International Psychogeriatrics (2011), 23:8, 1191–1196 © International Psychogeriatric Association 2011
doi:10.1017/S1041610211001220

GUEST EDITORIAL

Revised NIA-AA criteria for the diagnosis of Alzheimer's disease: a step forward but not yet ready for widespread clinical use

In clinical medicine, diagnostic criteria are not only useful everyday tools for the practicing physician, but also represent a conceptual concentrate of the understanding of the etiology and pathophysiology of diseases at a given point in time. Although different sets of diagnostic criteria for Alzheimer's disease (AD) have been developed, the most widely used and best validated by clinico-pathological study to date are the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association) criteria which were published in 1984 (McKhann *et al.*, 1984). These criteria are largely based on the exclusion of other conditions that may cause dementia and can be succinctly but fairly summarized as defining AD as an "acquired progressive cognitive, behavioral, and functional impairment with no other obvious cause". Clearly, the NINCDS-ADRDA criteria were etiology- and pathophysiology-agnostic in that they failed to point at any specific etiology, not even a degenerative one. They were also developed before other important causes of dementia, such as dementia with Lewy bodies, fronto-temporal dementia and subcortical vascular dementia had been fully described and characterized. The recent publication of a substantially revised version of these criteria (Sperling *et al.* 2011; Albert *et al.*, 2011; McKhann *et al.*, 2011), heralded by a largely European initiative four years ago (Dubois *et al.*, 2007) has been greeted with great interest by the field. The newly proposed criteria reflect the substantial insights on disease pathophysiology gained over the last decades, especially regarding the molecular pathology of AD and the time course of such pathology in relation to clinical symptoms and disease.

The conceptual framework

Longitudinal studies in patients with cognitive impairment of variable severity (from absent to moderate dementia) have led to the widely held view, rooted in the amyloid cascade hypothesis, that the pathophysiological process of AD (AD-P) starts at least ten years before the onset of even the mildest clinical symptoms (Figure 1) and that AD-P can be characterized by imaging and cerebrospinal fluid (CSF) biomarkers. Clinical symptoms usually – but not invariably – consist of amnestic and/or non-amnestic cognitive impairment, which do not impair functional abilities for a few years (mild cognitive impairment – MCI). With ongoing progression, cognitive impairment leads to disability and dementia within 5 to 7 years (2 to 3 years on average), and death usually ensues after 7–10 more years, though the disease course can be highly variable. Thus, by the time patients develop cognitive symptoms, the brain has been suffering amyloid-associated damage for many years. The practical consequence is that it is fully sensible to expect that patients with MCI due to AD-P will show an AD-like profile of biomarkers, consistent with the increased prevalence of AD-like changes that have been demonstrated in MCI cases over the past decade.

The molecular pathology of AD has been found to consist of cerebral β-amyloidosis and neurodegeneration (synaptic failure and neuronal loss), pathologically hallmarked by the classical extracellular senile plaques of amyloid $\beta_{1–42}$ and intracellular neurofibrillary tangles of hyperphosphorilated tau (HP-τ) protein, respectively. While the biological mechanisms linking the deposition of amyloid $\beta_{1–42}$ into plaques to accumulation of HP-τ into tangles are uncertain, the prevalent view posits that β-amyloidosis is the primary phenomenon, and neurodegeneration then follows (the "dynamic biomarkers" hypothesis) (Jack *et al.*, 2010). It is fair to acknowledge, however, that models alternative to the amyloidocentric hypothesis also exist. Recently, Braak and Del Tredici have proposed that the disease might start as tangles (or, rather, as "pre-tangles") in proximal axons of the noradrenergic locus ceruleus, and that via a prion-like transmission (neuron-to-neuron and tran-synaptic transport of tau protein aggregates), pathology spreads to the entorhinal cortex, and from here to the hippocampus and the rest of the neocortex (Braak and Del Tredici, 2011). This hypothesis will need to be tested in future studies.

The revised criteria, now more succinctly called NIA-AA (National Institute on Aging and Alzheimer's Association), build on the above

Table 1. The revised NIA-AA diagnostic criteria for Alzheimer's disease (Sperling *et al.*, 2011; Albert *et al.*, 2011; McKhann *et al.*, 2011)

AD DEMENTIA AND MCI: LIKELIHOOD OF AD PATHOLOGY			PRECLINICAL AD: THEORETICAL STAGES			
	Amy	**Ndg**		**Amy**	**Ndg**	**Ss**
High	+	+	Stage 1	+	+	−
Intermediate	+	**n.a.**	Stage 2	+	+	−
	n.a.	+	Stage 3	+	+	+
Low	−	−				
Uninformative	**UC / n.a.**	**UC / n.a.**				

NIA-AA = National Institute on Aging and Alzheimer's Association; AD = Alzheimer's disease; MCI = mild cognitive impairment; Amy = brain amyloidosis; Ndg = neurodegeneration; Ss = cognitive symptoms; n.a. = biomarker untested; UC = biomarker uninformative or conflicting.

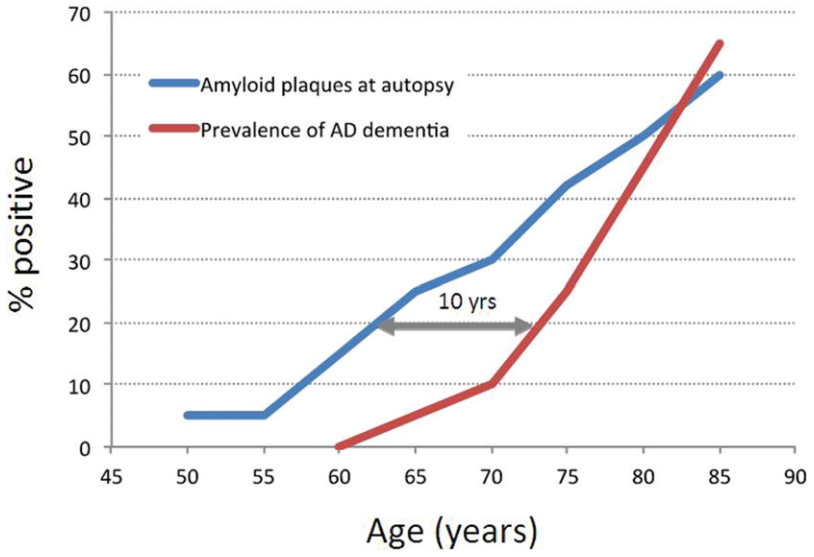

Figure 1. Temporal lag of approximately ten years between the deposition of amyloid and the clinical syndrome of AD dementia. Data on amyloid plaques at autopsy are taken from a large autopsy series (Braak and Braak, 1991), and those on the prevalence of AD dementia from three epidemiological studies (Hebert *et al.*, 1995; Ganguli *et al.*, 2000; Kukull *et al.*, 2002). Adapted from Sperling *et al.*, 2011.

scientific knowledge and propose the recognition of three stages of AD of increasing cognitive and functional severity: the preclinical, the MCI, and the dementia stage (Table 1). AD-P can be detected with markers of brain β-amyloidosis and neuronal injury (Table 2) at any one of the three stages. It should be noted that four of the six biomarkers with the best evidence of validity are imaging-based, and that two techniques (PET and CSF studies) allow assessment of both biomarkers of brain β-amyloidosis and neurodegeneration. This is relevant in view of the practical application of the criteria.

The operationalization

In agreement with the theoretical framework of dynamic biomarkers (Jack *et al.*, 2010), the preclinical stage is broken down into three sub-stages (Table 1) according to (i) the presence of brain amyloidodis only, (ii) brain amyloidosis with neurodegeneration, or (iii) brain amyloidosis with neurodegeneration and mild cognitive deficits not severe enough to qualify as MCI. Future prospective studies on representative samples of the general population will need to provide verification of this sequence of events. However, the detection of AD-P in the preclinical stage is not recommended in a clinical setting (Sperling *et al.*, 2011) as it is currently impossible to predict the proportion of persons with AD-P but with no or extremely mild cognitive symptoms who will subsequently develop MCI or dementia nor, importantly, when they will do so.

The new criteria for the mild cognitive impairment (MCI) (Albert *et al.*, 2011) and dementia stages (McKhann *et al.*, 2011) are potentially applicable in the clinic. The detection or exclusion of AD-P in a patient with MCI (Albert

https://doi.org/10.1017/S1041610211001220 Published online by Cambridge University Press

Table 2. Biomarkers of Alzheimer's disease pathophysiology in the revised NIA-AA diagnostic criteria for Alzheimer's disease (Sperling *et al.*, 2011; Albert *et al.*, 2011; McKhann *et al.*, 2011). Modified from Frisoni *et al.* (2011)

	Biomarkers of brain β-amyloidosis	• Increased uptake on amyloid imaging with PET • Decreased CSF Aβ42
MORE VALIDATED BIOMARKERS	Biomarkers of neurodegeneration (synaptic dysfunction and neuronal loss)	• Temporoparietal hypometabolism on 18F-FDG PET • Medial temporal (hippocampal) atrophy • Increased CSF τ/phospho-τ • Temporoparietal hypoperfusion on SPECT
LESS VALIDATED BIOMARKERS	Biomarkers of collateral damage, or serial biomarkers	• fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging • Inflammatory (cytokines) and oxidative stress biomarkers (isoprostanes) • Rates of brain atrophy

et al., 2011) (Table 1) can increase the confidence that the cognitive impairment is or is not due to AD and as such will or will not deteriorate in a matter of a few years leading to dementia. Similarly, the detection or exclusion of AD-P in a patient satisfying the traditional NINCDS-ADRDA criteria for "probable AD dementia" (McKhann *et al.*, 2011) can increase the confidence that the syndrome is due or not due to AD, which can be of clinical relevance in a significant proportion of cases where the differential diagnosis with non-AD dementias (e.g. dementia with Lewy bodies, frontotemporal degeneration, vascular dementia) is unclear on clinical grounds alone. Information provided by biomarkers is weighted according to two criteria: positivity/negativity of biomarkers, and fitting the theoretical dynamic biomarkers framework. Indeed, conflicting positivity/negativity of biomarkers (e.g. a negative amyloid biomarker in the presence of a positive neurodegeneration biomarker) is regarded as uninformative as if biomarkers information is not available.

An editorial accompanying publication of the revised criteria (Jack *et al.*, 2011) states that "in both the MCI and AD dementia criteria, clinical diagnoses are paramount and biomarkers are complementary". While stressing the relevance of history-taking and that the physical and neurological exam is a deonthological must to anyone who is a physician, it is also fair to acknowledge that the availability of biomarkers to ascertain AD-P clearly downgrades the clinical "diagnoses" of AD dementia and MCI to clinical *syndromes* with multiple possible etiologies. In the case of probable AD dementia, the most frequent etiology by far is indeed AD, but in the case of MCI the AD etiology is only between a half and two thirds of all cases, the remaining having either non-AD neurodegenerative diseases (rarely) or an unidentified cause most likely more related to the "normal" aging process (more frequently). It is not hard to imagine that, when biomarkers become available for routine use, the clinical criteria for AD dementia and MCI may be more loosely interpreted to increase their sensitivity, leaving to biomarkers the role of enhancing etiologic specificity.

Limiting factors for widespread use in the clinic

Clearly, the most pressing question for the practicing physician is whether the revised criteria are ready for use in their routine clinics. Here, the NIA-AA task force seems to have mixed feelings, possibly reflecting uncertainty in the community at large. While the revised criteria for AD dementia explicitly state that they "do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time", those of MCI due to AD state that the criteria "are designed to stimulate the application of biomarkers in clinical and research settings". While in theory biomarkers may have differential utility at different disease stages, the authors fail to provide clues that might help explain the different approaches.

We believe that several clinical and scientific factors currently limit widespread clinical adoption of the revised criteria. It is essential that the new criteria are fully validated in clinical-pathological series, as was the case for the NINCDS-ADRDA criteria. While initial clinical-pathological validation of individual markers has been undertaken under the pressure of the Food and Drugs Administration (FDA) for regulatory purposes (Clark *et al.*, 2011), studies will need to be undertaken including multiple biomarkers.

Research must further define the most efficient and effective diagnostic combination of biomarkers.

https://doi.org/10.1017/S1041610211001220 Published online by Cambridge University Press

The current formulation of the criteria requires positivity on at least one marker of amyloidosis and one of neurodegeneration, so a minimum of one lumbar tap with assessment of Aβ42 and τ might be sufficient. Alternatively, positron emission tomography (PET) imaging with FDG and an amyloid ligand might equally be effective but more acceptable to some patients – though substantially more expensive. On the other hand, the combination of medial temporal atrophy together with CSF Aβ42 might be the least expensive. Clearly, cost-effectiveness considerations will play a key role for widespread use.

Standardized procedures for biomarker assessment will need to be developed. Most biomarkers currently suffer from poor reproducibility across laboratories (Mattson *et al.*, 2010; Frisoni and Jack, 2011). In the case of hippocampal volume, despite high intra-laboratory reproducibility, normal hippocampal volume figures can vary 2.5-fold (Geuze *et al.*, 2005). This has so far prevented the definition of universally accepted norms and individually applicable normality thresholds. Current efforts are ongoing to develop standard operating procedures for the collection and measurement of biomarkers (Mattson *et al.*, 2010; Frisoni and Jack, 2011) that will allow widespread use of the criteria in clinical settings. Other uncertain issues include how the contribution of mixed pathologies (e.g. Lewy bodies or cerebrovascular disease) should be assessed, the effect of age on the penetrance of AD-P, and the interpretation of biomarker results when these are conflicting.

The one relatively straightforward set of criteria for AD has been replaced by three significantly more complicated sets. There will undoubtedly be issues not only regarding basic training in use of the criteria, but around how these are operationalized, and about reliability, not just of the biomarkers measurement but how these are integrated with clinical and demographic information to make a diagnosis. With increasing age, there is a decreasing relation between AD-P and clinical symptoms (Frisoni *et al.*, 2007; Bouwman *et al.*, 2009), and AD in the elderly is probably a more complex and even more heterogeneous condition than in younger patients. Considering that 75% of persons with dementia are aged over 75 years, it will be important to include a representative group of elderly patients in future studies of imaging and CSF biomarkers.

Communicating the various messages that these criteria bring to patients, carers, and society at large will require significant discussion among all involved stakeholders. New ethical problems arise when delivering to individuals a diagnosis that may cause anxiety and depression to both patients and relatives, in the absence of approved treatments. What will these individuals' reactions be, and how will we meet them? How might such early diagnosis impact on health and other insurance coverage? How will secular trends (Rocca *et al.*, 2011) affect the whole scenario? These key issues are already being debated in the literature (Porteri *et al.*, 2010).

Ready or not ready for clinical use?

The above shortcomings, however, do not preclude the use of the revised criteria under specific circumstances (Frisoni *et al.*, 2011). Uncertainties about the most efficient biomarker combination may restrict their use to those specialized centers with the ability to assess a large spectrum of biomarkers reliably and with good normative data. As with the diagnosis of any disease, the individual clinician will need to integrate the results of the biomarker analysis with clinical data in order to reach a final diagnosis.

A few European centers have found that the concept underlying the revised criteria for the diagnosis of MCI due to AD, i.e. the use of combined amyloid and neurodegeneration biomarkers, was applicable to the routine clinical population and was reasonably sensitive and specific to predict the development of incident dementia (Galluzzi *et al.*, 2010; Bouwman *et al.*, 2010). These results will undoubtedly encourage more centers to adopt a similar approach. Importantly, regulatory agencies such as the European Medicines Agency have indicated their interest in recommending the use of biomarkers for the selection of early AD cases to be enrolled in clinical trials and as markers of disease modification (Committee for Medicinal Products for Human Use, 2008; Hampel *et al.*, 2010). Scientific societies have become increasingly aware of the potential of AD biomarkers and are consequently considering their adoption into clinical guidelines (Hort *et al.*, 2010).

Clearly, the current lack of effective disease-modifying therapies will detract severely from their widespread clinical use. Their practical usefulness, and indeed, the value of the criteria – when validated – lies largely on improving patients' and families' knowledge. Even in the apparently pointless situation of the prediction of AD in asymptomatic young or middle-aged adults who might carry a pathogenic mutation, it has been shown that most individuals demonstrate effective coping skills and find the testing to be beneficial (Steinbart *et al.*, 2001). Many countries struggle to offer a basic assessment and diagnosis to those with established dementia, and even the routine use of

https://doi.org/10.1017/S1041610211001220 Published online by Cambridge University Press

routine structural imaging has been hotly debated in this journal (O'Brien, 2007), so the prospect of global use of several sophisticated biomarkers in some stretched healthcare systems might be a very distant and arguably unachievable prospect. Also, in high-income countries, the judgment on the opportunity to use health resources to provide mere patient knowledge will need to be made by politicians and healthcare decision-makers. The population prevalence of MCI might range between 1% and 3% of the general population (Fisk *et al.*, 2003), and from a societal perspective, such a large group of individuals at risk of developing AD places an extra burden on healthcare systems. Do health systems have sufficient resources? What will be the cost for society?

Everyone's hope is that ultimately one of the many disease-modifying drugs currently under trial (Mangialasche *et al.*, 2010) will show uncontroversial effectiveness. If so, then undoubtedly the field will need to have valid and reliable diagnostic criteria for AD that are fit for the purpose of delivering such treatments at the earliest possible opportunity to maximize benefit.

Conflict of interest declaration

GBF has acted as a consultant for Lilly, BMS, Bayer, Lundbeck, Elan, Astra Zeneca, Pfizer, Taurx, Wyeth, and has received unrestricted grants from Wyeth Int.l, Lilly Int.l, and Lundbeck Italia.

BW is/has been a member (on a consultancy basis) of the Scientific Advisory Boards for most companies with anti-dementia drugs: Merz Pharmaceuticals, Lundbeck Inc., Medivation, Inc., BMS, GSK, Janssen, Novartis, Pfizer Inc, Wyeth Int., l, Ely-Lilly. BW has been asked to comment on the revised criteria in Swedish for *Lakartidningen* (a journal for Swedish physicians).

JOB has acted as a consultant for GE Healthcare and Bayer healthcare and received honoraria for lectures from Pfizer, Novartis, Eisai, Lundbeck and Shire Pharmaceuticals.

Giovanni B. Frisoni,[1] Bengt Winblad[2] and John T. O'Brien[3]

[1]IRCCS Fatebenefratelli, Brescia, Italy
[2]Karolinska Institutet Alzheimer Disease Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
[3]Institute for Ageing and Health, Newcastle University, UK
Email: gfrisoni@fatebenefratelli.it

References

Albert, M. S. *et al.* (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, 270–279. doi:10.1016/j.jalz.2011.03.008.

Bouwman, F. H. *et al.* (2009). CSF biomarker levels in early and late onset Alzheimer's disease. *Neurobiology of Aging*, 30, 1895–1901. doi: 10.1016/j.neurobiolaging. 2008.02.007.

Bouwman, F. H. *et al.* (2010). New research criteria for the diagnosis of Alzheimer's disease applied in a memory clinic population. *Dementia and Geriatric Cognitive Disorders*, 30, 1–7. doi: 10.1159/000315542.

Braak, H. and Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*, 82, 239–259.

Braak, H. and Del Tredici, K. (2011). Alzheimer's pathogenesis: is there neuron-to-neuron propagation?. *Acta Neuropathologica*, 121, 589–595. doi: 10.1007/ s00401-011-0825-z.

Clark, C. M. *et al.* (2011). Use of florbetapir-PET for imaging beta-amyloid pathology. *JAMA*, 305, 275–283. doi: 10.1001/jama.2010.2008.

Committee for Medicinal Products for Human Use (2008). *Guideline on Medicinal Products for the Treatment of Alzheimer's Disease and Other Dementias*. Doc. Ref. CPMP/EWP/553/95 Rev. 1. London: Committee for Medicinal Products for Human Use.

Dubois, B. *et al.* (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology*, 6, 734–746. doi: 10.1016/S1474-4422(07)70178-3.

Fisk, J. D., Merry, H. R. and Rockwood, K. (2003). Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. *Neurology*, 61, 1179–1184.

Frisoni, G. B. and Jack, C. R. (2011). Harmonization of magnetic resonance-based manual hippocampal segmentation: a mandatory step for wide clinical use. *Alzheimer's & Dementia*, 7, 171–174. doi: 10.1016/j.jalz.2010.06.007.

Frisoni, G. B. *et al.* (2007). The topography of grey matter involvement in early and late onset Alzheimer's disease. *Brain*, 130, 720–730. doi: 10.1093/brain/awl377.

Frisoni, G. B., Hampel, H., O'Brien, J. T., Ritchie, K. and Winblad, B. (2011). Revised criteria for Alzheimer's disease: what are the lessons for clinicians?. *Lancet Neurology*, 10, 598–601. doi: 10.1016/ S1474-4422(11)70126-0

Galluzzi, S. *et al.* (2010). The new Alzheimer's criteria in a naturalistic series of patients with mild cognitive impairment. *Journal of Neurology*, 257, 2004–2014. doi: 10.1007/s00415-010-5650-0.

Ganguli, M., Dodge, H. H., Chen, P., Belle, S. and DeKosky, S. T. (2000). Ten-year incidence of dementia in a rural elderly US community population: the MoVIES Project. *Neurology*, 54, 1109–1116.

Geuze, E., Vermetten, E. and Bremner, J. D. (2005). MR-based in vivo hippocampal volumetrics: 1. Review of

https://doi.org/10.1017/S1041610211001220 Published online by Cambridge University Press

methodologies currently employed. *Molecular Psychiatry*, 10, 147–159. doi: 10.1038/sj.mp.4001580.

Hampel, H. *et al.* (2010). Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. *Nature Reviews: Drug Discovery*, 9, 560–574. doi: 10.1038/nrd3115.

Hebert, L. E. *et al.* (1995). Age-specific incidence of Alzheimer's disease in a community population. *JAMA*, 273, 1354–1359.

Hort, J. *et al.* (2010). EFNS guidelines for the diagnosis and management of Alzheimer's disease. *European Journal of Neurology*, 17, 1236–1248. doi: 10.1111/j.1468-1331.2010.03040.x; 10.1111/j.1468-1331.2010.03040.x.

Jack, C. R., Jr *et al.* (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurology*, 9, 119–128. doi: 10.1016/S1474-4422(09)70299-6.

Jack, C. R., Jr *et al.* (2011). Introduction to the recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, 257–262. doi: 10.1016/j.jalz.2011.03.004.

Kukull, W. A. *et al.* (2002). Dementia and Alzheimer disease incidence: a prospective cohort study. *Archives of Neurology*, 59, 1737–1746.

Mangialasche, F., Solomon, A., Winblad, B., Mecocci, P. and Kivipelto, M. (2010). Alzheimer's disease: clinical trials and drug development. *Lancet Neurology*, 9, 702–716. doi: 10.1016/S1474-4422(10)70119-8.

Mattsson, N., Blennow, K. and Zetterberg, H. (2010). Inter-laboratory variation in cerebrospinal fluid biomarkers for Alzheimer's disease: united we stand, divided we fall. *Clinical Chemistry and Laboratory Medicine*, 48, 603–607. doi: 10.1515/CCLM.2010.131.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34, 939–944.

McKhann, G. M. *et al.* (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, 263–269. doi: 10.1016/j.jalz.2011.03.005.

O'Brien, J. T. (2007). Introduction: for debate: should neuroimaging be a routine investigation in all cases of suspected dementia?. *International Psychogeriatrics*, 19, 525–526. doi: 10.1017/S1041610206214777.

Porteri, C., Galluzzi, S., Geroldi, C. and Frisoni, G. B. (2010). Diagnosis disclosure of prodromal Alzheimer disease-ethical analysis of two cases. *Canadian Journal of Neurological Sciences*, 37, 67–75.

Rocca, W. A. *et al.* (2011). Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimer's & Dementia*, 7, 80–93. doi: 10.1016/j.jalz.2010.11.002.

Sperling, R. A. *et al.* (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, 280–292. doi: 10.1016/j.jalz.2011.03.003.

Steinbart, E. J., Smith, C. O., Poorkaj, P. and Bird, T. D. (2001). Impact of DNA testing for early-onset familial Alzheimer disease and frontotemporal dementia. *Archives of Neurology*, 58, 1828–1831.