

In April 2011, the National Institute on Aging (NIA) and the Alzheimer's Association Work Groups proposed updated criteria for the diagnosis of Alzheimer's disease (AD), including dementia due to AD and mild cognitive impairment due to AD, as well as research criteria to begin defining the preclinical stages of AD. On April 25, Eric M. Reiman, MD, assembled several leading experts to discuss the updated diagnostic and research criteria for AD, including the conceptualization of AD as a sequence of biological changes that roughly correspond to the preclinical and increasingly severe clinical stages of the disorder, how the criteria might be related to developing the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) criteria and other suggested diagnostic criteria, and the potential implications and impact of those criteria on clinical practice. Their discussion appears here.

This special *Commentary* is another in a series of independent projects undertaken by the CME Institute of Physicians Postgraduate Press, Inc., as a service to its members and the broader academic and clinical community.

The roundtable teleconference was chaired by **Eric M. Reiman, MD**, Banner Alzheimer's Institute, Phoenix, Arizona. The faculty were **Guy M. McKhann, MD**, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland; **Marilyn S. Albert, PhD**, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland; **Reisa A. Sperling, MD**, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, and Massachusetts General Hospital, Boston; **Ronald C. Petersen, MD, PhD**, Department of Neurology, Mayo Clinic, Rochester, Minnesota; and **Deborah Blacker, MD, ScD**, Department of Psychiatry, Harvard Medical School and Massachusetts General Hospital, and the Department of Epidemiology, Harvard School of Public Health, Boston. Drs McKhann, Albert, and Sperling chaired NIA/Alzheimer's Association Dementia Due to AD, MCI Due to AD, and Preclinical AD Work Groups, respectively. Dr Petersen has participated in the MCI Due to AD Work Group, the *DSM-5* Task Force for the Diagnosis of Neurocognitive Disorders, and the International Working Group for New Research Criteria for the Diagnosis of AD. Dr Blacker has participated in the *DSM-5* Task Force for the Diagnosis of Neurocognitive Disorders; and Dr Reiman, Deputy Editor of *The Journal of Clinical Psychiatry*, participated in the Preclinical AD Work Group and has been actively involved in the development of strategies to evaluate preclinical AD treatments.

Financial disclosure appears at the end of this article.

The opinions expressed herein are those of the faculty and do not necessarily reflect the views of the CME provider and publisher.

J Clin Psychiatry 2011;72(9):1190-1196
(doi:10.4088/JCP.10087co1c)

© Copyright 2011 Physicians Postgraduate Press, Inc.

Alzheimer's Disease: Implications of the Updated Diagnostic and Research Criteria

Alzheimer's disease (AD) is the most common form of disabling cognitive impairment in older people. AD dementia has been estimated to affect an estimated 5.4 million Americans, and by 2050, it is projected to affect about 13.5 million older US adults.^{1,2} According to the World Alzheimer's Report,³ the number of afflicted people and the associated costs of AD are projected to skyrocket around the world due to the growing number of people living to older ages.

In 1984, Work Groups for the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, more commonly known as the Alzheimer's Association) developed the original clinical diagnostic criteria for AD.⁴ At that time, AD was considered a discrete clinicopathological entity, requiring evidence of dementia and likely or confirmed evidence of moderate-to-severe AD neuropathology.⁵

Progress in research during the past 27 years has led investigators to reconceptualize AD as a progressive sequence of biological changes, some of which can be measured using brain imaging and other biomarkers, which roughly correspond to preclinical and increasingly severe clinical stages of the disorder. Among several findings, researchers have shown that many patients with mild cognitive impairment (MCI) have biological evidence of AD and are at increased risk for progression to AD dementia⁶; identified pathophysiologic evidence of AD years before the onset of symptoms in cognitively normal people at increased risk for MCI and dementia due to AD; suggested that AD-modifying treatments might have the most profound effect if started before the onset of symptoms, when extensive neuropathology may already be evident; and characterized other disease processes that may contribute to disabling cognitive impairment (eg, Lewy bodies and vascular disease) in patients with or without pathophysiologic evidence of AD.

To begin the process of revising the diagnostic criteria, the National Institute on Aging (NIA) and the Alzheimer's Association held advisory meetings in 2009, during which attendees agreed that 3 separate work groups be formed in relationship to the dementia, MCI, and preclinical stages of AD.⁷ The work groups were asked to review scientific progress, propose diagnostic criteria for dementia due to AD and dementia due to MCI, and begin to establish research criteria for preclinical stages of AD. Five of the work group members participated in this *Commentary* discussion: Guy M. McKhann, MD, chaired the work group on AD dementia, as well as the work group that proposed the original NINCDS/ADRDA diagnostic criteria in 1984. Marilyn S. Albert, PhD, chaired the work group on MCI due to AD. Ronald C. Petersen, MD, PhD (a pioneer in MCI research), served as a member of the MCI due to AD work group. Reisa A. Sperling, MD, chaired the work group on preclinical AD, and Eric M. Reiman, MD, served as a member; both of these investigators have been actively involved in the use of brain imaging techniques in the preclinical stages of AD.

The recommendations established by each work group were presented at the 2010 International Conference on Alzheimer's Disease and were posted on the Alzheimer's Association's Web site for public review. After submitted comments were incorporated by the work groups as appropriate, a subcommittee reviewed the semi-final publications and made additional revisions,

FOR CLINICAL USE

- ◆ Alzheimer's disease (AD) consists of a progressive sequence of pathophysiologic changes, some of which can be measured by AD biomarkers, which correspond roughly to the preclinical and increasingly severe clinical stages of AD.
- ◆ The NIA and Alzheimer's Association have proposed new diagnostic criteria for dementia due to AD and MCI due to AD, as well as initial research criteria for preclinical AD.
- ◆ The new criteria for dementia due to AD reflect new information about the clinical course of the disease (such that memory impairment does not need to be a cardinal cognitive feature), consider other potential causes of dementia (eg, dementia with Lewy bodies, vascular dementia, frontotemporal dementia), and consider the existence of mixed pathology. The work group report anticipates the use of brain imaging, CSF, and other biomarkers to help improve confidence in the diagnosis of AD, but also notes the work needed to be completed before these biomarkers are routinely used in the clinical setting.
- ◆ The criteria for MCI due to AD reflect the understanding that AD symptoms are apparent before the onset of dementia and that many, but not all, patients with MCI will progress to AD dementia. The work group report includes types of cognitive tests to help support the diagnosis of MCI and anticipates the use of brain imaging, CSF, and other biomarkers to help improve confidence in the diagnosis of MCI due to AD and to help predict a person's cognitive course, as well as notes the work needed to be done before these biomarkers are routinely used in the clinical setting.
- ◆ The NIA and Alzheimer's Association have introduced research criteria to begin to define the preclinical stages of AD based primarily on AD biomarkers and/or genetic tests. The criteria evidence of characteristic AD biomarker changes, some of which begin many years before the clinical onset, is intended to provide a common language for researchers to compare their findings, clarify the extent to which individuals progress to the clinical stages of AD, and anticipate the evaluation of promising AD treatments in the preclinical stages, when they may be most effective. These criteria are proposed for research purposes only and are *not recommended* for use in the clinical setting to predict whether or when cognitively normal people may go on to develop symptoms.
- ◆ Amyloid imaging, other AD biomarker measurements, and genetic tests are not yet recommended for routine use in the clinical setting. However, the experts noted the emerging roles of these techniques in AD research, clinical assessment, and evaluation of treatments in the earliest clinical and preclinical stages of the disorder, and acknowledged some of the uncertainties that need to be addressed to fulfill their potential in these endeavors.
- ◆ *DSM-5* criteria are undergoing field trials and are expected to be published in 2013. Criteria for mild and major neurocognitive diseases correspond roughly to the NIA/Alzheimer's Association criteria for MCI due to AD and dementia due to AD, respectively. *DSM-5* criteria are designed for use in the clinical, legal, and clerical settings, and thus do not include research criteria for the preclinical stages of the disorder.

and then the publications were submitted for peer review. The criteria were published online ahead of print (Table 1)⁷ just before this *Commentary* discussion occurred.^{8,9}

In addition to the NIA and the Alzheimer's Association, other organizations have been actively involved in the development of revised diagnostic criteria for AD. The American Psychiatric Association (APA) began the process for revising the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, including the diagnostic criteria for AD dementia, over a decade ago. After several rounds of planning conferences and white paper submissions, a task force was formed and work group members were vetted and selected by 2008.

For AD, the *DSM-5* Neurocognitive Disorders Work Group, of which Deborah Blacker, MD, ScD, and Dr Petersen are members, developed a proposal¹⁰ based on literature reviews, data analyses, and questions, comments, and concerns submitted to the APA via a *DSM-5* preview Web site. In the proposed criteria, the work group recommended that the chapter be renamed "Neurocognitive Disorders" rather than the former "Delirium, Dementia, Amnesic, and Other Cognitive Disorders." This would include delirium and major and mild neurocognitive disorders, of which AD would be an etiologic subtype. Currently, field testing is being conducted with the proposed criteria, and, after revising the criteria according to the field test results, the *DSM-5* is slated to be published in 2013.

In addition, Bruno Dubois and colleagues in the International Working Group for New Research Criteria for the Diagnosis of AD¹¹ have proposed research criteria to capitalize on the development of promising brain imaging and cerebrospinal fluid (CSF) AD biomarkers in patients with dementia and MCI. Dr Petersen also served as a member of this working group.

Despite some differences in the terminology and intended use of the NIA/Alzheimer's Association diagnostic and research criteria, *DSM-5* diagnostic criteria (in development), and International Working Group Research Criteria, each has a number of common elements, and all are intended to reflect a work in progress, subject to modification with new research developments. The following discussion is intended to put the new and proposed criteria into context and to give clinicians practical advice about the NIA/Alzheimer's Association criteria.

WHY REVISE THE ORIGINAL NINCDS/ADRDA DIAGNOSTIC CRITERIA FOR AD?

Dr McKhann: The original criteria were developed because we recognized that AD was going to become a serious problem as the population aged and that we needed consistent, clinically applicable diagnostic criteria. The original criteria were meant to be preliminary but somehow lasted without revision until now.

Several limitations of the original criteria existed, which at the time either were not considered or were unknown. One limitation is the lack of the concept that AD progresses over

Table 1. Features of AD Phases as Described in the NIA/Alzheimer's Association Criteria^a

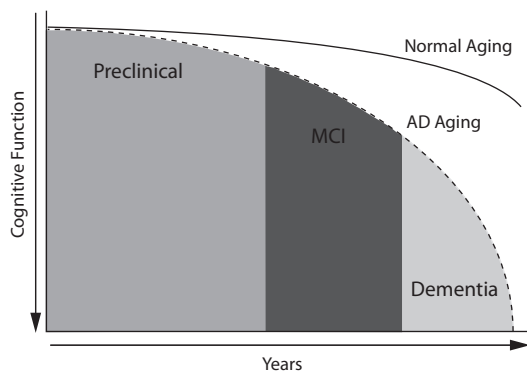
Phase	Patient Features
Preclinical AD (research criteria only)	Is biomarker-positive, ^b asymptomatic, and at risk for developing MCI due to AD and AD dementia Is biomarker-positive ^b and has subtle age-inappropriate cognitive decline Does not meet the criteria for MCI due to AD
MCI due to AD	Is concerned about a change in cognition (or concern is expressed by an informant or clinician) Has education- and age-inappropriate cognitive impairment in ≥ 1 of the following domains: Memory ^c Executive function Attention Language Visuospatial skills Has slight decline in performing functional tasks, but maintains independence Does not have vascular, traumatic, or medical causes of cognitive decline Does not meet the criteria for dementia
Probable dementia due to AD	Meets the criteria for all-cause dementia: Has gradual cognitive decline Has cognitive impairments that: Interfere with independence Are not due to delirium or another psychiatric disorder Have been designated via patient history and objective clinical assessment Are in ≥ 2 of the following domains: Memory Reasoning and judgment Visuospatial skills Language functions Personality or behavior Has either amnesic (learning and recall) or nonamnesic (language, visuospatial, and executive dysfunction) cognitive impairments Does not have evidence of any of the following conditions: Cerebrovascular disease Dementia with Lewy bodies Behavioral variant frontotemporal dementia, primary progressive aphasia (semantic variant or nonfluent/agrammatic variant), or another neurologic or medical disease or medication that could affect cognition

^aBased on Sperling et al,⁵ Albert et al,⁶ and McKhann et al.⁷

^bBiomarker-positive indicates that neuroimaging or cerebrospinal fluid assays have indicated that the individual has shown evidence of the pathophysiologic process associated with AD.

^cEpisodic memory impairment is most common in those who progress to AD dementia.

Abbreviations: AD = Alzheimer's disease, MCI = mild cognitive impairment, NIA = National Institute on Aging.

Figure 1. The Continuum of Alzheimer's Disease

Reprinted with permission from Sperling et al.⁵

time and manifests over a continuum (Figure 1).⁷ The disease starts long before patients present with impairment, possibly a decade or longer. Therefore, we should consider the possibility that AD pathophysiology can be detected preclinically via biomarker evidence, although it is not yet known whether everyone with preclinical biomarker evidence of AD pathophysiology progresses to the clinical phases of the illness. Additionally, most biomarkers did not exist 27 years ago;

imaging was primarily used to rule out other diagnostic entities rather than used as a measure of the disease itself. Those are some of the factors that prompted this revision.

Another limitation of the original criteria is the lack of discussion concerning causes of dementia other than AD, such as dementia with Lewy bodies, frontotemporal dementia (FTD), and vascular dementia.

Dr Albert: The reconceptualization of AD as existing on a continuum was a major advancement, particularly the concept of MCI due to AD. From a clinical perspective, patients with mild symptoms who did not have dementia were a critical population to address. Further, the concept of MCI had become widely accepted, largely based on work initiated by Dr Petersen and his colleagues.^{6,12,13}

WHAT ARE THE MAIN TAKE-HOME MESSAGES CONCERNING THE RECONCEPTUALIZATION OF AD?

Dr Albert: I would like to emphasize at least 3 take-home messages: (1) Viewing AD as existing on a spectrum is critical. Alzheimer's pathophysiologic processes begin in individuals who are cognitively normal, accumulate and are prevalent among those with MCI, and then cause the onset of AD dementia. Therefore, dementia is at the end of the

Table 2. Brain Imaging and CSF Biomarkers That Have Shown Promise in Improving Confidence in the Differential Diagnosis of MCI Due to AD and Dementia Due to AD

MRI measurements of atrophy in the hippocampus and other AD-affected brain regions
PET measurements of glucose hypometabolism in AD-affected brain regions
PET measurements of fibrillar A β deposition
CSF measurements of low A β 42, alone or in combination with high total tau and/or phospho-tau levels

Abbreviations: A β = amyloid-beta, AD = Alzheimer's disease, CSF = cerebrospinal fluid, MCI = mild cognitive impairment, PET = positron emission tomography.

spectrum and does not cover the entire range of individuals with AD pathology. (2) Wide consensus exists concerning the core clinical criteria for AD dementia and for MCI due to Alzheimer's pathology. (3) The implementation of biomarkers in research can help to elucidate the underlying pathology of clinical symptoms. I stress the research use of biomarkers because they are not yet clinically applicable; however, this research will help to advance the field to the point where biomarkers may be used in clinical care.

HOW HAVE ADVANCEMENTS IN BIOMARKER IDENTIFICATION INFLUENCED THE RECONCEPTUALIZATION OF AD?

Dr Sperling: As Dr Albert explained, the tremendous advances in the identification of biomarkers have allowed us to link clinical symptoms to the possible underlying etiology of MCI and AD dementia. We can also now detect early neuropathologic evidence of Alzheimer's pathology in patients who are clinically normal. Although we have identified early AD pathology via autopsies of older, clinically normal adults, biomarkers now allow us to detect this evidence *in vivo*, which presents an opportunity for longitudinal follow-up, again, to try to link the pathology to the eventual clinical course.

Dr Petersen: Also, patients with clinically diagnosed MCI have biomarkers that consistently fall between normal aging and dementia on the AD spectrum as evidenced in studies using magnetic resonance imaging (MRI), fluorodeoxyglucose positron emission tomography (FDG PET), and CSF assays (Table 2).¹⁴⁻¹⁶ These results corroborate the AD continuum concept showing that the pathophysiology is present at the MCI phase of AD, although not as severe as in the dementia phase. Thus, we may be able to detect AD much earlier than we could when the original NINCDS/ADRDA diagnostic criteria were developed.

WHAT ADVICE WOULD YOU GIVE CLINICIANS REGARDING THE USE OF NEUROIMAGING, CSF BIOMARKERS, AND GENETIC TESTING TO ASSESS PATIENTS FOR PRODROMAL AD, MCI, OR DEMENTIA?

Dr McKhann: Alzheimer's dementia and MCI due to AD are clinical entities, and the clinical criteria have not changed

much for practicing physicians. A major problem is applying biomarkers in the diagnosis of MCI and AD. The use of imaging and other biomarkers is not yet readily available or fiscally feasible in many clinical settings. Additionally, the use of biomarkers for preclinical detection and for clinical diagnosis is in a stage of evolution, and measurement is not yet standardized for practical purposes. Therefore, our recommendation at this time is that AD biomarkers be used primarily in research settings. Additional data are needed to clarify their role in clinical settings.

Dr Albert: Complete knowledge about biomarkers is still lacking, which is why the work groups reached a consensus that biomarkers be primarily used in research. As Dr McKhann stated, we have not established standardized measurement of biomarkers, which will account for the variability across institutions as well as establish cut-off points for distinguishing a diseased state from a normal state. Additionally, a majority of the research that has been conducted on biomarkers has focused on select populations. We need community studies to determine how using biomarkers will operate in real-world settings and to obtain generalizable and replicable results. So, much more work needs to be done before biomarkers can routinely be used in clinical practices.

Dr Petersen: And yet, some of these tests are available in clinical practice, which may present a conundrum for practitioners. For example, many clinicians would obtain an MRI scan for a patient who presents with memory impairment. Then, without standardization, interpreting the results becomes an issue.

In the meantime, practicing physicians can become more comfortable with looking at these scans and examining the relevant areas of the brain that may be involved early in the disease process, which may signal whether there is an underlying degenerative process, in addition to recognizing the other exclusionary information the MRI provides. Similarly, CSF tests are commercially available, although their predictive ability for disease progression has not been validated. Some insurance companies do reimburse for the use of FDG PET scans in the differential diagnosis of AD and FTD.

Therefore, becoming familiar with the tools through which biomarkers can be detected is advantageous for clinicians, although actually using those tools in practice at this time is not recommended.

Dr Sperling: To clarify, we are also not recommending neuroimaging or CSF assays for people who are asymptomatic or who are considered clinically normal and are not concerned about their memory.

Dr Blacker: Right. As Dr Albert pointed out, much research still needs to be done in community populations.

Dr Petersen: Some people have suggested that the role of genetic testing was underplayed in the new criteria.

Dr McKhann: The work groups for the NIA/Alzheimer's Association criteria discussed genetic testing, and we wanted to be very cautious about this topic. Therefore, we included very little about the genetic aspects of AD in the publications.

WHAT FACTORS WILL INFLUENCE YOUR USE AND INTERPRETATION OF AMYLOID PET SCANS (WHEN THEY BECOME AVAILABLE) OR CSF AMYLOID AND TAU ASSAYS?

Dr Petersen: At least one of the amyloid-labeling ligands may soon be approved for use in PET scans to detect the presence of amyloid plaques in the brain. A negative scan would show that amyloid plaques are not present, which may provide useful information to clinicians. However, once the imaging technique is available, clinicians probably will scan to see if amyloid plaques are present to account for the particular syndrome with which the patient is presenting.

Although it will be interesting to see how amyloid-labeling ligands are used, I caution that these are still research techniques and their future clinical implications are yet to be determined, particularly regarding the time frame of disease progression. For example, if a patient presents with a certain degree of cognitive impairment and if evidence of the presence of amyloid is found, either by CSF assays or neuroimaging, this result indicates that the disease will probably progress, but at what rate is unknown. Other measures, such as FDG PET, MRI, and CSF tau assays, may provide additional information as to the rate of disease progression for individual patients. Overall, more longitudinal data are needed before we can appropriately interpret biomarker results.

Dr Sperling: I completely agree and believe that finding negative results may be the greatest utility at this time for PET amyloid scans or CSF assays. Although these tests have limitations and cannot rule out AD, the data thus far suggest that these techniques are fairly sensitive in detecting amyloid plaques. Therefore, if a patient has AD dementia and does not have the presence of amyloid plaques in an imaging scan or spinal tap, then clinicians may need to re-evaluate the AD diagnosis and perhaps pursue additional tests or patient history. Finding an absence of amyloid plaques may be particularly helpful for patients who have an unusual clinical course or suspected early-onset AD. While nearly one-third of cognitively normal older adults may have a positive amyloid PET scan, more information is needed to determine what happens to these individuals over time. Until we have more information from longitudinal research studies or prevention trials, we do not recommend the clinical use of amyloid imaging to predict whether or when cognitively normal people might develop symptoms.

HOW WILL THE PROPOSED CRITERIA ADVANCE THE SCIENTIFIC UNDERSTANDING, TREATMENT, AND PREVENTION OF AD?

Dr Sperling: The new criteria can help us to begin planning and then, hopefully, implementing prevention trials of possible biologically active agents. The work group on preclinical AD developed the criteria around the idea of finding a specific population at risk for MCI due to AD and AD dementia. We could use biomarkers to track disease

progression in response to therapy in these individuals and use the emergence of clinical or cognitive impairment as an endpoint. So, my hope is that these criteria will move us to conduct studies of treatment earlier in the disease process.

Dr McKhann: I would like to emphasize the paradigm shift that is coupled with conducting earlier treatment trials. A majority of previous treatment trials have been conducted in AD dementia, most of which have not had promising clinical implications, possibly due to the irreversible neurodegeneration experienced in the late stage of the illness. As Dr Sperling said, we need to shift the emphasis from treating AD dementia to identifying preclinical AD and using therapies that prevent its conversion to MCI and dementia. Pharmaceutical companies and the US Food and Drug Administration (FDA) both appear to be moving in this direction as well.

Dr Petersen: It is incumbent upon the field to demonstrate the validity and utility of biomarkers. Currently, studies are being designed and conducted in the MCI phase of AD using imaging and other biomarkers to determine if the biomarkers correspond as expected with the clinical disease progression. Ideally, patients would respond to treatment at this phase of illness and the biomarkers would respond accordingly, establishing them as potential surrogate markers for the prevention trials described by Dr Sperling. So, I think these criteria are important to lend some credibility to the earlier stages of AD and to the use of biomarkers, either to stratify the populations or eventually as outcomes themselves.

Dr Reiman: While we will never give up on the effort to find demonstrably effective treatments for those patients in the most severe stages of AD, we have an opportunity to evaluate some of the most promising treatments at earlier clinical and preclinical stages when they might have the most profound benefit.

WHAT DSM-5 TERMINOLOGY AND CRITERIA MAY BE ANTICIPATED, AND HOW DO THEY COMPARE WITH THE NIA/ALZHEIMER'S ASSOCIATION CRITERIA?

Dr Petersen: The *DSM-5* category of neurocognitive disorders will describe not only the AD spectrum but also other forms of dementia and other causes of cognitive impairment. Nevertheless, the *DSM* will include criteria corresponding to 2 of the 3 stages of AD articulated in the NIA/Alzheimer's Association criteria and reflecting an increasingly severe continuum: (1) *mild neurocognitive disorder*, which is comparable to MCI, and (2) *major neurocognitive disorder*, which is consistent with dementia. The *DSM* has not previously included a predementia phase of cognitive impairment, so this development is new. The addition of preclinical AD criteria to the *DSM-5* is unlikely, as they have no diagnostic utility at this time. Currently, the proposed *DSM-5* criteria are undergoing field trials to test the criteria in various clinical settings. The criteria will then be revised and are slated to be published in 2013.

Dr Blacker: In general, the *DSM-5* Neurocognitive Disorders Work Group is trying to harmonize with expert groups

Table 3. Examples of Cognitive Tests by Domain to Assess Patients for MCI^a

Domain	Tests
Memory	Word-list learning (with multiple trials) Free and Cued Selective Reminding Test Rey Auditory Verbal Learning Test California Verbal Learning Test Episodic memory Logical Memory subtest of the Wechsler Memory Scale Revised Visual Reproduction subtest of the Wechsler Memory Scale Revised
Executive function	Trail Making Test
Language	Letter and Category Fluency on the Boston Naming Test
Spatial skills	Figure copying
Attention	Digit span forward

^aBased on Albert et al.⁶

on all etiologic subtypes. The work group was aware of the impending release of the NIA/Alzheimer's Association criteria, and plans to revise its earlier draft of the criteria for major and mild neurocognitive disorder due to AD to harmonize with the NIA/Alzheimer's Association criteria described here. Although the criteria are similar, the *DSM-5* has a broader mandate in terms of being used not only in clinical settings but also in legal and clerical settings. Therefore, the *DSM* criteria must be clear and concrete. But the 2 sets of criteria will be similar and would be used similarly by clinicians.

WHAT ADVICE WOULD YOU GIVE CLINICIANS TRYING TO GRAPPLE WITH THESE VARIOUS NEW CRITERIA?

Dr Petersen: Several criteria are emerging, including those from the NIA/Alzheimer's Association, the *DSM-5*, and also one we have not discussed, the International Working Group for New Research Criteria for the Diagnosis of AD by Dubois et al.¹¹ All of these criteria have a similar conceptual foundation, but some differ regarding the clinical characterization of diagnostic qualification for patients and specifics for using biomarkers and genetic testing.

Dr McKhann: Keep in mind that many of the criteria focused primarily on research purposes, particularly those from the NIA/Alzheimer's Association and the International Working Group for New Research Criteria for the Diagnosis of AD. Therefore, practicing clinicians will not need to implement a majority of the recommendations.

WHAT COGNITIVE TESTS CAN CLINICIANS USE TO HELP ASSESS MCI?

Dr Petersen: Memory impairment is central to most clinical presentations along the AD spectrum, and clinicians need to be sensitive to some assessment of memory. However, caution should be used for tools that require a minimal amount of recall (eg, 3 words) from patients after only a brief period of time has passed, such as is done with

the Mini-Mental State Examination. To truly assess memory, several items should be listed and followed by other cognitive activities and a substantial delay (eg, 10 to 30 minutes) before the patient is asked to recall the listed items. This method would allow patients more time to forget the items, which is a cardinal symptom present early in the development of AD and in mediotemporal lobe impairment. Although not all presentations of MCI with an AD substrate have memory loss, most clinicians would benefit from using an episodic memory assessment tool to evaluate patients.

Dr Albert: In the criteria for MCI due to AD, we recommended several appropriate tests that assess both immediate and delayed recall as well as other cognitive abilities, and they are helpful in identifying patients with MCI who are likely to develop AD dementia (Table 3).⁶ If formal tests are not available, informal tests may be used; however, informal tests are unlikely to be sensitive to the subtle memory problems seen in patients with early-stage MCI. Because patients are often impaired in several domains, not just in memory, multiple tests may need to be conducted to obtain a thorough and accurate clinical assessment.

WHAT WORK REMAINS TO SUPPORT OR FURTHER DEVELOP THE RESEARCH AND DIAGNOSTIC CRITERIA?

Dr Albert: The most pressing work that needs to be done is conducting community studies, establishing a standardization for the use of biomarkers, and verifying the longitudinal course of biomarkers during disease progression.

Dr Sperling: The community studies need to be completed in all 3 phases of the illness, particularly the preclinical phase. Compared with the general population, many volunteers for research studies have a higher socioeconomic status and a higher level of education. We need to get a better sense of whether epidemiologically-based community samples will reflect evidence of early AD pathology in the same proportions and at the same rate of progression as shown in the research groups.

Dr Petersen: Also, do the clinical criteria augmented with biomarkers function the same across age groups, eg, individuals aged 60 to 70 years versus individuals aged 80 years and older?

Dr McKhann: And, to emphasize Dr Petersen's remarks, we do not yet know if the biomarkers will change with effective treatment of AD. So, we need to know: (1) the progression of biomarkers in relation to disease state, both treated and untreated, and (2) if some neurodegeneration is potentially reversible, which is critical. A separate work group is evaluating pathological criteria in relation to the new clinical criteria.⁵

Dr Sperling: After the new criteria were published online, I received some criticism from colleagues about how cautious we were with regard to the implementation of biomarkers. From the comments in this discussion, I think that we all recognize that there is much that we still have to learn.

Disclosure of off-label usage: Dr Reiman has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this activity—other than the hopeful but cautious approach the experts expressed as amyloid PET and other AD biomarkers continue to be developed.

Financial disclosure: Dr Reiman has been a consultant for Amnestix, AstraZeneca, Bayer, Eisai, Elan, Eli Lilly, GlaxoSmithKline, Novartis, Siemens, and Takeda; his institution has received research grant support from AstraZeneca and Avid/Eli Lilly; he and his colleagues have proposed an “Alzheimer’s Prevention Initiative” to accelerate the evaluation of preclinical AD treatments; and he was a member of the NIA/Alzheimer’s Association Preclinical AD Work Group. Dr Albert has been a consultant for Eli Lilly and Genentech and has received grant/research support through Johns Hopkins University from GE Healthcare. Dr Petersen has been a consultant for Pfizer (Data Monitoring Committee), Janssen (Alzheimer’s Immunotherapy Data Monitoring Committee), Elan, and GE Healthcare. Dr Sperling has been a consultant for Pfizer, Janssen, Elan, Bristol-Myers Squibb, Bayer, Avid, Link, and Esai; has received grant/research support from Bristol-Myers Squibb, Janssen, and Elan; and has received honoraria from Pfizer and Avid (symposia). Drs Blacker and McKhann have no personal affiliations or financial relationships with any commercial interest to disclose relative to the activity.

REFERENCES

- Alzheimer’s Association, Thies W, Bleiler L. 2011 Alzheimer’s disease facts and figures. *Alzheimers Dement*. 2011;7(2):1–63. http://www.alz.org/downloads/Facts_Figures_2011.pdf. Accessed May 13, 2011.
- Alzheimer’s Association. *Changing the Trajectory of Alzheimer’s Disease: A National Imperative*. Chicago, IL: Alzheimer’s Association; 2010. http://www.alz.org/documents_custom/trajectory.pdf. Accessed May 13, 2011.
- Alzheimer’s Disease International. *World Alzheimer Report 2010: The Global Economic Impact of Dementia*. London, United Kingdom: Alzheimer’s Disease International; 2010. http://www.alz.org/documents/national/World_Alzheimer_Report_2010.pdf. Accessed July 5, 2011.
- McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer’s disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease. *Neurology*. 1984;34(7):939–944.
- Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging–Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers Dement*. 2011;7(3):257–262. <http://download.journals.elsevierhealth.com/pdfs/journals/1552-5260/PIIS1552526011001002.pdf>. Accessed August 5, 2011.
- Grundman M, Petersen RC, Ferris SH, et al, for the Alzheimer’s Disease Cooperative Study. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol*. 2004;61(1):59–66.
- Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer’s disease: recommendations from the National Institute on Aging–Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers Dement*. 2011;7(3):280–292. <http://download.journals.elsevierhealth.com/pdfs/journals/1552-5260/PIIS1552526011000999.pdf>. Accessed August 5, 2011.
- Albert MS, Dekosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer’s disease: recommendations from the National Institute on Aging–Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers Dement*. 2011;7(3):270–290. <http://download.journals.elsevierhealth.com/pdfs/journals/1552-5260/PIIS155252601100104X.pdf>. Accessed August 5, 2011.
- McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer’s disease: recommendations from the National Institute on Aging–Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers Dement*. 2011;7(3):263–269. <http://download.journals.elsevierhealth.com/pdfs/journals/1552-5260/PIIS1552526011001014.pdf>. Accessed August 5, 2011.
- Jeste DV, Blacker D, Blazer D, et al. Neurocognitive disorders: a proposal from the DSM-5 Neurocognitive Disorders Work Group. American Psychiatric Association. <http://www.dsm5.org/Proposed%20Revision%20Attachments/APA%20Neurocognitive%20Disorders%20Proposal%20for%20DSM-5.pdf>. Published January 7, 2010. Accessed May 10, 2011.
- Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer’s disease: a new lexicon. *Lancet Neurol*. 2010;9(11):1118–1127.
- Gauthier S, Reisberg B, Zaudig M, et al, for the International Psychogeriatric Association Expert Conference on mild cognitive impairment. Mild cognitive impairment. *Lancet*. 2006;367(9518):1262–1270.
- Petersen RC, O’Brien J. Mild cognitive impairment should be considered for DSM-V. *J Geriatr Psychiatry Neurol*. 2006;19(3):147–154.
- Landau SM, Harvey D, Madison CM, et al, for the Alzheimer’s Disease Neuroimaging Initiative. Comparing predictors of conversion and decline in mild cognitive impairment. *Neurology*. 2010;75(3):230–238.
- Smith EE, Egorova S, Blacker D, et al. Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Arch Neurol*. 2008;65(1):94–100.
- Oghabian MA, Batouli SA, Norouziyan M, et al. Using functional Magnetic Resonance Imaging to differentiate between healthy aging subjects, Mild Cognitive Impairment, and Alzheimer’s patients. *J Res Med Sci*. 2010;15(2):84–93.

For the CME Posttest for this article, see pages 1197–1198.
