Impact of the IWG/Dubois Criteria for Alzheimer's Disease in Imaging Studies

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13.1 The NINCDS-ADRDA Concept of AD

Alzheimer's disease (AD) has traditionally been defined as a type of dementia, a concept reified with the publication of the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria in 1984 (McKhann et al. 1984). Three major tenets of these criteria were that (1) the clinical diagnosis of AD could not be definitively made until there was a requisite postmortem confirmation, (2) the antemortem clinical diagnosis of AD could only be "probable," and (3) the diagnosis could only be applied when the disease was advanced to the functional disability threshold of dementia. Based on the NINCDS-ADRDA criteria, the diagnosis of probable AD requires that a dementia syndrome is established by clinical examination, documented by mental status questionnaire, and confirmed by

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neuropsychological testing with evidence of deficit in two or more areas of cognition, including memory with a progressive worsening over time responsible for a significant impact on activities of daily living (Association 2000). Therefore, the clinical diagnosis of AD is considered within a 2-step procedure with (1) an initial identification of a dementia syndrome and then (2) the exclusion of other possible etiologies of dementia with blood/CSF investigations for ruling out infectious, inflammatory, or metabolic diseases and with brain neuroimaging (CT scan or MRI) for excluding small vessel diseases, strategic lacunar infarcts, large vessel infarcts and/or cerebral hemorrhages, brains tumors, hydrocephalus, etc.

Considering AD as a dementia has left place to the concept of mild cognitive impairment (MCI), a label introduced by the Mayo Clinic group (Petersen et al. 1999) that refers to objective memory and/or cognitive impairment not severe enough to impact the daily living activity. The mild symptomatic phase of AD, which precedes the fully developed clinical syndrome of dementia, has no official clinical standing and was artificially included in the spectrum of MCI. The concept of MCI has a major limitation: collecting under a single label a variety of pathological entities (Dubois and Albert 2004). To decrease the clinical and pathological heterogeneity, subtyping MCI has been proposed. However, only 70 % of amnestic MCI cases that have progressed to dementia actually met neuropathological criteria for AD (Jicha et al. 2006). From the research point of view, heterogeneity of MCI may dilute the potential for a significant treatment effect and may have contributed to the negative outcomes where none of the tested medications were successful in delaying the time to diagnosis of AD (Jelic and Wahlund 2007). This discussion is not only theoretical. New approaches and drug compounds are currently under development (immunotherapy, gamma- or beta-secretase inhibitors, alpha-secretase activators…) that may slow down the disease process.

Two major considerations emphasized the need to revise the conceptual framework of AD:

The NINCDS-ADRDA criteria for AD have a low specificity against other dementias. This is mainly due to the fact at the time of these criteria, i.e., 1984, the clinical phenotype of AD was not specified and no reference to biomarkers of AD was proposed. This explains why AD was frequently misdiagnosed with other neurodegenerative diseases that can fulfill the NINCDS-ADRDA criteria (Varma et al. 1999). Two recently published clinical trials on passive immunotherapy in patients with AD dementia included in expert centers on the basis of the NINCDS-ADRDA criteria showed a high level of misdiagnosis in 31 and 36 % of the patients (Scheltens et al. 2012).

Since 1984, great progress has been made in several domains:

- The clinical phenotype of AD has been elucidated: in more than 85 % of the cases, AD presents as a progressive amnestic disorder (Dubois and Albert 2004). Postmortem studies of AD patients have shown a rather specific pattern of cortical neuronal lesions, which appear to begin within the medial temporal lobe structures (entorhinal cortex, hippocampal formations, parahippocampal gyrus) (Braak and Braak 1991; Delacourte et al. 1999), areas known to be critical for long-term episodic memory.

- Diagnostic accuracy of Alzheimer's disease (AD) has also been improved in the last years because of the characterization of new dementias through specific criteria, including the primary progressive aphasias, semantic dementia, corticobasal degeneration, posterior cortical atrophy, and Lewy body dementia. The individualization of these new diseases, which were previously confused with AD, has consequently decreased its apparent heterogeneity.
- Reliable biomarkers for AD have been isolated that are now available at least in expert centers. Although cognitive testing and episodic memory have shown discriminative utility for predicting conversion to AD (Gomar et al. 2011; Jagust et al. 2009; Schmand et al. 2011), the incremental gain of biomarkers on the accuracy of AD diagnosis is now well established (Hampel et al. 2008) and their diagnostic predictability has been extended to the predementia stage and even the preclinical states of AD (see below).

Considering AD as a dementia is too late. AD is already at work when the patients express the first cognitive symptoms, and there is no reason to link the diagnosis of a disease to a certain threshold of severity and to exclude from diagnosis and treatment a large number of patients who are not yet expressing a full-blown dementia. At a time where clinical trials of disease modifier treatments of AD dementia do not prove efficacy, at least on meaningful clinical outcomes, identification of AD at a prodromal stage and recruiting patients several years before dementia may be useful.

To conclude on this historical perspective, the classical definition of AD, based on the NINCDS-ADRDA diagnostic criteria (1984), had two major limitations: (1) they do not take into account the specific features of the disease, specific clinical phenotype and positive biomarkers; (2) they occur only when the dementia threshold is reached. The discovery and development of biomarkers, some of them being recognized as surrogate markers of the underlying neuropathological changes (Blennow et al. 2010; Hampel et al. 2008), has led the field to reconceptualize the disease definitions to both include biomarkers and apply them to enable earlier diagnosis. To be earlier and to be more specific, even at an early stage of the disease, were the two requirements of the new conceptual framework for the diagnosis of AD that we have recently proposed (Dubois et al. 2007, 2010).

13.2 A New Concept for AD

In 2007, an International Working Group (IWG) provided a new conceptual framework according to which AD moves from a clinicopathological entity to a *clinico-biological entity* (Dubois et al. 2007). The new IWG/Dubois criteria stipulate that AD can be recognized in vivo on the presence of a specific clinical phenotype ("an amnestic syndrome of the hippocampal type") or other specific clinical presentation in case of atypical AD) with a supportive evidence of biomarkers. The presence of biomarkers was proposed for the first time for the diagnosis of AD. The biomarkers of AD were divided into two groups: (1) *the pathophysiological markers* (these markers identify AD pathology since they are strongly correlated with postmortem

AD histopathological changes, and they are considered as markers of diagnosis and mainly consist in positive PET amyloid scan results or CSF changes) and (2) *topographical markers* (they reflect downstream damage and are rather markers of progression, more targeted at assessing change over time and predicting outcomes). They mainly consist in hippocampal atrophy on volumetric MRI or hypometabolism on fluorodeoxyglucose [FDG]- PET. The added value of biomarkers and therefore the specificity of the IWG/Dubois criteria for the diagnosis of AD were further confirmed. Retrospective studies demonstrated a moderate sensitivity and high specificity for the IWG/Dubois criteria (de Jager et al. 2010; Schoonenboom et al. 2008). Bouwman et al. (2010) have applied these criteria in a clinical setting and showed their high specificity, up to 100 % when biomarkers are combined, being feasible the diagnosis in the prodromal stage of the disease. In a naturalistic series of 90 consecutive MCI patients followed during 2 years, Galluzzi et al. (2010) also showed that the combination of biomarkers (medial temporal lobe atrophy and abnormal CSF) enhances prediction of conversion to AD. This is a requirement for research projects where a highly specific diagnosis is needed: (1) for the study of specific outcomes of AD that requires the follow-up of well-phenotyped cohorts of patients, (2) for the discovery or validation of new biomarkers which cannot be realized on heterogeneous populations with a low/intermediate likelihood of diagnostic accuracy, or (3) for inclusion in clinical trials. The 2007 IWG/Dubois criteria were successfully implemented in current Phase 2 clinical trials for prodromal AD with a gamma-secretase inhibitor, two immunotherapies, and the LipiDiDiet study, and they have been qualified by the European Medicine Agency (EMA) for use in AD clinical trials (Isaac et al. 2011).

The use of biomarkers allowed us to extend the concept of AD into the *prodromal* (predementia) stage because (i) the boundary between prodromal AD and dementia of the AD type is ambiguous and not clear-cut, and (ii) biomarkers are not so much linked to disease stages: their positivity reinforces the diagnosis of the disease at any stage, at least for the pathophysiological ones. Accordingly, the presence of a specific memory profile with a positivity of biomarker moves the patient from an undetermined MCI status to that of prodromal AD.

13.3 Further Refinements of the 2007 Criteria

13.3.1 Refinements of Clinical Entities

1. The first important refinements of these criteria came in 2010 where several clarifications were proposed (Dubois et al. 2010).

Typical vs. *Atypical AD.* The diagnostic framework introduced the concept of "atypical forms of AD." An amnestic presentation for AD may not always be the case, and other specific clinical phenotypes can be associated with postmortem evidence of AD pathology. These specific clinical phenotypes include non-amnestic focal cortical syndromes, such as logopenic aphasia, biparietal atrophy,

posterior cortical atrophy, and frontal-variant AD. With the advent of biomarkers providing in vivo confirmation of Alzheimer's pathology, it is now possible to include these clinical disorders as atypical AD if there is convincing biomarker support.

Preclinical States. There was also an elaboration beyond symptomatic stages of AD. In approximately 20–30 % of normal individuals over age 70, the presence of positive biomarkers (reduced CSF levels of Aβ 1–42 or increased deposits of Aβ in the brain as evaluated by amyloid PET) suggests an underlying AD pathology and predicts progression from normal to abnormal cognition (Morris et al. 2009; Resnick et al. 2010; Stomrud et al. 2007). However, the time course for progression to symptoms and the percent of persons who will progress to AD prior to death are currently not precisely known. According to recent data, around 20 % of PiB-positive subjects will convert to AD within 3 years of follow-up (Villemagne et al. 2011). The time frame for progression also is uncertain with some anticipated staying in this state for many years. It is considered that some of these normal individuals will never develop a clinical AD in line with postmortem evidence showing that a significant number of cases with histopathologically defined AD were cognitively normal at time of death (Bennett et al. 2012; O'Brien et al. 2009). In such cases, a successful cognitive aging might result from compensatory mechanisms that occur at the neuronal level or from protective factors such as cognitive reserve. It may also be postulated that some elderly with positive biomarkers will succumb from competitive age-related mortality before exhibiting cognitive decline and never develop AD symptoms.

As the percentage of persons who will progress from this state to symptomatic clinical conditions within their life span is still unknown (some elderly with positive biomarkers will never develop AD symptoms), these individuals without clinical symptoms but with positive biomarkers of Alzheimer's pathology (AP) should not be termed as preclinical Alzheimer's disease since this terminology has important legal, social, ethical, and emotional implications for those so labeled but should be considered as "asymptomatic at risk of AD" (ASR-AD). Asymptomatic at risk for AD refers to subjects with a normal cognitive condition and evidence of amyloidosis in the brain (on PET amyloid) or Alzheimer's-type changes in the CSF. If disease modifier treatments under investigation turn to be positive, there will be an interest to treat patients as early as possible. It will be important to identify subjects at risk who are under the way to convert to a clinical disease even before they become clearly symptomatic. The "dynamic process of conversion" may be identified in the brain functioning even in the absence of clinical symptoms. In that context, it may be justified to consider these subjects as having already AD as long as the identified underlying dynamic process has been invariably shown to prelude the occurrence of clinical symptoms. Additionally, a designation of the stage of "presymptomatic AD" was reserved for individuals carrying autosomal dominant monogenic AD mutations as they will inevitably develop clinical AD if they live enough. Since then the understanding of AD as a continuous clinico-biological entity encompassing both asymptomatic and symptomatic stages has grown in consensus.

13.3.2 Refinements in Biomarkers

2. No hierarchy between the biomarkers was proposed in the 2007 paper. Each biomarker was considered as having the same weight, in the absence of evidence for distinguishing between biomarker performance and accuracy at that time. Based on recent literature, it now possible to propose some line of evidence:

Recent Data on MRI Markers. Among all available MRI-related biomarkers, including (1) structural MRI with evaluation of atrophy of critical brain regions (parahippocampal gyrus, hippocampus, amygdala, posterior association cortex, and subcortical nuclei) of cortical thickness (Dickerson et al. 2012) and use of support vector machine-based classifier (Magnin et al. 2009); (2) functional MRI (Buckner et al. 2009; Jagust 2009); and (3) proton magnetic resonance spectroscopy (Fayed et al. 2008; Kantarci 2007; Qi et al. 2010), it is now well established that *medial temporal atrophy* is the best MRI marker at a prodromal stage of a further progression to AD dementia, hippocampal atrophy being the most robust (Rami et al. 2012; Risacher et al. 2009). However, the specificity of hippocampal volume for AD is influenced by several conditions, such as aging (van de Pol et al. 2006); several "neurotoxic" situations including diabetes, sleep apnea, and bipolar disorders (Fotuhi et al. 2012); and other conditions or dementias: hippocampal sclerosis, Lewy-related pathology, argyrophilic grain disease, and frontotemporal dementia (Barkhof et al. 2007; Galton et al. 2001). All these confounding factors make volumetric measure of medial temporal lobe structures less pertinent, at least on an individual level. Interestingly, the reliability of volumetric measures obtained from repeated MRI scans is high (Giedd et al. 1995) allowing to study the rate of atrophy over time, a good diagnostic marker for early AD as the progression of hippocampal loss is approximately two to four times faster in AD patients than in age-matched normal controls (den Heijer et al. 2010; Lo et al. 2011).

Recent Data on Genetic Markers. The presence of a rare autosomal dominant genetic mutation of AD on chromosome 1, 14, or 21 is a diagnostic marker of the disease even in the absence of clinical AD (presymptomatic state). By contrast, identification of relatively common risk variants such as CLU, C1R, and PICALM (Harold et al. 2009; Lambert et al. 2009) is of limited interest in the determination of risk for AD. Even the ApoE 4 allele, associated with AD risk, is neither necessary nor sufficient for development of the disease (Modrego 2006). However, ApoE4 homozygotes have a highly significant risk to develop AD (Devanand et al. 2005).

Recent Data on CSF Markers. The recent literature suggests that CSF changes are promising pathophysiological markers given their good correlations with postmortem AD changes (Buerger et al. 2006; Seppala et al. 2012; Strozyk et al. 2003; Tapiola et al. 2009). Engelborghs and collaborators (Engelborghs et al. 2008) showed that β-amyloid-1–42 (Aβ1-42), total tau (T-tau), and phospo-tau (P-tau) optimally autopsy-confirmed cases from controls and that Aβ1-42 and P-tau181P discriminated AD from non-AD dementias. In an autopsy cohort, Shaw with colleagues (Shaw et al. 2009) showed that low CSF Aβ1-42 levels had a sensitivity for AD detection of 96.4 %. A marked reduction in CSF of Aβ42 and of the Aβ42/Aβ40 ratio has consistently be found in patients with different stages of AD (Blennow et al. 2010). However, Aβ alone

may not be a sufficient marker given evidence of an overlap with other forms of dementias (such as diffuse Lewy body dementia and vascular dementia) and also its presence long before clinical AD. Numerous studies have shown that the combination of the three CSF biomarkers improves their discriminating accuracy (Blennow et al. 2010).

Taken together, it can be concluded that Aβ42 and tau (T-tau and P-tau) should be used in combination and that the CSF "AD signature" combining low Aβ42 and high tau levels increases significantly accuracy of the diagnosis of AD even at a prodromal as it is a strong predictor of dementia outcome (Hansson et al. 2006). The combination of the current candidates (Aβ and tau markers) reaches a sensitivity of 90–95 % and specificity about 90 % (de Souza et al. 2011) with a correct classification of patients with AD about 92 % (Schoonenboom et al. 2012). It should been pointed out, however, that there is a large variability in CSF biomarker levels between laboratories (Mattsson et al. 2009) with a marked variability across techniques (Mattsson et al. 2011) and across centers (Verwey et al. 2009). Thus, it is clear that measures need to be taken to standardize and optimize biomarker analysis, and several programs are running: quality control program for CSF biomarkers, BIOMARKAPD within the Joint Program for Neurodegenerative Diseases (JPND), and the Global Biomarker Standardization Consortium (GBSC).

Recent Data on Molecular Neuroimaging. FDG-PET has proven a good sensitivity to detect brain dysfunction and early changes in AD (Mosconi 2005) and to follow their evolution over time (Johnson et al. 2012). 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.

Amyloid PET imaging has shown very high postmortem validation (Clark et al. 2011; Ikonomovic et al. 2008) and good predictability for progression to AD dementia (Jack et al. 2010b; Koivunen et al. 2011) but low sensitivity to change in the clinical stages (Ossenkoppele et al. 2012). The performance of amyloid PET imaging with florbetapir was compared to amyloid pathology at autopsy (Clark et al. 2011). The specificity of florbetapir PET imaging for detection of moderate to frequent plaques was 100 %. Several issues remain to be resolved concerning the method of scan assessment and interpretation and the significance of the frequent cases of biomarker-positive asymptomatic individuals (Wolk et al. 2009). There are also rare cases of biomarker negative individuals with postmortem evidence of fibrillar amyloid (Cairns et al. 2009; Okello et al. 2009). The recent approval by the FDA of florbetapir (Av-45, Amyvid®) is the recognition of the interest of a neuroimaging biomarker in the clinical arena of AD diagnosis with the specification that a normal imagery should "rule out AD." Both retention of amyloid tracer in PET and changes in Abeta and tau CSF levels can be considered as good biomarkers of AD pathology.

In summary, based on these recent data, we propose the following statements:

- Although pathophysiological markers can be misleading in some cases (Cairns et al. 2009) and postmortem examination still remains the gold standard for a definite diagnosis of AD, the clinico-biological approach is justified by the necessity of the highest diagnosis accuracy at least for research perspective, a level of accuracy that the classical criteria did not afford.

- As discussed above, it has been shown that the CSF biomarkers correlate with brain Alzheimer's lesions and that their combination is more accurate than Aβ42 levels alone. Therefore, we recommend the presence of decreased Aβ42 *and* increased T-tau/P-tau levels as a marker for Alzheimer's pathology (Blennow et al. 2010).
- A high level of concordance, reaching 96 %, has also been shown recently between amyloid imaging and postmortem Alzheimer's pathology (Clark et al. 2011). Based on available evidence, it may be considered that (1) a negative PET amyloid excludes AD pathology and therefore is incompatible with AD diagnosis; (2) a positive PET amyloid testifies for brain amyloidosis, but it is not sufficient to certify an AD diagnosis; and (3) in case of a specific clinical phenotype of typical or atypical AD, the presence of a positive PET amyloid strongly favors the diagnosis of AD.
- At this stage, it is important to determine whether CSF markers (Aβ together with T-tau/P-tau) give a diagnostic accuracy that is equal to PET amyloid. Although there is no published large head-to-head comparison study, the available literature indicates that there is a high degree of correlation/agreement between CSF biochemical markers and PiB binding in the brain. In cognitively healthy subjects, Fagan and colleagues (Fagan et al. 2009) observed a strong inverse relationship of cortical PiB binding with CSF Aβ1-42. More recently, the same authors (Fagan et al. 2011) suggested that the ratios of tau(s) to Aβ1-42 outperformed each single biochemical analyte (including Aβ1-42) in discriminating PiB-positive from PiB-negative individuals. Jagust and colleagues (2009) demonstrated a substantial agreement between PiB-PET and CSF Aβ1-42 measures, but only a modest agreement between PiB-PET and P-tau. Similarly, Forsberg and colleagues (Forsberg et al. 2010) confirmed a significant correlation between PiB retention and CSF Aβ1-42. Tolboom and colleagues (Tolboom et al. 2009) suggested that the good agreement between these two different types of biomarkers (i.e., CSF and PET) provides converging evidence for their validity.
- Accordingly, we may consider that AD pathology in patients can be established by:
  - Evidence of an AD CSF signature: low Aβ42 *and* high T-tau or P-tau levels
  - Evidence of amyloid retention in amyloid PET

13.4 Added Value of the New Criteria

The main contribution of the new criteria was to establish AD as a single disease on a continuum that includes different stages (prodromal and dementia stages) that are identified with the same set of criteria defined by a clinical phenotype (an amnestic syndrome of the hippocampal type) supported by one or more positive biomarkers that can be a hippocampal atrophy on MRI, CSF changes, temporoparietal hypometabolism on PET-FDG, or significant retention of amyloid markers on PET. A hierarchy between the different biomarkers is the matter of an ongoing actualization of

the criteria which will highlight the value of pathophysiological markers such as CSF changes (low Aβ and high tau levels) and positive PET amyloid. It should be reminded that they are research criteria. They are particularly useful for research projects where a highly specific diagnosis is needed. However, they are more and more used in expert centers with facilities to assess a large spectrum of biomarkers and reliability of assessment procedures and with access to normative data: in these tertiary and expert centers, the criteria are applied for advanced diagnosis such as in case of young-onset AD or complex cases (posterior cortical atrophy, primary progressive aphasia, etc.), where biomarkers may increase the diagnosis accuracy. We can foresee that technically less demanding criteria for clinical settings might evolve from the more technically challenging research criteria once these are validated. Caution, however, is needed since there is no validation of their use in clinical settings. Cultural acceptability of biomarkers should also be taken into account. Whereas the use of CSF biomarkers is well developed in European countries, it is not the case in many Asian countries (Chiu and Lam 2007) and Latin America countries (Caramelli et al. 2011).

13.5 The NIA-AA Criteria

The NIA-AA diagnostic criteria published in 2011 (Jack et al. 2011) have the advantage to be used for clinical or research settings. They similarly advanced from the NINCDS-ADRDA framework to broaden the coverage of stages of disease from the asymptomatic (preclinical), through the predementia stages (MCI due to AD) and through the most severe stages of dementia. They share many features with the IWG criteria including recognition of an asymptomatic biomarker-positive phase and of a predementia symptomatic phase of AD. They also integrate biomarkers into the diagnostic process that were categorized into two types, one identifying amyloid abnormalities and the other the downstream neurodegeneration. The most interesting contribution of the NIA/AA criteria was the one concerning the preclinical stages of the disease. Based on the biomarker model proposed by Jack and colleagues (Jack et al. 2010a), it is proposed (Sperling et al. 2011) that (1) Ab accumulation biomarkers become abnormal first and a substantial Ab load accumulates before the appearance of clinical symptoms; (2) biomarkers of synaptic dysfunction, including FDG and functional MRI (fMRI), may demonstrate abnormalities very early, particularly in APOE gene allele carriers, who may manifest functional abnormalities before detectable Ab deposition (Reiman et al. 2004); (3) structural MRI is thought to become abnormal a bit later, as a marker of neuronal loss, and MRI retains a close relationship with cognitive performance through the clinical phases of MCI and dementia (Risacher et al. 2009); and (4) none of the biomarkers is static; rates of change in each biomarker change over time and follow a nonlinear time course.

The NIA/AA criteria differed conceptually in a number of important ways. At the preclinical stages, the position taken in this framework has been that the presence of AP indicates the diagnosis of AD and that this diagnosis is applicable at

this "in situ" stage for research purposes. At the predementia MCI stage, the framework applies a probabilistic likelihood based on the presence of AD biomarkers with designation either of biomarkers that reflect amyloidopathy (CSF Abeta or amyloid PET) or those that are "downstream" indicative of neuronal degeneration (CSF tau, FDG glucose, volumetric MRI). The probabilistic likelihood of "intermediate" or "high" is determined by the presence or absence of positive, negative, and indeterminate results on the "amyloid" and "downstream" biomarkers. At the difference of the IWG criteria, the MCI stage of AD is formally distinguished from the dementia stage, which has its own diagnostic criteria. In the dementia stage, ten categories of dementia of the AD type are established including probable AD dementia, possible AD dementia, probable or possible AD dementia with evidence of the AD pathophysiological process, and pathophysiologically proved AD dementia. The later stage retains most of the features of the past diagnosis of probable AD (McKhann et al. 1984) despite the low specificity, the limited positive predictive value, and the poor negative predictive value of these criteria (Varma et al. 1999).

The major advance of the IWG criteria and of the subsequent National Institute on Aging/Alzheimer's Association (NIA/AA) criteria (McKhann et al. 2011) was to support the diagnosis of AD prior to the onset of dementia and integrate biomarkers of Alzheimer's pathology into the diagnostic framework. Use of biomarkers in research may assist with clinical trials and possibly with regulatory decisions. They can set the stage for primary and secondary prevention. The emphasis on biomarkers builds on an increasingly robust scientific basis, but the data are still emerging, and the verification of the type of changes (reliability, reproducibility, validity, cutoff scores, sensitivity, and specificity for identifying AD), correlations with clinical outcomes, order of appearance, and consistency across populations is required. Even now, the additive value of multiple biomarkers and the challenges of biomarker inconsistency need investigation. Most biomarkers lack pathognomonic specificity: this is the case for topographic markers and downstream changes such as hippocampal atrophy and neocortical hypometabolism in FDG-PET which can result from many different brain disorders; this may also be the case for pathophysiological markers as amyloid retention can be observed in AD, in dementia with Lewy bodies, and in amyloid angiopathy. Furthermore, evidence of neurodegeneration is present in many neurodegenerative, vascular, and prion disorders.

The New Concept of Alzheimer's Disease

The NINCDS-ADRA concept of AD diagnosis (1984)	The IWG concept of AD diagnosis (2007)
The diagnosis of AD *cannot be certified* clinically and needs a postmortem confirmation to be ascertained	Pathological biomarkers can be considered as *surrogate* markers of the underlying AD pathology
Therefore, the clinical diagnosis of AD can only be "probable" and can only be made when the disease is advanced and reaches the threshold of *dementia*	Therefore, the clinical diagnosis can be established in vivo and *no more reference* to dementia is needed

Glossary

Alzheimer's disease (AD) The whole clinical phase, no longer restricted to the dementia syndrome.

AD dementia When cognitive symptoms interfere with activity of daily living.

Alzheimer's pathology Underlying neurobiological changes responsible for AD.

Asymptomatic at risk Cognitively normal individuals with positive pathophysiological biomarkers.

Atypical AD Less common but well-characterized clinical phenotypes that occur with Alzheimer's pathology. The diagnosis of AD needs in vivo evidence of pathophysiological markers.

Mixed AD Patients who fulfill the criteria for AD and additionally present with clinical and biomarkers evidence of other comorbid disorders.

Mild cognitive impairment (MCI) Patients for whom there is no disease clearly identified.

Pathophysiological markers Biological changes that reflect the underlying AD pathology (CSF changes; PET amyloid). They are markers of diagnosis.

Presymptomatic AD Cognitively normal individuals with a proven AD autosomal dominant mutation.

Prodromal AD The early symptomatic, predementia phase of AD.

Topographical biomarkers Downstream markers of neurodegeneration that can be structural (MRI) or metabolic (FDG-PET). They are markers of progression.

Typical AD The most common clinical phenotype of AD, characterized by an amnestic syndrome of the hippocampal type.

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