

UPDATE ARTICLE

Mild cognitive impairment (part 1): clinical characteristics and predictors of dementia

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Objective: To critically review and evaluate existing knowledge on the conceptual limits and clinical usefulness of the diagnosis of mild cognitive impairment (MCI) and the neuropsychological assessment and short- and long-term prognosis thereof.

Methods: We conducted a systematic search of the PubMed and Web of Science electronic databases, limited to articles published in English between 1999 and 2012. Based on the search terms mild cognitive impairment or MCI and epidemiology or diagnosis, we retrieved 1,698 articles, of which 248 were critically eligible (cross-sectional and longitudinal studies); the abstracts of the remaining 1,450 articles were also reviewed.

Results: A critical review on the MCI construct is provided, including conceptual and diagnostic aspects; epidemiological relevance; clinical assessment; prognosis; and outcome. The distinct definitions of cognitive impairment, MCI included, yield clinically heterogeneous groups of individuals. Those who will eventually progress to dementia may present with symptoms consistent with the definition of MCI; conversely, individuals with MCI may remain stable or return to normal cognitive function.

Conclusion: On clinical grounds, the cross-sectional diagnosis of MCI has limited prognostic relevance. The characterization of persistent and/or progressive cognitive deficits over time is a better approach for identification of cases at the pre-dementia stages, particularly if these cognitive abnormalities are consistent with the natural history of incipient Alzheimer's disease.

Keywords: Mild cognitive impairment; dementia; Alzheimer's disease; biomarkers

Introduction

The characterization of the transition between normal cognitive aging and the earliest manifestations of dementing disorders, particularly Alzheimer's disease (AD), has been an area of major interest in the last decades. Several definitions have attempted to describe these changes, such as benign forgetfulness of senescence (BFS),¹ age-associated memory impairment (AAMI),² age-associated cognitive decline (AACD),³ cognitive impairment but no dementia (CIND),⁴ and mild cognitive impairment (MCI).⁵ The latter has been the most widely employed definition both in clinical and research settings.⁶ The current diagnostic framework for MCI was first used approximately 13 years ago by Mayo Clinic researchers.⁵ MCI describes the cognitive state of non-demented individuals who report memory deficits, which should preferably be corroborated

by an informant, and measurable by objective testing; these deficits should not impair global cognitive function nor the ability to perform activities of daily living (ADLs). Individuals diagnosed with MCI have an increased risk of progression to dementia, AD being the putative outcome.

However, the experience accumulated in the last few years supports the notion that MCI is by no means a synonym of incipient dementia. Considering the insidious and progressive nature of most neurodegenerative disorders, we can assume that most patients who will progress to dementia will exhibit symptoms compatible with MCI at the earlier stages of the disease.⁷ However, the reverse may not be true, since many individuals who meet the diagnostic criteria for MCI in a given assessment may never progress to dementia.⁸ In this article, we aim to review the conceptual and practical aspects of MCI diagnosis, its clinical and neuropsychological assessment strategies, and the short and long-term prognosis associated with this condition.

Methods

We carried out a systematic search of the PubMed and Web of Science electronic databases using the following

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broad MeSH terms in the title or abstract, limited to articles published in English between 1999 and 2012: mild cognitive impairment OR MCI AND epidemiology OR diagnosis. We retrieved 1,698 articles, of which 248 were reviews. We reviewed the abstracts of the remaining 1,450 articles and critically summarized the most relevant publications in the following sections.

Results

Cognitive impairment in the elderly: the evolution of concepts

A number of overlapping definitions have been proposed since the 1950s to describe the transition between normal cognitive aging and pathological cognitive decline. These definitions developed from the concept of benign and malignant senescent forgetfulness described by Kral¹ more than 50 years ago and the age-related memory impairment described by Crook and Larrabee² in the late 1980s. Table 1 reviews the most commonly used terms and definitions, along with their major limitations.

The term mild cognitive impairment itself was firstly used by researchers at New York University⁹ to refer to a specific stage of cognitive deterioration identified through the Global Deterioration Scale (GDS). A grade 3 in this scale, which ranges from 1 to 7, indicates that an individual has cognitive complaints and shows subtle cognitive decline, but performance of usual occupational duties and social activities is preserved. A research group at Washington University in the early 1980s developed a similar dementia staging system, the Clinical Dementia Rating Scale (CDR).^{10,11} After a careful

clinical assessment, subjects may be classified into 5 major groups: CDR 0, CDR 0.5, CDR 1, CDR 2 and CDR 3, with higher scores indicating more severe cognitive impairment (CDR 0.5 through 1) or dementia (CDR 1 through 3). In addition to the CDR classification, subjects may be also classified according to the degree of overall functional impairment, as measured by the CDR sum of boxes (SoB), ranging from 0 to 18 points. A higher SoB score is indicative of more severe functional impairment. In several studies, a CDR 0.5 was used to include patients with incipient dementia; nonetheless, CDR 0.5 is also used interchangeably with MCI.

In the late 1990s, a group led by Ronald Petersen at the Mayo Clinic^{5,12} proposed five operational criteria for the clinical diagnosis of MCI (Table 2). In the original study,⁵ patients classified as having amnesic MCI showed a significant increase in the risk of progression to dementia (largely AD) during follow-up (i.e., 10% per year) as compared to elderly subjects with preserved cognitive function. In subsequent years, the criteria for MCI were revised to encompass other patterns of cognitive impairment in addition to memory per se.^{12,13} Therefore, one would be diagnosed in accordance to the number and type of functions affected: single-domain MCI, if only one cognitive domain was affected (memory or other cognitive domain); and multiple-domain MCI, if multiple cognitive domains were affected, including or not memory. However, the core aspect of MCI has been preserved, i.e., the presence of mild cognitive deficits that do not significantly interfere with the performance of ADLs. Figure 1 illustrates the distinct MCI subtypes according to the number and type of cognitive deficits within the core construct.

Table 1 Most common concepts used to define cognitive impairment/decline in the elderly

System	Criteria
Self-reported memory complaint	Complaints of memory loss in the absence of formal testing. When formal testing indicates no impairment, an individual would be classified as worried well.
Benign senescent forgetfulness	Inability to recall relatively unimportant data and parts of experience belonging to remote rather than the recent past; use of compensatory strategies.
Age-associated memory impairment	Gradual decline in memory (below young healthy norms), with other cognitive functions unimpaired. Adequate intellectual functioning.
Age-associated cognitive decline	Impairments (below age- and education-matched norms) in memory, learning, attention, thinking, language, or visuospatial functioning. Onset of decline is described as gradual and has been present for at least 6 months, which is confirmed by an informant.
Cognitive impairment no dementia	Cognitively impaired but no evidence of dementia according to DSM-IV criteria; cognitive impairment can be in one or multiple domains and have a variety of etiologies. More inclusive than age-associated memory impairment and age-related cognitive decline.
Mild cognitive impairment	Subjective complaint of cognitive impairment with objective cognitive impairment adjusted for age. Normal general intellectual function. Intact basic and instrumental activities of daily living.

Table 2 Operational criteria for the diagnosis of MCI^{5,12}

Mild cognitive impairment (MCI)
1. Consistent memory complaints which are preferentially corroborated by a close informant.
2. Objective characterization of specific deficits in memory and/or other cognitive domains, as indicated by a poor performance on validated cognitive and/or neuropsychological assessment tests (scores below than expected according to norms adjusted for age and educational level).
3. Preserved ability to perform activities of daily living (ADLs), or minimal impairment if considering instrumental ADLs.
4. Normal global cognitive function.
5. Absence of dementia.

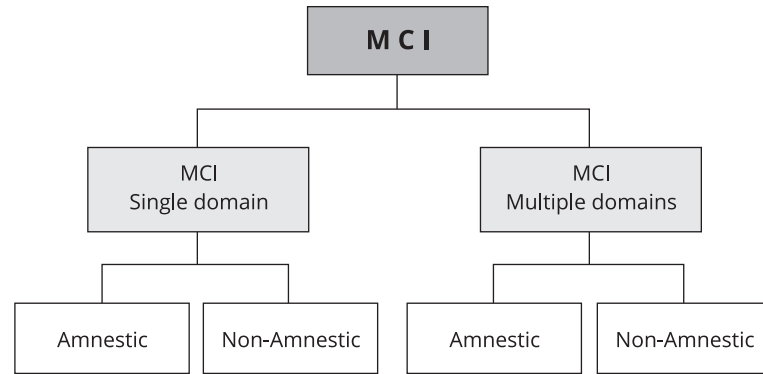


Figure 1 Classification of patients with mild cognitive impairment (MCI) according to the type and number of affected cognitive domains¹²

A recent task force, led by the U.S. National Institute on Aging (NIA) and the Alzheimer's Association (AA), proposed a revision of the MCI criteria and classification.¹⁴ Despite the similar clinical criteria for MCI diagnosis (known as the clinical core criteria), this revision placed greater emphasis on the probable etiologic mechanisms leading to cognitive impairment and its degree of certainty, with a major focus on the early diagnosis of AD in contrast to dementias of other etiologies (e.g., vascular dementia). These objectives would be achieved by a systematic evaluation of established disease biomarkers (e.g., cerebrospinal fluid, structural and functional neuroimaging, molecular amyloid imaging). In the second part of this review, we will address in detail the role of these biomarkers in the diagnosis and classification of AD.

Epidemiological characteristics of MCI in the elderly

The global prevalence of MCI in the elderly is estimated to be 15-20%.¹⁵ Yet, as in dementia, its prevalence rates depend heavily on the age range of the cohort under study, increasing from 3% in individuals aged 60 years or over to 15% among those aged 75 years or older. Nonetheless, prevalence rates of MCI show considerable variation in different studies, from 3 to 53%.¹⁶⁻¹⁹ In a recent systematic review, the incidence of all MCI subtypes ranged from 51 to 76.8 per 1,000 person-years; the incidence of amnestic MCI subtypes, from 9.9 to 40.6 per 1,000 person-years; and that of non-amnestic MCI subtypes, from 28 to 36.3 per 1,000 person-years.²⁰ The authors found that advanced age, low educational attainment, cerebral and cognitive reserve, and hypertension were the most significant risk factors for incident MCI.

Despite a wealth of data on the epidemiology of dementia, little information is available regarding its prodromal stages in the Brazilian population. In a clinical study, around one-third of elderly subjects assessed at a university memory center met the criteria for MCI; 60% of these subjects were classified as having multiple-domain MCI, 30% as amnestic MCI and 10% as non-amnestic

MCI.²¹ In a community-based study conducted in Southern Brazil, the incidence of MCI was 13 cases per 1,000 person-years.²² Thus, there is an urgent need for more epidemiological studies on the prevalence and incidence of MCI in the Brazilian elderly population.

Given the different definitions and conceptualizations that describe the cognitive dysfunction observed in the elderly, it is important to ascertain which is more suitable to illustrate the clinical framework of prodromal dementia. A notable analysis on how varied definitions work to detect early cognition changes in the general population was published in 2007, based on data from a large-scale multicenter study conducted in the United Kingdom, with a cohort of over 13,000 individuals aged 65 or older.²³ The authors showed that the classification of individuals as cognitively normal or cognitively impaired is highly dependent on how the inclusion criteria are defined. As a consequence, prevalence estimates can vary between 0.1 (adopting the most restrictive criteria) and 42% (when the definition was based only on the existence of subjective complaints). The prevalence of amnestic MCI as defined by the Mayo Clinic was 2.5% in this study.

Such wide variance could be explained by fundamental differences in the operationalization of the MCI diagnosis, including the requirement of objective measurement of cognitive decline (as opposed to self-reported complaints), the inclusion of cognitive functions other than episodic memory in the diagnostic workup, and the magnitude of cognitive impairment that delimits caseness (e.g., 1.5 SD below the mean). Hence, heterogeneity in methodological approaches may be the reason for the large variance in prevalence estimates, such as the definition of cognitive decline and diagnosis criterion employed; average age and educational level, among other demographic features; the coverage and sensitivity of batteries for cognitive testing; procedures for patients recruitment and the research setting (i.e., whether the study was conducted within the community or in specialized clinics; whether the patients applied voluntarily or were summoned by advertisements); and the presence of psychiatric comorbidities such as depression, anxiety, apathy or sleep disorders.

Diagnosis of MCI: is there a gold standard for clinical evaluation?

The clinical procedures for the diagnosis of MCI are complex and, in many instances, cognitive deficits are very mild, requiring more sophisticated cognitive assessments. In this scenario, a comprehensive neuropsychological evaluation may be considered a gold standard for the identification of patients with MCI.²⁴ However, formal neuropsychological testing may not be widely available, is time-consuming and expensive, requiring highly trained and skilled professionals to be carried out. Thus, there is a need for development of assessment strategies that are cost-effective, easy to administer and that generate results that are easy to interpret, while maintaining good sensitivity and specificity to identify MCI cases. Ultimately, these strategies should be widely available to all clinical settings. Many different approaches have been developed, with promising results.

The mini-mental state examination (MMSE) is the most widely used cognitive screening test in clinical and research settings.²⁵ Despite good sensitivity and specificity for diagnosis of dementia, its commonly used cutoff scores do not show good accuracy for discrimination of MCI, misidentifying most of these subjects as having normal cognitive function.²⁶ However, careful and qualitative analysis of performance on individual MMSE items and scores on relevant domains may yield more relevant information on mild cognitive disturbances rather than consideration of the total MMSE score alone. In a previous study, we showed that subjects with MCI had worse performance in specific MMSE subtests, according to their neuropsychological classification, despite having a similar total test score.²⁷ Individuals with amnesic MCI had worse performance only on the late recall subtest, while non-amnesic MCI patients had a worse performance on the three-stage command subtest. Subjects with multiple-domain MCI had a worse performance on the drawing task and on the late-recall subtest of the MMSE.

Other screening tests, such as the clock drawing test (CDT) and the semantic verbal fluency (VF), have also been tested for identification of MCI. As with other tests, they did not show good accuracy for the diagnosis of MCI, even when higher than usual cutoff scores were evaluated.^{28,29}

The Cambridge Cognitive test (CAMCOG) is a comprehensive cognitive assessment tool, part of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX), developed to provide the diagnosis of neuropsychiatric disorders - particularly dementia - in the elderly.³⁰ Despite good sensitivity and specificity to identify subjects with MCI (above 80%),²⁸ its administration is time-consuming (usually taking 20 to 30 minutes) and specific training is necessary for correct administration and interpretation of scores. These issues may limit its broad applicability in primary and secondary clinical settings. In a recent study by our group, Aprahamian et al.³¹ showed that scores on 4 out of 8 sub-items (language, memory, praxis, and calculation) retain the psychometric

properties of the whole test and similar accuracy to identify subjects with MCI (above 80%).

The combination of scores on two or more tests is a common strategy for increasing the accuracy of dementia diagnosis in clinical practice. In general, this yields better sensitivity and specificity to distinguish dementia from normal aging.^{32,33} In a series of studies, our group addressed whether the combination of cognitive screening tests would improve the identification of MCI. Abreu et al.³⁴ assessed whether the combination of an informant-based dementia screening test (Informant Questionnaire of Cognitive Decline in the Elderly - IQCODE) and an objective cognitive test (MMSE) would increase accuracy for identification of MCI. This combination did not significantly improve the sensitivity and specificity of each test alone in recognizing MCI cases as compared with healthy elderly subjects. In another study, Ladeira et al.³⁵ evaluated several possible combinations of the MMSE, CDT and VF tests. None of the chosen strategies were able to significantly improve the accuracy to differentiate MCI vs. healthy elderly controls beyond that found for the MMSE alone. These results are similar to previous studies with elderly populations.^{36,37}

Although some of the currently used cognitive screening tests yield good results for recognizing subjects with MCI, they still have important limitations, mainly because they were designed for the diagnosis of established dementia, not of its prodromal and milder manifestations. Therefore, it is important to develop new, more specific tools to tackle the challenge of identifying, with high accuracy, subjects with mild cognitive deficits. Indeed, some promising strategies have been developed and are being tested in several populations. The MoCA (Montreal Cognitive Assessment) is a brief cognitive test specifically developed to screen for mild cognitive deficits and has been regarded as a suitable test for initial workup of subjects with suspected MCI.^{38,39} It has been translated to and validated in European Portuguese⁴⁰ and Brazilian Portuguese,⁴¹ but further studies are still needed to assess its potential as a screening tool for MCI in our population, particularly among less educated samples. Another interesting assessment strategy is the use of computer-based cognitive tests. Several computer-based batteries have been developed, e.g., the Cambridge Neuropsychological Test Automated Battery (CANTAB)⁴² and the Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment (CANS-MCI),⁴³ which has recently been culturally adapted and validated into Brazilian Portuguese (Memória et al., Validation of the CANS-MCI in Brazilian older adults, submitted). This technology seeks to provide accurate and timely identification of MCI cases.

Longitudinal studies and MCI prognosis

In the seminal work of Petersen et al. at the Mayo Clinic,⁵ subjects with amnesic MCI showed a significantly higher risk of progression to AD as compared with cognitively preserved age-matched individuals (10-12%/year vs. 1-2%/year).¹³ Several studies have confirmed the higher

risk of progression to dementia in subjects with MCI, with rates ranging from 10 to 40% per year.⁴⁴⁻⁴⁷ Also, the Canadian Study of Health and Aging,⁴⁸ which adopted broader and more inclusive criteria to define cognitive loss in a large cohort of elderly without dementia (Cognitive Impairment No Dementia, CIND), showed that this population was at a higher risk of developing dementia than those with unimpaired cognition (47 versus 15%).

As the conceptual framework for MCI and its subtypes evolved, it was hypothesized that specific MCI subtypes would be associated with distinct outcomes. Pure amnesic MCI would be associated with higher risk of progression to AD, since impairment of episodic memory is considered the most common prodromal clinical symptom of AD. Multiple-domain MCI (amnesic and non-amnesic) would be associated with higher risk of progression to AD, vascular dementia (VD) or Lewy body dementia (LBD). Non-amnesic MCI, which is manifested by the involvement of one or more cognitive functions other than memory, would indicate higher risk of progression to frontotemporal dementia (FTD), primary progressive aphasia, or other non-dementia outcomes, e.g., major depression.⁴⁹

Despite this reasonable hypothetical foundation, the findings of several clinical and epidemiological studies did not corroborate the association between specific MCI subtypes and distinct outcomes. In The Vienna Trans-Danube Aging Study, the diagnosis of MCI was associated with higher rates of progression to AD on follow-up; however, this outcome was not subtype-specific, as the rate of conversion to AD of subjects presenting amnesic MCI was around 48.7%, vs. 26.8% in those with non-amnesic MCI.⁵⁰ Furthermore, the diagnosis of non-amnesic MCI was not predictive of other neurodegenerative dementias, such as LBD and FTD.⁵⁰ In a clinical study, the amnesic MCI and multiple-domain MCI subtype was as a predictor of both AD and VD, with no significant differences between these outcome.⁵¹

A large proportion of subjects classified as having MCI can resume normal cognitive function (backconversion or diagnostic instability) or maintain stable cognitive deficits, not progressing to dementia even on long-term follow-up.⁴⁴ In some studies, the rate of backconversion reached up to 40% of patients with MCI.^{52,53} In a longitudinal study carried out by our group, we found that 22% of patients initially diagnosed as MCI resumed normal cognitive function after 1 year of follow-up.⁵⁴ When the specific MCI subtype was taken into account, 37.5% of amnesic MCI subjects resumed normal cognitive function, as opposed to 12% of subjects with multiple-domain MCI and 14% of those with non-amnesic MCI. In this study, the best predictors of diagnostic instability were younger age and better global cognitive performance at baseline. These results were also observed in other studies.⁵⁵

Another key point when assessing individuals with MCI is to ascertain the predictors of conversion to dementia and AD. Most studies found that the main predictors of conversion from MCI to AD are older age, worse global

cognitive performance at baseline assessment and being an APOE ϵ 4 allele carrier.⁶ The presence of psychiatric symptoms, such as depression, apathy and anxiety, is also an important predictor of conversion.⁵⁶

In a recent study in Brazilian older adults, the most significant predictors of dementia in amnesic MCI subjects were older age, being an APOE ϵ 4 carrier, and worse performance on memory tests.⁵⁷ It is interesting to note that worsening of memory impairment was not shown to be a major predictor of MCI conversion in a large longitudinal study.⁵⁸ In this study, the emergence of executive dysfunction during follow-up was the most important determinant of conversion from MCI to AD. This finding highlights the importance of careful assessment of other cognitive domains beyond memory in these individuals.¹⁴

Despite the importance of characterizing the cognitive profile of MCI subjects and understanding the predictors of conversion to dementia, this provides little (or no) information on the trajectories from normal cognitive aging to MCI and, finally, to dementia. Therefore, we sought to determine the most common paths from normal cognition to AD.⁵⁹ In this work, we found that the most common pathway from cognitive aging and incipient AD was the emergence of single amnesic deficits (amnesic MCI) with the subsequent impairment of other cognitive domains (multiple-domain MCI, due to impairments in memory and executive functions) and, finally, the progression to more widespread cognitive and functional decline, characterizing the dementia syndrome. Similar results were also found in large community-based epidemiological studies.^{60,61}

Where lies the threshold between MCI and incipient dementia? The importance of functional assessment

The progression from MCI to dementia requires cognitive decline to be severe enough to impair one's ability to perform ADLs. According to the most recent criteria, MCI patients, unlike those with dementia, must have preserved global cognitive function, with no or minimal functional impairment, enabling them to perform ADLs independently.¹² However, recent studies have demonstrated that MCI subjects do have minimal functional deficits, in particular when facing more complex tasks, such as handling financial matters, paying bills, and shopping.⁶²⁻⁶⁵

However, when comes the time to decide whether a patient with MCI meets the diagnostic criteria for dementia on follow-up assessment (i.e., characterizing the actual conversion from MCI to AD), one must demonstrate that cognitive deficits do affect functioning.⁶⁶ This decision usually relies on the clinician's judgment, supported by relatively crude measures of functional ability.⁶⁷

The objective assessment of functional status is not a routine procedure when evaluating subjects with suspected cognitive impairment; rather, it usually relies on the subjective appraisal of a relative or caregiver, or even on the patient's self-judgment, rendering this information

inaccurate and subject to several sources of bias, including the informant's personality, mood, and cognitive state.⁶⁸ Therefore, the objective assessment of functional status may overcome some, if not most, of the limitation of informant-based scales. Also, the objective assessment of functional status not only helps to establish the threshold at which cognitive decline significantly impact ADL performance, but enables the investigation of which functional abilities are more sensitive to such alterations.

Considering the need for more objective functional assessment strategies, we validated the Brazilian Version of the Direct Assessment of Functional State, Revised (DAFS-R).⁶⁹ We have demonstrated that all MCI patients show mild objective functional impairments, but those who actually convert to AD show greater difficulties in performing specific tasks such as shopping and handling financial matters.⁷⁰ In addition, we found that functional impairment correlates significantly with executive dysfunction⁷¹ and with biological parameters intrinsic to the pathogenic process of AD.⁷⁰ Independent investigators have reported similar findings in a different population.⁷² Hence, the careful assessment of functional status may help the clinician to determine those MCI subjects most likely to progress to dementia.

Neuropsychiatric symptoms and risk of cognitive decline

Although patients with dementia commonly exhibit neuropsychiatric symptoms such as depression, anxiety, irritability, agitation, disinhibition, sleep disorders, and apathy, these occurrences have been consistently associated with faster cognitive decline and with increased risk of progressing to dementia across individuals with MCI.⁷³⁻⁷⁵ There is a growing tendency to admit that neuropsychiatric symptoms may accelerate the transitional state from MCI to dementia.^{74,75} These symptoms could confer a higher risk for dementia even among cognitively preserved persons.⁷³ Accordingly, neuropsychiatric symptoms now tend to be incorporated into any comprehensive clinical examination of individuals with MCI.

Despite wide acceptance by researchers and clinicians of the MCI construct as an important step toward understanding of the prodromal stages of dementia, others have harshly criticized the validity of this concept in light of the heterogeneity of its clinical setting and prognosis. Nonetheless, given the insidious progressive nature of most neurodegenerative diseases, including AD, it is reasonable to assume that most of the patients who tend to develop dementia will exhibit, at the earliest stages, symptoms consistent with MCI. However, the reverse may not be true, since many individuals who do meet the criteria for MCI in a given assessment resume normal cognitive function or do not progress to dementia at all.

Given the foregoing, is there an urgent need for improvement of the predictive accuracy of clinically defined MCI to aid the selection of subjects at risk of progressing to dementia? On clinical grounds, the best approach is to perform longitudinal reassessment of individuals diagnosed with MCI. Characterization of the

cognitive signs and symptoms that pertain to the natural history of the disease is undoubtedly an important aid to the early diagnosis of AD and other dementias. Massive efforts have been dedicated to increasing the accuracy of cross-sectional diagnosis of pre-dementia AD, and definite progress has been achieved in the development of biomarkers which reflect the core changes observed in the disease. In the future, the association of clinical and biological markers may help increase the specificity of MCI criteria, thus enabling identification of patients at actual risk of progression. Indeed, the use of biomarkers has been included in the most recent revisions of the diagnostic criteria for AD and MCI.⁷⁶⁻⁷⁸ In the second part of this review, we will address recent developments regarding biological markers of AD and how they can help improve the predictive accuracy of the clinical diagnosis of MCI.

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Disclosure

The authors report no conflicts of interest.

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