Opinions article

# The Diagnosis of Alzheimer's Disease in 2025 – Challenges of a Biological Paradigm in Brazil

## O Diagnóstico de Doença de Alzheimer em 2025-Desafios de um Paradigma Biológico no Brazil

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## ABSTRACT

In recent years, the definition of Alzheimer's Disease (AD) has evolved from a clinical paradigm to a biological one. This opinion article discusses the challenges of AD diagnosis in Brazil in light of the new guidelines proposed by the Alzheimer's Association, non-profit organization of United States, in 2024. The implementation of these new guidelines faces significant obstacles, including limited access to biomarkers, particularly within the Brazilian Unified Health System (SUS). Furthermore, the lack of representativeness in studies that support the diagnostic criteria, which predominantly focus on highly educated, white populations, raises concerns about their applicability in a population as diverse as Brazil's. Another factor to consider is the stigma associated with AD diagnosis, which can have a substantial psychological and social impact on asymptomatic individuals. The literature review was conducted as an open review, based on articles that address topics related to the impact of AD diagnosis and the implications of using biomarkers in medical practice, as well as research on Brazilian population data from the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística – IBGE) platform. This opinion article highlights the challenges of applying Alzheimer's Association criteria in Brazil, with the potential to exacerbate inequalities in the healthcare system.

**Keywords:** Alzheimer Disease, Neurology, Biomarkers, Diagnosis

## RESUMO

Nos últimos anos, a definição da Doença de Alzheimer (DA) evoluiu de um paradigma clínico para um biológico. Este artigo de opinião discute os desafios do diagnóstico da DA no Brasil à luz das novas diretrizes propostas pela Alzheimer's Association, organização sem fins lucrativos dos Estados Unidos, em 2024. A implementação dessas novas diretrizes enfrenta obstáculos significativos, incluindo o acesso limitado a biomarcadores, particularmente dentro do Sistema Único de Saúde brasileiro (SUS). Além disso, a falta de representatividade nos estudos que apoiam os critérios de diagnóstico, que se concentram principalmente em populações de elevado nível educacional e brancas, levanta preocupações sobre sua aplicabilidade em uma população tão diversa quanto a brasileira. Outro fator a considerar é o estigma associado ao diagnóstico da DA, que pode ter um impacto psicológico e social substancial em indivíduos assintomáticos. A revisão de literatura foi realizada como uma revisão aberta, com base em artigos que abordam tópicos relacionados ao impacto do diagnóstico da DA e às implicações do uso de biomarcadores na prática médica, bem como pesquisas sobre dados populacionais brasileiros na plataforma do Instituto Brasileiro de Geografia e Estatística (IBGE). Este artigo de opinião destaca os desafios de aplicar os critérios da Alzheimer's Association no Brasil, com o potencial de exacerbar as desigualdades no sistema de saúde.

**Palavras-chave:** Doença de Alzheimer, Neurologia, Biomarcadores, Diagnóstico

## ARTICLE INFO

DOI: https://doi.org/10.46979/rbn.v61i2.66976

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**Conflict of Interest:** The author declares no competing interests.
**Funding statement:** The author did not receive funding for this work.

## INTRODUCTION

In the past few years, the definition of Alzheimer's disease (AD) has been slowly shifting from a clinical paradigm to a biological/pathological one. In 2011[1], the National Institute on Aging – Alzheimer's Association (NIA-AA), non-profit organization of United States, for the first time differentiated the pathophysiological process of AD from the clinical syndromes – an important departure from the then prevailing clinical criteria established in 1984. This significant change was deemed appropriate due to the emergence of both fluid and imaging biomarkers, which made it possible to assess in vivo the presence of typical AD structural and functional abnormalities, as well as the existence in the brain of β-amyloid and phosphorylated tau, which are hallmarks of the AD pathology, in the brain.

This process of paradigm changing reached its peak with the publication of the "Revised criteria for diagnosis and staging of Alzheimer's disease" in 2024[2]. In this paper, the authors define AD as a biological process, characterized by the presence of specific neuropathologic changes, which may be assessed using biomarkers. These biomarkers are mainly divided into two categories: Core 1 biomarkers, which occur early in the process but are sufficient to diagnose AD even in the absence of symptoms, and Core 2 biomarkers, which occur later in the process and tend to be associated with AD clinical manifestations. The reader is advised to refer to the original paper by Jack et al.[2] for a detailed analysis of these diagnostic criteria.

Of note, the authors emphasize that these new diagnostic criteria are mostly intended to help in the expanding field of the development of disease-modifying drugs and should not be used in the present to diagnose asymptomatic individuals. Nevertheless, as it is probably not possible to control access to these biomarkers[3], it is likely that a strictly biological definition of AD results in an increase of asymptomatic individuals diagnosed with an incurable progressive disease.

This opinion article does not intend to debate the indications for monoclonal antibody drugs, such as Donanemab, currently approved by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária-ANVISA), Brazil's regulatory agency, as a disease-modifying therapy in the country. For a more in-depth view on the topic, we recommend the article "Use of anti-amyloid therapies for Alzheimer's disease in Brazil: a position paper from the Scientific Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology".[4]

In this article, we intend to discuss the expected challenges of this paradigm shift in the Brazilian healthcare scenario.

## INFRASTRUCTURE AND AVAILABILITY

The most obvious limitation for the implementation of this new paradigm is the low availability of biomarker testing, particularly in the public health care system, which is the only option for more than 70% of Brazilians[5]. In this setting, even basic diagnostic tools, like Computed Tomography and Magnetic Resonance are not sufficient for the current demand[6]– a scenario that can worsen with a hypothetical increase of AD diagnoses.

As of early 2025, neither tau - PET nor plasma biomarkers are available in Brazil and cerebrospinal fluid (CSF) biomarkers and amyloid-PET are not generally covered by health insurance plans. These tests are also only available in larger cities or in tertiary or quaternary centers. As a result, in Brazil biomarker testing is currently only available to individuals with better socioeconomical conditions and/or in metropolitan areas. Recent estimates suggest that between 70 and 90% of individuals with dementia are never diagnosed in Brazil, particularly in the North and Northeast regions[7]. It is reasonable to assume that making biomarkers necessary for the diagnosis of AD will increase the percentage of undiagnosed individuals and potentialize the already enormous inequities in health care access.

Another important question is the availability of qualified professionals to request biomarkers and interpret their results. A recent publication by the Scientific Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology[8] recommends that biomarkers should only be requested by well-trained physicians, ideally from the specialties of Geriatrics, Neurology or Psychiatry, a necessary measure to avoid overdiagnosis and decrease healthcare costs. However, access to these specialists is not easy in the Brazilian public health system, particularly in smaller cities or in rural areas[9].

## POPULATIONAL IDIOSYNCRASIES

One of the most significant issues of the 2024 diagnostic criteria is that most of the studies used to support them included only highly educated white participants, which compromises the representativity and generalizability of the findings. This question was, as a matter of fact, pointed by the authors of the original paper[2] as a limitation of the criteria.

When discussing the applicability of the biological paradigm to a Brazilian population, the problem becomes larger, as less than 45% of Brazilians identify themselves as white[10]. This is not, however, just a question of representativity, as different ethnicities tend to display different patterns of neuropathology, such as the higher prevalence of vascular pathology in black individuals, which was shown for example in a large recent Brazilian study using the Sao Paulo Brain Bank[11]. It is still unclear how the possible interaction of different pathological signatures may influence the interpretation of AD biomarkers.

As pointed above, another important limitation of the new diagnostic criteria is that it does not properly

encompass individuals with lower education. Low education is still a major problem in Brazil: although a significant improvement has occurred in the past decades, 7% of the Brazilian population was illiterate in 2022[10]. Considering that low education is one of the most important risk factors for the development of dementia [12] and that its diagnosis is significantly more difficult in patients with low education[9], the lack of good evidence for the role of AD biomarkers in these individuals increases inequities and leads to the worsening of the exclusion of a vulnerable population.

In summary, the 2024 diagnostic criteria are built around evidence that lack in diversity and representativity. Therefore, there is at this moment no solid foundation to justify the application of strictly biological criteria to a population such as the Brazilian, with high ethnic diversity and in contrasting socio-economic contexts.

## THE STIGMA OF ALZHEIMER`S DISEASE

An increase of AD diagnosis in asymptomatic individuals would also be troublesome because of the stigma associated with the disease. In Brazil it is usual that individuals avoid saying the terms "dementia" or "Alzheimer", as they consider them to have negative connotations. This is a phenomenon much more common in Brazil and Latin America than in European countries[7,9]. An interesting consequence of that is that only 58% of relatives of patients with dementia in Brazil want that the patients themselves become aware of their diagnosis[13]. Accordingly, around one third of the specialized physicians in Brazil do not inform the diagnosis of dementia to their patients[14]. This is, also, a phenomenon more common in Brazil and Latin America than in other regions of the world[15].

Considering that the new diagnostic criteria of AD would increase the diagnosis of a stigmatized disease among healthy asymptomatic individuals, we can expect psychologic and social consequences such as social withdrawal and segregation[7], as well as psychiatric manifestations such as anxious or depressive symptoms. It is, then, fundamental that the implementation of a biological paradigm to AD comes along the establishment of educational measures to raise awareness and mitigate inaccurate perceptions of the disease[9].

## CONCLUSION

The important advances in science in the last few years have drastically changed our understanding of AD, slowly shifting its concept towards a biological/pathological paradigm. Although this is an important step towards the development of effective treatments and prevention strategies, its application in real life, to real patients, is challenging, particularly when we consider a complex, idiosyncratic population such as the Brazilian one.

The diagnostic criteria suggested by the NIA-AA have the potential to increase the many inequities of health care in Brazil. The access to modern complementary tests and biomarkers is very limited, stigma will probably increase and affect healthy individuals and the evidence supporting the new criteria lacks representativity and diversity.

The clear limitations of the NIA-AA criteria have led to the proposal of other recommendations that may be much more palatable in our context. The most relevant one was the Clinical-Biological construct proposed by the International Working Group (IWG) in the end of 2024[3]. This recommendation acknowledges the important role of AD biomarkers and the value of the concept of presymptomatic AD, but strongly discourages the disclosure of an AD diagnosis to cognitively normal people. The reader is advised to refer to the original paper by Dubois et al[3] for a thorough analysis of their point of view.

Lastly, as care providers, researchers and policy makers, we should view this change of paradigm as a window of opportunity. There is an urge for new evidence regarding the role of biomarkers in our population, for educational measures to decrease stigma and misconceptions about AD and, most important of all, for the improvement of the access to biomarker testing and to specialized professionals capable of requesting and interpreting these tests.

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