Published in final edited form as:
Alzheimers Dement. 2011 May ; 7(3): 270–279. doi:10.1016/j.jalz.2011.03.008.

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

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With regard to potential conflicts of interest, Marilyn Albert serves as a consultant to Genentech and Eli Lilly and receives grants to her institution from GE Healthcare. Steven DeKosky serves as a consultant to Eisai, Merck, Elan/Wyeth, Novartis, he serves on the advisory board of Pfizer and provides clinical services to United Healthcare. Dennis Dickson report no conflicts. Bruno Dubois serves as a consultant to Affiris, Pierre Fabre, and Eisai, serving on a scientific advisory board for Bristol-Meyers Squibb, Roche, Pfizer, Eli Lilly, and GE Healthcare, and receives grants to his institution from Novartis, Roche, and Eisai. Howard Feldman is an employee of Bristol Meyers Squibb (BMS) and holds stock in BMS; he serves as a consultant to Servier, Glia Scientific, and Pfizer, and serves on a scientific advisory board for Elan, Janssen, Canada, and Wyeth. Nick Fox serves as a consultant (payment to Institute of Neurology) for BMS, Elan/Janssen, Eli Lilly, GE, Lundbeck, and Pfizer/Wyeth. The Institute of Neurology (Nick Fox) has conducted image analysis for Elan/Janssen, Lundbeck, and Pfizer/Wyeth. Anthony Gamst reports no conflicts. David Holtzman serves as a consultant for Bristol-Myers Squibb, Pfizer, and Innogenetics; he serves on a scientific advisory board for En Vivo, Satori, and C2N Diagnostics; and receives grants to his institution from Pfizer, Eli Lilly, and Astra Zeneca. William Jagust serves as a consultant to Genentech, Bayer Healthcare, GE Healthcare. Synarc, Otsuka Pharmaceuticals, Janssen Alzheimer Immunotherapy, Merck, and Tau Rx. Ronald Petersen serves as a consultant for Elan Pharmaceuticals and GE Healthcare and serves on data monitoring committees for Pfizer, Inc., Janssen Alzheimer Immunotherapy. Peter Snyder serves as a consultant to CogState Ltd. Maria Carrillo is an employee of the Alzheimer's Association and reports no conflicts. Bill Thies is an employee of the Alzheimer's Association and reports no conflicts. Creighton Phelps is an employee of the U.S. Government and reports no conflicts.

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Abstract

The National Institute on Aging and the Alzheimer's Association charged a workgroup with the task of developing criteria for the symptomatic predementia phase of Alzheimer's disease (AD), referred to in this article as mild cognitive impairment due to AD. The workgroup developed the following two sets of criteria: (1) core clinical criteria that could be used by healthcare providers without access to advanced imaging techniques or cerebrospinal fluid analysis, and (2) research criteria that could be used in clinical research settings, including clinical trials. The second set of criteria incorporate the use of biomarkers based on imaging and cerebrospinal fluid measures. The final set of criteria for mild cognitive impairment due to AD has four levels of certainty, depending on the presence and nature of the biomarker findings. Considerable work is needed to validate the criteria that use biomarkers and to standardize biomarker analysis for use in community settings.

Keywords

Mild cognitive impairment; AD dementia; Diagnosis

1. Introduction

The National Institute on Aging and the Alzheimer's Association convened a working group to revise the diagnostic criteria for the symptomatic predementia phase of Alzheimer's disease (AD). Details of the selection and the charge to the working group are outlined in the Introduction to the revised criteria for AD that accompanies this article [1]. The present article summarizes the recommendations of the working group.

The working group was assembled because of growing consensus in the field that there is a phase of AD when individuals experience a gradually progressive cognitive decline that results from the accumulation of AD pathology in the brain. When the cognitive impairment is sufficiently great, such that there is interference with daily function, the patient is diagnosed with AD dementia. The dementia phase of AD is the topic of a separate working group report [2]. It is important to note that, as AD is a slow, progressive disorder, with no fixed events that define its onset, it is particularly challenging for clinicians to identify transition points for individual patients. Thus, the point at which an individual transitions from the asymptomatic phase to the symptomatic predementia phase [3], or from the symptomatic predementia phase to dementia onset, is difficult to identify [2]. Moreover, there is greater diagnostic uncertainty earlier in the disease process. It is, nevertheless, important to incorporate this continuum of impairment into clinical and research practice.

Two general principles underlie the recommendations presented in this report: (1) The *Core Clinical Criteria* outlined later in the text are designed to be used in all clinical settings. The working group believes that it is essential to have clinical criteria that can be applied broadly, in any setting, without the need of highly specialized tests and/or procedures. (2) The *Clinical Research Criteria* outlined later in the text, which incorporate the use of biomarkers, are currently intended to be used only in research settings, including academic centers and clinical trials. There are several reasons for this limitation: (1) more research needs to be done to ensure that the criteria that include the use of biomarkers have been appropriately designed, (2) there is limited standardization of biomarkers from one locale to

another, and limited experience with cut-points for diagnosis, and (3) access to biomarkers may be limited in different settings.

As a result, some aspects of the clinical research criteria may need to be revised, as these criteria are put into practice and new findings emerge. The clinical research criteria include an outline of additional data that need to be acquired so as to refine and improve their application. From that perspective, the clinical research criteria are designed to be a work-in-progress that will be updated regularly, as new information becomes available.

In these recommendations, we use the term "mild cognitive impairment (MCI) due to AD" to refer to the symptomatic predementia phase of AD. This degree of cognitive impairment is not normal for age and, thus, constructs such as age-associated memory impairment and age-associated cognitive decline do not apply. From this perspective, MCI due to AD can be considered as a subset of the many causes of cognitive impairment that are not dementia (CIND), including impairments resulting from head trauma, substance abuse, or metabolic disturbance [4].

Thus, the concept of *"MCI due to AD"* is used throughout this article to reflect the fact that the ultimate focus of these criteria is to identify those symptomatic but nondemented individuals whose primary underlying pathophysiology is AD. Similar to AD dementia, MCI due to AD cannot be currently diagnosed by a laboratory test, but requires the judgment of a clinician. Thus, MCI is a syndrome defined by clinical, cognitive, and functional criteria [5,6]. Also, similar to AD dementia, etiologies in addition to AD pathophysiological processes may coexist in an individual who meets the criteria for MCI due to AD. Nevertheless, similar to the criteria proposed by the International Working Group of Dubois et al [7], these criteria assume that it is possible to identify those individuals with AD pathophysiological processes as the likely *primary* cause of their progressive cognitive dysfunction [8–10].

2. Core clinical criteria for the diagnosis of MCI

In this section, we outline the core clinical criteria for individuals with MCI. In considering the specifics of this clinical and cognitive syndrome, it is important to emphasize, as noted earlier in the text, that sharp demarcations between normal cognition and MCI and between MCI and dementia are difficult, and clinical judgment must be used to make these distinctions.

2.1. MCI—Criteria for the clinical and cognitive syndrome

2.1.1. Concern regarding a change in cognition—There should be evidence of concern about a change in cognition, in comparison with the person's previous level. This concern can be obtained from the patient, from an informant who knows the patient well, or from a skilled clinician observing the patient.

2.1.2. Impairment in one or more cognitive domains—There should be evidence of lower performance in one or more cognitive domains that is greater than would be expected for the patient's age and educational background. If repeated assessments are available, then a decline in performance should be evident over time. This change can occur in a variety of cognitive domains, including memory, executive function, attention, language, and visuospatial skills. An impairment in episodic memory (i.e., the ability to learn and retain new information) is seen most commonly in MCI patients who subsequently progress to a diagnosis of AD dementia. (See the section on the cognitive characteristics later in the text for further details).

2.1.3. Preservation of independence in functional abilities—Persons with MCI commonly have mild problems performing complex functional tasks which they used to perform previously, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors at performing such activities than in the past. Nevertheless, they generally maintain their independence of function in daily life, with minimal aids or assistance. It is recognized that the application of this criterion is challenging, as it requires knowledge about an individual's level of function at the current phase of their life. However, it is noteworthy that this type of information is also necessary for the determination of whether a person is demented.

2.1.4. Not demented—These cognitive changes should be sufficiently mild that there is no evidence of a significant impairment in social or occupational functioning. It should be emphasized that the diagnosis of MCI requires evidence of intraindividual change. If an individual has only been evaluated once, change will need to be inferred from the history and/or evidence that cognitive performance is impaired beyond what would have been expected for that individual. Serial evaluations are of course optimal, but may not be feasible in a particular circumstance.

2.2. Cognitive characteristics of MCI

It is important to determine whether there is objective evidence of cognitive decline, and if so, the degree of this decline in the reports by the individual and/or an informant. Cognitive testing is optimal for objectively assessing the degree of cognitive impairment for an individual. Scores on cognitive tests for individuals with MCI are typically 1 to 1.5 standard deviations below the mean for their age and education matched peers on culturally appropriate normative data (i.e., for the impaired domain(s), when available). It is emphasized that these ranges are guidelines and not cutoff scores.

2.2.1. Cognitive assessment—As noted earlier in the text, impairment in episodic memory (i.e., the ability to learn and retain new information) is most commonly seen in MCI patients who subsequently progress to a diagnosis of AD dementia. Research studies have shown that there are a variety of episodic memory tests that are useful for identifying those MCI patients who have a high likelihood of progressing to AD dementia within a few years. These tests share the characteristic that they assess both immediate and delayed recall, so that it is possible to determine retention over a delay. Many, although not all, of the tests that have proven useful in this regard are word-list learning tests with multiple trials. Such tests reveal the rate of learning over time, as well as the maximum amount acquired over the course of the learning trials. They are also useful for demonstrating that the individual is, in fact, paying attention to the task on immediate recall, which then can be used as a baseline to assess the relative amount of material retained on delayed recall. Examples of such tests include (but are not limited to): the Free and Cued Selective Reminding Test, the Rey Auditory Verbal Learning Test, and the California Verbal Learning Test. Other episodic memory measures include: immediate and delayed recall of a paragraph such as the Logical Memory I and II of the Wechsler Memory Scale Revised (or other versions) and immediate and delayed recall of nonverbal materials, such as the Visual Reproduction subtests of the Wechsler Memory Scale-Revised I and II.

Because other cognitive domains can be impaired among individuals with MCI, it is important to examine domains in addition to memory. These include: executive functions (e.g., set-shifting, reasoning, problem-solving, planning), language (e.g., naming, fluency, expressive speech, and comprehension), visuospatial skills, and attentional control (e.g., simple and divided attention). Many validated clinical neuropsychological measures are available to assess these cognitive domains, including (but not limited to): the Trail Making

Test (executive function), the Boston Naming Test, letter and category fluency (language), figure copying (spatial skills), and digit span forward (attention).

If formal cognitive testing is not feasible, then cognitive function can be assessed using a variety of simple, informal techniques. For example, the clinician can ask a patient to learn a street address and to recall it after a delay interval of a few minutes (e.g., John Brown, 42 Market Street, Chicago). Alternatively, the clinician can ask the patient to name three objects (e.g., a pen, a paper clip, and a dollar bill), place them in different locations around the room and subsequently ask the patient to recall the names of the objects and their locations, again after a brief delay. These types of approaches are relatively easy to perform during an office visit, and will yield informative results. It is important, however, for clinicians to recognize that these informal tests will likely be insensitive to subtle cognitive dysfunction during the early stages of MCI, and will often yield normal performance. In addition, these approaches typically do not assess cognitive domains beyond memory.

Finally, it must be recognized that atypical clinical presentations of AD may arise, such as the visual variant of AD (involving posterior cortical atrophy) or the language variant (sometimes called logopenic aphasia), and these clinical profiles are also consistent with MCI due to AD.

2.2.2. Summary of clinical and cognitive evaluation—The initiation of a clinical and cognitive evaluation typically includes a cognitive concern expressed by the patient, an informant, or a clinician observing the patient's performance. Cognitive decline can be documented by means of the history from the patient, preferably corroborated by an informant, or on the basis of observation by the clinician. Ideally, if serial assessments are available, they would be preferable, but in the setting of a single evaluation, this information is inferred from the history. The patient's cognition is assessed and found to be outside the normal range of function for the patient's age and educational background, but not sufficiently impaired to constitute dementia. The impairment can involve one or more cognitive domains. The clinician determines whether memory is prominently impaired, or whether the impairments in other cognitive domains predominate, such as spatial or language impairment. Typically, memory is the most common domain involved among patients who subsequently progress to AD dementia, as noted earlier in the text. There is generally mild functional impairment for complex tasks, but basic activities of daily living should be preserved, and the person should not meet criteria for dementia. It should be noted that the clinical syndrome, as summarized in this section and Table 1, is almost identical to the one previously described by Petersen et al [5,6,11].

2.2.3. Longitudinal cognitive evaluation—Evidence of progressive decline in cognition provides additional evidence that the individual has "MCI due to AD," as noted earlier in the text. Thus, it is important to obtain longitudinal assessments of cognition, whenever possible. It is recognized that a diagnosis will likely need to be given without the benefit of this information; however, obtaining objective evidence of progressive declines in cognition over time is important for establishing the accuracy of the diagnosis, as well as for assessing any potential treatment response.

2.2.4. Cautionary issues pertaining to cognitive assessment—It is important to emphasize that virtually all cognitive tests are sensitive to differences in age, education (i.e., literacy), and/or cultural variation among individuals. Age and educational norms are available for some tests, but few have norms that pertain to the oldest old (individuals aged ≥90 years). Moreover, considerable work remains to establish the reliability of cognitive tests across populations with wide cultural variation.

2.3. Etiology of the MCI clinical and cognitive syndrome consistent with AD

Once it has been determined that the clinical and cognitive syndrome of the individual is consistent with that associated with AD, but that the individual is not demented, the clinician must determine the likely primary cause, for example, degenerative, vascular, depressive, traumatic, medical comorbidities, or mixed disease. Typically, this information is derived from further historical information and ancillary testing (e.g., neuroimaging, laboratory studies, and neuropsychological assessment) that may prove informative.

To meet the core clinical criteria for MCI, it is necessary to rule out other systemic or brain diseases that could account for the decline in cognition (e.g., vascular, traumatic, medical). The goal of such an evaluation is to increase the likelihood that the underlying disease is a neurodegenerative disorder with characteristics consistent with AD. This diagnostic strategy is similar to the one that is used to diagnose "dementia due to AD." This may include seeking evidence for: (1) Parkinsonism, including prominent visual hallucinations, and rapid eye movement sleep abnormalities, often seen in dementia with Lewy bodies, (2) multiple vascular risk factors and/or the presence of extensive cerebrovascular disease on structural brain images, which is suggestive of vascular cognitive impairment, (3) prominent behavioral or language disorders early in the course of disease that may reflect frontotemporal lobar degeneration, or (4) very rapid cognitive decline that occurs over weeks or months, typically indicative of prion disease, neoplasm, or metabolic disorders. It should be noted that the pathological features of some of these disorders can exist in combination with AD (e.g., Lewy bodies and vascular disease), particularly among individuals at an advanced age.

The presence of vascular pathology, in the setting of MCI, is particularly challenging from a diagnostic perspective. Because AD pathology frequently coexists with vascular pathology, particularly at older ages, both may contribute to cognitive dysfunction. Thus, during life, it may be difficult to determine which pathological feature is the primary cause of the cognitive impairment.

Among the oldest old (i.e., those aged ≥90 years), there are additional difficulties in determining the etiology of the cognitive decline. For example, the pathological criteria for AD remain unclear for the oldest old.

2.3.1. Role of autosomal genetic mutations for AD—An additional issue is the role of genetics in the diagnosis. If an autosomal dominant form of AD is known to be present (i.e., mutation in *APP, PS1, PS2*), then the development of MCI is most likely the prodrome to AD dementia. The large majority of these cases develop early onset AD (i.e., onset below 65 years of age). There remains, however, variable certainty about the time course over which the progression from MCI to AD dementia will evolve in these individuals [12].

2.3.2. Role of genes that increase risk for AD—In addition, there are genetic influences on the development of late onset AD dementia. To date, the presence of one or two ε 4 alleles in the apolipoprotein E (*APOE*) gene is the only genetic variant broadly accepted as increasing risk for late-onset AD dementia, whereas the ε2 allele decreases risk. Evidence suggests that an individual who meets the clinical, cognitive, and etiologic criteria for MCI, and is also *APOE* ε4 positive, is more likely to progress to AD dementia within a few years than an individual without this genetic characteristic. It has been hypothesized that many additional genes play an important, but smaller role than *APOE*; these additional genes will also confer changes in risk for progression to AD dementia [13].

3. MCI—Research criteria incorporating biomarkers

In this section, we discuss the use of biomarkers in the diagnosis of "MCI due to AD." Much has been learned about the application of biomarkers to individuals with MCI. Thus, it seems important to incorporate this knowledge into the diagnostic framework outlined in these recommendations, recognizing as noted earlier in the text, that as new information emerges, it may be necessary to revise the way in which these recommendations incorporate biomarkers.

Two fundamental issues about individuals with MCI may be answered by the use of biomarkers: (1) To establish support for the underlying etiology of the clinical syndrome in an individual with MCI, which will have major importance for choosing the correct therapy, when effective treatments are available. (2) To determine the likelihood of cognitive and functional progression for an individual MCI patient to a more severe stage of MCI or to dementia, and the likelihood that this progression will occur within a defined period.

These questions are clearly interdependent, as different underlying etiologies can confer different prognoses for progression. However, a biomarker that is useful for defining an etiology may or may not be useful for prognostication, and vice versa. The different properties of biomarkers will ultimately drive their use in clinical situations, such as deciding whom to treat, as well as research situations that might include selection of subjects for clinical trials or for inclusion in longitudinal research studies. In addition, because the timing of progression to dementia is important, different biomarkers may have differential utility over the short- and long-term.

Biomarkers may be divided into several different classes. Some biomarkers directly reflect the pathology of AD by providing evidence of the presence of key proteins deposited in the brain during the course of AD, such as the beta-amyloid protein (Aβ) and tau [14]. Other biomarkers provide less direct or nonspecific evidence of AD by tracking a variety of indices of neuronal injury. These biomarkers may also have some specificity for AD, by virtue of the regional pattern of abnormalities. Conversely, other biomarker patterns can be useful in providing evidence of an alternative non-AD underlying cause.

The current pathological criteria for AD require evidence of Aβ deposition in plaques, along with evidence of tau deposition in neurofibrillary tangles. Evidence suggests that together the buildup of these two proteins in the brain is associated with neuronal injury. Thus, for the clinical research criteria proposed in this report to be based on the established pathological criteria, we have defined biomarkers in terms of whether they reflect Aβ deposition, tau deposition, or signs of neuronal injury.

Markers of Aβ deposition include both cerebrospinal fluid (CSF) measures of lower $A\beta_{42}$ levels [14–16] and positron-emission tomography (PET) evidence of Aβ deposition, using a variety of specific ligands [17]. Markers of tau accumulation include CSF measures of increased total tau or phosphorylated-tau (p-tau) [14–16].

It should be noted that increased Aβ deposition is seen in disorders other than AD (e.g., amyloid angiopathy). Likewise, although elevated levels of tau are clearly associated with AD, this finding may also occur in other neurodegenerative disorders (e.g., prion diseases). However, evidence of damage to neurons and synapses may also derive from direct measurement of tau (both total tau and p-tau) in the CSF, thus alterations in tau appear to be more nonspecific than the alterations in Aβ. Therefore, in these recommendations, CSF tau is considered to be a strong marker of the neuronal injury associated with AD. However, the two biomarkers in combination are extremely informative. Together with low CSF $A\beta_{42}$, elevated CSF tau provides a high likelihood of progression to AD in patients with MCI.

Measures of downstream neuronal injury include a number of structural and functional measures, including brain atrophy, and hypometabolism or hypoperfusion obtained with magnetic resonance imaging (MRI), PET, and single-photon emission computed tomography (SPECT) imaging [18–20].

A third group of biomarkers reflect biochemical changes related to processes such as cell death, synaptic damage, oxidative stress, or inflammation that may be part of the cascade of events that mediate damage, or the response to damage, in AD.

The major biomarkers in each of these categories are discussed later in the text and listed in Table 2.

3.1. Biomarkers reflecting Aβ

The amyloid plaques that are a hallmark feature of a pathological diagnosis of AD are reflected in biomarkers that can detect and quantify the Aβ protein that accumulates in the brain, as noted earlier in the text. This protein can be measured directly in CSF and plasma, however, the levels in CSF directly reflect the presence/amount of cerebral Aβ deposits (e.g., lower $A\beta_{42}$). PET scanning with a variety of ligands, some of which are still under development, can also detect fibrillar Aβ. CSF $A\beta_{42}$ and PET measures of fibrillar Aβ are strongly and inversely correlated with one another, and appear to reflect Aβ deposition in the brain [17].

Current evidence suggests that markers of amyloid pathology (i.e., CSF and PET) precede evidence of neuronal injury. This does not prove that Aβ is the initiating factor for the disease. However, it does suggest that these different categories of biomarkers seem to provide different sorts of information about the progress of disease in the brain.

3.2. Biomarkers reflecting neuronal injury

Elevated levels of tau are clearly associated with AD pathophysiological processes, as noted earlier in the text. However, changes in tau and phosphorylated-tau can also reflect general damage to neurons and synapses. In addition, AD also results in a wide range of structural and functional changes in the brain that have diagnostic and prognostic value in dementia and MCI, which appear to reflect damage to neurons and synapses. Many of these changes have topographic specificity for the neural damage or dysfunction that occurs in AD. Particular patterns of sequential involvement are characteristic of AD as well. Examples include loss of hippocampal volume seen on MRI, and reduction of glucose metabolism or perfusion in temporoparietal cortex that may be detected with PET or SPECT scanning. Although these biomarkers have been associated with the neuropathology of AD, regional atrophy, global atrophy, and regional hypometabolism and hypoperfusion are not specific for AD. These measures appear to provide evidence about the stage or severity of disease that may not be provided by Aβ biomarkers [21].

Other approaches to detection of downstream neuronal injury include the use of structural and functional measures that reflect more complex patterns of tissue loss or metabolic loss obtained with imaging procedures. These measures may be derived from data-driven statistical approaches in which many different brain regions are evaluated simultaneously. In these cases, replication and generalizability of findings must be demonstrated to develop data that can be used at the level of individual subject prediction.

Other techniques for which less data are currently available include diffusion tensor imaging, magnetic resonance spectroscopy, functional MRI, and resting BOLD functional connectivity. MRI perfusion has shown results similar to both SPECT/PET perfusion and PET metabolism, but available data are more limited.

3.3. Associated biochemical change

AD is characterized by numerous biochemical events, including oxidative stress (e.g., isoprostanes) and inflammation (e.g., cytokines). CSF, plasma, and imaging markers of these processes may provide information about specific pathways that are abnormal and could also provide information suggestive of underlying pathology. Additional work in this area is needed to know how useful these markers will be.

3.4. Limitations of current state of knowledge regarding biomarkers for AD

Many studies have used biomarkers to predict cognitive decline or progression to dementia among MCI patients, and most of the biomarkers in Table 2 are reported to be valuable in this situation. By contrast, there are several important limitations to current knowledge [22].

Few biomarkers have been compared with one another in multivariate studies, few have been validated with postmortem studies, and the use of combinations of biomarkers in studies has been limited. Therefore, it is currently difficult to understand the relative importance of different biomarkers when used together, and to interpret results when biomarker data conflict with one another.

Equally important, there is a dearth of truly predictive studies at the individual subject level or in unselected populations. Many biomarker studies report differences between “converters” and “stable” groups of subjects analyzed retrospectively (i.e., with subsequent knowledge of which subjects progressed to dementia).

Few studies define a specific cutoff value for a biomarker or biomarkers and then prospectively test its predictive accuracy. Effective use of biomarkers in the clinical arena will require the ability to assign a likelihood of decline or progression to dementia in an individual person over a specific time interval through the use of a single or multiple biomarkers.

Another major limitation is knowledge about the timing of decline or progression to dementia because the ability to detect change is dependent on the period of observation or prediction. Some biomarkers seem to have utility in predicting change over relatively short periods of observation, such as over 1 to 3 years. It seems likely that other types of biomarkers would be useful in predicting change over longer periods, such as many years or even decades. A complete understanding of the role of biomarkers in prediction of decline in MCI will require both short and long-term periods of observation.

Finally, little is known about outcome when biomarkers provide conflicting results, as noted earlier in the text. When a panel of biomarkers is used, it is possible that for some individuals, one biomarker will be positive, one negative, and one equivocal. This is complicated further by the fact that the biomarkers examined to date are not always clearly positive or clearly negative, but vary in degree. The long-term significance of such findings may also vary with the length of follow-up.

From a clinical perspective, it is important to emphasize, as noted earlier in the text, that although substantial deposits of Aβ and tau are required for a pathological diagnosis of AD, changes in these molecular markers in CSF are seen in other disorders (e.g., amyloid angiopathy, dementia with Lewy bodies, prion disease). Thus, the application of biomarkers as part of the clinical evaluation should consider other potential disorders, based on the overall clinical presentation of the patient.

3.5. Application of biomarkers to the clinical research diagnosis of MCI due to AD

In this section, we discuss the way in which biomarkers increase the likelihood that the MCI syndrome is due to the pathophysiological processes of AD. This diagnostic scheme is based on the wealth of biomarker and clinicopathological studies available. These data suggest that the conjoint application of clinical criteria and biomarkers can result in various levels of certainty that the MCI syndrome is due to AD pathophysiological processes.

For the purposes of the diagnostic approach we propose in these recommendations, two categories of biomarkers have been the most studied and applied to clinical outcomes. In this article, they are referred to as "Aβ" (which includes CSF $A\beta_{42}$ or PET amyloid imaging) and "biomarkers of neuronal injury" (which refers to CSF tau/p-tau, hippocampal, or medial temporal lobe atrophy on MRI, and temporoparietal/precuneus hypometabolism or hypoperfusion on PET or SPECT).

The criteria outlined later in the text are aimed at defining the level of certainty that the AD pathophysiological process is the underlying cause of the MCI syndrome in a given patient. The hypothesis underlying this classification scheme is that the evidence of both Aβ, and neuronal injury (either an increase in tau/p-tau or imaging biomarkers in a topographical pattern characteristic of AD), together confers the highest probability that the AD pathophysiological process is present. Conversely, if these biomarkers are negative, this may provide information concerning the likelihood of an alternate diagnosis. It is recognized that biomarker findings may be contradictory and that much remains to be learned about the outcome in these situations.

Currently, CSF $A\beta_{42}$ and tau measures, the ratio of CSF tau/$A\beta_{42}$, PET amyloid measures, and other biomarkers of neuronal injury such as hippocampal atrophy and temporoparietal hypometabolism have all been shown to predict progression of MCI to dementia. Whether one of these measures or a combination of them is more sensitive than the other, and whether quantitative values provide more information than a dichotomous rating are yet to be determined conclusively. It is also not yet known whether the best predictions of the actual rate of progression depend on the degree to which an individual expresses biomarkers of neuronal injury.

It is important to emphasize that standardization of these biomarkers is currently limited, and results often vary from laboratory to laboratory. Ultimately, it will be necessary to interpret biomarker data in the context of well-established normative values. "Positive" or abnormal values should fall within reliable and valid pathological ranges. Moreover, procedures for acquisition and analysis of samples need to be established to implement these biomarker criteria on a broad scale. Finally, although we consider biomarkers as "negative" or "positive" for purposes of classification, it is recognized that varying severities of an abnormality may confer different likelihoods or prognoses, which is currently difficult to quantify accurately for broad application.

In the coming years, when many of the unknown issues have been resolved, biomarkers reflecting AD pathophysiological processes in an individual with MCI will have two implications, depending on whether their levels fall within a range that supports the diagnosis of "MCI due to AD." First, if therapies directed at one or both of these two pathological proteins are being tested, or are effective for AD, then their detection with these biomarkers should indicate appropriate patient selection in terms of those most likely to derive therapeutic benefit. Second, detection of these biomarkers will predict a higher rate of cognitive and functional progression in patients with MCI whose biomarkers are positive as compared with MCI patients whose biomarkers are negative.

3.6. Biomarkers and levels of certainty for the diagnosis of MCI due to AD

In this section, we outline a probabilistic framework for the way in which biomarkers may be used to provide increasing levels of certainty that AD pathology is the cause of an individual's cognitive decline. That is, for those MCI subjects whose clinical and cognitive MCI syndrome is consistent with AD as the etiology, the addition of biomarkers would affect levels of certainty in the diagnosis.

In the most typical example in which the clinical and cognitive syndrome of MCI has been established, including evidence of an episodic memory disorder and a presumed degenerative etiology, the most likely cause is the neurodegenerative process of AD. However, the eventual outcome still has variable degrees of certainty. The likelihood of progression to AD dementia will vary with the severity of the cognitive decline and the nature of the evidence suggesting that AD pathophysiology is the underlying cause. Using the probabilistic framework proposed in these recommendations, positive biomarkers reflecting neuronal injury would increase the likelihood that progression to dementia will occur within a few years; however, positive findings reflecting both Aβ accumulation and neuronal injury together would confer the highest likelihood that the diagnosis is MCI due to AD.

In the example of the MCI patient who presents with an executive, spatial, or language impairment, it is still possible for such an individual to progress to AD dementia, although with a lower frequency. Thus, these presentations of MCI need to be recognized. The role of biomarkers may be particularly useful in this setting. For example, if a patient presents with a prominent visuospatial deficit and has significant atrophy in the parieto-occipital region on MRI, one might suspect a degenerative etiology likely leading to posterior cortical atrophy or the visual variant form of AD. If positive evidence of Aβ accumulation were also obtained on the basis of amyloid imaging or CSF measures, then the diagnosis of "MCI due to AD" would have a high likelihood.

In the following sections, we describe this hypothetical framework by which biomarkers may be used to increase diagnostic accuracy. As emphasized earlier, **this hypothetical framework will need to be tested by future studies and revised, as future data are generated.**

3.6.1. Biomarkers indicating a high likelihood that the MCI syndrome is due to AD

a. *A positive Aβ biomarker and a positive biomarker of neuronal injury.* The evidence to date indicates that this confers the highest likelihood that AD pathophysiological processes are the cause of the cognitive dysfunction. In addition, individuals with this biomarker profile are more likely to decline or progress to dementia due to AD in relatively short periods.

3.6.2. Biomarkers indicating an intermediate likelihood that the MCI syndrome is due to AD

a A positive Aβ biomarker in a situation in which neuronal injury biomarkers have not been or cannot be tested.

Or

b A positive biomarker of neuronal injury in a situation in which Aβ biomarkers have not been or cannot be tested.

Individuals falling within either of these categories show a major aspect of the AD pathological process, but without full evidence of both Aβ deposition and the downstream neuronal damage that characterize AD. Such individuals are considered to have a somewhat lower likelihood of underlying AD than individuals in whom both categories of biomarkers are positive. Note that this category does not include individuals in whom the two types of biomarkers provide conflicting information. This category accounts for situations in which one group of biomarkers cannot be tested because of access to technology, cost, or other reasons.

3.6.3. Situations in which biomarker information is uninformative

a. Results fall within ambiguous ranges (neither clearly positive nor negative) or biomarkers conflict with one another. In this category are also individuals in whom biomarkers have NOT been obtained.

There are many situations in which our current understanding of biomarkers limits the utility of biomarker testing. Clearly, there are many situations in which no biomarker testing can be or will be performed. This is likely to be the case in many routine clinical applications of the MCI criteria. Furthermore, there are many potential situations in which biomarkers could offer conflicting results (i.e., a positive Aβ biomarker and a negative biomarker of neuronal injury or the reverse). There is little available evidence to interpret the importance of the many different possible combinations of such biomarker outcomes; thus, these situations are classified together as uninformative. Finally, we recognize that results do not always fall into clearly “positive” and “negative” ranges but may be ambiguous, and the importance of such findings is unknown.

3.6.4. Biomarkers that suggest that the MCI syndrome is unlikely to be due to AD

a. *Negative biomarkers for both Aβ and neuronal injury.* The definitive absence of evidence of either Aβ deposition or neuronal injury strongly suggests that the MCI syndrome is not due to AD. In such situations, search for biomarkers that reflect alternative pathological processes should be considered. Such biomarkers are not as well established as those for AD. They may include: (1) prominent frontal or frontotemporal hypometabolism, hypoperfusion, or atrophy that often reflects frontotemporal lobar degeneration, (2) loss of dopamine transporters seen with SPECT imaging, often seen in dementia with Lewy bodies, (3) a periodic electroencephalogram, diffusion-weighted imaging changes on MRI, or an extremely high CSF tau protein in someone with very rapid dementia progression (progression from normal to moderate or severe dementia in ≤6 months) is typically indicative of prion disease, or (4) the presence of extensive cerebrovascular disease on structural brain images, without any biomarkers characteristic of AD, which is suggestive that the syndrome reflects vascular cognitive impairment. In all of these cases, the risk of subsequent decline is related to the most likely underlying pathology and the potential treatments that may be available.

4. Proposed terminology for classifying individuals with “MCI due to AD” with varying levels of certainty

We propose the terminology for “MCI due to AD” in the following sections, incorporating the use of biomarkers. It is fully recognized that there are limitations in our knowledge about these biomarkers, as noted earlier. These criteria are designed to stimulate the application of biomarkers in clinical research settings, thus permitting refinements in these criteria over time (Table 3).

4.1. MCI—Core clinical criteria

Individuals in this category meet the Core Clinical Criteria for MCI, based on the characteristics of the clinical syndrome and an examination of potential etiologic causes for the cognitive decline, as outlined earlier in the text. This evaluation process is designed to increase the likelihood that the underlying disease responsible for the cognitive dysfunction is a neurodegenerative disorder with characteristics consistent with AD. However, if biomarkers have been obtained, but the aggregate information is considered uninformative, this diagnosis will also apply. This would occur in situations in which biomarker results conflict with one another, or in situations in which results fall in an indeterminate range that is neither clearly negative nor positive. Patients in this category have the typical presentation of individuals who are at an increased risk of progressing to AD dementia. As noted earlier in the text, these individuals typically have a prominent impairment in episodic memory, but other patterns of cognitive impairment can also progress to AD dementia over time (e.g., visuospatial impairments). Note that this category also applies to situations in which biomarkers have NOT been tested. This category is still consistent with the possibility that the patient with MCI has underlying AD pathology

4.2. MCI due to AD—Intermediate likelihood

If the subject meets the Core Clinical Criteria for MCI, but in addition has either a positive biomarker reflecting Aβ deposition with an untested biomarker of neuronal injury, or a positive biomarker reflecting neuronal injury with an untested biomarker of Aβ, then there is increased likelihood that the outcome will be AD dementia. Thus, in the absence of one of these categories of biomarker information, the situation is still consistent with an *intermediate level of certainty* that the individual will progress to AD dementia over time. Therefore, patients who meet the criteria for this diagnosis have an intermediate level of certainty that they have “MCI due to AD.”

4.3. MCI due to AD—High likelihood

If the subject meets the Core Clinical Criteria for MCI, and in addition has positive biomarkers for both Aβ and neuronal injury, this provides *the highest level of certainty* that over time the individual will progress to AD dementia. Thus, patients who meet the criteria for this diagnosis have the highest level of certainty that they have “MCI due to AD,” and that they will progress to AD dementia over time.

4.4. MCI—Unlikely due to AD

Patients who have negative biomarkers for both Aβ and neuronal injury are considered to have the lowest likelihood of underlying AD pathophysiology. Although such individuals may still have AD, a search for an alternate cause of the MCI syndrome is warranted.

Acknowledgments

The authors would like to thank Dr. Cerise Elliott for her assistance with many of the organizational activities related to the preparation of this manuscript.

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Table 1

Summary of clinical and cognitive evaluation for MCI due to AD

Establish clinical and cognitive criteria
Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
Preservation of independence in functional abilities
Not demented
Examine etiology of MCI consistent with AD pathophysiological process
Rule out vascular, traumatic, medical causes of cognitive decline, where possible
Provide evidence of longitudinal decline in cognition, when feasible
Report history consistent with AD genetic factors, where relevant

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

Table 2

Biomarkers under examination for AD

Biomarkers of Aβ deposition
CSF $A\beta_{42}$
PET amyloid imaging
Biomarkers of neuronal injury
CSF tau/phosphorylated-tau
Hippocampal volume or medial temporal atrophy by volumetric measures or visual rating
Rate of brain atrophy
FDG-PET imaging
SPECT perfusion imaging
Less well validated biomarkers: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging, voxel-based and multivariate measures
Associated biochemical change
Inflammatory biomarkers (cytokines)
Oxidative stress (isoprostanes)
Other markers of synaptic damage and neurodegeneration such as cell death

Abbreviations: Aβ, beta-amyloid protein; CSF, cerebrospinal fluid; PET, positron emission tomography; FDG, fluorodeoxyglucose; SPECT, single photon emission tomography; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; BOLD, blood oxygen level-dependent; MR, magnetic resonance.

Table 3

MCI criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI-core clinical criteria	Uninformative	Conflicting/indeterminant/untested	Conflicting/indeterminant/untested
MCI due to AD—intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD—high likelihood	Highest	Positive	Positive
MCI—unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG. fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.