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## Editorial

## Expert opinion on Centiloid thresholds suitable for initiating anti-amyloid therapy. Summary of discussion at the 2024 spring Alzheimer's Association Research Roundtable

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## ABSTRACT

A 24–30 Centiloid (CL) threshold was collectively considered by a group of global dementia experts as a practical and implementable cut-off for anti-amyloid therapy intervention, in Alzheimer's disease patients who have been diagnosed at the mild cognitive impairment or mild dementia stage of their disease. Though additional validation is needed, knowledge of this threshold would be valuable to those involved in diagnosing and treating patients in the new AD care pathways, as well as entry into clinical trials. Therapy monitoring to determine future treatment response and assess amyloid clearance can be accomplished with amyloid PET with some technical details still to be elucidated.

## Brief Report

Recently in May 2024, the Alzheimer's Association Research Roundtable considered the theme of System Readiness and Patient Care Pathway for Alzheimer's Disease Diagnosis and Treatment. The issue of 'Optimizing the Use of Amyloid PET quantification in clinical routine settings' was one of the topics discussed at this meeting and is the focus of this short opinion piece. This article is particularly timely because of the recent FDA approvals of both lecanemab (Leqembi<sup>TM</sup>) and donanemab (Kisunla<sup>TM</sup>) where 'confirmed' amyloid pathology is a prerequisite of therapy initiation for both of these drugs.

Amyloid PET tracers (Amyvid<sup>TM</sup>, NeuraCeQ<sup>TM</sup>, Vizamy<sup>TM</sup>) have been approved in the USA and other global territories since 2013. All tracers were validated against neuropathology as the standard of truth [1]. According to the approved US Prescribing Information (which is consistent for all three radiopharmaceuticals), image interpretation of these scans is based upon a visual dichotomous yes or no for the presence or absence of tracer uptake in gray matter. In the pivotal Phase III studies

required for the registration of these amyloid PET tracers, the accuracy of image interpretation by visual inspection relative to histopathology as the standard of truth was approximately 90 % [2,3,4]. These studies were, however performed over 10 years ago, and since then new strategies of examining read performance have been reported.

In addition to pathology, quantitative measures of brain amyloid load are also used as a comparator to assess the accuracy of image interpretation, for example to assess possible differences between local and expert readers whose sensitivity may differ depending upon their levels of expertise. Whilst routine in research cohorts, the future use of quantitation methodology and increased visibility of the standardized 0–100 Centiloid (CL) scale [5] as an outcome measure in anti-amyloid therapy studies [6,7] has amplified the interest beyond Nuclear Medicine to the wider neurology community.

The US-based IDEAS study examined visual interpretation (positive or negative) results from local community-based readers of over 10,350 amyloid PET scans [8] using a neuropathology-based CL threshold of 24.4 and found an overall 86 % concordance rate (53 % V+/Q+, 33 %

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V-/Q-, 8 % V+/Q-, 6 % V-/Q+) [9] between robust PET-Only Processing (rPOP) based amyloid status and visual reads. In other studies, agreement between expert readers and quantitation however was higher at 93–95 % [10,11] suggesting that CL quantitation represents an opportunity for improved accuracy of PET amyloid imaging at the local level.

For initiation of anti-amyloid therapy, confirmation of positive biomarkers (either PET or CSF) indicative of AD are cited in both lecanemab and donanemab prescribing information as well as the Cummings et al (2023) [12] appropriate use recommendations for lecanemab. Regarding amyloid PET, neither give any direction as to an appropriate quantitative threshold which may be suitable to guide the inclusion of patients onto anti-amyloid therapies. With the advent of the CL measure being widely accepted for assessing cortical amyloid load [13], we thought it relevant to ask the questions 'What Centiloid value would you consider as a threshold for the inclusion specifically of MCI due to AD/early AD patients on to therapies, and why?'. The opinions of 38 global dementia experts with research and clinical expertise in both neurology and nuclear medicine/radiology were sought with 34 responding within a short period of time. The content of this short opinion piece summarizes their responses (with a list of participating experts at the end of the document).

The question specifically related to the therapy intervention of MCI due to AD/mild AD subjects, it is recognized that the CL measure in the future may have other intended uses such as targeting earlier patients with some cognitive deficits who may be 'accumulating' amyloid [13] or for facilitating the progress of the AD targeted drug development pipeline [14].

Although it is recognized that at about 12 CL amyloid pathology is emerging [15] seventy percent of the experts considered a threshold between 24–30 Centiloids suitable for therapy intervention. High concordance with reference neuropathology (ADNC/CERAD/Thal measures) and visual read methodology was most cited for this range [16]. It was acknowledged there is some 'noise' in the CL measure and that the upper figure of 30 CL represents a more conservative estimate where there is more certainty in the presence of amyloid and that potential false positive patients could be excluded from futile treatment regimens (data from IDEAs for example suggests that the false positive rate may be approximately 8 % [9]). As the current treatments have side effects that require continuous monitoring it may be prudent to limit those patients with lower CL values until treatments become less intensive or for inclusion into research studies (as is happening with the AHEAD 3–45 study where the lower bound of the A3 study is 20 CL [17]). Sites that have already implemented lecanemab therapy (such as the Mayo Clinic) also consider a cut-point (25CL) within the 24–30 CL range to supplement visual read methodology based upon the multisite pathology verification study of La Joie et al (2019) [16].

The value of the CL measure for monitoring purposes was also highlighted by many of the experts to determine future treatment response and assess amyloid clearance. CSF biomarkers are also capable to determine initial amyloid status but currently have limited precision for measuring longitudinal changes related to treatment effects. Indeed, the recent donanemab prescribing information states: 'consider stopping dosing based on reduction of amyloid plaques to minimal levels on amyloid PET imaging' [18]. Further clarification on specific quantitative levels of amyloid for treatment discontinuation (both 11 and 25 CL were part of the donanemab 'stopping' rules [7]) need to be articulated for wider scale implementation. It was also considered amongst the expert feedback that an amyloid scan at baseline for therapy initiation may also offer more detail that just the dichotomous yes/no for amyloid load with the CL value itself being useful for possibly predicting an approximate time for amyloid clearance/treatment cessation.

Several of our expert panel stated that from 25 CL the measure improves prediction of memory clinic patients with cognitive complaints progressing to dementia within 5 years [19]. Furthermore, in the Australian AIBL study, as baseline Centiloid values increased there was a

proportionate rise in the risk of progression to either MCI or dementia in older cognitively impaired participants [20]. Although there is strong research evidence for forecasting decline in cognition in the presence of amyloid, there is currently a 'limitation of use' for this application in the prescribing information for the amyloid PET tracers.

There was also the suggestion that lower CL levels in MCI cases may be due to alternative aetiologies such as LBD [5]. Lower CL values such as those between 15–20 may also be indicative of early patients accumulating amyloid but so far, the approved therapies are not indicated for these patients [13].

One expert pointed out that visual read sensitivity between different Nuclear Medics/Radiologists was often variable with experienced readers being able to consistently assess emerging pathology at 15 (personal communication from Professor Chris Rowe) to 17 CL [21] whilst other studies report a higher proportion of ambiguous scans between 20–35 CL [11]. Use of a standardised CL range could overcome this variation in read performance to ensure consistent inclusion of patients onto therapy.

Several experts were even more conservative than the 30 CL upper bound with 40 CL being cited to exclude anyone who may have amyloid due to other causes other than AD, as well as articulating the possible value of the tau measure. Although tau levels were utilised in the donanemab TRAILBLAZER ALZ-2 trial [7] for triaging patients, tau PET is not featured in the prescribing information.

Some impact of changing scanner model during longitudinal assessment was observed at higher CL levels [22]. From a cross section perspective this would not majorly impact initial treatment decisions as the impact was less than 2 CL at lower values hence the value of using the 24–30 CL range rather than a single measure. From an image interpretation perspective, our global dementia experts reiterated the importance of always visually inspecting the image in addition to producing a CL value as there are cases where the CL mask may sometimes include white matter, or the cerebellar reference region may be inaccurately positioned leading to a discordant visual/quantitation result. It is to be reinforced to the community at large using amyloid PET that quantitation via Centiloids (or any other measure) is not a substitute for visual inspection and that clinical interpretation may be optimized when the two methodologies are performed together. The use of the GAAIN atlas and whole cerebellum reference region originally proposed by Klunk et al (2015) [5] is highly recommended [23] and that for both initial and follow-up scanning consistency across tracer uptake times, image acquisition and processing pipelines should be observed [24]. Increasingly software products for image processing are including the CL measure and are both 510k cleared and CE marked with these recommended for clinical practice.

One expert pointed out that the CL measure was developed using data [5] from primarily Non-Hispanic White subjects and that group averages and CL thresholds may not be representative from other groups with different racial or socio-economic compositions; this is an area that should be considered for the future when performing larger registry or other research studies.

In summary, a 24–30 CL threshold was collectively considered as a practical and implementable cut-off for therapy intervention in patients with mild cognitive impairment or mild dementia. Knowledge of this threshold should be disseminated to those involved in diagnosing and treating patients in the new AD care pathways and can standardize patient inclusion. Therapy monitoring can be accomplished with amyloid PET with some technical details still to be elucidated.

#### Declaration of competing interest

GF is an employee of GE Healthcare who hold the Marketing Authorisation for Vizamy<sup>TM</sup>.

CW is a full-time employee of the Alzheimer's Association

GR has served on scientific advisory boards and/or as a consultant for Eli Lilly, Genentech/Roche, GE Healthcare, Alector and Merck,

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