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Perspective

Revisiting the framework of the National Institute on Aging-Alzheimer's Association diagnostic criteria

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Abstract In 2011, the National Institute on Aging and the Alzheimer's Association (NIA-AA) proposed revising the criteria for diagnosing Alzheimer's disease (AD), which had been established more than 25 years earlier by the National Institute on Neurologic and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA), now called the Alzheimer's Association. The NIA-AA initiative also built upon research criteria for AD proposed by the International Working Group (IWG) in 2007 and updated in 2010. These efforts to revise the criteria reflect the need to improve diagnostic accuracy, facilitate clinical trials, and establish a common set of criteria that are universally accepted across domains of clinical practice, research, and drug development. To ensure that the proposed NIA-AA criteria remain as current as possible, the Alzheimer's Association Research Roundtable convened a meeting in Washington, DC, on October 1 and 2, 2012, bringing together international stakeholders from industry, academia, and regulatory agencies to identify areas of agreement and research gaps respective of NIA-AA criteria and IWG recommendations.

Keywords: Diagnostic criteria; Dementia; Alzheimer's disease; Biomarkers

1. Introduction

In 2011, four workgroups (WGs) established by the National Institute on Aging and the Alzheimer's Association (NIA-AA) proposed revising the criteria for diagnosing Alzheimer's disease (AD) [1], which had been established more than 25 years earlier by the National Institute on Neurologic and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA). New criteria were deemed necessary because of an explosion of research on the epidemiology and clinical-pathological correlations of the disease and the development of numerous potential AD biomarkers. The NIA-AA WGs also built upon the research criteria proposed by the International Working Group (IWG) in 2007 [2].

These various efforts to revise the criteria reflect the need to improve diagnostic accuracy, facilitate clinical trials, and establish a common set of criteria that are universally accepted across domains of clinical practice, research, and drug development. As the field moves toward reaching a consensus on the new criteria, there remain unanswered questions about how best to implement the criteria in clinical and research settings, the implications of the revised criteria in the design and execution of clinical trials, how to validate these criteria, and their

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Table 1
Staging categories across the AD spectrum

Category	Subcategory	Cognitive/functional signs	Biomarkers
Preclinical	Stage 1	Asymptomatic	Aβ (PET or CSF)
	Stage 2	Asymptomatic	Aβ + neuronal injury (tau, FDG, sMRI)
	Stage 3	Subtle cognitive/behavioral decline	Aβ + neuronal injury (tau, FDG, sMRI)
MCI due to AD	Intermediate likelihood	Impairment in episodic memory	Aβ or neuronal injury (tau, FDG, sMRI)
	High likelihood	Possible impairment in other cognitive domains	Aβ + neuronal injury (tau, FDG, sMRI)
	Unlikely due to AD	Mild functional impairment Atypical presentations also possible	Biomarker negative for Aβ and neuronal injury
AD dementia	Probable; amnestic	Impairment in learning and recall and at least one other cognitive domain	Biomarkers increase certainty: Aβ + neuronal injury (tau, FDG, sMRI)
	Probable; non-amnestic	Language, visuospatial, or executive dysfunction	Biomarkers increase certainty: Aβ + neuronal injury (tau, FDG, sMRI)
	Possible	Meets clinical criteria for atypical or mixed etiology dementia	Biomarkers increase certainty: Aβ + neuronal injury (tau, FDG, sMRI)
	Unlikely due to AD	Meets clinical criteria for typical or atypical AD dementia	Biomarker negative for Aβ and neuronal injury

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-β; CSF, cerebrospinal fluid; PET, positron emission tomography; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging; MCI, mild cognitive impairment.

effect on regulatory requirements. To ensure the proposed NIA-AA criteria remain as current as possible, the Alzheimer's Association Research Roundtable convened international stakeholders from industry, academia, and regulatory agencies to identify potential areas for revision or update. Although dementia and preclinical states were discussed, the focus of the meeting was on the earliest symptomatic phase of AD, referred to as "mild cognitive impairment" (MCI) in the NIA-AA criteria and "prodromal AD" in the IWG criteria. This is the population that may be the hardest to define, but it is the most practical population for the development of therapies targeting the underlying disease pathology.

2. The NIA-AA revised guidelines

The 2011 NIA-AA criteria and research guidelines applied new terminology to AD, calling it Alzheimer's "dementia" in a manner very similar to how the clinical diagnosis of Alzheimer's "disease" was formulated in 1984 [3]. Alzheimer's dementia is now defined as cognitive impairment that interferes with work or daily activities, represents a decline from a previous level, and cannot be explained by other disorders, including psychiatric. The age range for Alzheimer's dementia was expanded to include those over age 90, and memory impairment was eliminated as a requirement. Therefore, a diagnosis of dementia requires deficits in two of five domains: memory, executive function, visuospatial performance, language, and personality/behavior [4]. The additional component in the Alzheimer's dementia revised criteria was the incorporation of biomarkers to increase certainty of a diagnosis when needed and appropriate (Table 1).

The NIA-AA criteria and recommendations labeled the symptomatic predementia phase of AD as MCI and developed guidelines for the diagnosis of MCI as a syndrome and MCI due to AD as a syndrome with an etiological diagnosis. Although this classification emphasizes that the disease exists along a continuum with unclear boundaries, it also posits that persons can be identified and characterized in the MCI stages even in the presence of uncertainty. Changes from previous MCI criteria include the acknowledgment that functional losses may occur even while maintaining some level of independence, and they accept that concerns about cognitive changes may be expressed by patients, family members, or others close to the patient. The term "mild cognitive impairment due to AD" [5] was introduced to denote a subgroup of MCI with high likelihood of underlying AD pathology. The new terminology is supported by data showing that most people along the AD continuum in the MCI stage (at least those diagnosed in specialized research centers) have AD pathology [6] (Table 1).

Finally, preclinical stages of AD were proposed, reflecting amyloidosis with or without neurodegeneration biomarkers and cognitive decline [7]. The preclinical framework was only designed for research and not for diagnostic purposes. The preclinical research recommendations recognize that more than one third of clinically normal individuals over the age of 65 harbor high levels of brain β-amyloidosis, and they recognize a growing interest in trials aimed at secondary prevention in these presymptomatic individuals [8]. Studies in individuals with autosomal dominant mutations leading to the development of early-onset AD show signs of disease long before onset: amyloid accumulation beginning at 20 years, neurodegeneration biomarkers at 10 years, and neuropsychological (Logical Memory Recall test) deficits 5 years before onset [9] (Table 1).

These recommendations and criteria have different implications when used for clinical practice compared with their use in research studies and clinical trials. For example, the clinical diagnosis of MCI is used in patient care, but it presents challenges in terms of determining a participant's appropriateness for a clinical trial, in which it is important to determine their position on the AD continuum and the