WhitePaper

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Amyloid PET Centiloid Scaling

Clinical Implementation in Alzheimer's Disease Care

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Table of Contents

Executive Summary

Amyloid PET imaging has become a central biomarker in the diagnostic work-up, therapeutic decision-making, and longitudinal monitoring of Alzheimer's disease (AD). While visual interpretation remains the regulatory standard, quantitative metrics are increasingly used to support clinical confidence.

Harmonization and Standardization: the Centiloid (CL) scale is a quantitative measure with continuous values typically beginning at 0 (set to be the average of young healthy controls) and ranging to 100 or higher (where typical AD patients would center at about 100) developed to harmonize Standard Uptake Value ratio (SUVr) results across amyloid tracers and scanners, and enable longitudinal and multicenter comparability, capture the continuum of amyloid accumulation and thus help identify pathological changes that may be missed or ambiguously classified by visual reads alone.

Enhanced Diagnostic Precision: in early stages of the disease, CL quantitative measures have demonstrated sensitivity to amyloid deposition prior to visual positivity. CL quantification has shown to improve inter-reader reliability and confidence, notably in challenging cases, by providing objective metrics that support or refine visual interpretations.

Trial Inclusion and Therapeutic Monitoring: particularly in anti-amyloid therapeutic studies, numerical CL thresholds are used to define eligibility, measure target engagement, and assess longitudinal treatment effects. Anti-amyloid monoclonal antibodies trials have employed CL cutoffs to guide inclusion and target management, reinforcing the role of quantification in treatment monitoring in both research and clinical practice.

Reimbursement: While not mandatory and not reimbursed separately, quantification is strongly favored in the therapy era because it provides objective evidence of amyloid burden and progression. Including quantification in the final report improves audit defensibility and amyloid PET reimbursement.

PET-only Centiloid Quantification: Since the development of the "standard CL method", an abundance of validated pipelines for quantifying amyloid PET across different tracers or analytic methods have become available. Robust validated PET-only CL pipelines allow accurate quantification of MRI-free studies. The quantification from dedicated brain PET-only amyloid scans can therefore be reported together with visual findings, facilitating the integration of such point of care PET devices as part of the MCI/AD early diagnosis in a decentralized model, for better patient management, faster treatment decisions and accelerated clinical workflows.

In this white paper, the rationale behind Centiloid (CL) quantification of static amyloid PET scans, the standard method for its calculation, and its utility in clinical practice and clinical research are briefly presented. The CL thresholds for clinical decision-making, the 'gray-zone' area, and some sources of variabilities between different CL pipelines are introduced. Examples of NeuroLF brain PET-only amyloid quantification results using a commercial software package for CL calculation are then presented. At the end, we summarize some current limitations of CL scaling.

Background: Rationale for Centiloid Quantification

Amyloid imaging using Positron Emission Tomography (PET) is pivotal to Alzheimer's Disease (AD) management as it detects the presence and spread of amyloid plaques in the brain, one of the earliest pathological hallmarks of AD. Large studies such as Amyloid imaging to prevent Alzheimer's Disease (AMYPAD, https://amypad.eu/) or Imaging Dementia - Evidence for Amyloid Scanning (IDEAS, https://www.ideas-study.org/) over years and thousands of scans, found that amyloid PET dramatically impacts diagnosis, patient management, and change of treatment plans. With increased payer coverage and the advent of anti-amyloid therapies, clinical use of amyloid PET is likely to increase to help guide the diagnosis and treatment of patients with cognitive impairment. The prescribing information for both Lecanemab and Donanemab mandates confirmation of amyloid pathology before initiating therapy. Additionally, the prescribing information for Donanemab recommends discontinuation of therapy once amyloid plaques have been reduced to minimal levels, as verified through amyloid PET imaging [1]. Three Fluorine-18 amyloid-PET tracers have regulatory-approval for routine clinical use: [18F]florbetapir (Amyvid™; Eli Lilly), [18F]flutemetamol (Vizamyl™; GE HealthCare), and [18F]florbetaben (Neuraceq®; Life Molecular Imaging), which compared to the 'gold standard' [11C]PiB, have shown high correlation of cortical binding and diagnostic classification performance [1].

In clinical practice, amyloid PET has traditionally been interpreted through binary visual reads that classify scans as "positive" or "negative" for amyloid plaque burden following visual interpretation guides . While these reads have high concordance with expert assessment and neuropathology, they are inherently categorical and reader-dependent, reducing a continuous biological process into a dichotomy, potentially obscuring early or subtle changes in plaque accumulation and limiting sensitivity to treatment effects or disease progression. Although phase III autopsy validation studies have shown that binary classification through visual assessment is approximately 90% accurate in advanced clinical and end-of-life subjects providing a useful stratification of amyloid-β (Aβ) status, in a heterogeneous clinical population visual assessment can be affected by partial volume effects compounded by cortical thinning or atrophy[2]. In addition, comorbidities such as other neurodegenerative disorders can further complicate visual assessment. Moreover, the proportion of subjective cognitive decline (SCD) subjects and pre-dementia patients assessed in memory clinics has significantly increased over the past few years for whom amyloid deposition may be emerging or focal, which makes visual assessment more challenging, especially by less experienced readers.

In summary, recent major developments make it essential to determine Aβ status with high certainty:

- AD diagnosis is more often made in an early stage of the disease such as Mild Cognitive Impairment (MCI) or mild dementia, or in uncertain cases after thorough workup where emerging Aβ pathology challenges high confidence assessments.
- The shift toward earlier diagnosis has led to the need for improvements in the risk stratification of pre-dementia patients.
- Anti-amyloid therapies and their availability in routine clinical practice require the accurate identification of Aβ pathology of potentially eligible patients and the assessment of treatment effects.

Quantification of static amyloid PET scans can be performed using software packages to calculate both regional and composite levels of amyloid burden and to generate a continuous measure of amyloid burden which can be used in addition to dichotomous visual reads[2]. The traditional and most widely used measure for quantifying PET is the Standard Uptake Value ratio (SUVr), defined

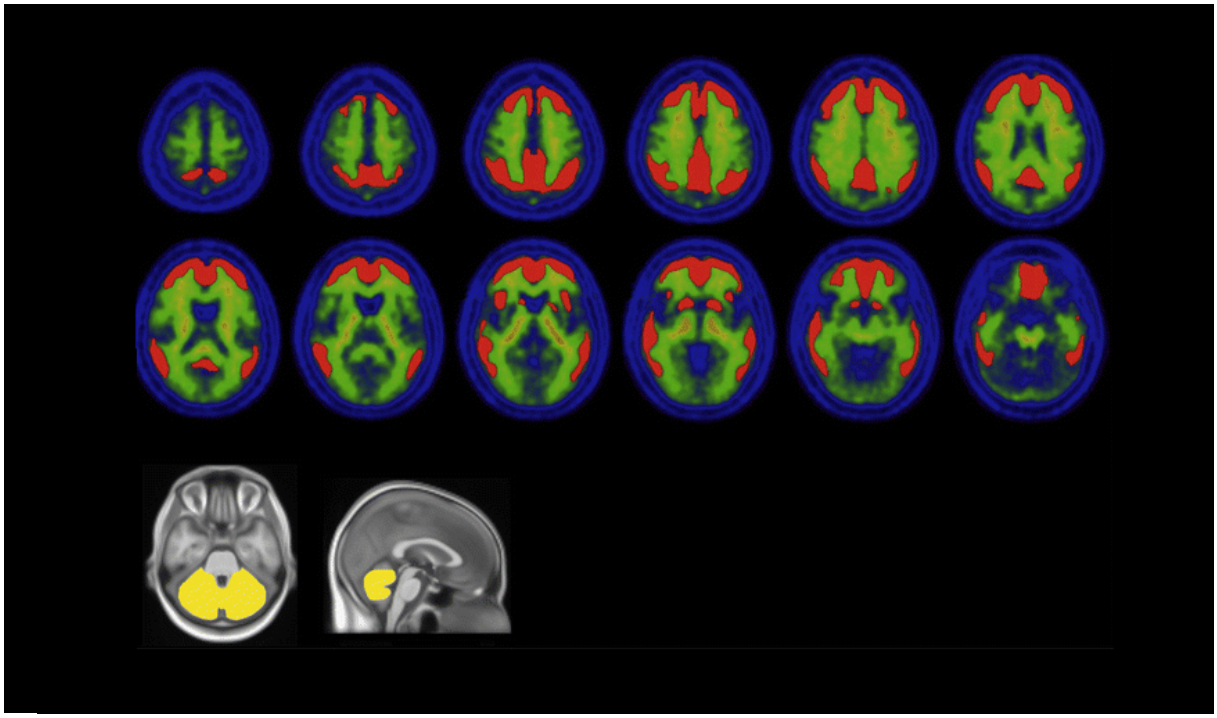


Figure 1: The standard Centiloid (CL) method cortical volume of interest (red) and the whole cerebellum reference region (yellow) normalized to MNI-152 space[3]

as the ratio of tracer uptake in a predefined target region to uptake in a reference region. The common SUVr target regions in the amyloid PET include the medial orbital frontal cortex, anterior cingulate, lateral temporal lobes, precuneus, posterior cingulate, parietal lobe, striatum cerebellum, or cerebellar cortex (Figure 1). However, variability in amyloid PET quantification using SUVr, due to various factors such as amyloid tracer, acquisition time duration, method of analysis, target and reference regions employed, partial volume correction, or instrumentation issues such as scanner model, reconstruction algorithm and method of attenuation correction, makes it challenging to quantitatively compare amyloid PET data acquired with different tracers or processed using different methods [3].

The Centiloid (CL) method was proposed to mitigate these limitations, to harmonize measures of Aβ across various amyloid PET tracers and analysis methods, and to provide a standardized scale that can be used to improve comparability of amyloid PET quantification and define common normative range [3]. Hence, the CL scale provides objective support to visual interpretation and longitudinal follow-ups.

Centiloid Scaling

The Centiloid (CL) method enables quantitative values from Aβ imaging to be expressed in a universal unit, allowing to standardize quantitative amyloid imaging measures by scaling the outcome of each particular analysis method or tracer to a 0 to 100 scale or higher (where typical Alzheimer's disease patients would center at about 100), anchored by young controls (≤45 years) and typical Alzheimer's disease (AD) patients [3]. The method was initially developed for [11C]PiB scans with CL=0 set as the average in young normal subjects and CL=100 the average in subjects with mild AD. However, as access to carbon-11[11C] is limited, scaling using fluorine-18 [18F] tracers was also further achieved.

In brief, to define the CL scale, PiB PET scans of young controls and AD patients were acquired at least 50–70 minutes after injection of 10–15 mCi injection dose at different sites and scanners. Various reconstruction algorithms by site and scanner-type were used: filtered back-projection, ordered-subsets expectation maximization (OSEM) or 3D-Ramla (row-action maximum likelihood algorithm). All subjects also underwent Magnetic Resonance Imaging (MRI). The Statistical Parametric Mapping, version 8 (SPM8), was used for all subsequent registration and normalization processes. Each PET image was registered to its MRI and the MRI and PET scans of each subject were manually reoriented to match the orientation of the MNI-152 T1-weighted template provided with the SPM8 software. Four reference Volumes of Interest (VOIs) were assessed in the development of the "CL standard method":

- Cerebellar Gray (CG)
- Whole Cerebellum (WC)
- Whole Cerebellum plus Brainstem (WC+B)
- Pons

Choice of the final standard reference was based on the variance observed in the data: the Pons gave the largest (worst) variance, the CG performed better, but was consistently outperformed by the WC and WC+B. Greater weight was given to the lower variance obtained using the WC reference. Therefore, the WC was chosen as the reference VOI for the "CL standard PiB method." Finally, the CL transformation is a linear, tracer-specific conversion equation of an individual's mean SUVr (referenced to WC).

The standard Centiloid value (CL) for each individual subject was then defined as [3]:

$$\mathbf{CL\ (PiB) = 93.7 \times SUVr\ (PiB) - 94.6}$$

Young control and patients scan data used to develop the method are available for free public access on the Global Alzheimer's Association Information Network (GAAIN; http://www.gaain.org) and has been used by different groups to generate conversion formulas for site-specific acquisition and processing pipelines, following the specific instructions and requirements outlined in the original framework publication.

Calibrating to the Standard Centiloid Scale

Calibration of a new method is a process that will need to be performed whenever a procedure other than the "Standard PiB Method" is used. This means a calibration is needed when:

- Using different cortical target regions or reference regions
- Direct PiB-to-MNI normalization without the use of MRI scan
- Using any other tracer by any method

For that, a calibrating site should acquire head-to-head data on at least 25 subjects comparing the new process to be calibrated with PiB-PET 50-70 minutes post injection scans using mean SUVr from the standard cortical target region and WC VOIs [3].

To perform the conversion from SUVr to CL for tracers other than PiB such as 18F-based amyloid PET tracers, head-to-head matching PiB and 18F-tracer PET scans from the same individuals according to the standard method have been performed. By applying the standard CL method to these scans, a linear conversion equation (scaling factor) is derived that can then be used to express the new tracer in CL units.

As part of this effort, the calibration for different [18F] tracers has resulted in CL equations below [4-6]:

CL [18F]florbeben = 153.4 × SUVr – 154.9

CL [18F]flutemetamol = 121.42 × SUVr – 121.16

CL [18F]florbetapir = 183 × SUVr – 177

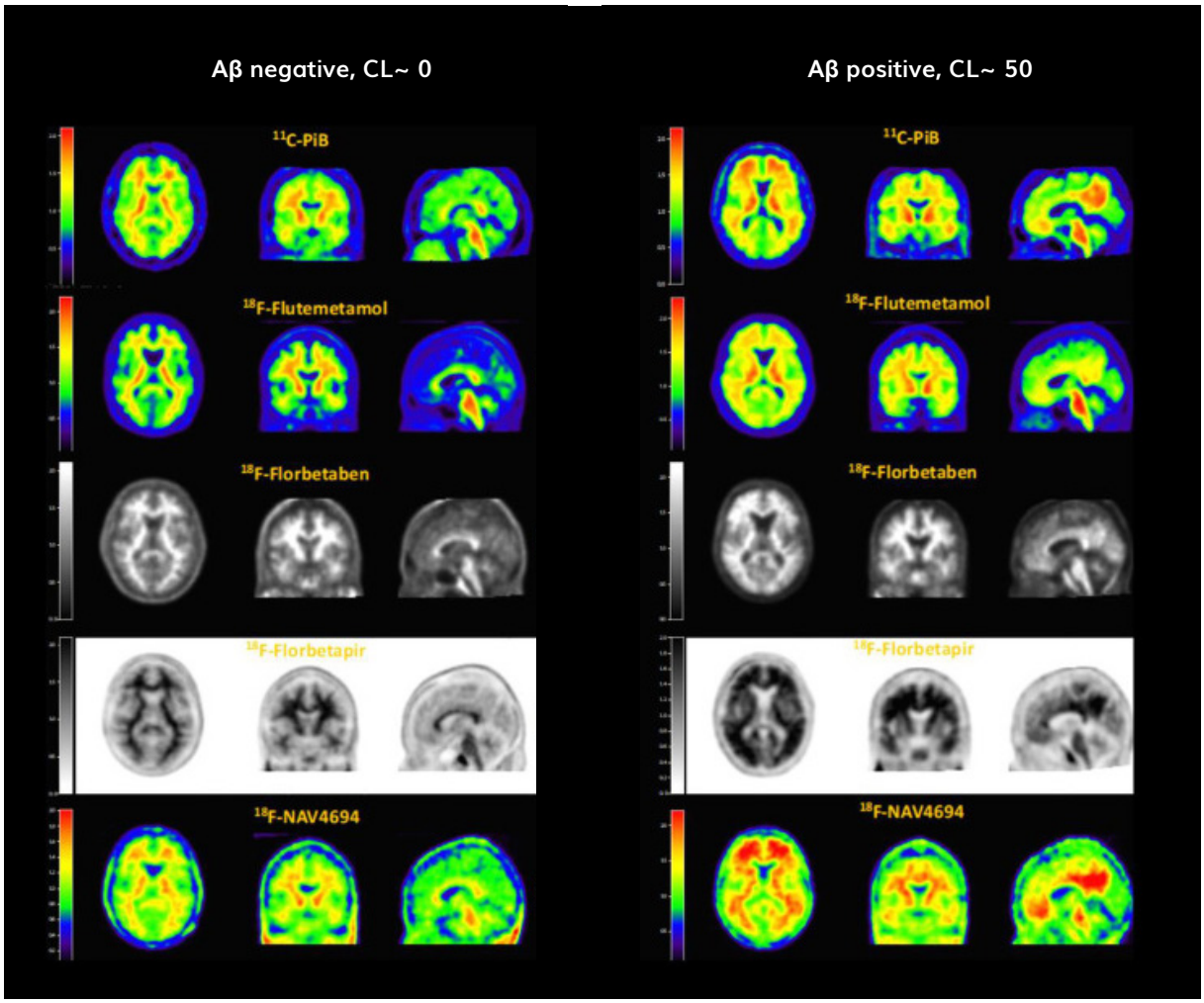


Figure 2: Illustrative PET images derived from the most commonly used amyloid tracers on different patients: left column: Aß negative subjects, CL ~0; right column: Aß positive subjects, CL ~50. [2]

Robustness of Centiloid Scale

The precision of the Centiloid scale requires consideration of the various inherent sources of potential variability. This includes the intrinsic test–retest variability (mean ± SD in CL units) of the specific amyloid-PET tracer and the reliability (variability) of the different methodologies or CL pipelines relative to the standard PiB method, calculated as correlation coefficient (R^2) for the linear regression between the site-acquired standard PiB SUVr data and the non-standard method data [3].

Test-Retest Variability: Methodological changes that are expected to affect the SUVr within the intrinsic test-retest tracer variability have shown minimal or negligible impact on the final CL quantitation. Intra-person test-retest variability expressed in CL units has been reported to be ~3CL [7]. Any change to the acquisition or analytical methodology that has a significant impact on the SUVr beyond the test–retest tracer variability, including among others, different tracer, image acquisition, pre and post processing, and adopted regions of interest, would require a new CL calibration process to generate a revised conversion formula.

Pipeline Impact: Overall, CL quantification using the standard CL pipeline is robust against tracer, and differences in image resolution. Within-pipeline 95% confidence intervals (CI) variability of <3CL for amyloid negative cases, ± 3.3 to ± 4.0 CL between 12 and 24 CL and ± 7CL for the amyloid positive group have been measured7,8. When analysed among different validated pipelines, the impact of different analytical pipelines on CL values were observed to be < 2CL for all tracers for scans visually read as negative. For scans visually read as positive, the absolute differences of ~1CL for [18F]florbetapir, ~9CL for [18F] florbetaben, and ~5CL for [18F]flutemetamol were also observed [7].

Clinical Utility of Centiloid Scaling

Since its development in 2015, the CL scale has been widely implemented in clinical practice and various clinical trials. Quantification of amyloid PET using CL scale has shown strong concordance with binary visual assessment, and using it alongside visual reads has shown to improve diagnostic confidence, accuracy, and consistency for [8,9]:

- early detection of amyloid (mild AD, MCI, and controls);
- less experienced readers, i.e. those with visual read accuracy of ≤ 90%;
- assessment of more challenging to interpret cases, such as patients with unclear diagnoses or weaker grey-white matter differentiation

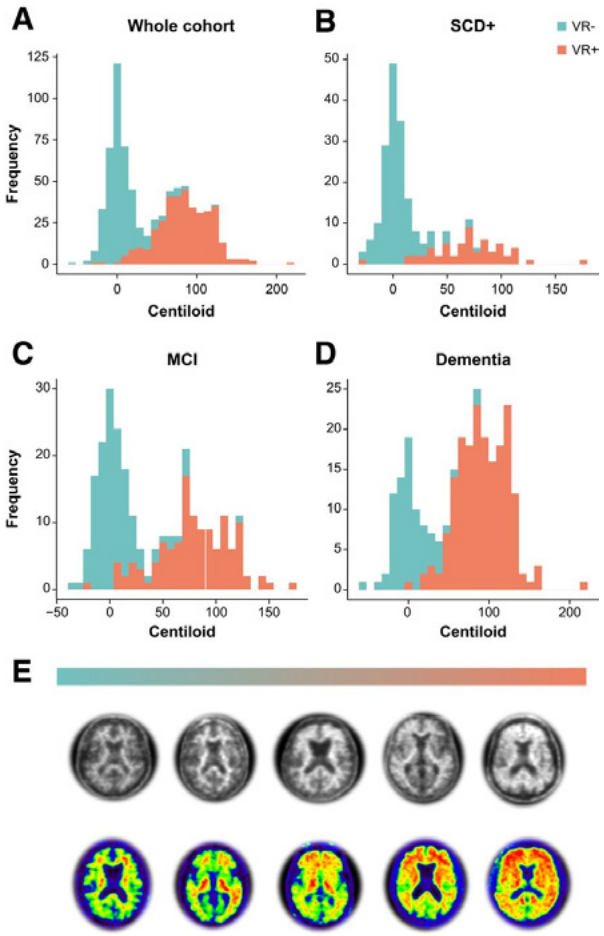


Figure 3: Agreement between local readers and Centiloid quantification for the whole AMYPAD study cohort, and within disease stages (SCD, MCI, Dementia) [9]

Centiloid Cut-offs in Clinical Practice

One of the key advantages of an "absolute" metric of amyloid burden is generalisation of quantitative thresholds across tracers and pipeline implementations. In the context of clinical use, the CL scale is recommended to robustly reflect the amount of Aβ pathology[8]. While CL thresholds may vary slightly across studies, CL < 10 and CL > 30 cutoffs are highlighted to reflect Aβ-negativity and Aβ-positivity thresholds with high certainty, respectively 8:

- <10 CL: Amyloid-negative; with high certainty excludes the presence of Aβ pathology.
- 10–30 CL: "intermediate range" or gray zone; borderline amyloid deposition; increased risk of disease progression.
- >30 CL: Amyloid-positive; high certainty presence of Aβ pathology

Dealing with gray zone values, typically defined as the range between 10–30 CL where amyloid levels are in a "borderline" or intermediate state, requires careful clinical interpretation, longitudinal monitoring, and corroboration with other biomarkers, as these levels indicate an increased risk of progression to AD although may not immediately confirm a diagnosis of Alzheimer's dementia.

Follow-up amyloid PET scans using the same tracer and processing pipeline can determine if the amyloid burden is increasing or remaining stable.

Centiloid in Clinical Trials

CL values are increasingly being incorporated into the design of clinical trials investigating AD treatments for[8]:

- population characterization
- participant selection (as eligibility criteria)
- treatment monitoring (e.g., detection of amyloid removal/clearance)

Universal cut-off or threshold values to denote amyloid status can be applied alongside visual reads and in longitudinal multi-center trial studies to facilitate inter-centre and inter-tracer comparisons and help distinguish between different levels of amyloid pathology. CL scale cut-offs improve patient selection for trials, identify the optimal window for therapeutic intervention, assess therapy response, potentially guide treatment endpoint decisions or determine strategies for reducing AD prevention trial sample sizes (Figure 4)[2].

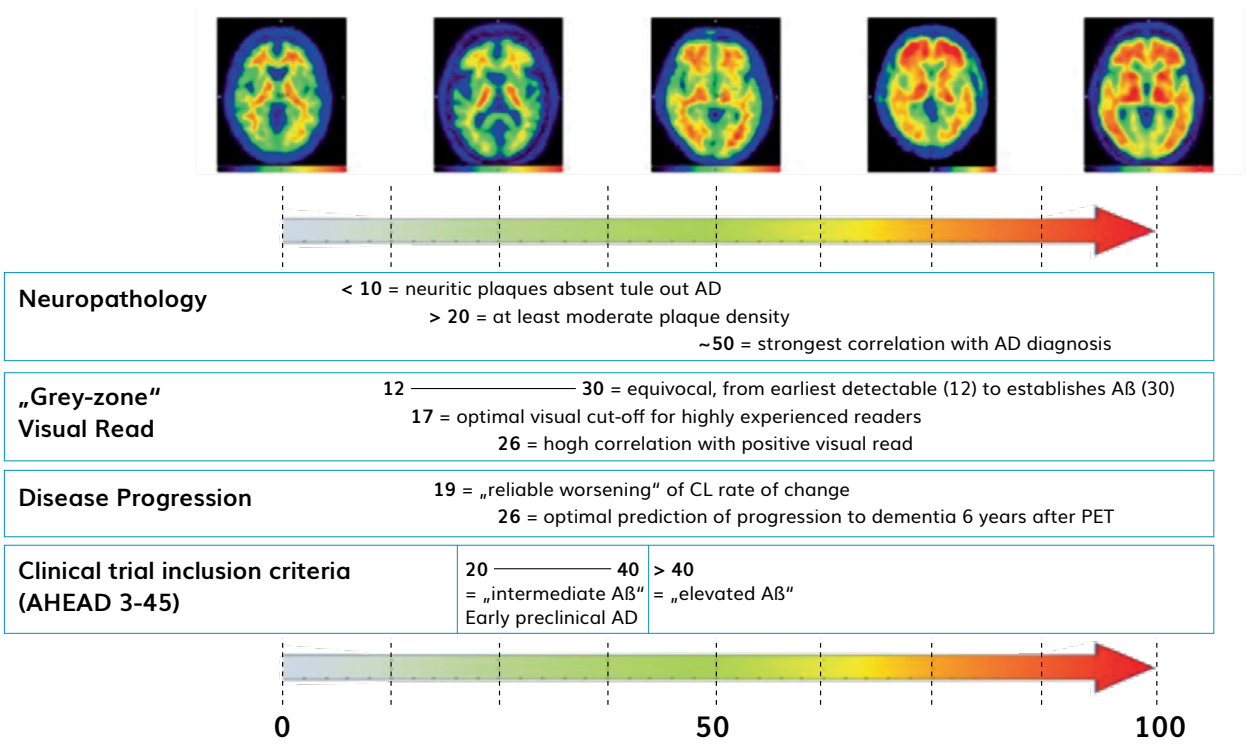


Figure 4: Summary of the various CL thresholds established in the literature and in use for clinical trial inclusion[2]

Patient Eligibility: As part of the Alzheimer's Association Research Roundtable (AARR) forum in 2024, 35 global experts were surveyed to identify an appropriate CL threshold for initiating therapy in patients with MCI or mild AD. Seventy percent of the panel recommended a CL range of 24 to 30 for this purpose. It was noted that while there may be some variability in the CL metric, a threshold of 24 CL aligns closely with visual read methodology, which is based upon a multisite pathology verification study, while 30 CL was suggested as a more conservative threshold, ensuring the presence of neuritic amyloid with greater certainty[1].

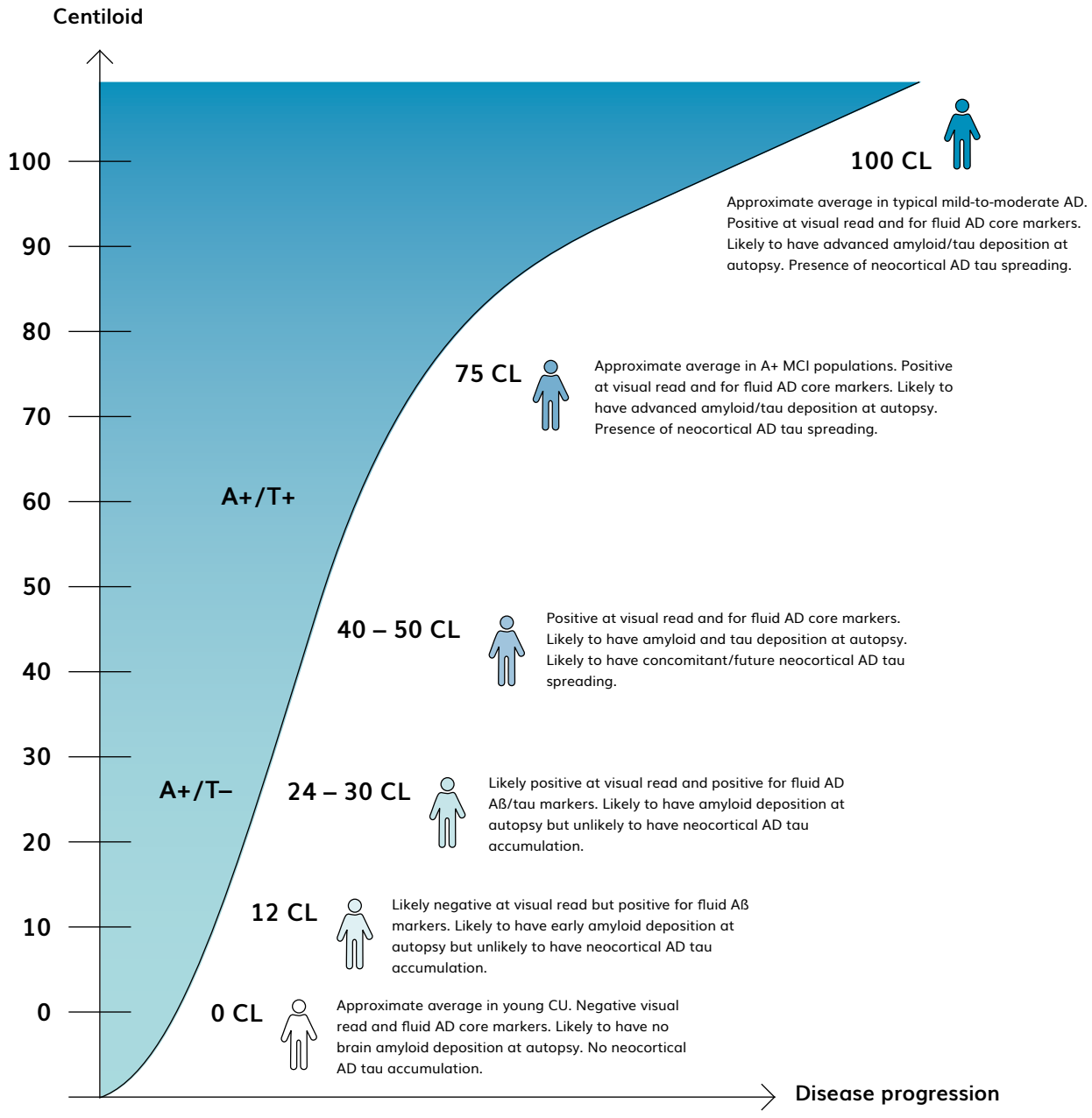


Figure 5: Schematic interpretation of CL values across the 0–100 continuum, with representative examples of the holistic interpretation of CL values according to their relationship with several outcomes and other biomarkers, as described in the literature.[7]

Treatment Monitoring: CL values have also been used in clinical trials for treatment monitoring, both to validate amyloid reduction in response to treatment and to report on number/rates of patients reaching amyloid-PET clearance during the trial. The use of CL values has allowed comparison of the rates of amyloid removal across clinical trials[7].

More recent frameworks such as Treatment-related amyloid clearance (TRAC)[10] have been proposed to characterize patients in the era of anti-amyloid therapies and guide clinical management by distinguishing responders from non-responders.

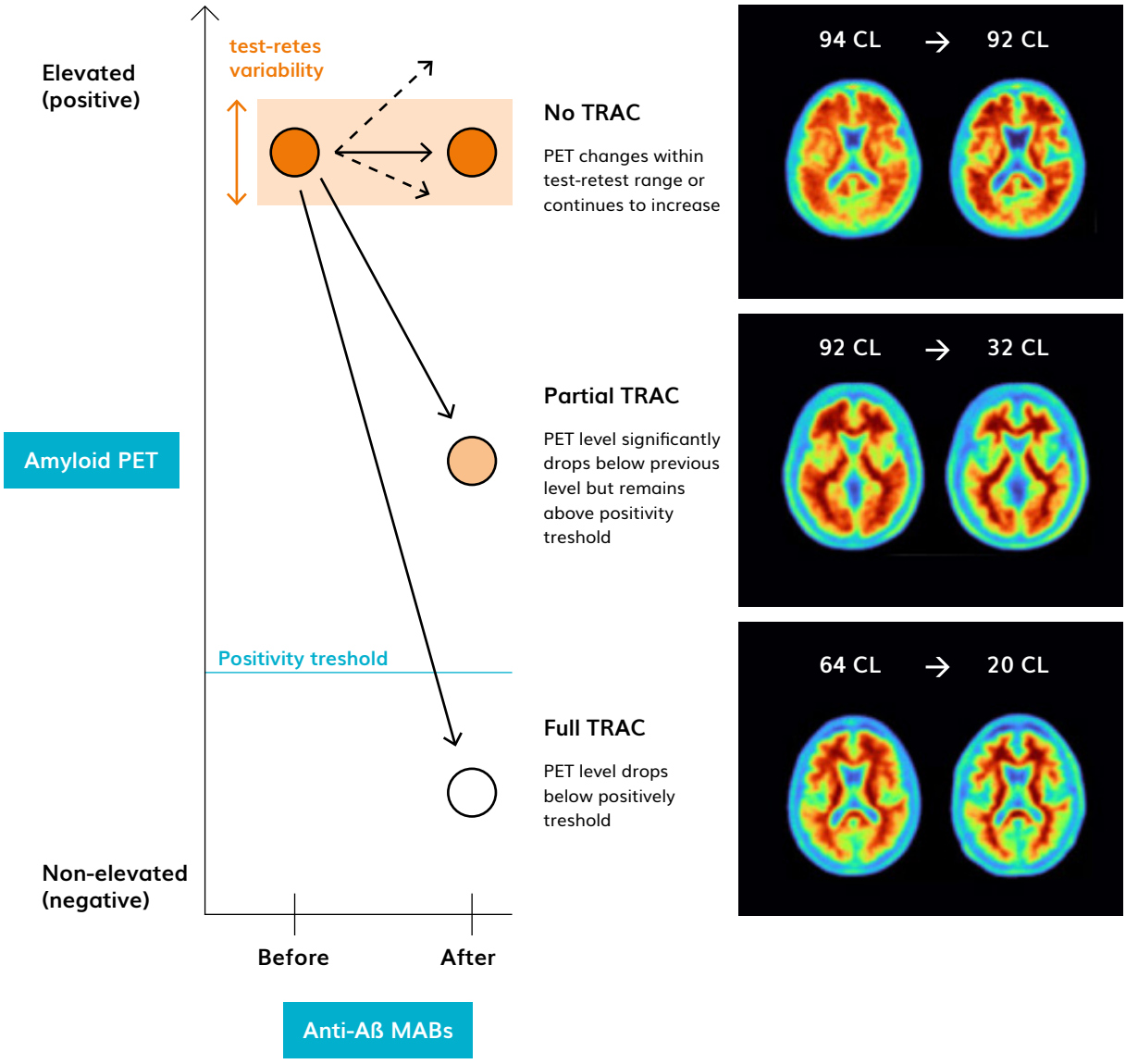


Figure 6: Treatment-related amyloid clearance (TRAC) framework[10]. Full TRAC describes individuals with amyloid-PET levels that have returned to the "negative" range, Partial TRAC describes participants whose amyloid-PET levels have significantly decreased with treatment but who remain above the predetermined positivity criterion.

Clinically available Software Packages

Various regulatory-approved software packages offer automated quantification of amyloid PET, including:

- Hermes Medical Solutions' BRASS (https://www.hermesmedical.com/neurology/)
- Syntermed's NeuroQ (https://www.syntermed.com/neuroq)
- MIM Software's MIMneuro (https://www.mimsoftware.com/nuclear_medicine/mim_neuro)
- GE Healthcare's CortexID (https://www.gehealthcare.com/courses/aw-cortex-id)
- Siemens Healthineers' syngo.MI Neurology Cortical Analysis (https://www.siemens-healthineers.com/molecular-imaging/mi-clinical-corner/whitepapers/syngo-mi-neurology-cortical-anyalsis)
- Combinostics (www.combinostics.com)
- Qubiotech's Neurocloud PET (https://www.qubiotech.com/en/solutions/neurocloud-pet/)
- Neurophet SCALE PET (https://www.neurophet.com/en/solutions/scale-pet)
- Brightonix Imaging BTXBRAIN (https://www.brtnx.com/en/product/product_ai_amyloid.php)
- Other tools available in research-only settings, such as PMOD (https://www.pmod.com/web/?portfolio=CL) or NiftyPET (https://github.com/NiftyPET/NiftyPET).

Although studies showed high quantification agreement between different products and an acceptable reliability for CL scores, software-specific biases have been observed [11-12]. Centiloid scores have been reported to differ by more than 10 CL in individual cases between methods, with CL calibrations contributing to their inconsistency. These differences did not impair their feasibility in aiding the image interpretation, as supported by the concordance with visual readings. Nevertheless, clinicians should recognize these platform-specific characteristics when applying diagnostic thresholds and use caution when interpreting longitudinal changes for amyloid positivity in individual cases.

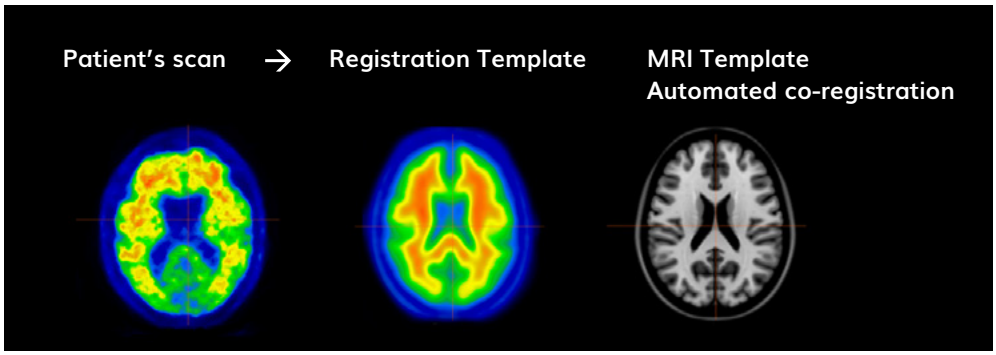
Dedicated Brain PET-only Centiloid Quantification

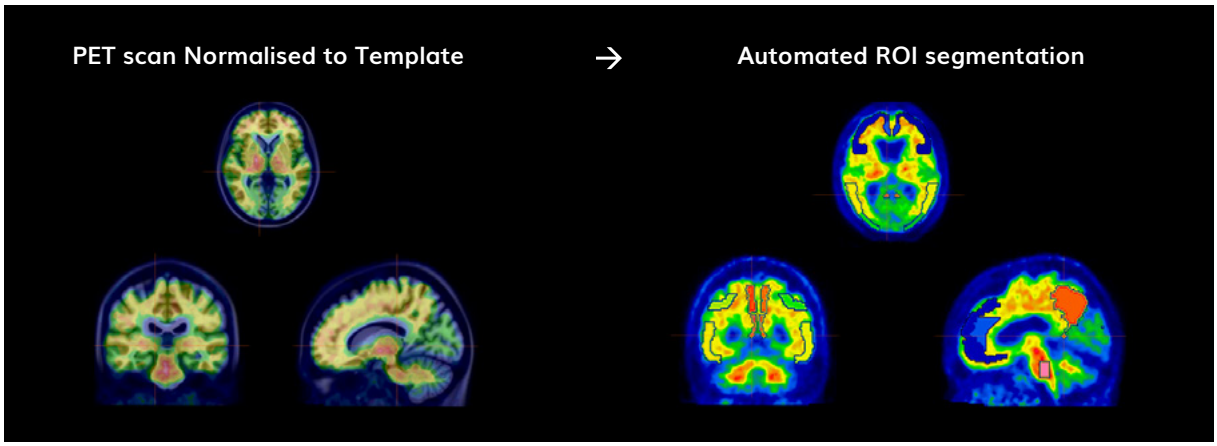
The need for an MRI scan for CL quantification as proposed in the original pipeline could limit its clinical implementation. Consequently, several PET-only pipelines have been developed, which do not rely on MR for accurate registration. For example, the IDEAS study developed a robust PET-Only Processing (rPOP) pipeline. The AMYPAD consortium performed a head-to-head study, comparing the standard PET-MR pipeline to the AmyPype PET-only pipeline to ensure consistent results regardless of the design and showed a strong correlation (R^2 = 0.97) between AmyPype and the standard PET-MR pipeline [8]. Other PET-only CL pipelines have been implemented with excellent performance against MR-based methods, such as the Computational Analysis of PET from AIBL (CapAIBL) or the Non-negative Matrix Factorization method.

Several commercially available software platforms mentioned earlier can also function as a "PET-only" analytical method to support automated co-registration of vendor-neutral PET images to a standard MRI template (e.g., MNI space) for normalization and automated segmentation of standard CL Regions of Interest (ROIs) to calculate the PET-only SUVr and the global CL value.

As an example, we applied CL quantification on amyloid PET scans from NeuroLF (Positrigo, Switzerland, https://www.positrigo.com/product/), a compact, seated, brain PET-only device, using the Hermes BRASS software package automated CL calculation. The NeuroLF PET-only compact design purpose is to fit in neurology or memory clinics and be used as a point-of-care scanner; a decentralized model independent from an imaging center, in order to increase access and allow faster PET imaging appointments.

The availability of validated and automated PET-only pipelines allows inclusion of SUVr and CL quantification values of NeuroLF amyloid PET scans in the final report for better patient management and treatment decisions at the point of care and therefore accelerate clinical workflows.





Global Centiloid (CL) value = 47.3		
REGION NAME Average Ratio SUVr	Voxels	Ratio (Z) SUVr 0.69 (2.60)
L Frontal Ctx	6541	0.68 (2.81)
R Frontal Ctx	6758	0.74 (3.49)
L Ant Cingulate	491	0.81 (4.59)
R Ant Cingulate	518	0.81 (5.30)
L Occipital Ctx	2150	0.54 (0.53)
R Occipital Ctx	2150	0.57 (0.80)
L Parietal Ctx	661	0.64 (1.67)
R Parietal Ctx	626	0.68 (1.86)
L Lat Temo Ctx	4649	0.67 (2.38)
R Lat Temo Ctx	4641	0.69 (2.56)
L PC2	1208	0.70 (2.46)
R PC2	1294	0.71 (2.80)
Pons	450	1.00 (nan)

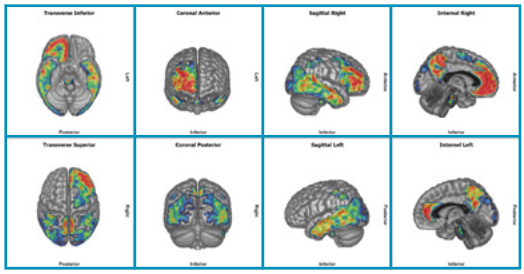


Figure 7: Workflow of reorientation and co-registration of NeuroLF Amyloid PET images with template MRI available in Hermes BRASS. Automated segmentation applies ROIs for SUVr and global CL calculation.

Conclusion

The clinical value of amyloid PET is entirely dependent on the quality of the images and accuracy of their interpretation. Semi-quantification using SUVr values traditionally used in PET imaging has several limitations in amyloid PET as it's dependent on the amyloid tracer used, duration of acquisition time, method of analysis, target and reference regions employed and partial volume correction. Instrumentation factors such as scanner model, reconstruction algorithm and method of attenuation correction also create variability and challenge efforts towards its universal use.

Quantitative amyloid PET using Centiloid (CL) scaling was developed as a continuous measure of amyloid burden (value between 0 and >100), to provide a standardized framework for amyloid PET quantification and to harmonize values across different tracers and processing methods using different pipelines. CL scaling has now matured into a clinically meaningful adjunct to visual interpretation. When implemented in a validated, standardized manner, it enhances diagnostic confidence, enables harmonization, and supports emerging therapeutic pathways. Although not mandatory and not reimbursed separately, quantification is strongly favored in the therapy era because it provides objective evidence of amyloid burden and progression and improves amyloid PET reimbursement.

While the standard CL pipeline as described by Klunk and colleagues is based on the [11C]PiB tracer and Statistical Parametric Mapping (SPM) for analysis, an abundance of alternative pipelines have been developed and are available. Any change to the acquisition or analytical methodology would require a new CL calibration to generate a revised SUVr to CL conversion formula, and head-to-head comparison with the standard pipeline. Hence, clinical validity of CL scaling pipelines relies on:

- Technical validation: repeatability, test–retest variability, and robustness to reconstruction changes
- Biological validation: concordance with visual reads and clinical diagnosis
- Cross-platform validation: agreement with the standard CL pipeline

With the availability of robust, validated PET-only CL pipelines, quantification results from dedicated brain PET-only amyloid scans can be reported together with final visual findings, facilitating the integration of such point of care devices as part of the MCI/AD early diagnosis in a decentralized model, for better patient management and faster treatment decisions at the point of care, and therefore accelerate clinical workflows.

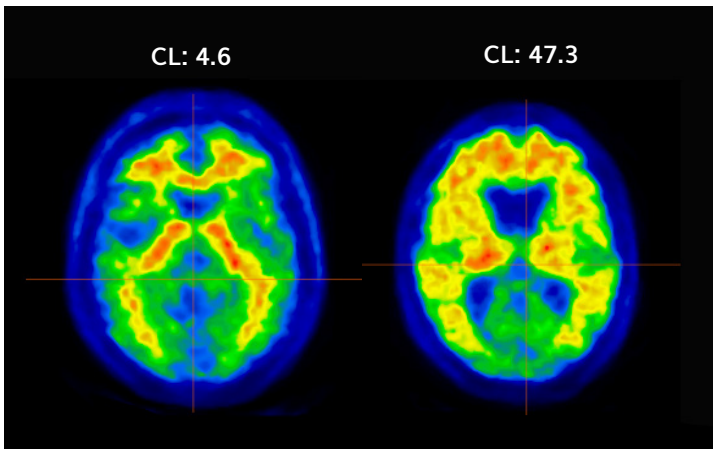


Figure 8: NeuroLF Amyloid PET images were acquired as part of clinical diagnostic routine and according to the standard protocol for [18F]flutemetamol, and uploaded in Hermes BRASS for automated quantification using template MRI (Courtesy of ProScan Imaging, Naples, Florida, the United States of America; **https://proscan.com/florida/**). Left image: CL: 4.6, Ratio (Z) SUVr: 0.53 (0.24); Right image: CL: 47.3, Ratio (Z) SUVr: 0.69 (2.60).

Limitations

Although standard, validated pipelines for CL calculation have shown to be robust, it is important to be aware of some limitations of CL scaling:

- Scale Anchoring: while scaled between 0–100, CL can sometimes be negative or in clinical practice may exceed 100.
- Variability (Reliability): while designed to harmonize quantification of amyloid PET images across tracers, scanners, and processing pipelines, CL values are still subject to variations based on image processing pipelines, and most notably, the chosen reference region. The choice of reference region has been reported to be the largest driver of CL variability.
- Studies indicate that the 95% CI for CL measurement uncertainty is roughly ±3 to ±8 CL units (for amyloid negative to amyloid positive images).
- CL thresholds are subject to ongoing refinement, and decisions should be made by specialized clinicians based on the patient's complete clinical picture. Variability matters most around the 'intermediate' or 'gray zone' which is 10–30 CL.
- Quantification should always be interpreted in conjunction with visual assessment, clinical context, and other biomarkers. It serves as a complementary clinical decision-support tool when robustly implemented and validated, enhancing diagnostic precision. False negatives – visually positive amyloid PET scans that are classified as negative by CL quantification, particularly due to substantial occipital uptake - represent a known limitation in current amyloid imaging analysis pipelines.
- CL quantification is sensitive to motion, particularly because it relies heavily on accurate spatial normalization and co-registration with an anatomical MRI. Patient movement during PET acquisition can induce image artifacts, leading to inaccurate definition of ROIs and subsequent errors in calculating the SUVr, which is then converted to a CL value.

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