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Review

# New Alzheimer's disease diagnostic criteria 2024: Biological vs Clinical-biological
# Nuevos criterios diagnósticos 2024 de enfermedad de Alzheimer: Biológicos vs Clínico-biológicos

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**Abstract**
Regarding the development of Alzheimer's disease biomarkers, the diagnostic criteria for the disease have been modified. Up to now, they have only been used in research, but with the advent of new biological treatments with anti-amyloid antibodies, they are beginning to be transferred to the clinic. In 2024, the working group sponsored by the Alzheimer's Association of the US (Jack et al., 2024) proposed biological criteria for the disease based on diagnosis with biomarkers. This brings with it the problem that there are normal subjects with positive biomarkers called by them patients with asymptomatic Alzheimer's disease. The latter was not shared by all the groups and the IWG (International Working Group) (Dubois et al., 2024) came out to mark the position that the latter are subjects "at risk" and not subjects with Alzheimer's disease. All of this brings with it a greater gap between developed countries and those that are developing, such as Latin America. Custodio et al. (2024) discuss these difficulties and the probable proposals to implement them in the clinic in Latin America and to be able to make use of these new medications.
*Keywords:* Diagnostic criteria; Alzheimer's; biomarkers; dementia; mild cognitive impairment; prodromal Alzheimer's.

**Resumen**
A partir del desarrollo de los biomarcadores de la enfermedad de Alzheimer se fueron modificando los criterios diagnósticos de la enfermedad. Hasta ahora los mismos se usaban solo en investigaciones, pero con el advenimiento de los nuevos tratamientos biológicos con anticuerpos anti-amiloideos se empiezan a trasladar los mismos a la clínica. En el 2024 el grupo de trabajo esponsoreado por la Asociación de Alzheimer de EEUU (Jack et al., 2024) propone criterios biológicos de la enfermedad a partir del diagnóstico con los biomarcadores. Esto lleva aparejado la problemática de que existen sujetos normales con biomarcadores positivos llamados por ellos pacientes con enfermedad de Alzheimer Asintomática. Esto último no fue compartido por todos los grupos y el IWG (International Working Group) (Dubois et al., 2024) salió a marcar la posición de que estos últimos son sujetos "en riesgo" y no sujetos enfermos de Alzheimer. Todo esto trae aparejado mayor brecha entre los países desarrollados y los que están en desarrollo como Latinoamérica. Custodio et al. (2024) discuten estas dificultades y las probables propuestas para implementar los mismos en la clínica en Latinoamérica y poder llegar al uso de estas nuevas medicaciones.
*Palabras claves:* Criterios diagnósticos; Alzheimer; biomarcadores; demencia; deterioro cognitivo leve; Alzheimer prodrómico.

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## INTRODUCTION

In 1904, Alois Alzheimer published his first patient, Augusta Deter, with Alzheimer's disease. Emil Kraepelin incorporated it into his Psychiatry book and described it as characteristic of what he called presenile dementia. He left the concept of senile dementia for vascular disease. This was maintained until the 1980s, when it could no longer be sustained, since Alzheimer's disease is an age-dependent disease, and its prevalence increases with age. Thus, the largest number of subjects with the disease were in the senile stage. To better define the disease, in 1984, McKhann et al. published the diagnostic criteria for Alzheimer's disease NINCDS ADRDA (McKhann et al., 1984). It was divided according to the possibilities of certainty into Possible (when there were doubts or another associated pathology), Probable (when the patient had a compatible clinical picture) and Definitive only by pathological anatomy (when the patient died). However, the advent of AD biomarkers has made it possible to reach an etiological diagnosis in living subjects. The AD biomarkers that have been developed and expanded since 2000 have been directed towards the search for amyloid (PET of the brain with amyloid labeling and measurement of AB40/AB42 in cerebrospinal fluid), tau (PET of the brain with tau labeling and measurement of phosphorylated tau in cerebrospinal fluid) and neurodegeneration (through volumetric MRI of the brain, PET with FDG metabolic study and measurement of total tau or neurofilament livin chain in cerebrospinal fluid).

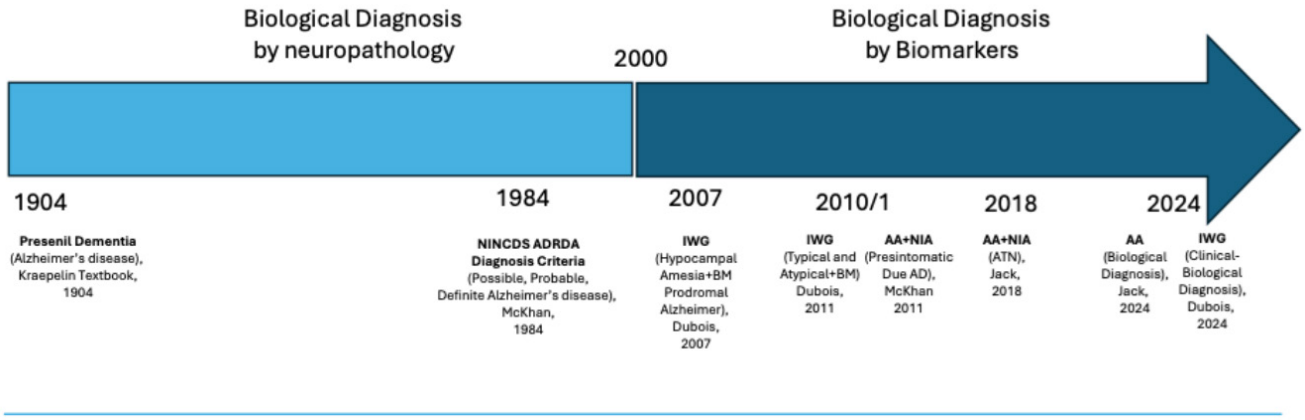
Currently, knowledge of the pathophysiology of Alzheimer's disease (AD) and biomarkers have developed rapidly, and with it, novel therapeutic approaches have appeared, some of them successful that in recent years have accessed approvals from regulatory agencies such as the FDA (Food and Drug Administration) of the USA (Anti-amyloid antibodies: Lecanemab-2023 and Donanemab-2024).

Recognizing dementia as a syndrome corresponding to the terminal stage of the disease (cognitive deterioration with compromised functionality and independence), these strategies advocate early intervention in mild cognitive impairment (which is when there is still no functional compromise) and mild dementia and foresee their future use in presymptomatic individuals.

Therapeutic attempts imply the demand for methods that confirm the diagnosis early, allow monitoring of adverse effects and subsequently evaluate the effectiveness of the intervention. The latter brings us to the central axis: the new 2024 criteria that define Alzheimer's disease as a biological or clinical biological construct even in its pre-dementia stages and its discrimination from other entities.

Two working groups made the initial effort to develop criteria of Alzheimer's disease diagnoses based on the success of using disease biomarkers. The international group (International Working Group - IGW) and the North American group of the National Institute on Aging (NIA) and the Alzheimer's Association of the USA (Alzheimer's Association - AA) (Jack et al., 2024). See Figure 1.

Figure 1: Evolution of Diagnosis Criteria for Alzheimer's Disease




References: IWG=International Working Group; AA=Alzheimer's Association; NIA=National Institute of Aging; BM=biomarkers; AD=Alzheimer's disease; MCI=mild cognitive impairment; A=amyloid; T=tau; N=neurodegeneration

*North American criteria (Alzheimer's Association Workgroup)*

Initially developed in 2011 by four working groups proposed by the National Institute on Aging (NIA) and sponsored by the Alzheimer's Association of the USA (AA-Alzheimer's Association). (Jack et al., 2011; Sperling et al., 2011; Albert et al., 2011; McKhann et al., 2011). Each group dealt with a topic approach, generalities of biomarkers and diagnostic approach in Alzheimer's disease (Jack et al., 2011); presymptomatic diagnosis ( Sperling et al., 2011), mild cognitive impairment due to Alzheimer's disease (Albert et al., 2011) and dementia due to Alzheimer's (McKhann et al., 2011)

AD biomarkers played a key role in supporting the diagnosis, which was based on clinical and clinical data. At this stage, the diagnostic criteria and recommendations were more aimed at clinical medical research, but given their low availability, their use in clinical practice was relativized. They defined stages of "Dementia or Mild Cognitive Impairment (MCI) due to Alzheimer's disease and even presymptomatic stages".

These criteria and recommendations were updated in 2012 at the neuropathological level (Hyman et al., 2012; Montine et al., 2012). In 2018, the new ATN concept for diagnosis with biomarkers was published in 2018 (Jack et al., 2018). A corresponded to amyloid, T to tau and N to neurodegeneration. The biomarkers were classified based on these and the diagnosis of the disease was addressed with them.

Recently, in 2024, after the approval of new anti-amyloid antibodies and the appearance of new biomarkers, criteria for the diagnosis of the disease were developed based solely on the biological aspects of the biomarkers (Jack et al., 2024). These constant changes show the rapid progress of research in both the diagnosis and treatment of the disease.

The latest version of 2024 (Jack et al., 2024) organized by the Alzheimer's Association already defines the disease biologically, replacing the traditional

syndromic definition. This concept based on the experience of oncology is being extended to all neurodegenerative diseases that move away from the syndrome to base the diagnosis on physiopathology and neuropathology.

The three most important developments for this change, as mentioned above, are based on the new treatments approved for the disease, the advances with blood biomarkers that are more accessible and cheaper than the traditional ones in PET and spinal fluid and redefines the ATN categories (amyloid, tau, neurodegeneration) based on the grouping of biomarkers (BM) into three: the core biomarkers of neuropathological changes of the disease, non-specific BM and BM of other co-pathologies such as alpha synuclein related to Parkinson's disease (see Table 1).

Table 1 Categorization of biomarkers

| BM Category | Fluids: CSF or Plasma | NeuroImages |
|---|---|---|
| Core Biomarkers for the diagnosis of AD | | |
| Core 1 | | |
| A ( ß-amyloid) | A ß 42 | Amyloid PET |
| T1 (p-tau) | p-tau217 / p-tau181<br>p-tau231 | |
| Core 2 | | |
| T2 (AD tau proteinopathy) | MTBR-tau243 | PET tau |
| Non-specific BM | | |
| N (Neurodegeneration) | NfL | RNM<br>PET FDG |
| I (Inflammation) | GFAP | |
| BM of other co-pathologies | | |
| V (Vascular) | | MRI (heart attacks) |
| S (Synuclein) | aSyn-SAA | |

Core 1 biomarkers are necessary and sufficient for the biological diagnosis of Alzheimer's disease. It is known that the biological alteration begins many years before the presence of clinical symptoms. However, according to these criteria, even though the symptoms may take years to appear, when the pathophysiology is present, the disease exists. These criteria call for Alzheimer's disease even when the subject only has the positive biomarker and does not yet have symptoms.

For those individuals diagnosed with Core 1, a "biological" staging (see Table 2) and a clinical staging (see Table 3) are proposed:

Table 2 Biological Staging of EA

| Stage | BM Initial stage (A) | BM Early stage (B) | BM Intermediate stage (C) | BM Late Stage (D) |
|---|---|---|---|---|
| PET | amyloid | Medial temporal tau | Moderate neocortical tau | Severe neocortical tau |
| Fluids | A ß 42/A ß 40<br>p-tau181/A ß 42;<br>t-tau/A ß 42 | Forms of<br>p-tau | MTBR-tau243 | Total Tau |

Clinical staging (see Table 3) describes 6 stages that can be correlated with those published in 2018.

Table 3 Clinical Staging of Alzheimer's Disease

| | Stadiums | Clinical and Biomarkers (BM) |
|---|---|---|
| 0 | Asymptomatic, genetic | Normal clinical and BM |
| 1 | Asymptomatic based on BM | Normal NPS clinic, abnormal BM |
| 2 | Transitional Decline | Normal NPS clinic but lower than the previous level of the same individual, abnormal BM |
| 3 | Mild cognitive impairment | Low NPS clinic, abnormal BM |
| 4 | Mild Dementia | Mild dementia + abnormal BM |
| 5 | Moderate Dementia | Moderate dementia + abnormal BM |
| 6 | Severe Dementia | Severe dementia + abnormal BM |

Finally, they propose to integrate both biological and clinical staging (See Table 4)

Table 4 Integration of both Alzheimer's Disease Staging

| | Clinical Stage 0 | Clinical Stage 1 | Clinical Stage 2 | Clinical Stage 3 | Clinical Stage 4-6 |
|---|---|---|---|---|---|
| Initial Biological Stage (TO) | X | 1A | 2A | 3A | 4-6A |
| Early Biological Stage (B) | X | 1B | 2B | 3B | 4-6B |
| Intermediate Biological Stage (C) | X | 1C | 2C | 3C | 4-6C |
| Advanced Biological Stage (D) | X | 1D | 2D | 3D | 4-6D |

Note: The typical expected trajectory is shown in light blue. However, there is considerable individual variability.

*International Alzheimer's Disease (IGW) criteria*

In 2007, the International Working Group (IWG) (Dubois et al., 2007) revised the 1984 criteria and redefined the clinical diagnosis of Alzheimer's disease.

To achieve this, it is based on two pillars: cognitive criteria and biomarkers, defining the latter as those methods (imaging, biochemical or genetic) that allow the biological manifestations of the disease to be found "in vivo". To add specificity, the "possible" category contained in the NINCDS-ADRDA criteria was abolished. The clinical criteria referred to a cognitive impairment described as hippocampal amnesia, in which the subject has memory loss, does not recover information with help or assistance, and also presents numerous intrusions. This is the type of memory loss characteristic of the disease. This group calls amnesic hippocampal mild cognitive impairment with positive biomarkers prodromal Alzheimer's disease.

Thus, although the clinical picture is the dominant criterion, the inclusion of biomarkers as a condition that supports the diagnosis of the disease is important.

In 2010, the same group (Dubois et al., 2010) added to the typical amnesic hippocampal form the so-called atypical variants of the disease (frontal, aphasic, posterior cortical, Down syndrome). This concept of typical and atypical was controversial in the literature because it only reflected the frequency of the clinical picture in the disease.

Thus, in 2021, these names were changed from typical or atypical to common phenotypes (hippocampal amnesic, logopenic aphasia, and posterior cortical atrophy) and uncommon phenotypes of Alzheimer's disease (corticobasal, behavioral, and dysexecutive).

In 2024, after the publication of the diagnostic criteria of the American AA group (Jack et al., 2024), the international group (Dubois et al., 2024) considers reviewing these criteria that were only based on biology and not on the clinic, proposing biological clinical criteria for practical clinical use.

Both groups (AA and IWG) agree on the description of cases with clinical cognitive impairment (mild cognitive impairment and mild, moderate and severe dementia) and the presence of biomarkers, but their concepts of cognitively normal subjects with positive biomarkers are different. The AA group considers them to be part of Alzheimer's disease and the IWG group considers them to be subjects "at risk" of the disease (see Table 5). All this brings differences not only in the definition (see Table 6) but also in the implications of the diagnosis in daily clinical practice, in the professional and even legal life of the subject, in the probable "endpoints" and what will be the expected demonstration of efficacy in clinical trials.

Table 5 IWG 2024 Definitions.

| | |
|---|---|
| Asymptomatic at risk for Alzheimer's disease (AD) | Cognitively normal individuals<br>BM: Isolated amyloidosis or with medial temporal p-tau or positive p-tau in fluids (CSF or blood)<br>Increased risk of progressing to AD<br>Should not be defined as EA |
| Presymptomatic Alzheimer's disease | Cognitively normal individuals<br>Family EA (APP, PSEN1, PSEN2)<br>Down syndrome<br>People Homozygous for APOE 44<br>Sporadic AD with amyloid and tau PET in neocortical regions |
| Alzheimer's disease | Individuals with cognitive impairment<br>Clinical phenotypes:<br>a) Common (hippocampal amnesic syndrome, logopenic aphasia, posterior cortical atrophy)<br>b) Uncommon (corticobasal syndrome, behavioral and dysexecutive variants)<br>CSF or PET positive. P-tau217 in plasma<br>Includes prodromal (mild cognitive impairment) and dementia (with functional loss) |

Table 6 Differential diagnostic approaches to Alzheimer's disease (AD).

| Definitions and implications | AA 2024 | IGW 2024 |
|---|---|---|
| Definition of Alzheimer's Disease | Biological (EA should be defined biologically not based on clinical data) | Clinical-biological (EA is a clinical-biological construct) |
| Possible Implications for Clinical Diagnosis | Abnormal presence of any BM core 1 of EA (A ß 42/40, p-tau) | A cognitive deficit and BM of EA are required |
| | A positive BM in a cognitively normal subject can be diagnosed with AD | A positive BM in a cognitively normal subject cannot be diagnosed as AD |
| Possible implications for the diagnostic disclosure of an individual | A cognitively normal person with a BM core 1 of EA can be said to have EA | A cognitively normal person with a positive BM for EA can be said to be at risk of having EA. |
| Potential implications for Phase 3 preventive clinical trials | BMs can be the primary endpoint | BMs cannot be primary endpoints |
| | Demonstrating clinical efficacy may not be necessary | Demonstrating clinical efficacy must be necessary |

*Need to adapt the 2024 Alzheimer's disease criteria in Latin America*

Both diagnostic criteria (AA and IWG) are clear for high-income countries (HIC) but complex for low- and middle-income countries (LMIC) such as those in Latin America. The available data on both diagnosis and treatment are from HIC and more globally representative and diverse research cohorts are needed (Jack et al., 2024).

The greatest barriers to adapting these diagnostic criteria in Latin America (Custodio et al., 2024) stem from the low availability of AD biomarkers. These criteria are limited to only a few centers in Argentina, Brazil, and Colombia. Although these criteria are basic for research, the development of new antibodies has complicated the situation and will soon bring these criteria into the clinic.

To this end, these authors describe local barriers in Latin America for both research and clinical use and generate proposals for their implementation, such as centralization of biomarker studies, regional validations of the same, and local guidelines.

Finally, a regional working group is proposed with knowledge of local resources (professionals and infrastructure) that can generate appropriate recommendations for using biomarkers in the new context of serum markers and potential treatments in the region.

## CONCLUSIONS

The approval of anti-amyloid antibodies for the treatment of Alzheimer's disease in early stages of the disease changes the perspectives on the need for AD biomarkers and necessarily leads to the definition of new diagnostic criteria in accordance with them. Both groups (AA and IGW) designate Alzheimer's disease in a similar way for symptomatic patients (cognitive impairment with positive biomarkers) but they are contrasted in asymptomatic subjects with positive biomarkers, which for the AA group are part of Alzheimer's disease and for the IGW are only subjects at risk of the disease. All this will be a major challenge in the coming times for LMICs.

## CONFLICTS OF INTEREST

The authors have no conflict of interest related to this review, except RFA for the tutorials of the cited articles Custodio et al., 2024; Dubois et al., 2024.

## CONTRIBUTOR ROLES

RFAllegri: Conceptualización, formal analysis, methodology, writing original draft

PBagnati: Validation, Writing-review

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