Updated Diagnostic Criteria for Alzheimer's Disease: Implications for Clinical Trials

Researchers and triallists from across the globe met in Paris this summer for the Alzheimer's Association International Conference on Alzheimer's Disease, to present and clarify the updated diagnostic criteria for Alzheimer's disease (AD) that were recently established by three working groups of the National Institute on Aging and the Alzheimer's Association, marking a major conceptual shift that affects both clinicians and researchers in the AD field. This CNS watch will review these new criteria, the role of biomarkers in the various stages of AD, the importance of early detection in emerging markets characterised by a predominance of undiagnosed cases, and the impact of these new criteria on drug development in terms of trial design, conduct, and subject selection in AD trials.

After more than a quarter of a century, the clinical diagnostic criteria for AD have been revised to reflect a deeper understanding of the etiology and the progress of the disease as it gradually changes over the course of many years. Since the original criteria were published in 1984[1], researchers have suggested that changes in the brain may occur decades before the appearance of AD symptoms, and that AD symptoms may be independent of brain changes. This is in stark contrast to prior axioms which asserted a direct correlation between brain changes and clinical symptomatology.

In order to address this new understanding, the updated guidelines distinguish three stages of AD: preclinical, mild cognitive impairment (MCI), and Alzheimer's dementia[2]. The first two stages apply only in research settings, while the latter one is most relevant clinically. The role of biomarkers is emphasised in characterising each stage with the goal of enhancing the clinical characterisation of the AD spectrum.

Among the revisions to the diagnostic guidelines is the inclusion of a "preclinical" phase of AD[3], a phase that is characterised by the pathophysiological process, and abbreviated as AD-P, that may occur decades prior to the onset of the clinical phase of the disease, or AD-C. Importantly, not all individuals with preclinical AD will develop symptomatic Alzheimer's dementia. Although biomarker signatures have yet to be enumerated, amyloid burden as measured by PET scanning or in CSF can still be useful for research purposes to help assess the risk of progression, but these are not sufficiently developed and standardised for clinical application.

The second stage proposed by the new criteria is classified as "mild cognitive impairment (MCI) due to AD"[4]. The workgroup actually developed two sets of criteria for MCI, a core clinical criteria for use by practitioners without access to biomarker tests and research criteria. The clinical criteria are characterised by problems with memory that may or may not progress to Alzheimer's dementia. Although individuals with MCI have measurable cognitive deficits, they are able to live and work independently. The research set of criteria for MCI incorporates the use of biomarkers based on cerebrospinal fluid measures (elevated tau and decreased Aβ) and neuroimaging (decreased glucose uptake on PET, and atrophy as measured by structural MRI). Due to the lack of access and standardisation, these criteria are to be used primarily by researchers but can be applied in the clinical context as a supplement to clinical testing in order to determine causes of symptoms.

The third proposed stage in the new criteria is specified as "Alzheimer's dementia"[2], and is the most relevant for clinicians, patients and care-givers. This final stage of the disease or AD-C is characterised by an insidious onset, a clear-cut decline in cognition by observation or report, and evidence of cognitive dysfunction on examination. The new guidance expands the role of cognition outside of memory and notes that a decline in other aspects of cognition such as word-finding, visual-spatial functioning and impaired reasoning/judgment may be the first symptom to be noticed. Biomarkers can be employed to help establish Alzheimer's dementia with a higher degree of certainty, and as such are helpful in addressing diagnostic certainty and distinguishing AD from other dementias.

The AD drugs approved to date are often inappropriately prescribed across a very broad spectrum of AD, encapsulating everything from Age Associated Memory Impairment to Severe Dementia. The adoption of these new criteria will allow researchers to better match appropriate trial design and eventual treatments to the specific stage of disease progression in a more precise manner, as opposed to approved drugs that were developed for a much more encompassing concept of AD.

The preclinical stage provides a fertile ground for future trials, as many researchers and clinicians now believe that early diagnosis may be the key to successfully treating AD. Biomarkers are needed to distinguish individuals who show evidence of the AD-P, and may be at an increased risk of cognitive decline and other clinical impairment. Trial design should be focused on early detection, disease prevention, and early therapeutic intervention. In this sense, this is not much different from markers of cardiovascular disease such as cholesterol. The members of the working group postulate a hypothetical model of the AD pathophysiological cascade displaying the social, medical, biomarker, and environmental factors' effect on cognitive decline. Research is necessary to isolate the impact of each factor, as well as their contribution to the overall health of a subject. Longitudinal studies in the preclinical population should focus on the conjunction of cognitive studies and biomarker assessment, and such trials may need to follow individuals for decades. This type

of setting is ideal for testing investigational projects that are targeted to prevent or slow the progression of the disease.

Trial design for the preclinical phases will need to recruit subjects prior to the onset of AD-C. Therefore, a cohort of older healthy normal subjects will need to be targeted using recruitment sources other than the typical primary care physician, neurology, or geriatrician office. Community outreach is vital to recruit subjects who are still working and living independently. Biomarker assessment will need to occur at regular intervals throughout the course of the trial in order to identify the conversion from normal brain health to AD-P and perhaps eventual AD-C. Effective screening measures that specify pre-clinical AD-P, conversion to MCI and eventual dementia are necessary to appropriately match individuals to trials specific to disease stage.

Effective screening strategies should also help improve the probability and occurrence of an earlier AD diagnosis. This is especially important in emerging markets, as low and middle income countries are more likely to exhibit a "treatment gap" between the number of individuals who have AD and those that have not yet received a formal diagnosis and treatment plan. The World Alzheimer Report 2011 reports a gap of 20-50% for high income countries, with an even larger gap for low to middle income countries[5] which has been suggested to be as high as 90% in countries like India. This report estimates that approximately 36 million people worldwide have dementia, a figure that is expected to double every 20 years to 66 million in 2030, and 115 million in 2050. This report speculates that much of this increase will be in low and middle income countries, as 58% of those with dementia currently live in low and middle income countries, rising to 71% by 2050.

Extrapolating this based on treatment gaps suggests that approximately 28 million of the 36 million people with dementia have not received a diagnosis, and therefore are not properly cared for. Barriers to diagnosis in emerging markets are multifactorial, and include a basic lack of awareness, stigma, inadequate provider skills, and a misperception that dementia is simply a normal part of the aging process. In addition to educating medical professionals about AD and strengthening the medical infrastructure, researchers and clinicians should focus on decreasing this gap via early detection paired with a treatment plan of psychosocial, psychological interventions and drug treatment. Documented diagnoses not only help provide patients and care-givers with an explanation of their current behaviour as well as what to expect in the future, but also render care and support services available, including the option of participating in clinical trials.

An emphasis on earlier detection should also translate into a re-emergence of AAMI and MCI trials using the new diagnostic criteria. Similar to the research agenda set forth for the preclinical stage, the establishment of standard biomarker parameters is necessary for research on the MCI stage due to the subtle differences that occur intra-individually, neuropsychological and behavioural assessments. MCI can be further classified to include the biomarker probability of AD etiology using $A\beta$ and neuronal imagery results. Prior conversion trials aimed at slowing the progression of AD were performed in patients who met common MCI criteria widely accepted at that time, and as such were conducted on a much more heterogeneous group of patients. Although there are many reasons for the failure of these trials, this variability appears to be a critical factor. Novel biomarker-based tools need to be developed to conduct new MCI trials much more efficiently than in the past, which typically involved 500-600 patients over the course of 3-5 years.

For researchers and clinicians working with the later stages of the disease who do not have access to neuroimaging and CSF biomarker testing, normative data on neuropsychological testing need to be established and disseminated to assist clinicians. Neuropsychological testing is less expensive for practitioners and is less invasive for patients. Therefore, establishing relevant age, gender, education and racial normative data for the common neuropsychological measures is a feasible achievement researchers should strive to complete in the near future, as it is vital to continue to measure the clinical, behavioural, and cognitive endpoints, as well as the more biologically-based endpoints.

The focus of Alzheimer's dementia trials will necessarily shift focus away from predominantly memory testing as a clinical endpoint to a much broader evaluation of the subject encompassing mood evaluations, behaviour, executive functioning, language, social participation, and other relevant domains. The cooperation of a knowledgeable informant is pertinent to evaluating the diminishing independence of the subjects and enrolment will be viewed in terms of a dyad (the patient and the care-giver participant). These trials will need to include repeated interviews with the informant, including assessments of activities of daily living (ADLs; e.g. dressing, hygiene), instrumental activities of daily living (IADLs; e.g. shopping, paying bills), and cognitive decline to corroborate neuropsychological testing of the subject.

These types of ecologically valid outcome measures may demand novel study conduct solutions such as the use of appropriately trained home health aides to collect relevant data in the home setting. It may not be practical to have patients come into a research institution to complete scales, blood work and biomarker assessments on a routine basis over a long period of time. These professional home health aide visits coupled with the use of internet-based assessment strategies should help reduce costs and make AD trials more efficient. This type of solution will also help deal with an inherent challenge of AD trials, namely the retention of informants and subjects over long trial periods.

Finally, the new guidance will permit the inclusion of novel endpoints that are salient to each diagnostic category, as well as the inclusion of novel patient groups that would typically be excluded from prior trials. For example, unlike prior criteria no age associations are made, and subjects would not be excluded from trial participation based on age criteria alone. As for novel endpoints, trials of preclinical and mild cognitive impairment patients will need to utilise scales other than the ADAS-Cog or measures of conversion to AD. Outcomes related to functional status and ecologically valid endpoints reflecting worker productivity and psychosocial outcomes may be required as these trials involve patients who are younger and higher-functioning at baseline. In these trials, volunteers are likely to lead to a selection bias, with those who have subjective cognitive complaints more

likely to volunteer, and therefore results may not generalise to the public at large. Given the course of the illness, designs must be longitudinal in nature and may have to follow a large sample from pre-dementia all the way through to eventual autopsy in order to demonstrate the roles of various biomarkers, depression, cognition, education, socioeconomic status, care-giving access etc. have on cognitive decline and disease progression. A repository of longitudinal data should be made available to clinicians and researchers to standardise analysis and interpretation of data.

These new criteria will need to be validated over the next several years, but are certainly being viewed positively as they will undoubtedly stimulate new trial designs and endpoints, and hopefully increase patient access to clinical trials, eventually resulting in approved medications better matched toward distinct patient populations.

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Henry J. Riordan, Ph.D. is Senior Vice President of Medical and Scientific Affairs at Worldwide Clinical Trials. Dr. Riordan has been involved in the assessment, treatment and investigation of various CNS drugs and disorders in both industry and academia for the past 20 years. He has been the primary author of >75 CNS protocols as well as several clinical development programs. Dr. Riordan specialises in clinical trials methodology and has advanced training in biostatistics, experimental design, neurophysiology, neuroimaging and clinical neuropsychology. He has over 65 publications including two books focusing on innovative CNS trials methods.
Email: henry.riordan@wwctrials.com

Erin B. Kornsey, MS is Clinical Manager of Medical and Scientific Affairs at Worldwide Clinical Trials. Ms. Kornsey has been examining clinical and psychosocial aspects of aging for over a decade. She has more recently focused her research efforts on issues surrounding clinical assessment methodology related to CNS trials including Alzheimer's disease.
Email: erin.kornsey@wwctrials.com