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Alzheimer's & Dementia 9 (2013) 160–168

Alzheimer's & Dementia

# Research and standardization in Alzheimer's trials: Reaching international consensus

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**Abstract** Alzheimer's disease (AD) is an epidemic facing the entire world. Increased knowledge gained during the past 25 years indicates that AD falls along a clinical and neuropathological spectrum represented as a continuum that extends from preclinical disease in which there are no symptoms, through early symptomatic phases, and finally to AD dementia. The Alzheimer's research community recognizes that imaging, body fluids, and cognitive biomarkers contribute to enhanced diagnostic confidence for AD. There has also been emerging consensus regarding the use of AD biomarkers in clinical trials. The use of biomarkers in clinical trials and practice is hampered by the lack of standardization. In response to the emerging need for standardization, an international meeting of AD researchers was held in Melbourne, Australia, in March 2012 to bring together key researchers, clinicians, industry, and regulatory stakeholders with the aim of generating consensus on standardization and validation of cognitive, imaging, and fluid biomarkers, as well as lifestyle parameters used in research centers worldwide.


*Keywords:* Alzheimer's disease; Diagnosis; Early detection; Biomarkers; Clinical outcomes; Cerebral spinal fluid; Amyloid imaging; Magnetic resonance imaging

## 1. Introduction

Alzheimer's disease (AD) is a core health issue facing the entire world. Increased knowledge gained during the past 25 years indicates that AD falls along a clinical and neuropathological spectrum, which is reflected in the new criteria proposed by both an international working group [1] and three workgroups established by the National Institute on Aging (NIA) and the Alzheimer's Association [2–4]. The AD continuum represented in the new criteria extends from preclinical disease, in which there are no symptoms, through early symptomatic phases, and finally to AD dementia. The revised criteria also operationalize functional independence more extensively than previous criteria and thus have compromised the categorical distinction between mild cognitive impairment and milder stages of AD dementia [5].

The NIA/Alzheimer's Association and international working group criteria recognize that biomarkers give enhanced diagnostic confidence for AD, including molecular biomarkers—in particular, low levels of cerebrospinal fluid

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http://dx.doi.org/10.1016/j.jalz.2012.10.006

(CSF), amyloid β 1–42 ($A\beta_{42}$), and elevated levels of CSF total tau (t-tau) and phosphorylated tau (phospho-tau)—and imaging biomarkers, including amyloid imaging with positron emission tomography (PET), reduced temporoparietal metabolism assessed using fluorodeoxyglucose (FDG)-PET, and whole brain and/or regional atrophy assessed with magnetic resonance imaging (MRI).

There has also been emerging consensus regarding the use of AD biomarkers in clinical trials, particularly for subject selection and assessment of target engagement and biological change [6]. Biomarkers are an integral component of the Dominantly Inherited Alzheimer's Network [7] and Alzheimer's Prevention Initiative [8] studies, which enroll individuals at high risk of developing AD because of their genetic background, as well as many recent clinical trials. However, the use of biomarkers in clinical trials is hampered by the lack of standardization and by the fact that nearly all biomarker research has been done in specialized research centers using in-house developed methods that have not been well validated in other sites and where enrolled populations are known to differ markedly from the general population. In addition, there are unintended consequences related to the greater use of biomarkers, including increased costs and the early identification of individuals when there is little known about prognosis and treatment. Furthermore, there remain many questions about the specificity of various biomarkers. For example, people with non-AD forms of dementia may also have CSF AD biomarker profiles, and many people who are clinically normal have positive CSF or imaging biomarkers. The extent and time course by which amyloid biomarkers, assessed either in CSF or by PET, predict the cognitive and functional trajectory of a patient remain to be established. Harmonization and standardization in clinical assessment is also needed to enable efficient and informative clinical trials.

The extent to which biomarkers reflect pathological changes that produce symptoms is another area of research that holds great promise but demands standardization. Recent studies, for example, indicate that Aβ accumulates prior to the onset of clinical symptoms and that by the time symptoms occur, other pathological factors such as neurodegeneration and tau accumulation may be more important [9]. This suggests that therapies targeting amyloid might be more effective if delivered during the preclinical stages of the disease and may explain why some clinical trials of antiamyloid therapies delivered to symptomatic patients may appear to have failed.

In response to the emerging consensus on the need for standardization, an international meeting of AD researchers was held in Melbourne, Australia, in March 2012 to build on previous work on standardization by bringing together key researchers, clinicians, industry, and regulatory stakeholders with the aim of generating consensus on standardization and validation of cognitive, imaging, and fluid biomarkers, and lifestyle parameters used in research centers worldwide.

## 2. Harmonizing cognitive data in longitudinal trials

Combining data from longitudinal studies conducted over many years and from different populations presents many challenges, but offers tremendous benefits in terms of acquiring a better understanding of both normal aging and the development of dementia. For example, the Mayo Clinic Study of Aging created a patient registry in 1986 using instruments available widely in the field to make their work applicable to practicing physicians [10]. Over time, advances in the field have resulted in changes in these instruments; however, the latent cognitive constructs underlying these tests, such as processing speed, are fairly constant over time, which allows the data to be combined, albeit with some nontrivial statistical modeling.

Although use of the same tests over and across studies makes it easier to pool data, there are also concerns that the most widely used tests, such as the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), lack sensitivity to detect cognitive change in high-functioning individuals and in the earliest stages of the disease. In the Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing (AIBL), for example, participants tend to be functioning at a higher level than the general population, with high levels of education and cognitive reserve that make it difficult to detect mild levels of cognitive impairment when compared with normative data sets. Using a simple test such as the Wechsler Test of Adult Reading as a measure of estimated IQ, which is impervious to strategic influence, could help; however, it is a blunt instrument with a low ceiling and does not target individuals with nonverbal strengths. Another strategy is to tap automatic rather than strategic processing, such as reaction time and error rate, and/or to assess intraindividual discrepancies in cognitive measures. However, when using these newer assessment tools, it will be important to correlate them with existing measures.

For diagnostic purposes and clinical trials, assessing change over time is more useful than a single cognitive test with a standardized cutoff. Moreover, cognitive assessment is most valuable when evaluated in the context of other biomarker tests as well as subjective memory complaints (ie, concerns about memory) obtained by informant interviews. Thus, in terms of cognitive tests, the field does need to develop standards regarding continuous variables and interpretation of findings with consideration of interpopulation differences.

## 3. Standardizing biomarker assessments

Although neuropathology has long been the gold standard for diagnosing AD, this may be changing as neuroimaging and other biomarkers, particularly in CSF, show utility in early diagnosis [11]. However, none of the currently available biomarkers by themselves capture fully the status of disease in an individual, and much of what we know about the pathophysiology of the disease is not captured by any