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FOR DEBATE: IS VERY EARLY DIAGNOSIS OF AD USING THE NEW CRITERIA BENEFICIAL FOR PATIENTS?

Introduction

The last few years have seen considerable progress in revisions of clinical diagnostic criteria for dementia. In relation to Alzheimer's disease (AD), the focus of this particular debate, the original McKhann criteria were described in 1984 (McKhann *et al.*, 1984) and represented a landmark in their field, allowing accurate categorisation of a type of dementia that was indeed shown subsequently by validation studies to largely represent AD. The criteria distinguished between "probable" AD, which despite its name was the highest level of clinical certainty available, "possible" AD, when there were variations in the course and presentation or the presence of another comorbidity that could be the cause of dementia, and "definite" AD for which autopsy validation was necessary. The impact of these criteria cannot be overestimated. Most of what we know regarding the natural history, and certainly the therapeutic response (and sadly non-response) of AD, is based upon cohorts diagnosed with these criteria, and most usually the probable Alzheimer type. Validation studies have shown reasonably good, and clinically applicable, sensitivity for the criteria of around 80%, but specificity has been lower, at around 70% (Knopman *et al.*, 2001). This low specificity is an issue, largely because of the lack of any positive features for ruling AD in (they have largely, though somewhat unfairly, been labelled criteria of exclusion). In addition, the low specificity is in part because the criteria often also include conditions that were not well defined or even recognised in the 1980s as separate disorders. For example, dementia with Lewy bodies, subcortical ischaemic vascular dementia, and various subtypes of frontotemporal dementia, which have now been shown to have distinct clinical, pathological and, in some cases, genetic components.

Tremendous progress has also been made in the area of biomarkers. At the time of the 1984 criteria, progressive atrophy on computed tomography imaging was really the only biomarker that had been described, and was incorporated in the 1984 criteria. Now, the situation has been transformed, with cerebrospinal fluid, tau and amyloid, multiple magnetic resonance (MR) biomarkers including serial whole-brain hippocampal atrophy on MR; temporoparietal hypometabolism on fluorodeoxyglucose-positron emission tomography (FDG-PET) or hypoperfusion on SPECT, and most recently amyloid PET imaging, to list but a few of the best validated biomarkers (Sinha *et al.*, 2012). Undoubtedly, others will emerge over time and despite the robustness of many of the aforementioned biomarkers, there remains interest in finding cheap, simple, and reliable alternatives, most especially those that could be easily collected, so for example blood biomarkers would represent a major advance.

On the background of these two major developments, demonstrating that the original 1984 McKhann criteria have limited specificity together with the advance in knowledge regarding biomarkers that can increase the certainty of AD diagnosis, various revisions to the clinical diagnostic criteria for AD have been proposed. Those of the International Working Group (IWG) of Dubois and colleagues (2007; 2010) represented a key step in arguing that the diagnosis of AD should be brought forward before the global cognitive impairment, or dementia, stage and also suggesting that biomarkers should be used to support the diagnosis. Similarly, a National Institute on Aging–Alzheimer's Association (NIA–AA) workgroup reformed and, under Guy McKhann's leadership, published revised proposed criteria for AD (McKhann *et al.*, 2011). Other associated workgroups also proposed criteria for mild cognitive impairment due to AD (Albert *et al.*, 2011) and most controversially of all asymptomatic or preclinical AD (Sperling *et al.*, 2011). The publication of these various sets of criteria has caused considerable interest, but also controversy. How valid and reliable are they? Do they really represent a major advance over current criteria? How should they be used: are they strictly criteria for research or should we be using them in the clinic?

In view of these key issues, we decided to commission a debate between Bruno Dubois, Serge Gautier, and Jeff Cummings, who make the case for the utility of the new research diagnostic criteria for AD, focussing on the IWG criteria though similar

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arguments apply to the NIA–AA criteria, and Helen Chiu and Henry Brodaty who argue from a number of different areas including technical, ethical, and social that use of these criteria more widely may be premature. I hope you enjoy this very timely and topical debate.

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The utility of the new research diagnostic criteria for Alzheimer's disease

Alzheimer's disease (AD) has traditionally been defined as a type of dementia, a concept reinforced by the publication of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders (NINCDS–ADRDA) criteria in 1984 (Isaac *et al.*, 2011). Three major tenets of these criteria were that (i) the clinical diagnosis of AD cannot be made with certainty and requires post-mortem confirmation; (ii) for that reason, the clinical diagnosis of AD can only be "probable"; and (iii) the diagnosis can be made only when the disease is advanced and reaches the threshold of dementia.

The discovery of biomarkers for AD, considered as surrogate markers of the underlying neuropathological changes of the disorder, led an international work group (IWG) organized by Bruno Dubois to propose a new conceptual framework for AD in 2007 (Albert *et al.*, 2011). According to the IWG, AD is now defined as a dual clinicobiological entity that can be recognized *in vivo*, prior to the onset of the dementia syndrome, on the basis of (i) a specific core clinical phenotype consisting of an amnestic syndrome of the hippocampal type and (ii) supportive evidence from biomarkers reflecting the location or the nature of Alzheimer-type changes. Therefore, AD is diagnosed with the same criteria throughout all symptomatic phases of the disease on a biologically based approach to diagnosis independent of clinical expression of disease severity. The definitions were further clarified in 2010 (Bouwman *et al.*, 2010). The major advance of the IWG criteria and of the subsequent National Institute on Aging/Alzheimer's Association (NIA/AA) criteria (Albert *et al.*, 2011) was to integrate biomarkers of Alzheimer pathology into a diagnostic framework for earlier clinical diagnosis. The use of biomarkers in research will assist with clinical trials and possibly with regulatory decisions. They will set the stage for primary and secondary prevention. The emphasis on biomarkers is justified by an increasing body of knowledge, primarily from the Alzheimer Disease Neuroimaging Initiative, but the data are still emerging and verification of the type of changes, correlations with clinical outcomes, duration of biomarker-related phase of AD, order of appearance, and consistency across populations is required. Although both sets of criteria – IWG and NIA/AA – were intended for research application while additional data are accrued, their wide discussion, the approval by the Food and Drug Administration (FDA) in the United States of florbetapir amyloid imaging for the detection of neuritic amyloid plaques and the impending approval of more biomarkers suggest that they will be integrated rapidly into clinical practice.

The key conceptual advances of the IWG/Dubois criteria for AD

1. The new criteria for Alzheimer disease published in 2007 (Albert *et al.*, 2011) and the subsequent proposal for a Lexicon revision (Dubois *et al.*, 2010) in 2010 have significantly changed the conceptual framework of AD and its diagnosis. The new criteria have introduced biomarkers for the diagnosis of AD. The IWG/Dubois criteria divide biomarkers into pathophysiologic markers that identify AD pathology (i.e. cerebrospinal fluid [CSF] Aβ and tau levels; and positron emission tomography [PET] amyloid imaging) and topographical markers that reflect downstream damage (i.e. medial temporal atrophy on magnetic resonance imaging [MRI]; parietal/temporal hypometabolism on fluorodeoxyglucose [FDG] PET). The new criteria allow a positive diagnosis of AD in life and no longer depend on excluding other diseases as the basis for AD diagnosis.
2. The new criteria have introduced the concept of AD as a clinicobiological entity. As biomarkers can be considered as surrogate markers of the histopathological changes, the clinical diagnosis can now be established *in vivo*. Post-mortem

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examination is no longer needed to verify the histologic diagnosis and reference to "probable" AD is no longer required or warranted if compelling biomarker evidence of AD is present.

3. The new criteria have introduced the concept of "prodromal AD," extending the concept of AD into a symptomatic pre-dementia stage. Biomarkers obviate the need to link the diagnosis of the disease to a specific threshold of severity and to arbitrarily divide patients into those with and without functional impairment. The ambiguous nature of any boundary between prodromal AD and dementia of the AD type argues in favor of a unified diagnostic approach that uses the same criteria for diagnosis of AD regardless of the severity of the accompanying cognitive and functional deficits. Therefore, no reference to dementia is required. Biomarkers are signatures of the disease and allow diagnosis independent of disease stage. Indeed, they reinforce the diagnosis of the disease at any stage, even at the earliest prodromal ones. Recognizing AD at a prodromal stage may have several advantages: obtain appropriate treatment earlier; stop searching for other causes; help the family to understand and accept; decide financial and legal plans while competent; enable the patient and family to make lifestyle choices; induce better adherence and management of other medical conditions; take appropriate steps to prevent injury (driving, weapons); get greater access to help within the healthcare system and within communities; and participate in clinical trials with disease modifying treatments.
4. The new criteria apply specifically to AD and do not rely on the non-specific syndromic diagnosis of mild cognitive impairment (MCI). MCI patients have variable underling pathology and variable outcomes; IWG/Dubois criteria apply specifically to AD including its prodromal stage and do not rely on the concept of MCI. MCI may be a useful term for patients whose memory impairment has not been characterized and who have not been studied with biomarkers.
5. The new criteria have introduced the concept of a continuum of AD with a simple diagnostic procedure based on a clinical–biological entity using cognitive assessment and biomarker evidence that provides a framework for diagnosing AD throughout any phase of AD following the onset of symptoms. There is no reason to propose different criteria for different phases of the same disease. The combination of a specific phenotype (episodic memory impairment characterized by poor free recall that is not normalized by cueing) and a biomarker supportive of the presence of Alzheimer pathology is the basis for diagnosis of AD at any stage of the disease. Preliminary retrospective studies of the criteria support the utility of this approach with modest sensitivity and high specificity demonstrated (Bouwman *et al.*, 2010; Galluzzi *et al.*, 2010). This has significantly changed the definition of the disease: from a clinic-pathological to a clinic-biological entity.
6. The new criteria have introduced the concept of typical AD highlighting the importance of episodic memory disorders and that of an "amnestic syndrome of the hippocampal type." With the added value of a cueing paradigm, memory performance can account for up to 90% of the diagnostic certainty for AD and can predict time of conversion to dementia (Aizenstein *et al.*, 2008). The amnestic syndrome of the hippocampal type, as evidenced by the Free and Cued Selective Reminding Test, was recently shown to be highly specific for AD pathology (Isaac *et al.,* 2011). The new criteria acknowledged the fact that several cognitive changes can be encountered in AD, even at a prodromal stage of the disease, but none are specific of AD and their presence adds little to the diagnosis.
7. The IWG/Dubois criteria have introduced the concept of atypical forms of AD. An amnestic presentation may not always be the presenting feature of AD and other clinical phenotypes can be associated with post-mortem evidence of AD pathology. There are well-defined clinical phenotypic variant presentations of AD that do not exhibit the amnestic memory impairment described above. These include non-amnestic focal cortical syndromes, such as logopenic aphasia, posterior cortical atrophy, and frontal variant AD. With the advent of biomarkers providing *in vivo* confirmation of Alzheimer's pathology, it is now possible to include these clinical disorders as atypical AD if there is convincing biomarker support. These disorders might develop an amnestic deficit only later in the disease course.
8. The criteria are aimed at reaching the highest specificity of diagnosis. The IWG recognizes that applying the criteria requires significant expertise, technical skills, and financial resources to allow the comprehensive evaluation with MRI, PET, and CSF. The aim of the new criteria is to support the high likelihood of the presence of AD because this is a priority for research purposes or clinical trials.
9. The IWG/Dubois criteria have introduced that the diagnosis of AD should be restricted to the clinical phase of the disease and that it starts with the first clinical symptoms. The new lexicon proposes that pathological lesions or neuronal changes reported by neuropathologists in post-mortem studies should be called "Alzheimer pathology" in order to disambiguate the name of AD. This proposal is retained in the ongoing revision of the Consensus Guidelines for the Neuropathologic Criteria of AD, where the term "AD neuropathological changes" is proposed to reflect the characteristic histopathological changes of AD in order to disentangle the clinical disease from AD lesions. AD as a diagnosis is reserved for those with clinical symptoms avoiding the challenges associated with diagnosing a disease when no symptoms are present.

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10. The new criteria have introduced for the first time the concept of two distinct preclinical stages of AD. Approximately 20%–30% of individuals older than 70 years have reduced $A\beta_{1-42}$ protein in the CSF and deposits of fibrillar $A\beta$ in the brain that can be visualized by amyloid imaging (Aizenstein *et al.*, 2008). These individuals are recognized to be at risk for progressive cognitive decline. Positive amyloid imaging or low CSF $A\beta$ predicts progression from normal to abnormal cognition; the time course for progression to symptoms and the percentage of persons who will progress to AD prior to age-related death are not currently known (Aizenstein *et al.*, 2008). The conceptual framework recognizes preclinical states distinguishing (i) "Asymptomatic at risk for AD" (ASR-AD) with a normal cognitive condition and evidence of amyloidosis in the brain or in the CSF. This neutral nomenclature was chosen to acknowledge that the percentage and the time frame for progression to symptomatic clinical conditions is unknown; it is not expected that all these individuals will progress to symptomatic AD. This state should not be described as preclinical AD because this nomenclature may imply progression, suggesting that "preclinical" is a predecessor state for "clinical" AD. There will be reservations concerning the assignment of a disease diagnosis when there are no symptoms to anchor such a diagnosis. (ii) "Presymptomatic AD" (PS-AD) with normal condition and autosomal dominant monogenic AD mutation. Because of the full penetrance of these mutations, these individuals will inevitably develop clinical AD.

To conclude, the IWG/Dubois criteria embrace the entire continuum of symptomatic AD from the prodromal to the dementia forms in a single diagnostic framework; integrate biomarkers into all phases of the diagnostic approach; use biomarkers to improve on the diagnostic specificity of less specific syndromes such as MCI and probable AD dementia; emphasize episodic memory impairment as the key AD phenotype; and have the advantage of simplicity of application. Conceptually, they advance the idea of AD as a clinical–biological entity. The research criteria require validation studies and further investigation of the sensitivity, specificity, positive and negative predictive values, and clinical utility. They have already shown their potential utility for research studies and clinical trials: they have been successfully implemented in current Phase 2 clinical trials for prodromal AD with a γ-secretase inhibitor, two immunotherapies, and the Lipididiet study, and they have been accepted by the European Medicine Agency (Aizenstein *et al.*, 2008) for use in AD clinical trials. They are also starting to be used in clinical settings, at least in expert centers, in case of young-onset AD or of complex cases such as posterior cortical atrophy or primary progressive aphasia, where the evidence to date is that biomarkers can increase diagnostic accuracy. The recent approval by the US FDA of the PET–amyloid scan (florbetapir, Av-45, Amyvid®), together with the inclusion in both sets of new diagnostic criteria for AD of both the CSF changes and MRI hippocampal volume, creates an opportunity to move the criteria from research to clinical settings, where they may be expected to significantly increase the diagnostic accuracy of AD.

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Arguments against the biomarker-driven diagnosis of AD

Impressive developments in the biomarker diagnosis of Alzheimer's disease (AD and pre-symptomatic states, using cerebrospinal fluid (CSF), positron emission tomography (PET), magnetic resonance imaging (MRI), and proteomics, have been at the forefront of research in the last decade. With the publication of the criteria of Dubois *et al.* (2007) and the revised National Institute on Aging and Alzheimer's Association (NIA–AA) criteria for the diagnosis of AD (Jack *et al.*, 2011), this has further ignited the interest and enthusiasm for researchers and clinicians in the field. In some of the major conferences on dementia in recent years, the topic of the biomarker-driven diagnosis of AD has dominated the research agenda. But many questions arise as to how this research will translate into practice. Here, we would like to put forward our arguments against a biomarker-driven diagnosis of AD, and we would caution that very early diagnosis of AD may not result in better care of the subjects.

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Conceptual aspect

A basic conceptual issue is the definition of a complex disease like AD. Historically, AD has been regarded as a clinicopathological disorder with a clinical picture of dementia as well as specific AD neuropathology. With the proposed new lexicon and definition of AD by Dubois *et al.* (2007) and the revised NIA–AA criteria (Jack *et al.*, 2011), there is a distinction of the clinical manifestations from the underlying AD neuropathology. Two essential differences from the criteria of AD by McKhann *et al.* (1984) are the incorporation of biomarkers and formalization of the different stages of disease in the new diagnostic criteria (Jack *et al.*, 2011). Thus, "asymptomatic at risk state for AD" (Dubois *et al.*, 2007) and "preclinical AD" (Sperling *et al.*, 2011) have become "disease entities." This has raised a fundamental question on the concept of what is a "disease." According to the World Health Organization (WHO), a "disease" is associated with malfunction and suffering (Giaccone *et al.*, 2011). Paradoxically, "asymptomatic" and "preclinical" AD, conditions when a person has no symptoms or signs, are now designated as "disease" in these new AD criteria.

The new criteria of AD rely heavily on biomarkers of amyloidosis and neurodegeneration. It is hypothesized that amyloid biomarkers may be abnormal 10–20 years before the onset of symptoms, while abnormalities in biomarkers of neurodegeneration occur later (Jack *et al.*, 2011). In reality, we do not know with certainty that people with AD neuropathology will develop cognitive impairment and dementia in the future. Despite growing evidence that a positive amyloid PET scan with Pittsburgh compound B or low CSF A Beta 42 predicts cognitive decline or dementia, the relationship for progression of mild cognitive impairment (MCI) to dementia and for normal to MCI is probabilistic rather than deterministic (Blacker, 2010). We have to be mindful of the pitfalls of labeling at-risk status defined by biomarkers as disease, since many factors might influence the development of cognitive impairment or dementia. In particular, compensatory mechanisms and cognitive reserve should be given due consideration. For instance, a recent study on 249 subjects found that education had a positive effect on late-life cognitive ability, and it counteracts the deleterious effects of cerebrovascular disease and AD as assessed by neuroimaging biomarkers (Murray *et al.*, 2011).

In addition, a major challenge in the new framework of the diagnosis of AD is the multiple brain pathologies frequently encountered in dementia. Around 40% of patients with AD have significant cerebrovascular disease, and around 90% of patients with dementia with Lewy bodies (DLB) have concurrent AD pathology (Ballard *et al.*, 2011). This is particularly the case in very old age where multiple pathologies are frequent (Wharton *et al.*, 2011); indeed, there is a decrease in the correlation between AD pathology and clinical symptoms with older age (Wharton *et al.*, 2011). Further complicating the picture is that about 20%–30% of people with the neuropathology of AD at postmortem did not have dementia in life (Neuropathology Group of MRC CFAS, 2001).

AD is a heterogeneous condition, and subtypes may be better defined by clinical phenotypes rather than biomarkers. None of the existing biomarkers has been shown to have good criterion validity. For instance, Oksengard *et al.* (2010) tested the Dubois 2007 criteria and found that they lacked accuracy for predicting AD. The Dubois criteria were valid in only 55% of patients clinically diagnosed as AD. In addition, only 7.3% of prodromal AD subjects were identified from a group of 96 patients with subjective cognitive impairment and/or MCI in this study.

Technical aspect

Biomarkers are biological parameters that reflect disease-related pathophysiological processes. An ideal biomarker should be (1) sensitive, specific, reliable, reproducible, and inexpensive; (2) able to detect a fundamental feature of the disease and reflect some basic pathophysiological processes; and (3) obtained through simple non-invasive procedures (Humpel and Marksteiner, 2009). In addition, it has been recommended that an ideal biomarker of AD should indicate the actual presence of AD, not merely increased risk, and it should change with disease severity (Klunk, 1998). Unfortunately, none of the existing biomarkers for AD satisfies all these criteria.

Before the adoption of biomarkers in clinical use, standardized procedures for biomarker assessment need to be developed. It is noteworthy that all biomarkers are continuous measures and hence there should be agreement on the interpretation of findings and optimal cut-off points. Currently, most AD biomarkers suffer from poor standardization and reproducibility across centers (Frisoni *et al.*, 2011). In addition, the duration of follow-up of abnormal biomarkers in the literature is insufficient for us to know how accurately they will predict the progression of preclinical dementia to MCI or dementia.

In the case of neuroimaging, there is variability between machines and even longitudinal variability

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within machines. Hippocampal atrophy is not linear and, hence, discrimination between normal subjects and MCI subjects may be poor. Normal hippocampal volume can vary a lot and this has prevented universally accepted norms (Frisoni *et al.*, 2011). Volumetric change is only seen after excessive neuronal loss and imaging biomarkers may give opposite results in volumetric and tracer studies. Information provided by biomarkers may be conflicting and do not fit in the theoretical framework of dynamic biomarkers, which suggests that biomarkers of A β-amyloid are indicative of initiating events while biomarkers of neurodegeneration become dynamic later (Jack *et al.*, 2011).

Turning to CSF, there is a similar variability in the collection methods, standardization between laboratories, stability of chemicals, and platforms for analysis. Hort *et al.* (2010a) reported on the use of CSF biomarkers in the diagnosis of dementia across 23 European countries, Israel, and Georgia, and found that each laboratory had its own norms in half of the countries.

In addition, CSF changes are not specific. Aβ is decreased, whereas total tau (T-tau) is increased in AD, as well as other types of dementia, such as vascular dementia, Creutzfeldt–Jakob disease, frontotemporal dementia, and DLB. Phosphorylated tau (p-tau) is increased in AD and DLB, although different epitopes of p-tau may be more specific, including p-tau 231 and p-tau 181. Furthermore, the diagnostic performance of CSF biomarkers decreases with age (Mattsson *et al.*, 2012).

Albeit the risk is small but lumbar puncture is an invasive procedure with potential side effects. Blood biomarkers are non-invasive and would be more acceptable to subjects. However, the currently available blood biomarkers are not yet ready for use in the diagnosis of AD. For example, plasma levels for β-amyloid (1–42) are unstable and influenced by various drugs. In addition, it is not sensitive and specific for early diagnosis of AD (Humpel and Marksteiner, 2009).

Definitional aspect

The new criteria of AD appear to offer a simple and straightforward way of making a diagnosis with the use of biomarkers in addition to the clinical picture, and this is very appealing to clinicians. However, there are practical difficulties in operationalizing the criteria.

In the case of MCI due to AD (Albert *et al.*, 2011), the proposed criteria for MCI are as follows: (1) Concern regarding a change in cognition, (2) impairment in one or more cognitive domains, (3) preservation of independence in functional abilities, and (4) not demented. The authors stated that cognitive test scores in people with MCI are typically 1–1.5 standard deviations (SD) below the mean for their age- and education-matched peers. On a practical level, it is unclear whether clinicians should use 1 SD or 1.5 SD, and the number of cognitive tests to be used per cognitive domain. It is important to recognize the wide cultural variation in the applicability of cognitive testing. Assessment of cognitive function is influenced by cultural factors and literacy levels. Many older adults in developing countries have low literacy levels and low acceptance of formal cognitive testing (Chiu and Lam, 2007). Another limitation is that norms are not well established for the oldest-old population even in developed countries.

Ultimately, the decision of making a diagnosis of MCI rests on "clinical judgment." While this is acceptable practice for experts and experienced clinicians, these criteria may result in a massive over-diagnosis in the field.

Utilitarian aspect

Despite the exponential studies on the use of biomarkers, the advances appear to be associated with only incremental gain on the accuracy of diagnosis above a good history, clinical examination, and cognitive testing. Interestingly, a recent study on the discriminative utility of different biomarkers and cognitive markers examined their ability to predict conversion from MCI to AD. The authors concluded that cognitive markers were more robust predictors of conversion than most biomarkers (Gomar *et al.*, 2011). Schmand *et al.* (2011) reported that neuropsychological tests and structural MRI scans were most accurate at identifying AD and that CSF and fluorodeoxyglucose (FDG) PET were less accurate and did not significantly add to accuracy of neuropsychological tests or MRI. This was especially so for those older than 75 years, where presumably multiple pathologies were operating. This study did not include amyloid imaging.

An important result of early diagnosis should be early treatment. However, at present there is no effective disease-modifying treatment. Although a very early diagnosis of AD may facilitate advance planning for the future of the individual, the predictive values of the new criteria of preclinical AD and MCI due to AD are uncertain and there may be misdiagnosis. These factors seriously undermine the clinical utility of very early or preclinical diagnosis of AD. One might argue

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that lifestyle strategies including exercise, mental activities, and social activities as well as legal planning should be implemented for people who are in the preclinical or MCI stage to prevent dementia. However, these lifestyle preventative strategies and contingency planning could be and should be encouraged universally anyway, for brain health, as well as physical and mental health.

Social and cultural aspects

Much of the development and discussion on the use of biomarkers in the diagnosis of AD are by experts in developed countries, and the views and perspectives from researchers and clinicians in developing countries are missing.

According to a report of Alzheimer's Disease International (ADI, 2009), 57.7% of people with dementia lived in low- and middle-income countries in 2010, rising to 70.5% in 2050. With the majority of people suffering from dementia residing in developing countries, it is essential to consider the perspectives of people from these countries. Three factors regarding the use of biomarkers are important globally, but are particularly pertinent in developing countries: availability, affordability, and acceptability.

Even in developed countries, there is a lack of availability of the high-tech investigations, including PET scans, MRI scans, and CSF biomarker essay, outside tertiary centers or research centers. In developing countries, these high-tech investigations are only available in a few specialized centers in big cities. For instance, according to the information from the Organization for Economic Co-operation and Development Health Data 2011 (OECD, 2011), there are 97.3 computed tomography scanners per 1 million population, and 43.1 MRI scanners per 1 million population in Japan, compared with 4.3 and 1.9 per million, respectively, in Mexico.

Apart from the lack of high-tech investigations, there is a paucity of specialists as well as infrastructure for doing the biomarkers. For instance, there is up to a 200-fold difference in the number of psychiatrists and up to a 100-fold difference in the number of neurologists in low-income countries compared with high-income countries (WHO, 2004; 2005).

Affordability of these biomarkers also varies significantly across countries. To quote an example, the gross national income per capita in current US$ was $47,350 in the United States compared with $1,260 in India in 2010 (The World Bank, 2012). Considering the low income of people living in developing countries, many of the biomarkers are hardly affordable, and the high costs of the investigations are prohibitive to their use.

Cultural acceptability is another factor to consider. In particular, while the use of CSF biomarkers is considered to be important in the diagnostic workup of dementia in many European countries (Hort *et al.*, 2010a), lumbar puncture and the use of CSF biomarkers are not routine in the diagnosis of dementia for research or clinical purpose in many Asian countries (Chiu and Lam, 2007).

In Chinese communities, CSF is regarded as precious fluid, and there is a great reluctance in the general population to do a lumbar puncture unless the condition is very serious and potentially lethal. In addition, there are many myths about lumbar puncture prevalent in the lay community, including the belief that lumbar puncture is harmful to health and is very painful.

In developing countries, the priority in terms of dementia care is in raising awareness of dementia, as well as to enhance primary health care and other community services (ADI, 2009). It is difficult to conceive how the stretched resources in these countries should be diverted from care of people with dementia to expensive investigations. In the scenario in which biomarkers are incorporated in the diagnostic criteria of AD, this may end up with a much lower prevalence of AD in developing countries, as many sufferers will not undergo these investigations.

Even for developed countries, resources are not unlimited. If clinicians order biomarkers for all subjects with memory complaints, it would result in a dramatic rise in health expenditure, and possibly a marked increase in the diagnosis of AD. We must bear in mind that at present there is no effective treatment to modify disease progression, and there is no study that addresses the cost–benefit ratio of early diagnosis of AD. Therefore, it is uncertain if the additional costs of these biomarkers may be offset by the savings in the early detection of people at risk of AD.

Ethical aspect

There are major ethical concerns in the use of biomarkers in very early diagnosis of AD, given the uncertain specificity and sensitivity of these tests in the new criteria for the diagnosis of AD in the preclinical and MCI stages. What are the implications of a pre-symptomatic or preclinical diagnosis in the absence of disease-modifying treatments? What will be the consequences for insurance, work, driving, and family relationships? Will there be prejudice against the person in job opportunities and insurance? Will the person be stigmatized by his or her family and society?

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Even if biomarkers can deliver earlier diagnosis, the advantages of knowing one's diagnosis earlier are imputed and not empirically proved. There are very few studies on the effects on subjects after disclosure of early diagnosis of dementia, but catastrophic reactions are a definite risk. In addition, there is a possible increased risk of suicide and euthanasia after disclosure of early diagnosis (Draper *et al.*, 2010). In the absence of effective disease-modifying treatments, early diagnosis may do more harm than good to the subject, the family, and the society. The diagnosis of a person as preclinical AD is particularly problematic as it might lead to personal suffering and anguish for many years, long before any manifestation of dementia. In case of misdiagnosis, the consequences can be very serious for the person and frequently the family as well.

In an interesting study, Boustani *et al.* (2005) carried out a screening study of primary care patients aged 65 or older based on cognitive battery. Only half of the screen positive subjects consented to further diagnostic assessment. The authors speculated that fear of stigmatization, discrimination, loss of independence, as well as a perception that dementia is a severe untreatable disease had led to the low acceptance rate of early diagnosis.

As mentioned earlier, lifestyle preventative strategies could be implemented without early diagnosis of AD. Therefore, on balance, it appears that very early diagnosis of AD with the new criteria may not be associated with improved treatment or quality of life in the subjects with AD pathology. Another pertinent area is that we have to be cautious that the drive to diagnose more people with AD pathology is not fuelled by market considerations for treatment development or use of diagnostic procedures.

Conclusions

Developments in biomarker research represent a clear advance heuristically, are useful as research tools, and are helpful in the diagnosis of difficult cases in tertiary clinics. However, we must also recognize that core clinical criteria provide very good diagnostic accuracy and utility in most patients with AD (McKhann *et al.*, 2011). Clearly, more research needs to be done to ensure that the proposed biomarker-driven criteria have been appropriately designed, and that standardization of biomarkers is essential before they can be adopted for clinical use.

In addition, one must beware of the dangers in the widespread adoption of these revised criteria. First, clinicians might ignore the cautions raised by authors of the new criteria that the diagnostic criteria for preclinical AD are for research purposes, and adopt these criteria in making day-to-day diagnoses. Some scientific associations are already considering the integration of the AD biomarkers into clinical guidelines (Hort *et al.*, 2010b), which will have a major impact on clinical practice. Second, commercial interests may drive the usage of biomarker techniques, so that healthcare providers and consumers may demand tests without clear understanding of the limitations of these tests. Third, the focus on biomarkers might result in their domination of the research agenda which is not healthy or desirable. Fourth, the impact on the public use of resources can be enormous, especially in developing countries. Fifth, the negative and harmful effects of a diagnosis without treatment and of misdiagnosis should be seriously considered. Sixth, these criteria are not applicable globally because of a lack of consideration of various cultural and social factors, including affordability, availability, and acceptability. Thus, we are of the view that the new biomarker-driven diagnostic criteria of AD are not yet ready for routine clinical use. Until a time when there is an effective disease-modifying treatment, it is too soon to tell if very early diagnosis with these criteria will result in better care of people with AD.

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Commentary

Dubois, Gauthier, and Cummings argue strongly and coherently for the need for revision of the Alzheimer's diagnostic accuracy and the many benefits to moving to a new diagnostic system. What they propose represents a fundamental paradigm shift in our field, moving Alzheimer's disease from a clinic-pathological to a clinic-biological entity, and separating the diagnosis of Alzheimer's disease from

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Alzheimer's dementia. In other words, recognising that people can have Alzheimer's disease for many years before they develop the global cognitive decline needed to fulfil current clinical criteria for dementia. The new diagnostic criteria are strongly supported by a very large body of research over the last 25 years and seek to advance the previous McKhann *et al.* (1984) criteria by, in particular, enhancing diagnostic specificity since, for the first time, CSF and imaging biomarkers are needed to "rule in" rather than simply rule out other disorders. The authors emphasise that these are research criteria and that they require validation and further investigation of clinical utility, whilst also pointing out that they have already been implemented in current Phase 2 clinical studies. Such a parallel introduction of criteria to our field whilst validation is ongoing is nothing new for psychiatry, or indeed dementia, and the same happened for the original Alzheimer's disease criteria as well. Dubois, Gauthier, and Cummings end with a stated aspiration to move the criteria from research to clinical settings, and by doing so hopefully increase the accuracy of the clinical diagnosis of Alzheimer's disease and ultimately improve patient care.

In a thoughtful and very carefully argued piece, Chiu and Brodaty acknowledge and agree that there have been major and fundamental developments in the research field in relation to biomarkers, but raise some extremely important issues that need to be addressed before the criteria can be more widely applied in clinical practice. From a nosological perspective, they ask whether Alzheimer's disease can really be a disease when there are no signs or symptoms, which would be the case if the diagnosis is pushed back to the "preclinical" phase. They highlight the potential over-reliance on biomarkers, particularly as biomarkers may be abnormal for 20 years before the onset of symptoms, question how multiple pathologies will be taken into account, argue the need for better standardisation of biomarkers and the need for them to be more widely (and cheaply) available and argue that there is a need in ongoing research to demonstrate the "added value" of the new criteria and use of biomarkers over current clinical practice. The practical difficulties of the high cost of using investigations and ethical issues over the labelling of those with preclinical disease are eloquently addressed. Finally, Chiu and Brodaty conclude by cautioning against the widespread adoption of the criteria without the appropriate validation studies and the need for financial, ethical, and practical issues to be properly addressed.

Like many of the thoughtful debates we have carried in the pages of this journal, the two sides appear to start from very different perspectives but arrive at some common ground. Both articles argue that the new criteria represent a potential advance, that there are issues that need to be addressed and that the criteria are currently for research rather than clinical practices. Thus, all authors seem to agree on the direction of travel, the main difference appears essentially to be that Dubois, Gauthier, and Cummings are occupying the outer lane, arguing for a fast and rapid pace of movement from research to clinical use, whilst Chiu and Brodaty feel that if the key issues that they eloquently highlight are not properly addressed first, then more harm than good may result. As usual, the final arbiter of the strength or otherwise of the different arguments is you, our highly valued readers.

Conflict of interest

J. O'Brien has acted as a consultant to Bayer Healthcare, GE Healthcare, and received research funding from Lilly. B. Dubois has acted as a consultant for Lilly. S. Gauthier has acted as consultant to Affiris, Astellas, Astra-Zeneca, Bayer, Baxter, BMS, Elan, Epix, ExonHit, GE Health Care, Janssen-Cilag, Lundbeck, Lilly, Merz, Myriad, Neurochem, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Sonexa, UBC, Wyeth. J. Cummings, H. Chiu, and H. Brodaty have no conflict of interest.

Description of authors' roles

J. O'Brien wrote the introduction and the commentary. B. Dubois, S. Gauthier, J. Cummings, H. Chiu, and H. Brodaty contributed to the writing of the paper.

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