

Topics for Discussion

Profile status

Proposed approach to address PET-MR in profile

Claim and Supporting paragraphs

Blood flow and clearance impact

Profile status

Red-line and comment response worksheet are almost ready to post!

Projection is within 1.5 to 2 weeks

90 comments addressed

PET-MR

1. Executive Summary

56 This QIBA Profile documents specifications and requirements to provide comparability and consistency for
57 the use of PET imaging using 18F labeled tracers which target amyloid across scanners in neurology. The
58 document primarily addresses PET/CT imaging; however, a dedicated PET that has transmission capabilities
59 can also be used. PET/MR scanners are excluded in this version because of their novelty and unknown
60 quantification differences as compared to PET/CT and dedicated PET scanners.

PET/MR scanners are not strictly excluded in this version as long as the repeatability of the SUVs from
these scanners is conformant with the assumptions underlying the claims.

...

Summary for Clinical Trial Use

96 institutions considering specifications for procuring new PET/CT (or PET/MR in subsequent document
97 versions) equipment.

98 Radiologists, nuclear medicine physicians, technologists, and physicists designing PET/CT (and PET/MR)
99 acquisition protocols.

(or PET/MR if the repeatability of the SUVs is conformant with the assumptions underlying the claims)

...

PET-MR

3.2. Image Data Acquisition

359 This section summarizes the imaging protocols and procedures that shall be performed for an amyloid-PET
360 exam by using either a PET/CT or a dedicated PET scanner with the requirement that a Germanium source
361 can be used to perform attenuation correction. Note that PET scanners that do not measure in some way
362 the attenuation of the brain and use a calculated algorithm for estimating the attenuation and scatter
363 corrections are excluded from this profile. In addition, due to their novelty, PET/MR scanners are not
364 covered in this version of the profile. More research and data need to be done with these scanners to
365 understand any differences they may have in quantifying PET amyloid data as compared to PET/CT and
366 dedicated PET scanners. Going forward in this document, PET scanner can mean either a PET/CT or a
367 dedicated PET scanner.

PET/MR scanners are not strictly excluded in this version as long as the repeatability of the SUVRs from these scanners is conformant with the assumptions underlying the Claims. This work was not yet published when this Profile was released. Since the claims of this profile are only valid for the same patient being scanned on the same scanner with the same protocols and analysis, only the repeatability of the PET/MR SUVRs needs to be validated in the context of the Claims, and not the difference in SUVRs as compared to PET/CT scanners.

PET-MR

3.6.3 Amyloid- PET Acquisition Scanner

1016 Amyloid-PET studies as described in this Profile require either a PET/CT scanner or a dedicated PET scanner
1017 with the ability to acquire a transmission image. PET/MR scanners may be added in future versions of this
1018 Profile.

PET/MR scanners may be added in future versions of this Profile or may already be included in this Profile
if the repeatability of the SUVRs from these scanners is conformant with the assumptions underlying the claims.

Claim and Clinical Utilization

Claim:

If Profile criteria are met, then:

Claim 1: Brain amyloid burden as reflected by the SUVR is measurable from 18F amyloid tracer PET with a within subject coefficient of variation (wCV) of $\leq 1.94\%$.

Clinical Utilization

It is acknowledged that because amyloid accumulation rates reported in the literature are in the range of one percent to a few percent per year, SUVR confidence intervals derived from the wCV may not be relevant to the assessment of individual change over the duration of a typical clinical trial. They may be more relevant to individual amyloid removal by certain therapeutic agents. In addition, the wCV value can be used to guide the number of subjects to include in clinical trials targeting measurement of longitudinal change in amyloid SUVR. A few examples of practical uses of the Claim are described below, and further guidance is found in the [“Statistical Planning for a Clinical Trial Guidance document”](#) posted on the QIBA website.

1. Powering of clinical trial to measure rate of amyloid accumulation. As an example, if the likely rate of amyloid accumulation is 1.5% per year with a standard deviation of x in a selected trial population, then to detect amyloid accumulation over a period 2 years with 80% power will require y subjects. The derivation of this is based upon: <to be completed>
2. Powering of a clinical trial to measure a reduction in the rate of amyloid accumulation (e.g. due to treatment intervention). If the likely rate of amyloid accumulation is 1.5% per year with a standard deviation of y , then the number of subjects to detect a 50% reduction in the rate of accumulation over a 2 year period would be z . This is based on the following derivation <to be completed>
3. Confidence interval around individual percent change. The confidence intervals for a single true change associated with the wCV of Claim 1 are shown in the graph below for confidence levels of 70%, 80%, 90%, and 95%:

<Add graph>

Claim and Considerations

Considerations for claim:

The following important considerations are noted:

1. The technical performance claim was derived from a review of the literature summarized in Appendix B, where 18F amyloid PET tracers were used and data acquisition and processing procedures were considered to be adequately aligned with the recommendations in this profile. The wCV cited is the highest of the test-retest studies that occurred within a 60 day period. The wCV values in these studies of less than 60 days ranged from 1.15% in healthy controls using a cerebellar cortex reference region to 1.94% in AD patients using a whole cerebellum reference region. The wCV values derived from studies over a 2 year duration in amyloid negative normal controls from the ADNI data set ranged from 1.25% (white matter reference region) to 1.6% (whole cerebellum reference region) and in one case up to 3.38% (whole cerebellum reference region, different cerebellum boundary definition, different authors).
2. Conformance to the Claim depends upon many factors, including minimized subject motion, alignment of Em/Tx scans, and stability in detection sensitivity from scan to scan in reference region slices compared to target region slices. In particular, choice of reference region can greatly impact wCV due to the sensitivity of different regions to technical factors. In published longitudinal studies over periods of 2 year intervals, the wCV was less than 1.94% across studies only when reference regions incorporating subcortical white matter were used. A more extensive discussion of the considerations in selecting reference region is found in section 3.4.3.2.2.
3. This Claim is applicable for single or multi-center studies assuming that the same 18F-amyloid PET tracer, scanner, scanner software version, image acquisition parameters, image reconstruction method and parameters, and image processing methods are used for each subject at each time point as described in the Profile.

Claim and Considerations

4. It is presumed that a) the wCV is constant over the range of SUVR values and b) any bias in the measurements is constant over the range of SUVR values (linearity).

5. The SUVR has been selected due to its logistical feasibility in multi-site trials, and its use to date in large reference studies such as ADNI. However, from the fundamental kinetic properties of radiotracers it can be understood that changes in SUVR may not represent only a change in specific signal (amyloid) but could, at least in part, be the result of changes or variability in perfusion (van Berckel et al, J Nucl Med. 2013) and/or tissue clearance (Carson RE et al, 1993). This impact, when random, is another source of variability included that contributes to the wCV. However, changes in perfusion and/or clearance can be systematic due to the action of certain pharmacological agents or due to disease progression (for example, in dementia stages of AD), creating artificial change in amyloid SUVR. Changes to SUVR can be on the order of 2% to 5% or greater, becoming significant in studies of amyloid accumulation, prevention, or modest removal. Whether or not a change in SUVR is affected by changes in perfusion and/or clearance ideally should be first demonstrated in a small (e.g. 20 subjects) cohort before SUVR is used in the larger clinical trial. These contributions can be quantified by using a full acquisition from time of tracer injection through late timeframes, and kinetic modelling. At the very least these validation studies should be performed to assess the minimally required decrease in SUVR that is needed to rule out false positive findings because of disease and/or drug related perfusion effects. In the case of a new PET tracer, studies that include blood sampling should be conducted to confirm that the SUVR approach and use of a reference region are a suitable approach to measure tracer binding. For further details regarding considerations in kinetic modeling please see Appendix I.

Appendix I

Appendix I. Kinetic modeling and comparison to

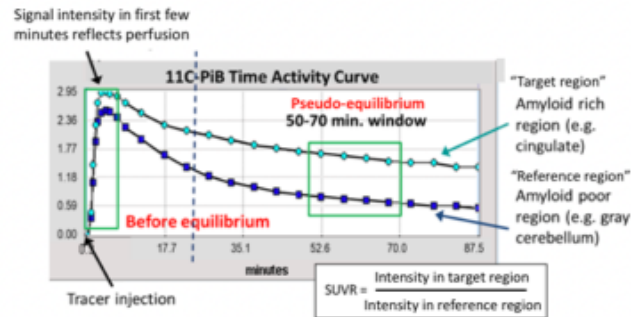
This section is intended as a reference to illustrate the difference between measurement and full kinetic modeling, and why and how these two approaches may differ.

The contributors to amyloid PET signal

The signal intensity measured in a particular image voxel (image) reflects the amount of radiotracer present in that voxel. However, since PET image resolution is generally a few centimeters, the signal intensity of an amyloid PET tracer in a voxel is a combination of blood and various other tissue compartments. It is necessary to separate out the contributions from each of these compartments is dependent upon blood flow, the rate of tracer diffusion into tissue, the presence of amyloid, and the rate at which the tracer is cleared from the body.

Stages of tracer uptake and clearance

Figure 1 below shows the signal intensity measured for the different regions of the brain from the time of tracer injection. In the initial minutes, the signal intensity reflects the rate at which the tracer enters the tissue (perfusion), which is driven by the combination of blood flow and permeability. Studies of amyloid tracers including ¹¹C demonstrated a strong correlation between the early rapid increase in signal intensity and the early rapid increase in blood flow. Following the first few minutes, the tracer binds to amyloid in tissue that contains amyloid to which it is bound. The rate of tracer influx to tissue is in equilibrium with the rate of tracer efflux from the tissue. The signal intensity curve for any region of the brain at a time following achievement of relative equilibrium (TAC).



Kinetic modeling

Several different models have been developed that use simultaneous differential equations to solve for the "flux" into and out of compartments, and ultimately the amount of tracer bound to target (in this case, amyloid). The gold standard approach uses a full kinetic model to obtain the actual tracer concentration in blood. However, this approach is labor-intensive and can be impacted by variability in the blood measurements. Alternate modeling approaches eliminate the need for blood sampling by using reference measurements in tissue that does not contain the target. This is often the cerebellar cortex, which is generally devoid of amyloid. In Alzheimer's disease, certain familial forms of AD, or certain of the reference region approach as an approximation for blood flow. Each new tracer, as it has been for ¹¹C-PIB (ref), ¹⁸F-amyloid (for ¹⁸F-florbetaben, ¹⁸F-florbetapir, and ¹⁸F-florbetaben, ref). All kinetic models require the course of tracer measurement (TAC) from time of injection to equilibrium has been reached. The creation of a full TAC using a time window has also been demonstrated (ref). The measure of amyloid derived from a kinetic model is called the Distribution Volume Ratio (DVR) or alternatively state the Binding Potential (BP_{ND}) + 1. Published studies state the DVR value or alternatively state the BP_{ND} value when necessary to capture a full TAC. Using the scanner for a full hour or more also precludes its use for other patients during that entire time.

Standardized Uptake Value Ratio

Despite the advantages provided by full kinetic modeling in terms of blood flow, binding, and clearance, there are practical drawbacks, particularly those with disease, to lie still in the scanner for the duration of a dynamic scan. Acquiring dynamic scans presents additional challenges as time of injection may require two technicians to be present for acquisition or memory capacity required to acquire the data.

necessary to capture a full TAC. Using the scanner for a full hour or more also precludes its use for other patients during that entire time.

For these reasons, the SUVr is often used as an approximation for DVR. This measurement uses only a "late timeframe" segment during which the tracer is in equilibrium. In true equilibrium, and assuming that blood flow rates are the same in target and reference tissue, the ratio of the two tissues provides a relative measure of the signal contribution due to amyloid binding. In reality, equilibrium is "pseudo", in that local differences in blood flow rates and directional tracer movement can occur. However, numerous studies have demonstrated that the simpler SUVr approach can provide discrimination between normal, MCI, and AD groups (refs) and, with adequate numbers of subjects, measure group level increases (ref) or decreases (Biogen ref) over time.

Caveats to measurement approaches

Kinetic modeling. Not always same. Logan reference biased upward. Blood sampling vs. reference region models. For amyloid negative scans, noise and error. Kinetic modeling does NOT overcome error introduced by subject motion, misalignment between emission and transmission scan, or other technical sources of noise. Since the risk of subject movement increases with longer times in the scanner, these variables can outweigh the benefits unless provisions are made to align each timeframe prior to image reconstruction.

SUVr values are in general biased upward relative to kinetic modeling results (Sulistein 2007, Carson 1993, Zhou, van Berckel 2013). This artificial increase is caused when plasma clearance rate is close to the slowest tissue clearance rate (Carson), and becomes larger with later timeframes.

Reference for ranges of longitudinal accumulation

TABLE 3
24-Month SUVR Changes with Pontine, Cerebellar, and Cerebral White Matter ROIs*

ROI	AD Aβ+	AD Aβ-	P†	MCI Aβ+	MCI Aβ-	P†	NC Aβ+	NC Aβ-	P†	NC ε4+	NC ε4-	P†
Pons	-0.000 ± 0.030	-0.013 ± 0.017	0.34	0.007 ± 0.028 [‡]	0.000 ± 0.018	0.02	0.014 ± 0.024 [§]	0.005 ± 0.017 [‡]	0.03	0.010 ± 0.019 [‡]	0.006 ± 0.019 [‡]	0.32
Cerebellum	0.004 ± 0.064	0.011 ± 0.039	0.80	0.007 ± 0.051	0.004 ± 0.023	0.33	0.024 ± 0.045 [‡]	0.006 ± 0.022 [§]	0.006	0.018 ± 0.039 [‡]	0.008 ± 0.025 [‡]	0.08
Cerebral white matter	0.043 ± 0.037 [§]	0.019 ± 0.027	0.15	0.024 ± 0.028 [§]	0.008 ± 0.020 [§]	<0.001	0.026 ± 0.021 [§]	0.011 ± 0.019 [§]	0.001	0.020 ± 0.02 [§]	0.012 ± 0.021 [§]	0.08
White matter vs. pons	<0.001	0.04		<0.001	0.003		0.065	0.031		0.055	0.04	
White matter vs. cerebellum	0.01	0.69		0.02	0.13		0.86	0.15		0.85	0.19	

Chen K et al, J Nucl Med, 2015

*Data are reported as mean ± SD SUVR changes unless otherwise indicated.

[‡]P values reflect differences between respective Aβ+ vs. Aβ- or NC APOE4 carrier vs. noncarrier SUVR changes.

Table 5

Mean (± SD) % changes over two years in [¹⁸F]-AV45 uptake when assessed by the ten different COMP-SUVR methodological configurations (column 1) for the three diagnosis groups (columns 2–4) for all subjects. Columns 5–7 display corresponding results when only Aβ-positive subjects were considered. Significant differences of all different configurations when contrasted against the COMP-SUVR-REF configuration are indicated by: *p < 0.05; **p < 0.01; ***p < 0.001.

Configuration	All subjects			Aβ-positive subjects		
	HC (N = 88)	MCI (N = 148)	AD (N = 22)	HC (N = 26)	MCI (N = 66)	AD (N = 16)
2-year-Δ-COMP-SUVR-FULL _{CBL}	1.0 ± 5.5%***	0.6 ± 6.3%***	-0.4 ± 8.8%**	2.1 ± 7.2%***	0.9 ± 7.7%***	-1.2 ± 7.7%***
2-year-Δ-COMP-SUVR-FULL _{BST}	1.0 ± 4.3%	0.5 ± 4.5%*	-1.5 ± 4.3%	2.4 ± 5.0%	1.2 ± 4.8%	-1.1 ± 4.7%
2-year-Δ-COMP-SUVR-FULL _{WM}	0.9 ± 1.6%	1.2 ± 1.7%	1.1 ± 1.3%	1.0 ± 1.2%	1.6 ± 1.6%	1.4 ± 1.1%
2-year-Δ-COMP-SUVR-GM _{CBL}	1.6 ± 6.3%	1.3 ± 7.0%***	0.6 ± 9.6%	2.9 ± 8.3%	1.8 ± 8.5%***	-0.6 ± 8.5%*
2-year-Δ-COMP-SUVR-GM _{BST}	1.9 ± 4.5%	1.7 ± 4.7%	-0.1 ± 4.3%	3.5 ± 5.3%	2.9 ± 4.9%	0.6 ± 4.6%
2-year-Δ-COMP-SUVR-GM _{WM}	1.7 ± 3.0%	2.4 ± 3.4%	2.4 ± 2.9%	2.1 ± 2.5%	3.3 ± 3.5%	3.0 ± 2.4%
2-year-Δ-COMP-SUVR-PVEC _{CBL}	4.6 ± 9.9%***	4.2 ± 10.6%***	4.2 ± 12.7%*	6.5 ± 12.7%*	5.4 ± 12.2%***	2.7 ± 12.7%
2-year-Δ-COMP-SUVR-PVEC _{BST}	3.6 ± 7.5%	3.3 ± 7.1%*	1.6 ± 6.3%	5.6 ± 6.5%	5.2 ± 7.1%**	2.8 ± 6.0%
2-year-Δ-COMP-SUVR-PVEC _{WM}	3.4 ± 6.5%	4.0 ± 6.7%***	4.2 ± 5.9%	4.2 ± 4.2%	5.5 ± 6.3%*	5.1 ± 4.2%*
2-year-Δ-COMP-SUVR-REF	1.9 ± 5.4%	1.8 ± 6.3%	1.0 ± 8.2%	3.2 ± 7.5%	2.6 ± 7.8%	0.5 ± 7.7%

Reference for ranges of longitudinal accumulation

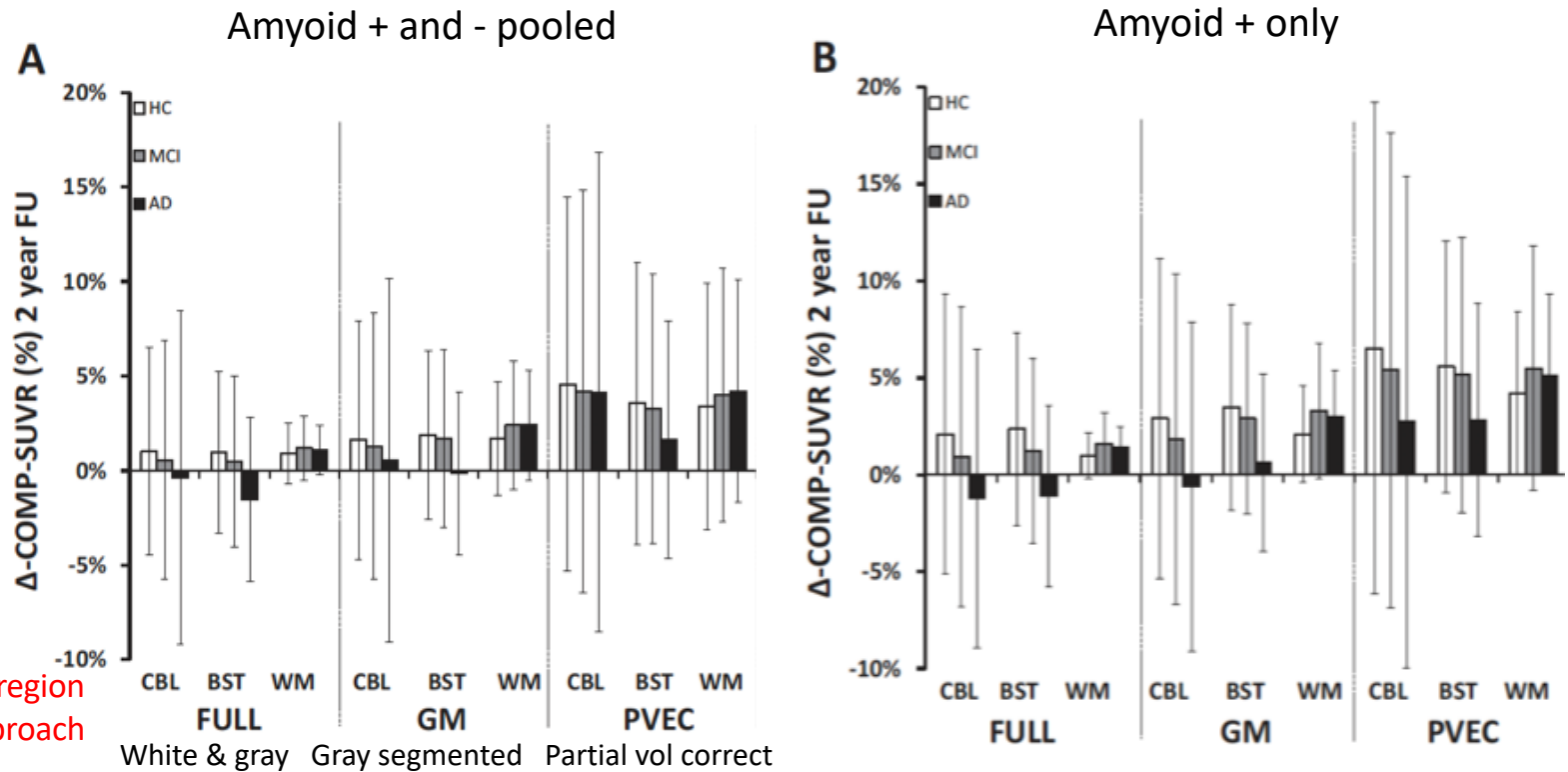


Fig. 5. Changes in longitudinal [^{18}F]-AV45 uptake. Longitudinal % changes in [^{18}F]-AV45 uptake (\pm SD) as assessed for HC (white; $N = 88$), MCI (gray; $N = 148$) and AD (black; $N = 22$) subjects and calculated for the ten COMP-SUVR configurations (A), as well as corresponding longitudinal % changes in [^{18}F]-AV45 uptake (\pm SD) when only A β positive subjects were considered (B). Either full atlas VOIs (FULL), gray matter segmented VOIs (GM) or gray matter segmented VOIs after partial volume effect correction (PVEC) were used and scaled by either the cerebellum (CBL), the brainstem (BST) or the white matter (WM). An additional standard configuration consisted of GM segmented VOIs scaled by the whole cerebellum (REF).

Brendel et al,
Neuroimage, 2015