



Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

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In the past 8 years, both the International Working Group (IWG) and the US National Institute on Aging–Alzheimer's Association have contributed criteria for the diagnosis of Alzheimer's disease (AD) that better define clinical phenotypes and integrate biomarkers into the diagnostic process, covering the full staging of the disease. This Position Paper considers the strengths and limitations of the IWG research diagnostic criteria and proposes advances to improve the diagnostic framework. On the basis of these refinements, the diagnosis of AD can be simplified, requiring the presence of an appropriate clinical AD phenotype (typical or atypical) and a pathophysiological biomarker consistent with the presence of Alzheimer's pathology. We propose that downstream topographical biomarkers of the disease, such as volumetric MRI and fluorodeoxyglucose PET, might better serve in the measurement and monitoring of the course of disease. This paper also elaborates on the specific diagnostic criteria for atypical forms of AD, for mixed AD, and for the preclinical states of AD.

Introduction

In 2007, the International Working Group (IWG) for New Research Criteria for the Diagnosis of Alzheimer's Disease (AD) provided a new conceptual framework that proposes to anchor the diagnosis of AD on the presence of biomarkers.¹ A goal of these diagnostic criteria, and of the subsequent National Institute on Aging–Alzheimer's Association (NIA–AA) criteria,² has been to expand coverage of the full range of disease stages, from the asymptomatic through the most severe stages of dementia. Potentially, their most important practical application is to allow earlier intervention in the prodromal stages of the disease and to facilitate research studies into secondary prevention of AD in the preclinical states. As we learn more through the research application of these criteria, common ground is being found for the eventual development of a universal set of criteria that truly captures the essence of AD.

In parallel, research into biomarkers has helped to clarify the potential value of each marker in the diagnosis of AD. Data highlight the value of cued recall measures for the assessment of episodic memory impairment; the relevance of atrophy of the hippocampus and related structures has been revisited; the value, relation with pathology, and significance of CSF biomarkers are better known; and interpretation of data from amyloid PET imaging has improved, its correlation with pathology clarified, and new ligands have been introduced. The objectives of the proposed revision are to clarify, in the context of this consensus framework, how the criteria can be applied, maintaining the principle of a high specificity. Our aims are as follows: (1) to present a new diagnostic algorithm for typical AD; (2) to advance the diagnostic criteria for atypical AD; (3) to refine the diagnostic criteria for mixed AD; (4) to elaborate the criteria for the diagnosis of the preclinical states of AD;

and (5) to differentiate the biomarkers of AD diagnosis from those of AD progression.

Conceptual advances of the new criteria

AD has traditionally been defined as a type of dementia, a notion brought into existence with the publication of criteria from the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) in 1984.³ Two major tenets of these criteria were as follows: (1) the clinical diagnosis of AD could only be designated as “probable” while the patient was alive and could not be made definitively until Alzheimer's pathology had been confirmed post mortem; and (2) the clinical diagnosis of AD could be assigned only when the disease had advanced to the point of causing significant functional disability and met the threshold criterion of dementia. The absence at that time of clinical criteria for the other dementias and the lack of biomarkers resulted in a low specificity in differentiation of AD from other dementias.⁴

In 2007, the IWG for New Research Criteria for the Diagnosis of AD provided a new conceptual framework that moved AD from a clinicopathological to a clinicobiological entity.⁵ These 2007 IWG criteria proposed that AD could be recognised in vivo and independently of dementia, in the presence of two requisite features. The first was a core clinical phenotypic criterion that required evidence of a specific episodic memory profile characterised by a low free recall that is not normalised by cueing.⁵ This memory profile differs from that observed in patients with non-AD disorders, such as frontotemporal dementias, progressive supranuclear palsy, Huntington's disease, major depression, or even normal ageing, in which the frontal-related retrieval deficit is normalised by the cueing procedure.^{6–9} This pattern was secondarily shown to

correlate significantly with hippocampal volume and, more precisely, with the CA1 field in three-dimensional hippocampal surface-based shape analysis.¹⁰ It was included as a core criterion because no other cognitive changes in “typical AD”, whether at a prodromal (predementia) or dementia stage, are as specific to the disease. The second criterion was the presence of biomarker evidence consistent with and supportive of AD on: (1) structural MRI; (2) molecular neuroimaging with PET (¹⁸F-2-fluoro-2-deoxy-D-glucose PET [FDG PET] or ¹¹C-labelled Pittsburgh compound B PET [PiB PET]); or (3) CSF analysis of amyloid β (A β) or tau protein (total tau [T-tau] and phosphorylated tau [P-tau]) concentrations. The most innovative aspect of the 2007 criteria was the first introduction of biomarkers into the core diagnostic framework. This change enabled AD diagnosis to be extended into the prodromal stage, where the disease can be diagnosed with supportive biomarkers. The ambiguous nature of any categorical boundary between prodromal AD and AD dementia argues in favour of a unified and dimensional diagnostic approach that uses the same criteria for diagnosis irrespective of the severity of cognitive and functional deficits. The recognition of prodromal AD was an important advance over the broader and more heterogeneous state of mild cognitive impairment (MCI). Furthermore, the IWG diagnostic criteria served to disconnect the clinicobiological diagnosis of AD from the diagnostic requirement of having dementia and functional disability that impairs everyday life. The framework offered a single set of criteria that were applicable at all clinical stages of disease across the entire disease continuum. Their main limitations were the focus on only typical AD with amnesic presentations and the absence of ordering or weighting of the supportive biomarkers.

The first important refinements to the 2007 criteria were made by the IWG in 2010.¹¹ A lexicon was proposed that clearly drew a distinction between the clinical disease (AD) and disease pathology (Alzheimer’s pathology)—which is defined by specific neuronal lesions observed post mortem, including senile plaques and neurofibrillary tangles associated with neuronal loss, synaptic loss, and frequently with cerebral amyloid angiopathy—because this pathological process might not have been symptomatic during life. In turn, this distinction broadened the spectrum of the disease to include its preclinical states, in which Alzheimer’s pathology exists without clinical symptoms. Two states were proposed for preclinical AD: “asymptomatic at-risk state for AD” and “presymptomatic AD”. The former group includes individuals with biomarkers of Alzheimer’s pathology but without clinical symptoms or signs. These individuals are classified as being asymptomatic at risk of AD because the percentage of individuals with positive biomarkers who will progress to symptomatic clinical conditions is not yet established, and because it is recognised that significant Alzheimer’s pathology can

exist at post mortem in individuals who were not judged to be symptomatic in their lifetime.^{12–15} The designation of presymptomatic AD was proposed for the few individuals who carry an autosomal dominant monogenic AD mutation with virtually full penetrance, in view of the inevitability that they will develop clinically manifest AD. The 2010 lexicon also proposed working definitions of “atypical AD” and “mixed AD”. Biomarkers were further categorised as “pathophysiological” if they were direct in-vivo indicators of brain amyloidosis and tauopathy, including amyloid tracer PET scans and CSF concentrations of A β _{1–42}, T-tau, and P-tau. On the assumption that Alzheimer’s pathology leads to metabolic changes or neuronal loss in connected regions, biomarkers were considered to be “topographical” if they identified downstream brain changes indicative of the regional distribution of Alzheimer’s pathology, including medial temporal lobe atrophy on MRI or reduced glucose metabolism in temporoparietal regions on FDG PET. No changes were made to the diagnostic algorithm itself (clinical core plus supportive biomarker evidence), except for the specification of atypical forms of AD, which described the less frequent but well defined clinical phenotypic variants of non-amnesic focal cortical syndromes, including logopenic aphasia, posterior cortical atrophy, and frontal variant AD.

The NIA-AA diagnostic criteria, published in 2011,² similarly advanced the NINCDS-ADRDA framework to cover the full staging of the disease: asymptomatic (preclinical AD),¹⁶ predementia (MCI due to AD),¹⁷ and dementia (due to AD).¹⁸ These criteria shared many features with the IWG criteria, including the integration of biomarkers in the diagnostic process and the recognition of an asymptomatic biomarker-positive stage. The NIA-AA criteria differ conceptually from the IWG criteria on several points. The NIA-AA proposed three different sets of diagnostic criteria, one for each disease stage. Although both the IWG and NIA-AA criteria recognise that the disease starts before the occurrence of clinical symptoms, the NIA-AA criteria support the diagnosis of AD in asymptomatic individuals with biomarker evidence of A β accumulation,¹⁶ whereas the IWG considers this to be only an at risk of disease state. At both the MCI¹⁷ and dementia stages,¹⁸ the NIA-AA diagnostic framework provides different levels of probabilistic likelihood (high, intermediate, or unlikely) that the syndrome is due to AD based on biomarker information. The NIA-AA criteria have the advantage of being applicable when no supportive biomarkers are available, albeit at the expense of diagnostic specificity. The IWG criteria are less complex in their semiology, have the advantage of consistency, and are more readily applicable in clinical trials and in clinical diagnosis when biomarkers are available.

Validation of both the IWG and NIA-AA diagnostic criteria is fundamental to progress in the field. Preliminary studies (both retrospective and prospective) done mostly

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with patients referred to memory clinics indicate moderate sensitivity and high specificity for the IWG criteria, with a good diagnostic accuracy (from 93% to 100% compared with the NINCDS–ADRDA clinical criteria and, for one study, with the neuropathological Consortium to Establish a Registry for Alzheimer's disease [CERAD] criteria) when several biomarkers are combined.^{19–23} The emphasis and progress on biomarkers builds on an increasingly robust scientific foundation as data emerge about biomarker performance (reliability, reproducibility, validity) and operationalisation (cutoff scores, sensitivity and specificity for AD).²⁴ The most challenging questions for both the IWG and NIA–AA frameworks focus on the multitude of proposed biomarkers, their inter-relationships particularly with regard to producing additive value, and their putative weight in the diagnosis. A temporal order has been proposed in the NIA–AA research criteria for preclinical AD, in which amyloid biomarker changes precede neuronal injury in the progression to symptomatic stages.² This ordering is not settled, although it has received some support from the cross-sectional baseline data of genetically identified early-onset familial AD cases with various presenilin and amyloid precursor protein mutations.^{25–27}

In this Position Paper, the IWG presents evidence to support a refinement of its diagnostic algorithm based on the weighting of biomarkers, which is achieved by reconsidering the biomarker categories and their role as markers of Alzheimer's pathology.

Methods

The IWG recognised the limitations of the initial criteria and the need to take advantage of rapid progress in the field, and considered that the criteria for the diagnosis of AD might be improved in the light of a more comprehensive body of evidence than was available at their initial formulation in 2007. For this update, an extensive review of the literature was undertaken by BD and LCdS with key search themes (AD diagnosis, preclinical states, prodromal AD, atypical and mixed AD, CSF and neuroimaging, amyloid PET) in PubMed from 2007 until January, 2013. On the basis of a review of selected papers (BD and LCdS), an early draft of the revised conceptual framework was developed (BD, HHF, CJ, PS, and JLC), which was then circulated to the IWG experts for their extensive feedback and electronic consultations within the group. The feedback resulted in a more advanced version of the diagnostic framework and the draft manuscript. It was then proposed to a broader group of experts (JLM, KB, DS, SCa, SE, M-OH, AN, GR, CR, BV, and LS) for their additional comments in specific areas. The final version was approved by all the authors.

A revised diagnostic algorithm for typical AD

New evidence on tests to identify AD memory disorders Memory disorders that manifest as free recall deficits occur in many brain diseases other than AD.^{28–30} A

specific episodic memory disorder has been reported in AD, which is the manifestation of a hippocampal dysfunction⁴ and can be identified by tests that include list learning. Of these, the free and cued selective reminding test (FCSRT) was specifically recommended in the 2007 criteria because of two major advantages: it controls for a successful encoding (achieved by cued recall) and it facilitates retrieval processing (with the same semantic cues).³¹ There is evidence to support the choice of the FCSRT as a valid clinical marker of typical AD. On one version of the test applied in patients referred to a specialised memory clinic, a low total recall performance, despite retrieval facilitation with cueing, had an excellent specificity for AD,³² whereas a low free recall had a specificity of 92% for identification of people with amnesic MCI who would progress to AD dementia.³³ The FCSRT had better reported predictive validity than did the Wechsler Memory Scale (WMS) logical memory immediate recall test for identification of both individuals from a community-based cohort with memory complaints who went on to develop incident AD dementia³⁴ and patients referred to a memory clinic who fulfilled broad criteria for MCI and had a characteristic positive CSF profile for Alzheimer's pathology.³⁵ Furthermore, impaired FCSRT performance can be correlated with hippocampal atrophy,¹⁰ grey matter loss of the medial temporal lobe,²³ and the presence of Alzheimer's pathology as shown by CSF changes,^{23,35–37} even at a prodromal stage.³⁴ Different cutoff scores have been considered³³ and are currently being deployed in several clinical trials in prodromal or early AD, including studies of γ -secretase inhibitors, BACE inhibitors, monoclonal antibodies, and medical foods. The challenge of prescribing cutoff points lies in the variations in the tests used and in the adjustments across populations for age and education. For research purposes—clinical trials, validation of new biomarkers, or follow-up of patient cohorts—the general approach is to recommend that cutoff points are selected within given target populations that have high specificity for an early AD diagnosis, potentially at the expense of lower sensitivity. Optimisation of the specificity of the memory screen might be a goal to minimise unnecessary additional testing.³⁴ Simplified versions of the test based on cued recall can be used for bedside testing. These versions were reported to predict progression to AD dementia in patients with MCI with specificity around 90%.^{38–40}

Other memory tests, particularly those based on list learning and delayed recall, can also be effective in identification of the amnesic syndrome of AD. These tests include different versions of the paired-associate learning and the Rey auditory verbal learning tasks.^{41–48} Other promising neuropsychological tests to detect the amnesic impairments that are specific for early pathological involvement of the entorhinal-perirhinal cortex include the DMS48,⁴⁹ a visual recognition test that

is correlated with an AD pattern in patients with MCI,⁵⁰ and the topographical memory test.⁵¹ The short-term memory binding test might also be a good marker for AD,⁵² given its high specificity in patients with familial AD and in asymptomatic carriers with *PSEN1* autosomal dominant gene mutations.⁵³ For all of these tests, evidence for their diagnostic utility for AD should be available before they can be recommended for use within the diagnostic algorithm.

In conclusion, the aggregate evidence continues to support the presence of an amnesic syndrome of the hippocampal type as the clinical core criterion for typical AD, which can be best identified with a list-learning memory test such as the FCSRT or other episodic memory tests with established high specificity for AD across the disease.

The evidence for refining the biomarker criteria

CSF biomarkers and amyloid PET have both shown the highest specificity when correlated with the underlying Alzheimer's pathology in post-mortem studies. Conceptually, they are the most specific biomarkers to determine that an individual is within the AD continuum even several years before the clinical onset of disease.

CSF pathophysiological markers for AD include $A\beta_{1-42}$, which inversely reflects the brain amyloid burden; T-tau, which directly reflects the intensity of neuronal degeneration; and P-tau, which is believed to be a direct marker of tangle pathology.⁵⁴ Recent studies suggest that CSF markers of $A\beta_{1-42}$ and tau correlate closely with post-mortem Alzheimer's pathology.⁵⁵⁻⁶⁰ In an autopsy cohort, low CSF $A\beta_{1-42}$ concentrations had a sensitivity of 96.4% for AD detection⁵⁵ and CSF markers significantly increased the diagnostic accuracy in clinically uncertain cases.⁶¹ Of CSF markers, P-tau₁₈₁ concentrations were the most accurate to distinguish AD from non-AD dementias, even in autopsy-confirmed dementia patients.^{56, 62} A marked reduction in CSF $A\beta_{1-42}$ and in the $A\beta_{1-42}/A\beta_{1-40}$ ratio has consistently been noted in patients at different stages of AD.^{54, 63} However, an isolated low $A\beta_{1-42}$ is not sufficiently specific to diagnose AD, in view of similar findings in some patients with non-AD dementias (Lewy body disease or vascular dementia), given its presence long before onset of clinical AD, or given AD copathology in patients with Lewy body disease.⁶⁴ Additionally, $A\beta_{1-42}$ concentrations are particularly sensitive to preanalytical and analytical biases⁶⁵ and make it difficult to achieve the requisite low coefficient of variation and quality control.⁶⁶ Numerous studies have shown that a combination of these CSF biomarkers is required because it significantly improves their discriminative accuracy,⁶⁷⁻⁷² but no consensus has been agreed yet as to which specific combination has the greatest utility in AD diagnosis.

The added value of the combinations of CSF markers has been tested in predictive studies of progression to AD dementia. Individuals with a high ratio of T-tau to

$A\beta_{1-42}$ or of P-tau₁₈₁ to $A\beta_{1-42}$ progress to symptomatic cognitive impairment (ie, CDR >0) more quickly than do the remainder of the cohort.⁶⁷ This result was not observed for $A\beta_{1-42}$ concentrations alone for the duration of the longitudinal studies (3–5 years) completed to date. The combination of T-tau, $A\beta_{1-42}$, and P-tau is highly predictive of AD dementia,⁷²⁻⁷⁴ which has been confirmed in three large multicentre studies—namely, the Alzheimer's Disease Neuroimaging Initiative (ADNI) study,⁶² the Development of Screening Guidelines and Criteria for Predementia Alzheimer's Disease (DESCRIPA) study,⁷⁵ and the Swedish Brain Power (SBP) project.⁷⁶ A meta-analysis recently confirmed that the combination of CSF $A\beta_{1-42}$ with either T-tau or P-tau has the highest predictive accuracy, whereas individual markers were also predictive but with lower accuracy (odds ratio [OR] 7.5–8.1).⁷⁷ Studies of autosomal dominant mutation carriers, including the Dominantly Inherited Alzheimer's Disease (DIAN) project, also show that high CSF T-tau and P-tau combined with a decrease in CSF $A\beta_{1-42}$ and the ratio of $A\beta_{1-42}$ to $A\beta_{1-40}$ are present 10–15 years before the first symptoms of dementia.^{25,78,79} Thus, data so far indicate that the combination of $A\beta_{1-42}$ with either T-tau or P-tau has the best specificity, but evidence is insufficient with regard to the predictive value and diagnostic accuracy (sensitivity, specificity, negative predictive value, and positive predictive value) of $A\beta_{1-42}$ alone. Additionally, the combined analysis of the CSF biomarkers provides the best accuracy in the differential diagnosis between AD and other degenerative dementias,⁸⁰⁻⁸² with a good concordance with post-mortem diagnosis.^{81,83} In particular, the ratio of T-tau to $A\beta_{1-42}$ was the best biomarker to differentiate AD from frontotemporal lobar degeneration, and showed a specificity of 96.6% in a series of patients with diagnostic confirmation either by genetics or by post-mortem examination.⁸⁰

In conclusion, $A\beta_{1-42}$ and tau (T-tau or P-tau) should be used in combination, and the CSF AD signature, which combines low $A\beta_{1-42}$ and high T-tau or P-tau concentrations, significantly increases the accuracy of AD diagnosis even at a prodromal stage.^{67,73,77,83,84} This combination reaches a sensitivity of 90–95% and a specificity of about 90% in AD.^{81,85} CSF biomarkers cannot be used as standalone tests, and should be interpreted in a larger clinical context with confounding factors taken into account. An important concern is the large variability in CSF measures between laboratories⁸² and across techniques,⁸⁶ and the lack of agreement on cutoff thresholds.⁸⁷ These variations have made direct comparison of study results difficult. Several programmes of standardisation, including the Alzheimer's Association Quality Control programme for CSF biomarkers, initiatives within the Joint Program for Neurodegenerative Diseases, and the Global Biomarker Standardisation Consortium,⁸⁸⁻⁹⁰ and by industry, will minimise between-laboratory variations in the future and allow identification of uniform cutoff levels.

PET imaging with amyloid tracers, including ^{11}C -PiB, florbetapir (AV-45),⁹¹ flutemetamol (^{18}F -PiB derivative), florbetaben (AV-1), and AZD4694,⁹² provides important information about the extent of A β neuritic plaque burden in the brain. Amyloid PET is therefore considered as a surrogate marker of brain fibrillar amyloid pathology. Both quantitative and qualitative measures of amyloidopathy with PET ligands have correlated strongly with post-mortem senile neuritic plaque pathology across PET ligands^{93–97} and shown good predictability for progression to AD dementia in heterogeneous groups of patients with MCI.^{98–101} Agreement between florbetapir amyloid PET images and post-mortem results reaches 96%.⁹³

In conclusion, amyloid PET is a validated pathophysiological marker for fibrillar amyloid, particularly neuritic plaques and amyloid angiopathy. In view of the good correlation with post-mortem diagnosis of AD, a positive amyloid PET can be considered, by extension, as a good marker of Alzheimer's pathology.

As with CSF, there are several issues with the methods of assessment and their interpretation. Visual interpretations of ^{18}F amyloid tracers require experienced raters. Tracer sensitivity for moderate amyloid burden is less established and varies according to the age of patients.¹⁰² The significance of the frequent cases of amyloid PET positivity in asymptomatic individuals requires further investigation,^{97,103,104} which also holds true for the rare cases of amyloid PET-negative individuals with AD autosomal dominant mutations¹⁰⁵ or post-mortem evidence of fibrillar amyloid.^{106,107}

For the purposes of the proposed refinement of the IWG diagnostic criteria, it is important to compare the diagnostic accuracy of CSF markers (low A β and high T-tau or P-tau concentrations) to that of a positive fibrillar amyloid PET scan, given that they gauge somewhat different aspects of AD pathophysiology. CSF A β_{1-42} measures soluble forms of A β , and a low concentration suggests that significant parenchymal deposition has occurred, whereas amyloid imaging directly identifies fibrillar A β . CSF T-tau and CSF P-tau reflect neuronal degeneration and hyperphosphorylation of tau in the brain, respectively. Despite these distinctions, a recent study has shown equal ability of CSF and amyloid imaging markers to identify individuals at risk of incident cognitive impairment.¹⁰⁸ Results from this study showed that individuals with increased ligand retention in amyloid imaging typically have decreased CSF A β and increased CSF tau concentrations, rather than A β alone. In the pathophysiological evolution of AD, substantial deposition of fibrillar amyloid is likely to co-occur with changes in both CSF A β_{1-42} and tau, at least at a time shortly before the onset of clinical symptoms. Despite reports of discrepancies,¹⁰⁵ a high degree of correlation and agreement exists between CSF markers of A β_{1-42} and tau, and brain amyloid binding. Amyloid ligand retention on PET has consistently correlated inversely with CSF concentrations of A β_{1-42} ,^{109–111} even in

cognitively healthy patients,¹¹² which supports the concept of a physiological link between CSF A β_{1-42} concentrations and brain amyloidosis. By contrast with the well documented correlation between brain amyloid retention and CSF A β_{1-42} concentrations, only a modest agreement was noted between amyloid PET and P-tau.¹¹³ More recently, the ratios of tau(s) to A β_{1-42} outperformed each single biochemical analyte (including A β_{1-42}) in distinguishing PiB-positive from PiB-negative individuals.⁸⁷ The good agreement between CSF markers and PET amyloid imaging provides converging evidence for their validity.¹¹⁴

In conclusion, Alzheimer's pathology can be suspected *in vivo* at any stage of the disease, including preclinical states, by a CSF signature of low A β_{1-42} and high T-tau or P-tau concentrations, or by evidence of significant PET amyloid retention (either by visual assessment in advanced cases or by assessment of global cortical threshold in intermediate or difficult cases).

Proposed revision for typical AD

A research diagnosis of typical AD can be made in the presence of an amnesic syndrome of the hippocampal type that can be associated with various cognitive or behavioural changes, and at least one of the following changes indicative of *in-vivo* Alzheimer's pathology: a CSF profile consisting of decreased A β_{1-42} levels together with increased T-tau or P-tau concentrations, or an increased retention on amyloid tracer PET. The proposed diagnostic change for typical AD is to include only pathophysiological markers of Alzheimer's pathology (panel 1).

A revised diagnostic algorithm for atypical AD The case for refining the diagnostic algorithm

In an estimated 6–14% of cases,^{115–117} the presentation of AD varies from the typical amnesic form. Patients with an atypical clinical presentation probably account for most of the 11% of AD cases with an atypical pathological distribution at autopsy.¹¹⁸ Each of these atypical forms of AD presents with a relative preservation of memory plus a recognisable (or characteristic) phenotype that might be accompanied by topographical evidence of brain damage (regional atrophy or hypometabolism) in related regions. Atypical forms of AD generally occur with an earlier age at onset than does typical amnesic AD. It is now possible to propose more precise definitions for atypical AD presentations, including a posterior variant of AD, a logopenic variant of AD, and a frontal variant of AD.

The posterior variant of AD presents as a posterior cortical atrophy¹¹⁹ and generally results in several signs and symptoms that distinguish two subtypes:¹²⁰ an occipitotemporal variant,¹¹⁵ with a predominant impairment in the visual identification of objects, symbols, words, or faces; and a more common biparietal variant,¹²¹ with predominant visuospatial dysfunction, as well as features of Gerstmann or Balint syndrome, limb apraxia, or neglect. The logopenic variant of AD, which presents as the

logopenic primary progressive aphasia, is defined by a progressive impairment in single-word retrieval and in repetition of sentences in the context of spared semantic, syntactic, and motor speech abilities.¹²² The frontal variant of AD presents as a behavioural variant of frontotemporal dementia, with progressive apathy or behavioural disinhibition and stereotyped behaviours, or with predominant executive dysfunction at testing.^{123–128}

Although most cases of posterior cortical atrophy and logopenic primary progressive aphasia are linked to Alzheimer's pathology,^{126,129} only a few patients who present with prominent frontal behavioural symptoms have Alzheimer's pathology detected post mortem.^{126,128,130}

As for typical AD, the IWG emphasises the necessity of pathophysiological biomarkers to support a diagnosis of AD in these atypical cases (panel 2). The topographical biomarkers can help to characterise the clinical phenotype (regional cortical hypometabolism in FDG PET, circumscribed cortical atrophy on structural MRI), whereas a positive pathophysiological biomarker is required to link the phenotype to the underlying Alzheimer's pathology.^{131–133} Although a positive pathophysiological biomarker supports the presence of Alzheimer's pathology, it does not exclude the co-occurrence of non-AD pathology, which might be a significant contributor to the atypical syndromes, particularly in the frontal variant,¹³⁴ which is less predictive of pure underlying AD than the logopenic or posterior variants. By definition, these atypical syndromes can be diagnosed within their prodromal phase as well as into the dementia continuum along a spectrum of severity. Further work is needed to distil the specific clinical core related to Alzheimer's pathology in each of these atypical presentations, with the aim of characterising the clinically atypical cores with the same conceptual foundation in cognitive theory and operationalisation in terms of test paradigms as has been done for the amnesic core in typical AD.

The occurrence of a dementia in patients with Down's syndrome can be classified as an atypical AD because the clinical phenotype associated with the occurrence of Alzheimer's pathology is dominated by changes in behaviour, executive functions, and functional activities.¹³⁵ The premorbid intellectual disability creates a specific setting for the assessment of the cognitive impairment associated with Alzheimer's pathology. Although episodic memory changes can be identified with testing procedures, the presenting functional and behavioural symptoms lead to their consideration as atypical AD.

Proposed revision for atypical AD

A diagnosis of atypical AD can be made in the presence of the following: a clinical phenotype that is consistent with one of the known atypical presentations (posterior variant, logopenic variant of primary progressive aphasia, frontal variant) and at least one of the changes indicating in-vivo Alzheimer's pathology (panel 2).

Panel 1: IWG-2 criteria for typical AD (A plus B at any stage)

A Specific clinical phenotype

- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
 - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
 - Objective evidence of an amnesic syndrome of the hippocampal type,* based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

B In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

Exclusion criteria† for typical AD

History

- Sudden onset
- Early occurrence of the following symptoms: gait disturbances, seizures, major and prevalent behavioural changes

Clinical features

- Focal neurological features
- Early extrapyramidal signs
- Early hallucinations
- Cognitive fluctuations

Other medical conditions severe enough to account for memory and related symptoms

- Non-AD dementia
- Major depression
- Cerebrovascular disease
- Toxic, inflammatory, and metabolic disorders, all of which may require specific investigations
- MRI FLAIR or T2 signal changes in the medial temporal lobe that are consistent with infectious or vascular insults

AD=Alzheimer's disease. *Hippocampal amnesic syndrome might be difficult to identify in the moderately severe to severe dementia stages of the disease, in which in-vivo evidence of Alzheimer's pathology might be sufficient in the presence of a well characterised dementia syndrome. †Additional investigations, such as blood tests and brain MRI, are needed to exclude other causes of cognitive disorders or dementia, or concomitant pathologies (vascular lesions).

A revised diagnostic algorithm for mixed AD

The case for refining the diagnostic algorithm

The IWG initially defined mixed AD as the co-occurrence of Alzheimer's pathology with other pathologies that might contribute to the cognitive decline, such as normal pressure hydrocephalus, hippocampal sclerosis, and most often cerebrovascular disease or Lewy body disease.¹¹ Mixed AD has been reported to represent at least 50% of all AD cases at autopsy, with a particularly high prevalence in people older than 80 years.^{136,137} The recognition of mixed pathology in clinical diagnosis is challenging.¹³⁸ Our current proposal for mixed AD diagnosis is that there must be evidence of AD based on clinical phenotype, either typical or atypical, with concurrent in-vivo evidence of Alzheimer's pathology. Additionally, clinical as well as

Panel 2: IWG-2 criteria for atypical AD (A plus B at any stage)**A Specific clinical phenotype (one of the following)**

- Posterior variant of AD (including)
 - An occipitotemporal variant defined by the presence of an early, predominant, and progressive impairment of visuo-perceptive functions or of visual identification of objects, symbols, words, or faces
 - A biparietal variant defined by the presence of early, predominant, and progressive difficulty with visuospatial function, features of Gerstmann syndrome, of Balint syndrome, limb apraxia, or neglect
- Logopenic variant of AD defined by the presence of an early, predominant, and progressive impairment of single word retrieval and in repetition of sentences, in the context of spared semantic, syntactic, and motor speech abilities
- Frontal variant of AD defined by the presence of early, predominant, and progressive behavioural changes including association of primary apathy or behavioural disinhibition, or predominant executive dysfunction on cognitive testing
- Down's syndrome variant of AD defined by the occurrence of a dementia characterised by early behavioural changes and executive dysfunction in people with Down's syndrome

B In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- Alzheimer's disease autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

Exclusion criteria* for atypical AD*History*

- Sudden onset
- Early and prevalent episodic memory disorders

Other medical conditions severe enough to account for related symptoms

- Major depression
- Cerebrovascular disease
- Toxic, inflammatory, or metabolic disorders

AD=Alzheimer's disease. *Additional investigations, such as blood tests and brain MRI, are needed to exclude other causes of cognitive disorders or dementia, or concomitant pathologies (vascular lesions).

Panel 3: IWG-2 criteria for mixed AD (A plus B)**A Clinical and biomarker evidence of AD (both are required)**

- Amnesic syndrome of the hippocampal type or one of the clinical phenotypes of atypical AD
- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF, or increased tracer retention on amyloid PET

B Clinical and biomarker evidence of mixed pathology*For cerebrovascular disease (both are required)*

- Documented history of stroke, or focal neurological features, or both
- MRI evidence of one or more of the following: corresponding vascular lesions, small vessel disease, strategic lacunar infarcts, or cerebral haemorrhages

For Lewy body disease (both are required)

- One of the following: extrapyramidal signs, early hallucinations, or cognitive fluctuations
- Abnormal dopamine transporter PET scan

AD=Alzheimer's disease.

neuroimaging or biochemical evidence of a non-AD contributing disorder should be present. For example, in the case of Lewy body disease, additional clinical features of visual hallucinations, extrapyramidal signs, rapid eye movement (REM) sleep behaviour disorder, or cognitive fluctuations¹³⁹ would be supported by a positive dopamine transporter imaging test.¹⁴⁰ For cerebrovascular disease, the clinical presentation would include a history of stroke, appropriate vascular risk factors or focal neurological findings (or both), which should be supported by neuroimaging evidence of cerebrovascular disease in the form of lacunar disease, evidence of cerebral amyloid angiopathy, large or small vessel territory infarctions, extensive leukoariosis, or small vessel disease (panel 3).

The clinical phenotype of mixed AD is uncertain. AD and non-AD dementias are not easily catalogued into distinct, non-overlapping clinical and neuropsychological profiles.¹⁴¹ A few autopsy-based studies on AD associated with Lewy body disease have shown episodic memory impairment similar to that noted in AD alone, with visuospatial deficits unusually severe for AD¹⁴² and with milder impairment in executive functioning than usually found in Lewy body disease.¹⁴³ AD combined with cardiovascular disease might also present with a distinct profile of deficits, probably broader than that of AD alone.^{144,145} These and other mixed AD clinical presentations need to be carefully characterised, particularly at the prodromal stage.

Proposed revision for mixed AD

A diagnosis of mixed AD can be made in patients with typical or atypical clinical phenotypic features of AD and the presence of at least one biomarker of Alzheimer's pathology. This evidence is needed to establish the AD contribution to the mixed disorder. The coexisting disorder within the mixed diagnosis is identified by additional evidence of specific clinical and biological features of the other disease, such as parkinsonism or cerebrovascular disease (panel 3).

Criteria for the preclinical states of AD**The case for new criteria for the diagnosis of preclinical states**

The disappointing results of drugs targeting $A\beta$ in recent clinical trials for patients with mild to moderately severe AD have engendered the belief that these therapies are being tested too late in the process of the disease and that earlier intervention is needed to ameliorate the course of AD.^{146,147} In turn, interest has intensified in defining the preclinical states of AD through research projects on the natural history and trajectory of the disease, to design secondary preventive clinical trials.^{148,149} Pathophysiological biomarkers of disease, independent of disease stage, makes it possible to identify patients considered to be asymptomatic at risk for AD.¹² In preclinical states, data for early CSF changes are needed because it may be possible that an isolated low $A\beta_{1-42}$ concentration is

sufficient to identify asymptomatic at-risk patients at this time.³⁶ Cognitively normal patients with isolated low concentrations of A β present significant changes in both cortical thickness and fMRI,^{36,150} which suggests that at the start of the preclinical state, amyloid might be the only positive marker, as proposed by Jack and colleagues.⁹⁹ By contrast, the identification of relatively common genetic risk variants such as *CLU*, *CRI*, and *PICALM*^{51,152} is of limited interest in the determination of risk of the preclinical state of AD in the general population. Even the *APOE* ϵ 4 allele, associated with AD risk, is neither necessary nor sufficient for development of the disease.¹⁵³

Although a long insidious preclinical state of the disease can precede the onset of clinical symptoms by many years, the risk factors and timing for development of clinically expressed AD from the asymptomatic at-risk state are not characterised sufficiently well to move beyond this diagnostic designation. To be asymptomatic at risk, individuals should not have clinical evidence of prodromal AD. The existence of any cognitive changes or complaints does not necessarily signify progression to clinical AD because these could be non-specific changes. There is an emerging trend to consider that AD can be identified clinically in the case of subtle cognitive changes.¹⁷ Isolated subjective memory complaints and the recent concept of subjective cognitive decline¹⁵⁴ could be predictors of subsequent cognitive decline and progression to dementia¹⁵⁵ and might be associated with brain amyloid deposition on amyloid PET.^{156,157} However, subjective memory complaints are only a risk factor for AD, because they might result from many other causes frequently encountered in the ageing population, including attention difficulties, depressed mood, sleep disorders, and drug side-effects. According to the refined IWG criteria proposed here, the diagnosis of AD requires the identification of one of the specific clinical phenotypes of the disease. A similar approach is advocated for presymptomatic AD, with progression to clinical AD certified only by the presence of objective clinical symptoms characteristic of the disease (panel 1).

Proposed revision for preclinical states

Research criteria for preclinical states of AD require: the absence of clinical symptoms of AD (typical or atypical phenotypes); and the presence of at least one biomarker of Alzheimer's pathology for the identification of asymptomatic at-risk state, or the presence of a proven AD autosomal dominant mutation on chromosomes 1, 14, or 21 for the diagnosis of presymptomatic state (panel 4).

Differentiation of biomarkers of AD diagnosis from biomarkers of AD progression

Refining the use of pathophysiological and topographical biomarkers

Alzheimer's pathology consists of brain amyloid deposition and neurofibrillary tangles, generally associated with synaptic loss and vascular amyloid deposits. Where

they develop, these lesions induce functional deficits and neuronal death. Variations in the hierarchy and relationships between A β load, cerebral hypometabolism, and atrophy have been reported.¹⁵⁸ However, these changes account for regional hypometabolism, atrophy of specific structures, and cognitive disorders in relation to the location of the neuronal lesions. Downstream topographical markers, particularly hippocampal atrophy assessed by MRI, cortical hypometabolism measured by FDG PET, and the subsequent cognitive and behavioural changes lack pathological specificity for AD, but they might be particularly valuable for detection and quantification of disease progression. These changes might be good markers to monitor time to disease milestones—eg, dementia onset—or for determination of disease stages.^{25,99}

Among all MRI-related biomarkers—including structural MRI with assessment of atrophy of critical brain regions (parahippocampal gyrus, hippocampus, amygdala, posterior association cortex, and subcortical nuclei including the cholinergic basal forebrain), assessment of cortical thickness,¹⁵⁹ and with use of support vector machine-based classifier,¹⁶⁰ functional MRI^{161,162} with studies of activation or functional connectivity; and proton magnetic resonance spectroscopy for the N-acetylaspartate (NAA)/creatinine ratio in specific areas (posterior cingulate gyri)^{163–165}—it is now established that medial temporal atrophy is the best MRI marker at a prodromal stage of further progression to AD dementia, and hippocampal atrophy is the most robust.¹⁶⁶ However, hippocampal volume is reduced in several conditions, including old age, and several neurotoxic situations including diabetes, sleep apnoea, bipolar disorder, and other conditions or dementia

Panel 4: IWG-2 criteria for the preclinical states of AD

IWG-2 criteria for asymptomatic at risk for AD (A plus B)

- A Absence of specific clinical phenotype (both are required)
- Absence of amnesic syndrome of the hippocampal type
 - Absence of any clinical phenotype of atypical AD
- B In-vivo evidence of Alzheimer's pathology (one of the following)
- Decreased A β _{1–42} together with increased T-tau or P-tau in CSF
 - Increased retention on fibrillar amyloid PET

IWG-2 criteria for presymptomatic AD (A plus B)

- A Absence of specific clinical phenotype (both are required)
- Absence of amnesic syndrome of the hippocampal type
 - Absence of any clinical phenotype of atypical AD
- B Proven AD autosomal dominant mutation in *PSEN1*, *PSEN2*, or *APP*, or other proven genes (including Down's syndrome trisomy 21)

AD=Alzheimer's disease.

(hippocampal sclerosis, Lewy-related pathology, argyrophilic grain disease, and frontotemporal dementia).^{167–169} Additionally, some pathological studies have documented the existence of hippocampal sparing in AD, often associated with early age-of-onset and non-amnesic clinical presentations, in which cortical degeneration is predominant while the medial temporal lobes are relatively spared.^{118,170,171} The association of all these non-AD disorders decreases the diagnostic utility of volumetric measures of medial temporal lobe structures for individual diagnostic purposes. However, the reliability of volumetric measures obtained from repeated MRI scans is high,¹⁷² which allows the study of the rate of atrophy over time as a reliable modality to measure disease progression. For example, hippocampal loss occurs at a rate that is approximately two to four times faster in patients with AD than in age-matched healthy controls.^{173,174}

Among topographical markers, FDG PET has been shown to have good sensitivity in detection of early brain dysfunction in AD^{175–177} and to follow disease evolution over time,^{178–181} including in AD mutation carriers.^{182,183} FDG uptake is believed to be a sensitive marker of synaptic dysfunction,^{184,185} and understandably the topography of hypometabolism accurately maps on clinical symptoms. Patients with AD with predominant memory impairment show the classic default mode network pattern (temporoparietal association areas including the precuneus and posterior cingulate cortex), whereas in patients with AD with focal neuropsychological deficits (language, praxis, or visuospatial dysfunction) hypometabolism affects the pertinent neocortical area.^{186,187} A study of the accuracy to predict progression from MCI to dementia in 102 patients reported values of 95% sensitivity and 79% specificity,¹⁸⁸ and a meta-analysis noted a positive likelihood ratio of 7.5 (0.4–14.7) and a negative likelihood ratio of 0.50 (0.14–0.86).²⁴ Changes have also been noted in asymptomatic patients at risk for AD.^{189–191} FDG uptake is

reduced, predominantly in temporoparietal association areas including the precuneus and posterior cingulate cortex, and these changes are closely related to cognitive impairment as demonstrated in cross-sectional and longitudinal studies.¹⁸⁶

Therefore, functional tracers such as FDG PET, in addition to their ability to differentiate AD from other neurodegenerative dementias,^{192–194} can help to show the extent to which Alzheimer's pathology affects brain function, particularly in individuals with high cognitive reserve.^{195–197}

Proposed revision

We propose that pathophysiological biomarkers of Alzheimer's pathology and downstream topographical markers of AD should be reconceptualised, whereby biomarkers of Alzheimer's pathology are restricted to those indicating the specific presence of tau pathology (CSF or PET tau) and amyloid pathology (CSF or PET amyloid) (panel 5). These biomarkers have the necessary specificity for a diagnosis of AD at any point on the disease continuum. Downstream topographical markers of brain regional structural and metabolic changes have insufficient pathological specificity and are therefore now removed from the IWG diagnostic algorithm. These markers can be used to measure disease progression.

Discussion

In this paper, we refine the IWG research diagnostic criteria for AD to provide a more simplified algorithm based on specific AD clinical phenotypes with in-vivo evidence of Alzheimer's pathology through either a molecular AD signature in CSF or positive amyloid imaging (figure). This simplified diagnostic algorithm reinforces our understanding of AD as a clinicobiological entity and allows the application of a single set of diagnostic criteria at any stage of the disease. We broaden the clinical core criteria to include the challenging phenotypic characterisations of atypical and mixed AD. The proposed refinements will place great demands on the clinical core diagnosis, for which the clinician now needs to identify a range of potential AD phenotypes, including mixed AD phenotypes and focal non-amnesic disease presentations.

We reconsider the biomarker support required for these diagnoses by anchoring all diagnostic criteria to the requirement of in-vivo evidence of AD pathophysiology, defined as increased brain amyloid retention on PET imaging (and perhaps of tau ligand on tau imaging PET in the near future), or as decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF. Low CSF $A\beta_{1-42}$ concentrations alone are not specific enough for an AD diagnosis. These refinements are based on evidence supporting the high specificity of CSF biomarkers and PET amyloid imaging for AD. An important change in the current criteria is that topographical markers of AD are now recommended for the assessment of disease

Panel 5: Definition of AD biomarkers

Diagnostic marker

- Pathophysiological marker
- Reflects in-vivo pathology
- Is present at all stages of the disease
- Observable even in the asymptomatic state
- Might not be correlated with clinical severity
- Indicated for inclusion in protocols of clinical trials

Progression marker

- Topographical or downstream marker
- Poor disease specificity
- Indicates clinical severity (staging marker)
- Might not be present in early stages
- Quantifies time to disease milestones
- Indicated for disease progression

AD=Alzheimer's disease.

stage and progression rather than as diagnostic markers. The classification in the NINCDS–ADRDA criteria of “clinically probable” AD could be discarded now that we are able to identify Alzheimer’s pathology in vivo. Additionally, we now integrate the presence of an autosomal dominant genetic mutation for AD as a diagnostic marker of the disease.

Within the proposed refinements of the IWG diagnostic criteria, we address the problem of the diversity of AD biomarkers and their potential weighting in the diagnostic algorithm. The IWG previously identified pathophysiological and topographical markers but attributed equal utility to both in the diagnosis of AD. The NIA–AA distinguishes between markers of A β deposition and neuronal injury, and assigns each type an equal role in diagnosis. We advance this categorisation through a redefinition of purpose or role of the biomarkers. We view pathophysiological markers as indicators of Alzheimer’s pathology in the brain, rather than as markers linked to disease stages. That is, they describe the presence of disease pathology at any stage. These markers of Alzheimer’s pathology are largely static, at least in the symptomatic stage of the disease, whereas topographical markers that are linked to the evolution of disease have greater dynamic range and changes over time. These proposed refinements simplify the diagnostic approach by designating a single in-vivo pathophysiological signature of AD, measured either in CSF or by use of amyloid PET.

The proposed revisions still rely on the two fundamental tenets that underlined the initial IWG criteria. The first is that they characterise a disease (AD) and not a syndrome (MCI or dementia). The combination of a specific cognitive profile, consistent with typical or atypical AD, and a positive pathophysiological marker moves the patient from an undetermined status of MCI to that of prodromal AD. The concept of MCI remains useful for cases that are negative for pathophysiological biomarkers. The second tenet is to maintain the principle of high specificity, at least for criteria that apply for research purposes including clinical trials. The 2007 IWG criteria were successfully implemented in current phase 2 clinical trials for prodromal AD and they were qualified for use in AD clinical trials by the European Medicines Agency (EMA).¹⁹⁸ Identification of patients with typical AD is thought to be more accurate and more reliable based on the refined algorithm. Once the well defined and operationalised core amnesic criterion is met, confirmation from a single positive pathophysiological marker is sufficient for inclusion purposes (except in rare cases of AD in which memory and MRI changes precede amyloid positivity).¹⁹⁹ To date, we have integrated evidence-based, clinically established, atypical forms of AD. In the future, new potential atypical presentations of AD might be considered and incorporated into our model. Research on patients with atypical or mixed AD will also benefit from the refined algorithm with reference to biomarkers

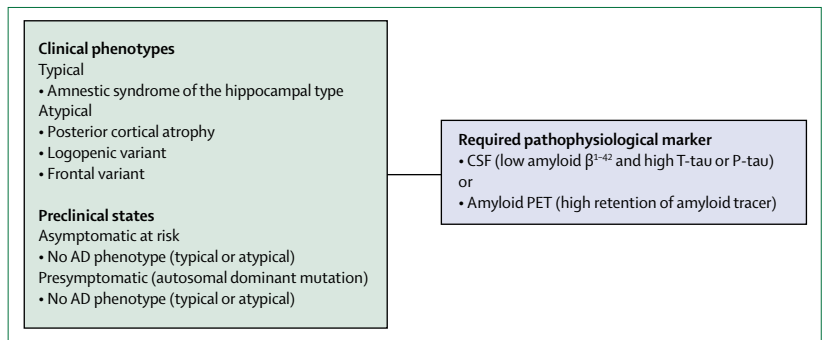


Figure: AD is defined as a clinicobiological entity

A simplified algorithm is proposed: in any condition and at any stage of the disease, the diagnosis of AD relies on the presence of a pathophysiological marker. AD=Alzheimer’s disease.

of amyloid pathology. This diagnostic framework should promote more systematic studies of these disorders.

Although the revised algorithm is meant to apply to all stages of the disease, it should be implemented with caution for some conditions, such as for patients with AD at moderately severe or severe stages for whom intellectual deterioration has progressed to a point at which memory testing is no longer possible. In such circumstances, positive markers of Alzheimer’s pathology should be considered as sufficient for inclusion in research on the basis of a history consistent with AD and after exclusion of a mixed disease with appropriate investigations. Disagreement between pathophysiological markers needs to be considered, and longitudinal observations should help to solve this issue in the future. There might also be age-related limitations. In older patients (>85 years), the clinical expression of AD and neuroimaging changes might be less salient.²⁰⁰ The phenotypic expression of AD is relatively mild in the oldest-old (>85 years) with a frequently indolent course.^{201–203} The diagnostic performance of CSF biomarkers and of structural MRI-based regional brain atrophy decreases with age,²⁰⁴ as does the association between neuritic plaques and dementia.²⁰⁵ This decrease in performance might affect the ability to distinguish AD from normal ageing in this group,²⁰⁶ for which high fibrillar amyloid is also very often detected. Furthermore, these patients have an increased risk of other systemic comorbidities¹³⁶ and general health problems including inflammatory conditions, anaemia, cancer, frailty, comedications, and other factors, which undoubtedly can interfere with the occurrence, expression, and progression of AD symptoms²⁰⁷ and might render the proposed algorithm less accurate. One refinement for a research perspective might be to separate younger patients, for which AD is rather pure with fewer or no comorbidities, high diagnostic accuracy, and reliability, from the oldest-old patients with a higher risk of comorbidities and a more complex underlying pathology. Research into individuals with identified risk of AD will continue to present challenges despite our efforts to

better define the preclinical states of AD. Important clinical issues exist in distinguishing between normal ageing, subtle early AD symptoms, and non-AD symptoms, and careful assessment will be needed to establish whether cognitive changes constitute an early expression of AD. Isolated low CSF levels of $A\beta_{1-42}$ might be present long before the appearance of the disease, and further evidence will tell us whether it might be sufficient to define asymptomatic at-risk patients.

In our view, the proposed criteria, which are designed for the accurate diagnosis of AD for rigorous research purposes, might in the future be used for clinical diagnosis in practice, at least for young-onset AD or atypical presentations in which biomarkers might increase diagnostic accuracy. Expert centres with adequate resources could use the algorithm proposed here and assess its performance to move the field forward and to determine utility within clinical practice. Important work has already been done in application of the 2007 IWG criteria in outpatient clinics, with excellent specificity and acceptable sensitivity.²⁰⁻²³ There is no a priori reason against a general move of the proposed criteria from research into clinical settings, at least in specific cases, although several caveats need to be considered. Not all centres have PET scanning equipment and expertise, and some participants might not readily accept a lumbar puncture for CSF assays. Further studies are needed to clarify conflicting results that can occur between the different CSF markers, and between CSF markers and amyloid PET. The lack of financial support for these costly investigations may limit the practicality of the IWG-2 criteria for general clinical use. Studies to determine the cost-effectiveness of diagnosis might also be required. Pathophysiological markers allow the identification of Alzheimer's pathology, including amyloidopathy or tauopathy, but do not preclude the presence of other non-AD conditions. MRI and other investigations are still necessary for the identification of comorbid or non-AD conditions and will continue to be part of the diagnostic approach. Cultural acceptance should also be taken into account. Although the use of CSF biomarkers is advancing well in European countries, this is not the case in many Asian²⁰⁸ and Latin American countries,²⁰⁹ and to some extent even in North America. An important issue in transitioning of the proposed algorithm to general clinical settings is the rendering of a diagnosis of AD at the prodromal stage, in an era for which effective disease-modifying treatments are not yet available. The potential benefits of such a diagnosis should be weighed against any potential psychological and emotional effects.^{210,211} Alternatively, a misdiagnosis of AD has strong ethical implications, which emphasise the value of high diagnostic accuracy. The choice of a highly specific clinical criterion decreases the risk of a false-positive diagnosis anchored on biomarker results.

In conclusion, we propose a number of refinements to the 2007 IWG diagnostic algorithm and 2010 lexicon for the research diagnosis of AD. The current refinements

have been made possible because rapid progress in the field in the past 4 years has improved our characterisation of clinical phenotypes and the expression of disease captured by in-vivo biomarkers of Alzheimer's pathology. We foresee that progress will continue to be rapid and we anticipate that studies of the very early stages of disease will represent a paradigm shift that will result in more successful therapeutic developments.

Contributors

All authors contributed to the writing and revision of the paper and approved the final version. BD had final responsibility for the decision to submit for publication.

Declaration of interests

BD has collaborated with Eli Lilly and Affiris, and has received grants for his institution from Roche and Pfizer. HHF was a full-time paid employee of Bristol-Myers Squibb from 2009 to 2011, on leave from the University of British Columbia (UBC), and received salary and stock holdings in this role. Since 2012, he has provided consulting through service agreements with Biogen Idec, Eli Lilly Pharmaceuticals, Kyowa Hakko Kirin, and GE Healthcare, for which UBC received payments. He received a speaker's honorarium from Danone, and has served on advisory boards with Fidelity Biosciences, for which he received travel and meeting expenses. HH has received honoraria, travel expenses, consulting fees, or research grants from Boehringer Ingelheim, Bristol-Myers Squibb, Elan Corporation, Wyeth, Novartis, Eisai, Pfizer, Schwabe, Sanofi-Aventis, Roche Pharmaceuticals and Diagnostics, GE Healthcare, AstraZeneca, Avid, Eli Lilly and Company, Janssen-Cilag, Merz Pharmaceuticals, GlaxoSmithKline Biologicals, Jung Diagnostics, and Thermo Fisher Scientific Clinical Diagnostics BRAHM S GmbH. KB has served on advisory boards for Innogenetics, Pfizer, and Roche. STDK has worked as a consultant for drug development for Pfizer, Merck, Lilly, Genzyme, AstraZeneca, and Helicon Therapeutics. He is also the principal investigator at the University of Virginia Memory Disorders Clinics for Elan, Novartis, Janssen, Pfizer, and Baxter. DS has been a consultant for Elan Corporation. RB is co-founder and part owner of C2N Diagnostics. He has received grants, consultancy fees, or speaker's fees from AstraZeneca, Merck, a pharma consortium (Biogen Idec, Elan Pharmaceuticals, Eli Lilly and Company, Hoffman-La Roche, Genentech, Janssen Alzheimer's Immunotherapy, Mithridion, Novartis Pharma AG, Pfizer Biotherapeutics R&D, Sanofi-Aventis, Eisai), Genentech, Roche, and Sanofi. SCA has received honoraria as a conference speaker for Novartis and Serono, and reimbursement for travel grants from Novartis and Nutricia. NCF has received research funding from Janssen, Elan Corporation, Lundbeck, Pfizer, Sanofi, and Wyeth; he has received no personal compensation for these activities. DG has received funding for research and clinical trials from Eli Lilly; he serves on Data and Safety Monitoring Boards for Pfizer, Elan Corporation, and Balance Pharmaceuticals. AN received honoraria for her participation on scientific advisory boards with Elan Corporation, Merck, GE Healthcare, Lundbeck AB, Pfizer, Avid Radiopharmaceuticals, (a wholly owned subsidiary of Eli Lilly), Johnson & Johnson, and Cytex; and as a speaker for Novartis, Bayer Health, Janssen-Cilag, Pfizer, Merz, and Envivo. Her department has received grants from GE Healthcare and Bayer Health. FP has received fees for participation on scientific advisory boards for Eli Lilly, Sanofi, Novartis, Janssen, Pfizer, and Nutricia. GR has received consulting fees from Eli Lilly and speaker's honoraria from GE Healthcare. He receives research support from Avid Radiopharmaceuticals. PR has received an honorarium from Lundbeck and Eisai, and has participated in expert meetings for Roche, Lilly, and Elan. CR has received research grants from Bayer/Piramal, GE Healthcare, Avid Radiopharmaceuticals, and AstraZeneca. SS has received honoraria from GE Healthcare, Avid Radiopharmaceuticals/Lilly, Bayer, Bristol-Myers Squibb, Athena, Pfizer, Merck, Roche, Baxter, and Janssen Alzheimer's Immunotherapy; and research grants to his institution from Avid, Janssen Alzheimer's Immunotherapy, Baxter, Bristol-Myers Squibb, Pfizer, Genentech, GE Healthcare, Roche, Merck, and Biogen. PJV has served as an advisory board member for Bristol-Myers Squibb. He receives, and has received, research grants from Bristol-Myers Squibb. LS has received grants and

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