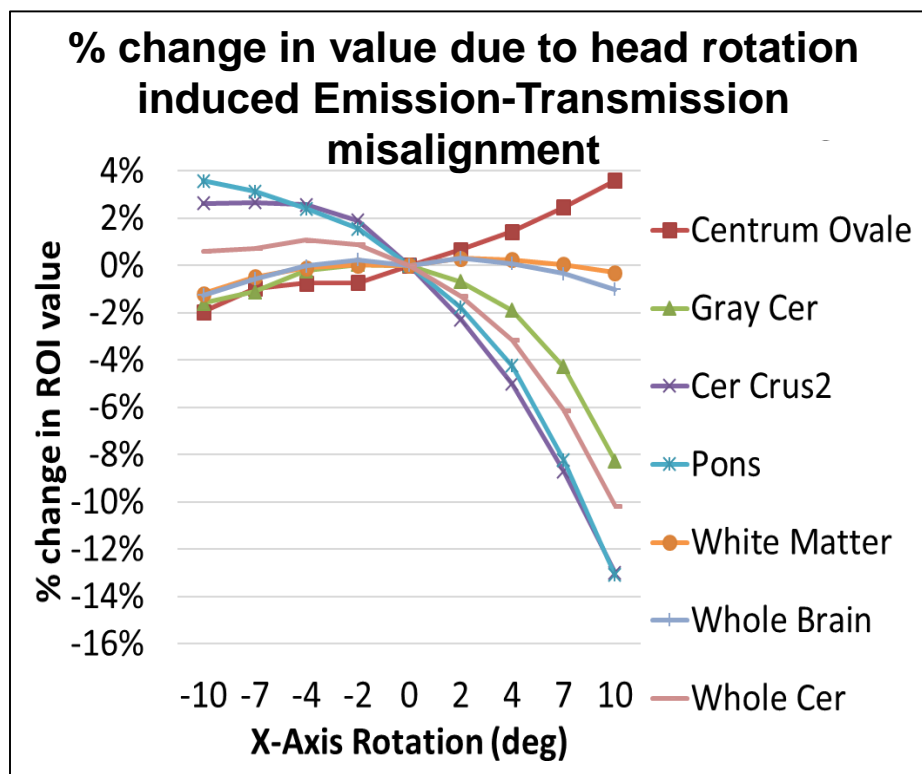
The profile identifies critical factors and recommendations impacting test-retest variability at each stage in image acquisition, processing and analysis, with highlights summarized here.

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 from scan to scan.
- ❑ **Subject motion: Major contributor to error,** must minimize between and within transmission and emission 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

- ❑ **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

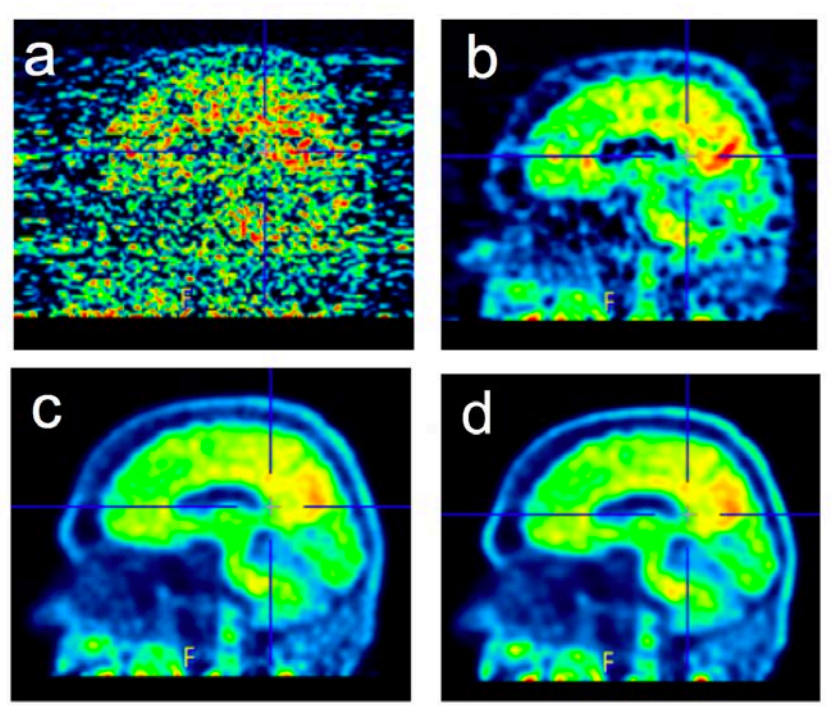
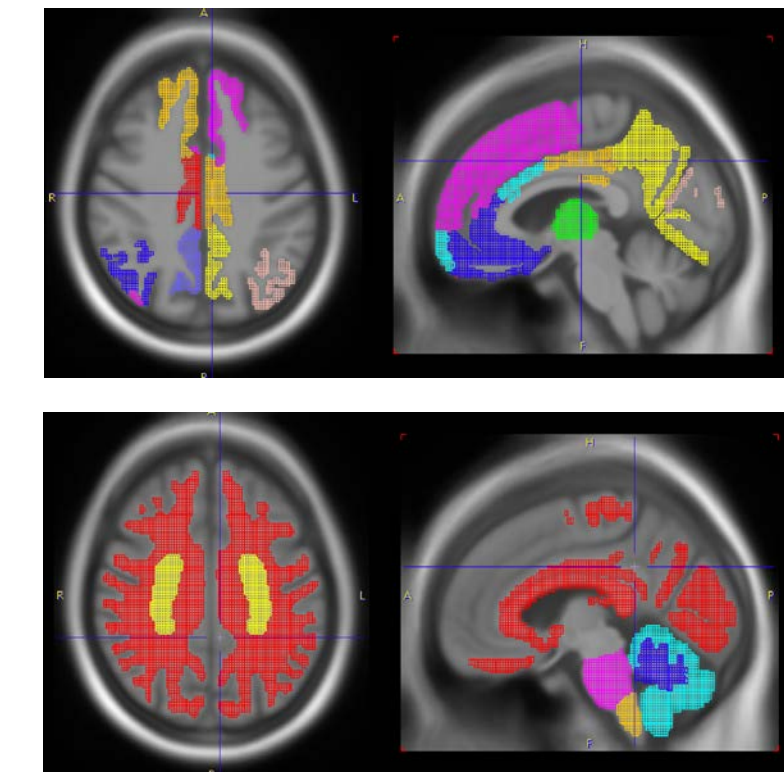


Image reconstructed using (a) FBP 0mm smooth; (b) FBP 5mm; (c) OSEM 4i24s 5mm; (d) OSEM+PSF 4i24s 5mm.

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).

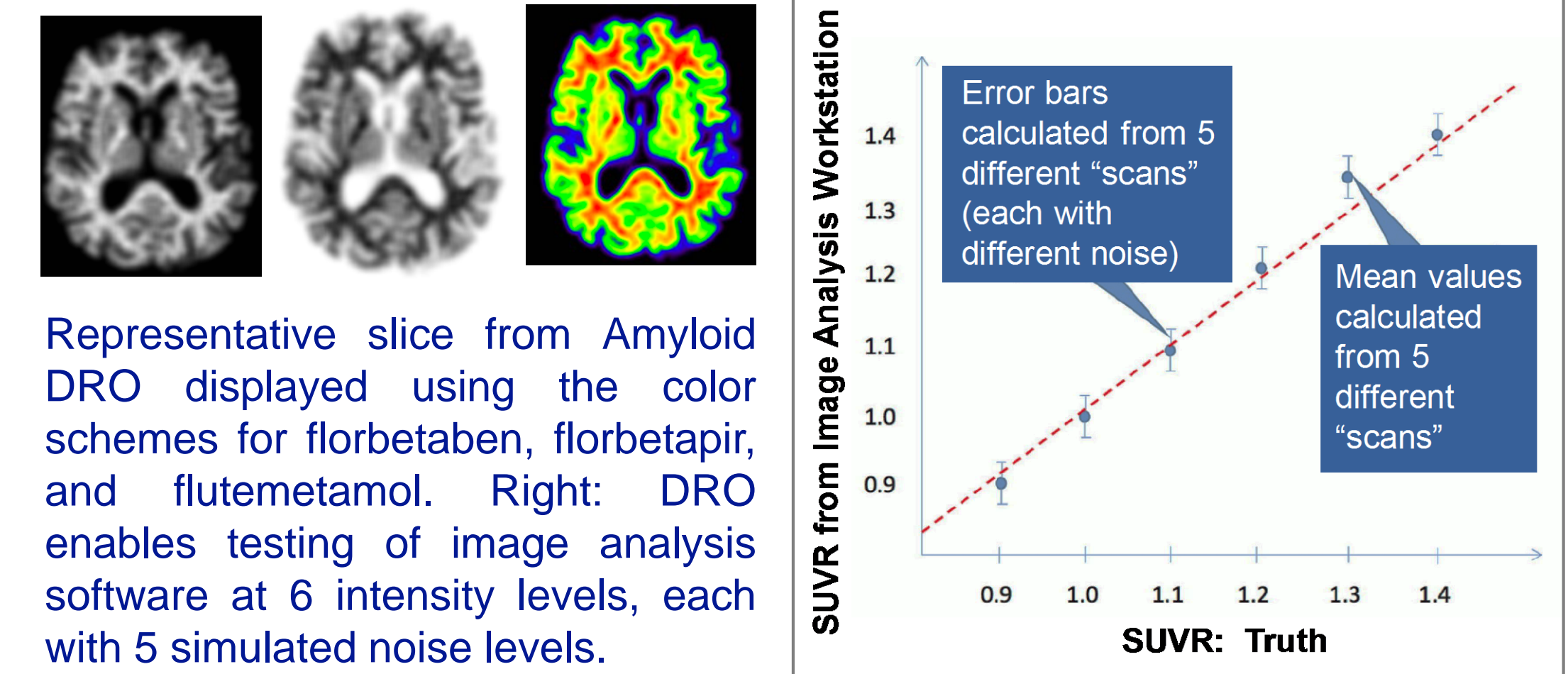
QUALITY CONTROL

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 using the color schemes for florbetaben, florbetapir, and flutemetamol. Right: DRO enables testing of image analysis software at 6 intensity levels, each with 5 simulated noise levels.

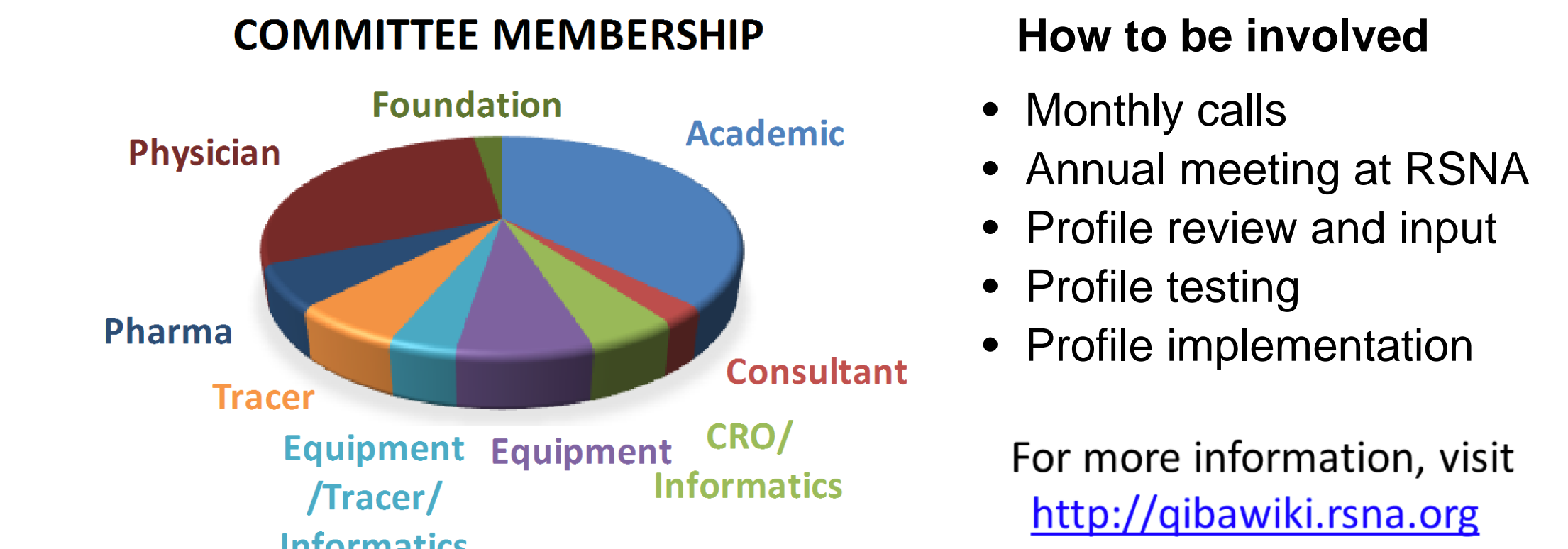
Amyloid PET Profile Development Status



Profile has been distributed for public comment and feedback tabulated. Open issues and comments are being addressed.

- Next steps**
 - Finalize version 1 claims
 - Finalize conformance testing
 - Integrate public comments
 - Profile testing
- Version 2 Plans**
 - Accuracy (cross-sectional) claim
 - Expanded guidelines that may include: PET-MR, Centiloid, partial volume correction, Kinetic modeling

Amyloid Biomarker Committee



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.