Agenda

- Public comment
  - Feedback Summary
  - Selected topics
- Claim(s)
  - Review
  - Proposed approach
- Response coordination and timeline
- Poster
- Other topics

Public comment feedback

- At least 9 responders (6 through formal link), of which some represent multiple reviewers within organizations
- 82 comments
- Approximately 30 categories organized into 9 broader categories

Public comment feedback

Category	Topic	Comments
Use	Appropriate Use	1
	Off label	1
Claim	Claim	5
Scanner and QC	Scanner QC	1
	Phantom	1
	CT parameters	1
	PET/MR	1
Radiotracer	Radiotracer label	6
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	Full dynamic modeling	2
	Acquisition parameters	1
	Reconstruction parameters	2
Image analysis	Image analysis	2
	Reference region	3
	Ref. region /analysis (refs)	6
	Cortical average calculation	1
	Software availability	1
	Atrophy correction	1
	Centiloid	4
	Reporting	1
Actors	Personnel qualifications	2
	Responsibilities	1
	Review	2
Terminology	Relevance	4
	Terminology	24

Public comment: Radiotracer related

- Labeling for at least 2 radiotracers has been updated
  - Update in profile
  - Since further updates are possible, refer to manufacturer labeling as a superseding standard
- Broader point regarding label for all tracers:
  - Clarify that quantitative read is an off label use in clinical use despite FDA approval of measurement software
- Some comments regarding administration, personnel
- NAV4694 status and associated inclusion

Public comment: Topics addressed via description

The following topics have been described in the profile but are not associated with guidelines in Version 1:

Topic	Rationale
PET-MRI scanners	Attenuation correction has been evolving; lack of test-retest data
Partial Volume Effects correction	Mixed results; sensitivity but also variability
Centiloid conversion	Still under refinement and adoption
Full dynamic modeling	Feasible for fewer centers, modeling complexity, BUT doable in several centers and very important to describe advantages, caveats

However, they should be described adequately, with potential benefit or relevance, and for further inclusion in version 2 of the profile.

Profile Framework

Measurement Approach	Approach in Profile
SUVR • Practical implementation • Existing & in process data • Caveat re: blood flow	Primary focus and basis for guidelines, claim
Full dynamic modeling • Advantage wrt blood flow contribution measurement • Acquisition and analysis more complex, not routinely used in clinic	Communicate aspects of variability (e.g. blood flow) addressed by this approach, as well as the impact of modeling assumptions

Claim(s) – a History

Claims

Longitudinal (repeatability)

- Confidence interval
- Does not imply that the value is accurate

Cross-sectional (accuracy)

- Is measurement accurate
- Requires bias data that was not available at the time of profile initiation

Literature basis

↓

Criterion: Test-retest window (≤60 days)

↓

Pooled results for F18 studies

Group	TRV%	S.D.	RC%	95% CI
HC	3.12	6.52	10.41	4.8-14.9
AD	2.77	3.82	10.36	3.3-20.3

↓

Claim: A true change if >14.9%

↓

Concerns that this range is not reflective of controls in profile

↓

Revised claim: A true change if >8% (reduced estimate); Status: OPEN ITEM

Claim – Issues

- Over a typical clinical trial period, physiological accumulation rates are below 8% (rather, 1 – 3% per year based upon statistically powered studies, difficult to show this with human autopsy)
    - Claim as stated would not be useful for accumulation studies, even if confidence interval is further reduced
- A change of 8% or more within a short period of time typically implies a technical artifact, not a real physiologic change
- The 8% was an estimate without direct data support
- The current statement (“framing”) of the claim is not directly relevant to a clinical trial measurement used for subject inclusion, or to a radiologist in the clinic, where the goal might be to establish whether a single subject’s measurement is reliable wrt repeatability (accuracy aside)

Claim – Goals

- State claim(s) in a framework that is relevant for the intended audience
- Support claims with data

Claim - Studies originally used as basis for 95% CI

Author	N	Tracer	Ref. region	Window (minutes)	M	SD	RC%	95%CI
Joshi et al, 2012	10 AD, 10 HC	Florbetapir	cerebellum	50-70	2.4 1.5	0.84 1.41	5.38 3.32	3.76, 9.44 2.32, 5.84
Cseleyni et al, 2012	3 AD, 4 HC	AZD4694	cerebellum	51-63	5.6 9.0	7.93 6.02	16.75 20.30	9.49, 62.44 12.16, 58.35
Vandenberghe et al, 2010	5 AD	Flutemetamol	cerebellar cortex	85-115	1.5	0.7	3.18	1.99, 7.81
Villemagne et al, 2011	8 AD, 8 HC	Florbetaben	cerebellar cortex	90-110	6.2 2.9	3.99 3.71	14.18 8.84	9.48, 27.17 5.97, 16.94
Aalto et al, 2009	6 AD, 4 HC	11C-PIB	cerebellar cortex	60-90	4.3 3.5	0.61 1.48	8.49 7.30	5.47, 18.7 4.37, 20.99
Villemagne et al, 2011	4 HC + 2 HC	11C-PIB	cerebellar cortex	40-70	3.5 3.7	2.74 3.18	8.24 8.41	4.94, 23.69 4.38, 52.69
Tolboom et al, 2009	6 AD, 6 HC	11C-PIB	cerebellar cortex	60-90	8.0 4.4	7.01 4.19	20.05 11.43	12.92, 44.17 7.37, 25.18

Claim – Studies originally used - considerations

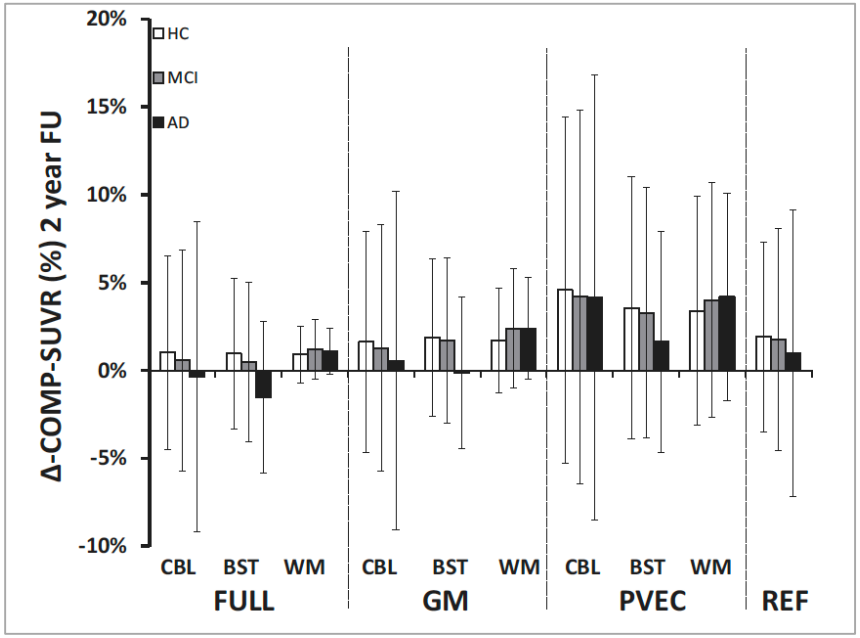
Author	N	Tracer	Ref. region	Window (min)	Issues as reference data
Joshi et al, 2012	10 AD, 10 HC	Florbetapir	cerebellum	50-70	• None; caveat of ref region used
Cseleyni et al, 2012	3 AD, 4 HC	AZD4694	cerebellum	51-63	• Tracer in development, 12 minute window, full dynamic scans - subject to increased motion in late frames
Vandenberghe et al, 2010	5 AD	Flutemetamol	cerebellar cortex	85-115	• None; caveat of ref region used
Villemagne et al, 2011	8 AD, 8 HC	Florbetaben	cerebellar cortex	90-110	• Mass dose changed in second scan, not designed for test-retest
Aalto et al, 2009	6 AD, 4 HC	11C-PIB	cerebellar cortex	60-90	• 60-90 minutes subsequently recommended against for SUVR due to low signal/noise • Subjects in scanner for an hour by this point, misalignment potential
Villemagne et al, 2011	4 HC + 2 HC	11C-PIB	cerebellar cortex	40-70	
Tolboom et al, 2009	6 AD, 6 HC	11C-PIB	cerebellar cortex	60-90	• 60-90 minutes subsequently recommended against for SUVR due to low signal/noise • Subjects in scanner for an hour by this point, misalignment potential

*highlighted studies may best serve as references

Claim – Longer timeframe studies for comparison and relevance to clinical trial timeframes

	Chen et al 2015	Chen et al 2015	Chen et al 2015	Brendel et al 2015	Brendel et al 2015
	CN	CN	CN	CN	CN
	88	88	88	62	62
Amyloid status	Negative	Negative	Negative	Negative	Negative
Time between scans	2 years	2 years	2 years	2 years	2 years
Reference Region	Pons	Cerebellum	White	Full cerebellum	White
Mean intra-subject	0.50%	0.60%	1.10%	0.54%	0.85%
S.D. intra-subject	1.70%	2.20%	1.90%	4.79%	1.76%
RC%	3.45%	4.45%	4.28%	9.37%	3.81%
95% CI	3.01%	3.87%	3.73%	7.97%	3.24%
	4.05%	5.21%	5.02%	11.36%	4.61%

(estimates)



Brendel et al, 2015

Claim – Impact of reference region on variability and required "N"

TABLE 4
Number of Participants Needed Per Arm to Detect Aβ-Modifying Treatment Effect in 12-Month Clinical Trial with 80% Power and 2-Tailed *P* of 0.05

No. of participants needed to detect…	Reference ROI	AD Aβ+	AD Aβ−	MCI Aβ+	MCI Aβ−	NC Aβ+	NC Aβ−	NC ε4+	NC ε4−
25% attenuation in further SUVR increases	Cerebral white matter	187	515	325	1,547	162	819	252	770
	Cerebellum	62,809	3,040	8,076	10,844	853	2,938	1,180	2,453
	Pons	N/A	N/A	2,718	724,200	697	3,318	907	2,519
25% decrease in SUVR from baseline	Cerebral white matter	8	21	13	62	7	33	11	31
	Cerebellum	2,513	122	324	434	35	118	48	99
	Pons	N/A	N/A	109	28,968	28	133	37	101

N/A = not applicable because SUVR was decreasing with this reference ROI.

Chen et al, 2015

Claim – Goals (recap)

- State claim(s) in a framework that is relevant for the intended audience
- Support claims with data

Claim – Proposed Approach

- State the claim for individual, single time-point scan in the context of a confidence interval for test-retest consistency on an individual subject rather than % that constitutes real longitudinal change
- Develop table or provide the necessary inputs for table construction that determines the number of subjects required to detect a longitudinal change of x% (or a reduction in the rate of accumulation)
    - Reference, separately, short and longer timeframe scan re-scan data
- Associate claims with narrower acquisition and analysis parameters (“if then”; include constraints on acquisition consistency, reconstruction consistency, motion, processing, reference region)
- Describe the additional blood flow related error that could be reduced with full dynamic modeling, while pointing out assumptions and caveats regarding variability associated with this approach
- Include description of the additional data needed to establish an accuracy (cross-sectional) claim.

Relating profile claims to clinical trial design

- A goal is to help the audience relate the profile guidance and confidence intervals to practical use in clinical trial design
- Nancy Obuchowski has drafted a document (section, appendix, or standalone) that could provide this information
- The original version was drafted at the request of the DaTscan SPECT group, which is in a similar position to the amyloid profile with regard to being able to support a longitudinal, but not yet a cross-sectional, claim at this time
- Making use of this translation guide (tailored) for both profiles has additional benefits with regard to profile standardization and implementation

Public comment: response coordinators

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Poster

To maintain topic uniformity across all posters, content should address each of the following:

1. **Organizational structure updates**: brief description of new Biomarker Committees, Task Forces or new biomarkers being considered, *etc.*
2. **Profile development status:** current status and plans for advancing Profile to next stage
3. **Profile impact / implications for clinical trials and patient care:** address the expected "value add" for the Profile and/or specific examples of how the Profile has been used (in whole or in part) or could be used to provide better clinical trial or patient care management decisions, including the mitigation of potential pitfalls
4. **Conformance procedure update:** checklist development, feasibility testing plans/result
5. **Groundwork project status/results:** optional

- No smaller than **30 pt** for section titles
- No smaller than **24 pt** for body text
- Text should be easy to read from a **three-foot distance**.
- Use a sans-serif font, e.g. **Arial** or **Helvetica**.
- We encourage incorporating a **QR code** to link to relevant supplemental information.

Poster

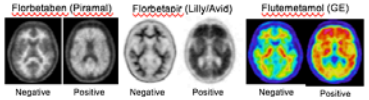
QIBA PET Amyloid Biomarker Committee: Overview and 2017 Update

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

[1]Perlman Advisory Group, [2]Siemens Healthineers, [3]University of Utah, [4]ADM Diagnostics, [5]Washington University Mallinckrodt Institute of Radiology, [6]GE Healthcare, [7]Piramal, [8]University of Groningen, [9]GE Healthcare, [10]University of Washington, [11]Roche, [12]VU Medical Center, [13]Cleveland Clinic Foundation, [14]Johns Hopkins University, [15]University of Iowa, [16]JLVMI Consulting

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. A positive amyloid burden is now a criterion for a diagnosis of preclinical AD in cognitively normal persons. 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.



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

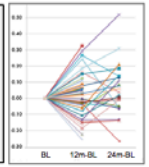
- An inclusion criterion, confirming presence of AD pathology
- An endpoint for anti-amyloid therapeutics

In patient care, the IDEAS study (ref) has demonstrated in approximately 4,000 subjects that amyloid imaging changed the diagnosis in 29% of dementia patients and 46% of patients with mild cognitive impairment who were clinically misdiagnosed as having AD.

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. Similarly, accurate measurement of amyloid removal requires quantitation. However, amyloid measurement is influenced by many technical factors beyond the amyloid present. The graphs below illustrate the impact upon (a) measured trajectory and (b) the number of subjects required to detect a treatment effect, due to technical factors.

Figure description



Reference region	Required number of subjects
White	325
Pons	2,718
Cerebellum	8,076

Table description

Amyloid Profile: Scope and Claims

SCOPE (SUVR, description of kinetic modeling)

CLAIMS, BASIS, AND PRACTICAL USE

Profile Activities and Guidelines

Intro wording

SUBJECT HANDLING

IMAGE ACQUISITION

(incorporate findings from groundwork project)

IMAGE RECONSTRUCTION AND POST PROCESSING

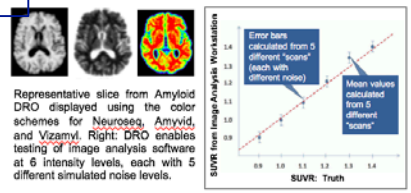
(incorporate findings from groundwork project)

IMAGE ANALYSIS

REPORTING

QUALITY CONTROL

Conformance Testing



Representative slice from Amyloid DRO displayed using the color schemes for Neuroseq, Amyvid, and Vizamyl. Right: DRO enables testing of image analysis software at 6 intensity levels, each with 5 different simulated noise levels.

Amyloid Profile Development Status

Profile Drafted → Public Comment → Publicly Reviewed → Technically Confirmed → Claim Confirmed

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

COMMITTEE MEMBERSHIP

How to be involved

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

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.

3

5

2

1

5

4

Poster

Poster

...iew and 2017 Update

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...althcare, [9]University of Washington, [10]Roche, [15]VU Medical Center, [13]Cleveland Clinic Foundation, [14]Johns Hopkins University, [15]University of Iowa,

Quantitative Imaging Biomarkers Alliance

RSNA

IMAGE RECONSTRUCTION AND POST PROCESSING

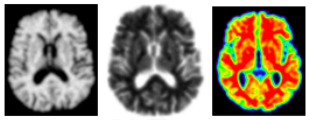
(incorporate findings from groundwork project)

IMAGE ANALYSIS

REPORTING

QUALITY CONTROL

Conformance Testing



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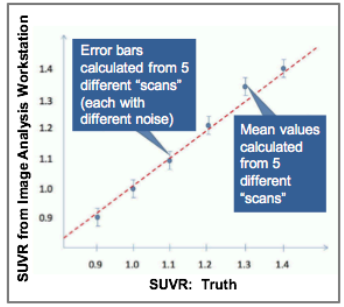

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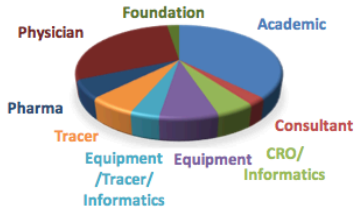

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Next steps

- Compile any additional feedback
- Column in feedback table indicating how addressed or response, for review by working group
- Claim consensus
- Conformance
- Review poster for 10/31 submission