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View point

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ABSTRACT

The recently announced revision of the Alzheimer's disease (AD) diagnostic ATN classification adds to an already existing disregard for clinical assessment the rejection of image-based in vivo assessment of the brain's condition.

Abbreviations: Aβ, amyloid-beta; AD, Alzheimer's disease; ATN, amyloid, tau, neurodegeneration; FDA, Food and Drug Administration; NIA-AA, National Institute on Aging and Alzheimer's Association.

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Amyloid-PET
Dementia
Revision

The revision suggests that the diagnosis of AD should be based solely on the presence of cerebral amyloid-beta and tau, indicated by the "A" and "T". The "N", which stands for neurodegeneration – detected by imaging – should no longer be given importance, except that A+ ± T + = AD with amyloid PET being the main method for demonstrating A+ . We believe this is an artificial and misleading suggestion. It is artificial because it relies on biomarkers whose significance remains obscure and where the detection of "A" is based on a never-validated PET method using a tracer that marks much more than amyloid-beta. It is misleading because many patients without dementia will be falsely classified as having AD, but nonetheless candidates for passive immunotherapy, which may be more harmful than beneficial, and sometimes fatal.

In 1787 Prince Potemkin-Taurichеski of Russia was tasked with settling more Russians in the country of Crimea, which had been annexed from the Ottoman Empire in 1783. To impress Empress Catherine II of Russia, who decided to visit the land of 'New Russia', Potemkin took the empress down the Dnipro River on a royal barge and showed her the rural villages, which were filled with villagers every day, making it look like the resettlement was going very well. What the empress did not know was that these villages were simply facades that looked like buildings from the river's perspective. Every night, while the empress slept, Potemkin's workers would pack up the facades, move them to the next stop on the river and rebuild them to look like another village.

Unfortunately, this story also has similarities with the announced revision of Alzheimer's diagnostic criteria (Alzforum, 2023). The diagnostic criteria for Alzheimer's disease (AD) have undergone a number of changes since 1984 (Knopman et al., 2019). Initially, they were based mainly on clinical assessment, and from 1997 onward primarily on postmortem neuropathological findings, namely neuritic plaques and neurofibrillary tangles. In 2011, the US National Institute on Aging and Alzheimer's Association (NIA-AA) endorsed, for research purposes, a diagnosis of preclinical AD based on the presence of positive AD biomarkers in the cerebrospinal fluid or according to cerebral amyloid-PET imaging (Sperling et al., 2011), which had emerged in 2004 with the appearance of the tracer ^{11}C-Pittsburgh Compound-B (Klunk et al., 2024) and later more long-lived ^{18}F-labeled PET tracers. ^{18}F-florbetapir (Camus et al., 2012), in particular, has been widely used for detecting "amyloid positivity" and for monitoring perceived therapy-induced removal of cerebral amyloid in clinical trials. It is important to note here that amyloid-PET also marks inflammation, myelin and myelin damage where amyloid is not present (Kepe et al., 2013; Surmak et al., 2020; Høilund-Carlsen et al., 2022). Cognitive impairment was left out as a criterion (Sperling et al., 2011).

In 2018, a series of authors created an NIA-AA Research Framework including the "ATN" classification (Jack et al., 2018) based on an "unbiased descriptive classification scheme for Alzheimer disease biomarkers" proposed by themselves in 2016 (Jack et al., 2016). The "A/T/(N)" classification, as it was written in 2018, put crucial emphasis on "A", biomarkers of amyloid-beta (Aβ) plaques, and "T", biomarkers of tau. In contrast, biomarkers of neurodegeneration "(N)", including FDG-PET hypometabolism and atrophy on MRI, were in parenthesis, indicating a lesser diagnostic role (Jack et al., 2018).

The latest proposed revision is not only devoid of clinical assessment; it also drops the "N" for diagnosis and staging of Alzheimer's. It relies solely on biomarker molecules, the pathogenic roles of which have never been proven, and has been praised with statements such as "This is great progress, absolutely the direction we need to go," and "This [system] matches the biology so well. You've nailed it" (Alzforum, 2023). The proposers wish to endorse it not only for research but also for clinical practice. In the case of clinical trials, there is an unambiguous effort to define the disease as the presence of surrogate markers (A and T) alone. One hypothetical outcome of this scenario is the following: a new drug inhibits neuronal degeneration without affecting the presence of amyloid and tau. That hypothetical drug, although disease modifying, would be considered a "failure" in clinical trials, while patients are "binned" into two groups: Alzheimer's disease with cognitive impairment or Alzheimer's disease without cognitive impairment. The omission of cognitive impairment from the definition of AD doesn't make sense because people who exhibit brain amyloidosis and no dementia (about 1/3 of all people older than 75) would also be identified as AD patients.

Everyone agrees that AD is a form of cognitive decline caused by neurodegeneration, but neither cognitive decline nor neurodegeneration are tested for or given diagnostic value in the revised ATN system, which the authors now want clinicians to use "by selecting the best-validated biomarkers", none of which have been properly validated. The lack of correlation between cognitive status and the biomarkers in question was highlighted some 25 years ago, as was the lack of a causal relationship between Aβ and AD (Robakis and Pangalos, 1994; Neve and Robakis, 1998), two serious discrepancies that no one has since been able to explain (Morris et al., 2018).

There is no hook in the ceiling to hang the definition on, i.e., an infallible reference to refer to and test against. The latest proposed revision lacks justification in medical science. We propose a definition based on clinical assessment and in vivo evidence of increased neurodegeneration that most clinicians would be able to relate to and use in their daily work (Høilund-Carlsen et al., 2023) supplemented by biomarkers with the proviso that the biomarkers are acknowledged to be surrogates that have not yet been shown to be causal despite a 20-year effort to do so.

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Declaration of Competing Interest

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Data Availability

No data was used for the research described in the article.

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