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Who Should Use the New Diagnostic Guidelines? The Debate Continues

Ever since new criteria came out for a research diagnosis of prodromal/preclinical Alzheimer's disease, plus criteria for a research and clinical diagnosis of the MCI and dementia stages of the disease, they have engendered spirited discussion in the field. This revision was the first major update of AD diagnostic guidelines in more than 20 years. Alzforum covered this important milestone with commentary (see Dubois et al., 2007), in the news (see ARF related conference story), and in a Webinar with some of the developers of an international and a U.S. set of criteria (see ARF Webinar). However, conversation in the research and clinical community is far from over.

One particular question concerns how these new criteria will be implemented outside of the small core of specialized dementia clinics at leading academic medical centers or federally funded Alzheimer's Disease Centers. Are the criteria useful to clinicians everywhere? Will their application radiate out appropriately from tertiary into secondary and primary care sites throughout the community? Has the time come to apply the new guidelines in those settings?

What do diagnosticians think who were not part of the expert panels that produced the guidelines? Alzforum is inviting physicians from across the country to comment on these questions. Are you already using the new guidelines? If yes, how are they working? Are they helping to diagnose patients earlier and better? If no, what other guidance would you like to see?

This discussion arose from concerns previously articulated by Allen Frances of Duke University, Raleigh, North Carolina. Frances chaired the DSM-IV Task Force when it revised diagnostic guidelines for a wide range of psychiatric diseases. In essence, Frances cautions Alzforum readers that the guidelines "can be misused in less skilled, less careful, and less scrupulous hands." Read Frances' full comment to set the stage for this conversation.

Alzforum editors invited **Andrew Budson** at the VA Boston Health Care System and **Paul Solomon** at the Memory Clinic in Bennington, Vermont, to start further conversation on the questions. Both are experienced dementia diagnosticians. They did not participate in the National Institute on Aging/Alzheimer's Association or International Working Group panels that drew up the new criteria. Besides seeing patients every week, they published a guidebook in 2011 on differential diagnosis of dementing illnesses (see Alzforum Book Review). Budson and Solomon address Frances' concerns, and then offer detailed guidance on how clinics in a variety of settings can implement the new criteria. We continue the discussion with commentary from clinicians in different cities and settings. Do you see aging patients in primary care? As a secondary care

specialist? In tertiary care? What is your experience with the new guidelines?

Comment by: Andrew E. Budson, Paul R. Solomon

Using the New Diagnostic Criteria for Alzheimer's Disease and Mild Cognitive Impairment in Clinical Practice

We would like to comment on the usefulness in clinical practice now, and as we anticipate it in the future, of the new diagnostic criteria from the National Institute on Aging (NIA) and the Alzheimer's Association (AA) that were published earlier this year (1,3,4). These criteria updated the prior 1984 criteria by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association work group. A number of factors have changed since 1984, prompting the development of new criteria. These factors include:

- That the AD pathophysiological process likely starts years prior to cognitive changes and decades prior to the onset of clinical dementia (2). The concept of the "AD pathophysiological process" is thus separated from "AD dementia."
- Many patients whose cognition is not normal for their age do not meet criteria for dementia.
- Genetics of AD are better understood.
- Biomarkers of AD are available in some centers.
- New criteria are needed for research.
- Specific treatments for the AD pathophysiological process are being developed; it is therefore critical to know if patients have that process.

The new criteria define three stages of AD:

- ***Preclinical AD*** is characterized by measureable changes in biomarkers and poor performance on challenging cognitive tests.
- ***MCI due to AD*** is characterized by the first clinical changes. Mild changes in memory and other cognitive abilities are noticeable to patients and families, and can be detected through careful evaluation, but do not interfere with day-to-day activities.
- ***Dementia due to AD*** is characterized by changes in two or more aspects of cognition and behavior that interfere with function in everyday life.

Questions have been raised regarding the utility of these new criteria for clinical practice, in particular, for MCI due to AD. We do find these criteria useful in current clinical practice, and expect that they will be more useful in the future. The specific areas in which we find them useful include:

- Reminding clinicians that, because of the aging population, numbers of patients with all stages of AD will likely triple in the next 50 years.
- Helping clinicians to recognize that AD is the end of a long process, spanning years or perhaps decades.

- Talking with patients and families regarding the difference between the AD pathophysiological process versus AD dementia.
- Evaluating patients with cognitive impairment and dementia to determine etiology, with special attention to amnestic and non-amnestic presentations of AD.
- Considering biomarkers in the diagnosis of all stages of AD. Our current recommendations are to use biomarkers for those cases that present diagnostic quandaries (2).
- Enabling clinicians to diagnose (and perhaps treat) AD at the earliest possible stage. At present, that is MCI due to AD, but eventually (with new disease-modifying medications), it may be preclinical AD.
- Helping primary care providers, community practicing psychiatrists, psychologists, neurologists, geriatricians, and others understand better what to do with the new diagnostic markers being developed when they become available.

There are, however, a number of situations in which we would not use the new criteria and the tests they invoke. These situations are those in which we may detect AD pathology at an asymptomatic state and be unable to offer any treatment options. Because there are no FDA-approved treatments that have been proven to alter the underlying AD pathophysiological process, we do not currently use the preclinical AD criteria in a clinical setting. For example, we would not obtain PET amyloid imaging or CSF Aβ and tau in asymptomatic individuals, regardless of their family history or concern that they may develop the disease in the future. Because these tests—particularly the PET amyloid imaging—may detect disease pathology a decade prior to clinical symptoms, we would not use them in asymptomatic patients until disease-modifying treatments are available.

We understand the concerns raised by Dr. Frances in his comment, but disagree that we should wait for additional experts to weigh in and cost-allocation studies to be performed prior to the new criteria being used by practicing clinicians. Although these new criteria are not perfect, they represent a much-needed step forward in linking the scientific discoveries over the last 25+ years with clinical practice. Once these new criteria are operationalized, additional studies can examine the important concerns raised by Dr. Frances such as test utilization and resource allocation. Moreover, given that we are on the edge of an approaching epidemic of new cases of AD, and given that a crucial aspect of managing this disease will be early detection using biomarkers and early treatment with disease-modifying compounds, waiting any longer for more contemporary criteria that herald state-of-the-art diagnosis and treatment may not be the most productive approach.

Rather, we suggest that it would be beneficial to embrace the new criteria as a harbinger of what day-to-day practice might encompass in the near future. This goal is best accomplished if practitioners become familiar with the new criteria and use them as a roadmap for the future of diagnosis. For example, although the new criteria are explicit in stating that the use of biomarkers is not now appropriate for diagnosis, CSF biomarkers are already commercially available for use and can be helpful in certain diagnostic circumstances (2), and a PET-based amyloid imaging marker has been submitted to the FDA for approval and could

be widely available in the next few years. Additionally, there are multiple disease-modifying medications in clinical trials. Data from several of these new compounds could be submitted to the FDA within the next few years, raising the possibility that these treatments could be clinically available before the additional information that Dr. Frances would like is available. Given these possibilities regarding both diagnosis and treatment, we may not have the luxury of waiting for the new diagnostic guidelines to be perfected.

Below we share our views on how we use these criteria in current clinical practice in our respective centers. We also discuss our use of the new criteria in more detail elsewhere (2).

Table 1 presents several biomarkers of Aβ deposition or neurodegeneration that are currently in use in clinical or research settings. In clinical practice, we tend to divide the biomarkers by how they are obtained: structural MRI, PET, and CSF studies.

Table 1: Putative Biomarkers for the AD Pathophysiologic Process Currently Being Used

1. Markers of amyloid-beta (Aβ) protein deposition in the brain
   a) low CSF Aβ42
   b) positive PET amyloid imaging
2. Markers of downstream neurodegeneration
   a) elevated cerebrospinal fluid tau (total and phosphorylated)
   b) decreased metabolism in temporal and parietal cortex on [18]flurodeoxyglucose (FDG) positron emission tomography
   c) atrophy on MRI in temporal (medial, basal, and lateral) and medial parietal cortex

While volumetric MRI analyses are not routinely available, we encourage all clinicians to look for qualitative patterns of atrophy in temporal (medial, basal, and lateral) and medial parietal cortex (2).

Decreased metabolism may be observed on FDG PET scans in temporal and parietal cortex when the AD pathophysiological process has caused neurodegeneration (2). These studies are available to the clinician now, and are covered by Medicare in the United States. Note that we do not recommend using these scans routinely when the history, physical examination, cognitive testing, and structural imaging are all consistent with AD—it simply is not necessary (2). However, in situations in which one suspects an atypical neurodegenerative disease or the patient is younger than 66 years of age (when the prevalence of AD is similar to that of many other etiologies), an FDG PET scan can help distinguish AD from another disorder (such as dementia with Lewy bodies or frontotemporal dementia).

Available CSF biomarkers for AD are Aβ42, total tau, and p-tau. When all three markers are combined, the accuracy of the diagnosis is highest, with sensitivity and specificity of 85-90 percent. As in the case of FDG PET scans, we view these tests as helpful in situations in which one suspects an atypical neurodegenerative

disease or the patient is younger than 66 years of age; we do not believe obtaining CSF is necessary for routine clinical practice.

Table 2 shows how we have operationalized the criteria for MCI due to the AD pathophysiological process. Following Albert et al. (3), we first present criteria for the clinical and cognitive syndrome of MCI, then criteria regarding the etiology of the MCI syndrome being consistent with AD.

Table 2: Clinical and Cognitive Evaluation for MCI Due to AD

Step 1: Establish clinical and cognitive criteria: Determine that the clinical and cognitive syndrome is consistent with MCI and the patient is not demented

Guideline	**Procedures**
Concern regarding a change in cognition	**History & Observation** • Concern of a *change* in cognition from prior level • Reported by patient and/or informant, or observed by clinician
Objective evidence of impairment in one of more areas of cognition (e.g., memory, attention, language, visuospatial skills, executive function)	**Neurocognitive Testing** • Impairment in episodic memory (learning and retention of new information such as word lists), the most common symptom & best predictor of progression to AD dementia. • Other cognitive areas should also be evaluated. • Sample battery: Rey Auditory Verbal Learning Test (memory), the Trail Making Test Parts A & B (executive function), the Boston Naming Test, letter and category fluency (language), figure copying (spatial skills), and digit span forward (attention). (See Budson & Solomon [2] for discussion.) • Patients with MCI typically score 1 to 1.5 standard deviations below the mean on cognitive tests. • Note that cognitive assessments are influenced by age, education, motivation, and cultural variation. Not all tests provide normative data taking these factors into account. • Evaluation by a neuropsychologist is appropriate & helpful in these patients with mild deficits. Brief or informal office testing may not be sensitive enough to detect

	deficits.
Preservation of independence in functional abilities	**History, Questionnaires** • MCI patients *maintain independence of function in daily life* although they may experience more difficulty or take longer in carrying out complex tasks (e.g., balancing the checkbook, household projects, meal planning & preparation). • Interviews with friends or family will usually detect these changes • Standardized and validated scales completed by family or friends can be helpful (see Budson & Solomon [2] for a discussion specific scales)
Not demented	**History, Observation, Questionnaires** • There is no significant impairment in occupational or social function

Step 2: Examine etiology of MCI consistent with AD pathophysiological process: Determine the likely primary cause of signs & symptoms

Guideline	Procedures
Rule out other possible causes of cognitive decline. Possibilities include: vascular, Lewy body other degenerative disease, traumatic, depression, medical comorbidities, mixed dementia, other (see Budson & Solomon [2] for complete list & description of the various disorders).	**History, neurocognitive testing, imaging, & laboratory studies** • History & testing may be consistent with various clinical phenotypes • CT & MRI may show vascular infarcts & patterns of atrophy • Laboratory studies (e.g., B12, TSH, Lyme titer) may find other causes of cognitive deficits
Provide evidence of longitudinal decline in cognition	**History, serial neuropsych testing** • Documentation of progressive cognitive decline increases the probability of MCI due to AD. • Decline can be determined by history and / or neuropsychological testing.
Report history consistent with AD genetic factors	**Genotyping** • Genotyping is not part of the routine

	workup for MCI or AD; however, if an autosomal-dominant form is known to be present (i.e. mutation in APP, PS1, PS2), then the development of MCI is highly likely to be the prodrome of AD. • Most of these patients develop early-onset AD in their 40s or 50s. • The presence of one or two ε4 alleles in the apolipoprotein protein E increases risk for late-onset AD.
Evaluate for atrophy of temporal (medial, basal, and lateral) and medial parietal cortex and other biomarkers when available and clinically useful.	**Biomarkers** • Although the use of biomarkers is not recommended routinely, they are available to the clinician when desired. • There are two categories of biomarkers, those associated with Aβ protein deposition and those associated with downstream neurodegeneration (see Table 1). • We recommend routine review of CT & MRI patterns of atrophy, a marker of downstream neurodegeneration. • Presence of one biomarker category makes the "biomarker probability of AD etiology" "intermediate;" both categories must be positive for the "highest" probability. The "lowest" probability is present if both categories are negative.

Table 3 shows how we have operationalized the new criteria for AD using a four-step approach (4). Step 1 determines dementia is present, Step 2 determines that the dementia is due to AD, Step 3 provides an increased level of certainty to the diagnosis, and Step 4 evaluates the biomarker probability of AD etiology. Finally, Tables 4 and 5 show criteria for possible AD and for dementia unlikely to be AD, respectively (4).

Table 3: Clinical and Cognitive Evaluation for All Cause Dementia and AD

Step 1: Criteria for "All Cause Dementia"

Guideline	**Procedures**
• Interferes with the ability to function at work or with usual abilities ***and*** • Represents a decline from previous ability **and** • Cannot be explained by delirium or major psychiatric disorder	**History & observation** • Evidence of changes in functioning reported by either patient and/or informant, or observed by clinician.
Presence of cognitive impairment	**History, observation, neuropsychological testing** • History-taking from a knowledgeable informant • Objective mental status testing and/or neuropsychological testing • Neuropsychological testing is recommended when history and mental status testing cannot provide a confident diagnosis.
The cognitive or behavioral impairment involves a minimum of two domains	**History, observation, neuropsychological testing** • Impaired ability to acquire/ remember new information (e.g., repeating questions, forgetting events or appointments, becoming lost in familiar places). • Impaired reasoning and handling of complex tasks, poor judgment (e.g., inability to handle finances, poor decision making) • Impaired visuospatial abilities (e.g., difficulty recognizing faces or common objects) • Impaired language (speaking, reading, writing; e.g., difficulty thinking of common words while speaking, hesitations in speech) • Changes in personality, behavior, comportment (e.g., agitation, apathy, social withdrawal)
The cognitive or behavioral impairment	**History, observation, neuropsychological testing**

involves a minimum of two domains.	• Impaired ability to acquire/ remember new information (e.g., repeating questions, forgetting events or appointments, becoming lost in familiar places) • Impaired reasoning and handling of complex tasks, poor judgment (e.g., inability to handle finances, poor decision making) • Impaired visuospatial abilities (e.g., difficulty recognizing faces or common objects) • Impaired language (speaking, reading, writing; e.g., difficulty thinking of common words while speaking, hesitations in speech) • Changes in personality, behavior, comportment (e.g., agitation, apathy, social withdrawal)
Difference between MCI and dementia	**History & observation** • The fundamental difference between a diagnosis of dementia versus MCI depends upon whether there is a significant change in the ability to function at work or in daily activities. This requires clinical judgment based upon the information provided by the patient and a knowledgeable informant.

Step 2: Criteria for "Probable AD Dementia"

Guideline	**Procedures**
Meets criteria for dementia	See criteria above for dementia, Step 1.
Insidious onset – symptoms have a gradual onset over months or years, not sudden over hours or days.	**History** • From patient and knowledgeable informant
Clear-cut history of worsening of cognition	**History, serial neuropsych testing** • From patient and knowledgeable informant
Initial cognitive deficits are evident and most prominent in one of the following categories: • Amnestic presentation – the most common presentation	**History, neuropsychological testing** Amnestic Presentation: • Impairment of learning and recall of recently learned information • Deficit in at least one other cognitive

• Non-amnestic presentations: 1) Language presentation, 2) Visuospatial presentation, 3) Executive dysfunction	area) Non-amnestic presentations: • Language – most prominent deficits are word finding, but should also be deficits in other cognitive areas • Visuospatial – most prominent deficits are spatial cognition, but should also be deficits in other cognitive areas • Executive – most prominent deficits are reasoning, judgment and problem solving, but should also be deficits in other cognitive areas
Do not make diagnosis of AD when there is evidence of another dementing illness.	**History, neuropsychological testing, imaging studies, laboratory studies** Disorders to rule out include: • Vascular cognitive impairment / vascular dementia • Dementia with Lewy bodies • Frontotemporal dementia – behavioral variant • Primary progressive aphasia • Evidence of neurological disease or non-neurological condition or medication that could have a substantial effect on cognition

Note: patients who would have met criteria under the 1984 guidelines would also meet criteria under the current guidelines.

Step 3: Criteria for "Probable AD Dementia with increased level of certainty"

Guideline	Procedures
Meets criteria for AD dementia	See above, Step 2.
Probable AD dementia with documented decline	**History, serial neuropsych testing** Evidence of progressive cognitive decline on subsequent evaluations from: • knowledgeable informant **or** • cognitive testing (either formal neuropsychological evaluation or standardized mental status examinations)
Probable AD dementia in a carrier of a causative AD genetic mutation	**Laboratory studies** Presence of early-onset familial mutation • APP, PSEN1, or PSEN2 (Note that the apolipoprotein E ε4 allele was not considered specific enough to meet criteria.)

Step 4: Evaluate the "Biomarker probability of AD etiology"

Guideline	Procedures
Evaluate for atrophy of temporal (medial, basal, and lateral) and medial parietal cortex and other biomarkers when available and clinically useful.	**Biomarkers** • Although the use of biomarkers is not recommended routinely, they are available to the clinician when desired. • There are two categories of biomarkers, those associated with Aβ protein deposition and those associated with downstream neurodegeneration (see Table 1). • We recommend routine review of CT & MRI patterns of atrophy, a marker of downstream neurodegeneration. • Presence of one biomarker category makes the "biomarker probability of AD etiology" "intermediate;" both categories must be positive for a "high" probability. The "lowest" probability is present if both categories are negative.

Table 4: Clinical and Cognitive Evaluation for Possible AD

Criteria for "Possible AD Dementia"

Guideline	Procedures
Atypical course	**History, neuropsychological testing, imaging studies, laboratory studies** Meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either • has a sudden onset of cognitive impairment or • demonstrates insufficient historical detail or objective cognitive documentation of progressive decline
Etiologically mixed presentation	**History, neuropsychological testing, imaging studies, laboratory studies** Meets all core clinical criteria for AD dementia but has evidence of • concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or**or** • features of Dementia with Lewy bodies other than the dementia itself; or • evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition

Table 5: Criteria for Dementia Unlikely to be Due to AD

1. Does not meet clinical criteria for AD dementia
2. Regardless of meeting clinical criteria for probable or possible AD dementia
   a) There is sufficient evidence for an alternative diagnosis such as HIV dementia, dementia of Huntington's disease, or others that rarely overlap with AD
   b) Biomarkers for both Aβ and neuronal degeneration are negative.

(Adapted from McKhann et al. [4])

▫ Comments to this discussion are invited on the Alzforum Webinar page or by e-mail to tfagan@alzforum.org.

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