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Current guidelines for dementia screening: shortcomings and recommended changes

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SUMMARY

The availability of various guidelines regarding the diagnosis of Alzheimer's disease (AD) leaves most primary care providers with the task of having to decide which guidelines to follow. This review will help them navigate these different guidelines and understand how they differ from previous guidelines. Challenges related to the use of these guidelines are discussed, including biomarker testing, the lack of recognition in the community of what constitutes memory impairment and how to best screen for it, and recommendations for easy and early detection and diagnosis in the clinical settings are made. Adoption of biomarkers in clinical practice will give primary care providers the means to establish with certainty the underlying pathology responsible for the observed clinical symptoms and increase their ability to establish the presence of AD pathology before symptoms occur and, therefore, potentially help prevent or slow down the progression to AD.

Whether referring to infectious or chronic conditions, the need for diagnostic guidelines cannot be overemphasized. Such guidelines can positively impact both research and clinical practice efforts to identify affected individuals and develop effective interventions, with the final goal of reducing disease burden and improving quality of life of those affected, including caregivers. In the case of Alzheimer's disease (AD), a progressive neurodegenerative disease in which accumulating brain pathology (e.g., amyloid plaques, neurofibrillary tangles, inflammation and loss of synapses) can lead to declines in cognitive and functional abilities, it is critically important to develop diagnostic guidelines that can be readily applied and interpreted by clinicians and researchers alike.

From a public health perspective, clear and reliable diagnostic guidelines for AD can aid efforts to correctly estimate incidence and prevalence of AD, and initiate therapeutic interventions at the earliest possible stage. From a research perspective, uniform diagnostic guidelines can help the identification and enrolment of participants in AD-related research to characterize the longitudinal course of the disease, develop new diagnostics and biomarkers, and test new therapies. These approaches could be applied not only to those with AD, but also in those individuals at risk of developing AD, but who have not yet manifested clinical signs or symptoms [101]. In this sense, uniform sets of criteria can assist research efforts to

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develop the most effective interventions by ensuring comparable trial populations; therefore, aiding the process of comparing results among these different studies [1] and also helping to determine the need for such interventions. For the health provider interested in identifying patients at-risk of AD or treating those with AD, clear guidelines can provide the needed blueprint for good screening and diagnostic practices. Finally, guidelines can provide insights into the correct diagnosis and prognosis, and help clinicians direct patients and caregivers to the most appropriate resources to address and cope with the challenges posed by AD.

Past guidelines for AD diagnosis

Until recently, the diagnosis of AD had been guided by clinical criteria established by a workgroup organized by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA). Reflecting the limited knowledge of AD, which at the time was regarded as a binary (yes/no) clinicopathologic outcome, the workgroup report published in 1984 called for a distinction to be made between three types of AD [1]. A diagnosis of probable AD would be warranted in the presence of progressive decline in memory and other cognitive domains as suggested by clinical examination and confirmed through neuropsychological tests, which could not be attributed to other systemic or brain diseases. Impaired activities of daily living (ADL), family history and assessments to rule out other causes of dementia were proposed as supporting the diagnosis of probable AD. In the presence of variations in the onset, presentation, progression of disease, other systemic or brain diseases, even if not sufficient to produce dementia, or the presence of progressive severe cognitive deficit, the diagnosis of possible AD was suggested. Finally, definite AD could only be diagnosed if the diagnosis of probable AD was supplemented by evidence of postmortem AD-specific neuropathology. The 1984 guidelines align well with the DSM-IV definition of AD [2]; although the latter requires the presence of ADL impairment as a threshold for the AD diagnosis, while the former only considered ADL limitations/ impairment as supporting the diagnosis of probable AD.

Current guidelines

Revised NINCDS–ADRDA research criteria

Since the publication of the 1984 criteria, our understanding of AD has advanced to the point that, in 2005, an International working group for New Research Criteria for the Diagnosis of AD consisting of dementia experts from North America, Europe and Asia was assembled to discuss the need to revise these guidelines based on new scientific evidence of a continuous progressive disease process that starts many years before clinical symptoms are observed and involves intermediate stages [3]. Another important reason was the recent identification of biomarkers of AD-related pathology that could be used to diagnose patients in earlier stages of the disease. The recommendations of the International Working Group were published in 2007 and called for a revision of the NINCDS–ADRDA criteria, to include a core diagnostic criteria for probable AD consisting of early memory impairment and supported by the presence of at least one biomarker of AD pathology [3]. According to the revised criteria, the possible AD diagnosis was excluded and a definite diagnosis

requires either a combination of clinical and histopathological (brain biopsy or autopsy), or clinical and genetic (mutation on chromosome 1, 14 or 21) evidence of the disease. Presence of early memory impairment has to be ascertained by both subjective report from the patient or informants, and objective evidence from performance tests, has to have occurred gradually, be sustained for at least 6 months, not be due to other medical conditions and does not necessarily need to be accompanied by impairment in other cognitive domains. The biomarkers to support a diagnosis of probable AD include medial temporal lobe atrophy by structural MRI, low amyloid-β_{1-42} (Aβ), increased total and phosphotau concentrations in cerebrospinal fluid, reduced glucose metabolism in bilateral temporal parietal regions by functional neuroimaging with PET and familial autosomal dominant mutations. These biomarkers were recognized as important in helping with the diagnosis of AD in earlier stages, including prodromal AD/mild cognitive impairment (MCI) and preclinical AD, which were detailed in a subsequent report published by the International Working Group in 2010 with the goal of advancing the 2007 research criteria by providing a framework that covers the entire spectrum of the disease [4].

According to this new lexicon, AD consists of three stages: preclinical, prodromal and AD dementia; the last two of which combine to constitute the clinical phase of AD. Two preclinical states have been proposed to capture the long period of time between the development of brain lesions and occurrence of first symptoms: an asymptomatic at-risk state for AD, in which patients do not have clinical evidence of AD, but would show *in vivo* evidence of amyloidosis in the brain or the cerebrospinal fluid; and a presymptomatic state that is exclusively dedicated to individuals without clinical AD, but with familial autosomal dominant mutations. The clinical stage encompasses the predementia state, which according to this new definition includes prodromal AD in which clinical symptoms are present but are not severe enough to affect social roles and functionality, and MCI, which is defined similarly to prodromal AD, but either memory impairment is not characteristic to AD or biomarker testing is negative. When cognitive symptoms have become severe enough to affect social functioning and instrumental ADL, the disease has reached its dementia phase. Although a core diagnostic criterion, clinical symptoms are not sufficient to warrant a diagnosis of AD in these revised guidelines. Evidence of AD pathology through biomarkers is needed for such a diagnosis, and can also be used to diagnose preclinical and predementia stages [4]. It is important to emphasize that these revisions to the 1984 clinical diagnosis criteria were designed for research purposes and may not be appropriate for use in clinical settings.

National Institute on Aging–Alzheimer's Association clinical diagnosis criteria

A set of new AD diagnosis criteria was published in 2011 by three working groups under the auspices of the National Institute on Aging (NIA) and the Alzheimer's Association (AA) following a series of advisory roundtable meetings including academia and industry members from countries around the globe, and allowing for a period of public comment [5]. Recognizing the continuity and different stages in the disease process, the guidelines were published separately for the three stages of AD: preclinical, MCI due to AD and dementia.

Preclinical AD diagnostic criteria—Similarly to the 2007 research criteria, the NIH–AA guidelines describe the preclinical stage as the earliest phase in the continuum of disease, in which, while no clinical symptomatology is evident, AD-related pathologic processes have already begun and can be detected with biomarkers of amyloidosis and neurodegeneration [6]. The NIH–AA report also provides an estimate for the lag between pathology initiation and symptomatology occurrence of at least 10 years. Moreover, it goes one step further and describes the preclinical stage as a continuous process of its own in which asymptomatic patients with biomarker pathology and those with familial AD-related genetic mutations would be in the very early preclinical stage, while those who are asymptomatic but show evidence of slight cognitive decline not sufficient enough to be diagnosed with MCI or dementia would be in a later stage of preclinical AD and one step closer to clinical AD. To reflect this idea of a continuous preclinical stage as well as a proposed temporal ordering of AD pathology in which Aβ deposition is considered an upstream event associated with downstream pathology (i.e., neuronal death, tangle formation and synaptic dysfunction) and increased risk of progression to AD, a staging framework for preclinical AD has been proposed to help identify the group of patients most likely to progress to the clinical stage. This staging framework recognizes three stages: stage 1 in which only amyloidosis is present; stage 2 in which both amyloidosis and biomarker evidence of neurodegeneration are present; and stage 3 in which, besides amyloidosis and neurodegeneration, there is also evidence of subtle cognitive decline (Boxes 1-4).

MCI diagnostic criteria—The NIH–AA guidelines for the diagnosis of MCI define it as the symptomatic predementia phase of AD in which the patient shows evidence of mild cognitive decline in the absence of significant impairment in ADL [7]. This definition of the early symptomatic predementia stage is in line with that from the 2007 report, differing from it only in terms of terminology, in that the International working group [4] defines this stage as prodromal AD, while the NIH–AA report calls it MCI due to AD. Recognizing the difficulty of obtaining biomarker data in the clinical setting, the NIH–AA report proposes two sets of criteria for MCI diagnosis: a set to be used when diagnosing MCI in the clinical setting and another one for clinical diagnosis for research purposes. The difference between the two mainly comes from the use of biomarkers, the clinical criteria allowing MCI diagnosis on the basis of clinical (subjective and objective) evidence of mild cognitive decline, consistent with AD, and not meeting the requirements for dementia, while the research criteria incorporates Aβ and neurodegeneration biomarkers with the scope of defining the level of certainty that the AD pathophysiological process explains the clinical evidence of MCI. Based on the clinical and research criteria, a new terminology for classifying individuals with MCI due to AD with varying levels of certainty was proposed and includes (Boxes 1-4):

- MCI – core clinical criteria reserved for patients who meet the core clinical criteria but do not have biomarker studies;
- MCI – intermediate likelihood includes those with clinical MCI and either one of the two types of AD biomarkers: positive Aβ biomarkers (e.g., cerebrospinal fluid $A\beta_{42}$ or PET amyloid imaging) or positive markers for neuronal injury (cerebrospinal fluid tau/phospho-tau, hippocampal or medial temporal lobe

atrophy on MRI, temporoparietal/precuneus hypometabolism or hypoperfusion on PET or single-photon emission computed tomography);

- MCI – high likelihood captures those with clinical MCI and evidence of both AD biomarkers;
- MCI – unlikely due to AD, which is warranted in the absence of both biomarkers.

AD dementia diagnostic criteria—The new revisions [8] of the AD diagnostic criteria retained the framework for probable AD as described in the 1984 report, but redefined the term possible AD dementia, renamed the category of definite AD as pathophysiologically proved AD dementia, and integrated biomarker evidence in the diagnostic criteria for the probable and possible categories (for research use only). Therefore, according to the new guidelines, probable AD dementia is diagnosed when insidious onset of decline in at least two cognitive domains with either amnestic (impaired ability to acquire or remember new information) or nonamnestic (language impairment, visuospatial impairment, changes in personality and executive dysfunction) presentation is evidenced by both subjective report (from the patient or a knowledgeable informant) and objective performance (through mental status examination or neuropsychological testing), and it affects the ability to perform ADL and is not explained by other diseases affecting cognition (e.g., cerebrovascular disease, Lewy body dementia and frontotemporal dementia). The certainty of probable AD dementia is increased by documented decline using informant report (someone who knows the patient well) and cognitive testing, evidence of a causative genetic mutation and/or positive biomarker studies. An atypical dementia course (sudden onset or unclear evidence of progressive decline) or an etiologically mixed presentation (evidence of AD dementia, but also of other non-AD dementias) would warrant a diagnosis of possible AD dementia, and certainty would be increased by AD-related biomarker evidence or postmortem neuropathological evidence of AD. Similar to the 1984 guidelines, a presentation that meets the requirements for a clinical diagnosis of probable AD dementia and is confirmed by neuropathological examination would indicate pathophysiologically proven AD dementia, the ultimate diagnosis (Boxes 1-4).

Innovation of the most current clinical diagnostic criteria (NIH–AA)

Scientific advances in our understanding of AD over the past three decades are reflected in the new diagnostic guidelines. The recommendations for diagnosis of preclinical AD, MCI due to AD and AD dementia were driven by the growing evidence that the cognitive deficits that accompany AD pathology evolve gradually [3,5] and that identifying patients in stages that precede dementia, which represents the culmination of a long process of pathology accumulation, is essential. The new recommendations were also guided by a better understanding of the distinctions and overlaps between AD and different non-AD dementias (e.g., Lewy body dementia, vascular dementia and frontotemporal degeneration), by the new insights into the sequenced process that characterizes AD pathology accumulation [9], and by the evidence that, although a common presentation in AD patients, memory impairment is not always present. Moreover, the accumulated evidence that AD biomarkers may assist diagnosis at all stages of the disease [10] has led to the incorporation of biomarkers into the

new diagnostic criteria. It is important to note that when it comes to using biomarker evidence to diagnose AD, biomarkers are useful in establishing the presence of AD pathology in the preclinical stage (research only), while in the case of MCI and dementia, biomarkers represent complimentary evidence, and diagnosis of disease only requires clinical evidence [5–8]. The two hallmarks of the new diagnostic guidelines, inclusion of biomarkers and the staging of AD, are important in that they help pave the way to identification with more certainty of at-risk individuals earlier in the process of disease, when the benefits are highest and prevention of the disease may be possible in patients at preclinical stages.

Challenges

The Institute of Medicine Forum on Neuroscience and Nervous System Disorders identified the incorporation of biomarker testing in the diagnosis criteria as the main challenge given the conflicting biomarker results, and suggested standardization and validation of each of the proposed biomarkers before they are used in clinical practice [101]. A recent review of biomarkers used to detect AD argues that adding to the problem is the fact that the specificity of each marker varies with some biomarkers being able to detect disease presence but not progression (e.g., cerebrospinal fluid $A\beta_{42}$), while others are sensitive to progression but not the presence of disease (e.g., MRI atrophy) and others are able to mark both disease presence and progression (e.g., fludeoxyglucose-PET) [10].

Moreover, biomarker testing is rarely available outside of specialty clinics (e.g., memory assessment clinics) and, therefore, many primary care providers lack this type of technology. Other challenges to the implementation of the diagnostic guidelines in the clinical setting that do not relate to the use of biomarkers for diagnostic purposes include a lack of recognition of a memory problem by both the patient/informants and the primary care doctor, time constraints, lack of screening because of widespread perceptions that effective therapies are still eluding us, and unfamiliarity with available screening tools and resources to address further needs of patients with memory problems [11]. It is for these reasons, as well as a lack of evidence for their predictive power for AD, that these new criteria are being described as ‘research criteria’ with more research needed before they are applied on a large scale in clinical settings.

Other diagnostic guidelines

Other diagnostic guidelines are available from professional associations such as the American Academy of Neurology (AAN) and the American Geriatric Society (AGS). Similar to the NINCDS–ADRDA criteria, AAN [102] characterizes patients with MCI as having memory impairment but not being demented, and encourages clinicians to be alert in regards to cognitive impairment in all patients and to screen those who are impaired and continue to monitor MCI patients for progression to AD using the ten warning signs of AD published by the AA [12]. A diagnosis of MCI is recommended for patients with memory impairment who are not demented, in that their general cognitive function is within normal limits, and their ability to perform ADL is intact. In terms of AD dementia diagnosis, AAN suggests using NINCDS–ADRDA and/or DSM-IV diagnostic criteria, while excluding other

non-AD dementias. Regarding use of biomarkers to diagnose AD, the AAN guidelines recognize the importance of structural neuroimaging in the initial evaluation of patients with memory impairments, but no other AD biomarker is recommended for use in clinical practice for diagnostic purposes.

AGS guidelines for diagnosis of AD include evidence of dementia syndrome defined as chronic decline in memory and at least one other cognitive function sufficient enough to affect daily life; progressive onset and continuing decline; and exclusion of other conditions that could affect cognition [103]. However, while these guidelines recognize that AD is a continuous process, its progression is described in four stages, starting with MCI, which is considered to represent the preclinical stage of AD, mild impairment (1–3 years from onset of symptoms), moderate impairment (2–8 years) and, finally, severe impairment (6–12 years). The different cognitive functions likely to be affected are described for each AD stage and scores on various neuropsychological tests are provided for each stage to guide practitioners in their attempts to stage patients. Regarding biomarkers, AGS recommends use of fludeoxyglucose-PET scans for atypical AD with evidence of frontotemporal dementia.

Neither of these sets of guidelines places emphasis on biomarker testing as a means to diagnosing AD. However, clinical criteria that are in line with other published guidelines (e.g., NINCDS–ADRDA and DSM-IV) are considered essential for AD diagnosis in clinical settings. This may limit the usefulness of these types of guidelines as newer disease-modifying medications are developed, for which it will be more essential to identify specific protein pathologies.

Implications for public health

In the context of AD, the most effective public health interventions are the ones that address secondary prevention. Identification of affected individuals as early in the disease process as possible when the likelihood of success is highest can be accomplished through dementia screening. Screening in the preclinical stage as described in the current guidelines is not feasible in the usual clinical setting, because biomarker testing may not be available and the clinical interpretation at this time may be unclear. However, the period between the first development of symptoms and the moment that medical care is sought may be a good interval of time in which to screen at-risk individuals [13]. Although not all screening tools are equally able to detect AD at the earliest stages of decline, the AD8 [14], a reliable and validated informant-based instrument, has been found to correlate with changes in AD biomarkers and to better correspond to underlying AD pathology than performance-based screening measures such as Mini-Mental State Examination and Short Blessed Test [15]. Therefore, the combination of simple tools such as the AD8 (to collect informant observations) and the Mini-Cog [16] (to measure performance) represent important strategies to improve detection of dementia in the community, where biomarker studies may not be available. Recent changes in the US healthcare system (Patient Protection and Affordable Care Act) calling for a Personalized Prevention Plan [104], including screening for cognitive disorders reimbursable through Medicare, may provide incentives for better screening practices and may potentially help the adoption of biomarker technology in

clinical practice, offering the possibility of detection of AD pathology in early preclinical stages when interventions to prevent progression to MCI or dementia may be most effective.

Recommendations for clinical practice

The availability of the various guidelines regarding the diagnosis of AD leaves most primary care providers with the task of having to decide which guidelines to follow. While these different sets of diagnostic criteria may vary in the terminology they use, all are based on a framework that defines AD as a continuous process involving several progressive stages. The real challenge that most practitioners may face, however, is to make use of biomarker technology. Obtaining biomarkers can be invasive, uncomfortable and expensive, especially in the context of little coverage by most insurance plans for AD diagnostic purposes. This, along with a lack of established standardized measurements of biomarkers and cutoff points for distinguishing abnormal from normal state [17], the scarce availability of this technology outside of specialty clinics and research centers and the fact that many individuals who meet the criteria for preclinical AD may never develop AD symptomatology [6], has prompted the organizations releasing the diagnostic guidelines as well as other experts in the field to recommend against using biomarkers for the diagnosis of AD at any stage, particularly among asymptomatic patients [17].

Therefore, at this point in time, primary care providers are advised to focus on the core criteria for diagnosis of clinical AD, which do not require use of biomarker evidence, but rely on clinical evaluation and neuropsychological testing. In fact, a practical guide to the early detection and diagnosis of AD consisting of five easy-to-follow steps has been recently proposed [18]. Given the better prospects for patients with AD, early detection before the irreversible damage sets in is of particular importance. To achieve this, healthcare providers are encouraged to start the diagnostic process by running prediagnostic tests and looking for early warning signs (step 1). A thorough patient history, physical examination, input from knowledgeable informants and laboratory tests can all help rule out other potential explanations for cognitive decline (e.g., depression) and identify risk factors that may put the patient at increased risk of dementia, including mobility problems, unplanned weight loss and general physical frailty. The next step is to use validated instruments that can be performance based (e.g., Mini-Cog), informant based (e.g., AD8) or a combination of the two to screen for AD (step 2). A positive screening test would suggest a cognitive impairment exists, warranting the need for an assessment of functioning (e.g., instrumental ADL) to establish the extent of the patient's physical limitations and dependence on those around him/her (step 3). The next step would be to assess the presence of behavioral symptoms such as anxiety, agitation and depression (step four). Standardized tools exist to help with this process (e.g., Neuropsychiatric Behavioral Pathology in Alzheimer's Disease [19]). The last step in the diagnosis process should include an evaluation of the caregivers' needs (step 5). Addressing caregivers' medical and other needs is critical to ensure optimal care for AD patients, because addressing their needs may help improve patient–caregiver relationships, delay institutionalization of the patient, and improve the quality of life for both the patient and caregiver.

A need for education of primary care providers on both what constitutes dementia and the tools that are available to screen and diagnose AD has been identified [11]. Instruments such as the Mini-Cog and AD8 are brief and easy to administer in any physician's office, and family physicians are encouraged to become familiar and proficient in using them to screen and diagnose AD [18]. This is particularly important as it may help avoid misclassification of patients. Ethical considerations need to be taken into account in the case of potential false positive as this may have ramifications relating to the individual's health insurance, workplace, and the patients' and their families' emotional wellbeing. By contrast, false negatives can negatively influence the likelihood of early intervention in affected individuals.

Conclusion & future perspective

Even though the use of biomarkers is not currently recommended, many physicians are ordering MRIs to evaluate patients with memory impairment [17], suggesting that steps toward the adoption in clinical practice of at least some biomarkers are already being taken. In Europe, for example, cerebrospinal fluid biomarkers are widely used and an infrastructure for their use in clinical practice already exists in many countries; although great variability of cutoff values has been reported [20]. Once the issues regarding cutoff points, standardization and validation for use in clinical settings are sorted out, these biomarkers will probably be widely adopted, especially if insurance companies start including them among covered diagnostic tools. In fact, some biomarkers (i.e., fludeoxyglucose-PET) are reportedly being covered by Medicare [105] as well as some insurance companies [17] to distinguish AD from other forms of dementia. Adoption of biomarkers in the clinical practice will not only give many physicians the means to establish with certainty the underlying pathology responsible for the observed clinical symptoms, but it will also increase their ability to establish the presence of AD pathology before symptoms occur; therefore, potentially helping patients to prevent or slow down progression to AD. As our knowledge of the predictive power of biomarkers to diagnose disease at its different stages will evolve, and primary care providers and neurologists become more familiar with using them to assess dementia risk, the new diagnosis guidelines will be regarded not only as research but also as clinical criteria. Moreover, as we learn more and more about pathological changes in the brain, the possibility of disease-modifying interventions will become a more reachable goal with a direct impact on the lives of all those affected.

Box 1

Preclinical Alzheimer's disease diagnostic criteria (research only).

NIH–AA guidelines

- Stage 1: asymptomatic amyloidosis
- Stage 2: amyloidosis + neuronal injury
- Stage 3: amyloidosis + neuronal injury + subtle cognitive decline

International Working Group guidelines

- Asymptomatic at-risk state: brain/cerebrospinal fluid amyloidosis

- Presymptomatic (monogenic AD): rare autosomal dominant AD mutations (on chromosomes 1, 14 or 21)

AA: Alzheimer's Association; AD: Alzheimer's disease.

Box 2

Mild cognitive impairment diagnostic criteria.

NIH–AA guidelines (MCI due to AD)

- Core clinical criteria: concern about change in cognition; lower performance in ≥1 cognitive domain; independence in functional abilities not affected; and not demented
- Intermediate likelihood: MCI core clinical criteria and positive for Aβ or neuronal injury biomarker
- High likelihood: MCI core clinical criteria and positive for Aβ and neuronal injury biomarker
- Unlikely due to AD: biomarkers for Aβ and neuronal injury

International Working Group guidelines

- Prodromal AD: episodic memory loss of the hippocampal type; ability to perform IADL not affected; not demented; and supportive biomarker evidence of AD pathology

AAN guidelines

- MCI: memory impairment; normal general cognitive function; intact ADL/IADL; and not demented

AGS guidelines

- MCI: report of memory loss; objective assessment of memory impairment; mild impairment in ≥1 other cognitive function; no functional impairment; MMSE: 26–30; CDR: 0.5; FAST: 3; and MoCA: <26

Aβ: Amyloid-β; AA: Alzheimer's Association; AAN: American Academy of Neurology; AD: Alzheimer's disease; ADL: Activities of daily living; AGS: American Geriatric Society; CDR: Clinical Dementia Rating; FAST: Reisberg Functional Assessment Staging Scale; IADL: Instrumental Activities of Daily Living; MCI: Mild cognitive impairment; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment.

Box 3

Alzheimer's disease diagnostic criteria.

NIH–AA guidelines

- Probable AD: insidious onset of cognitive decline in ≥2 domains or amnestic/nonamnestic behavior interfering with functionality; clear-cut history of decline; impairment assessed subjectively and objectively; no evidence of neurological conditions to explain cognitive decline; and supportive biomarker evidence
- Possible AD: meets criteria for probable AD but has atypical course; an etiologically mixed presentation; and supportive biomarker evidence
- Pathophysiologically proven AD: clinical evidence of AD and histopathological evidence

International Working Group guidelines

- Probable AD: early and significant episodic memory impairment; progressive self-reported change in memory function >6 months; objective evidence of impaired memory; other cognitive changes are possible; and supportive biomarker evidence of AD pathology
- Definite AD: both clinical and histopathological evidence; and both clinical and genetic evidence

AAN guidelines

- Probable AD: subjective and objective deficits in memory and ≥1 other area of cognition; progressive, significant and continuous decline; late onset; absence of other disorders to explain deficits; impaired ADL/IADL; and laboratory results including cerebral atrophy on computed tomography

AGS guidelines

- Mild AD: disorientation to time; language problems, IADL limitations; judgement problems; mood change; social withdrawal; MMSE: 21–25; CDR: 1; and FAST: 4
- Moderate AD: disorientation to time/place; problem-solving difficulties; ADL/IADL limitations; neuropsychiatric symptoms; MMSE: 11–20; CDR: 2; and FAST: 5–6
- Severe AD: remote memory gone; language abilities gone; severe problem-solving difficulties; ADL dependent; agitation; MMSE: 0–10; CDR: 3; and FAST: 7

AA: Alzheimer's Association; AAN: American Academy of Neurology; AD: Alzheimer's disease; ADL: Activities of daily living; AGS: American Geriatric Society; CDR: Clinical Dementia Rating; FAST: Reisberg Functional Assessment Staging Scale; IADL: Instrumental Activities of Daily Living; MMSE: Mini-Mental State Examination.

Box 4

Recommendations for biomarker use.

NIH–AA guidelines

- Used for diagnostic purposes at all three stages (research only)

AAN guidelines

- Structural neuroimaging with either a noncontrast computed tomography or MRI is recommended in the initial evaluation of patients with dementia

International Working Group guidelines

- Used for diagnostic purposes at all three stages (research only)

AGS guidelines

- FDG-PET scans recommended for atypical AD when frontotemporal dementia is suspected

AA: Alzheimer's Association; AAN: American Academy of Neurology; AD: Alzheimer's disease; AGS: American Geriatric Society; FDG: Fludeoxyglucose.

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Practice Points

- Reflecting a new understanding of Alzheimer's disease (AD) as a progressive disease, current diagnostic guidelines help identify at-risk individuals earlier in the disease process when benefits are highest.
- Three stages are currently recognized as capturing the long disease process. The preclinical stage is the period between brain lesion development and clinical symptoms; the prodromal stage is the early symptomatic predementia phase; and the AD dementia stage is the symptomatic end stage.
- Use of biomarkers to diagnose AD at all three stages is another hallmark of new diagnostic guidelines; although it is currently limited to the research setting.
- The main challenge for most primary care providers is the use of biomarkers to diagnose AD. Recommendations include use of a five-step guide to detect and diagnose AD in the early states in the clinical setting.