



Quinn, T. J., McCleery, J., Flicker, L. and Richard, E. (2019) When is Alzheimer's not dementia—Cochrane commentary on The National Institute on Ageing and Alzheimer's Association Research Framework for Alzheimer's Disease. *Age and Ageing*, 48(2), pp. 174-177. (doi:[10.1093/ageing/afy167](https://doi.org/10.1093/ageing/afy167)).

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Deposited on: 12 September 2018

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When is Alzheimer's not dementia - Cochrane commentary on The National Institute on Ageing and Alzheimer's Association Research Framework for Alzheimer's disease.

Abstract:Early 2018 saw the release of new diagnostic guidance on Alzheimer's Disease from the National Institute on Ageing and the Alzheimer's Association (NIA-AA). This proposed research framework represents a fundamental change in how we think about Alzheimer's disease, moving from diagnosis based on clinical features to diagnosis based solely on biomarkers. These recommendations are contentious and have important implications for patients, clinicians, policy makers and the pharmaceutical industry. In this commentary, we offer a summary of the NIA-AA research framework. We then focus on five key areas: divorcing neuropathology from the clinical syndrome; the emphasis placed on one dementia subtype; validity of available biomarkers; the changing meaning of the term 'Alzheimer's disease'; and the potential for a research framework to influence clinical practice.

Key points:

- The NIA-AA research framework proposes a new view of Alzheimer's disease that is based solely on CSF and imaging biomarkers.
- Although presented as guidance for research only, the framework has far reaching implications for clinical practice and for society.
- The biomarkers described are neither sensitive nor specific to the clinical diagnosis of dementia.
- A particularly contentious aspect is redefining Alzheimer's disease based only on a biomarker profile and requiring no corresponding symptoms.

Keywords: Alzheimer's disease, biomarkers, Cochrane, dementia, evidence-based medicine, guidelines, research

Introduction:In order to understand a concept and use it effectively, we first have to define it. Medical conceptualisation of the common form of dementia experienced by older people has seen many iterations. Initially labelled ‘senile dementia’, it was considered an inevitable consequence of ageing and was generally presumed to be due to cerebral atherosclerosis. By the mid-twentieth century, this dogma was shaken by the observations that many people with so-called senile dementia had post-mortem neuropathological changes similar to those described by Alois Alzheimer.[1] Since then, creating consensus on how to classify and identify common forms of dementia, including Alzheimer’s disease dementia (AD), has proven challenging. Various criteria have been suggested and these continue to evolve as our knowledge of the condition increases. In 2012 the United States National Institute on Ageing and the Alzheimer’s Association (NIA-AA) issued dementia diagnostic guidance that incorporated new technologies such as cerebrospinal fluid (CSF) biomarkers as an adjunct to the traditional tools of history taking and examination[2] For the first time, a state of pre-clinical dementia was defined based solely on biomarker patterns suggestive of underlying disease, without the need for any discernible clinical symptoms.

In response to the exponential growth of biomarker research since the publication of the 2012 guidelines, the NIA-AA convened an international expert panel to further collate the evidence. The results, published in early 2018, were a set of new diagnostic guidance materials entitled ‘A Research Framework: Towards a biological definition of Alzheimer’s Disease’.[3] Although described as a ‘framework’ and for research only, the NIA-AA materials make a number of suggestions that fundamentally challenge our current understanding of AD.

Summary of the guidance:The main thrust of the research framework is to change the definition of AD from a clinical syndrome to a disease identified by specific biological features alone. The justification for this change in emphasis is that the *disease* of Alzheimer’s is characterised by neuropathological change of amyloid plaque and neurofibrillary tangle and that it is this biological disease, rather than symptoms, that should be the focus of research attention.

We now have a substantial body of longitudinal data showing detectable change in various proteins many years prior to clinical symptoms of AD. Based on these data, and since in-vivo neuropathological diagnosis is unlikely, the framework proposes that biomarkers are used as a proxy for the neuropathology of AD in living subjects. The biomarkers of choice are: markers of amyloid deposition (A); markers of fibrillary tau (T) and markers of neurodegeneration (N). For each category both a CSF and a neuroimaging biomarker are suggested. An AD spectrum disease is defined by the presence of at least one positive amyloid (A) biomarker, while the other biomarkers help to ‘stage’ the pathological process. Thus a series of biomarker profiles based on differing combinations of A, T and N are possible, akin to the tumour, node, metastasis (TNM) system used in oncology. Accompanying cognitive symptoms can be added to the ATN system, but are not mandated or indeed necessary for diagnosis.

The full NIA-AA research framework documents along with commentary and supporting materials are available open access online.[3]

Reception:Following publication of the framework, the NIA-AA invited comment and discussion. There has been substantial positive published comment, often from specialist centres already experienced in the use of biomarkers. There have even been calls for the immediate application of the framework in the clinic, particularly to support reimbursement of biomarker tests in insurance-based systems. However, critical voices have also been raised at recent scientific meetings.

Our remit in the Cochrane Dementia Group is to provide evidence-based appraisal of developments in dementia research and practice. We have previously been a critical friend of the 2011 diagnostic guidance, commenting that the evidence supporting biomarker-based diagnosis was not yet definitive and that wide-scale adoption would be premature.[4] Our concerns are magnified in relation to the new framework. Some of the aims of the new guidance are clearly laudable. For example, better biological characterisation of trial participants should allow for more efficient studies and a common language with which to discuss the complex field of AD biomarkers is needed. However, we believe that this new guidance has some serious and worrying conceptual and practical implications that should be widely debated.

Separating the clinical from the pathological - a messy divorce:A recurring theme in the materials is that *'(clinical symptoms) are neither sensitive nor specific for the neuropathologic changes that define the disease'*. It is true that many individuals with a clinical picture of amnesic cognitive decline do not have the expected AD biomarker profile and that this may have had consequences for trials of interventions based on the amyloid hypothesis. However, it is equally true that many with a biomarker profile that would be labelled 'Alzheimer's' in the new guidance are cognitively unimpaired and will remain so for the rest of their lives.[5] In fact, one could turn the statement round and say that the biomarkers are not sufficiently sensitive or specific for the clinical syndrome. We must ask ourselves what is the 'target condition' here? In other words, which is more important to clinicians, patients and the public, the neuropathological signature or the clinical symptoms?

How good are the biomarkers:Data validating the suggested biomarkers against the development of clinical dementia are still sparse. Where data are available, these are often confined to unrepresentative populations and fail to adhere to best methodological practice.[6] The predictive value of individual biomarkers in persons with cognitive complaints, is low and the added value over and above simple cognitive tests has not been unequivocally shown.[7] As explained in the framework paper itself, up to 60% of cognitively unimpaired people aged over 80 would be classified within the Alzheimer's spectrum proposed, yet many of them would never develop cognitive symptoms.

Even within the exclusive neuropathological framework there are validity issues. The chosen CSF and imaging markers are described as interchangeable but the agreement between them is far from perfect. The NIA-AA state that this apparent discrepancy reflects choice of cut-points used to define biomarker positivity and the properties of the different assays. However, the framework does not offer practical guidance on standardising the measurement processes or interpreting conflicting biomarker results. The anticipation is that results will inevitably converge over a longer timescale, but this entails a certain amount of wishful thinking.

No disease is an island:The framework applies only to AD and all other potential contributors to cognitive decline are lumped together as ‘suspected non-Alzheimer pathologic change’. It is now possible to identify growing number of pathologies which may affect the aging brain, but we have only very limited understanding of what initiates these pathologies, how they are related to each other, how they develop over time and how they relate to cognitive decline. Many would argue that the focus on AD in this guidance is overly reductionist. Dementia processes are not always separate and distinct. Many patients do not fit neatly within a single disease category and complexity is the rule rather than the exception. Too exclusive a focus on one type of pathology may discourage research on the interaction between different pathological processes, an approach which could open up much-needed new therapeutic avenues. Further, the idea that early intervention trials will inevitably be improved by delineating a population of people with homogeneous underlying neuropathology is open to question, since the external validity of such trials will be limited.

What’s in a name:The use of the term “Alzheimer’s disease” to describe everyone with positive biomarker tests, regardless of symptoms, can only cause confusion. For the public and clinicians the term “Alzheimer’s disease” is synonymous with clinical dementia. We suggest that it will not be possible to communicate a change in the meaning of “Alzheimer’s disease” to the wider community and that the various additional terms proposed (‘dementia due to Alzheimer’s disease’, ‘Alzheimer’s disease with dementia’ and ‘Alzheimer’s clinical syndrome’) will be of little help in this regard. In our view, this new terminology, as well as being unnecessary for the stated purpose of facilitating research, will lead inevitably to a serious problem of over-diagnosis.

Clinical creep:The framework’s authors recognise that clinical adoption of their new criteria could fuel over-diagnosis and emphasise that the definitions are for research purposes only *at the moment*. However, research criteria and nomenclature do not, and arguably should not, exist in a separate space to clinical practice. These proposals will inevitably shift the disease boundary in the clinic. In doing so, they will provide a powerful impetus to the spread of biomarkers into diagnostic practice. Such changes are already occurring, under commercial pressure, despite the lack of validation and the absence of any evidence of improved outcomes. The definition of what constitutes an improved clinical outcome is also being stretched, with recent studies addressing the value of these investigations including such inconsequential outcomes as clinical trial referrals or additional tests.[8] We note that the UK National Institute for Health and Care Excellence has promoted use of CSF and imaging biomarker tests in its recent guidance on dementia diagnosis, which is intended to inform clinical practice.[9] When considering the risk of clinical creep, we should be aware that the proposed disease definitions will be, in practice, inapplicable in low income settings and probably also beyond the available resources in many higher income settings, leading to serious inconsistencies in practice.

The framework also has important implications for drug development and the pharmaceutical industry. Defining disease on the basis of biomarkers alone is a very large step towards the approval of treatments on the basis of effects on those biomarkers, rather than on the basis of demonstrable benefits to patients. The large and growing proportion of older adults in the population makes this a potentially lucrative market.

The authors of the framework envisage that additional biomarker domains will be incorporated into the model. The implication is that more and more asymptomatic people will be identified as having a neurodegenerative disease, with no requirement for the disease labels to be accompanied by either symptoms or a thorough understanding of prognosis or treatment implications. This is an alarming expansion of the concept of disease which may have far-reaching psychological, social, legal and financial consequences for individuals, consequences which are hard to study or to quantify.[10]

Alternative approaches:In our view, this guidance goes beyond what was needed for its stated aims. Better communication about biomarkers and better characterisation of trial participants for interventions targeting a highly specific mechanism could be achieved by a purely descriptive vocabulary, such as the ATN labels, without linking these to disease categories. This would be consistent with the reality that cognitive impairment arises in a multidimensional space in which the nature and degree of proteinopathy is only one factor determining whether or not an individual will develop cognitive decline. This 'space' in which symptoms are determined can look quite different from different perspectives and may be influenced by the organisation of services and the politics of research funding as well as by biology. Alternatives to a model which relies on discrete diagnostic labels are available. Dementia could be the prototypical condition which would benefit from a research framework eschewing dichotomisation (disease / no disease) and embracing instead a model focused on patient prognosis and the likelihood of future outcome.[11]

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